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Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome (Review)

Chen Y, Schieppati A, Chen X, Cai G, Zamora J, Giuliano GA, Braun N, Perna A

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Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD004293.

DOI: 10.1002/14651858.CD004293.pub3.

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Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Yizhi Chen^{1,2}, Arrigo Schieppati³, Xiangmei Chen¹, Guangyan Cai¹, Javier Zamora^{4,5}, Giovanni A Giuliano², Norbert Braun^{6,7}, Annalisa Perna²

¹Department of Nephrology, Chinese PLA General Hospital, Chinese PLA Institute of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing, China. ²Department of Renal Medicine, Laboratory of Biostatistics, Clinical Research Center for Rare Diseases “Aldo e Cele Daccò”, Mario Negri Institute for Pharmacological Research, Ranica (Bergamo), Italy. ³Unit of Nephrology, Azienda Ospedaliera “Ospedali Riuniti di Bergamo”, Bergamo, Italy. ⁴Clinical Biostatistics Unit, Ramon y Cajal Institute for Health Research (IRYCIS), CIBER Epidemiology and Public Health (CIBERESP) and Cochrane Collaborating Centre, Madrid, Spain. ⁵CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain. ⁶Department of Internal Medicine, MediClin Müriz-Klinikum Waren, Waren/Müriz, Germany. ⁷Renal Services, Mueritz-Klinik, Klink, Germany

Contact address: Annalisa Perna, Department of Renal Medicine, Laboratory of Biostatistics, Clinical Research Center for Rare Diseases “Aldo e Cele Daccò”, Mario Negri Institute for Pharmacological Research, Ranica (Bergamo), 24020, Italy. perna@marionegri.it.

Editorial group: Cochrane Kidney and Transplant Group.

Publication status and date: Edited (no change to conclusions), published in Issue 11, 2014.

Citation: Chen Y, Schieppati A, Chen X, Cai G, Zamora J, Giuliano GA, Braun N, Perna A. Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. *Cochrane Database of Systematic Reviews* 2014, Issue 10. Art. No.: CD004293. DOI: 10.1002/14651858.CD004293.pub3.

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ABSTRACT

Background

Idiopathic membranous nephropathy (IMN) is the most common form of nephrotic syndrome in adults. The disease shows a benign or indolent course in the majority of patients, with a rate of spontaneous complete or partial remission of nephrotic syndrome as high as 30% or more. Despite this, 30% to 40% of patients progress toward end-stage kidney disease (ESKD) within five to 15 years. The efficacy and safety of immunosuppression for IMN with nephrotic syndrome are still controversial. This is an update of a Cochrane review first published in 2004.

Objectives

The aim of this review was to evaluate the safety and efficacy of immunosuppressive treatments for adult patients with IMN and nephrotic syndrome. Moreover it was attempted to identify the best therapeutic regimen, when to start immunosuppression and whether the above therapies should be given to all adult patients at high risk of progression to ESKD or only restricted to those with impaired kidney function.

Search methods

We searched Cochrane Renal Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Chinese databases, reference lists of articles, and clinical trial registries to June 2014. We also contacted principal investigators of some of the studies for additional information.

Selection criteria

Randomised controlled trials (RCTs) investigating the effects of immunosuppression in adults with IMN and nephrotic syndrome.

Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome (Review)

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Data collection and analysis

Study selection, data extraction, quality assessment, and data synthesis were performed using the Cochrane-recommended methods. Summary estimates of effect were obtained using a random-effects model, and results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes, and mean difference (MD) and 95% CI for continuous outcomes.

Main results

Thirty nine studies with 1825 patients were included, 36 of these could be included in our meta-analyses. The data from two studies could not be extracted and one study was terminated due to poor accrual. Immunosuppression significantly reduced all-cause mortality or risk of ESKD ((15 studies, 791 patients): RR 0.58 (95% CI 0.36 to 0.95, $P = 0.03$) and risk of ESKD ((15 studies, 791 patients): RR 0.55, 95% CI 0.31 to 0.95, $P = 0.03$), increased complete or partial remission ((16 studies, 864 patients): RR 1.31, 95% CI 1.01 to 1.70, $P = 0.04$), and decreased proteinuria ((9 studies, 393 patients): MD -0.95 g/24 h, 95% CI -1.81 to -0.09, $P = 0.03$) at the end of follow-up (range 6 to 120 months). However this regimen was associated with more discontinuations or hospitalisations ((16 studies, 880 studies): RR 5.35, 95% CI 2.19 to 13.02, $P = 0.0002$). Combined corticosteroids and alkylating agents significantly reduced death or risk of ESKD ((8 studies, 448 patients): RR 0.44, 95% CI 0.26 to 0.75, $P = 0.002$) and ESKD ((8 studies, 448 patients): RR 0.45, 95% CI 0.25 to 0.81, $P = 0.008$), increased complete or partial remission ((7 studies, 422 patients): RR 1.46, 95% CI 1.13 to 1.89, $P = 0.004$) and complete remission ((7 studies, 422 patients): RR 2.32, 95% CI 1.61 to 3.32, $P < 0.00001$), and decreased proteinuria ((6 studies, 279 patients): MD -1.25 g/24 h, 95% CI -1.93 to -0.57, $P = 0.0003$) at the end of follow-up (range 9 to 120 months). In a population with an assumed risk of death or ESKD of 181/1000 patients, this regimen would be expected to reduce the number of patients experiencing death or ESKD to 80/1000 patients (range 47 to 136). In a population with an assumed complete or partial remission of 408/1000 patients, this regimen would be expected to increase the number of patients experiencing complete or partial remission to 596/1000 patients (range 462 to 772). However this combined regimen was associated with a significantly higher risk of discontinuation or hospitalisation due to adverse effects ((4 studies, 303 patients): RR 4.20, 95% CI 1.15 to 15.32, $P = 0.03$). Whether this combined therapy should be indicated in all adult patients at high risk of progression to ESKD or only restricted to those with deteriorating kidney function still remained unclear. Cyclophosphamide was safer than chlorambucil ((3 studies, 147 patients): RR 0.48, 95% CI 0.26 to 0.90, $P = 0.02$). There was no clear evidence to support the use of either corticosteroid or alkylating agent monotherapy. Cyclosporine and mycophenolate mofetil failed to show superiority over alkylating agents. Tacrolimus and adrenocorticotrophic hormone significantly reduced proteinuria. The numbers of corresponding studies related to tacrolimus, mycophenolate mofetil, adrenocorticotrophic hormone, azathioprine, mizoribine, and Tripterygium wilfordii are still too sparse to draw final conclusions.

Authors' conclusions

In this update, a combined alkylating agent and corticosteroid regimen had short- and long-term benefits on adult IMN with nephrotic syndrome. Among alkylating agents, cyclophosphamide was safer than chlorambucil. This regimen was significantly associated with more withdrawals or hospitalisations. It should be emphasised that the number of included studies with high-quality design was relatively small and most of included studies did not have adequate follow-up and enough power to assess the prespecified definite endpoints. Although a six-month course of alternating monthly cycles of corticosteroids and cyclophosphamide was recommended by the KDIGO Clinical Practice Guideline 2012 as the initial therapy for adult IMN with nephrotic syndrome, clinicians should inform their patients of the lack of high-quality evidence for these benefits as well as the well-recognised adverse effects of this therapy. Cyclosporine or tacrolimus was recommended by the KDIGO Clinical Practice Guideline 2012 as the alternative regimen for adult IMN with nephrotic syndrome; however, there was no evidence that calcineurin inhibitors could alter the combined outcome of death or ESKD.

PLAIN LANGUAGE SUMMARY

Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Idiopathic membranous nephropathy (IMN) is a disease in which glomerular basement membrane becomes thickening by light microscopy on renal biopsy and it represents a major cause of primary nephrotic syndrome in adults. A combined alkylating agent and corticosteroid regimen had short- and long-term benefits on adult IMN with nephrotic syndrome. Among alkylating agents, cyclophosphamide was safer than chlorambucil. It should be emphasised that the number of included randomised studies with high-quality design was relatively small and most of the included studies did not have adequate follow-up and enough power to assess the prespecified outcomes. Meanwhile, this regimen was significantly associated with more withdrawals or hospitalisations. Although a

six-month course of alternating monthly cycles of corticosteroids and cyclophosphamide was recommended by the KDIGO Clinical Practice Guideline 2012 as the initial therapy for adult IMN with nephrotic syndrome, clinicians should inform their patients of the lack of high-quality evidence for these benefits as well as the well-recognised adverse effects of this therapy. Whether this combined therapy should be indicated in all adult patients at high risk of progression to ESKD or only restricted to those with deteriorating kidney function still remained unclear.

Cyclosporine or tacrolimus was recommended by the KDIGO Clinical Practice Guideline 2012 as the alternative regimen for adult IMN with nephrotic syndrome; however, there was no evidence that calcineurin inhibitors could alter the definite endpoints such as all-cause mortality or risk of ESKD. There was no clear evidence to support the use of either corticosteroid or alkylating agent monotherapy. The numbers of corresponding studies related to tacrolimus, mycophenolate mofetil, adrenocorticotrophic hormone, azathioprine, mizoribine, and Tripterygium wilfordii are still too sparse to draw final conclusions.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Immunosuppressive treatments versus no treatment or angiotensin-converting enzyme inhibitor (ACEi) for adult IMN with nephrotic syndrome					
Patient or population: adults with IMN and nephrotic syndrome Settings: Intervention: immunosuppressive treatments Comparison: no treatment or ACEi					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No treatment or ACEi	Immunosuppressive treatments			
Death or ESKD (dialysis/transplantation) Follow-up: 6 to 120 months	Study population		RR 0.58 (0.36 to 0.95) P = 0.03	791 (15)	⊕⊕⊕⊖ Moderate ¹
	167 per 1000	97 per 1000 (60 to 159)			
	Moderate				
	91 per 1000	53 per 1000 (33 to 86)			
ESKD (dialysis/transplantation) Follow-up: 6 to 120 months	Study population		RR 0.55 (0.31 to 0.95) P = 0.03	791 (15)	⊕⊕⊕⊖ Moderate ¹
	125 per 1000	69 per 1000 (39 to 119)			
	Moderate				
	71 per 1000	39 per 1000 (22 to 67)			

Complete or partial remis- sion Follow-up: 6 to 120 months	Study population		RR 1.31 (1.01 to 1.70) P = 0.04	864 (16)	⊕⊕⊕⊖ Moderate ²
	296 per 1000	388 per 1000 (299 to 504)			
	Moderate				
	306 per 1000	401 per 1000 (309 to 520)			
Temporary or permanent discontinuation or hospi- talisation due to adverse effects Follow-up: 6 to 120 months	Study population		RR 5.35 (2.19 to 13.02) P = 0.0002	880 (16)	⊕⊕⊕⊕ high
	2 per 1000	13 per 1000 (5 to 31)			
	Moderate				
	0 per 1000	0 per 1000 (0 to 0)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹The relatively small number of included RCTs with high-quality design and adequate follow-up did not guarantee enough power to appropriately assess the definite endpoint

²Substantial heterogeneity (P = 0.004, I² = 53%)

ESKD - end-stage kidney disease; IMN - idiopathic membranous nephropathy

BACKGROUND

This is an update of a Cochrane review investigating the effects of immunosuppressive treatments in adult patients with idiopathic membranous nephropathy (IMN) and nephrotic syndrome (Schieppati 2004).

Description of the condition

IMN is the most common form of primary nephrotic syndrome in adults (Hofstra 2012). The disease shows a benign or indolent course in about one third of patients, with a high rate of spontaneous remission. Approximately another one third continues to have nephrotic syndrome but maintains normal kidney function. Despite this, 10% to 30% of patients progress toward end-stage kidney disease (ESKD) within 10 years (Waldman 2009). If follow-up is extended to 10 to 20 years, progression to ESKD may occur in 50% to 60% of patients without treatment (Ponticelli 2010).

Description of the intervention

Several immunosuppressive treatments have been used (Hofstra 2010a; Hofstra 2012; Ponticelli 2010; Ruggenenti 2009; Waldman 2009), including corticosteroids (Coggins 1979), alkylating agents (chlorambucil and cyclophosphamide) (Donadio 1974a; Imbasciati 1980), azathioprine (Silverberg 1976), and mizoribine (Shibasaki 2004). More recently, calcineurin inhibitors (cyclosporine and tacrolimus) (Cattran 1995; Praga 2007), mycophenolate mofetil (Chan 2007), adrenocorticotrophic hormone (Arnadottir 2006), Tripterygium wilfordii (a traditional Chinese immunosuppressive medicine) (Liu 2009b), and newer therapeutic approaches such as biologics (rituximab and eculizumab) (Appel 2002; Remuzzi 2002) and high-dose gamma-globulin (JPRN-UMIN000006939) have been proposed. However due to the uncertain risk-benefit profile of these regimens and the lack of definite evidence on altering the long-term course of the disease, the most appropriate therapy still cannot be easily identified.

Why it is important to do this review

Four meta-analyses have been performed in this field (Couchoud 1994; Hogan 1995; Imperiale 1995; Schieppati 2004). Meta-analysis of data from eight randomised controlled trials (RCTs) enrolling 526 patients showed that there was a tendency in favour of immunosuppressive treatments (corticosteroids, alkylating agents and azathioprine) in two surrogate outcomes (improvement in proteinuria and impairment of kidney function). However, there was no statistically significant difference in complete remission and renal survival rate (Couchoud 1994). Imperiale 1995 included five prospective studies, four RCTs and one non-RCT, in which

alkylating agents were compared with corticosteroids, placebo or symptomatic treatments. They found a beneficial effect of alkylating agents on complete or partial remission in 228 patients, of whom 202 were included in RCTs. However there was not enough evidence related to the long-term effects of alkylating agents on the definite endpoints. Hogan 1995 performed a pooled analysis of 35 retrospective and prospective studies in 1815 patients, of whom 475 were included in RCTs. Complete remission was more frequently with the use of alkylating agents compared with no treatment or corticosteroids. However, there was still no evidence that corticosteroids or alkylating therapy could improve renal survival in the long run.

In 2004, a Cochrane systematic review (Schieppati 2004) was published with the aim to assess the role of available immunosuppressive treatments. A total of 18 RCTs with 1025 patients were selected and analysed. Immunosuppressive treatments, especially alkylating agents (chlorambucil and cyclophosphamide) and cyclosporine, could increase complete or partial remission. However, the long-term effects of immunosuppressive treatments on definite endpoints such as all-cause mortality or renal survival rate could not be demonstrated. As expected, immunosuppressive treatments led to a significantly higher risk of severe adverse effects.

During the latest decade some RCTs evaluating newer immunosuppressive therapies have been published. These alternative agents were expected to be more effective and less toxic. However Dussol 2008 failed to demonstrate the effect of mycophenolate mofetil on complete or partial remission. Chen 2010a reported that tacrolimus was associated with high risk for relapse. There was no evidence related to the favourable impact of adrenocorticotrophic hormone on all-cause mortality or risk of ESKD (Arnadottir 2006; Ponticelli 2006). More studies that evaluated the effects of corticosteroids, alkylating agents, and cyclosporine have also been published (Jha 2007; Kosmadakis 2010; Naumovic 2011). Thus there is need to update the previously published Cochrane systematic review in order to explore whether adding novel agents could modify previous findings.

OBJECTIVES

The aim of this review was to evaluate the safety and efficacy of immunosuppressive treatments for adult patients with IMN and nephrotic syndrome. Moreover it was attempted to identify the best therapeutic regimen, when to start immunosuppression and whether the above therapies should be given to all adult patients at high risk of progression to ESKD or only restricted to those with impaired kidney function.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs aimed to assess the effects of immunosuppressive treatments in adult patients with IMN and nephrotic syndrome were included. All the included RCTs had a follow-up of at least six months. Quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) were excluded.

Types of participants

Inclusion criteria

- Adults
- Histologically proven diagnosis of IMN
- Diagnosis of nephrotic syndrome as defined by the authors in each single study. In studies that included a minority of non-nephrotic patients analyses were restricted to nephrotic patients only. In absence of an explicit definition of nephrotic syndrome, the cut-off value of proteinuria above 3.5 g/24 h was used

Exclusion criteria

Secondary forms of membranous nephropathy were excluded. We also excluded studies where it was impossible to identify how many adult IMN patients had nephrotic syndrome, unless it was assessed that the majority of adult patients had IMN and nephrotic syndrome and/or this information could be inferred by baseline characteristics.

Types of interventions

The widely recognised immunosuppressive treatments included corticosteroids, alkylating agents (chlorambucil and cyclophosphamide), calcineurin inhibitors (cyclosporine and tacrolimus), sirolimus, mycophenolate mofetil, and synthetic adrenocorticotrophic hormone (Hofstra 2012; Ponticelli 2010; Waldman 2009). Other seldom studied immunosuppressive regimens such as Tripterygium wilfordii (a traditional Chinese immunosuppressive medicine) (Cameron 2011; Chen 2010a; Goldbach-Mansky 2009; Tao 2002; Xu 2009), leflunomide (Chen 2010b; Tam 2006), azathioprine (Ahuja 1999), mizoribine (Yoshioka 2000), methotrexate (Lehman 2004), and levamisole (Srivastava 1991) were also investigated. Furthermore, biologics (eculizumab and rituximab) and high-dose gamma-globulin were considered to be potentially eligible for this review (Appel 2002; Remuzzi 2002; Ruggerenti 2009; JPRN-UMIN000006939).

The following interventions, nonimmunological in nature, were excluded: drugs aimed to reduce proteinuria through the inhibition of renin-angiotensin system (e.g. angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or

aliskiren); drugs aimed to correct dyslipidaemia (e.g. statins); anti-aldosterone drugs (e.g. spironolactone); nonsteroidal anti-inflammatory drugs (e.g. indomethacin).

Types of outcome measures

Primary outcomes

- Composite definite endpoints (death or ESKD), death alone (all causes), and risk of ESKD (need renal replacement therapy) alone at the last follow-up

Secondary outcomes

- 100% or 50% serum creatinine (SCr) increase from baseline at different time points and at the last follow-up
 - SCr ($\mu\text{mol/L}$) or glomerular filtration rate (GFR) (mL/min/1.73 m^2) at different time points and at the last follow-up
 - Complete or partial remission, complete remission alone, and partial remission alone at different time points and at the last follow-up.
 - Complete and partial remission of nephrotic syndrome was assessed according to the definition provided in each single study.
 - In the absence of an explicit definition, complete remission was defined as proteinuria less than 0.3 g/24 h and with a normal or stable SCr (within 50% of baseline value).
 - In the absence of an explicit definition, partial remission was defined as proteinuria reduced by at least 50% and remained between 0.3 - 3.5 g/24 h with a normal or stable SCr (within 50% of baseline value).
 - Proteinuria (g/24 h) at different time points and at the last follow-up.
 - Severe adverse events (defined as those leading to patient temporary or permanent withdrawal or hospitalisation).

Search methods for identification of studies

For this update we searched the Cochrane Renal Group's Specialised Register (June 2014) through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's specialised register contains studies identified from the following sources.

- Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
- Weekly searches of MEDLINE OVID SP
- Handsearching of renal-related journals and the proceedings of major renal conferences
- Searching the current year of EMBASE OVID SP
- Weekly current awareness alerts for selected renal journals
- Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the [Cochrane Renal Group](#). See [Appendix 1](#) for search terms used in strategies for this review. We also searched the following databases in order to further identify potentially eligible RCTs (all accessed in June 2012).

- United States National Institutes of Health Clinical Trial Registry (<http://clinicaltrials.gov/>)
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/>)
- Chinese Clinical Trial Registry (ChiCTR) (<http://www.chictr.org/en/>)
- China Biomedicine Database (CBM) (<http://sinomed.imicams.ac.cn/>)
- China National Knowledge Infrastructure (CNKI) (<http://www.cnki.net/>)
- China Wei Pu Database (<http://www.cqvip.com/>)
- China Wang Fang Database (<http://www.wanfangdata.com.cn/>)
- The University of Hong Kong (HKU) Clinical Trial Register (<http://www.hkclinicaltrials.com/>)

Please refer to our review published in 2004 for the original search strategies used ([Schieppati 2004](#)).

Data collection and analysis

Selection of studies

The initial 2004 version of this review was undertaken by six authors. The search strategy was initially performed independently by two authors in December 2003. Two authors independently inspected all articles identified in abstract form. For studies that could possibly be RCTs, or in the case of disagreement between the two authors, the full articles were obtained. In turn, the same authors compiled an 'ad hoc' questionnaire and they revised these articles independently. The questionnaires were then cross-checked and discrepancies were resolved by discussion with a third author. One author provided unpublished material, handsearched abstract books in German language and helped preparing the manuscript. In this update, selection of studies was done by four authors. The titles and abstracts of retrieved citations, and where necessary the full-text articles, were independently evaluated by two authors. A third author helped search for studies published in Chinese. Disagreements were resolved by consulting a fourth author.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals, were translated before assessment. In case of duplicates, reports were grouped together and the publication with the most complete data was included. When relevant outcomes were only published in earlier versions these data were used. Any differences between published versions were highlighted. A third author addressed the resolved these discrepancies. If needed, further details were requested by written correspondence to principal investigators and any relevant information obtained in this manner was included in this review. We also contacted principal investigators for missing data whenever necessary. Disagreements were resolved by consultation with a third author.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool ([Higgins 2011](#)) (see [Appendix 2](#)).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
 - Participants and personnel
 - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

Data were quantitatively combined by two independent authors. Dichotomous outcomes were expressed as risk ratio (RR) with 95% confidence intervals (CI). When a continuous scale of measurement was used, the mean difference (MD) was chosen or the standardised mean difference (SMD) was considered if a different scale was adopted.

Unit of analysis issues

Studies with multiple intervention arms were analysed by entering each pair-wise comparison separately. For dichotomous outcomes, both the number of events and the total number of patients were halved. For continuous outcomes, only the total numbers of participants were halved, while the means and standard deviations were left unchanged ([Higgins 2011](#)).

Dealing with missing data

Missing data were assessed for each included study. For missing participants due to drop-out, intention-to-treat analysis (ITT) was performed and compared with per-protocol analysis (PP) for the dichotomous data; while the continuous data remained unchanged due to the difficulty of application of ITT for this type of data (Moher 2010). For missing statistics such as standard deviations, these studies were not considered in the meta-analysis unless the missing data could be appropriately imputed using methods recommended by the Cochrane Collaboration (Higgins 2011). We also contacted principal investigators to request the missing data if possible.

Assessment of heterogeneity

Heterogeneity was assessed by using Q test and quantified by using I^2 statistic (Higgins 2011). The threshold P value of heterogeneity was 0.10. The I^2 statistic of 25%, 50%, and 75% was interpreted as indicating low, medium, and high levels of heterogeneity, respectively.

Assessment of reporting biases

Reporting biases such as publication bias were firstly addressed by using funnel plots and then further quantified by using Harbord test if there was adequate number of identified RCTs (i.e. at least 10 studies) (Harbord 2006; Harbord 2009, Higgins 2011). Harbord test was performed by using STATA software (version 11.2).

Data synthesis

A random-effects model was used for analyses of both dichotomous and continuous data. Robustness of study findings was also confirmed by using the fixed-effect model when appropriate. The quality of evidence was assessed by using GRADE Profiler software (version 3.6).

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity (e.g. participants and interventions). Heterogeneity among participants could be related to age, renal pathology, and disease severity. Heterogeneity in treatments could be related to the route, dose and duration of therapies during the studies and whether relative agents were previously used before entry to studies. Subgroup analysis was also performed to explore the following covariates, i.e. language of publication, source of funding, sample size calculation.

Sensitivity analysis

We performed sensitivity analysis in order to explore the influence of following factors.

- Repeating the analysis excluding unpublished studies or low quality studies based on the assessment of risk of bias;
- Repeating the analysis excluding any very long or very large study to determine the extent to which they unduly influenced the results.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#).

Results of the search

in our 2004 original review (Schieppati 2004) after screening 943 records, 18 studies (19 records) were identified (Ahmed 1994; Branten 1998; Braun 1995; Cameron 1990; Cattran 1989; Cattran 1995; Cattran 2001; Coggins 1979; CYCLOMEN Study 1994; Donadio 1974a; Falk 1992; Imbasciati 1980; Murphy 1992; Pahari 1993; Ponticelli 1992; Ponticelli 1998; Reichert 1994; Silverberg 1976).

In this update the Cochrane Renal Group's Specialised Register was searched and 17 new studies (Arnadottir 2006; Chan 2007; Chen 2010a; Dussol 2008; Dyadyk 2001; Hofstra 2010; Jha 2007; Jurubita 2012; Kosmadakis 2010; Naumovic 2011; Ponticelli 2006; Praga 2007; Saito 2009; Senthil Nayagam 2008; Shibasaki 2004; Tiller 1981; Xu 2010) were identified. One Japanese study (Koshisawa 1993) was identified in the list of references of Shibasaki 2004 and one Chinese study (Liu 2009b) was identified by searching the Chinese databases. Two studies previously identified as awaiting assessment on 2004 have been added to the included studies (Austin 1996a; Stegeman 1994).

Included studies

A total of 39 studies (1825 patients) were included in this updated review (Figure 1). The median sample size was 31 (range 9 to 120). The median follow-up was 24 months (range 6 to 120). Eight studies were only published as abstracts (Arnadottir 2006; Austin 1996a; Braun 1995; Dyadyk 2001; Jurubita 2012; CYCLOMEN Study 1994; Saito 2009; Xu 2010) and unpublished data were provided by the authors of two studies (Braun 1995; CYCLOMEN Study 1994). Two studies (Austin 1996a; Dyadyk 2001) could not be included in the meta-analyses as we were unable to extract the necessary data and one study was prematurely terminated due to low accrual rate (Stegeman 1994). Three studies were included in more than one comparison category (Braun 1995; Kosmadakis 2010; Naumovic 2011).

Figure 1. Study selection flow diagram.

Six studies included patients with declining kidney function (baseline SCr 203 to 260 $\mu\text{mol/L}$ or GFR 43 to 51 mL/min/1.73 m^2) (Austin 1996a; Branten 1998; Cattran 1995; CYCLOMEN Study 1994; Falk 1992; Reichert 1994). Five studies involved patients who were resistant to corticosteroids monotherapy (Koshisawa 1993; Saito 2009; Shibasaki 2004) or corticosteroids plus alkylating agents (Cattran 2001; Naumovic 2011). Subgroup analysis was performed to investigate the impact of baseline characteristics. The 39 included studies were divided into three categories according to financial ties. Eight studies had industrial support (Dussol 2008; Praga 2007; Senthil Nayagam 2008) or both industrial support and non-profit support (Cattran 1995; Cattran 2001; Chan 2007; Saito 2009; Silverberg 1976); 16 studies declared non-profit support (Cattran 1989; Coggins 1979; Donadio 1974a; Falk 1992; Hofstra 2010; Imbasciati 1980; Liu 2009b; Naumovic 2011; Ponticelli 1998; Ponticelli 2006; Reichert 1994; Tiller 1981) or had no support (Braun 1995; CYCLOMEN Study 1994; Jha 2007; Kosmadakis 2010); 14 studies did not declare financial support (Ahmed 1994; Arnadottir 2006; Austin 1996a; Branten 1998; Cameron 1990; Chen 2010a; Dyadyk 2001; Jurubita 2012; Koshisawa 1993; Murphy 1992; Pahari 1993; Ponticelli 1992; Shibasaki 2004; Xu 2010). Subgroup analysis was carried out to determine whether industrial support was associated with more favourable results.

Eight studies provided a priori sample size calculation (Cattran 1989; Cattran 2001; Dussol 2008; Hofstra 2010; Ponticelli 1992; Ponticelli 1998; Praga 2007; Tiller 1981). Subgroup analysis was conducted to inspect the influence of a priori sample size estimation.

The majority of studies were published in English. For the studies published in Chinese (Liu 2009b) and Japanese (Koshisawa 1993) there were not enough data to perform subgroup analyses based on language.

Studies awaiting classification

There are eight studies awaiting assessment (Berg 2007; Gaskin 2004; Hirayama 2006; Liu 2006; Liu 2007; Howman 2012; Appel 2002; Saito 2006). All were due to be completed between 2005 and 2009 but as yet no full-text reports have been identified.

Ongoing studies

We have identified 14 ongoing studies (ChiCTR-TRC-08000098; ChiCTR-TRC-11001144; CTRI/2010/091/000231; EUCTR2007-005410-39-ES; JPRN-UMIN000001099; JPRN-UMIN000006939; NCT00805753; NCT00843856; NCT01093157; NCT01161459; NCT01180036; NCT01282073; NCT01386554; NCT01508468) and these will be assessed and included or excluded in a future update.

Excluded studies

Twenty three studies (35 records) were excluded. Reasons for exclusion were: 10 were not randomised (Alexopoulos 2006; Austin 2008; Dominguez-Gil 1999; du Buf-Vereijken 2004; Goumenos 2007; Li 2008; Michail 2004; Polenakovic 1997; Rashid 1995; Yao 2001); the exact number of adult IMN patients with nephrotic syndrome was unavailable in each intervention group in 11 studies (Ambalavanan 1996; Black 1970; Lagrue 1975; Majima 1990; MRCWP 1971; Nand 1997; Plavljanic 1998; Edefonti 1988; Ponticelli 1993a; Sahay 2002; Shilov 1998); one study only enrolled children (Tejani 1991); and one study did not complete the scheduled follow-up (Sun 2008).

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Selective reporting (reporting bias)-Death	Selective reporting (reporting bias)-ESKD	Selective reporting (reporting bias)-Creatinine increase	Selective reporting (reporting bias)-Creatinine	Selective reporting (reporting bias)-GFR	Selective reporting (reporting bias)-Remission	Selective reporting (reporting bias)-Proteinuria	Selective reporting (reporting bias)-Side effects	Other bias
Ahmed 1994	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Amadottir 2006	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Austin 1996a	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Branten 1998	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Braun 1995	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Cameron 1990	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Cattran 1989	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Cattran 1995	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Cattran 2001	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Chan 2007	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Chen 2010a	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Coggins 1979	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
CYCLOMEN Study 1994	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Donadio 1974a	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Dussol 2008	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Dyadyk 2001	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Falk 1992	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Hofstra 2010	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Imbasciati 1980	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Jha 2007	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Jurubita 2012	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Koshisawa 1993	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Kosmadakis 2010	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Liu 2009b	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Murphy 1992	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Naumovic 2011	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Pahari 1993	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Ponticelli 1992	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Ponticelli 1998	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Ponticelli 2006	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Praga 2007	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Reichert 1994	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Saito 2009	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Senthil Nayagam 2008	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Shibasaki 2004	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Silverberg 1976	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Stegeman 1994	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Tiller 1981	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Xu 2010	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?

Allocation

Random sequence generation

Twenty-two studies (56%) specified appropriate methods for random sequence generation and were considered to be at low risk of bias. Appropriate methods of randomisation were not reported in the remaining 17 studies (44%). These studies were thus considered to have unclear risk of bias.

Allocation concealment

Fifteen studies (38%) reported appropriate allocation concealment methods and were considered to be at low risk of bias, while the remaining 24 studies (62%) did not provide details about allocation concealment and were considered to have unclear risk of bias.

Blinding

Blinding of participants

Appropriate procedure related to blinding of participants was confirmed in six studies (15%) and were considered to be at low risk of bias. Three studies (8%) were considered to have unclear risk of bias, and the remaining 30 studies (77%) did not perform adequate blinding of participants and were considered to be at high risk of bias.

Blinding of personnel and outcome assessors

Adequate blinding of personnel and outcome assessors was confirmed in four studies (10%) and were considered to be at low risk of bias. Three studies (8%) were considered to have unclear risk of bias, and the remaining 32 studies (82%) did not perform adequate blinding of personnel and outcome assessors and were considered to be at high risk of bias.

Incomplete outcome data

Thirty-two studies (82%) were considered to be at low risk of bias; two studies (5%) were considered to have unclear risk of bias; and five studies (13%) were considered to be at high risk of bias.

Selective reporting

Thirty studies (83%) were considered to be at low risk of bias and, nine studies (17%) were considered to be at high risk of bias. Six studies did not provide any data related to primary outcomes - all-cause mortality or risk of ESKD. The reporting rates of secondary outcomes - increase of SCr, SCr, GFR, complete or partial remission, proteinuria, and severe adverse effects - were 59% (23/39), 38% (15/39), 33% (13/39), 82% (32/39), 56% (22/39), and 79% (31/39), respectively. Two studies did not provide data that could be extracted and meta-analysed, and one study was terminated due to poor accrual.

Other potential sources of bias

Fourteen studies (36%) were considered to be at low risk of bias; seven studies (18%) were considered to have unclear risk of bias. The remaining 18 studies (46%) were considered to be at high risk of bias. The underlying rationale has been detailed in the risk of bias tables in [Characteristics of included studies](#).

Publication bias

It has been recommended that tests for publication bias should be used only when at least 10 studies were included in the meta-analysis ([Harbord 2009](#)). Thus, tests were restricted to the comparison of immunosuppressive treatments versus no treatment or ACEi (18 studies). There was no evidence of publication bias for composite definite endpoints ($Z = 0.81$, 95% CI -1.13 to 2.76, $SE = 0.87$, $N = 12$, $P = 0.374$) ([Figure 4A](#); [Figure 4C](#)) and complete or partial remission ($Z = -1.19$, 95% CI -3.50 to 1.12, $SE = 1.08$, $N = 17$, $P = 0.290$) ([Figure 4B](#); [Figure 4D](#)). Publication bias could be partially responsible for the significant heterogeneity in complete or partial remission when alkylating agents and corticosteroids were compared with no treatment in three studies. Beneficial intervention effects were reported in two published studies ([Imbasciati 1980](#); [Jha 2007](#)), while neutral findings remained unpublished in one study ([Braun 1995](#)) (RR 2.04, 95% CI 1.46 to 2.86 versus RR 0.73, 95% CI 0.36 to 1.48; $I^2 = 85\%$, subgroup differences $P = 0.0010$).

Figure 4. Publication bias of comparison: I Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, outcome: I.1 all-cause mortality or risk of ESKD (Harbord test) (A); I.6 complete or partial remission (Harbord test) (B); I.1 all-cause mortality or risk of ESKD (funnel plot) (C); and I.6 complete or partial remission (funnel plots) (D).

Sensitivity analysis

Seventeen studies were classified to be totally or partially unpublished or have low quality design (Ahmed 1994; Arnadottir 2006; Branten 1998; Braun 1995; Cattran 1989; CYCLOMEN Study 1994; Jurubita 2012; Koshisawa 1993; Kosmadakis 2010; Liu 2009b; Murphy 1992; Naumovic 2011; Pahari 1993; Saito 2009; Shibasaki 2004; Tiller 1981; Xu 2010). Sensitivity analysis, designed to exclude these studies, was performed to detect publication bias (Harbord 2006; Harbord 2009; Higgins 2011). Since no studies were of long duration and most enrolled < 100 patients, sensitivity analyses were not performed.

Effects of interventions

See: [Summary of findings for the main comparison Immunosuppressive treatments versus no treatment or](#)

[angiotensin-converting enzyme inhibitors \(ACEi\); Summary of findings 2 Alkylating agents and corticosteroids versus no treatment or angiotensin-converting enzyme inhibitors \(ACEi\) or corticosteroids](#)

Immunosuppressive treatments versus no treatment or ACEi

Immunosuppressive treatment significantly reduced the composite outcome of death or ESKD ([Analysis 1.1](#) (15 studies, 791 patients): RR 0.58, 95% CI 0.36 to 0.95, $P = 0.03$; $I^2 = 21\%$), and ESKD alone ([Analysis 1.3](#) (15 studies, 791 patients): RR 0.55, 95% CI 0.31 to 0.95, $P = 0.03$; $I^2 = 16\%$) at the end of follow-up (range 6 to 120 months) ([Summary of findings for the main comparison](#)). There was no significant difference in all-cause mortality ([Analysis 1.2](#) (15 studies, 791 patients): RR 0.65, 95% CI 0.29 to 1.44, $P = 0.29$; $I^2 = 0\%$).

Immunosuppressive treatment significantly reduced the risk of 100% increase in SCr ([Analysis 1.4](#) (8 studies, 409 patients): RR 0.42, 95% CI 0.26 to 0.67, $P = 0.0003$; $I^2 = 52\%$) and the risk of 50% increase in SCr ([Analysis 1.5](#) (8 studies, 414 patients): RR 0.52, 95% CI 0.33 to 0.81, $P = 0.004$; $I^2 = 12\%$) and increased GFR ([Analysis 1.7](#) (8 studies, 287 patients): MD 9.77 mL/min/1.73 m², 95% CI 3.92 to 15.62, $P = 0.001$; $I^2 = 0\%$), but significantly increased SCr ([Analysis 1.6](#) (5 studies, 198 patients): MD 25.43 μ mol/L, 95% CI 10.09 to 40.78, $P = 0.001$; $I^2 = 0\%$) at the end of follow-up.

Immunosuppressive treatments significantly increased complete or partial remission ([Analysis 1.8](#) (16 studies, 864 patients): RR 1.31, 95% CI 1.01 to 1.70, $P = 0.04$; $I^2 = 53\%$) and reduced proteinuria ([Analysis 1.11](#) (8 studies, 393 patients): MD -0.95 g/24 h, 95% CI -1.81 to -0.09, $P = 0.03$; $I^2 = 59\%$) at the end of follow-up (range 6 to 120 months). Significant heterogeneity was found for complete or partial remission ($I^2 = 53\%$, $P = 0.004$) and proteinuria ($I^2 = 59\%$, $P = 0.009$). There were no significant differences in complete remission ([Analysis 1.9](#) (15 studies, 761 patients): RR 1.59, 95% CI 0.87 to 2.88, $P = 0.13$; $I^2 = 46\%$) or partial remission ([Analysis 1.10](#) (15 studies, 761 patients): RR 1.16, 95% CI 0.86 to 1.57, $P = 0.33$; $I^2 = 27\%$).

Immunosuppressive treatments resulted in a significantly higher risk of severe adverse effects ([Analysis 1.12](#) (16 studies, 880 patients): RR 5.35, 95% CI 2.19 to 13.02, $P = 0.0002$; $I^2 = 0\%$).

Sensitivity analysis

Nine of 18 studies ([Arnadottir 2006](#); [Braun 1995](#); [Cattran 1989](#); [CYCLOMEN Study 1994](#); [Koshisawa 1993](#); [Kosmadakis 2010](#); [Murphy 1992](#); [Shibasaki 2004](#); [Tiller 1981](#)), which provided unpublished data or had low quality design, were excluded for the sensitivity analysis. There were no significant changes to the outcomes ([Cameron 1990](#); [Cattran 1995](#); [Coggins 1979](#); [Donadio 1974a](#); [Dussol 2008](#); [Jha 2007](#); [Imbasciati 1980](#); [Praga 2007](#); [Silverberg 1976](#)).

Subgroup analysis

According to the baseline characteristics, two studies involved patients with significantly declining kidney function (baseline GFR: 46 to 51 mL/min/1.73 m²) ([Cattran 1995](#); [CYCLOMEN Study 1994](#)). There were no statistically significant subgroup differences in the outcomes. Four studies were partially or totally supported by drug companies ([Cattran 1995](#); [Dussol 2008](#); [Praga 2007](#); [Silverberg 1976](#)). Industrial support was not associated with more favourable results. Four studies estimated sample size in advance ([Cattran 1989](#); [Dussol 2008](#); [Praga 2007](#); [Tiller 1981](#)). A priori sample size calculation was associated with more conservative results in complete remission (RR 0.50, 95% CI 0.24 to 1.02 versus

RR 2.42, 95% CI 1.40 to 4.17; $I^2 = 91.5\%$, subgroup differences $P = 0.0006$).

Corticosteroid monotherapy versus no treatment

There were no significant differences in any of the considered outcomes at the end of follow-up (range 24 to 48 months) ([Cameron 1990](#); [Cattran 1989](#); [Coggins 1979](#)) ([Analysis 2.1](#); [Analysis 2.2](#); [Analysis 2.3](#); [Analysis 2.4](#); [Analysis 2.5](#); [Analysis 2.6](#); [Analysis 2.7](#); [Analysis 2.8](#); [Analysis 2.9](#); [Analysis 2.10](#); [Analysis 2.11](#); [Analysis 2.12](#)).

Alkylating agent monotherapy versus no treatment

Alkylating agents significantly increased the risk of temporary or permanent discontinuation or hospitalisation due to adverse events ([Analysis 3.12](#) (3 studies, 102 patients): RR 7.18, 95% CI 1.33 to 38.70, $P = 0.02$; $I^2 = 0\%$) at the end of follow-up (range 12 to 36 months) ([Donadio 1974a](#); [Murphy 1992](#); [Tiller 1981](#)). There were no significant differences in any of the other outcomes at the end of follow-up ([Analysis 3.1](#); [Analysis 3.2](#); [Analysis 3.3](#); [Analysis 3.4](#); [Analysis 3.5](#); [Analysis 3.6](#); [Analysis 3.7](#); [Analysis 3.8](#); [Analysis 3.9](#); [Analysis 3.10](#); [Analysis 3.11](#)).

Alkylating agents plus corticosteroids versus no treatment, ACEi or ARB, or corticosteroids

Alkylating agents plus corticosteroids significantly reduced the composite outcome of death or ESKD ([Analysis 4.1](#) (8 studies, 448 patients): RR 0.44, 95% CI 0.26 to 0.75, $P = 0.002$; $I^2 = 0\%$) and ESKD alone ([Analysis 4.3](#) (8 studies, with 448 patients): RR 0.45, 95% CI 0.25 to 0.81, $P = 0.008$; $I^2 = 0\%$) at the end of follow-up (range 9 to 120 months) ([Summary of findings 2](#)). There was no significant difference in all-cause mortality ([Analysis 4.2](#) (8 studies, 448 patients): RR 0.57, 95% CI 0.16 to 1.98, $P = 0.38$; $I^2 = 0\%$).

Alkylating agents plus corticosteroids significantly increased GFR ([Analysis 4.7.1](#) (2 studies, 102 patients): MD 11.70 mL/min/1.73 m², 95% CI 1.50 to 21.91, $P = 0.02$; $I^2 = 15\%$) at the end of follow-up (range 9 to 120 months).

Alkylating agents plus corticosteroids significantly increased complete or partial remission ([Analysis 4.8.1](#) (7 studies, 442 patients): RR 1.46, 95% CI 1.13 to 1.89, $P = 0.004$; $I^2 = 53\%$) and complete remission ([Analysis 4.9.1](#) (7 studies, 442 patients): RR 2.32, 95% CI 1.61 to 3.32, $P < 0.00001$; $I^2 = 11\%$) and decreased proteinuria ([Analysis 4.11.1](#) (6 studies, 279 patients): MD -1.25 g/24 h, 95% CI -1.93 to -0.57, $P = 0.0003$; $I^2 = 50\%$) at the end of follow-up (range 9 to 120 months). Significant heterogeneity was found for complete or partial remission ($I^2 = 53\%$, $P = 0.05$) and proteinuria ($I^2 = 50\%$, $P = 0.08$). There was no significant difference in partial remission ([Analysis 4.10.1](#) (7 studies, 442 patients): RR 0.94, 95% CI 0.56 to 1.57, $P = 0.82$; $I^2 = 0\%$).

Sensitivity analysis

Four unpublished or low quality studies (Ahmed 1994; Braun 1995; Kosmadakis 2010; Pahari 1993) were excluded. This did not affect efficacy outcomes, while the risk of severe adverse effects significantly increased (Analysis 4.12 (8 studies, 448 patients): RR 2.11 95% CI 0.77 to 5.79, $P = 0.15$ versus 4 studies, 303 patients: RR 4.20, 95% CI 1.15 to 15.32, $P = 0.03$) (Falk 1992; Jha 2007; Ponticelli 1992; Imbasciati 1980).

Subgroup analysis

One study involved patients with established renal insufficiency (baseline SCr: 203-239 $\mu\text{mol/L}$) (Falk 1992) and there were no statistically significant subgroup differences in the outcomes. No study declared to receive financial support from drug companies, and the planned subgroup analysis was not conducted. One study estimated the sample size in advance (Ponticelli 1992) and there were no statistically significant subgroup differences in the outcomes.

Alkylating agents plus corticosteroids versus no treatment

Alkylating agents plus corticosteroids significantly reduced the composite outcome of death or ESKD (Analysis 4.1.1 (3 studies, 211 patients): RR 0.33, 95% CI 0.17 to 0.64, $P = 0.001$; $I^2 = 0\%$) and ESKD alone (Analysis 4.3.1 (3 studies, 211 patients): RR 0.31, 95% CI 0.15 to 0.65, $P = 0.002$; $I^2 = 0\%$) at the end of follow-up (range 60 to 120 months). There was no significant difference in all-cause mortality (Analysis 4.2.1 (3 studies, 211 patients): RR 0.48, 95% CI 0.12 to 1.97, $P = 0.31$; $I^2 = 0\%$).

Alkylating agents plus corticosteroids significantly reduced the risk of 100% increase in SCr (Analysis 4.4.2 (3 studies, 211 patients): RR 0.39, 95% CI 0.17 to 0.89, $P = 0.02$; $I^2 = 52\%$). Imbasciati 1980 reported a significantly reduced risk of 50% increase of SCr (Analysis 4.5.2 (1 study, 81 patients): RR 0.33, 95% CI 0.15 to 0.68, $P = 0.003$), and Jha 2007 reported a significant increase in GFR (Analysis 4.7.2 (1 study, 93 patients): MD 14.00 mL/min/1.73 m², 95% CI 5.82 to 22.18, $P = 0.0008$) at the end of follow-up (60 to 120 months). However Imbasciati 1980 reported this combined treatment significantly increased SCr (Analysis 4.6.2 (1 study, 56 patients): MD 26.86 $\mu\text{mol/L}$, 95% CI 10.14 to 43.58, $P = 0.002$) at the end of follow-up (120 months).

Alkylating agents plus corticosteroids significantly increased complete remission (Analysis 4.9.2 (3 studies, 211 patients): RR 3.18, 95% CI 1.23 to 8.21, $P = 0.02$; $I^2 = 39\%$) and decreased proteinuria (Analysis 4.11.2 (2 studies, 174 patients): MD -2.06 g/24 h, 95% CI -3.69 to -0.44, $P = 0.01$; $I^2 = 77\%$) at the end of follow-up (range 60-120 months). There was no significant difference in complete or partial remission (Analysis 4.8.2 (3 studies, 211 patients): RR 1.52, 95% CI 0.85 to 2.73, $P = 0.16$; $I^2 = 71\%$) or partial remission (Analysis 4.10.2 (3 studies, 211 patients): RR

1.00, 95% CI 0.50 to 2.02, $P = 0.99$; $I^2 = 56\%$) at the end of follow-up (range 60-120 months). Significant heterogeneity was found for complete or partial remission ($I^2 = 71\%$, $P = 0.03$) and proteinuria ($I^2 = 77\%$, $P = 0.04$).

Alkylating agents plus corticosteroids led to a significantly higher risk of severe adverse effects (Analysis 4.12.1 (3 studies, 211 patients): RR 9.79, 95% CI 1.28 to 75.01, $P = 0.03$; $I^2 = 0\%$).

Alkylating agents plus corticosteroids versus ACEi

Kosmadakis 2010 (9 patients) reported no significant differences in any of the considered outcomes at the end of follow-up (9 months).

Alkylating agents plus corticosteroids versus corticosteroids (same dose)

Alkylating agents and corticosteroids significantly increased complete or partial remission (Analysis 4.8.15 (2 studies, 112 patients): RR 1.52, 95% CI 1.07 to 2.15, $P = 0.02$; $I^2 = 0\%$) at the end of follow-up (range 12 to 54 months).

Alkylating agents + corticosteroids versus corticosteroids (low dose)

Pahari 1993 reported alkylating agents and corticosteroids significantly increased complete or partial remission (Analysis 4.8.20 (90 patients): RR 1.71, 95% CI 1.21 to 2.42, $P = 0.002$) and complete remission (Analysis 4.9.20 (90 patients): RR 2.51, 95% CI 1.61 to 3.94, $P < 0.0001$) at the end of follow-up (46 months).

Cyclophosphamide plus corticosteroids versus chlorambucil plus corticosteroids

Cyclophosphamide plus corticosteroids led to a significantly lower risk of severe adverse effects (Analysis 5.11 (3 studies, 147 patients): RR 0.48, 95% CI 0.26 to 0.90, $P = 0.02$; $I^2 = 0\%$) at the end of follow-up (15 to 39 months).

There were no significant differences in any of the other outcomes at the end of follow-up (Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4; Analysis 5.5; Analysis 5.6; Analysis 5.7; Analysis 5.8; Analysis 5.9; Analysis 5.10).

Cyclosporine with or without corticosteroids versus no treatment, ACEi, or corticosteroids with or without alkylating agents/azathioprine

There were no significant differences in any of the considered outcomes at the end of follow-up (range 12 to 21 months) (Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4; Analysis 6.5; Analysis 6.6; Analysis 6.7; Analysis 6.8; Analysis 6.9; Analysis 6.10; Analysis 6.11; Analysis 6.12).

Cyclosporine versus placebo or no treatment

There were no significant differences in any of the considered outcomes at the end of follow-up (range 12 to 21 months) (2 studies, 38 patients).

Cyclosporine plus corticosteroids versus no treatment

Braun 1995 reported no significant differences in any of the considered outcomes at the end of follow-up (60 months) (33 patients).

Cyclosporine plus corticosteroids versus ACEi

Kosmadakis 2010 reported no significant differences in any of the considered outcomes at the end of follow-up (9 months) (10 patients).

Cyclosporine plus corticosteroids versus placebo of cyclosporine plus corticosteroids

Cattran 2001 reported no significant differences in any of the considered outcomes at the end of follow-up (18 months) (51 patients).

Cyclosporine plus corticosteroids versus alkylating agents plus corticosteroids

There were no significant differences in any of the considered outcomes at the end of follow-up (range 9 to 60 months) (2 studies, 47 patients).

Cyclosporine plus corticosteroids versus azathioprine plus corticosteroids

Naumovic 2011 reported no significant differences in any of the considered outcomes at the end of follow-up (36 months) (23 patients).

Cyclosporine (1.5 mg/kg twice/d) plus corticosteroids versus cyclosporine (3.0 mg/kg once/d) plus corticosteroids

Saito 2009 reported cyclosporine (1.5 mg/kg twice/d) significantly reduced proteinuria (Analysis 7.2 (33 patients): MD -0.70, 95% CI -0.96 to -0.44, $P < 0.00001$) at the end of follow-up (12 months) (33 patients). There was no significant difference reported for complete remission at 12 months (Analysis 7.1 (33 patients): RR 1.06, 95% CI 0.66 to 1.72).

Tacrolimus with or without corticosteroids versus no treatment or corticosteroids plus alkylating agents

Tacrolimus with or without corticosteroids significantly decreased proteinuria (Analysis 8.9.1 (2 studies, 145 patients): MD -1.06 g/24 h, 95% CI -1.66 to -0.47, $P = 0.0004$; $I^2 = 0\%$) at the end of follow-up (range 9 to 30 months).

Tacrolimus versus no treatment

Praga 2007 reported no significant differences in any of the considered outcomes at the end of follow-up (30 months) (48 patients).

Tacrolimus plus corticosteroids versus alkylating agents plus corticosteroids

Tacrolimus plus corticosteroids significantly reduced proteinuria (Analysis 8.9.5 (2 studies, 84 patients): MD -1.03 g/24 h, 95% CI -1.69 to -0.37, $P = 0.002$; $I^2 = 7\%$) at the end of follow-up (9 to 12 months).

Mycophenolate mofetil with or without corticosteroids versus no treatment or corticosteroids with alkylating agents

There were no significant differences in any of the considered outcomes at the end of follow-up (range 12-24 months) (3 studies, 77 patients).

Mycophenolate mofetil versus no treatment

Dussol 2008 reported no significant differences in any of the considered outcomes at the end of follow-up (12 months) (36 patients).

Mycophenolate mofetil plus corticosteroids versus alkylating agents plus corticosteroids

There were no significant differences in any of the considered outcomes at the end of follow-up (range 15 to 24 months) (2 studies, 41 patients).

Mycophenolate mofetil plus cyclosporine (2 mg/kg/d) plus corticosteroids versus cyclosporine (5 mg/kg/d) plus corticosteroids

Jurubita 2012 reported no significant differences in any of the considered outcomes at the end of follow-up (12 months) (18 patients).

Adrenocorticotrophic hormone versus no treatment or corticosteroids plus alkylating agents

[Ponticelli 2006](#) reported ACTH significantly reduced proteinuria ([Analysis 11.10.1](#) (32 patients): MD -1.80 g/24 h, 95% CI -3.19 to -0.41, $P = 0.01$) at the end of follow-up (22 months).

Adrenocorticotrophic hormone versus no treatment

[Arnadottir 2006](#) reported ACTH significantly increased complete or partial remission ([Analysis 11.7.2](#) (30 patients): RR 7.00, 95% CI 1.91 to 25.62, $P = 0.003$) and complete remission ([Analysis 11.8.2](#) (30 patients): RR 11.00, 95% CI 1.62 to 74.88, $P = 0.01$) at the end of follow-up (21 months).

Adrenocorticotrophic hormone versus alkylating agents plus corticosteroids

[Ponticelli 2006](#) reported ACTH significantly reduced proteinuria ([Analysis 11.10.2](#) (32 patients): MD -1.80 g/24 h, 95% CI -3.19 to -0.41, $P = 0.01$) at the end of follow-up (22 months).

Azathioprine with or without corticosteroids versus placebo or cyclosporine plus corticosteroids

Azathioprine versus placebo or no treatment at 12 months

[Silverberg 1976](#) reported no significant differences in any of the considered outcomes at the end of follow-up (12 months) (9 patients).

Azathioprine plus corticosteroids versus cyclosporine plus corticosteroids at 36 months

[Naumovic 2011](#) reported no significant differences in any of the considered outcomes at the end of follow-up (36 months) (23 patients).

Mizoribine versus no treatment

Mizoribine significantly increased complete or partial remission ([Analysis 13.2.1](#) (2 studies, 114 patients): RR 2.24, 95% CI 1.14 to 4.38, $P = 0.02$; $I^2 = 0\%$) at the end of follow-up (range 6 to 24 months).

Tripterygium wilfordii plus corticosteroids versus Tripterygium wilfordii

[Liu 2009b](#) reported Tripterygium wilfordii and corticosteroids significantly increased complete or partial remission ([Analysis 14.6.1](#) (84 patients): RR 2.03, 95% CI 1.31 to 3.16, $P = 0.002$) and complete remission ([Analysis 14.7.1](#) (84 patients): RR 7.63, 95% CI 1.87 to 31.13, $P = 0.005$) at the end of follow-up (12 months).

Early versus late immunosuppressive treatments

[Hofstra 2010](#) reported no significant differences in any of the considered outcomes at the end of follow-up (72 months).

Other results

The reported results of the three studies which could not be included in our meta-analyses can be found in [Table 1](#).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Alkylating agents and corticosteroids versus no treatment or ACEi or corticosteroids monotherapy for adult IMN with nephrotic syndrome					
Patient or population: adults with IMN and nephrotic syndrome					
Settings:					
Intervention: alkylating agents and corticosteroids					
Comparison: no treatment or ACEi or corticosteroids monotherapy					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No treatment or ACEi or corticosteroids	Alkylating agents and corticosteroids			
Death or ESKD (dialysis/transplantation) Follow-up: 9 to 120 months	Study population		RR 0.44 (0.26 to 0.75) P = 0.002	448 (8)	⊕⊕⊕⊖ Moderate ¹
	181 per 1000	80 per 1000 (47 to 136)			
	Moderate				
	77 per 1000	34 per 1000 (20 to 58)			
ESKD (dialysis/transplantation) Follow-up: 9 to 120 months	Study population		RR 0.45 (0.25 to 0.81) P = 0.008	448 (8)	⊕⊕⊕⊖ Moderate ¹
	150 per 1000	68 per 1000 (38 to 122)			
	Moderate				
	67 per 1000	30 per 1000 (17 to 54)			

Complete or partial remis- sion Follow-up: 9 to 120 months	Study population		RR 1.46 (1.13 to 1.89) P = 0.004	422 (7)	⊕⊕⊕⊖ Moderate ²
	408 per 1000	596 per 1000 (462 to 772)			
	Moderate				
	458 per 1000	669 per 1000 (518 to 866)			
Temporary or permanent discontinuation or hospi- talisation due to adverse effects Follow-up: 9 to 120 months	Study population		RR 2.11 (0.77 to 5.79) P = 0.15	448 (8)	⊕⊕⊖⊖ Low ³
	31 per 1000	65 per 1000 (24 to 179)			
	Moderate				
	0 per 1000	0 per 1000 (0 to 0)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹The relatively small number of included RCTs with high-quality design and adequate follow-up did not guarantee enough power to appropriately assess the definite endpoint

²Moderate heterogeneity (P = 0.05, I² = 53%)

³Sensitivity analysis revealed a statistically significant difference (P = 0.03, RR 4.20, 95% CI 1.15 to 15.32), whereby four low quality studies were excluded and only four high quality studies were analysed

ESKD - end-stage kidney disease; IMN - idiopathic membranous nephropathy

DISCUSSION

Summary of main results

Immunosuppressive treatments significantly reduced the composite definite endpoints and risk of ESKD. In a population with an assumed risk of ESKD of 125/1000 patients, immunosuppressive treatments would be expected to reduce the number of patients experiencing ESKD to 69/1000 patients (95% CI 39 to 119) ([Summary of findings for the main comparison](#)). However, there was no significant difference in the all-cause mortality. Immunosuppressive treatments significantly reduced the risks of 100% and 50% increase of SCr and increased GFR but were also associated with a significantly increased SCr at the end of follow-up. It should be noted that these three outcomes - increase of SCr, GFR, and SCr - were reported in 8, 8, and 5 of 18 studies, respectively. Thus, the inconsistent results could be attributed to the selective reporting bias. Immunosuppressive treatments significantly increased complete or partial remission but not complete remission alone or partial remission alone. In a population with an assumed complete or partial remission of 296/1000 patients, this regimen would be expected to increase the number of patients experiencing complete or partial remission to 388/1000 patients (95% CI 299 to 504) ([Summary of findings for the main comparison](#)). Moreover, the prespecified subgroup analysis indicated that a priori sample size calculation resulted in more conservative estimate in complete remission. Immunosuppressive treatments resulted in more temporary or permanent discontinuations or hospitalisations due to adverse effects. The type of adverse effects was not assessed because different immunosuppressive treatments have different safety profiles. The proportion of patients experiencing mild adverse effects was also not considered because they were quite common for immunosuppressive treatments and very likely under-reported, particularly in the control group of non-double-blind studies. Conversely, permanent or temporary discontinuation or hospitalisation due to adverse effects was more likely reported in sufficient detail.

It should be noted that not all immunosuppressive treatments are equal. Which treatments could be confidently discarded or recommended? The role of corticosteroids monotherapy or alkylating agents monotherapy remained very uncertain not only for definite but also for surrogate endpoints. Furthermore, safety concerns with the use of alkylating agent monotherapy could be raised. So far, only three studies compared corticosteroids plus alkylating agents with no treatment: two published studies with positive results ([Imbasciati 1980](#); [Jha 2007](#)) and one unpublished study with neutral results ([Braun 1995](#)). Meta-analysis of these three studies (211 patients) showed that this regimen significantly reduced the composite outcome of death or ESKD, increased complete remission and decreased proteinuria, but significantly increased the risk of adverse effects leading to withdrawals or hospitalisations. When compared with no treatment or ACEi or corticosteroids

monotherapy in eight studies (448 patients), combined corticosteroids and alkylating agents significantly reduced the composite outcome of death or ESKD, increased complete or partial remission and complete remission, and decreased proteinuria. In a population with an assumed risk of all-cause mortality or ESKD of 181/1000 patients, this regimen would be expected to reduce the number of patients experiencing death or ESKD to 80/1000 patients (95% CI 47 to 136). In a population with an assumed complete or partial remission of 408/1000 patients, this regimen would be expected to increase the number of patients experiencing complete or partial remission to 596/1000 patients (95% CI 462 to 772) ([Summary of findings 2](#)). However, it should be noted that four of these eight studies were classified as unpublished or having low quality design. The number of included high quality studies was relatively small. Furthermore, most of included studies did not have adequate follow-up to appropriately assess definite endpoints. Among alkylating agents, cyclophosphamide was safer than chlorambucil.

The superiority of cyclosporine or mycophenolate mofetil plus corticosteroids over alkylating agents plus corticosteroids was not identified, but this conclusion was based on four small studies totalling < 150 participants. In contrast, tacrolimus and adrenocorticotrophic hormone significantly reduced proteinuria. Two studies demonstrated a significant benefit of mizoribine monotherapy on complete or partial remission in Japanese patients ([Koshisawa 1993](#); [Shibasaki 2004](#)). Tripterygium wilfordii might have beneficial effects on “complete or partial remission” and complete remission for Chinese patients ([Liu 2009b](#)). There was no clear evidence to support the use of corticosteroid monotherapy, alkylating agent monotherapy, or azathioprine. A better understanding of genetic susceptibility and pathogenic mechanisms of IMN may allow the discovery of newer drugs. The recent identification of M-type phospholipase A2 receptor and the utilization of rituximab represent major milestones in understanding the pathogenesis and searching for new therapeutic strategies for IMN ([Beck 2009](#); [Beck 2011](#); [Herrmann 2012](#); [Stanescu 2011](#); [Waldman 2012](#)). Numerous non-randomised studies have demonstrated that rituximab is a promising new immunosuppressive drug, but these pioneering studies are still ongoing ([NCT01508468](#); [NCT01180036](#)).

Overall completeness and applicability of evidence

One major limitation was the relatively small numbers of included studies in some immunosuppressive regimens, especially for the newer immunosuppressive drugs, such as tacrolimus, mycophenolate mofetil, and adrenocorticotrophic hormone. This issue is common in systematic reviews carried out in the field of glomerulonephritis. Another major concern relied in the relatively short follow-up in most of the included studies (median follow-up 24 months). It has been recognised that for definite endpoints such as ESKD a follow-up of at least seven to 10 years should be consid-

ered. For surrogate outcomes such as complete or partial remission an adequate follow-up should be of at least two to three years ([du Buf-Vereijken 2005](#)).

Quality of the evidence

Due to the paucity of studies, subgroup analysis allowing for variations in interventions (different doses, routes and duration of therapies used and previously-used relative agents before entry to the studies) and in populations (age, race, and renal pathology) could not be properly carried out. Language bias was not addressed by subgroup analysis. Sensitivity analysis could not be performed to explore the effect of dominating studies with very long follow-up or very large same size. However, we performed sensitivity analysis to investigate the impact of unpublished or low quality studies and subgroup analysis to investigate covariate effects of clinical baseline characteristics, industrial support, and a priori sample size estimation. Heterogeneity was found to be statistically significant in certain comparisons when complete or partial remission and proteinuria were assessed. Differences in immunosuppressive therapeutic approaches, in the choices of the control arm, in adequacy of sample size, and more generally in study quality could at least partially account for heterogeneity. There was no clear evidence of publication bias in the comparison of immunosuppressive treatments versus no treatment or ACEi. However, publication bias cannot be completely excluded in other comparisons with insufficient number of studies.

Potential biases in the review process

The Cochrane Renal Group's Trial Search Co-ordinator implemented comprehensive search strategies for this update. We also searched clinical trials registries such as ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform. The major difference in the review process between this update and 2004 initial version was the addition of studies published in Chinese language, which contributed to reduce the impact of language bias. However, the authenticity of randomised studies published in Chinese language constituted a non-negligible issue ([Wu 2009](#)). Finally, only one study related to Tripterygium wilfordii (a traditional Chinese immunosuppressive medicine) was included ([Liu 2009b](#)). This study was not combined with other studies.

Agreements and disagreements with other studies or reviews

Three systematic reviews were published before 1995 ([Couchoud 1994](#); [Hogan 1995](#); [Imperiale 1995](#)). During the past few years there was no published systematic review or meta-analysis of RCTs related to immunosuppressive treatments for adult patients with

IMN and nephrotic syndrome. In 2004, we published the first version of this systematic review. The present update of systematic review (39 studies, 1825 patients) seemed to be more powerful than the 2004 original version (18 studies, 1025 patients). However, after careful scrutiny there was no improvement neither in median sample size/study (42 patients/study in the 2004 version versus 31 patients/study in this update) nor in the proportion of studies without potential methodological problems (61% in the 2004 version versus 53% in this update).

AUTHORS' CONCLUSIONS

Implications for practice

In this update, a combined alkylating agent and corticosteroid regimen had short- and long-term benefits on adult IMN with nephrotic syndrome. Among alkylating agents, cyclophosphamide was safer than chlorambucil. It should be emphasised that the number of included studies with high-quality design was relatively small and most of the included studies did not have adequate follow-up and enough power to assess the prespecified definite endpoints. This regimen was significantly associated with more withdrawals or hospitalisations. Although a six-month course of alternating monthly cycles of corticosteroids and cyclophosphamide was recommended by the KDIGO Clinical Practice Guideline 2012 as the initial therapy for adult IMN with nephrotic syndrome ([KDIGO 2012](#)), clinicians should inform their patients of the lack of high-quality evidence for these benefits as well as the well-recognised adverse effects of this therapy. Whether this combined therapy should be indicated in all adult patients at high risk of progression to ESKD or only restricted to those with deteriorating kidney function still remained unclear.

Cyclosporine or tacrolimus was recommended by the KDIGO Clinical Practice Guideline 2012 as the alternative regimen for adult IMN with nephrotic syndrome ([KDIGO 2012](#)); however, there was no evidence that calcineurin inhibitors could alter the combined outcome of death or ESKD. There was no clear evidence to support the use of corticosteroid monotherapy or alkylating agent monotherapy. The numbers of corresponding studies related to tacrolimus, mycophenolate mofetil, adrenocorticotrophic hormone, azathioprine, mizoribine, and Tripterygium wilfordii are still too sparse to draw final conclusions.

Implications for research

There is need for more methodologically sound studies with an emphasis on adequate sample size and follow-up. Furthermore, priority should be given to the choice of definite rather than surrogate endpoints. Any immunosuppressive treatments (including calcineurin inhibitors (cyclosporine and tacrolimus), sirolimus, mycophenolate mofetil, synthetic adrenocorticotrophic hormone,

Tripterygium wilfordii (a traditional Chinese immunosuppressive medicine), leflunomide, azathioprine, mizoribine, methotrexate, levamisole, and even biologics (eculizumab and rituximab) and high-dose gamma-globulin), should be further directly compared with alkylating agents and corticosteroids after the superiority over placebo or no treatment or non-immunosuppressive treatments are clearly established. More studies are needed to assess whether immunosuppressive treatments should be given to all adult patients at high risk of progression to ESKD or only restricted to those with established renal insufficiency. Ideally, optimal doses, routes, and durations of therapies that are most beneficial and least harmful to patients of different races, ages, and clinical and pathological severity still remain to be clarified.

ACKNOWLEDGEMENTS

The authors thank Professor Giuseppe Remuzzi, who had the idea and revised the manuscript for the original review and the review update.

The authors are also indebted to Dr Antonietta Chianca, who provided statistical advice for the review update, Dr Lisa A Tjosvold,

who helped perform the electronic search for the original review, Dr Luciana Tammuzzo, who hand-searched the Journal of Nephrology for the original review, and principal investigators of the completed and ongoing studies considered in the review, who provided additional information or clarification for the original review (Professor Daniel C Cattran, Professor Peter Mathieson, Dr Roberto Pisoni, and Professor Teut Risler).

The authors also thank Ms Ruth Mitchell, the Cochrane Trials Search Coordinator, who provided us with the Cochrane Library search strategy and relevant information, and Ms Narelle Willis, the Cochrane Renal Group Coordinator, for her help and support.

The review update was partially supported by the Key Science and Technology Planning of Science and Technology Commission Foundation of Beijing (D131100004713003, D131100005313006), the National Key Technology Research and Development Program of the Ministry of Science and Technology of China (2011BAI10B08), and the National Basic Research Program Project of China (2011CB944004). The sponsors had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

REFERENCES

References to studies included in this review

Ahmed 1994 {published data only}

* Ahmed S, Rahman M, Alam MR, Islam S, Chowdhury MN, Chowdhury SM, et al. Methyl prednisolone plus chlorambucil as compared with prednisolone alone for the treatment of idiopathic membranous nephropathy - a preliminary study. *Bangladesh Renal Journal* 1994;**13**(2): 51-4. [EMBASE: 1995085509]
Rahman M, Ahmed S, Alam MR, Selim SI, Chowdhury MN, Chowdhury SM, et al. Methyl prednisolone plus chlorambucil as compared with prednisolone alone for the treatment of idiopathic membranous nephropathy - a preliminary study [abstract]. 10th Asian Colloquium in Nephrology; 1994, Dec 2-6; Karachi, Pakistan. 1994:66.

Arnadottir 2006 {published data only}

Arnadottir M, Stefansson B, Berg A. A randomized study on treatment with adrenocorticotrophic hormone in idiopathic membranous nephropathy [abstract no: F-PO1112]. *Journal of the American Society of Nephrology* 2006;**17** (Abstracts):571A. [CENTRAL: CN-00782355]

Austin 1996a {published data only}

Austin HA, Vaughan EM, Boumpas DT, Balow JE. Randomized trial of pulse cyclophosphamide and prednisone vs. prednisone alone in idiopathic membranous nephropathy [abstract no: A0410]. *Journal of the American*

Society of Nephrology 1996;**7**(9):1327. [CENTRAL: CN-00583858]

Branten 1998 {published data only}

Branten AJ, Reichert LJ, Koene RA, Wetzels JF. Cyclophosphamide is superior to chlorambucil in the treatment of patients with membranous nephropathy and renal insufficiency [abstract no: A0395]. *Journal of the American Society of Nephrology* 1997;**8**(Programs & Abstracts):82A. [CENTRAL: CN-00444527]
* Branten AJ, Reichert LJ, Koene RA, Wetzels JF. Oral cyclophosphamide versus chlorambucil in the treatment of patients with membranous nephropathy and renal insufficiency. *Qjm* 1998;**91**(5):359-66. MEDLINE: 9709470

Braun 1995 {published and unpublished data}

Braun N, Dietz K, Vonthein R, Erley C, Risler T. Remission and relapses in idiopathic membranous nephropathy. Description by a longitudinal multi-state Markov-model [abstract]. 41st Congress. European Renal Association. European Dialysis and Transplantation Association; 2004 May 15-18; Lisbon, Portugal. 2004:34-5. [CENTRAL: CN-00509101]
Braun N, Erley CM, Benda N, Zauner I, Kanis R, Grupp C, et al. Therapy of membranous glomerulonephritis with nephrotic syndrome. 5 years follow-up of a prospective, randomized multi-centre study [abstract]. *Nephrology*

Dialysis Transplantation 1995;**10**(6):967.

* Braun N, Erley CM, Benda N, Zauner I, Kanis R, Grupp C, et al. Therapy of membranous glomerulonephritis with nephrotic syndrome. 5 years follow-up of a prospective, randomized multi-center study [abstract]. *Journal of the American Society of Nephrology* 1995;**6**(3):413. [CENTRAL: CN-00261096]

Cameron 1990 {published data only}

* Cameron JS, Healy MJ, Adu D. The Medical Research Council trial of short-term high-dose alternate day prednisolone in idiopathic membranous nephropathy with nephrotic syndrome in adults. The MRC Glomerulonephritis Working Party. *Quarterly Journal of Medicine* 1990;**74**(2):133–56. MEDLINE: 2189149
Cameron JS, Working Party of the MRC Glomerulonephritis Registry. The MRC trial of prednisolone in membranous nephropathy. The Working Party of the MRC Glomerulonephritis Registry [abstract]. *Nephrology Dialysis Transplantation* 1988;**3**(6):844. [CENTRAL: CN-00260412]
Cameron JS, Working party of the UK MRC Glomerulonephritis Registry. The MRC trial of prednisolone in membranous nephropathy. The Working Party of the UK MRC Glomerulonephritis Registry [abstract]. *Nephrology Dialysis Transplantation* 1988;**3**(4): 507–8. [CENTRAL: CN-00260389]

Catran 1989 {published data only}

Catran D, Cardella C, Charron R, Roscoe J, Cole E, Bear R, et al. Results of a controlled trial of alternate day prednisone (ADS) in idiopathic membranous glomerulonephritis (IMGN) [abstract]. *Kidney International* 1985;**27**(3):600. [CENTRAL: CN-00550495]
Catran D, Cardella C, Charron R, Roscoe J, Rance P, Cusimano M, et al. Preliminary results of controlled trial of alternate-day prednisone in idiopathic membranous glomerulonephritis [abstract]. *Kidney International* 1981;**19**(2):388–9. [CENTRAL: CN-00644365]
Catran DC, Cole E, Cardella C, Charron R, Roscoe J, Delmore T, et al. Results of a controlled trial of alternate day prednisone (P) in membranous nephropathy (IMGN) [abstract]. *Kidney International* 1989;**35**(1):208. [CENTRAL: CN-00644367]
* Catran DC, Delmore T, Roscoe J, Cole E, Cardella C, Charron R, et al. A randomized controlled trial of prednisone in patients with idiopathic membranous nephropathy. *New England Journal of Medicine* 1989;**320**(4):210–5. MEDLINE: 2643046

Catran 1995 {published data only}

Catran D, Greenwood CM, Ritchie S, Bernstein K, Churchill DN, Clarke WF, et al. A controlled trial of cyclosporine in patients with progressive membranous nephropathy [abstract]. *Journal of the American Society of Nephrology* 1993;**4**(Program & Abstracts):271. [CENTRAL: CN-00483446]
Catran DC. Cyclosporine in the treatment of membranous nephropathy (MGN) [abstract]. 12th International

Congress of Nephrology; 1993, Jun 13-18; Jerusalem, Israel. 1993:535. [CENTRAL: CN-00602121]

* Catran DC, Greenwood C, Ritchie S, Bernstein K, Churchill DN, Clark WF, et al. A controlled trial of cyclosporine in patients with progressive membranous nephropathy. Canadian Glomerulonephritis Study Group. *Kidney International* 1995;**47**(4):1130–5. MEDLINE: 7783410

Catran 2001 {published data only}

* Catran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl MA, Hoy WE, et al. Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. *Kidney International* 2001;**59**(4):1484–90. MEDLINE: 11260412
Catran DC, Pohl M, Maxwell D, Appel G, Hunsicker GP, Kunis C, et al. Randomized controlled trial of cyclosporine (D) vs placebo (P) in steroid resistant, nephrotic patients (NS) with membranous nephropathy (SR-MGN) [abstract]. *Journal of the American Society of Nephrology* 1998;**9**(Program & Abstracts):85A. [CENTRAL: CN-00444711]
Catran DC, Wald R, Brencley PE, Coupes B, for the North American Nephrotic Syndrome Group and the Genes Gender and Glomerulonephritis Group. Clinical correlates of serial urinary membrane attack complex estimates in patients with idiopathic membranous nephropathy. *Clinical Nephrology* 2003;**60**(1):7–12. MEDLINE: 12872852

Chan 2007 {published data only}

Chan TM, Lin AW, Tang SC, Qian JQ, Lam MF, Ho YW, et al. Prospective controlled study on mycophenolate mofetil and prednisolone in the treatment of membranous nephropathy with nephrotic syndrome. *Nephrology* 2007;**12**(6):576–81. MEDLINE: 17995584

Chen 2010a {published data only}

Chen M, Chen J, Li X, Lu F, Xu FF, Qian JQ, et al. A randomized controlled study comparing prednisone plus tacrolimus versus prednisone plus cyclophosphamide in patients with membranous nephropathy and nephrotic syndrome [abstract no: SA-PO1086]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):802A. [CENTRAL: CN-00782317]
* Chen M, Li H, Li XY, Lu FM, Ni ZH, Xu FF, et al. Tacrolimus combined with corticosteroids in treatment of nephrotic idiopathic membranous nephropathy: a multicenter randomized controlled trial. *American Journal of the Medical Sciences* 2010;**339**(3):233–8. MEDLINE: 20220333

Coggins 1979 {published data only}

* Coggins CH, Pinn V, Glasscock RR, Blades JM, Cotran R, Cohen J, et al. A controlled study of short-term prednisone treatment in adults with membranous nephropathy. Collaborative Study of the Adult Idiopathic Nephrotic Syndrome. *New England Journal of Medicine* 1979;**301**(24): 1301–6. MEDLINE: 388220
Coggins CH, The Collaborative Study of the Adult Nephrotic Syndrome. The effect of short-term prednisone treatment in adult nephrotics with minimal change (MC) and membranous (M) histology [abstract].

Kidney International 1977;**12**(6):463. [CENTRAL: CN-00784389]

CYCLOMEN Study 1994 {published and unpublished data}

Laurens W, Ruggenenti P, Perna A, Vanrenterghem Y, Remuzzi G. A randomised and controlled study to assess the effect of cyclosporin in nephrotic patients with membranous nephropathy and reduced renal function (CYCLOMEN). *Journal of Nephrology* 1994;**7**(4):237–47. [EMBASE: 1994281713]
Pisoni R, Grinyo JM, Salvadori M, Laurens W, Garini G, Oliver YA, et al. Cyclosporine versus conservative therapy in patients with idiopathic membranous nephropathy (IMN) and deteriorating renal function: Results of the CYCLOMEN trial [abstract]. *Journal of the American Society of Nephrology* 2000;**11**(Sept):95A. [CENTRAL: CN-00583866]

Donadio 1974a {published data only}

Donadio JV, Holley KE, Anderson CF, Taylor WF. Controlled trial of cyclophosphamide in idiopathic membranous nephropathy. *Kidney International* 1974;**6**(6): 431–9. MEDLINE: 4613934

Dussol 2008 {published data only}

* Dussol B, Morange S, Burtsey S, Indreies M, Cassuto E, Mourad G, et al. Mycophenolate mofetil monotherapy in membranous nephropathy: a 1-year randomized controlled trial. *American Journal of Kidney Diseases* 2008;**52**(4): 699–705. MEDLINE: 18585835
Dussol B, Sichez H, Burtsey S, Cassuto E, Kaarasslan H, Villar E, et al. Mycophenolate mofetil (MMF) in patients with idiopathic membranous nephropathy with nephrotic syndrome: a multicenter randomized trial [abstract no: TH-F-DS1092]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):566A. [CENTRAL: CN-00653744]

Dyadyk 2001 {published data only}

Dyadyk AI, Bagriy AE, Yarovaia NF, Dyadyk IA. Results of long-term randomised study of immunosuppressive treatment of patients with idiopathic membranous glomerulonephritis [abstract]. *Nephrology Dialysis Transplantation* 2001;**16**(6):A64. [CENTRAL: CN-00487685]

Falk 1992 {published data only}

Falk RJ, Hogan SL, Muller KE, Jennette JC. Treatment of progressive membranous glomerulopathy. A randomized trial comparing cyclophosphamide and corticosteroids with corticosteroids alone. The Glomerular Disease Collaborative Network. *Annals of Internal Medicine* 1992; **116**(6):438–45. MEDLINE: 1371211

Hofstra 2010 {published data only}

Branten AJ, Du Buf-Vereijken PW, Wetzels JF. Early versus late start of immunosuppressive therapy in patients with membranous nephropathy; a randomized study. [abstract no: SA-PO188]. *Journal of the American Society of Nephrology* 2004;**15**(Oct):341A. [CENTRAL: CN-00583772]
Branten AJ, du Buf-Vereijken PW, Wetzels JF. Defining the optimal time of treatment start in patients with

membranous nephropathy: a randomized study [abstract no: SU-PO969]. *Journal of the American Society of Nephrology* 2002;**13**(September, Program & Abstracts): 668A. [CENTRAL: CN-00444526]

Hofstra JM, Branten AJ, Wetzels FM. No benefit of early start of immunosuppressive therapy in idiopathic membranous nephropathy [abstract no: F-FC264]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):60A. [CENTRAL: CN-00747283]

* Hofstra JM, Branten AJ, Wirtz JJ, Noordzij TC, du Buf-Vereijken PW, Wetzels JF. Early versus late start of immunosuppressive therapy in idiopathic membranous nephropathy: a randomized controlled trial. *Nephrology Dialysis Transplantation* 2010;**25**(1):129–36. MEDLINE: 19666912

Imbasciati 1980 {published data only}

Imbasciati E, Cagnoli L, Case N, Pasquali S, Di Filippo G, Limido D, et al. Controlled study of treatment of steroids and chlorambucil, in alternate months, for membranous nephropathy and focal glomerulosclerosis. Preliminary evaluation of the results [Studio controllato di un trattamento a mesi alterni di steroidi e clorambucil nella nefropatia membranosa e nella glomerulosclerosi focale. Valutazione preliminare dei risultati]. *Minerva Nefrologica* 1980;**27**(4):571–5. MEDLINE: 7019771
Ponticelli C. Treatment of membranous nephropathy (MN) [abstract]. 9th Asian Colloquium in Nephrology; 1992, May 17–21; Seoul, Korea. 1992:22–4. [CENTRAL: CN-00461530]
Ponticelli C. Treatment of membranous nephropathy [abstract]. 12th International Congress of Nephrology; 1993, Jun 13–18; Jerusalem, Israel. 1993:565.
Ponticelli C, Zucchelli P, Imbasciati E, Cagnoli L, Pozzi C, Grassi C, et al. Controlled trial of monthly alternated courses of steroid and chlorambucil for idiopathic membranous nephropathy. *Proceedings of the European Dialysis & Transplant Association* 1983;**19**:717–23. MEDLINE: 6348763
Ponticelli C, Zucchelli P, Imbasciati E, Cagnoli L, Pozzi C, Passerini P, et al. Controlled trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. *New England Journal of Medicine* 1984;**310**(15):946–50. MEDLINE: 6366560
Ponticelli C, Zucchelli P, Locatelli F, Grassi G, Limido D, Volpini T, et al. Controlled trial of monthly alternated courses of steroid and chlorambucil in idiopathic membranous nephropathy [abstract]. *Kidney International* 1983;**23**(3):554. [CENTRAL: CN-00644373]
Ponticelli C, Zucchelli P, Passerini P, Cagnoli L, Cesana B, Pozzi C, et al. A randomized trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. *New England Journal of Medicine* 1989;**320**(1):8–13. MEDLINE: 2642605
* Ponticelli C, Zucchelli P, Passerini P, Cesana B, Locatelli F, Pasquali S, et al. A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. *Kidney International* 1995;**48**(5):1600–4.

- MEDLINE: 8544420
- Zucchelli P, Cagnoli L, Pasquali S, Casanova S, Donini U. Clinical and morphologic evolution of idiopathic membranous nephropathy. *Clinical Nephrology* 1986;**25**(6): 282–8. MEDLINE: 3524923
- Zucchelli P, Ponticelli C, Cagnoli L, Aroldi A, Beltrandi E. Prognostic value of T lymphocyte subset ratio in idiopathic membranous nephropathy. *American Journal of Nephrology* 1988;**8**(1):15–20. MEDLINE: 2967032
- Jha 2007** *{published data only}*
- * Jha V, Ganguli A, Saha TK, Kohli HS, Sud K, Gupta KL, et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. *Journal of the American Society of Nephrology* 2007;**18**(6):1899–904. MEDLINE: 17494881
 - Jha V, Kohli HS, Sud K, Gupta KL, Sakhuja V. A randomized controlled trial of steroids and cyclophosphamide in adults with idiopathic membranous nephropathy [abstract no: FC3-02]. *Nephrology* 2003;**8**(Suppl):A16.
 - Jha V, Kohli HS, Sud K, Krishan L, Joshi K, Sakhuja V. Randomized controlled trial of steroids and cyclophosphamide in adults with idiopathic membranous nephropathy [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):213A. [CENTRAL: CN-00445921]
 - Jha V, Saha TK, Kohli HS, Sud K, Gupta KL, Joshi K, et al. A randomized controlled trial of steroids and cyclophosphamide in adults with idiopathic membranous nephropathy [abstract]. 35th Congress. European Renal Association. European Dialysis and Transplantation Association; 1998, Jun 6-9; Rimini, Italy. 1998:114.
- Jurubita 2012** *{published data only}*
- Jurubita R, Ismail G, Bobeica G, Rusu E, Zilisteanu D, Andronesi A, et al. Efficacy and safety of triple therapy with MMF, cyclosporine and prednisolone versus cyclosporine and prednisolone in adult patients with idiopathic membranous nephropathy and persistent heavy proteinuria [abstract]. *Nephrology Dialysis Transplantation* 2012;**27** (Suppl 2):FP347.
- Koshisawa 1993** *{published data only}*
- Koshisawa S, Sato M, Narita M, Sakai O, Nakajima M. Clinical evaluation of an immunosuppressive drug, mizoribine (HE-69) on steroid-resistant nephrotic syndrome. A multicenter double-blind comparison study with placebo. *Jin To Tohseki [Kidney & Dialysis]* 1993;**34**(4): 631–50.
- Kosmadakis 2010** *{published data only}*
- Kosmadakis G, Filiopoulos V, Smirloglou D, Skarlas P, Georgoulas C, Michail S. Comparison of immunosuppressive therapeutic regimens in patients with nephrotic syndrome due to idiopathic membranous nephropathy. *Renal Failure* 2010;**32**(5):566–71. MEDLINE: 20486839
- Liu 2009b** *{published data only}*
- Liu ZH, Li SJ, Wu Y, Zuo K, Wang B, Zeng CH, et al. Treatment of membranous nephropathy with Tripterygium wilfordii and steroid: a prospective randomized control trial. *Shenzangbing Yu Touxu Shenyizhi Zazhi [Chinese Journal of Nephrology Dialysis & Transplantation]* 2009;**18**(4):303–9.
- Murphy 1992** *{published data only}*
- Murphy BF, McDonald I, Fairley KF, Kincaid-Smith PS. Randomized controlled trial of cyclophosphamide, warfarin and dipyridamole in idiopathic membranous glomerulonephritis. *Clinical Nephrology* 1992;**37**(5): 229–34. MEDLINE: 1606772
- Naumovic 2011** *{published data only}*
- Naumovic R, Jovanovic D, Pavlovic S, Stosovic M, Marinkovic J, Basta-Jovanovic G. Cyclosporine versus azathioprine therapy in high-risk idiopathic membranous nephropathy patients: A 3-year prospective study. *Biomedicine & Pharmacotherapy* 2011;**65**(2):105–10. MEDLINE: 21109389
- Pahari 1993** *{published data only}*
- Pahari DK, Das S, Dutta BN, Banerjee D. Prognosis and management of membranous nephropathy. *Journal of the Association of Physicians of India* 1993;**41**(6):350–1. MEDLINE: 8005970
- Ponticelli 1992** *{published data only}*
- Ponticelli C. Treatment of idiopathic membranous nephropathy (IMN) [abstract]. Pakistan Society of Nephrology & Urology. 10th Asian Colloquium in Nephrology; 1994, Dec 2-6; Karachi, Pakistan. 1994:38.
- * Ponticelli C, Zucchelli P, Passerini P, Cesana B. Methylprednisolone plus chlorambucil as compared with methylprednisolone alone for the treatment of idiopathic membranous nephropathy. The Italian Idiopathic Membranous Nephropathy Treatment Study Group. *New England Journal of Medicine* 1992;**327**(9):599–603. MEDLINE: 1640953
- Ponticelli 1998** *{published data only}*
- Ponticelli C, Altieri P, Scolari F, Passerini P, Roccatello D, Cesana B, et al. A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. *Journal of the American Society of Nephrology* 1998;**9**(3):444–50. MEDLINE: 9513907
- Ponticelli 2006** *{published data only}*
- Ponticelli C, Passerini P, Salvadori M, Manno C, Viola BF, Pasquali S, et al. A randomized pilot trial comparing methylprednisolone plus a cytotoxic agent versus synthetic adrenocorticotrophic hormone in idiopathic membranous nephropathy. *American Journal of Kidney Diseases* 2006;**47** (2):233–40. MEDLINE: 16431252
- Praga 2007** *{published data only}*
- Praga M, Barrio V, Juárez GF, Luño J, Grupo Español de Estudio de la Nefropatía Membranosa. Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial. *Kidney International* 2007;**71**(9):924–30. MEDLINE: 17377504
- Reichert 1994** *{published data only}*
- * Reichert LJ, Huysmans FT, Assmann K, Koene RA, Wetzels JF. Preserving renal function in patients with membranous

- nephropathy: daily oral chlorambucil compared with intermittent monthly pulses of cyclophosphamide. *Annals of Internal Medicine* 1994;**121**(5):328–33. MEDLINE: 8042821
- Reichert LJ, Koene RA, Wetzels JF. Chlorambucil but not pulse cyclophosphamide reverses the deterioration of renal function in patients with membranous glomerulonephropathy [abstract]. *Journal of the American Society of Nephrology* 1993;**4**(Program & Abstracts):285.
- Saito 2009** *{published data only}*
Saito T, Watanabe M, Ogahara S, Shuto H, Kataoka Y. Significance of blood concentration of cyclosporine at 2 hours after administration for the treatment of idiopathic membranous nephropathy with steroid resistant nephrotic syndrome [abstract no: SA285]. World Congress of Nephrology; 2009 May, 22–26; Milan, Italy. 2009.
- Senthil Nayagam 2008** *{published data only}*
Senthil Nayagam L, Ganguli A, Rathil M, Kohli HS, Gupta KL, Joshi K, et al. Mycophenolate mofetil or standard therapy for membranous nephropathy and focal segmental glomerulosclerosis: a pilot study. *Nephrology Dialysis Transplantation* 2008;**23**(6):1926–30. MEDLINE: 17989103
- Shibasaki 2004** *{published data only}*
Shibasaki T, Koyama A, Hishida A, Muso E, Osawa G, Yamabe H, et al. A randomized open-label comparative study of conventional therapy versus mizoribine onlay therapy in patients with steroid-resistant nephrotic syndrome (postmarketing survey). *Clinical & Experimental Nephrology* 2004;**8**(2):117–26. MEDLINE: 15235928
- Silverberg 1976** *{published data only}*
Western Canadian Glomerulonephritis Study Group. Controlled trial of azathioprine in the nephrotic syndrome secondary to idiopathic membranous glomerulonephritis. *Canadian Medical Association Journal* 1976;**115**(12):1209–10. MEDLINE: 793706
- Stegeman 1994** *{published data only}*
De Jong PE. ACE inhibition versus corticosteroids in membranous nephropathy (ACIMEN). *European Union biomedical and health research: the BIOMED 1 programme*. Vol. 1, Amsterdam: IOS Press, 1995:606–607. [ISBN 0929–6743]
Stegeman CA, De Zeeuw D, De Jong PE. ACE inhibition versus corticosteroids in membranous nephropathy (ACIMEN). *Journal of Nephrology* 1994;**7**(5):294–300. [EMBASE: 1994344069]
- Tiller 1981** *{published data only}*
Mathew TH. The treatment of idiopathic glomerulonephritis. Proceedings of the Second Asian Pacific Congress of Nephrology. 1983:164–72.
Tiller D. Australian glomerulonephritis trial: membranous glomerulonephritis, mesangiocapillary glomerulonephritis [abstract]. *Australian & New Zealand Journal of Medicine* 1981;**11**(4):603. [CENTRAL: CN–00583749]
* Tiller DJ, Clarkson AR, Mathew T, Thompson N, Row G, Lauer C, et al. A prospective randomised trial of cyclophosphamide, dipyridamole and warfarin in membranous and mesangiocapillary glomerulonephritis. In: Zuruksoglu W, Papadimitriou M, Pypasopoulos M, Sion M, Zamboulis C editor(s). *Advances in Basic and Clinical Nephrology. 8th International Congress of Nephrology; 1981 June 7–12; Athens, Greece*. Basel: Karger, 1981:345–51.
- Xu 2010** *{published data only}*
Xu J, Zhang W, Xu YW, Chen N. A double-blinded prospective randomised study on the efficacy of corticosteroid plus cyclophosphamide or FK506 in idiopathic membranous nephropathy patients with nephrotic syndrome [abstract]. *NDT Plus* 2010;**3**(Suppl 3):iii431. [EMBASE: 70484584]

References to studies excluded from this review

- Alexopoulos 2006** *{published data only}*
Alexopoulos E, Papagianni A, Tsamelashvili M, Leontsini M, Memmos D. Induction and long-term treatment with Cyclosporin A in membranous glomerulonephritis with the nephrotic syndrome [abstract no: SA-PO1020]. *Journal of the American Society of Nephrology* 2005;**16**(Nov):780A. [CENTRAL: CN–00644271]
Alexopoulos E, Papagianni A, Tsamelashvili M, Leontsini M, Memmos D. Induction and long-term treatment with cyclosporine in membranous nephropathy with the nephrotic syndrome. *Nephrology Dialysis Transplantation* 2006;**21**(11):3127–32. MEDLINE: 16968719
- Ambalavanan 1996** *{published data only}*
Ambalavanan S, Fauvel J-P, Sibley RK, Myers BD. Mechanism of the antiproteinuric effect of cyclosporine in membranous nephropathy. *Journal of the American Society of Nephrology* 1996;**7**(2):290–8. MEDLINE: 8785399
- Austin 2008** *{published data only}*
Austin HA, Braun MJ, Howard LV, Kopp JB, Balow JE. Sirolimus therapy in idiopathic and lupus membranous nephropathy [abstract]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):561A.
- Black 1970** *{published data only}*
Black DA, Rose G, Brewer DB. Controlled trial of prednisone in adult patients with the nephrotic syndrome. *British Medical Journal* 1970;**3**(5270):412–6. MEDLINE: 4916790
- Dominguez-Gil 1999** *{published data only}*
Dominguez-Gil B, Hernandez E, Segura J, Carreno A, Morales E, Herrero JC, Praga M. Immunosuppressive treatment in idiopathic membranous glomerulonephritis (MGN) with progressive renal function worsening [abstract]. *Nephrology Dialysis Transplantation* 1999;**14**(9):A155. MEDLINE: CN–00583436
Torres A, Dominguez-Gil B, Carreno A, Segura J, Gonzalez E, Ortiz M, et al. Immunosuppressive treatment in idiopathic membranous glomerulonephritis (MGN) with progressive renal function worsening [abstract]. *Journal*

- of the American Society of Nephrology 2000;**11**(Sept):99A. [CENTRAL: CN-00783416]
- Torres A, Domínguez-Gil B, Carreño A, Hernández E, Morales E, Segura J, et al. Conservative versus immunosuppressive treatment of patients with idiopathic membranous nephropathy. *Kidney International* 2002;**61**(1):219–27. MEDLINE: 11786104
- du Buf-Vereijken 2004** {published data only}
- du Buf-Vereijken PW, Branten AJ, Wetzels JF, Membranous Nephropathy Study Group. Cytotoxic therapy for membranous nephropathy and renal insufficiency: improved renal survival but high relapse rate. *Nephrology Dialysis Transplantation* 2004;**19**(5):1142–8. MEDLINE: 14993502
- Edefonti 1988** {published data only}
- Edefonti A, Ghio L, Bettinelli A, Paterlini G. Unconjugated hyperbilirubinemia due to cyclosporin a (CyA) administration in children with nephrotic syndrome (NS) [abstract]. *Pediatric Nephrology* 1987;**1**(4):C8. [CENTRAL: CN-00465774]
- Edefonti A, Ghio L, Bettinelli A, Paterlini G, Giani M, Nebbia G, et al. Unconjugated hyperbilirubinemia due to ciclosporin administration in children with nephrotic syndrome. *Contributions to Nephrology* 1988;**67**:121–4. MEDLINE: 3208520
- Edefonti A, Ghio L, Rizzoni G, Rinaldi S, Gusmano R, Lama G, et al. Cyclosporine (CSA) vs cyclophosphamide (CYC) for children with frequently relapsing/steroid dependant nephrotic syndrome (FR/SDNS): long term study [abstract]. 9th Congress. International Pediatric Nephrology Association; 1992 Aug 30 - Sept 4; Jerusalem, Israel. 1992:C70. [CENTRAL: CN-00483820]
- Edefonti A, Ghio L, Rizzoni G, Rinaldi S, Gusmano R, Lama G, et al. Cyclosporine (CSA) vs cyclophosphamide (CYC) for children with frequently relapsing/steroid dependent nephrotic syndrome (FR/SDNS): long term study [abstract]. *Journal of the American Society of Nephrology* 1992;**3**(3):310. [CENTRAL: CN-00520331]
- Ponticelli C. A multicenter controlled prospective trial with cyclosporine vs cyclophosphamide in frequent relapsers and steroid dependent patients with idiopathic nephrotic syndrome. *Journal of Nephrology* 1989;**2**(2):147–51. [EMBASE: 1991014828]
- Ponticelli C. Ciclosporin in the treatment of idiopathic nephrotic syndrome [abstract]. 10th Asian Colloquium in Nephrology; 1994, Dec 2–6; Karachi, Pakistan. 1994:116.
- Ponticelli C, Edefonti A, Ghio L, Rizzoni G, Rinaldi S, Gusmano R, et al. Cyclosporin versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: a multicentre randomized controlled trial. *Nephrology Dialysis Transplantation* 1993;**8**(12):1326–32. MEDLINE: 8159300
- Ponticelli C, Rivolta E. Ciclosporin in minimal-change glomerulopathy and in focal segmental glomerular sclerosis. [Review] [39 refs]. *American Journal of Nephrology* 1990;**10**(Suppl 1):105–9. MEDLINE: 2256469
- Goumenos 2007** {published data only}
- Goumenos DS, Katopodis KP, Passadakis P, Vardaki E, Liakopoulos V, Dafnis E, et al. Corticosteroids and ciclosporin A in idiopathic membranous nephropathy: higher remission rates of nephrotic syndrome and less adverse reactions than after traditional treatment with cytotoxic drugs. *American Journal of Nephrology* 2007;**27**(3):226–31. MEDLINE: 17389782
- Laguerre 1975** {published data only}
- Laguerre G, Bernard D, Bariety J, Druet P, Guenel J. Treatment with chlorambucil and azathioprine in primary glomerulonephritis. Results of a “controlled” study [Traitement par le chlorambucil et l’azathioprine dans les glomérulonéphrites primitives: Résultats d’une étude “contrôlée”]. *Journal d’Urologie et de Néphrologie* 1975;**81**(9):655–72. MEDLINE: 765492
- Li 2008** {published data only}
- Li X, Lv R, He Q, Li H, Du X, Lin W, et al. Early initiation of tacrolimus or cyclophosphamide therapy for idiopathic membranous nephropathy with severe proteinuria. *Journal of Nephrology* 2008;**21**(4):584–91. MEDLINE: 18651550
- Majima 1990** {published data only}
- Majima K, Hori Y, Inoue T, Ishizaki K, Kinoshita E, Nomura G. The effects of treatment with prednisolone in patients with idiopathic membranous nephropathy [abstract]. 11th International Congress of Nephrology; 1990, Jul 15–20; Tokyo, Japan. 1990:117A. [CENTRAL: CN-00784437]
- Michail 2004** {published data only}
- Michail S, Filiopoulos V, Kosmadakis G, Tentolouris N, Georgoulas C, Gobou A, et al. Comparison of three regimens in patients with idiopathic membranous nephropathy (IMN) associated with nephrotic syndrome (NS) [abstract no: SP053]. 41st Congress. European Renal Association. European Dialysis and Transplantation Association; 2004, May 15–18; Lisbon, Portugal. 2004:34. [CENTRAL: CN-00509354]
- MRCWP 1971** {published data only}
- Anonymous. Controlled trial of azathioprine and prednisone in chronic renal disease. Report by Medical Research Council Working Party. *British Medical Journal* 1971;**2**(5756):239–41. MEDLINE: 4929367
- Nand 1997** {published data only}
- Nand N, Das R, Jaswal TS. Evaluation of efficacy of methylprednisolone, prednisolone and chlorambucil in idiopathic glomerulonephritis. *Journal of the Indian Medical Association* 1997;**95**(6):163–5, 174. MEDLINE: 9420390
- Plavljanić 1998** {published data only}
- Plavljanić D, Spoljar-Scukanec M, Milutinovic S. Tubular damage in patients with membranous nephropathy. The response to treatment [abstract]. 35th Congress. European Renal Association. European Dialysis and Transplantation Association; 1998, Jun 6–9; Rimini, Italy. 1998:193. [CENTRAL: CN-00485443]

Polenakovic 1997 {published data only}

Polenakovic M, Grcevska L, Polenakovic H. Long-term follow-up of patients with stage II idiopathic membranous nephropathy (IMN)- good response to steroid and chlorambucil treatment [abstract]. *Nephrology Dialysis Transplantation* 1997;**12**(9):A76. [CENTRAL: CN-00520378]

Ponticelli 1993a {published data only}

Ponticelli C, Rizzoni G, Edefonti A, Altieri P, Rivolta E, Rinaldi S, et al. A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. *Kidney International* 1993;**43**(6):1377-84. MEDLINE: 8315953

Rashid 1995 {published data only}

Rashid HU, Khanam A, Islam KM. Treatment of membranous nephropathy with prednisolone and ACE-inhibitor [abstract]. ISN XIII International Congress of Nephrology; 1995, Jul 2-6; Madrid, Spain. 1995:269.

Sahay 2002 {published data only}

Gopal KA, Sahay M, Raman A, Narayan G. Ponticelli regime for membranous nephropathy - do Indians respond differently? [abstract]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):615. [CENTRAL: CN-00445523]
Sahay M, Anuradha, Narayan G. Ponticelli regimen for membranous nephropathy - do Indians respond differently? [abstract]. *Indian Journal of Nephrology* 2002;**12**(4):180. [CENTRAL: CN-00461642]

Shilov 1998 {published data only}

Shilov EM, Krasnova TN, Ivanov AA, Ivanova LV, Shnyakina OV, Tareyeva IE. Oral cyclophosphamide versus cyclophosphamide (CPA) pulses in membranous and mesangial GN [abstract]. 35th Congress. European Renal Association. European Dialysis and Transplantation Association; 1998, Jun 6-9; Rimini, Italy. 1998:116. [CENTRAL: CN-00485850]

Sun 2008 {published data only}

Sun GD, Xu ZG, Luo P, Miao LN. The effect of tacrolimus combined with small dose of hormone on idiopathic membranous nephropathy. *Zhongguo Shiyong Neike Zazhi [Chinese Journal of Practical Internal Medicine]* 2008;**28**(7): 542-545. [ChiCTR-TRC-09000539]

Tejani 1991 {published data only}

Tejani A, Suthanthiran M, Pomrantz A. A randomized controlled trial of low-dose prednisone and ciclosporin versus high-dose prednisone in nephrotic syndrome of children. *Nephron* 1991;**59**(1):96-9. MEDLINE: 1944755

Yao 2001 {published data only}

Yao X, Chen H, Wang Q, Tang Z, Hu W, Yin G, et al. Cyclosporin A treatment for idiopathic membranous nephropathy. *Chinese Medical Journal* 2001;**114**(12): 1305-8. MEDLINE: 11793859
Yao XD, Li L, Tang Z, Hu WX, Ying G, Chen HP. Prospective clinical trial of Cyclosporin A in idiopathic membranous nephropathy [abstract]. 6th Asian Pacific Congress of Nephrology; 1995, Dec 5-9; Hong Kong. 1995:52. [CENTRAL: CN-00462029]

References to studies awaiting assessment**Appel 2002 {published data only}**

Appel G, Nachman P, Hogan S, Radhakrishnan J, Old C, Hebert L, et al. Eculizumab (C5 complement inhibitor) in the treatment of idiopathic membranous nephropathy (IMN): preliminary baseline and pharmacokinetic (PK)/ pharmacodynamic (PD) data [abstract no: SU-PO970]. *Journal of the American Society of Nephrology* 2002;**13** (Program & Abstracts):668A.

Berg 2007 {published data only}

Berg AL. Treatment with adrenocorticotrophic hormone in idiopathic membranous nephropathy. <http://www.controlled-trials.com> 2007.

Gaskin 2004 {published data only}

Gaskin G. A national, randomised controlled trial of immunosuppressive therapy in idiopathic membranous nephropathy with declining renal function. 2004. http://www.nihr.ac.uk/Profile/Pages/NRRResults.aspx?publication_id=N0016094239 (accessed 3 April 2014).

Hirayama 2006 {published data only}

Hirayama K, Koyama A. CYPMEN (CYclosporine with/without Prednisolone in MEMbranous Nephropathy) study. 2006. <http://www.anzctr.org.au/ACTRN12609000996268.aspx> (accessed 3 April 2014).

Howman 2012 {published data only}

Howman A, Chapman TL, Langdon MM, Ferguson C, Adu D, Feehally J, et al. Immunosuppression for progressive membranous nephropathy: a UK randomised controlled trial. *Lancet* 2013;**381**(9868):744-51. MEDLINE: 23312808
Mathieson PW. The UK randomized controlled trial of Immunosuppression for progressive membranous nephropathy [abstract no: THOR048]. *Journal of the American Society of Nephrology*. 2011; Vol. 22:11A.

Liu 2006 {published data only}

Liu Z. Tacrolimus treatment of patients with idiopathic membranous nephropathy. <http://clinicaltrials.gov/ct2/show/NCT00302523> (accessed 3 April 2014).

Liu 2007 {published data only}

Liu Z. To compare the efficacy and safety of Tripterygium wilfordii (TW) versus valsartan in the membranous nephropathy (MN). <http://clinicaltrials.gov/ct2/show/NCT00518219> (accessed 3 April 2014).

Saito 2006 {published data only}

Saito T. Combined therapy of prednisolone and mizoribine in membranous nephropathy with refractory nephrotic syndrome. www.who.int/trialsearch/trial.aspx?trialid=JPRN-C000000368 (accessed 3 April 2014).

References to ongoing studies**ChiCTR-TRC-08000098 {published data only}**

ChiCTR-TRC-08000098. Research on integrated therapy of traditional Chinese medicine for membranous

- nephropathy. <http://www.chictr.org/en/proj/show.aspx?proj=1290> (accessed 3 April 2014).
- ChiCTR-TRC-11001144** *{published data only}*
ChiCTR-TRC-11001144. A prospective randomized study on the efficacy of steroid combined with CTX or tacrolimus in IMN patients with NS. <http://www.chictr.org/en/proj/show.aspx?proj=261> (accessed 3 April 2014).
- CTRI/2010/091/000231** *{published data only}*
CTRI/2010/091/000231. Comparison of efficacy of tacrolimus versus cyclophosphamide in idiopathic membranous nephropathy. <http://apps.who.int/trialsearch/Trial.aspx?TrialID=CTRI/2010/091/000231> (accessed 3 April 2014).
- EUCTR2007-005410-39-ES** *{published data only}*
EUCTR2007-005410-39-ES. Randomized pilot study comparing tacrolimus vs. cyclophosphamide-prednisone in idiopathic membranous nephropathy - MEMTAC [Estudio piloto aleatorizado comparativo de tacrolimus vs ciclofosfamida-prednisona en la nefropatía membranosa idiopática - MEMTAC]. <http://apps.who.int/trialsearch/Trial.aspx?TrialID=EUCTR2007-005410-39-ES> (accessed 3 April 2014).
- JPRN-UMIN000001099** *{published data only}*
JPRN-UMIN000001099. Optimal use of ciclosporin in membranous nephropathy (OCIM-NS study). <http://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000001321&language=E> (accessed 3 April 2014).
- JPRN-UMIN000006939** *{published data only}*
JPRN-UMIN000006939. High-dose gamma-globulin therapy for nephrotic membranous nephropathy patients. <http://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000007975&language=E> (accessed 93 April 2014).
- NCT00805753** *{published data only}*
NCT00805753. Dose-finding pilot study of ACTH in patients with idiopathic membranous nephropathy (MN). <http://www.clinicaltrials.gov/ct2/show/NCT00805753> (accessed 3 April 2014).
- NCT00843856** *{published data only}*
NCT00843856. Mycophenolate mofetil and tacrolimus versus tacrolimus for the treatment of idiopathic membranous glomerulonephritis (IMG) (MTAC). <http://www.clinicaltrials.gov/ct2/show/NCT00843856> (accessed 3 April 2014).
- NCT01093157** *{published data only}*
NCT01093157. A dose escalation study of long-acting ACTH gel in membranous nephropathy. <http://www.clinicaltrials.gov/ct2/show/NCT01093157> (accessed 3 April 2014).
- NCT01161459** *{published data only}*
NCT01161459. Treatment of idiopathic membranous nephropathy with Tripterygium wilfordii plus steroid vs tacrolimus plus steroid. <http://www.clinicaltrials.gov/ct2/show/NCT01161459> (accessed 3 April 2014).
- NCT01180036** *{published data only}*
NCT01180036. A randomized controlled trial of rituximab versus cyclosporine in the treatment of membranous nephropathy (IMN). <http://www.clinicaltrials.gov/ct2/show/NCT01180036> (accessed 3 April 2014).
- NCT01282073** *{published data only}*
NCT01282073. Mycophenolate mofetil in patients with progressive idiopathic membranous nephropathy (MMFPRIMER). <http://www.clinicaltrials.gov/ct2/show/NCT01282073> (accessed 3 April 2014).
- NCT01386554** *{published data only}*
NCT01386554. Acthar for treatment of proteinuria in membranous nephropathy patients (CHART). <http://www.clinicaltrials.gov/ct2/show/NCT01386554> (accessed 3 April 2014).
- NCT01508468** *{published data only}*
NCT01508468. Evaluate rituximab treatment for idiopathic membranous nephropathy (GEMRITUX). <http://www.clinicaltrials.gov/ct2/show/NCT01508468> (accessed 3 April 2014).

Additional references

Ahuja 1999

Ahuja M, Goumenos D, Shortland JR, Gerakis A, Brown CB. Does immunosuppression with prednisolone and azathioprine alter the progression of idiopathic membranous nephropathy?. *American Journal of Kidney Diseases* 1999;**34**(3):521–9. MEDLINE: 10469864

Beck 2009

Beck LH Jr, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *New England Journal of Medicine* 2009;**361**(1):11–21. MEDLINE: 19571279

Beck 2011

Beck LH Jr, Fervenza FC, Beck DM, Bonegio RG, Malik FA, Erickson SB, et al. Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. *Journal of the American Society of Nephrology* 2011;**22**(8):1543–50. MEDLINE: 21784898

Cameron 2011

Cameron M, Gagnier JJ, Chrusasik S. Herbal therapy for treating rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2011;**2**:CD002948. DOI: 10.1002/14651858.CD002948.pub2

Chen 2010a

Chen YZ, Gao Q, Zhao XZ, Chen XM, Zhang F, Chen J, et al. Meta-analysis of tripterygium wilfordii hook F in the immunosuppressive treatment of IgA nephropathy. *Internal Medicine* 2010;**49**(19):2049–55. MEDLINE: 20930429

Chen 2010b

Chen YZ, Zhao XZ, Wu J, Mei CL. Combination regimen of leflunomide plus methylprednisolone in a female patient with reactive arthritis and concomitant IgA nephropathy.

- Chinese Medical Journal* 2010;**123**(3):375–8. MEDLINE: 20193265
- Couchoud 1994**
Couchoud C, Laville M, Boissel JP. Treatment of membranous nephropathy: a meta-analysis. *Nephrology Dialysis Transplantation* 1994;**9**(5):469–70. MEDLINE: 8090324
- du Buf-Vereijken 2005**
du Buf-Vereijken PW, Branten AJ, Wetzels JF. Idiopathic membranous nephropathy: outline and rationale of a treatment strategy. *American Journal of Kidney Diseases* 2005;**46**(6):1012–29. MEDLINE: 16310567
- Goldbach-Mansky 2009**
Goldbach-Mansky R, Wilson M, Fleischmann R, Olsen N, Silverfield J, Kempf P, et al. Comparison of Tripterygium wilfordii Hook F versus sulfasalazine in the treatment of rheumatoid arthritis: a randomized trial. *Annals of Internal Medicine* 2009;**151**(4):229–40, W49–51. MEDLINE: 19687490
- Harbord 2006**
Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**(20): 3443–57. MEDLINE: 16345038
- Harbord 2009**
Harbord RM, Harris RJ, Sterne JAC. Updated tests for small-study effects in meta-analyses. *The Stata Journal* 2009;**9**(2):197–210.
- Herrmann 2012**
Herrmann SM, Sethi S, Fervenza FC. Membranous nephropathy: the start of a paradigm shift. *Current Opinion in Nephrology & Hypertension* 2012;**21**(2):203–10. MEDLINE: 22240444
- Higgins 2011**
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
- Hofstra 2010a**
Hofstra JM, Wetzels JF. Alkylating agents in membranous nephropathy: efficacy proven beyond doubt. *Nephrology Dialysis Transplantation* 2010;**25**(6):1760–6. MEDLINE: 20133280
- Hofstra 2012**
Hofstra JM, Wetzels JF. Management of patients with membranous nephropathy. *Nephrology Dialysis Transplantation* 2012;**27**(1):6–9. MEDLINE: 21737514
- Hogan 1995**
Hogan SL, Muller KE, Jennette JC, Falk RJ. A review of therapeutic studies of idiopathic membranous glomerulopathy. *American Journal of Kidney Diseases* 1995;**25**(6):862–75. MEDLINE: 7771482
- Imperiale 1995**
Imperiale TF, Goldfarb S, Berns JS. Are cytotoxic agents beneficial in idiopathic membranous nephropathy? A meta-analysis of the controlled trials. *Journal of the American Society of Nephrology* 1995;**5**(8):1553–8. MEDLINE: 7756587
- KDIGO 2012**
KDIGO. Idiopathic membranous nephropathy. *Kidney International - Supplement* 2012;**2**:186–97. DOI: 10.1038/kisup.2012.20
- Lehman 2004**
Lehman TJ, Edelheit BS, Onel KB. Combined intravenous methotrexate and cyclophosphamide for refractory childhood lupus nephritis. *Annals of the Rheumatic Diseases* 2004;**63**(3):321–3. MEDLINE: 14962970
- Moher 2010**
Moher D, Hopewell S, Schulz KF, Montori V, Gotszche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c869. MEDLINE: 20332511
- Ponticelli 2010**
Ponticelli C, Passerini P. Management of idiopathic membranous nephropathy. *Expert Opinion on Pharmacotherapy* 2010;**11**(13):2163–75. MEDLINE: 20707756
- Remuzzi 2002**
Remuzzi G, Chiurciu C, Abbate M, Brusegan V, Bontempelli M, Ruggenti P. Rituximab for idiopathic membranous nephropathy. *Lancet* 2002;**360**(9337):923–4. MEDLINE: 12354476
- Ruggenti 2009**
Ruggenti P, Cravedi P, Remuzzi G. Rituximab for membranous nephropathy and immune disease: less might be enough. *Nature Clinical Practice Nephrology* 2009;**5**(2): 76–7. MEDLINE: 19048001
- Srivastava 1991**
Srivastava RN, Vasudev AS, Bagga A. Levamisole in nephrotic syndrome. *Lancet* 1991;**338**(8777):1275. MEDLINE: 1682671
- Stanescu 2011**
Stanescu HC, Arcos-Burgos M, Medlar A, Bockenhauer D, Kottgen A, Dragomirescu L, et al. Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy. *New England Journal of Medicine* 2011;**364**(7):616–26. MEDLINE: 21323541
- Tam 2006**
Tam LS, Li EK, Wong CK, Lam CW, Li WC, Szeto CC. Safety and efficacy of leflunomide in the treatment of lupus nephritis refractory or intolerant to traditional immunosuppressive therapy: an open label trial. *Annals of the Rheumatic Diseases* 2006;**65**(3):417–8. [PUBMED: 16474039]
- Tao 2002**
Tao X, Younger J, Fan FZ, Wang B, Lipsky PE. Benefit of an extract of Tripterygium Wilfordii Hook F in patients with rheumatoid arthritis: a double-blind, placebo-controlled study. *Arthritis & Rheumatism* 2002;**46**(7):1735–43. MEDLINE: 12124856

Waldman 2009

Waldman M, Austin HA 3rd. Controversies in the treatment of idiopathic membranous nephropathy. *Nature Reviews Nephrology* 2009;**5**(8):469–79. MEDLINE: 19581908

Waldman 2012

Waldman M, Austin HA 3rd. Treatment of idiopathic membranous nephropathy. *Journal of the American Society of Nephrology* 2012;**23**(10):1617–30. MEDLINE: 22859855

Wu 2009

Wu T, Li Y, Bian Z, Liu G, Moher D. Randomized trials published in some Chinese journals: how many are randomized?. *Trials [Electronic Resource]* 2009;**10**:46. MEDLINE: 19573242

Xu 2009

Xu G, Tu W, Jiang D, Xu C. Tripterygium wilfordii Hook F treatment for idiopathic refractory nephrotic syndrome in adults: a meta-analysis. *Nephron Clinical Practice* 2009;**111**(4):c223–8. MEDLINE: 19287181

Yoshioka 2000

Yoshioka K, Ohashi Y, Sakai T, Ito H, Yoshikawa N, Nakamura H, et al. A multicenter trial of mizoribine compared with placebo in children with frequently relapsing

nephrotic syndrome. *Kidney International* 2000;**58**(1): 317–24. MEDLINE: 10886577

References to other published versions of this review**Chen 2013**

Chen Y, Schieppati A, Cai G, Chen X, Zamora J, Giuliano GA, et al. Immunosuppression for membranous nephropathy: a systematic review and meta-analysis of 36 clinical trials. *Clinical Journal of The American Society of Nephrology: CJASN* 2013;**8**(5):787–96. MEDLINE: 23449768

Perna 2004

Perna A, Schieppati A, Zamora J, Giuliano GA, Braun N, Remuzzi G. Immunosuppressive treatment for idiopathic membranous nephropathy: a systematic review. *American Journal of Kidney Diseases* 2004;**44**(3):385–401. MEDLINE: 15332211

Schieppati 2004

Schieppati A, Perna A, Zamora J, Giuliano GA, Braun N, Remuzzi G. Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. *Cochrane Database of Systematic Reviews* 2004, Issue 4. DOI: 10.1002/14651858.CD004293.pub2

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ahmed 1994

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT Study duration: prior to 1994
Participants	<ul style="list-style-type: none"> Country: Bangladesh Setting: single centre Patients with biopsy-proven IMN with nephrotic syndrome; SCr < 1.7 mg/dL <ul style="list-style-type: none"> Pathology stage: NS Proteinuria (g/24 h): treatment group 1 (6.11 ± 1.86); treatment group 2 (7.61 ± 1.99) Hypertension: treatment group 1 (0/10); treatment group 2 (2/10) Serum albumin: NS SCr (mg/dL): treatment group 1 (1.35 ± 0.13); treatment group 2 (1.22 ± 0.16) GFR: NS Use of ACEi or ARB during follow-up: NS Previous immunosuppressive treatment: none Number: treatment group 1 (10); treatment group 2 (10) Mean age $\pm$ SD (years): treatment group 1 (32 ± 7); treatment group 2 (38 ± 14) Sex (M/F): treatment group 1 (8/2); treatment group 2 (8/2)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Methylprednisolone: 1 g/d IV for 3 consecutive days Prednisolone: 0.5 mg/kg/d for 27 days Chlorambucil: 0.2 mg/kg/d for 1 month for 3 cycles (6 months) <p>Treatment group 2</p> <ul style="list-style-type: none"> Prednisolone: 1.0 to 1.5 mg/kg/d for 8 weeks and then in tapering dose and finally withdrawal after 8 weeks
Outcomes	<ul style="list-style-type: none"> Death ESKD 50% or 100% creatinine increase Final SCr Partial or complete remission Final proteinuria Side effects leading to patient withdrawal or hospitalisation
Notes	<ul style="list-style-type: none"> Baseline comparison: NS Follow-up period (months): treatment group 1 (14.6 ± 1.15); treatment group 2 (15.6 ± 2) Funding information: NS Sample size calculation: NS Confounding factors: one patient in the treatment group 1 developed hypertension at the end of follow-up

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	No information was provided, however, it could not be done
Blinding of personnel (performance bias)	High risk	No information was provided, however, it could not be done
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information was provided, however, it could not be done
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported

Ahmed 1994 (Continued)

Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Unclear risk	No information provided

Arnadottir 2006

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: before 2006
Participants	<ul style="list-style-type: none"> Countries: Iceland; Sweden Setting: international multicentre Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> Pathology stage: NS Proteinuria: NS Hypertension: NS Serum albumin: NS SCr ($\mu\text{mol/L}$): treatment group (107); control group (104) GFR: NS Baseline declining kidney function: NS Use of ACEi or ARB during follow-up: yes Previous immunosuppressive use: NS Number: treatment group (15); control group (15) Mean age $\pm$ SD (years): NS Sex (M/F): NS
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> ACTH: SC 1.0 mg once/wk, 0.75 mg twice/wk or 1.0 mg twice/wk for 9 months <p>Control group</p> <ul style="list-style-type: none"> No specific treatment
Outcomes	<ul style="list-style-type: none"> Partial or complete remission Proteinuria GFR
Notes	<ul style="list-style-type: none"> Baseline characteristics: comparable Follow-up period: at least 21 months in each patient Funding information: NS Sample size calculation: NS Confounding factors: NS Only abstract was available and unpublished data were not used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	NS
Blinding of personnel (performance bias)	High risk	NS
Blinding of outcome assessment (detection bias) All outcomes	High risk	NS
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Data was unable to be extracted from the abstract
Selective reporting (reporting bias)-Death All outcomes	High risk	Not reported
Selective reporting (reporting bias)-ESKD All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Data was unable to be extracted from the abstract
Selective reporting (reporting bias)-Remission All outcomes	High risk	Data was unable to be extracted from the abstract
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Data was unable to be extracted from the abstract

Arnadottir 2006 (Continued)

Selective reporting (reporting bias)-Side effects All outcomes	High risk	Data was unable to be extracted from the abstract
Other bias	High risk	Only abstract was available and unpublished data were not used

Austin 1996a

Methods	<ul style="list-style-type: none"> Study design: RCT Study duration: NS
Participants	<ul style="list-style-type: none"> Country: USA Setting: NS Patients with IMN <ul style="list-style-type: none"> Pathology stage: NS Proteinuria: NS Hypertension: NS Serum albumin: NS SCr ($\mu\text{mol/L}$): NS GFR: 24 to 156 mL/min Baseline declining kidney function: NS Use of ACEi or ARB during follow-up: NS Previous immunosuppressive use: NS Number: treatment group 1 (17); treatment group 2 (14) Mean age $\pm$ SD (years): NS Sex (M/F): NS
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> IV CPA: (0.5.0 g/m² every other month) Prednisone: 40 mg/m² every other day for 2 months tapered to 10 mg/m² <p>Treatment group 2</p> <ul style="list-style-type: none"> Prednisone: 40 mg/m² every other day for 2 months tapered to 10 mg/m²
Outcomes	<ul style="list-style-type: none"> Partial or complete remission GFR Proteinuria
Notes	<ul style="list-style-type: none"> Baseline characteristics: comparable Follow-up period: 1 year Funding information: NS Sample size calculation: NS Confounding factors: NS Only abstract was available and data could not used

Risk of bias

Bias	Authors' judgement	Support for judgement
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Austin 1996a (Continued)

Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants (performance bias)	Unclear risk	NS
Blinding of personnel (performance bias)	Unclear risk	NS
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NS
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Data could not be extracted
Selective reporting (reporting bias)-Death All outcomes	High risk	Not reported
Selective reporting (reporting bias)-ESKD All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Nor reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Data could not be extracted
Selective reporting (reporting bias)-Remission All outcomes	High risk	Data could not be extracted
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Side effects All outcomes	High risk	Not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: 1989 to 1996
Participants	<ul style="list-style-type: none"> • Country: Netherlands • Setting: NS • Patients with biopsy-proven IMN with nephrotic syndrome and deteriorating kidney function <ul style="list-style-type: none"> ◦ Pathology stage: NS ◦ Proteinuria (g/24 h): treatment group 1 (9 ± 2.6); treatment group 2 (11 ± 5.3) ◦ Hypertension: NS ◦ Serum albumin (g/L): treatment group 1 (22 ± 5.6); treatment group 2 (22 ± 6.0) ◦ SCr ($\mu\text{mol/L}$): treatment group 1 (219 ± 73); treatment group 2 (274 ± 126) ◦ GFR (mL/min): treatment group 1 (46 ± 17); treatment group 2 (43 ± 23) ◦ Baseline declining kidney function: yes ◦ Use of ACEi or ARB during follow-up: treatment group 1 (7/15), treatment group 2 (9/17) received ACEi before, no confounding effect was found during follow-up ◦ Previous immunosuppressive status: treatment group 1 (prednisone (6)); Treatment group 2 (prednisone (4); prednisone and chlorambucil (4)) • Number: treatment group 1 (15); treatment group 2 (17) • Mean age $\pm$ SD (years): treatment group 1 (51 ± 12); treatment group 2 (53 ± 14) • Sex (M/F): treatment group 1 (15/0); treatment group 2 (15/2)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Monthly cycles of steroids and chlorambucil <ul style="list-style-type: none"> ◦ Steroids: 1g IV methylprednisolone on 3 consecutive days, followed by oral prednisone 0.5 mg/kg/d, months 1, 3 and 5 ◦ Chlorambucil: 0.15 mg/kg/d months 2, 4 and 6 ◦ The cumulative dosage was 9.8 ± 4.1 mg/kg. ◦ Because of deteriorating kidney function, 5 patients received a second course of therapy consisting of oral CPA and prednisone (four patients) or AZA and prednisone (one patient). <p>Treatment group 2</p> <ul style="list-style-type: none"> • CPA and steroids <ul style="list-style-type: none"> ◦ Oral CPA: 1.5-2.0 mg/kg/d for 1 year ◦ Steroids in a comparable dose ◦ The median daily dose was 1.56 mg/kg
Outcomes	<ul style="list-style-type: none"> • Death • ESKD • 50% or 100% creatinine increase • Final SCr • Partial or complete remission • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation

Notes	<ul style="list-style-type: none">● Baseline comparison: comparable● Follow-up period (months): mean (32 ± 18); treatment group 1 (median 38, range 8-71); treatment group 2 (median 26, range 5-68)● Funding information: NS● Sample size calculation: NS● Confounding factors: no● This study was not fully randomised. Furthermore, this study partially overlapped with Reichert 1994	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	No information was provided, however, it could not be done
Blinding of personnel (performance bias)	High risk	No information was provided, however, it could not be done
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information was provided, however, it could not be done
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported

Branten 1998 (Continued)

Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	High risk	This study was not fully randomised

Braun 1995

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT Study duration: 1986 to 1996
Participants	<ul style="list-style-type: none"> Country: Germany Setting: multicentre Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> Pathology stage (I/II/III/IV): treatment group 1 (2/18/4/4); treatment group 2 (1/23/4/9); control group (1/11/2/4) Proteinuria (g/24 h): treatment group 1 (9.3 ± 6.3); treatment group 2 (7.2 ± 3.9); control group (6.5 ± 5.4) Hypertension: treatment group 1 (13/31); treatment group 2 (33/44); control group (9/22) Serum albumin (% of total protein): treatment group 1 (53 ± 12); treatment group 2 (52 ± 9); control group 3 (52 ± 9) SCr (mg/dL): treatment group 1 (1.0 ± 0.3); treatment group 2 (1.2 ± 0.4); control group (1.0 ± 0.4) GFR (mL/min): treatment group 1 (103 ± 31); treatment group 2 (102 ± 43); control group (107 ± 33) Baseline declining kidney function: no Use of ACEi or ARB during follow-up: yes, no confounding effect Previous immunosuppressive status: no Number: treatment group 1 (31); treatment group 2 (44); control group (22) Mean age $\pm$ SD (years): treatment group 1 (42.5 ± 13.9); treatment group 2 (43.0 ± 15.7); control group (46.9 ± 16.1) Sex (M/F): treatment group 1 (25/6); treatment group 2 (21/23); control group

	(13/9)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Monthly cycles of steroids and chlorambucil <ul style="list-style-type: none"> Steroids: IV methylprednisolone 1g over 20 to 30 min for 3 consecutive days, followed by oral prednisone 0.5 mg/kg/d or methylprednisolone 0.4 mg/kg/d, months 1, 3 and 5 Chlorambucil: 0.2 mg/kg/d, months 2, 4 and 6; the dose was lowered if the leukocyte count fell below 5000/mm³ <p>Treatment group 2</p> <ul style="list-style-type: none"> CSA + steroids <ul style="list-style-type: none"> Oral CSA and prednisone for 6 months <p>Control group</p> <ul style="list-style-type: none"> Symptomatic treatments as the above two groups
Outcomes	<ul style="list-style-type: none"> Death ESKD 50% or 100% creatinine increase Partial or complete remission Side effects leading to patient withdrawal or hospitalisation
Notes	<ul style="list-style-type: none"> Baseline comparison: more patients in the two treatment groups had more severe nephrotic syndrome and aggressive IMN than the control group Follow-up period: 68/97 patients completed the 5-year follow-up Funding information: NS Sample size calculation: NS Confounding factors: no Only abstract was available and unpublished data were included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The patients were randomised into one of the two treatment groups (1986 to 1990) using sealed envelopes that contained the treatment protocol and that were numbered according to a table of randomisation. The study group decided to change the randomisation protocol in 1990 by adding a control group to the two treatment arms. Patients were then randomised into one of the two treatment groups or the control group (1991 to 1996) using a computer based-randomisation table
Allocation concealment (selection bias)	Unclear risk	Randomisation method described could usually not allow investigators/participants to know or influence intervention group

		before eligible participant entered in the study. But the authors failed to clarify the randomisation was centrally performed and it was possible for investigators to open the sealed envelopes in advance
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	A total of 97/124 (78%) randomised patients were entered to the final analysis. Furthermore, of these 97 patients 18 were lost to follow-up and 11 did not complete the five-year follow-up. Eventually only 68/124 (55%) completed the five-year follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported

Braun 1995 (Continued)

Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	High risk	Only abstract was available and unpublished data were included

Cameron 1990

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: November 1981 to February 1985
Participants	<ul style="list-style-type: none"> • Country: UK • Setting: multicentre • Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> ◦ Pathology stage: 89/103 biopsies were reviewed by a central panel after the local judgement was made in each working party. Of these 89, 70 were graded (4 as I, 32 as II, 26 as III, and 8 as IV) ◦ Proteinuria (g/24 h): treatment group (10.8 ± 5.9); control group (10.4 ± 5.3) ◦ Hypertension: treatment group (9/52); control group (16/51) ◦ Serum albumin (g/L): treatment group (26 ± 6); group (25 ± 5) ◦ SCr ($\mu\text{mol/L}$): treatment group (114 ± 42); control group (115 ± 43) ◦ GFR (mL/min): treatment group (87 ± 30); control group (89 ± 34) ◦ Baseline declining kidney function: 13/103 patients with an initial SCr $\geq 150 \mu\text{mol/L}$ ◦ Use of ACEi or ARB during follow-up: NS ◦ Previous immunosuppressive status: no • Number: treatment group (52); control group (51) • Mean age $\pm$ SD (years): treatment group (45 ± 11.6); control group (44 ± 12.1) • Sex (M/F): treatment group (43/9); control group (43/8)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Prednisolone: 125 mg was given every alternate day for 8 weeks. Patients who weighted more than 80 kg received 150 mg on alternative days <p>Control group</p> <ul style="list-style-type: none"> • Placebo: identical tablets as prednisolone for 8 weeks
Outcomes	<ul style="list-style-type: none"> • Death • ESKD • 50% or 100% creatinine increase • Final SCr • Final GFR • Partial or complete remission • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation.

Notes	<ul style="list-style-type: none">● Baseline comparison: comparable● Follow-up period: mean 49 (36-72) months● Funding information: NS● Sample size calculation: NS● Confounding factors: At the last follow-up (49 months) a higher proportion of females were in remission or had stable function than corresponding males (P = 0.012)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed centrally, and coded tablets given locally from bottles supplied from the coordinator
Allocation concealment (selection bias)	Low risk	Randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants (performance bias)	Low risk	Identical tablets contained either 5mg of prednisolone or placebo. It could be done
Blinding of personnel (performance bias)	Low risk	Identical tablets contained either 5mg of prednisolone or placebo. It could be done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identical tablets contained either 5mg of prednisolone or placebo. It could be done
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 patients (8%) in the treatment group were lost at 4, 6, 21, and 24 months and 3 (6%) in the placebo group at 9, 18, and 21 months. Their data to the point of loss have been included in the analysis on an intention-to-treat basis. No patient lost was in remission or had a plasma creatinine of over 400μmol/L when lost. Thus, missing outcome data balanced in numbers across intervention groups and have been imputed using appropriate methods
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified

Cameron 1990 (Continued)

Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias.

Cattran 1989

Methods	<ul style="list-style-type: none"> • Study design: open, parallel RCT • Study duration: 1977 to 1985
Participants	<ul style="list-style-type: none"> • Country: Canada • Setting: single centre • Patients with biopsy-proven IMN; 120/158 patients with IMN had nephrotic-range proteinuria (64 in prednisone group and 56 in control group), while the remaining 38 patients did not have the diagnosis of nephrotic syndrome <ul style="list-style-type: none"> ◦ Pathology stage (I/II/III/IV): treatment group (6/33/33/9); control group (7/35/28/7) ◦ Proteinuria (g/24 h): treatment group (6.9 ± 0.8); control group (5.2 ± 0.9) ◦ Hypertension: treatment group (28/81); control group (24/77) ◦ Serum albumin (g/L): treatment group (27 ± 1.3); control group (30 ± 1) ◦ SCr ($\mu\text{mol/L}$): treatment group (120 ± 10); control group (103 ± 9) ◦ GFR (mL/sec/1.73 m^2): treatment group (1.3 ± 0.08); control group (1.5 ± 0.08).

	<ul style="list-style-type: none">○ Baseline declining kidney function: a portion had○ Use of ACEi or ARB during follow-up: NS○ Previous immunosuppressive status: the use of any immunosuppressive agent other than prednisone was not allowed in the 6 months before entry● Number: treatment group (81); control group (77)● Median age, range (years): treatment group (46, 18-77); control group (45, 16-83)● Sex (M/F): treatment group (61/20); control group (44/33)	
Interventions	Treatment group <ul style="list-style-type: none">● Prednisone: 45 mg/m² in a single dose on alternate days for 6 months. The cumulative dose was 0.6 ± 0.05 mg/kg/d Control group 2 <ul style="list-style-type: none">● No specific treatment for 6 months	
Outcomes	<ul style="list-style-type: none">● Death● ESKD● Partial or complete remission● Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">● Baseline comparison: comparable● Follow-up period: 48 ± 3.2 months. 72% of the 158 patients were followed for 3 years or more● Funding information: supported by grants from the Kidney Foundation of Canada● Sample size calculation: the estimated total sample size was 150 patients; enrolled 158● Confounding factors: no	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were assigned by the study coordinator in Toronto Glomerulonephritis Registry according to a table of random numbers
Allocation concealment (selection bias)	Low risk	Central Randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding

Blinding of outcome assessment (detection bias) All outcomes	High risk	No information was provided, however, it could not be done
Incomplete outcome data (attrition bias) All outcomes	Low risk	27/158 (17%) patients were lost during follow-up of 48 months: 10/81 (12%) in the prednisolone group and 17/77 (22%) in the control group
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	High risk	158 patients were properly randomised, only 120 of them were diagnosed with nephrotic syndrome. The randomisation was not stratified according to nephrotic syndrome or non-nephrotic syndrome

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: before 1994
Participants	<ul style="list-style-type: none"> • Country: Canada • Setting: multicentre • Patients with biopsy-proven IMN with nephrotic-range proteinuria and progressive decline of kidney function (the decline of CrCl was ≥ 8 mL/min 8-12 months before entry to the study) <ul style="list-style-type: none"> ◦ Pathology stage: NS ◦ Proteinuria (g/24 h): treatment group (11.5, 9-18); control group (12.8, 4-21) ◦ Hypertension: NS ◦ Serum albumin (g/L): treatment group (29 ± 6.6); control group (30 ± 9.2) ◦ SCr ($\mu\text{mol/L}$): treatment group (186 ± 65); control group (204 ± 81) ◦ GFR (mL/min): treatment group (51 ± 20); control group (46 ± 16) ◦ Baseline declining kidney function: yes ◦ Use of ACEi or ARB during follow-up: yes, no confounding effect. No ACEi were allowed unless the patient had been on such therapy a minimum of 3 months prior to entry ◦ Previous immunosuppressive status: No corticosteroids, immunosuppressive drugs or nonsteroidal anti-inflammatory agents were allowed 8-12 months before entry to the study • Number: treatment group (9); control group (8) • Median age, range (years): treatment group (44, 22-59); control group (40, 20-61) • Sex (M/F): treatment group (8/1); control group (6/2)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • CSA: 100 mg/mL, was initiated at 3.5 mg/kg/d taken in 2 divided doses, and periodic adjustments were made as necessary to achieve a 12-hour trough level of between 110 and 170 ng/mL. The mean dose of CSA was 3.8 mg/kg with a range between 2.5 and 4.9 <p>Group 2</p> <ul style="list-style-type: none"> • Placebo: made of the identical carrier except CSA was excluded. It was initially prescribed at 0.035 mL/kg/d, taken in 2 divided quantities with periodic arbitrary adjustments in dose to match the CSA group
Outcomes	<ul style="list-style-type: none"> • Death. • ESKD • Final GFR • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation
Notes	<ul style="list-style-type: none"> • Baseline comparison: comparable • Follow-up period: total observation was 21 months <ul style="list-style-type: none"> ◦ Treatment group: 10.1 (4-13) months for the study and 20 (0-41) months for the extension observation ◦ Control group: 8.9 (4-13) months for the study and 22 (6-56) months for the extension observation • Funding information: grant support was in part by the Ontario Ministry of

	Health, Kidney Foundation of Canada, Metropolitan Toronto Community Foundation and Sandoz Canada Limited <ul style="list-style-type: none">● Sample size calculation: NS● Confounding factors: no● An automatic dose reduction was reached because of a 30% rise in SCr in 10 patients (6 in CSA group, 4 in placebo group). With medication adjustment this reversed in 5 in CS group but none in placebo group	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The patients were randomly assigned to either CSA or placebo in blocks stratified by centre
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	Low risk	The patients were masked in regards to their assignment
Blinding of personnel (performance bias)	High risk	The patients were masked in regards to their assignment, but for safety reasons the physician in charge was not
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided, however, it could not be done
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported.
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported

Cattran 1995 (Continued)

Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Remission All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Cattran 2001

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: before 2001
Participants	<ul style="list-style-type: none"> • Countries: Canada, USA • Setting: multicentre (11) • Patients with biopsy-proven steroid-resistant IMN and nephrotic-range proteinuria. All patients must have failed to achieve remission of their proteinuria after a minimum of 8 weeks of prednisone treatment at ≥ 1 mg/kg/d <ul style="list-style-type: none"> ◦ Pathology stage (I-IV): treatment group 1 (2.2, 1-4); treatment group 2 (2.4, 1-4) ◦ Proteinuria (g/24 h): treatment group 1 (9.7 ± 5.3); treatment group 2 (8.8 ± 4.7) ◦ Hypertension: NS ◦ Serum albumin (g/L): treatment group 1 (28 ± 6); treatment group 2 (27 ± 6) ◦ SCr (mg/dL): treatment group 1 (1.3 ± 0.5); treatment group 2 (1.1 ± 0.3) ◦ GFR (mL/min/1.73 m²): treatment group 1 (95 ± 37); treatment group 2 (90 ± 27) ◦ Baseline declining kidney function: CrCl was ≥ 42 mL/min/1.73 m² in all included patients ◦ Use of ACEi or ARB during follow-up: yes, no confounding effect ◦ Previous immunosuppressive status: no immunosuppressive agents, plasma exchange therapy, or antilymphocyte products were allowed in the 6 months prior to entry to the study. The average per patient prednisone dose given prior to the 6-month run-in period was not different in the 2 groups. In the placebo group, the mean total

	<p>dose was 92 mg/kg (range 65 to 120), and in the CSA group, it was 108 mg/kg (range 60 to 140). The mean duration of treatment was also similar at 12 weeks in the placebo patients (range 8 to 22) and 14 weeks in the CSA patients (range 8 to 28). In addition, in the prestudy period, 18 patients (placebo (10), CSA (8)) had failed a course of a cytotoxic agents (CPA (9),</p> <ul style="list-style-type: none"> ○ chlorambucil (5), AZA (4)) for an average of 4 months (range 2 to 12). ● Number: treatment group 1 (28); treatment group 2 (23) ● Mean age $\pm$ SD (years): treatment group 1 (47 ± 11); treatment group 2 (49 ± 14) ● Sex (M/F): treatment group 1 (26/2); treatment group 2 (16/7)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> ● CSA + prednisone <ul style="list-style-type: none"> ○ CSA: started at a dose of 3.5 mg/kg/d in 2 equal doses at 12-hour intervals. Adjustments in dosages were made to achieve a whole-blood 12-hour trough level measured by monoclonal assay between 125 and 225 mg/L. It was continued for 26 weeks and then tapered to zero over 4 weeks ○ Prednisone: 0.15 mg/kg/d up to a maximum dose of 15 mg. This was reduced after 26 weeks by thirds at 4-week intervals and was stopped after 8 weeks ● Early stop points included a confirmed $\geq 30\%$ rise in baseline creatinine. Confirmed meant that the creatinine was not improved by two 25% reductions in the dose of the test medication spaced out over a four-week period. Other premature stop points included doubling of baseline liver enzymes and intolerable side effects. The test medication was also stopped if a complete remission of proteinuria was achieved and persisted for 1 month or more. The mean CSA dose was 3.7 ± 2.0 mg/kg. The mean trough level at 26 weeks was 148 ± 29 ng/L. All patients completed the 6 months of the test medications except 1 case of complete remission, where the CSA was stopped at week 20 after 4 week with no proteinuria <p>Treatment group 2</p> <ul style="list-style-type: none"> ● Placebo + prednisone <ul style="list-style-type: none"> ○ Placebo: started at a dose of 0.035 mL/kg/d. A comparable number of adjustments were made in the placebo patient's medication volume to ensure that masking was maintained. It was continued for 26 weeks and then tapered to zero over 4 weeks ○ Prednisone: 0.15 mg/kg/d up to a maximum dose of 15 mg. This was reduced after 26 weeks by thirds at 4-week intervals and was stopped after 8 weeks
Outcomes	<ul style="list-style-type: none"> ● Death ● ESKD ● 50% or 100% creatinine increase ● Final SCr ● Partial or complete remission ● Final proteinuria ● Side effects leading to patient withdrawal or hospitalisation
Notes	<ul style="list-style-type: none"> ● Baseline comparison: comparable ● Follow-up period: 18 months ● Funding information: supported by the Kidney Foundation of Canada and Novartis Canada ● Sample size calculation: the estimated total sample size was 50 patients. The

number of finally included patients was similar to the estimate (51).

- Confounding factors: no. At randomisation, 53% (27) of the patients were hypertensive (CSA (16), placebo (11)). Nineteen were on ACEi (CSA (11), placebo (8)), and 8 were on other antihypertensive medications. During the CS period, there was an increase in the number of patients in both groups that required antihypertensive medication, but more in the CSA than in the placebo group (8 versus 5). Despite this, no significant differences in supine, sitting, or mean arterial pressure measurements were noted during the active medication period or during the post-CSA period. Since ACEi could not be introduced in this period, these additional cases resulted in a decreased percentage of the hypertensive patients within each group on this class of CSA. In the CSA group, this fell from 69% to 46% and in the placebo group from 73% to 50%. During the post-test medication period, neither the percentage of patients with hypertension nor the use of ACEi changed significantly. There was no difference in the CSA group between those on ACEi compared with those not on an ACEi in either baseline proteinuria or in the amount of protein reduction by week 26. The number as well as the severity of hypertension was greater in the CSA compared with the placebo group in the active treatment period. A new antihypertensive agent (8) or an increase in the dose of the antihypertensive drugs (2) was required in the CSA group versus a new agent (5) in the placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed by the clinical coordinating centre from a table of random numbers and was stratified by centre in blocks of two to ensure a balance between groups
Allocation concealment (selection bias)	Low risk	Central randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants (performance bias)	Low risk	The patients were masked in regards to CSA versus placebo assignment. Novartis Canada Ltd. (Whitby, Ontario, Canada) provided CSA in a drink solution (100 mg/mL) and an identical placebo made from the same carrier
Blinding of personnel (performance bias)	High risk	The physicians were not masked in regards to CSA versus placebo assignment for safety reasons

Blinding of outcome assessment (detection bias) All outcomes	High risk	The end points were objective and measured centrally by a lab blinded to patient designation. No further information was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients except 2 patients completed the study. The reasons were relocation outside of North America and noncompliance
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Methods	<ul style="list-style-type: none"> • Study design: open, parallel RCT • Study duration: before 2007
Participants	<ul style="list-style-type: none"> • Country: China • Setting: NS • Patients with biopsy-proven IMN with proteinuria of ≥ 3 g/d <ul style="list-style-type: none"> ◦ Pathology stage: NS ◦ Proteinuria (g/24 h): 5.7 ± 2.7 ◦ Hypertension: 14/20 ◦ Serum albumin (g/L): 26.5 ± 7.5 ◦ SCr ($\mu\text{mol/L}$): treatment group 1 (103.3 ± 48.7); treatment group 2 (85.7 ± 31.8) ◦ GFR (mL/min): treatment group 1 (87.1 ± 38.5); treatment group 2 (101.8 ± 40.6) ◦ Baseline declining kidney function: initial creatinine was $< 300 \mu\text{mol/L}$ in all included patients 3/20 patients (2 in the MMF group and 2 in the control group) had abnormal SCr at baseline. ◦ Use of ACEi or ARB during follow-up: in view of their confounding effects on proteinuria and kidney function, ACEi and ARB were not started during the study, and if a patient was already on either medication at the start of the study, the dose was kept unchanged. Only 1 patient was receiving ACEi prior to the study, and the dose was kept unchanged ◦ Previous immunosuppressive status: those who had received cytotoxic or CSA treatment within the previous 12 months, or who had received prednisolone at ≥ 20 mg/d for 4 weeks or more within the past 6 months, were excluded • Number: treatment group 1 (11); treatment group 2 (9) • Mean age $\pm$ SD (years): 49.5 ± 13.5 • Sex (M/F): 13/7
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • MMF + prednisolone <ul style="list-style-type: none"> ◦ MMF: 1 g twice/d was given for 6 months. ◦ Oral prednisolone: started at 0.8 mg/kg/d, then tapered by 5 mg/d every fortnight until reaching 10 mg/d at around 4 months, then tapered by 2.5 mg/d every fortnight, till total withdrawal at around 6 months from baseline. The cumulative dose of prednisolone was 3.80 ± 0.28 g <p>Treatment group 2</p> <ul style="list-style-type: none"> • Modified Ponticelli regimen • IV methylprednisolone 1 g/d for 3 days, followed by oral prednisolone 0.4 mg/kg/d. for 3 weeks, then 0.2 mg/kg/d till the end of the month, alternating with chlorambucil 0.2 mg/kg/d for 1 month, for a total duration of 6 months. The cumulative dose of prednisolone was 9.93 ± 0.25 g
Outcomes	<ul style="list-style-type: none"> • Death • ESKD • Final GFR • Partial or complete remission • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation

Notes	<ul style="list-style-type: none">● Baseline comparison: comparable● Follow-up period: 15-24 months● Funding information: the study received partial funding support from the Wai Hung Charity Foundation and Roche Pharmaceuticals (Hong Kong). The donors had no role in the study design and execution, data analysis and interpretation, or writing of the report● Sample size calculation: NS● Confounding factors: no	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No information provided. However, it could be done
Allocation concealment (selection bias)	Unclear risk	Patients who satisfied the selection criteria were randomised by drawing envelope into either one of two treatment groups
Blinding of participants (performance bias)	High risk	Open-label
Blinding of personnel (performance bias)	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information was provided, however, it could not be done
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported

Chan 2007 (Continued)

Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Unclear risk	No information provided

Chen 2010a

Methods	<ul style="list-style-type: none"> • Study design: open, parallel RCT • Study duration: July 2004 to August 2008
Participants	<ul style="list-style-type: none"> • Country: China • Setting: multicentre • Patients with biopsy-proven IMN and nephrotic syndrome <ul style="list-style-type: none"> ◦ Pathology stage (I/II/III): treatment group 1 (16/21/2); treatment group 2 (16/17/1) ◦ Proteinuria (g/24 h): treatment group 1 (7.71 ± 3.93); treatment group 2 (7.28 ± 3.91) ◦ Hypertension: NS ◦ Serum albumin (g/L): treatment group 1 (23.1 ± 4.25); treatment group 2 (23.1 ± 4.81) ◦ SCr ($\mu\text{mol/L}$): treatment group 1 (75.7 ± 22.4); treatment group 2 (85.0 ± 37.5) ◦ GFR (mL/min/1.73m^2): treatment group 1 (105.5 ± 28.7); treatment group 2 (97.0 ± 34.3) ◦ Baseline declining kidney function: initial creatinine was $< 221 \mu\text{mol/L}$ in all included patients ◦ Use of ACEi or ARB during follow-up: yes, no confounding effect. To exclude the interference of ACEi or ARB on the level of proteinuria, patients who were taking ACEi or ARB before initiation of immunosuppressive therapy were instructed to maintain the dose of ACEi or ARB; those not taking ACEi or ARB before initiation of immunosuppressive therapy were instructed not to take ACEi or ARB; and other antihypertensive drugs were prescribed in those patients who did not reach the above target values. There were no significant differences in both systolic and diastolic BP between the two groups during follow-up. 12/39 patients in tacrolimus group received ACEi or ARB; while 7/34 patients in CPA group received ACEi or ARB ($P = 0.32$). Five new patients in tacrolimus group were diagnosed as hypertension and none in

	<p>CPA were diagnosed ($P = 0.09$)</p> <ul style="list-style-type: none"> ○ Previous immunosuppressive status: No immunosuppressive treatment was allowed within previous 3 months before entry ● Number: treatment group 1 (39); treatment group 2 (34) ● Mean age $\pm$ SD (years): treatment group 1 (47.2 ± 11.9); treatment group 2 (48.6 ± 11.6) ● Sex (M/F): treatment group 1 (23/16); treatment group 2 (18/16)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> ● Tacrolimus + steroids <ul style="list-style-type: none"> ○ Tacrolimus: started at a dose of 0.1 mg/kg/d, divided into 2 daily doses at a 12-hour interval. Later doses for the first 6 months were adjusted to achieve a whole blood 12 hours trough level between 5 and 10 ng/mL. Treatment was tapered for the next 3 months with a target trough level between 2 and 5 ng/mL. Doses were reduced by 25% every 2 weeks in the presence of a 50% Scr increase. If increasing of SCr persisted 50% of baseline values for 2 to 4 weeks after 75% reduction of tacrolimus doses, definition of end point was established. The daily dose was 4.43 ± 2.42 mg/d during the first 6 months ○ Oral prednisone: 1 mg/kg/d for 4 weeks, tapered gradually, and discontinued by 8 months <p>Treatment group 2</p> <ul style="list-style-type: none"> ● CPA + steroids <ul style="list-style-type: none"> ○ Oral CPA: 100 mg/d for 4 months (accumulated dosage was 12 g). The dosage was reduced by 50 mg/d if the total white blood cell count fell below 4000/L (when it returns to the normal range, the dosage can be increased with careful monitoring). ○ Oral prednisone: 1 mg/kg/d for 4 weeks, tapered gradually, and discontinued by 8 months
Outcomes	<ul style="list-style-type: none"> ● Death ● ESKD ● 50% or 100% creatinine increase ● Final GFR ● Partial or complete remission ● Final proteinuria ● Side effects leading to patient withdrawal or hospitalisation
Notes	<ul style="list-style-type: none"> ● Baseline comparison: comparable ● Follow-up period: 12 months ● Funding information: NS ● Sample size calculation: NS ● Confounding factors: No ● Glucose intolerance was only noted in 11 patients in the tacrolimus group (including 3 patients developed diabetes mellitus) ($P = 0.00$). Infection and hypertension tended to be more common in the tacrolimus group than in the CPA group although the P value did not reach statistical significance (8 versus 1 with $P = 0.55$ for infection; 5 versus 1 with $P = 0.09$ for hypertension) ● Relapse occurred in 11 patients, 6 in the tacrolimus group and 5 in the CPA group. All the patients experiencing relapse had partial remission to the initial

	treatment. All the relapses in the tacrolimus group took place within 3 months after withdrawal of tacrolimus. There was no significant difference of relapse rate between the 2 groups. For the 6 patients experiencing relapse in the tacrolimus group, 2 were retreated with tacrolimus; 2 were retreated with CPA, and the other 2 received conservative therapies (ACEi and/or ARB). For the 5 patients experiencing relapse in the CPA group, 2 received MMF, 1 received CSA, and the other 2 received conservative therapies (ACEi and/or ARB)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed by a clinical coordinating centre using a table of random numbers and was stratified by centres
Allocation concealment (selection bias)	Low risk	Allocation concealment was performed by enclosing assignments in sequentially numbered, opaque-closed envelopes
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 13/73 patients (18%) did not finish the 12-month follow-up. 6/39 patients (15%) withdrew in the tacrolimus group (infection (3); severe gastrointestinal complaint (1); elevated aminotransferase (1); patient's intention (1)). In the CPA group 7/34 patients (21%) did not finish the follow-up: 3 patients withdrew (severe gastrointestinal complaint (1); elevated aminotransferase (1); patient's intention(1)) and 4 patients were lost to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported

Chen 2010a (Continued)

Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Unclear risk	No information provided

Coggins 1979

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: before 1979
Participants	<ul style="list-style-type: none"> • Country: USA • Setting: multicentre (Interhospital Group) • Patients with biopsy-proven IMN and nephrotic syndrome <ul style="list-style-type: none"> ◦ Pathology stage (I/II/III-IV/Indeterminate): treatment group (5/18/9/2); control group (9/20/8/1) ◦ Proteinuria (g/24 h): treatment group (9.4 ± 6); control group (8.3 ± 4) ◦ Hypertension: NS ◦ Serum albumin: NS ◦ SCr (mg/dL): treatment group (1.1 ± 0.2); control group (1.0 ± 0.2) ◦ GFR (L/d/1.73 m²): > 60 ◦ Baseline declining kidney function: no ◦ Use of ACEi or ARB during follow-up: NS ◦ Previous immunosuppressive status: no patient received before • Number: treatment group (34); control group (38) • Mean age, range (years): 39, 16-65 • Sex (M/F): treatment group (22/12); control group (20/18)

Interventions	<p>Treatment group</p> <ul style="list-style-type: none">● Prednisone<ul style="list-style-type: none">○ Weight 45 to 80 kg: 125 mg, given as a single dose every other morning○ Weight < 45 kg: 100 mg every other day○ Weight > 80 kg: 150 mg, every other day● If no response at the end of 8 weeks, prednisone was tapered within an additional 4-week period. If a partial or complete response occurred, the drug was reduced by 25 mg/dose each week until a dosage of 25 mg was reached, and tapered 5 mg/dose/wk thereafter. If a patient relapsed after a complete or partial remission, the dosage was returned to the original level, maintained at that level for 1 month, and tapered as before <p>Control group</p> <ul style="list-style-type: none">● Placebo: identical placebo control tablets (supplied by Upjohn Company)● If no response at the end of 8 weeks, placebo was tapered within an additional 4-week period. If a partial or complete response occurred, the drug was reduced by 25 mg/dose each week until a dosage of 25 mg was reached, and tapered 5 mg/dose/wk thereafter. If a patient relapsed after a complete or partial remission, the dosage was returned to the original level, maintained at that level for 1 month, and tapered as before	
Outcomes	<ul style="list-style-type: none">● Death● ESKD● 50% or 100% creatinine increase● Partial or complete remission● Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">● Baseline comparison: comparable● Follow-up period: 23 ± 4.4 (4-52) months. Only 31/72 patients were followed for 24 months, and 21/72 were still under observation at 3 years● Funding information: The Collaborative Study, its members, and their institutions were supported by the following grants from the National Institutes of Health: AM15646, USPHS 5-M01-RR-00058, USPHS HL-05949, NIH 5 T32 AM 07241-02, 5K0 HL 4418, and USPHS RR-109● Sample size calculation: NS● Confounding factors: no	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Immediately after admission to the study, patients were randomly allocated to prednisone or placebo. Randomization was stratified according to initial histologic diagnosis with the light microscope (before review by the Central Pathology Board) in the participating hospital. No further information was provided, however, it could be done

Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	Low risk	Patients were assigned without the knowledge of either the patient or physician to prednisone therapy or identical placebo control tablets (supplied by the Upjohn Company)
Blinding of personnel (performance bias)	Low risk	Patients were assigned without the knowledge of either the patient or physician to prednisone therapy or identical placebo control tablets (kindly supplied by the Upjohn Company)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No further information was provided, however, it could be done
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported

Coggins 1979 (Continued)

Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias

CYCLOMEN Study 1994

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT
Participants	<ul style="list-style-type: none"> Country: Europe Setting: multicentre Patients with biopsy-proven IMN with nephrotic syndrome and worsening kidney function <ul style="list-style-type: none"> Pathology stage: NS Proteinuria (g/24 h): treatment group (6.8 ± 0.9); control group (4.0 ± 0.5) Hypertension: NS Serum albumin: NS SCr: NS GFR (mL/min/1.73 m²): treatment group (49.3 ± 6.5); control group (47.8 ± 7.3) Baseline declining kidney function: yes Use of ACEi or ARB during follow-up: yes, no confounding effect Previous immunosuppressive status: NS Number: treatment group (10); control group (11) Age: 49 years Sex (M/F): treatment group (9/1); control group (8/3)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> CSA: 5 mg/kg/d for 6 months <p>Control group</p> <ul style="list-style-type: none"> Conservative therapy for 6 months
Outcomes	<ul style="list-style-type: none"> Death ESKD Final SCr Final GFR Partial or complete remission Final proteinuria Side effects leading to patient withdrawal or hospitalisation

Notes	<ul style="list-style-type: none">● Baseline comparison: the baseline proteinuria was not balanced (P < 0.05)● Follow-up period: 12 (6-25) months● Funding information: NS● Sample size calculation: The estimated total sample size was 186 patients. This study was prematurely stopped and the number of finally included patients was far from the estimate (21)● Confounding factors: NS● Only abstract was available and unpublished data were included	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Central Randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	21/22 (95%) randomised completed the treatment and were finally analysed
Selective reporting (reporting bias)	Low risk	The study protocol was available and it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported
Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported

CYCLOMEN Study 1994 (Continued)

Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported.
Other bias	High risk	Only abstract was available and unpublished data were included

Donadio 1974a

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT Study duration: May 1971 to June 1973
Participants	<ul style="list-style-type: none"> Country: USA Setting: single centre Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> Pathology stage (I/II/III): treatment group (3/7/1); control group (2/8/1) Proteinuria (g/24 h): treatment group (7.8, 2-16.6); control group (7.6, 2-12.1) Hypertension: treatment group (2/11); control group (2/11) Serum albumin (g/L): treatment group (27, 19-34); control group (23, 16-37). SCr (mg/dL): treatment group (1.2, 0.8-1.9); control group (1.1, 0.8-2.2) GFR (mL/min/1.73 m²): treatment group (75, 44-117); control group (80.6, 33-112) Baseline declining kidney function: no Use of ACEi or ARB during follow-up: NS Previous immunosuppressive status: no patients had received prior cytotoxic drug treatment. 3 patients in treatment group (27%) and 4 in control group (36%) had received or were currently receiving prednisone treatment; such treatment was tapered off and then stopped within 30 days. <ul style="list-style-type: none"> Number: treatment group (11); control group (11) Mean age, range (years): treatment group (males: 41, 25-74; females: 48.5, 40-59); control group (males: 47.6, 34-69; females: 41, 26/65) Sex (M/F): treatment group (9/2); control group (8/3)
Interventions	Treatment group <ul style="list-style-type: none"> Oral CPA: 1.5 to 2.5mg/kg/d (mean: 1.8) for 1 year. If the leukocyte count was < 3000/mm³ or if the platelet count was < 80000/mm³ the drug was stopped for a

	minimum of 7 days. When the counts increased to above these limits, treatment was started again at one-half the previous dose and then increased to the initial dose level if possible. The cumulative dose was 538 ± 120 (310-665) mg/kg in the 9 patients who completed the 12 month treatment	
	Control group <ul style="list-style-type: none">• No treatment	
Outcomes	<ul style="list-style-type: none">• Death• ESKD• 50% or 100% creatinine increase• Final GFR• Partial or complete remission• Final proteinuria• Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">• Baseline comparison: comparable• Follow-up period: 19/22 patients were followed at least 12 months (treatment group (9); control group (10)). 17/22 patients were followed for an average of 1 year beyond the 1 year of treatment (treatment group (7); control group (8))• Funding information: supported by a grant from the Mayo Foundation and by Public Health Service grant RR-585 from the National Institutes of Health Clinical Research Center• Sample size calculation: NS• Confounding factors: NS• Nine patients in each group had the nephrotic syndrome on initial evaluation. Two in each group presented with non-nephrotic proteinuria, but all had previously been documented to have the nephrotic syndrome	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Only after a patient was deemed eligible was the treatment ascertained by referral to a list created from a table of random numbers (by WFT). The table was maintained by the renal pathologist (KEH) and was not seen by the clinicians (JVD. and CFA)
Allocation concealment (selection bias)	Low risk	Neither patient nor clinician knew what treatment was going to be given before the patient agreed to enter study
Blinding of participants (performance bias)	High risk	No placebo was used and no blinding was used
Blinding of personnel (performance bias)	High risk	No placebo was used and no blinding was used

Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo was used and no blinding was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/11 patients (18%) in the CPA group and 1/11 patients (9%) in the no-drug group did not complete the 12-month follow-up. In 2 patients in the CPA group, the drug was stopped after 8 months, on the advice of the clinicians, when data analysis to that point revealed no treatment benefit either to these patients or to the 19 patients who had completed the study. 1 patient in the no-drug group was dropped from the study because the patient was not considered to have purely IMN
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported

Other bias	Low risk	The study appeared to be free of other sources of bias
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Dussol 2008

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT Study duration: January 2004 to January 2008
Participants	<ul style="list-style-type: none"> Country: France Setting: multicentre Patients with biopsy-proven IMN and nephrotic syndrome <ul style="list-style-type: none"> Pathology stage (I/II): treatment group (8/9); control group (13/6) Proteinuria (g/24 h): treatment group (6.2 ± 3.5); control group (9.5 ± 5.8) Hypertension: NS Serum albumin (g/L): treatment group (23.2 ± 7.3); control group (20.2 ± 6.0) SCr (mg/dL): treatment group (1.01 ± 0.34); control group (1.09 ± 0.39) GFR (mL/min/1.73 m²): treatment group (92.1 ± 29.8); control group (80.7 ± 25.4) Baseline declining kidney function: initial creatinine was $< 200 \mu\text{mol/L}$ in all included patients. Use of ACEi or ARB during follow-up: yes, no confounding effect. In the control group, 14 patients received ACEi, 1 received ARB, and 2 received a combination of ACEi and ARB. In the MMF group, 17 patients received ACEi, 1 received ARB, and 1 received a combination of ACEi and ARB Previous immunosuppressive status: no patient received previous immunosuppressive treatment before entry Number: treatment group (19); control group (17) Mean age $\pm$ SD (years): treatment group (47.8 ± 15.2); control group (55.9 ± 15.2) Sex (M/F): treatment group (17/2); control group (15/2)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> MMF + conservative treatment <ul style="list-style-type: none"> MMF: 250 mg/d, progressively increased by 250 mg every other day to 2 g/d for 12 months. MMF therapy was then progressively stopped in 15 days. Mean dose of MMF was 1,850 mg. Sixteen patients could achieve the target dose of 2 g/d. Two patients were maintained on 1.5 g/d, and 1 was maintained on 1 g/d because of gastrointestinal symptoms <p>Control group</p> <ul style="list-style-type: none"> Conservative treatment <ul style="list-style-type: none"> Renin-angiotensin blockers, statins, low-salt and low-protein diet, and diuretics in case of oedema
Outcomes	<ul style="list-style-type: none"> Death ESKD 50% or 100% creatinine increase Final GFR

	<ul style="list-style-type: none">● Partial or complete remission● Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">● Baseline comparison: comparable● Follow-up period: 12 months● Funding information: partial support for this study was provided by Roche through technical assistance and financing for the clinical research assistant. Roche did not intervene in the design or conduct of the study, analysis and interpretation of the data, or preparation of the article● Sample size calculation: estimated total sample size was 34 patients. The number of finally included patients was similar to the estimate (35)● Confounding factors: no	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed by each centre through a centralized Internet on-line application provided by the sponsor (minimization method). Randomization was stratified according to sex and centre
Allocation concealment (selection bias)	Low risk	Central randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients were lost to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported

Dussol 2008 (Continued)

Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	No reported
Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	No reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Dyadyk 2001

Methods	<ul style="list-style-type: none"> • Study design: RCT • Study duration: NS
Participants	<ul style="list-style-type: none"> • Country: Ukraine • Setting: NS • Patients with IMN <ul style="list-style-type: none"> ◦ Pathology stage (I/II): NS ◦ Proteinuria (g/24 h): NS ◦ Hypertension: NS ◦ Serum albumin (g/L): NS ◦ SCr (mg/dL): NS ◦ GFR (mL/min/1.73 m²): NS ◦ Baseline declining kidney function: NS ◦ Use of ACEi or ARB during follow-up: NS ◦ Previous immunosuppressive status: NS • Number: treatment group 1 (16); treatment group 2 (16) • Mean age ± SD (years): NS • Sex (M/F): treatment group 19/13

Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> CPA <ul style="list-style-type: none"> Initial dose: 1.5 to 3.5 mg/kg/d Mean treatment duration: 5.8 months <p>Treatment group 2</p> <ul style="list-style-type: none"> Azathioprine <ul style="list-style-type: none"> Initial dose: 1.4 to 2.0 mg/kg/d Mean treatment duration: 6.6 months
Outcomes	<ul style="list-style-type: none"> Proteinuria Creatinine
Notes	<ul style="list-style-type: none"> Baseline comparison: comparable Follow-up period: 12-48 months Funding information: NS Sample size calculation: NS Confounding factors: NS Only abstract was available and data could not be used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants (performance bias)	Unclear risk	NS
Blinding of personnel (performance bias)	Unclear risk	NS
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NS
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Data could not be extracted
Selective reporting (reporting bias)-Death All outcomes	High risk	Not reported
Selective reporting (reporting bias)-ESKD All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Data could not be extracted

Dyadyk 2001 (Continued)

Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Data could not be extracted
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Data could not be extracted
Selective reporting (reporting bias)-Side effects All outcomes	High risk	Not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Falk 1992

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT Study duration: March 1986 to November 1990
Participants	<ul style="list-style-type: none"> Country: USA Setting: multicentre (Glomerular Disease Collaborative Network) Patients with biopsy-proven progressive IMN with either deteriorating kidney function or persistent proteinuria associated with morbid complications <ul style="list-style-type: none"> Pathology stage: NS Proteinuria (g/24 h): treatment group 1 (12.4 ± 9.9); treatment group 2 (11.1 ± 6.7) Hypertension: NS Serum albumin: NS SCr (mg/dL): treatment group 1 (2.3 ± 1.0); treatment group 2 (2.7 ± 1.6) GFR: NS Baseline declining kidney function: yes Use of ACEi or ARB during follow-up: yes, no confounding effect. Previous immunosuppressive status: all patient had received a course of corticosteroids therapy. All patients had received initial therapy with prednisone at a dose of 2.0 mg/kg body weight every other day (not exceeding a maximum single dose of 120 mg) for 8 weeks; the drug was then tapered by 25%/dose/wk over 4 weeks. Patients were not eligible if they had previously been treated with CPA or chlorambucil Number: treatment group 1 (13); treatment group 2 (13) Mean age $\pm$ SD (years): treatment group 1 (43.3 ± 14.8); treatment group 2 (46.0 ± 13.7) Sex (M/F): treatment group (9/4); control group (7/6)

Interventions	Treatment group 1 <ul style="list-style-type: none">CPA + steroids: IV CPA in conjunction with a 3-day course of pulse methylprednisolone and alternate-day corticosteroids<ul style="list-style-type: none">Steroids: IV pulse methylprednisolone at a dose of 7 mg/kg (not exceeding a single maximum dose of 1000 mg) given on 3 consecutive days. Forty-eight hours after completing therapy with pulse methylprednisolone, patients began treatment with oral corticosteroids (prednisone, 1mg/kg every other day, not exceeding 80mg per single dose) for 2 months; drug was tapered 25%/dose/wk over the next 4 weeks.CPA: monthly IV CPA was given at an initial dose of 0.5g/m². Leukocyte counts were monitored to maintain counts at levels no lower than 3x10⁶/L. If leukocyte nadir counts remained above 5x10⁶/L after each treatment, the subsequent cyclophosphamide dose was raised by 250mg/m². The maximum single dose did not exceed 1000 mg/m². CPA was administered monthly for 6 months Treatment group 2 <ul style="list-style-type: none">Prednisone: oral 2.0 mg/kg prednisone on alternate days for 8 weeks, and then tapered by 25%/dose/wk over 4 weeks	
Outcomes	<ul style="list-style-type: none">DeathESKD50% or 100% creatinine increaseFinal SCrFinal proteinuriaSide effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">Baseline comparison: comparable except the racial distribution (P = 0.003). The numbers of Whites/Blacks/Others were 11/1/1 and 6/7/0 in treatment group 1 and treatment group 2, respectivelyFollow-up period: 29.2 ± 17.1 monthsFunding information: in part by the Jessie Bell DuPont Religious, Charitable and Educational Fund, the Telephone Pioneers of North Carolina (Chapter 35, and the National Institutes of Health General Clinical Research Center) (grant RR00046)Sample size calculation: NSConfounding factors: noTo be included in the study, patients had to have either deteriorating kidney function or persistent proteinuria associated with morbid complications. Deterioration in kidney function was defined by a sustained doubling of the SCr over, at most, 2 years of follow-up or by a 50% fall in the GFR during the same interval. Additionally, patients were accepted into the protocol if they had a sustained SCr > 2.0 mg/dL (reciprocal value, 0.5) (two successive measurements at least 2 weeks apart). Patients were also eligible if they had an entry SCr < 2.0 mg/dL (reciprocal value, 0.5) but had persistent proteinuria with morbid complications	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All patients were randomised under the same computer generated randomisation

		table through the central Glomerular Disease Collaborative Network office. Patients were stratified on the basis of whether they had deterioration in kidney function or persistent proteinuria with morbid complications
Allocation concealment (selection bias)	Low risk	Central randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two (one in each group) patients had less than 18 months of follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	High risk	Not reported

Falk 1992 (Continued)

Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Hofstra 2010

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT Study duration: May 1998 to May 2005
Participants	<ul style="list-style-type: none"> Country: Netherlands Setting: multicentre Patients with biopsy-proven IMN with nephrotic syndrome and high risk for ESKD. The high risk for ESKD was defined as urinary B₂ microglobulin > 0.5 µg/min and urinary IgG > 125 mg/24 h <ul style="list-style-type: none"> Pathology stage: NS Proteinuria (g/10 mmol Cr): treatment group 1 (9.6, 5.9-14.4); treatment group 2 (12.0, 5.6-17.2) Hypertension: NS Serum albumin (g/L): treatment group 1 (22.6 ± 4.8); treatment group 2 (22.3 ± 3.8) SCr (mg/dL): treatment group 1 (94, 68-122); treatment group 2 (101, 75-126) GFR (mL/min/1.73 m²): treatment group 1 (81 ± 17); treatment group 2 (76 ± 13) Baseline declining kidney function: no; SCr was < 135 µmol/L in all patients at randomisation Use of ACEi or ARB during follow-up: all patients were aggressively treated to decrease BP (target value 130/80 mmHg), primarily by using ACEi and/or ARB Previous immunosuppressive status: patients who had previously been treated with immunosuppressive drugs were excluded Number: treatment group 1 (14); treatment group 2 (12) Mean age ± SD (years): treatment group 1 (48 ± 13); treatment group 2 (49 ± 10) Sex (M/F): treatment group 1 (13/1); treatment group 2 (11/1)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Early treatment: started immunosuppressive therapy immediately after randomisation <ul style="list-style-type: none"> Oral CPA: 1.5 mg/kg BW/d for 12 months, IV methylprednisolone: 1 g on days 1, 2, 3, 60, 61, 62, 120, 121 and 122 Oral prednisone: 0.5 mg/kg BW/d for 6 months, and subsequently tapered by decreasing the dose by 5 mg/week.

	<ul style="list-style-type: none">○ For prevention of gastric symptoms, famotidine 1 daily dose 20 mg was added.○ From 1999 onwards, trimethoprim-sulfamethoxazole was added 480 mg/d in the first 4-6 months, to prevent pneumocystis jiroveci pneumonia. In young fertile patients, the treatment regimen was modified because of the infertility risk associated with the use of CPA; in these patients, after 3 months of treatment CPA was replaced by AZA 1.5 mg/kg BW/day for the remaining 9 months. Three patients were treated according to the modified treatment scheme with AZA Treatment group 2 <ul style="list-style-type: none">● Late treatment: started treatment when kidney function deteriorated, defined as an increase of SCr with $\geq 25\%$ reaching a level of $\geq 135 \mu\text{mol/l}$ or an increase of SCr with $\geq 50\%$● Two patients received modified treatment with AZA after 3 months	
Outcomes	<ul style="list-style-type: none">● Death● ESKD● Partial or complete remission● Final proteinuria● Final SCr● Final GFR● Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">● Baseline comparison: comparable● Follow-up period: 72 $\pm$ 22 months; treatment group 1 (73 $\pm$ 20); treatment group 2 (71 $\pm$ 26)● Funding information: supported by grants from the Dutch Kidney Foundation (NSN OW08 and NSN PC152).● Sample size calculation: the estimated total sample size was 30 patients. The number of finally included patients was similar to the estimate (26).● Confounding factors: NS● Relapse re-treatment<ul style="list-style-type: none">○ Treatment group 1: 3 patients (23%) relapsed to nephrotic syndrome 36 months after treatment (range 25-106 months). One patient achieved a spontaneous complete remission, and another was retreated with CPA and steroids for 6 months, followed by a course of AZA. With this regimen, a partial remission was achieved. In the third patient, the relapse was only recently diagnosed.○ Treatment group 2: 3 patients (27%) relapsed to nephrotic syndrome 38 months after treatment (range 13-76 months). Two were retreated. The first patient received 6 months of CPA and steroid therapy, followed by AZA for 1 year and achieved a complete remission. The second patient started re-treatment with 3 months of CPA and steroids, followed by MMF. At the end of the follow-up, the patient had just started this treatment and nephrotic proteinuria still persisted. The third patient has not been retreated yet, as the relapse was diagnosed shortly before the last follow-up date	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	No information provided. However, it could be done
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	Open-label
Blinding of personnel (performance bias)	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	During the first year of the study, 3 patients were excluded because of the following reasons: discovery of a malignancy and withdrawal from the study within 3 months; protocol violation (start of prednisone by a physician in another hospital) and loss to follow-up due to emigration 7 months after randomisation. Thus, the final analysis included 26 patients
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported
Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported

Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Unclear risk	No information provided

Imbasciati 1980

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT Study duration: 1976 to 1985
Participants	<ul style="list-style-type: none"> Country: Italy Setting: multicentre Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> Pathology stage (I/II/III/IV): treatment group (11/21/8/2); control group (7/23/7/2) Proteinuria (g/24 h): treatment group (6.18 ± 2.98); control group (5.30 ± 2.84) Hypertension: treatment group (8/42); control group (12/39) Serum albumin: NS SCr (μmol/L): treatment group (93.8 ± 21.5); control group (93.1 ± 25.3) GFR: NS Baseline declining kidney function: no Use of ACEi or ARB during follow-up: yes; 2 (1 per group) were recorded to receive captopril during the 5-year follow-up Previous immunosuppressive status: patients who had previously received steroids or cytotoxic therapy were excluded Number: treatment group (42); control group (39) Mean age, range (years): treatment group (43.5, 15-70); control group (42, 16-74) Sex (M/F): treatment group (34/8); control group (29/10)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Chlorambucil + steroids <ul style="list-style-type: none"> i) IV methylprednisolone: 1g was given for 20 to 30 minutes on 3 consecutive days ii) Cycle A: on day 4, oral methylprednisolone (0.4 mg/kg/d) or prednisone (0.5 mg/kg/d) was given in a single morning dose for 27 days. At the end of the first month, the steroid was discontinued iii) Cycle B: chlorambucil (0.2 mg/kg/d) for 1 month; the dose was lowered if the leukocyte count fell below $5.0 \times 10^9/L$. After one month the chlorambucil was discontinued iv) Cycle A v) Cycle B vi) Cycle A

	vii) Cycle B <ul style="list-style-type: none">The entire duration of the treatment period was six months. During the study it was decided that clinicians would be free to treat the patients again, but not until 2 years after the first 6 month course of therapy. No patient relapsed within the first 2 years Control group <ul style="list-style-type: none">No specific therapy Both the treatment and control groups received low salt diets and were given diuretic and antihypertensive agents as needed	
Outcomes	<ul style="list-style-type: none">DeathESKD50% or 100% creatinine increaseFinal SCrPartial or complete remissionFinal proteinuriaSide effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">Baseline comparison: comparableFollow-up period: median 5 years (2-11) in the first report and 10 years in the second report<ul style="list-style-type: none">Funding information: supported in part by a grant (82.01308.04) from the Consiglio Nazionale delle RicercheSample size calculation: NSConfounding factors: absence of tubulointerstitial lesions reduced the risk of a deterioration of kidney function significantly (P = 0.0073) at the 5-year follow-up, this significance disappeared at the 10-year follow-up<ul style="list-style-type: none">The first report of the study analysed the data at 5-years follow-up; the second report analysed the data at 10-year follow-upIn the treatment group, 4 of relapsed patients were treated again. Three patients who had partial remissions after treatment were given new courses of therapy because of recurrence of the nephrotic syndrome at 24, 38, and 39 months, respectively. Another patient who had a recurrence of the nephrotic syndrome after having a complete remission with therapy was retreated 36 months later. Two controls, one still nephrotic and the other one with kidney function deterioration asked to be treated because of the deterioration of kidney function and then were lost to follow-up 22 and 29 months after randomisation with unchanged clinical conditions. Their data were analysed according to the intention-to-treat principle	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	For all patients, the indications for therapy were contained in sealed, completely opaque envelopes numbered in sequence according to a table of random numbers

Allocation concealment (selection bias)	Low risk	Randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four patients in the treatment group did not complete the 6-month therapy, these patients were continued to be followed up because of side effects. They were considered to be treated patients in the data analysis, according to the intention-to-treat principle. In the case of patients who died, data obtained before the time of death were included. 3/81 patients (3%) were lost to 5-year follow-up: two controls and one treated patient were lost to follow-up 22, 28, and 24 months after randomisation, respectively. At the second analysis, 9/42 (21%) treated patients and 10/39 (26%) controls were lost to follow-up from 12 to 96 months after randomisation. These 3 patients were also considered in the analyses
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported

Imbasciati 1980 (Continued)

Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Jha 2007

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT Study duration: March 1993 to February 1995
Participants	<ul style="list-style-type: none"> Country: India Setting: Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> Pathology stage: the majority of the patients had stage II IMN with minimal interstitial scarring Proteinuria (g/24 h): treatment group (6.11 ± 2.5); control group (5.91 ± 2.2) Hypertension: treatment group (5/47); control group (7/46) Serum albumin (g/L): treatment group (23.4 ± 5.8); control group (24.2 ± 8.1) SCr (mg/dL): treatment group (1.21 ± 0.31); control group (1.17 ± 0.22) GFR (mL/min): treatment group (89 ± 26); control group (84 ± 22) Baseline declining kidney function: a portion had Use of ACEi or ARB during follow-up: ACEi and ARB were withheld for at least 1 year after randomisation. During follow-up more control group patients developed hypertension that required drugs for control (16/47 versus 7/35 at the 10-year follow-up, $P < 0.01$). Treatment group patients exhibited significantly lower prevalence of ACEi/ARB use at various time points (13/47 versus 32/46 at the 10-year follow-up, $P < 0.01$). The actual mean BP values were not different between the two groups either at baseline or during follow-up Previous immunosuppressive status: patients who had received steroids or immunosuppressive drugs for ≥ 2 months were excluded <ul style="list-style-type: none"> Number: treatment group (47); control group (46) Mean age $\pm$ SD (years): treatment group (38.0 ± 13.6); control group (37.2 ± 12.4)

	<ul style="list-style-type: none"> Sex (M/F): treatment group (30/17); control group (27/19)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> CPA + steroids <ul style="list-style-type: none"> IV methylprednisolone 1 g/d for 3 consecutive days followed by oral prednisolone 0.5 mg/kg/d for 27 d in the first, third, and fifth months Oral CPA 2 mg/kg/d in the second, fourth, and sixth months. It was withheld temporarily when the counts fell to 3500/mm³ until recovery to 4000/mm³. Treatment was halted when a patient exhibited any evidence of active ulcer disease, neoplasm, diabetes, and/or life-threatening infections <p>Control group</p> <ul style="list-style-type: none"> Supportive therapy that consisted of dietary sodium restriction, diuretics, and antihypertensive agents
Outcomes	<ul style="list-style-type: none"> Death ESKD 50% or 100% creatinine increase Final GFR Partial or complete remission Final proteinuria Side effects leading to patient withdrawal or hospitalisation
Notes	<ul style="list-style-type: none"> Baseline comparison: comparable Follow-up period: median 11 years (10.5 to 12) Funding information: NS Sample size calculation: NS Confounding factors: no Patients in control group were given the choice of opting for the immunosuppressive regimen 24 months after randomisation. Finally, 15 patients elected to receive the experimental protocol 24 to 54 months after randomisation. All of them had nephrotic-range proteinuria at the time of treatment. Data were analysed on an intention-to-treat basis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	11/104 (11%) patients were lost to follow-up, 4/51 (8%) in treatment group and 7/53 (13%) in control group, between 18 to 48 month of randomisation and excluded from analysis
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Methods	<ul style="list-style-type: none">● Study design: parallel RCT● Study duration: before 2012	
Participants	<ul style="list-style-type: none">● Country: Romania● Setting: single centre● Patients with biopsy-proven IMN with persistent heavy proteinuria (> 8 g/d, minimum 6 months)<ul style="list-style-type: none">○ Pathology stage: NS○ Proteinuria (g/24 h): treatment group 1 (10.4, 8.4-14.9); treatment group 2 (10.26, 8-14.1).○ Hypertension: NS○ Serum albumin: NS○ SCr: NS○ GFR (mL/min/1.73 m²): > 60○ Baseline declining kidney function: NS○ Use of ACEi or ARB during follow-up: NS○ Previous immunosuppressive status: NS● Number: treatment group 1 (9); treatment group 2 (9)● Age: NS● Sex: NS	
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none">● MMF + CSA + steroids for 12 months<ul style="list-style-type: none">○ MMF: 1 g/ d○ CSA: 2 mg/kg/d, but not exceeding 150 mg/d○ Prednisolone: 0.15 mg/kg/d <p>Treatment group 2</p> <ul style="list-style-type: none">● CSA + steroids<ul style="list-style-type: none">○ CSA: 5 mg/kg/d, but not exceeding 150 mg/d○ Prednisolone: 0.15 mg/kg/d	
Outcomes	<ul style="list-style-type: none">● Partial or complete remission	
Notes	<ul style="list-style-type: none">● Baseline comparison: NS● Follow-up period: 12 months● Funding information: NS● Sample size calculation: NS● Confounding factors: NS● Only abstract was available and unpublished data were not used	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement

Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patient was lost to follow-up, and an intention-to-treat analysis was used
Selective reporting (reporting bias)	High risk	Only remission data were provided in that abstract
Selective reporting (reporting bias)-Death All outcomes	High risk	Not reported
Selective reporting (reporting bias)-ESKD All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Side effects All outcomes	Unclear risk	Not reported
Other bias	Unclear risk	Only abstract was available and unpublished data were not used

Koshisawa 1993

Methods	<ul style="list-style-type: none">• Study design: parallel RCT• Study duration: April 1989 to June 1992	
Participants	<ul style="list-style-type: none">• Country: Japan• Setting: NS• Patients with biopsy-proven IMN with steroid-resistant nephrotic syndrome<ul style="list-style-type: none">◦ Pathology stage: NS◦ Proteinuria: NS◦ Hypertension: NS◦ Serum albumin: NS◦ SCr: NS◦ GFR (mL/min): ≥ 50◦ Baseline declining kidney function: NS◦ Use of ACEi or ARB during follow-up: NS◦ Previous immunosuppressive status: receiving a daily maintenance dose of 20 mg prednisolone-equivalent a day (including zero dosage) before entry was allowed. <p>Other immunosuppressant medication should be stopped at the start of the study</p> <ul style="list-style-type: none">• Number: treatment group (48); control group (41)• Age: > 15 years• Sex (M/F): NS	
Interventions	Treatment group <ul style="list-style-type: none">• Mizoribine: 50 mg 3 times/d after meals for 24 weeks Control group <ul style="list-style-type: none">• Placebo.	
Outcomes	<ul style="list-style-type: none">• 50% or 100% creatinine increase• Partial or complete remission• Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">• Baseline comparison: NS• Follow-up period: 24 weeks• Funding information: NS• Sample size calculation: NS• Confounding factors: the data were abstracted from a RCT aiming to investigate the effect of mizoribine on steroid-resistant primary nephrotic syndrome. This study included all different pathologic variants of nephrotic syndrome. The randomisation were not stratified according to the pathologic diagnosis• Published in Japanese	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement

Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	Low risk	Double-blind
Blinding of personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No information provided. However, it could be done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2/48 patients in the treatment group did not complete 24-week follow-up
Selective reporting (reporting bias)	High risk	The primary outcome such as death and ESKD were NS
Selective reporting (reporting bias)-Death All outcomes	High risk	Not reported
Selective reporting (reporting bias)-ESKD All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported.
Other bias	High risk	The data were abstracted from a RCT aiming to investigate the effect of mizoribine on steroid-resistant primary nephrotic syn-

		drome. This study included all different pathologic variants of nephrotic syndrome. The randomisation were not stratified according to the pathologic diagnosis
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Kosmadakis 2010

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT Study duration: before 2010
Participants	<ul style="list-style-type: none"> Country: Greece Setting: single centre Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> Pathology stage: NS Proteinuria (g/24 h): treatment group 1 (6.6 ± 1.0); treatment group 2 (7.0 ± 0.7); treatment group 3 (5.2 ± 0.8) Hypertension: patients with prior history of essential hypertension were excluded Serum albumin (g/L): treatment group 1 (27 ± 7); treatment group 2 (28 ± 2); treatment group 3 (22 ± 1.4) SCr: NS GFR (mL/min/1.73 m²): treatment group 1 (81.6 ± 8); treatment group 2 (51.5 ± 7); treatment group 3 (65.7 ± 5.6) Baseline declining kidney function: a portion had Use of ACEi or ARB during follow-up: used only in the ACEi group Previous immunosuppressive status: NS Number: treatment group 1 (10); treatment group 2 (8); treatment group 3 (10) Mean age $\pm$ SD (years): treatment group 1 (50.5 ± 4.9); treatment group 2 (55.4 ± 2.8); treatment group 3 (51.8 ± 5.4) Sex (M/F): treatment group 1 (8/2); treatment group 2 (4/4); treatment group 3 (5/5)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> CSA + steroids for 9 months <ul style="list-style-type: none"> Oral CSA: 3-3.5 mg/kg/d Oral methylprednisolone: 12.5 mg/d <p>Treatment group 2</p> <ul style="list-style-type: none"> CPA + steroids for 9 months <ul style="list-style-type: none"> Oral CPA: 2 mg/kg/24 h Oral methylprednisolone: 1.5 mg/kg/48 h <p>Treatment group 3</p> <ul style="list-style-type: none"> ACEi for 9 months <ul style="list-style-type: none"> : Lisinopril
Outcomes	<ul style="list-style-type: none"> Death ESKD Final GFR Partial or complete remission Final proteinuria

	<ul style="list-style-type: none">Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">Baseline comparison: GFR was worsen in CPA group than other 2 groupsFollow-up period: At least 9 monthsFunding information: NSSample size calculation: NSConfounding factors: NS	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported

Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	High risk	There was a significant difference in the baseline GFR (P = 0.021). The sample size was also small for a 3-arm study

Liu 2009b

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: January 2006 to December 2007
Participants	<ul style="list-style-type: none"> Country: China Setting: NS Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> Pathology stage: NS Proteinuria (g/24 h): treatment group 1 (6.04 ± 2.52); treatment group 2 (5.66 ± 2.28) Hypertension: treatment group 1 (10/43); treatment group 2 (11/41) Serum albumin (g/L): treatment group 1 (24.1 ± 3.66); treatment group 2 (27.3 ± 4.96) SCr (mg/dL): treatment group 1 (0.79 ± 0.31); treatment group 2 (0.88 ± 0.38) GFR: NS Baseline declining kidney function: 9/84 patients with an initial SCr of between 1.25 and 1.5 mg/dL (treatment group 1 (4); treatment group 2 (5)). No patients had SCr > 1.5 mg/dL Use of ACEi or ARB during follow-up: 15 in treatment group 1 and 14 in treatment group 2 received before the entry of study. 14 in treatment group 1 and 12 in treatment group 2 received during the follow-up Previous immunosuppressive status: patients treated with steroids or immunosuppressive therapy within the 3-month period before screening were excluded. There were no differences in the number of patients that had been previously treated with steroids alone or in combination with cytotoxics. Previous treatment with steroids/steroids plus cytotoxics: treatment group 1 (13/4); treatment group 2 (14/3) Number: treatment group 1 (43); treatment group 2 (41)

	<ul style="list-style-type: none"> • Mean age $\pm$ SD (years): treatment group 1 (40.5 ± 12.0); treatment group 2 (48.6 ± 10.3) • Sex (M/F): treatment group 1 (31/12); treatment group 2 (30/11)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Tripterygium wilfordii + steroids <ul style="list-style-type: none"> ◦ Tripterygium wilfordii: 120 mg/d for 3 months. If the patients had complete remission, then gradually reduced to 60 mg/d for remaining 9 months. If the patients did not reach complete remission, then continued the 120 mg-dosage to a maximum of 6 months and then gradually reduced to 60 mg/d for the remission 6 months ◦ Prednisone: 30 mg/d for 8 weeks, and gradually reduced by 5 mg every 2 weeks and then maintained at 10 mg every two days <p>Treatment group 2</p> <ul style="list-style-type: none"> • Tripterygium wilfordii: 120 mg/d for 3 months. If the patients had complete remission, then gradually reduced to 60 mg/d for remaining 9 months. If the patients did not reach complete remission, then continued the 120 mg-dosage to a maximum of 6 months and then gradually reduced to 60 mg/d for the remission 6 months
Outcomes	<ul style="list-style-type: none"> • Death • ESKD • 50% or 100% creatinine increase • Partial or complete remission • Side effects leading to patient withdrawal or hospitalisation
Notes	<ul style="list-style-type: none"> • Baseline comparison: comparable except that the percentage of males and serum albumin was significantly higher in treatment group 2 at baseline. • Follow-up period: 12 months • Funding information: supported by Chinese grants (06G040, BK2007718, and 06Z025) • Sample size calculation: NS • Confounding factors: baseline age was lower in patients with complete remission than patients with no-response ($P < 0.01$) • Published in Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding

Liu 2009b (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3/84 patients (all in treatment group 2) losses to 12-month follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	High risk	Published in Chinese

Methods	<ul style="list-style-type: none">• Study design: open, parallel RCT• Study duration: 1978 to 1986	
Participants	<ul style="list-style-type: none">• Country: Australia• Setting: multicentre (2)• Patients with biopsy-proven IMN<ul style="list-style-type: none">◦ Pathology stage (I/II/III): treatment group (4/14/1); control group (5/15/1)◦ Proteinuria (g/24 h): treatment group (5.0, 0.9-13); control group (3.9, 0.5-12)◦ Hypertension: treatment group 6/19); control group (6/21)◦ Serum albumin (g/L): treatment group (28, 16-42); control group (30, 19-41)◦ SCr ($\mu\text{mol/L}$): treatment group (110, 50-280); control group (90, 50-200)◦ GFR: NS◦ Baseline declining kidney function: 2 patients had the SCr > 200 $\mu\text{mol/L}$ (one in each group)◦ Use of ACEi or ARB during follow-up: NS◦ Previous immunosuppressive status: patients who had received any immunosuppressive therapy within 12 months prior to consideration of study entry were excluded• Number: treatment group (19); control group (21)• Mean age, range (years): treatment group (47, 26-66); control group (40, 18-65)• Sex (M/F): treatment group (12/7); control group (14/7)	
Interventions	<p>Treatment group</p> <ul style="list-style-type: none">• CPA + warfarin + dipyridamole<ul style="list-style-type: none">◦ Oral CPA: maximum dosage of 1.5 mg/kg/d for 6 mouths◦ Dipyridamole and sodium warfarin therapy were continued for 2 years• Symptomatic treatment <p>Control group</p> <ul style="list-style-type: none">• Symptomatic treatment only	
Outcomes	<ul style="list-style-type: none">• Death• ESKD• 50% or 100% creatinine increase• Final SCr• Partial or complete remission• Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">• Baseline comparison: comparable• Follow-up period: At least 24 months in all patients• Funding information: NS• Sample size calculation: NS• Confounding factors: no	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Murphy 1992 (Continued)

Random sequence generation (selection bias)	Low risk	Insufficient information about the sequence generation process to permit judgement. However, it could be done
Allocation concealment (selection bias)	Low risk	After consent was obtained from patient, randomisation was performed by opening sealed envelopes
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All except 1 patient completed the 2 years of follow-up. One treatment group patient died 8 months after study entry, 2 months after cessation of CPA. As this patient had a severe nephrotic syndrome and was the only patient with progressive deterioration in kidney function, his death and consequent removal from the remainder of the study could have biased data at time points subsequent to 6 months in favour of a benefit of therapy. Accordingly, it was decided to enter dummy values for SCr and proteinuria. These dummy values were chosen so as to be higher (900 $\mu\text{mol/L}$ for SCr and 30g/24 h for proteinuria) than all the other patients at that time point, in order to ensure that any bias introduced due to the death of this patient would be against an effect of treatment
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported

Murphy 1992 (Continued)

Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	High risk	40 patients were properly randomised, only 26 were diagnosed with nephrotic syndrome, 13 in each group. The randomisation was not stratified according to nephrotic syndrome or non-nephrotic syndrome

Naumovic 2011

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: 1995 to 2002
Participants	<ul style="list-style-type: none"> • Country: Serbia • Setting: single centre • Patients with biopsy-proven high-risk IMN; all had nephrotic syndrome with average proteinuria of 9 g/d <ul style="list-style-type: none"> ◦ Pathology stage (I/II/III/IV): treatment group 1 (mean 2.2); treatment group 2 (mean 2.08) ◦ Proteinuria (g/24 h): treatment group 1 (11.6 ± 4.7); treatment group 2 (7.0 ± 2.7) ◦ Hypertension: NS ◦ Serum albumin (g/L): treatment group 1 (22.9 ± 4.8); treatment group 2 (28.3 ± 6.4) ◦ SCr (μmol/L): treatment group 1 (124.5 ± 75.9); treatment group 2 (120.5 ± 46.5) ◦ GFR (mL/min): treatment group 1 (80.7±27.5); treatment group 2 (76.2 ± 31.3) ◦ Baseline declining kidney function: 22% of the patients exhibited elevated SCr values, and nearly 40% had lower CrCl

	<ul style="list-style-type: none"> ○ Use of ACEi or ARB during follow-up: yes, no confounding effect. ACEi were also given to all patients either in doses needed for adequate regulation of arterial hypertension, or in normotensive patients in smaller amounts in order to achieve an antiproteinuric effect. During the 3-year follow-up newly diagnosed hypertension was recorded in two patients of CSA group that required an increased dose of ACEi or addition of another antihypertensive. Hypertension developed in three new patients of AZA was successfully regulated by ACEi and calcium channel antagonists ○ Previous immunosuppressive status: all the patients previously received the so-called Ponticelli protocol (chlorambucil and corticosteroids for six months). The lead-time between the end of the Ponticelli protocol and the beginning of the new treatment was at least 1 year: 17.9 ± 4.9 months in CSA group and 19.5 ± 8.1 months in AZA group <ul style="list-style-type: none"> ● Number: treatment group 1 (10); treatment group 2 (13) ● Mean age $\pm$ SD (years): treatment group 1 (39.2 ± 13.1); treatment group 2 (47.5 ± 8.2) ● Sex (M/F): treatment group 1 (9/1); treatment group 2 (10/3)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> ● CSA + steroids <ul style="list-style-type: none"> ○ CSA: 3 mg/kg/d. During the follow-up, the CSA dose was adjusted to achieve 12-h trough levels of 80-100 ng/mL. ○ Prednisone: 0.5 mg/kg/d 8 weeks. The dose was gradually reduced to 5 to 10 mg/d, and remained unchanged until the end of the treatment. ○ CSA and prednisone, were slowly discontinued over 2 weeks at the end of the 24-month period <p>Treatment group 2</p> <ul style="list-style-type: none"> ● AZA + steroids <ul style="list-style-type: none"> ○ AZA: 1.5-2 mg/kg for 6 months, and afterwards 50 mg/d. AZA was temporarily withdrawn or the dose was reduced if the white cell count fell below $4 \times 10^9/L$ ○ Prednisone: 0.5 mg/kg/d 8 weeks. The dose was gradually reduced to 5 to 10 mg/d, and remained unchanged until the end of the treatment. ○ AZA and prednisone, were slowly discontinued over 2 weeks at the end of the 24-month period
Outcomes	<ul style="list-style-type: none"> ● Death ● ESKD ● 50% or 100% creatinine increase ● Final SCr ● Final GFR ● Partial or complete remission ● Final proteinuria ● Side effects leading to patient withdrawal or hospitalisation
Notes	<ul style="list-style-type: none"> ● Baseline comparison: average proteinuria was significantly greater in the CSA group ($P = 0.003$). In addition, patients in the CSA group had significantly higher serum triglyceride and lower total protein and albumin concentrations ● Follow-up period: at least 36 months ● Funding information: funded by the Ministry of Science and Technology of the

	Republic of Serbia (project number 145043) <ul style="list-style-type: none">• Sample size calculation: NS• Confounding factors: no	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	No information was provided, however, it could not be done
Blinding of personnel (performance bias)	High risk	No information was provided, however, it could not be done
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information was provided, however, it could not be done
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported

Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	High risk	This study was not fully randomised

Pahari 1993

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: before 1993
Participants	<ul style="list-style-type: none"> Country: India Setting: NS Patients with biopsy-proven IMN and > 2.0 g/24 h proteinuria <ul style="list-style-type: none"> Pathology stage: NS Proteinuria (g/24 h): ≥ 2 Hypertension: NS Serum albumin: NS SCr (mg/dL): ≤ 2 GFR: NS Baseline declining kidney function: no Use of ACEi or ARB during follow-up: NS Previous immunosuppressive status: NS Number: treatment group 1 (36); treatment group 2 (35) Mean age $\pm$ SD (years): treatment group 1 (35 $\pm$ 16); treatment group 2 (32 $\pm$ 20) Sex (M/F): treatment group 1 (25/11); treatment group 2 (24/11)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> CPA + steroids <ul style="list-style-type: none"> Oral prednisolone: 4 mg/kg/d from 1 to 3 days followed by oral prednisolone 0.5 mg/kg/d from 4 to 30 days (Injection dexamethasone 1 mg/kg/d from 1 to 3 days in cases who are intolerant to high dose oral prednisolone) Oral CPA: 2 mg/kg/d from 1 to 30 days of next months (oral chlorambucil was used in patients intolerant to oral CPA). The treatment was continued for 1 year. <p>Treatment group 2</p> <ul style="list-style-type: none"> Oral prednisolone: 60 mg/d was given for 12 weeks
Outcomes	<ul style="list-style-type: none"> Death ESKD 50% or 100% creatinine increase

	<ul style="list-style-type: none">● Partial or complete remission● Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">● Baseline comparison: NS● Follow-up period: 46 ± 10.2 months● Funding information: NS● Sample size calculation: NS● Drop-out rate: treatment group 1 (2/42); treatment group 2 (8/48)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	No information provided, however, it could not be done
Blinding of personnel (performance bias)	High risk	No information provided, however, it could not be done
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided, however, it could not be done
Incomplete outcome data (attrition bias) All outcomes	High risk	90 patients were randomised, only 71/90 (79%) were finally analysed. The missing outcome data were not balanced in numbers across intervention groups: 6/42 (14%) in CPA group and 13/48 (27%) in prednisolone group
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported

Pahari 1993 (Continued)

Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	High risk	The inclusion criteria of proteinuria was rather 2 g/24 h than 3.5 g/24 h

Ponticelli 1992

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: before December 1989
Participants	<ul style="list-style-type: none"> • Country: Italy • Setting: multicentre (Italian Idiopathic Membranous Nephropathy Treatment Study Group) • Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> ◦ Pathology stage (I-II/III-IV): treatment group 1 (27/18); treatment group 2 (29/18) ◦ Proteinuria (g/24 h): treatment group 1 (7.6 ± 4.2); treatment group 2 (7.0 ± 4.1) ◦ Hypertension: treatment group 1 (15/45); treatment group 2 (14/47) ◦ Serum albumin: NS ◦ SCr (mg/dL): treatment group 1 (1.0 ± 0.3); treatment group 2 (1.0 ± 0.3) ◦ GFR: NS ◦ Baseline declining kidney function: no. Patients with SCr >1.7 mg/dL ($150 \mu\text{mol/L}$) were excluded ◦ Use of ACEi or ARB during follow-up: NS ◦ Previous immunosuppressive status: patients with previous treatment with corticosteroids or cytotoxic agents were excluded • Number: treatment group 1 (45); treatment group 2 (47)

	<ul style="list-style-type: none">• Mean age, range (years): treatment group 1 (46, 14-65); treatment group 2 (47, 14-64)• Sex (M/F): treatment group 1 (32/13); treatment group 2 (27/20)	
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none">• Chlorambucil + steroids (3 cycles of each for 6 months)<ul style="list-style-type: none">◦ Methylprednisolone: 3 cycles of IV 1 g on 3 consecutive days and then 0.4 mg/kg/d given orally for 27 days, in a single morning dose◦ Oral chlorambucil: 0.2 mg/kg/d <p>Treatment group 2</p> <ul style="list-style-type: none">• IV methylprednisolone: 1 g on 3 consecutive days at the beginning of treatment and again 2 and 4 months• Oral methylprednisolone: 0.4 mg/kg every other day, except during the period of IV administration, for six months	
Outcomes	<ul style="list-style-type: none">• Death• ESKD• 50% or 100% creatinine increase• Final SCr• Partial or complete remission• Final proteinuria• Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">• Baseline comparison: comparable• Follow-up period: treatment group 1 (54 ± 16 months); treatment group 2 (54 ± 17 months). 63/92 (68%) patients completed the 48-month follow-up and were analysed for the outcomes of partial or complete remission (treatment group 1 (32/45, 71%), treatment group 2 (31/47, 66%). 50/92 (54%) patients had data for final proteinuria at 48 months (treatment group 1 (26/45, 58%); treatment group 2 24/47 (51%))• Funding information: NS• Sample size calculation: the estimated total sample size was unclear and this study was prematurely stopped. The number of finally included patients (N = 92) gave the study a power of 0.80 to demonstrate an increase of 0.30 in clinical response in the intervention group, assuming a 0.50 response in the control group, at the 5% level of significance with a two-tailed test• Confounding factors: several factors influenced remission of nephrotic syndrome: baseline proteinuria and SCr, presence of mesangial sclerosis. The more severe the disease, the poorer the response to therapy	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The coordinating centre assigned the patients consecutively to one of the two treatment regimens in random order

Allocation concealment (selection bias)	Low risk	Central Randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants (performance bias)	High risk	No information provided, however, it could not be done
Blinding of personnel (performance bias)	High risk	No information provided, however, it could not be done
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information provided, however, it could not be done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patients who could not complete treatment were included in the analysis according to the intention-to-treat principle. For the two patients who died and the one who was lost to follow-up, data obtained at the last observation were considered
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported

Ponticelli 1992 (Continued)

Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Ponticelli 1998

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT
Participants	<ul style="list-style-type: none"> Country: Italy Setting: multicentre Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> Pathology stage (I-II/III-IV): treatment group 1 (32/18); treatment group 2 (27/18) Proteinuria (g/24 h): treatment group 1 (7.96 ± 5.19); treatment group 2 (6.85 ± 3.51) Hypertension: treatment group 1 (15/50); treatment group 2 (14/45) Serum albumin: NS SCr (mg/dL): treatment group 1 (1.06 ± 0.27); treatment group 2 (1.04 ± 0.27) GFR: NS Baseline declining kidney function: patients with SCr > 1.7 mg/dL were excluded Use of ACEi or ARB during follow-up: yes, no confounding effect. The use of ACEi was discouraged but not prohibited Previous immunosuppressive status: patients who had previously received corticosteroids, immunosuppressive drugs, or CSA were excluded Number: treatment group 1 (50); control group 2 (45) Mean age, range (years): treatment group 1 (50, 18-65); control group 2 (48, 17-55) Sex (M/F): treatment group 1 (37/13); control group 2 (29/16)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Chlorambucil + steroids (3 cycles of each for 6 months) <ul style="list-style-type: none"> Methylprednisolone: 1 g IV on 3 consecutive days and then 0.4 mg/kg/d given orally for 27 d, in a single morning dose Chlorambucil: 0.2 mg/kg/d, orally for 1 month. The total duration of treatment, therefore, was 6 mo for both groups; 3 mo with the same doses of methylprednisolone and 3 mo with either of the two cytotoxic drugs. Steroids were completely stopped at the end of the study period. Two relapse patients were retreated with steroids and chlorambucil. One did not respond, and the other attained partial remission

	Treatment group 2 <ul style="list-style-type: none">● CPA + steroids (3 cycles of each for 6 months)<ul style="list-style-type: none">○ Methylprednisolone: 1 g IV on 3 consecutive days and then 0.4 mg/kg/d given orally for 27 d, in a single morning dose○ Oral CPA: 2.5 mg/kg/d. Two relapse patients were retreated. One patient was retreated with steroids and cyclophosphamide and had complete remission. Another patient was treated with steroids and chlorambucil and had partial remission.	
Outcomes	<ul style="list-style-type: none">● Death● ESKD● 50% or 100% creatinine increase● Final SCr● Partial or complete remission● Final proteinuria● Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">● Baseline comparison: comparable● Follow-up period: treatment group 1 (36, 12-78 months); treatment group 2 (42, 12-72 months)● Funding information: supported in part by a grant from Ospedale Maggiore di Milano● Sample size calculation: The estimated total sample size was 100 patients. The number of finally included patients was similar to the estimate (95)● Confounding factors: NS	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	At the coordinating centre, patients were assigned consecutively to one of the two treatment regimens, according to a centre-stratified random order
Allocation concealment (selection bias)	Low risk	Central Randomisation method described above could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 8/95 (8%) patients did not complete the 6-month regimen and then excluded in some final analyses: treatment group 1 (6/50), treatment group 2 (2/

		45). Two patients did not present at the follow-up visit and a 51-yr-old woman died because of a deep-vein thrombosis with acute kidney failure and cardiac shock 3 mo after the diagnosis of membranous nephropathy, before treatment was started. Four patients in treatment group 1 and one in treatment group 2, who completed the treatment, did not present at the follow-up visit and were considered lost to follow-up after the sixth month
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT Study duration: September 2001 to December 2003
Participants	<ul style="list-style-type: none"> Country: Italy Setting: multicentre Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> Pathology stage (I-II/III-IV): treatment group 1 (12/4); treatment group 2 (14/2) Proteinuria (g/24 h): treatment group 1 (5.5 ± 2.0); treatment group 2 (6.7 ± 2.8) Hypertension: treatment group 1 (9/16); treatment group 2 (9/16) Serum albumin: NS SCr (mg/dL): treatment group 1 (0.9 ± 0.17); treatment group 2 (1.0 ± 0.36) GFR: NS Baseline declining kidney function: no; patients with SCr concentrations > 1.9 mg/dL (168 mol/L) were excluded Use of ACEi or ARB during follow-up: yes, no confounding effect. Eleven patients in treatment group 2 and 12 patients in treatment group 1 were treated with ACEi and/or ARB during the study. There was no significant difference between the 2 groups in the probability of remission between patients administered ACEi and/or ARB or statins and those not administered either of these drugs Previous immunosuppressive status: patients who previously received treatment with corticosteroids or cytotoxic agents were excluded Number: treatment group 1 (16); control group 2 (16) Mean age $\pm$ SD (years): treatment group 1 (51.4 ± 9.5); control group 2 (48 ± 12.9) Sex (M/F): treatment group 1 (7/9); control group 2 (12/4)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> CPA/chlorambucil + steroids (3 cycles of each for 6 months) <ul style="list-style-type: none"> Methylprednisolone: 1 g, administered IV on 3 consecutive days, and then 0.4 mg/kg/d 27 days, administered orally in a single morning dose. Oral chlorambucil (0.2 mg/kg/d orally) or oral CPA (2.5 mg/kg/d) for 1 month <p>Treatment group 2</p> <ul style="list-style-type: none"> Synthetic ACTH (tetracosactide): IM 1 mg between 7:00 and 9:00 AM. Administration of ACTH was increased from 1 injection every other week to 2 injections/wk for a total treatment period of 1 year
Outcomes	<ul style="list-style-type: none"> Death ESKD 50% or 100% creatinine increase Final SCr Partial or complete remission Final proteinuria Side effects leading to patient withdrawal or hospitalisation
Notes	<ul style="list-style-type: none"> Baseline comparison: comparable Follow-up period (months): treatment group 1 (21.8 ± 7.5); treatment group 2

	(21.8 ± 7.6) <ul style="list-style-type: none">• Funding information: spontaneous clinical study sponsored by the grant “Project Glomerulonephritis” in memory of Pippo Neglia. The corresponding author was an external consultant to Novartis, which produces tetracosactide used in this study• Sample size calculation: estimated total sample size was too large to validate the study assumption. The author decided to perform a pilot study with a limited number of patients (32)• Confounding factors: no	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The coordinating centre assigned patients consecutively by telephone to 1 of the 2 treatment regimens in a centralized randomised order, with assignation produced by a table from a statistical textbook
Allocation concealment (selection bias)	Low risk	The sequence was concealed until intervention was assigned
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported

Ponticelli 2006 (Continued)

Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Praga 2007

Methods	<ul style="list-style-type: none"> • Study design: open, parallel RCT • Study duration: January 2003 to September 2006
Participants	<ul style="list-style-type: none"> • Country: Spain • Setting: multicentre • Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> ◦ Pathology stage (I/II/III/IV): treatment group (4/15/3/0); control group (4/18/1/0) ◦ Proteinuria (g/24 h): treatment group (7.2 ± 3.3); control group (8.4 ± 5.4) ◦ Hypertension: NS ◦ Serum albumin (g/L): treatment group (27 ± 8); control group (29 ± 8) ◦ SCr (mg/dL): treatment group (0.98 ± 0.2); control group (1.1 ± 0.3) ◦ GFR (mL/min/1.73 m²): treatment group (104 ± 26); control group (107 ± 63) ◦ Baseline declining kidney function: no; GFR by Cockcroft-Gault formula was ≥ 50 mL/min/1.73 m² in all included patients. ◦ Use of ACEi or ARB during follow-up: yes, no confounding effect. Included patients who also had to be treated with an ACEi or an ARB at their maximal tolerated doses for at least 2 months before screening. All the patients were instructed to maintain the same doses of ACEi or ARB that they were taking at randomisation until the end of the study ◦ Previous immunosuppressive status: patients treated with steroids or immunosuppressive therapy within the 6-month period before screening were excluded. There were no differences in the number of patients that had been previously

	treated with steroids alone or in combination with cytotoxics (previous treatment with steroids/steroids plus cytotoxics: treatment group (5/4); control group (6/4)) <ul style="list-style-type: none">• Number: treatment group (25); control group (23)• Mean age ± SD (years): treatment group (3.7 ± 12.1); control group (50.1 ± 12.2)• Sex (M/F): treatment group (20/5); control group (20/3)	
Interventions	Treatment group <ul style="list-style-type: none">• Tacrolimus: 0.05 mg/kg/d, divided into two daily doses at 12-h interval. Later doses were adjusted to achieve a whole blood 12-h trough level between 3 and 5 ng/mL. When a remission was not obtained after the first 2 months of treatment, doses were increased to achieve levels between 5 and 8 ng/mL. Tacrolimus treatment was continued for 12 months and then gradually tapered off for the next 6 months; a 25% tacrolimus dose reduction was indicated at months 12, 14, and 16 and treatment was withdrawn by month 18. Tacrolimus doses were reduced by 25% every 2 weeks in the presence of a 50% SCr increase. If SCr persisted > 50% of baseline values 2-4 weeks after > 75% reduction of tacrolimus doses, definition of end point was established Control group <ul style="list-style-type: none">• No specific immunosuppressive treatment	
Outcomes	<ul style="list-style-type: none">• Death• ESKD• 50% or 100% creatinine increase• Partial or complete remission• Final proteinuria• Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">• Baseline comparison: comparable except that diastolic BP was significantly higher in control group than in tacrolimus group at baseline• Follow-up period: 30 months• Funding information: partially supported by Astellas. Astellas did not intervene in the design or conduct of the study, analysis, and interpretation of the data or preparation of this paper• Sample size calculation: estimated total sample size was 48. The number of finally included patients was 48.• Confounding factors: by multivariate analysis, baseline eGFR (OR 1.06, 95% CI: 1.02 to 1.09, P = 0.004) and the treatment group (OR 16.1, 95% CI: 2.7 to 96.1, P = 0.002) were the only factors statistically significantly correlated with the achievement of a partial remission or complete remission	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed by the clinical coordinating centre using a table of random numbers and was stratified by centres

Praga 2007 (Continued)

Allocation concealment (selection bias)	Low risk	Allocation concealment was performed by enclosing assignments in sequentially numbered, opaque-closed envelopes
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 8/48 (17%) randomised patients did not complete the 18-month regimen. Two patients of the treated group (personal decision because lack of response after 6 months of treatment and a partial seizure in a patient with history of epilepsy) and one of the control group (severe oedema six months after randomisation and deafness attributed to high-dose diuretics) withdrew from the study. Five patients (three in the control group and two in the treatment group) were lost to follow-up between 3 and 18 months after randomisation. But they were all included in the final analyses according to the intention-to-treat basis
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported

Praga 2007 (Continued)

Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Reichert 1994

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT Study duration: June 1989 to November 1992
Participants	<ul style="list-style-type: none"> Country: Netherlands Setting: university hospital and teaching hospitals Patients with <ul style="list-style-type: none"> Pathology stage (I-II/III/unavailable): treatment group 1 (6/2/1); treatment group 2 (6/3/0) Proteinuria (g/10 mmol of creatinine): treatment group 1 (8.5 ± 2.5); treatment group 2 (9.8 ± 4.8) Hypertension: treatment group 1 (7/9); treatment group 2 (5/9) Serum albumin (g/L): treatment group 1 (22.9 ± 6.4); treatment group 2 (25.9 ± 9.7) SCr ($\mu\text{mol/L}$): treatment group 1 (260 ± 112); treatment group 2 (218 ± 85) GFR: NS Baseline declining kidney function: yes Use of ACEi or ARB during follow-up: yes, no confounding effect. Three patients in the treatment group 1 and 5 patients in the treatment group 2 received ACEi. Previous immunosuppressive status: six patients in the treatment group 1 and 5 patients in treatment group 2 had been treated previously with short-term, high-dose prednisone according to Coggins 1979 <ul style="list-style-type: none"> Number: treatment group 1 (9); treatment group 2 (9) Mean age, range (years): treatment group 1 (45, 31-65); treatment group 2 (49, 24-65) Sex (M/F): treatment group 1 (9/0); treatment group 2 (8/1)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Chlorambucil + steroids <ul style="list-style-type: none"> Oral chlorambucil: 0.15 mg/kg/d in months 2, 4, and 6 Prednisone; 3 IV pulses of 1 g of methylprednisolone followed by oral

	<p>prednisone at 0.5 mg/kg/d in months 1, 3, and 5)</p> <ul style="list-style-type: none"> • Three patients were retreated with new immunosuppressive therapy <p>Treatment group 2</p> <ul style="list-style-type: none"> • CPA + steroids <ul style="list-style-type: none"> ◦ IV CPA: 750 mg/m² body surface area once every month for 6 months ◦ Methylprednisolone: (3 IV 1 g pulses in months 1, 3, and 5) • One patient were retreated with new immunosuppressive therapy
Outcomes	<ul style="list-style-type: none"> • Death • ESKD • 50% or 100% creatinine increase • Final SCr • Partial or complete remission • Side effects leading to patient withdrawal or hospitalisation
Notes	<ul style="list-style-type: none"> • Baseline comparison: comparable • Follow-up period: Mean 15 (6-36) months: treatment group 1 (26 ± 12 months); treatment group 2 (13 ± 5.8 months) • Funding information: NWO grant 900/716-111 from the Netherlands Foundation of Scientific Research • Sample size calculation: NS • Confounding factors: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No information was provided, however, it could be done
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	No information was provided, however, it could not be done
Blinding of personnel (performance bias)	High risk	No information was provided, however, it could not be done
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information was provided, however, it could not be done
Incomplete outcome data (attrition bias) All outcomes	Low risk	18/20 patients completed the study. 2 (1 from each treatment group) immediately withdrew after assignment: one had to receive regular dialysis before treatment with methylprednisolone and CPA had begun,

Reichert 1994 (Continued)

		and the other became psychotic 2 weeks after starting prednisone treatment. Because these 2 patients received neither chlorambucil nor CPA, their data are not used for analysis
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Unclear risk	No information provided

Saito 2009

Methods	<ul style="list-style-type: none"> Study design: parallel RCT
Participants	<ul style="list-style-type: none"> Country: Japan Setting: NS Patients with biopsy-proven IMN with steroid-resistant nephrotic syndrome <ul style="list-style-type: none"> Pathology stage: NS

	<ul style="list-style-type: none"> ○ Proteinuria (g/24 h): treatment group 1 (3.5 ± 0.3); treatment group 2 (3.7 ± 0.5) ○ Hypertension: NS ○ Serum albumin: NS ○ SCr: NS ○ GFR: NS ○ Baseline declining kidney function: NS ○ Use of ACEi or ARB during follow-up: NS ○ Previous immunosuppressive status: steroids ● Number: treatment group 1 (16); treatment group 2 (17) ● Mean age $\pm$ SD (years): NS ● Sex (M/F): NS
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> ● CSA + steroids continued for 48 weeks <ul style="list-style-type: none"> ○ CSA: 1.5 mg/kg twice a day ○ Prednisolone: initially prescribed at 40 mg/d and tapered <p>Treatment group 2</p> <ul style="list-style-type: none"> ● CSA + steroids continued for 48 weeks <ul style="list-style-type: none"> ○ CSA: 3 mg/kg once a day before breakfast ○ Prednisolone: initially prescribed at 40 mg/d and tapered
Outcomes	<ul style="list-style-type: none"> ● Complete remission ● Final proteinuria
Notes	<ul style="list-style-type: none"> ● Baseline comparison: NS ● Follow-up period: 48 weeks ● Funding information: Kidney Foundation, Japan, and Novartis Pharma, Japan ● Sample size calculation: NS ● Confounding factors: NS ● Only abstract was available and unpublished data were not used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding

Saito 2009 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	High risk	Only remission and final proteinuria data were provided in that abstract
Selective reporting (reporting bias)-Death All outcomes	High risk	Not reported
Selective reporting (reporting bias)-ESKD All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	High risk	Not reported
Other bias	High risk	Only abstract was available and unpublished data were not used

Senthil Nayagam 2008

Methods	<ul style="list-style-type: none"> • Study design: open, parallel RCT • Study duration: before 2008
Participants	<ul style="list-style-type: none"> • Country: India • Setting: single centre • Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> ◦ Pathology stage: NS ◦ Proteinuria: NS ◦ Hypertension: NS ◦ Serum albumin (g/L): treatment group 1 (27 ± 7); treatment group 2 (27 ± 4)

	<ul style="list-style-type: none">○ SCr: NS○ GFR (mL/min): treatment group 1 (85 ± 10.8); treatment group 2 (80 ± 13.4)○ Baseline declining kidney function: a small number of patients○ Use of ACEi or ARB during follow-up: yes, no confounding effect. All patients with GFR of > 60 mL/min were started on escalating doses of ACEi and/or ARB before entry and during study.○ Previous immunosuppressive status: patients who had received steroids or immunosuppressive drugs previously were excluded<ul style="list-style-type: none">● Number: treatment group 1 (11); treatment group 2 (10)● Mean age ± SD (years): adults● Sex (M/F): NS	
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none">● MMF + steroids<ul style="list-style-type: none">○ MMF: 2 g/day in 2 divided doses for 6 months. MMF dose was decreased by 25-33% for persistent gastrointestinal symptoms, discontinued temporarily if the white blood cell count decreased to < 4000 μL, platelets below 100,000 μL or if the patient developed severe infections or unacceptable gastrointestinal symptoms. It was permanently discontinued if there was any evidence of development of malignancy.○ Prednisolone: 0.5 mg/kg/d for 8-12 wk. The cumulative dose was 1.8 ± 0.3 g <p>Treatment group 2</p> <ul style="list-style-type: none">● CPA + steroids (3 cycles for 6 months)<ul style="list-style-type: none">○ Methylprednisolone: IV 1 g/d for 3 consecutive days followed by oral prednisolone 0.5 mg/kg/d for 27 days. The cumulative prednisolone dose was 2 ± 0.4 g○ Oral CPA: 2 mg/kg/d for 30 days	
Outcomes	<ul style="list-style-type: none">● Death● ESKD● Final GFR● Partial or complete remission● Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">● Baseline comparison: NS● Follow-up period: treatment group 1 (18.2 (14.6-20.8) months); treatment group 2 (16.1 (13.1-18.8) months)● Funding information: supported by a grant from M/s Panacea Biotec Ltd, New Delhi, India● Sample size calculation: NS● Confounding factors: NS	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment allocation was on the basis of minimization, using the following parameters: (MN or FSGS), sex and GFR. Minimization is a valid alternative to randomi-

		sation, and ensures uniformity between the two groups with respect to the characteristics used in the allocation process
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	Open label
Blinding of personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/11 patients in MMF group was lost to follow-up after 1.5 months and was included in the non-responder category
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported

Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Shibasaki 2004

Methods	<ul style="list-style-type: none"> Study design: open, parallel RCT Study duration: April 1996 to June 2001
Participants	<ul style="list-style-type: none"> Country: Japan Setting: multicentre Patients with biopsy-proven IMN with steroid-resistant nephrotic syndrome. Steroids resistance was defined as absence of a satisfactory response to corticosteroid therapy for 3 months <ul style="list-style-type: none"> Pathology stage: NS Proteinuria: NS Hypertension: NS Serum albumin: NS SCr (mg/dL): < 2.0 GFR (mL/min): ≥ 40 Baseline declining kidney function: NS Use of ACEi or ARB during follow-up: yes, no confounding effect. <p>Concomitant use of ACEi, antiplatelet agents, and anticoagulants was allowed, and the same method of administration of these drugs was followed during the study period as is usual for these drugs.</p> <ul style="list-style-type: none"> Previous immunosuppressive status: receiving a daily maintenance dose of 20 mg prednisolone-equivalent a day (including zero dosage) before entry was allowed. Other immunosuppressant medication should be stopped at the start of the study Number: treatment group (14); control group (11) Mean age $\pm$ SD (years): NS Sex (M/F): NS
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Mizoribine: 50 mg, 3 times/d. after meals No particular restriction was placed on the use of corticosteroids during the study period <p>Control group</p> <ul style="list-style-type: none"> Conservative therapy No particular restriction was placed on the use of corticosteroids during the study period
Outcomes	<ul style="list-style-type: none"> Partial or complete remission

Notes	<ul style="list-style-type: none">● Baseline comparison: NS● Follow-up period: 2 years● Funding information: NS● Sample size calculation: NS● Confounding factors: The data were abstracted from a RCT aiming to investigate the effect of mizoribine on steroid-resistant nephrotic syndrome. This study included all different pathologic variants of nephrotic syndrome. The randomisation were not stratified according to the pathologic diagnosis	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	No blinding
Blinding of personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Approximate 32% (8/25) of patients were lost in the two-year follow-up: 21% (3/14) in the mizoribine group and 45% (5/11) in the control group. The proportion of loses in the follow-up could have an substantial influence on the results. The reason for missing data were not specified and the missing data were not imputed using appropriate methods
Selective reporting (reporting bias)	High risk	Only complete or partial remission were reported. The primary outcome such as death and ESKD were not stated; side effects leading to patient withdrawal were not recorded
Selective reporting (reporting bias)-Death All outcomes	High risk	Not reported

Shibasaki 2004 (Continued)

Selective reporting (reporting bias)-ESKD All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Side effects All outcomes	High risk	Not reported
Other bias	High risk	The data were abstracted from a RCT aiming to investigate the effect of mizoribine on steroid-resistant nephrotic syndrome. This study included all different pathologic variants of nephrotic syndrome. The randomisation were not stratified according to the pathologic diagnosis

Silverberg 1976

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: before 1976
Participants	<ul style="list-style-type: none"> • Country: Canada • Setting: multicentre (4) (Western Canadian Glomerulonephritis Study Group) • Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> ◦ Pathology stage (I/II/III): treatment group (0/4/1); control group (1/3/0) ◦ Proteinuria (g/24 h): treatment group (12.2 ± 4.9); control group (9.1 ± 5.9) ◦ Hypertension: treatment group (2/5); control group (1/4) ◦ Serum albumin (g/L): treatment group (24 ± 5); control group (25 ± 3) ◦ SCr (mg/dL): treatment group (1.1 ± 0.4); control group (1.5 ± 0.5) ◦ GFR (mL/min/1.73 m²): treatment group (95 ± 37); control group (74 ± 22) ◦ Baseline declining kidney function: CrCl > 50 mL/min/1.73 m² in all

	included patients <ul style="list-style-type: none">○ Use of ACEi or ARB during follow-up: NS○ Previous immunosuppressive status: patients were required to have received no AZA, CPA or nitrogen mustard for at least 1 year before entry into the study, and no steroids for at least 4 months● Number: treatment group (5); control group (4)● Mean age ± SD (years): treatment group (41 ± 15); control group (45 ± 18)● Sex (M/F): treatment group (3/2); control group (3/1)	
Interventions	Treatment group <ul style="list-style-type: none">● AZA: 2.5 mg/kg/d (in 50 mg tablets) once-a-day for 1 year Control group <ul style="list-style-type: none">● Placebo: similar number of placebo tablets as AZA	
Outcomes	<ul style="list-style-type: none">● Death● ESKD● 50% or 100% creatinine increase● Final SCr● Final GFR● Partial or complete remission● Final proteinuria● Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">● Baseline comparison: comparable● Follow-up period: 12 months● Funding information: supported by the Medical Research Council of Canada, grant MA 4718, and by Burroughs-Wellcome Ltd● Sample size calculation: NS● Confounding factors: NS	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Insufficient information about the sequence generation process to permit judgement. However, it could be done
Allocation concealment (selection bias)	Low risk	Closed-envelope technique
Blinding of participants (performance bias)	Low risk	Double-Blind. Only the pharmacist knew which tablets were AZA and which were placebo
Blinding of personnel (performance bias)	Low risk	Double-Blind. Only the pharmacist knew which tablets were AZA and which were placebo

Silverberg 1976 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	No information provided, however, it could be done
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	Low risk	Reported
Selective reporting (reporting bias)-Creatinine All outcomes	Low risk	Reported
Selective reporting (reporting bias)-GFR All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Remission All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Unclear risk	No information provided

Stegeman 1994

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: January 1994 to January 1996
Participants	<ul style="list-style-type: none"> Countries: Europe Setting: multicentre Patients with biopsy-proven IMN with nephrotic syndrome <ul style="list-style-type: none"> Pathology stage: stages: 1-IV Proteinuria: ≥ 3 g/d Hypertension: NS Serum albumin (g/L): NS SCr (mg/dL): NS CrCl: > 60 mL/min/1.73 m² Baseline declining kidney function: NS Use of ACEi or ARB during follow-up: no Previous immunosuppressive status: no previous antiproteinuric treatments with cytotoxic drugs and/or steroids Number: treatment group 1 (50); treatment group 2 (50); control group (50) Age range: 18 to 65 years Sex (M/F): NS
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> ACEi <ul style="list-style-type: none"> Dose: 10 mg/d for study period <p>Treatment group 2</p> <ul style="list-style-type: none"> Steroids <ul style="list-style-type: none"> Prednisolone: 6 month treatment, dose adjusted for body weight at the start of the study and tapered from 8 weeks <p>Control group</p> <ul style="list-style-type: none"> No specific treatment <ul style="list-style-type: none"> Continuation of salt restriction and diuretics as needed
Outcomes	<ul style="list-style-type: none"> Partial or complete remission Relapse after complete or partial remission
Notes	<ul style="list-style-type: none"> Follow-up: 60 months This study was terminated due to poor accrual rate Data presented here is from the published study protocol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients stratified centrally according to the clinical characteristics during the pre-treatment phase
Allocation concealment (selection bias)	Low risk	Central trial coordinator will randomly allocate eligible patients after stratification

Stegeman 1994 (Continued)

Blinding of participants (performance bias)	Unclear risk	NS
Blinding of personnel (performance bias)	Unclear risk	NS
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NS
Incomplete outcome data (attrition bias) All outcomes	High risk	Study terminated due to poor accrual rate
Selective reporting (reporting bias)	High risk	Study terminated due to poor accrual rate
Selective reporting (reporting bias)-Death All outcomes	High risk	Study terminated due to poor accrual rate
Selective reporting (reporting bias)-ESKD All outcomes	High risk	Study terminated due to poor accrual rate
Selective reporting (reporting bias)-Creatinine increase	High risk	Study terminated due to poor accrual rate
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Study terminated due to poor accrual rate
Selective reporting (reporting bias)-GFR All outcomes	High risk	Study terminated due to poor accrual rate
Selective reporting (reporting bias)-Remission All outcomes	High risk	Study terminated due to poor accrual rate
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Study terminated due to poor accrual rate
Selective reporting (reporting bias)-Side effects All outcomes	High risk	Study terminated due to poor accrual rate
Other bias	High risk	Study terminated due to poor accrual rate

Tiller 1981

Methods	<ul style="list-style-type: none">● Study design: parallel RCT● Study duration: May 1974 to November 1980	
Participants	<ul style="list-style-type: none">● Country: Australia● Setting: multicentre● Patients with biopsy-proven IMN<ul style="list-style-type: none">○ Pathology stage: NS○ Proteinuria (g/24 h): treatment group (5.0); control group (4.2)○ Hypertension: NS○ Serum albumin: NS○ SCr: patients with SCr > 350 μmol/L were excluded○ GFR: patients with GFR < 0.33 mL/sec/1.73 m²(20 mL/min/1.73 m²) were excluded○ Baseline declining kidney function: no.○ Use of ACEi or ARB during follow-up: NS○ Previous immunosuppressive status: previous treatment did not preclude patients from the study, provided that they had been on no “specific” treatment for a period of 6 months before entering the study● Number: treatment group (27); control group (27)● Mean age ± SD (years): patients were not excluded on account of age● Sex (M/F): NS	
Interventions	<p>Treatment group</p> <ul style="list-style-type: none">● CPA + warfarin + dipyridamole<ul style="list-style-type: none">○ CPA was given at a dosage of 1.5 mg/kg/d for 6 mouths○ Dipyridamole and sodium warfarin therapy were prescribed○ Symptomatic treatment <p>Control group</p> <ul style="list-style-type: none">● Symptomatic treatment	
Outcomes	<ul style="list-style-type: none">● Death● ESKD● Side effects leading to patient withdrawal or hospitalisation	
Notes	<ul style="list-style-type: none">● Baseline comparison: comparable● Follow-up period: 36 months● Funding information: supported by a grant from the National Health and Medical Research Council of Australia● Sample size calculation: sample size calculation not reported, however It was proposed to enter a minimum of 50 patients into study protocol. The number of finally included patients was similar to the estimate (54)● Confounding factors: NS● The full text was published at a conference	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

Tiller 1981 (Continued)

Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	High risk	No information was provided, however, it could not be done
Blinding of personnel (performance bias)	High risk	No information was provided, however, it could not be done
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information was provided, however, it could not be done
Incomplete outcome data (attrition bias) All outcomes	High risk	29/54 patients (54%) completed the 36-month follow-up: 14/27 (52%) in the treatment group and 15/27 (56%) in the control group. The missing numbers of patients were balanced and the missing reason was specified in each patient. The rate of loss to follow-up was high (54%), intention to treat principle was used to deal with these data to avoid potential bias
Selective reporting (reporting bias)	Low risk	The primary outcomes and key adverse effects were detailed in the publication, although other outcomes were not available to be included in this meta-analysis
Selective reporting (reporting bias)-Death All outcomes	Low risk	Reported
Selective reporting (reporting bias)-ESKD All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported
Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported

Tiller 1981 (Continued)

Selective reporting (reporting bias)-Remission All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Proteinuria All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Side effects All outcomes	Low risk	Reported
Other bias	Unclear risk	No information provided

Xu 2010

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: November 2006 to January 2008
Participants	<ul style="list-style-type: none"> Country: China Setting: NS Patients with biopsy-proven IMN with severe NS (urinary protein excretion > 5 g/24 h or albumin < 25 g/L) or kidney dysfunction <ul style="list-style-type: none"> Pathology stage: NS Proteinuria (g/24 h): > 5.0 Hypertension: NS Serum albumin: NS SCr: NS GFR: NS Baseline declining kidney function: some patients had kidney dysfunction Use of ACEi or ARB during follow-up: NS Previous immunosuppressive status: NS Number: treatment group 1 (11); treatment group 2 (12) Mean age $\pm$ SD (years): treatment group 1 (55.0 $\pm$ 13.5); treatment group 2 (54.6 $\pm$ 13.5) Sex (M/F): treatment group 1 (6/5); treatment group 2 (9/4)
Interventions	Treatment group 1 <ul style="list-style-type: none"> FK506 + steroids Treatment group 2 <ul style="list-style-type: none"> CPA +steroids
Outcomes	<ul style="list-style-type: none"> Final proteinuria
Notes	<ul style="list-style-type: none"> Baseline comparison: comparable Follow-up period: 9 months Funding information: NS Sample size calculation: NS

	<ul style="list-style-type: none">• Confounding factors: NS• Only abstract was available and unpublished data were not used	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants (performance bias)	Low risk	It was claimed that double-blind was performed, we still judged that it could not be done because it was only published in the conference abstract and there was no further information
Blinding of personnel (performance bias)	Low risk	It was claimed that double-blind was performed, we still judged that it could not be done because it was only published in the conference abstract and there was no further information
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It was claimed that double-blind was performed, we still judged that it could not be done because it was only published in the conference abstract and there was no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	22 of 24 randomised patients completed the study. Only 2 patients in FK506 group dropped out at 2 years
Selective reporting (reporting bias)	High risk	Only final proteinuria data were provided in that abstract
Selective reporting (reporting bias)-Death All outcomes	High risk	Not reported
Selective reporting (reporting bias)-ESKD All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Creatinine increase	High risk	Not reported

Selective reporting (reporting bias)-Creatinine All outcomes	High risk	Not reported
Selective reporting (reporting bias)-GFR All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Remission All outcomes	High risk	Not reported
Selective reporting (reporting bias)-Proteinuria All outcomes	Low risk	Reported
Selective reporting (reporting bias)-Side effects All outcomes	High risk	Not reported
Other bias	High risk	Only abstract was available and unpublished data were not used

AZA - azathioprine, BP - blood pressure; ACEi - angiotensin converting enzyme inhibitors; ACTH - adrenocorticotrophic hormone; ARB - angiotensin receptor blockers; CPA - cyclophosphamide; CSA - cyclosporine; GFR - glomerular filtration rate; IMN - idiopathic membranous nephropathy; IV - intravenous; NS - not stated; RCT - randomised controlled trial; SC - subcutaneous; SCr - serum creatinine

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alexopoulos 2006	Not a RCT
Ambalavanan 1996	This RCT with cross-over design compared the efficacy of CSA versus ACEi in the treatment of adult IMN and secondary membranous nephropathy. We could not determine the number of patients with IMN in each intervention group. The first period of the cross-over was only 3 months (< 6 months)
Austin 2008	A pilot uncontrolled trial to investigate the effects of sirolimus on adult IMN patients with nephrotic syndrome. This study was prematurely terminated owing to the unfavourable risk-benefit ratio
Black 1970	A RCT compared prednisone and supportive treatment in patients with nephrotic syndrome; we could not determine the number of patients diagnosed with IMN and nephrotic syndrome in each intervention group
Dominguez-Gil 1999	A retrospective study

(Continued)

du Buf-Vereijken 2004	A controlled clinical trial of one treatment group versus one historical control group
Edefonti 1988	RCT compared CSA to CPA in patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome; only 35/66 patients received renal biopsy and all patients were diagnosed with minimal change nephropathy and focal segmental glomerulosclerosis. No IMN were included
Goumenos 2007	Retrospective study
Lagrue 1975	RCT compared chlorambucil, AZA and placebo; we could not determine the number of patients diagnosed with IMN and nephrotic syndrome in each intervention group
Li 2008	A prospective non-randomised cohort study
Majima 1990	RCT compared prednisone with non-prednisone in the treatment of IMN; we could not determine whether all included patients had the diagnosis of nephrotic syndrome. The age of included patients were not available for us to make sure they were all adults
Michail 2004	It was unclear whether randomisation was used
MRCWP 1971	RCT compared AZA with prednisone in CKD; we could not determine the number of patients with IMN and nephrotic syndrome in each intervention group
Nand 1997	RCT evaluated the efficacy of methylprednisolone, prednisolone and chlorambucil in idiopathic glomerulonephritis; we could not determine the number of patients with IMN and nephrotic syndrome in each intervention group
Plavljanić 1998	RCT compared methylprednisolone plus CPA to no treatment in patients with MN; it was uncertain that MN were idiopathic or secondary. The clinical diagnosis of nephrotic syndrome was also unclear
Polenakovic 1997	Not a RCT
Ponticelli 1993a	RCT compared the efficacy and safety of CSA with those of supportive therapy in patients with steroid-resistant idiopathic nephrotic syndrome; all patients were diagnosed with minimal change nephropathy and focal segmental glomerulosclerosis. No IMN were included
Rashid 1995	Not a RCT
Sahay 2002	RCT compared the Ponticelli regimen, ACEi and non-specific treatment; the number of patients in each comparison group was not available
Shilov 1998	RCT included 12 membranous nephropathy, 16 mesangial proliferative glomerulonephropathy, 3 mesangiocapillary glomerulonephropathy. We could not determine the number of patients with IMN and nephrotic syndrome in each intervention group
Sun 2008	RCT compared 24-month tacrolimus plus steroids with 6-month tacrolimus plus steroids in 20 adults diagnosed as IMN and nephrotic syndrome. The recruiting of patients was from March 2004 to August 2007; the publication of this study was submitted to that journal on February 2008. Thus, we concluded that some of randomised patients did not complete the 24-month treatment of tacrolimus plus steroids

(Continued)

Tejani 1991	Participants were children
Yao 2001	Not a RCT

ACEi - angiotensin-converting enzyme inhibitors; ARB - angiotensin receptor blockers; AZA - azathioprine; CPA - cyclophosphamide; CKD - chronic kidney disease; CSA - cyclosporine; IMN - idiopathic membranous nephropathy; RCT - randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Appel 2002

Methods	Phase II double-blind, placebo-controlled RCT of the effect of h5G1.1-mAb on the reduction of proteinuria
Participants	Adults (18 years of age and older) IMN
Interventions	Group 1: infusion of h5G1.1-mAb every 2 weeks Group 2: alternating infusions of h5G1.1-mAb and placebo every 2 weeks Group 3: infusion of placebo every 2 weeks
Outcomes	Not specified
Notes	End data: 01/06/2005. A preliminary analysis results were available in a published abstract in 2002; no data were available to be included in this meta-analysis

Berg 2007

Methods	Open-label RCT
Participants	IMN
Interventions	Depot preparation of a synthetic fragment of ACTH versus no specific treatment
Outcomes	The primary outcomes were complete remissions and the combination of complete and partial remissions at the end of the treatment period (nine months after study start) and at the end of the follow-up period (21 months after study start) The secondary outcomes were the changes at the end of the treatment period and the end of the follow-up period, as compared to baseline, in the serum concentrations of albumin, creatinine, apolipoprotein A1, apolipoprotein B and lipoprotein(a), the urinary excretion/24 h of albumin, immunoglobulin G and protein HC, glomerular filtration rate and mean arterial pressure
Notes	Anticipated completion before 31/01/2005

Gaskin 2004

Methods	National RCT (All UK renal units were invited to participate)
Participants	IMN with declining kidney function
Interventions	Immunosuppressive therapy
Outcomes	Kidney function (GFR); proteinuria; adverse effects
Notes	End date: 01/06/2005

Hirayama 2006

Methods	RCT
Participants	IMN in adults with nephrotic syndrome
Interventions	CSA with/without low-dose prednisolone
Outcomes	Primary outcomes: rates of patients with complete remission or partial remission, and rates of patients with relapse or recurrence by urinary examinations at the follow-up clinic visiting until 24 months after the initiation of the treatment Secondary outcome: excretion of urinary protein (g/d), serum levels of protein and albumin (mg/dL), CrCl (mL/min), SCr level (mg/dL), adverse effects until 24 months after the initiation of the treatment
Notes	Completed before 18/11/2009

Howman 2012

Methods	Multicentre open label RCT
Participants	120 patients aged between 18 and 75 years, with IMN
Interventions	120 (40 in each group), interim follow-up at 2 years, final follow-up at 5 years Randomisation will be between three groups Group 1: Supportive treatment only Group 2: 12 months treatment with CSA Group 3: 6 months treatment with a combination of prednisolone and chlorambucil
Outcomes	Change in GFR with a further decline of 20% being an end-point. Secondary outcome measures include proteinuria and adverse effects
Notes	Completed in 31/03/2009. Added 23/09/09: Closed to recruitment, 108 recruited, in follow-up

Liu 2006

Methods	RCT
Participants	Biopsy-proven IMN. Nephrotic syndrome with proteinuria (> 4 g/d) and serum albumin < 30 g/dL. Age 18-60 years with informed consent
Interventions	Tacrolimus versus IV CPA pulse
Outcomes	Proteinuria, kidney function, and adverse effects
Notes	Primary completion date: December 2008 (final data collection date for primary outcome measure)

Liu 2007

Methods	RCT
Participants	Biopsy-proven IMN nephrotic syndrome with proteinuria (> 4 g/d) and serum albumin < 30 g/dL. Age over 18 with informed consent
Interventions	Tripterygium Wilfordii (TW) versus valsartan
Outcomes	Not specified
Notes	Primary completion date: March 2009 (Final data collection date for primary outcome measure)

Saito 2006

Methods	Parallel, open-label RCT
Participants	Membranous nephropathy with primary steroid resistant nephrotic syndrome
Interventions	Group 1: oral mizoribine once a day administration (150 mg) after breakfast for 2 years Group 2: oral mizoribine 3 times a day administration (50 mg each) after meals for 2 years
Outcomes	Primary outcomes: urine protein excretion (g/d), remission status of nephrotic syndrome Key secondary outcomes: kidney function (CrCl), serum total protein and albumin levels
Notes	Last follow-up date was 2009/12

ACTH - adrenocorticotrophic hormone; CPA - cyclophosphamide; CrCl - creatinine clearance; CSA - cyclosporine; GFR - glomerular filtration rate; IMN - idiopathic membranous nephropathy; RCT - randomised controlled trial; SCr - serum creatinine

Characteristics of ongoing studies [ordered by study ID]

ChiCTR-TRC-08000098

Trial name or title	Research on integrated therapy of traditional Chinese medicine for membranous nephropathy
Methods	RCT
Participants	<ol style="list-style-type: none"> 1. Diagnosed with IMN by renal biopsy 2. Age 18 to 75 years, without gender or nation restrict 3. CKD $\leq$ phase 3 (GFR $>$ 30 mL/min), 24 h urinary albumin $\geq$ 3.5 g
Interventions	<p>Group 1: integrated therapy of TCM</p> <p>Group 2: prednisone and CPA</p>
Outcomes	Kidney function and TCM symptoms and signs, blood, stool and urine routine, liver function and ECG, Serum lipid, GFR, and renal biopsy, 24 h urinary albumin, creatinine and serum albumin
Starting date	2007/12/01
Contact information	Yueyi Deng, Yiping Chen, Tel: +86 021 28333352, +86 0 13661791159, Fax: +86 021 64871762, +86 021 54363399, dengyueyi@medmail.com.cn, chenylonghua@medmail.com.cn, No.725, Wanping South Road, Shanghai, 200032, Longhua Hospital Affiliated to Shanghai University of TCM
Notes	Recruiting in December 2011

ChiCTR-TRC-11001144

Trial name or title	A prospective randomized study on the efficacy of steroid combined with CTX or tacrolimus in IMN patients with NS
Methods	RCT
Participants	<ol style="list-style-type: none"> 1. IMN patients proven by biopsy within 24 weeks 2. 24 h urinary protein excretion at admission $\geq$ 5 g or serum albumin $<$ 25 g/L 3. The patient had renal insufficiency defined as CKD 2-3 stage with moderate proteinuria or severe NS with pleural effusion, ascites, renal venous thrombosis 4. Nephrotic syndrome patients without severe oedema, follow-up 3 months, 24 h urinary protein excretion $>$ 5 g or serum albumin $<$ 25 g/L 5. Written informed consent
Interventions	<p>Group 1: CPA + prednisone</p> <p>Group 2: Tacrolimus + prednisone</p>
Outcomes	24 h urinary protein excretion, SCr, and serum albumin
Starting date	2008/01/01
Contact information	Chen Nan, Zhang Wen, Tel: +86 021 64370045, Fax: +86 021 64456419, chen-nan@medmail.com.cn, zhangwen255@163.com, nephrology department, Shanghai Jiaotong university affiliated Ruijin hospital, No.

	197, Ruijin NO.2 Road, Luwan District, Shanghai, 200025, China
Notes	Recruiting in December 2011

CTRI/2010/091/000231

Trial name or title	Comparison of efficacy of tacrolimus versus cyclophosphamide in idiopathic membranous nephropathy
Methods	Clinical controlled trial
Participants	1. Adults (age > 18 y) 2. Nephrotic range proteinuria (urine P/Cr ratio > 3 g/d) 3. Biopsy-proven primary membranous glomerulonephritis (IMN) 4. GFR > 30 mL/min (MDRD)
Interventions	Group 1: Tacrolimus + prednisolone: tacrolimus (0.1 mg/kg/d); prednisolone (0.5 mg/kg/d) Group 2: CPA + prednisolone: CPA (2 mg/Kg/d); prednisolone (0.5 mg/kg/d)
Outcomes	Not specified
Starting date	04/05/2010
Contact information	Dr SK Agarwal and Dr PM Dogra, Dept of Nephrology, 4th Floor, AIIMS, Ansari Nagar 110029 New Delhi, DELHI India, Telephone: 01126594911, Email: skagarwal58@yahoo.co.in and dodgemanu@gmail.com
Notes	Open to Recruitment in December 2011

EUCTR2007-005410-39-ES

Trial name or title	Estudio piloto aleatorizado comparativo de tacrolimus vs ciclofosfamida-prednisona en la nefropatía membranosa idiopática - MEMTAC
Methods	RCT
Participants	IMN
Interventions	tacrolimus versus CPA
Outcomes	Efficacy and safety
Starting date	11/06/2008
Contact information	Spain
Notes	None

[JPRN-UMIN000001099](#)

Trial name or title	Optimal use of cyclosporine in idiopathic membranous nephropathy associated with nephrotic syndrome
Methods	Parallel open RCT
Participants	IMN associated with nephrotic syndrome
Interventions	Group 1: Steroid + CSA Group 2: Steroid
Outcomes	Primary outcomes: quantity of urinary protein, frequency of relapse, kidney function (SCr, eGFR), time to remission, total dose of steroid (until remission) Key secondary outcomes: adverse effects of steroid and CSA, total dose of steroid (in all treatment period), duration of hospitalisation, serum albumin, serum total protein, serum total cholesterol, degree of oedema
Starting date	2007/07
Contact information	Masaaki Izumi, Hyogo College of Medicine, Division of Kidney and Dialysis, Department of Internal Medicine, 1-1, Mukogawa, Nishinomiya, Hyogo, Japan, TEL +81-798-45-6521, Email izumi@hyo-med.ac.jp
Notes	Last follow-up date: 2010/07

[JPRN-UMIN000006939](#)

Trial name or title	High-dose gamma-globulin therapy for nephrotic membranous nephropathy patients
Methods	Parallel RCT
Participants	Nephrotic membranous nephropathy
Interventions	Immunoglobulin versus ARB or ACEi with or without statin
Outcomes	Remission rate, alteration of proteinuria or kidney function, complication of infectious diseases or cardiovascular diseases
Starting date	2012/02/01
Contact information	Hitoshi Yokoyama, Kanazawa Medical University Hospital Nephrology, 1-1 Daigaku, Uchinada, Ishikawa, Japan, Telephone: 076-286-2211(3401), Email: h-yoko@kanazawa-med.ac.jp
Notes	Not yet recruiting in May 2012

NCT00805753

Trial name or title	A dose-finding pilot study of ACTH on the serum lipoprotein profile and proteinuria in patients with idiopathic membranous nephropathy (MN)
Methods	RCT
Participants	IMN with diagnostic biopsy performed < 36 months from the time of dose randomisation
Interventions	Group 1: ACTH 40 units subcutaneously for up to 12 weeks. If at day 91 no response has been shown, you will have the option to increase the dose of ACTH to 80 units for up to an additional 120 days Group 2: ACTH 80 units subcutaneously for up to 12 weeks
Outcomes	Primary outcome measures: change in proteinuria, change in LDL cholesterol, HDL cholesterol, and triglycerides, and side effects/toxicity Secondary outcome measures: complete or partial remission, and the effect of maximizing angiotensin II blockade on proteinuria
Starting date	January 2009
Contact information	Lori Riess 507-266-1047 riess.lori@mayo.edu; Shirley Jennison 507-255-0231 jennison.shirley@mayo.edu; Fernando C. Fervenza, M.D., Ph.D
Notes	Estimated primary completion date: December 2011 (final data collection date for primary outcome measure)

NCT00843856

Trial name or title	Mycophenolate mofetil and tacrolimus vs tacrolimus alone for the treatment of idiopathic membranous glomerulonephritis
Methods	RCT
Participants	Idiopathic membranous glomerulonephritis on renal biopsy
Interventions	Group 1: tacrolimus Group 2: tacrolimus and MMF
Outcomes	Primary outcome measures: efficacy of MMF in preventing relapse of nephrotic syndrome secondary to membranous glomerulonephritis on withdrawal of tacrolimus therapy. This will be initially measured at 6 months post withdrawal of tacrolimus therapy Secondary outcome measures: the time to obtaining remission from proteinuria. The degree of remission of proteinuria obtained (complete or partial). The rate of decline of kidney function measured by the MDRD equation for GFR
Starting date	February 2009
Contact information	Megan E Griffith, MB ChB (hons) PhD 02083835272 megan.griffith@imperial.nhs.uk; Tom D Cairns 02083835272 tom.cairns@nhs.net
Notes	Estimated primary completion date: February 2014 (final data collection date for primary outcome measure)

NCT01093157

Trial name or title	A dose-finding pilot study of ACTH (adrenocorticotrophic hormone) on the proteinuria and serum lipoprotein profile in patients with idiopathic membranous nephropathy (MN)
Methods	RCT
Participants	IMN with diagnostic biopsy performed less than 36 months from the time of dose randomisation
Interventions	Group 1: ACTH (HP Acthar gel) 40 units Group 2: ACTH (HP Acthar gel) 80 units Note: one arm receive 40 units and the second arm 80 units of the ACTH gel subcutaneously both given in a dose escalating frequency beginning at once every two weeks escalating to a maximum of twice/wk over a total of three months exposed
Outcomes	Primary outcome measures: change in proteinuria from baseline to value at 3 months. Secondary outcome measures: complete remission or partial remission at 3 months and adverse effects
Starting date	February 2010
Contact information	Daniel Cattran, MD 416-340-4187; Paul Ling 416-340-3514
Notes	Estimated primary completion date: August 2011 (Final data collection date for primary outcome measure)

NCT01161459

Trial name or title	Treatment of idiopathic membranous nephropathy with Tripterygium wilfordii plus steroid vs tacrolimus plus steroid
Methods	RCT
Participants	Biopsy-proven IMN
Interventions	Group 1: Tripterygium wilfordii plus steroid Group 2: tacrolimus plus steroid
Outcomes	Primary outcome measures: the number of complete remission and partial remission Secondary outcome measures: number of participants with adverse events as a measure of safety and tolerability steroid
Starting date	June 2010
Contact information	Ke Zuo, Master 00862580860734 ext 210002 alexzuo_3000@yahoo.com.cn
Notes	Estimated primary completion date: November 2011 (final data collection date for primary outcome measure)

NCT01180036

Trial name or title	A randomized controlled trial of rituximab versus cyclosporine in the treatment of idiopathic membranous nephropathy (IMN)
Methods	RCT
Participants	IMN with diagnostic biopsy performed within the past 36 months
Interventions	Group 1: rituximab Group 2: CSA
Outcomes	Primary outcome measures: remission status Secondary outcome measures: remission status Note: complete remission or partial remission, and complete remission alone at 6, 12, 18, 24, and 27 months. Frequency of and time to relapse rate of change in urinary protein at 6 and 12 months and beyond time to complete remission or partial remission and to complete remission alone. Toxicity quality of life as measured by SF-36 frequency of PRA2 antibodies and its relation to therapy and proteinuria response
Starting date	May 2011
Contact information	Fernando C Fervenza, M.D., Ph.D. 507-266-7083 fervenza.fernando@mayo.edu; Shirley A Jennison 507-255-0231 jennison.shirley@mayo.edu
Notes	Estimated primary completion date: January 2015 (Final data collection date for primary outcome measure)

NCT01282073

Trial name or title	A randomized controlled multi-center trial of mycophenolate mofetil for the patient with high risk membranous nephropathy
Methods	Multicentre RCT
Participants	Patients with IMN
Interventions	Group 1: MMF + low dose steroid Group 2: CSA + low dose steroid
Outcomes	Primary outcome measures: percentage of complete and partial remission Secondary outcome measures: eGFR, relapse, proteinuria, and side effects
Starting date	March 2011
Contact information	Se-Hee Yoon, MD +82-11-9403-9623 sehei@hanmail.net
Notes	Estimated primary completion date: March 2013 (Final data collection date for primary outcome measure)

NCT01386554

Trial name or title	A randomized, placebo-controlled, parallel-group, double-blind study of H.P. Acthar gel (Acthar) in treatment-resistant subjects with persistent proteinuria and nephrotic syndrome due to idiopathic membranous nephropathy (IMN)
Methods	Parallel, placebo-controlled RCT
Participants	A history of nephrotic syndrome due to IMN as confirmed by documented results from a kidney biopsy performed within 4 years prior to screening
Interventions	Group 1: 0.5 mL acthar Group 2: 0.5 mL placebo Group 3: 1.0 mL acthar Group 4: 1.0 mL placebo
Outcomes	Primary outcome measures: complete or partial remission in proteinuria Secondary outcome measures: proportion of subjects that have sustained complete or partial remission
Starting date	August 2011
Contact information	Jay Elliott, PhD (513) 579-9911 ext 2032 j.elliott@medpace.com; Mary Nyberg, MBA (410) 480-7500 ext 315 mnyberg@questcor.com
Notes	Estimated primary completion date: March 2013 (final data collection date for primary outcome measure)

NCT01508468

Trial name or title	Evaluate rituximab treatment for idiopathic membranous nephropathy (GEMRITUX)
Methods	Multicentre open-label RCT
Participants	IMN proved by renal biopsy
Interventions	Rituximab and symptomatic treatment versus symptomatic treatment
Outcomes	Primary outcomes: rate of proteinuria Secondary outcomes: progression of CKD, Percentage of proteinuria variation, percentage of nephrotic syndrome complication, rituximab tolerance in IMN at 3 and 6 months
Starting date	January 2012
Contact information	Karine Dahan, MD, + 33 (0) 1 56 01 66 39, karine.dahan@tnn.aphp.fr, department of Nephrology, Tenon hospital Paris, France
Notes	Estimated primary completion date: July 2014 (Final data collection date for primary outcome measure)

ACEi - angiotensin converting enzyme inhibitors; ACTH - adrenocorticotrophic hormone; ARB - angiotensin receptor blockers; CKD - chronic kidney disease; CPA - cyclophosphamide; CrCl - creatinine clearance; CSA - cyclosporine; ECG - electrocardiogram, eGFR - estimated glomerular filtration rate; GFR - glomerular filtration rate; IMN - idiopathic membranous nephropathy; P/Cr - protein/creatinine; RCT - randomised controlled trial; SCr - serum creatinine; TCM - traditional Chinese medicine

DATA AND ANALYSES

Comparison 1. Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or ESKD (dialysis/transplantation) (ITT analysis)	15	791	Risk Ratio (IV, Random, 95% CI)	0.58 [0.36, 0.95]
1.1 Steroids versus placebo/no treatment at final follow-up (24-48 months)	3	295	Risk Ratio (IV, Random, 95% CI)	0.75 [0.34, 1.63]
1.2 CPA versus placebo/no treatment at final follow-up (12-36 months)	3	102	Risk Ratio (IV, Random, 95% CI)	0.62 [0.03, 12.27]
1.3 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months)	3	211	Risk Ratio (IV, Random, 95% CI)	0.33 [0.17, 0.64]
1.4 Alkylating agents+steroids versus ACEi/ARB at final follow-up (9 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 CSA versus placebo/no treatment at final follow-up (12-21 months)	2	38	Risk Ratio (IV, Random, 95% CI)	1.04 [0.15, 7.21]
1.6 CSA+steroids versus placebo/no treatment at final follow-up (60 months)	1	33	Risk Ratio (IV, Random, 95% CI)	1.5 [0.18, 12.80]
1.7 CSA+steroids versus ACEi/ARB at final follow-up (9 months)	1	10	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.8 TAC versus placebo/no treatment at final follow-up (30 months)	1	48	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.20]
1.9 MMF versus placebo/no treatment at final follow-up (12 months)	1	36	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.10 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Death (ITT analysis)	15	791	Risk Ratio (IV, Random, 95% CI)	0.65 [0.29, 1.44]
2.1 Steroids versus placebo/no treatment at final follow-up (24-48 months)	3	295	Risk Ratio (IV, Random, 95% CI)	0.58 [0.11, 2.97]
2.2 CPA versus placebo/no treatment at final follow-up (12-36 months)	3	102	Risk Ratio (IV, Random, 95% CI)	0.75 [0.05, 10.61]

2.3 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months)	3	211	Risk Ratio (IV, Random, 95% CI)	0.48 [0.12, 1.97]
2.4 Alkylating agents+steroids versus ACEi/ARB at final follow-up (9 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 CSA versus placebo/no treatment at final follow-up (12-21 months)	2	38	Risk Ratio (IV, Random, 95% CI)	2.7 [0.13, 58.24]
2.6 CSA+steroids versus placebo/no treatment at final follow-up (60 months)	1	33	Risk Ratio (IV, Random, 95% CI)	1.57 [0.07, 35.57]
2.7 CSA+steroids versus ACEi/ARB at final follow-up (9 months)	1	10	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.8 TAC versus placebo/no treatment at final follow-up (30 months)	1	48	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.20]
2.9 MMF versus placebo/no treatment at final follow-up (12 months)	1	36	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.10 Azathioprine versus placebo/no treatment at the final follow-up (12 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 ESKD (dialysis/transplantation) (ITT analysis)	15	791	Risk Ratio (IV, Random, 95% CI)	0.55 [0.31, 0.95]
3.1 Steroids versus placebo/no treatment at final follow-up (24-48 months)	3	295	Risk Ratio (IV, Random, 95% CI)	0.81 [0.34, 1.93]
3.2 CPA versus placebo/no treatment at final follow-up (12-36 months)	3	102	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.84]
3.3 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months)	3	211	Risk Ratio (IV, Random, 95% CI)	0.31 [0.15, 0.65]
3.4 Alkylating agents+steroids versus ACEi/ARB at final follow-up (9 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 CSA versus placebo/no treatment at final follow-up (12-21 months)	2	38	Risk Ratio (IV, Random, 95% CI)	0.84 [0.06, 11.76]
3.6 CSA+steroids versus placebo/no treatment at final follow-up (60 months)	1	33	Risk Ratio (IV, Random, 95% CI)	1.0 [0.10, 9.86]
3.7 CSA+steroids versus ACEi/ARB at final follow-up (9 months)	1	10	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

3.8 TAC versus placebo/no treatment at final follow-up (30 months)	1	48	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.9 MMF versus placebo/no treatment at final follow-up (12 months)	1	36	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.10 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 100% increase in serum creatinine (ITT analysis)	8	409	Risk Ratio (IV, Random, 95% CI)	0.42 [0.26, 0.67]
4.1 Steroids versus placebo/no treatment at final follow-up (24 months)	1	72	Risk Ratio (IV, Random, 95% CI)	0.20 [0.05, 0.85]
4.2 CPA versus placebo/no treatment at final follow-up (12-24 months)	2	48	Risk Ratio (IV, Random, 95% CI)	0.92 [0.15, 5.73]
4.3 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months)	3	211	Risk Ratio (IV, Random, 95% CI)	0.39 [0.17, 0.89]
4.4 CSA+steroids versus placebo/no treatment at final follow-up (60 months)	1	33	Risk Ratio (IV, Random, 95% CI)	0.67 [0.18, 2.47]
4.5 MMF versus placebo/no treatment at final follow-up (12 months)	1	36	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.6 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.8 [0.07, 9.18]
5 50% increase in serum creatinine (ITT analysis)	8	414	Risk Ratio (IV, Random, 95% CI)	0.52 [0.33, 0.81]
5.1 Steroids versus placebo/no treatment at final follow-up (36 months)	1	103	Risk Ratio (IV, Random, 95% CI)	0.57 [0.34, 0.94]
5.2 CPA versus placebo/no treatment at final follow-up (12-24 months)	2	48	Risk Ratio (IV, Random, 95% CI)	0.99 [0.20, 4.91]
5.3 Alkylating agents+steroids versus placebo/no treatment at final follow-up (120 months)	1	81	Risk Ratio (IV, Random, 95% CI)	0.33 [0.15, 0.68]
5.4 TAC versus placebo/no treatment at final follow-up (30 months)	1	48	Risk Ratio (IV, Random, 95% CI)	0.15 [0.02, 1.18]
5.5 MMF versus placebo/no treatment at final follow-up (12 months)	1	36	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.6 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Risk Ratio (IV, Random, 95% CI)	4.17 [0.25, 68.16]

5.7 Mizoribine versus placebo/ no treatment at final follow-up (6 months)	1	89	Risk Ratio (IV, Random, 95% CI)	0.71 [0.23, 2.16]
6 Final serum creatinine	5	198	Mean Difference (IV, Random, 95% CI)	25.43 [10.09, 40.78]
6.1 Steroids versus placebo/ no treatment at final follow-up (36 months)	1	87	Mean Difference (IV, Random, 95% CI)	48.00 [-42.71, 138. 71]
6.2 CPA versus placebo/no treatment at final follow-up (24 months)	1	25	Mean Difference (IV, Random, 95% CI)	19.98 [-43.38, 83. 34]
6.3 Alkylating agents+steroids versus placebo/no treatment at final follow-up (120 months)	1	56	Mean Difference (IV, Random, 95% CI)	26.86 [10.14, 43.58]
6.4 CSA versus placebo/no treatment at final follow-up (12 months)	1	21	Mean Difference (IV, Random, 95% CI)	11.5 [-50.19, 73.19]
6.5 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Mean Difference (IV, Random, 95% CI)	-53.10 [-219.98, 113.78]
7 Final GFR [mL/min/1.73 m²]	8	287	Mean Difference (IV, Random, 95% CI)	9.77 [3.92, 15.62]
7.1 Steroids versus placebo/ no treatment at final follow-up (36 months)	1	86	Mean Difference (IV, Random, 95% CI)	8.0 [-11.49, 27.49]
7.2 CPA versus placebo/no treatment at final follow-up (12 months)	1	19	Mean Difference (IV, Random, 95% CI)	-5.33 [-26.46, 15. 80]
7.3 Alkylating agents+steroids versus placebo/no treatment/ ACEi/ARB at final follow-up (9-120 months)	2	102	Mean Difference (IV, Random, 95% CI)	11.70 [1.50, 21.91]
7.4 CSA versus placebo/no treatment at final follow-up (12-24 months)	2	29	Mean Difference (IV, Random, 95% CI)	0.85 [-18.34, 20.03]
7.5 CSA+steroids versus ACEi/ARB at final follow-up (9 months)	1	10	Mean Difference (IV, Random, 95% CI)	9.20 [-19.01, 37.41]
7.6 MMF versus placebo/no treatment at final follow-up (12 months)	1	32	Mean Difference (IV, Random, 95% CI)	12.37 [-4.93, 29.67]
7.7 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Mean Difference (IV, Random, 95% CI)	33.0 [-19.01, 85.01]
8 Complete or partial remission (ITT analysis)	16	864	Risk Ratio (IV, Random, 95% CI)	1.31 [1.01, 1.70]
8.1 Steroids versus placebo/ no treatment at final follow-up (24-48 months)	3	295	Risk Ratio (IV, Random, 95% CI)	1.18 [0.64, 2.16]
8.2 CPA versus placebo/no treatment at final follow-up (12-24 months)	2	48	Risk Ratio (IV, Random, 95% CI)	2.14 [0.99, 4.63]

8.3 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months)	3	211	Risk Ratio (IV, Random, 95% CI)	1.52 [0.85, 2.73]
8.4 Alkylating agents+steroids versus ACEi/ARB at final follow-up (9 months)	1	9	Risk Ratio (IV, Random, 95% CI)	1.0 [0.68, 1.46]
8.5 CSA versus placebo/no treatment at final follow-up (21 months)	1	21	Risk Ratio (IV, Random, 95% CI)	0.55 [0.13, 2.38]
8.6 CSA+steroids versus placebo/no treatment at final follow-up (60 months)	1	33	Risk Ratio (IV, Random, 95% CI)	0.94 [0.59, 1.49]
8.7 CSA+steroids versus ACEi/ARB at final follow-up (9 months)	1	10	Risk Ratio (IV, Random, 95% CI)	0.64 [0.31, 1.30]
8.8 Tacrolimus versus placebo/no treatment at final follow-up (30 months)	1	48	Risk Ratio (IV, Random, 95% CI)	1.31 [0.60, 2.87]
8.9 MMF versus placebo/no treatment at final follow-up (12 months)	1	36	Risk Ratio (IV, Random, 95% CI)	0.89 [0.39, 2.03]
8.10 ACTH versus placebo/no treatment at final follow-up (21 months)	1	30	Risk Ratio (IV, Random, 95% CI)	7.00 [1.91, 25.62]
8.11 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.28 [0.01, 5.43]
8.12 Mizoribine versus placebo/no treatment at final follow-up (6-24 months)	2	114	Risk Ratio (IV, Random, 95% CI)	2.24 [1.14, 4.38]
9 Complete remission (ITT analysis)	15	761	Risk Ratio (IV, Random, 95% CI)	1.59 [0.87, 2.88]
9.1 Steroids versus placebo/no treatment at final follow-up (24-48 months)	2	192	Risk Ratio (IV, Random, 95% CI)	0.64 [0.29, 1.42]
9.2 CPA versus placebo/no treatment at final follow-up (12-24 months)	2	48	Risk Ratio (IV, Random, 95% CI)	2.0 [0.21, 19.44]
9.3 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months)	3	211	Risk Ratio (IV, Random, 95% CI)	3.18 [1.23, 8.21]
9.4 Alkylating agents+steroids versus ACEi/ARB at final follow-up (9 months)	1	9	Risk Ratio (IV, Random, 95% CI)	6.0 [0.37, 98.16]
9.5 CSA versus placebo/no treatment at final follow-up (21 months)	1	21	Risk Ratio (IV, Random, 95% CI)	0.36 [0.02, 8.03]

9.6 CSA+steroids versus placebo/no treatment at final follow-up (60 months)	1	33	Risk Ratio (IV, Random, 95% CI)	1.25 [0.29, 5.44]
9.7 CSA+steroids versus ACEi/ARB at final follow-up (9 months)	1	10	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.8 TAC versus placebo/no treatment at final follow-up (30 months)	1	48	Risk Ratio (IV, Random, 95% CI)	0.55 [0.15, 2.06]
9.9 MMF versus placebo/no treatment at final follow-up (12 months)	1	36	Risk Ratio (IV, Random, 95% CI)	0.45 [0.04, 4.50]
9.10 ACTH versus placebo/no treatment at final follow-up (22 months)	1	30	Risk Ratio (IV, Random, 95% CI)	11.00 [1.62, 74.88]
9.11 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.28 [0.01, 5.43]
9.12 Mizoribine versus placebo/no treatment at final follow-up (6-24 months)	2	114	Risk Ratio (IV, Random, 95% CI)	4.08 [0.73, 22.81]
10 Partial remission (ITT analysis)	15	761	Risk Ratio (IV, Random, 95% CI)	1.16 [0.86, 1.57]
10.1 Steroids versus placebo/no treatment at final follow-up (24-48 months)	2	192	Risk Ratio (IV, Random, 95% CI)	1.63 [0.62, 4.25]
10.2 CPA versus placebo/no treatment at final follow-up (12-24 months)	2	48	Risk Ratio (IV, Random, 95% CI)	2.19 [0.90, 5.34]
10.3 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months)	3	211	Risk Ratio (IV, Random, 95% CI)	1.00 [0.50, 2.02]
10.4 Alkylating agents+steroids versus ACEi/ARB at final follow-up (9 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.55 [0.22, 1.35]
10.5 CSA versus placebo/no treatment at final follow-up (21 months)	1	21	Risk Ratio (IV, Random, 95% CI)	0.73 [0.15, 3.53]
10.6 CSA+steroids versus placebo/no treatment at final follow-up (60 months)	1	33	Risk Ratio (IV, Random, 95% CI)	0.83 [0.41, 1.69]
10.7 CSA+steroids versus ACEi/ARB at final follow-up (9 months)	1	10	Risk Ratio (IV, Random, 95% CI)	0.45 [0.17, 1.21]
10.8 TAC versus placebo/no treatment at final follow-up (30 months)	1	48	Risk Ratio (IV, Random, 95% CI)	3.22 [0.74, 13.95]
10.9 MMF versus placebo/no treatment at final follow-up (12 months)	1	36	Risk Ratio (IV, Random, 95% CI)	1.07 [0.40, 2.89]

10.10 ACTH versus placebo/ no treatment at final follow-up (22 months)	1	30	Risk Ratio (IV, Random, 95% CI)	3.0 [0.35, 25.68]
10.11 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.12 Mizoribine versus placebo/no treatment at final follow-up (6-24 months)	2	114	Risk Ratio (IV, Random, 95% CI)	1.89 [0.90, 3.97]
11 Final proteinuria	9	393	Mean Difference (IV, Random, 95% CI)	-0.95 [-1.81, -0.09]
11.1 Steroids versus placebo/ no treatment at final follow-up (36 months)	1	86	Mean Difference (IV, Random, 95% CI)	0.0 [-1.99, 1.99]
11.2 CPA versus placebo/no treatment at final follow-up (12 months)	1	19	Mean Difference (IV, Random, 95% CI)	-0.49 [-3.60, 2.62]
11.3 Alkylating agents+steroids versus placebo/ no treatment/ACEi/ARB at final follow-up (9-120 months)	3	183	Mean Difference (IV, Random, 95% CI)	-1.62 [-2.49, -0.76]
11.4 CSA versus placebo/no treatment at final follow-up (12-21 months)	2	38	Mean Difference (IV, Random, 95% CI)	-0.08 [-9.29, 9.13]
11.5 CSA+steroids versus ACEi/ARB at final follow-up (9 months)	1	10	Mean Difference (IV, Random, 95% CI)	0.40 [-1.10, 1.90]
11.6 TAC versus placebo/no treatment at final follow-up (18 months)	1	48	Mean Difference (IV, Random, 95% CI)	-1.30 [-3.75, 1.15]
11.7 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Mean Difference (IV, Random, 95% CI)	1.10 [-2.79, 4.99]
12 Temporary or permanent discontinuation or hospitalisation due to adverse events	16	880	Risk Ratio (IV, Random, 95% CI)	5.35 [2.19, 13.02]
12.1 Steroids versus placebo/ no treatment	3	295	Risk Ratio (IV, Random, 95% CI)	2.22 [0.38, 13.12]
12.2 CPA versus placebo/no treatment	3	102	Risk Ratio (IV, Random, 95% CI)	7.18 [1.33, 38.70]
12.3 Alkylating agents+steroids versus placebo/ no treatment	3	211	Risk Ratio (IV, Random, 95% CI)	9.79 [1.28, 75.01]
12.4 Alkylating agents+steroids versus ACEi/ ARB	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.5 CSA versus placebo/no treatment	2	38	Risk Ratio (IV, Random, 95% CI)	5.45 [0.29, 101.55]
12.6 CSA+steroids versus placebo/no treatment	1	33	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

12.7 CSA+steroids versus ACEi/ARB	1	10	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.8 TAC versus placebo/no treatment	1	48	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.9 MMF versus placebo/no treatment	1	36	Risk Ratio (IV, Random, 95% CI)	8.10 [0.47, 140.24]
12.10 Azathioprine versus placebo/no treatment	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.11 Mizoribine versus placebo/no treatment	1	89	Risk Ratio (IV, Random, 95% CI)	4.29 [0.21, 86.80]

Comparison 2. Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or ESKD (dialysis/transplantation) (ITT analysis)	3	295	Risk Ratio (IV, Random, 95% CI)	0.75 [0.34, 1.63]
1.1 At final follow-up (24 months)	1	72	Risk Ratio (IV, Random, 95% CI)	0.16 [0.02, 1.23]
1.2 At final follow-up (48 months)	2	223	Risk Ratio (IV, Random, 95% CI)	0.94 [0.48, 1.81]
2 Death (ITT analysis)	3	295	Risk Ratio (IV, Random, 95% CI)	0.58 [0.11, 2.97]
2.1 At final follow-up (24 months)	1	72	Risk Ratio (IV, Random, 95% CI)	0.22 [0.01, 4.48]
2.2 At final follow-up (48 months)	2	223	Risk Ratio (IV, Random, 95% CI)	0.79 [0.08, 8.04]
3 ESKD (dialysis/transplantation) (ITT analysis)	3	295	Risk Ratio (IV, Random, 95% CI)	0.81 [0.34, 1.93]
3.1 At final follow-up (24 months)	1	72	Risk Ratio (IV, Random, 95% CI)	0.22 [0.03, 1.82]
3.2 At final follow-up (48 months)	2	223	Risk Ratio (IV, Random, 95% CI)	1.05 [0.47, 2.38]
4 100% increase in serum creatinine	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4.1 At final follow-up (24 months) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 At 24 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 50% increase in serum creatinine	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5.1 At final follow-up (36 months) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 At 36 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Final serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 At final follow-up (36 months)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 At 6 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 At 12 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.4 At 24 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

6.5 At 36 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Final GFR [mL/min/1.73 m ²]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 At final follow-up (36 months)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 At 36 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Complete or partial remission	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.1 At final follow-up (24-48 months) (ITT analysis)	3	295	Risk Ratio (IV, Random, 95% CI)	1.18 [0.64, 2.16]
8.2 At 6 months	1	63	Risk Ratio (IV, Random, 95% CI)	1.47 [0.36, 6.03]
8.3 At 12 months	2	153	Risk Ratio (IV, Random, 95% CI)	1.90 [1.17, 3.07]
8.4 At 24 months	1	31	Risk Ratio (IV, Random, 95% CI)	2.4 [0.93, 6.17]
8.5 At 36 months	2	156	Risk Ratio (IV, Random, 95% CI)	1.09 [0.76, 1.56]
8.6 At 48 months	2	128	Risk Ratio (IV, Random, 95% CI)	1.01 [0.48, 2.12]
9 Complete remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.1 At final follow-up (24-48 months) (ITT analysis)	2	192	Risk Ratio (IV, Random, 95% CI)	0.64 [0.29, 1.42]
9.2 At 6 months	1	63	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 At 12 months	2	153	Risk Ratio (IV, Random, 95% CI)	1.21 [0.09, 16.41]
9.4 At 24 months	1	31	Risk Ratio (IV, Random, 95% CI)	5.33 [0.70, 40.54]
9.5 At 36 months	1	80	Risk Ratio (IV, Random, 95% CI)	0.66 [0.33, 1.33]
9.6 At 48 months	1	55	Risk Ratio (IV, Random, 95% CI)	0.49 [0.21, 1.14]
10 Partial remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
10.1 At final follow-up (24-48 months) (ITT analysis)	2	192	Risk Ratio (IV, Random, 95% CI)	1.63 [0.62, 4.25]
10.2 At 6 months	1	63	Risk Ratio (IV, Random, 95% CI)	1.47 [0.36, 6.03]
10.3 At 12 months	2	153	Risk Ratio (IV, Random, 95% CI)	2.48 [0.73, 8.44]
10.4 At 24 months	1	31	Risk Ratio (IV, Random, 95% CI)	1.42 [0.38, 5.33]
10.5 At 36 months	1	80	Risk Ratio (IV, Random, 95% CI)	1.61 [0.77, 3.37]
10.6 At 48 months	1	55	Risk Ratio (IV, Random, 95% CI)	1.12 [0.52, 2.41]
11 Final proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.1 At final follow-up (36 months)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 At 6 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.3 At 36 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12 Temporary or permanent discontinuation or hospitalisation due to adverse events	3	295	Risk Ratio (IV, Random, 95% CI)	2.22 [0.38, 13.12]

Comparison 3. Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or ESKD (dialysis/transplantation) (ITT analysis)	3	102	Risk Ratio (IV, Random, 95% CI)	0.62 [0.03, 12.27]
1.1 At final follow-up (12 months)	1	22	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

1.2 At final follow-up (36 months)	1	54	Risk Ratio (IV, Random, 95% CI)	0.14 [0.01, 2.64]
1.3 At final follow-up (24 months)	1	26	Risk Ratio (IV, Random, 95% CI)	3.0 [0.13, 67.51]
2 Death (ITT analysis)	3	102	Risk Ratio (IV, Random, 95% CI)	0.75 [0.05, 10.61]
2.1 At final follow-up (12 months)	1	22	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 At final follow-up (24 months)	1	26	Risk Ratio (IV, Random, 95% CI)	3.0 [0.13, 67.51]
2.3 At final follow-up (36 months)	1	54	Risk Ratio (IV, Random, 95% CI)	0.2 [0.01, 3.98]
3 ESKD (dialysis/transplantation) (ITT analysis)	3	102	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.84]
3.1 At final follow-up (12 months)	1	22	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 At final follow-up (24 months)	1	26	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 At final follow-up (36 months)	1	54	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.84]
4 100% increase in serum creatinine	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1 At final follow-up (12-24 months) (ITT analysis)	2	48	Risk Ratio (IV, Random, 95% CI)	0.92 [0.15, 5.73]
4.2 At 6 months	1	26	Risk Ratio (IV, Random, 95% CI)	3.0 [0.13, 67.51]
4.3 At 12 months	2	44	Risk Ratio (IV, Random, 95% CI)	0.56 [0.06, 5.14]
4.4 At 18 months	1	25	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.5 At 24 months	1	25	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 50% increase in serum creatinine	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1 At final follow-up (12-24 months) (ITT analysis)	2	48	Risk Ratio (IV, Random, 95% CI)	0.99 [0.20, 4.91]
5.2 At 6 months	1	26	Risk Ratio (IV, Random, 95% CI)	3.0 [0.13, 67.51]
5.3 At 12 months	2	44	Risk Ratio (IV, Random, 95% CI)	0.56 [0.06, 5.14]
5.4 At 18 months	1	25	Risk Ratio (IV, Random, 95% CI)	3.23 [0.14, 72.46]
5.5 At 24 months	1	25	Risk Ratio (IV, Random, 95% CI)	1.08 [0.08, 15.46]
6 Final serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 At final follow-up (24 months)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 At 6 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 At 12 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.4 At 18 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.5 At 24 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Final GFR [mL/min/1.73 m²]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 At final follow-up (12 months)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 At 12 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Complete or partial remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.1 At final follow-up (12-24 months) (ITT analysis)	2	48	Risk Ratio (IV, Random, 95% CI)	2.14 [0.99, 4.63]
8.2 At 6 months	1	26	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 At 12 months	2	44	Risk Ratio (IV, Random, 95% CI)	1.80 [0.79, 4.07]
8.4 At 18 months	1	25	Risk Ratio (IV, Random, 95% CI)	2.44 [1.01, 5.87]

8.5 At 24 months	1	25	Risk Ratio (IV, Random, 95% CI)	2.17 [0.87, 5.37]
9 Complete remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.1 At final follow-up (12-24 months) (ITT analysis)	2	48	Risk Ratio (IV, Random, 95% CI)	2.0 [0.21, 19.44]
9.2 At 6 months	1	26	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 At 12 months	2	44	Risk Ratio (IV, Random, 95% CI)	0.36 [0.02, 8.05]
9.4 At 18 months	1	25	Risk Ratio (IV, Random, 95% CI)	0.36 [0.02, 8.05]
9.5 At 24 months	1	25	Risk Ratio (IV, Random, 95% CI)	2.17 [0.22, 20.94]
10 Partial remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
10.1 At final follow-up (12-24 months) (ITT analysis)	2	48	Risk Ratio (IV, Random, 95% CI)	2.19 [0.90, 5.34]
10.2 At 6 months	1	26	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 At 12 months	2	44	Risk Ratio (IV, Random, 95% CI)	2.19 [0.89, 5.35]
10.4 At 18 months	1	25	Risk Ratio (IV, Random, 95% CI)	3.25 [1.14, 9.24]
10.5 At 24 months	1	25	Risk Ratio (IV, Random, 95% CI)	2.17 [0.69, 6.79]
11 Final proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.1 At final follow-up (12 months)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 At 12 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12 Temporary or permanent discontinuation or hospitalisation due to adverse events	3	102	Risk Ratio (IV, Random, 95% CI)	7.18 [1.33, 38.70]

Comparison 4. Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or ESKD (dialysis/transplantation) (ITT analysis)	8	448	Risk Ratio (IV, Random, 95% CI)	0.44 [0.26, 0.75]
1.1 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months)	3	211	Risk Ratio (IV, Random, 95% CI)	0.33 [0.17, 0.64]
1.2 Alkylating agents+steroids versus ACEi/ARB at final follow-up (9 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Alkylating agents+steroids versus steroids (same dose) at final follow-up (15-54 months)	3	138	Risk Ratio (IV, Random, 95% CI)	0.80 [0.29, 2.23]
1.4 Alkylating agents+steroids versus steroids (low dose) at final follow-up (46 months)	1	90	Risk Ratio (IV, Random, 95% CI)	0.57 [0.05, 6.08]
2 Death (ITT analysis)	8	448	Risk Ratio (IV, Random, 95% CI)	0.57 [0.16, 1.98]

2.1 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months)	3	211	Risk Ratio (IV, Random, 95% CI)	0.48 [0.12, 1.97]
2.2 Alkylating agents+steroids versus ACEi/ARB at final follow-up (9 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Alkylating agents+steroids versus steroids (same dose) at final follow-up (15-54 months)	3	138	Risk Ratio (IV, Random, 95% CI)	1.04 [0.07, 16.20]
2.4 Alkylating agents+steroids versus steroids (low dose) at final follow-up (46 months)	1	90	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 ESKD (dialysis/transplantation) (ITT analysis)	8	448	Risk Ratio (IV, Random, 95% CI)	0.45 [0.25, 0.81]
3.1 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months)	3	211	Risk Ratio (IV, Random, 95% CI)	0.31 [0.15, 0.65]
3.2 Alkylating agents+steroids versus ACEi/ARB at final follow-up (9 months)	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Alkylating agents+steroids versus steroids (same-dose) at final follow-up (15-54 months)	3	138	Risk Ratio (IV, Random, 95% CI)	0.88 [0.31, 2.49]
3.4 Alkylating agents+steroids versus steroids (low dose) at final follow-up (46 months)	1	90	Risk Ratio (IV, Random, 95% CI)	0.57 [0.05, 6.08]
4 100% increase in serum creatinine	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1 Alkylating agents+steroids versus placebo/no treatment/steroids at final follow-up (15-120 months) (ITT analysis)	5	257	Risk Ratio (IV, Random, 95% CI)	0.51 [0.25, 1.04]
4.2 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months) (ITT analysis)	3	211	Risk Ratio (IV, Random, 95% CI)	0.39 [0.17, 0.89]
4.3 Alkylating agents+steroids versus placebo/no treatment at 60 months	2	107	Risk Ratio (IV, Random, 95% CI)	0.39 [0.07, 2.25]
4.4 Alkylating agents+steroids versus placebo/no treatment at 120 months	1	93	Risk Ratio (IV, Random, 95% CI)	0.38 [0.21, 0.69]
4.5 Alkylating agents+steroids versus steroids (same dose) at final follow-up (15-24months) (ITT analysis)	2	46	Risk Ratio (IV, Random, 95% CI)	1.05 [0.40, 2.76]
4.6 Alkylating agents+steroids versus steroids (same dose) at 6 months	1	26	Risk Ratio (IV, Random, 95% CI)	0.14 [0.01, 2.52]

4.7 Alkylating agents+steroids versus steroids (same dose) at 12-15 months	2	46	Risk Ratio (IV, Random, 95% CI)	0.86 [0.31, 2.41]
4.8 Alkylating agents+steroids versus steroids (same dose) at 24 months	1	26	Risk Ratio (IV, Random, 95% CI)	1.25 [0.43, 3.63]
5 50% increase in serum creatinine	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1 Alkylating agents+steroids versus placebo/no treatment/steroids at final follow-up (24-120 months) (ITT analysis)	4	289	Risk Ratio (IV, Random, 95% CI)	0.56 [0.28, 1.11]
5.2 Alkylating agents+steroids versus placebo/no treatment at final follow-up (120 months) (ITT analysis)	1	81	Risk Ratio (IV, Random, 95% CI)	0.33 [0.15, 0.68]
5.3 Alkylating agents+steroids versus placebo/no treatment at 60 months	1	81	Risk Ratio (IV, Random, 95% CI)	0.24 [0.10, 0.59]
5.4 Alkylating agents+steroids versus placebo/no treatment at 120 months	1	81	Risk Ratio (IV, Random, 95% CI)	0.33 [0.15, 0.68]
5.5 Alkylating agents+steroids versus steroids (same dose) at final follow-up (24-54 months) (ITT analysis)	2	118	Risk Ratio (IV, Random, 95% CI)	0.88 [0.47, 1.63]
5.6 Alkylating agents+steroids versus steroids (same dose) at 6 months	1	26	Risk Ratio (IV, Random, 95% CI)	0.25 [0.03, 1.95]
5.7 Alkylating agents+steroids versus steroids (same dose) at 12 months	1	26	Risk Ratio (IV, Random, 95% CI)	1.0 [0.32, 3.17]
5.8 Alkylating agents+steroids versus steroids (same dose) at 24 months	1	26	Risk Ratio (IV, Random, 95% CI)	1.2 [0.49, 2.96]
5.9 Alkylating agents+steroids versus steroids (same dose) at 54 months	1	92	Risk Ratio (IV, Random, 95% CI)	0.66 [0.28, 1.56]
5.10 Alkylating agents+steroids versus steroids (low dose) at final follow-up (46 months) (ITT analysis)	1	90	Risk Ratio (IV, Random, 95% CI)	0.23 [0.03, 1.88]
5.11 Alkylating agents+steroids versus steroids (low dose) at 46 months	1	71	Risk Ratio (IV, Random, 95% CI)	0.19 [0.02, 1.58]
6 Final serum creatinine	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Alkylating agents+steroids versus placebo/no treatment/steroids at final follow-up (12-120 months)	4	150	Mean Difference (IV, Random, 95% CI)	-21.48 [-85.96, 42.99]

6.2 Alkylating agents+steroids versus placebo/no treatment at final follow-up (120 months)	1	56	Mean Difference (IV, Random, 95% CI)	26.86 [10.14, 43.58]
6.3 Alkylating agents+steroids versus placebo/no treatment at 6 months	1	56	Mean Difference (IV, Random, 95% CI)	10.61 [0.22, 21.00]
6.4 Alkylating agents+steroids versus placebo/no treatment at 12 months	1	56	Mean Difference (IV, Random, 95% CI)	14.15 [1.41, 26.89]
6.5 Alkylating agents+steroids versus placebo/no treatment at 24 months	1	56	Mean Difference (IV, Random, 95% CI)	26.52 [15.48, 37.56]
6.6 Alkylating agents+steroids versus placebo/no treatment at 36 months	1	56	Mean Difference (IV, Random, 95% CI)	22.98 [9.19, 36.77]
6.7 Alkylating agents+steroids versus placebo/no treatment at 48 months	1	56	Mean Difference (IV, Random, 95% CI)	23.87 [9.64, 38.10]
6.8 Alkylating agents+steroids versus placebo/no treatment at 60 months	1	56	Mean Difference (IV, Random, 95% CI)	25.64 [11.25, 40.03]
6.9 Alkylating agents+steroids versus placebo/no treatment at 72 months	1	56	Mean Difference (IV, Random, 95% CI)	29.17 [14.17, 44.17]
6.10 Alkylating agents+steroids versus placebo/no treatment at 84 months	1	56	Mean Difference (IV, Random, 95% CI)	29.17 [12.85, 45.49]
6.11 Alkylating agents+steroids versus placebo/no treatment at 96 months	1	56	Mean Difference (IV, Random, 95% CI)	27.4 [10.89, 43.91]
6.12 Alkylating agents+steroids versus placebo/no treatment at 108 months	1	56	Mean Difference (IV, Random, 95% CI)	25.64 [9.08, 42.20]
6.13 Alkylating agents+steroids versus placebo/no treatment at 120 months	1	56	Mean Difference (IV, Random, 95% CI)	26.86 [10.14, 43.58]
6.14 Alkylating agents+steroids versus steroids (same dose) at final follow-up (24-54 months)	3	94	Mean Difference (IV, Random, 95% CI)	-59.17 [-120.09, 1.75]
6.15 Alkylating agents+steroids versus steroids (same dose) at 6 months	1	23	Mean Difference (IV, Random, 95% CI)	-59.76 [-206.64, 87.12]
6.16 Alkylating agents+steroids versus steroids (same dose) at 12-15 months	3	134	Mean Difference (IV, Random, 95% CI)	-5.37 [-54.86, 44.13]
6.17 Alkylating agents+steroids versus steroids (same dose) at 24 months	2	102	Mean Difference (IV, Random, 95% CI)	-29.71 [-70.58, 11.15]

6.18 Alkylating agents+steroids versus steroids (same dose) at 36 months	1	84	Mean Difference (IV, Random, 95% CI)	-27.0 [-81.49, 27.49]
6.19 Alkylating agents+steroids versus steroids (same dose) at 48 months	1	63	Mean Difference (IV, Random, 95% CI)	-47.00 [-121.64, 23.64]
7 Final GFR [mL/min/1.73 m ²]	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Alkylating agents+steroids versus placebo/no treatment/ACEi/ARB at final follow-up (9-120 months)	2	102	Mean Difference (IV, Random, 95% CI)	11.70 [1.50, 21.91]
7.2 Alkylating agents+steroids versus placebo/no treatment at final follow-up (120 months)	1	93	Mean Difference (IV, Random, 95% CI)	14.0 [5.82, 22.18]
7.3 Alkylating agents+steroids versus placebo/no treatment at 12 months	1	93	Mean Difference (IV, Random, 95% CI)	0.0 [-6.12, 6.12]
7.4 Alkylating agents+steroids versus placebo/no treatment at 24 months	1	93	Mean Difference (IV, Random, 95% CI)	3.0 [-4.37, 10.37]
7.5 Alkylating agents+steroids versus placebo/no treatment at 48 months	1	93	Mean Difference (IV, Random, 95% CI)	8.0 [1.29, 14.71]
7.6 Alkylating agents+steroids versus placebo/no treatment at 72 months	1	93	Mean Difference (IV, Random, 95% CI)	15.0 [7.27, 22.73]
7.7 Alkylating agents+steroids versus placebo/no treatment at 96 months	1	93	Mean Difference (IV, Random, 95% CI)	14.0 [8.51, 19.49]
7.8 Alkylating agents+steroids versus placebo/no treatment at 120 months	1	93	Mean Difference (IV, Random, 95% CI)	14.0 [5.82, 22.18]
7.9 Alkylating agents+steroids versus ACEi/ARB at final follow-up (9 months)	1	9	Mean Difference (IV, Random, 95% CI)	-0.10 [-24.22, 24.02]
7.10 Alkylating agents+steroids versus ACEi/ARB at 9 months	1	9	Mean Difference (IV, Random, 95% CI)	-0.10 [-24.22, 24.02]
8 Complete or partial remission	7		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.1 Alkylating agents+steroids versus placebo/no treatment/ACEi/ARB/steroids at final follow-up (9-120 months) (ITT analysis)	7	422	Risk Ratio (IV, Random, 95% CI)	1.46 [1.13, 1.89]
8.2 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months) (ITT analysis)	3	211	Risk Ratio (IV, Random, 95% CI)	1.52 [0.85, 2.73]
8.3 Alkylating agents+steroids versus placebo/no treatment at 12 months	2	173	Risk Ratio (IV, Random, 95% CI)	4.59 [1.74, 12.08]

8.4 Alkylating agents+steroids versus placebo/no treatment at 24 months	2	172	Risk Ratio (IV, Random, 95% CI)	4.02 [2.38, 6.77]
8.5 Alkylating agents+steroids versus placebo/no treatment at 36 months	2	165	Risk Ratio (IV, Random, 95% CI)	3.21 [2.03, 5.10]
8.6 Alkylating agents+steroids versus placebo/no treatment at 48 months	2	152	Risk Ratio (IV, Random, 95% CI)	2.34 [1.41, 3.86]
8.7 Alkylating agents+steroids versus placebo/no treatment at 60 months	3	173	Risk Ratio (IV, Random, 95% CI)	1.54 [0.82, 2.88]
8.8 Alkylating agents+steroids versus placebo/no treatment at 72 months	1	93	Risk Ratio (IV, Random, 95% CI)	2.22 [1.41, 3.48]
8.9 Alkylating agents+steroids versus placebo/no treatment at 84 months	1	93	Risk Ratio (IV, Random, 95% CI)	2.22 [1.41, 3.48]
8.10 Alkylating agents+steroids versus placebo/no treatment at 96 months	1	93	Risk Ratio (IV, Random, 95% CI)	2.08 [1.35, 3.21]
8.11 Alkylating agents+steroids versus placebo/no treatment at 108 months	1	93	Risk Ratio (IV, Random, 95% CI)	2.08 [1.35, 3.21]
8.12 Alkylating agents+steroids versus placebo/no treatment at 120 months	2	174	Risk Ratio (IV, Random, 95% CI)	1.98 [1.43, 2.75]
8.13 Alkylating agents+steroids versus ACEi/ARB at final follow-up (9 months) (ITT analysis)	1	9	Risk Ratio (IV, Random, 95% CI)	1.0 [0.68, 1.46]
8.14 Alkylating agents+steroids versus ACEi/ARB at 9 months	1	9	Risk Ratio (IV, Random, 95% CI)	1.0 [0.68, 1.46]
8.15 Alkylating agents+steroids versus steroids (same dose) at final follow-up (12-54 months) (ITT analysis)	2	112	Risk Ratio (IV, Random, 95% CI)	1.52 [1.07, 2.15]
8.16 Alkylating agents+steroids versus steroids (same dose) at 12-15 months	2	112	Risk Ratio (IV, Random, 95% CI)	1.76 [1.05, 2.95]
8.17 Alkylating agents+steroids versus steroids (same dose) at 24 months	1	91	Risk Ratio (IV, Random, 95% CI)	1.71 [1.04, 2.81]
8.18 Alkylating agents+steroids versus steroids (same dose) at 36 months	1	84	Risk Ratio (IV, Random, 95% CI)	1.67 [1.08, 2.56]
8.19 Alkylating agents+steroids versus steroids (same dose) at 48 months	1	63	Risk Ratio (IV, Random, 95% CI)	1.49 [0.91, 2.44]

8.20 Alkylating agents+steroids versus steroids (low dose) at final follow-up (46 months) (ITT analysis)	1	90	Risk Ratio (IV, Random, 95% CI)	1.71 [1.21, 2.42]
8.21 Alkylating agents+steroids versus steroids (low dose) at 46 months	1	71	Risk Ratio (IV, Random, 95% CI)	1.46 [1.11, 1.92]
9 Complete remission	7		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.1 Alkylating agents+steroids versus placebo/no treatment/ ACEi/ARB/steroids at final follow-up (9-120 months) (ITT analysis)	7	422	Risk Ratio (IV, Random, 95% CI)	2.32 [1.61, 3.32]
9.2 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months) (ITT analysis)	3	211	Risk Ratio (IV, Random, 95% CI)	3.18 [1.23, 8.21]
9.3 Alkylating agents+steroids versus placebo/no treatment at 12 months	2	173	Risk Ratio (IV, Random, 95% CI)	7.68 [1.39, 42.56]
9.4 Alkylating agents+steroids versus placebo/no treatment at 24 months	2	172	Risk Ratio (IV, Random, 95% CI)	13.86 [2.70, 71.21]
9.5 Alkylating agents+steroids versus placebo/no treatment at 36 months	2	165	Risk Ratio (IV, Random, 95% CI)	16.14 [3.19, 81.69]
9.6 Alkylating agents+steroids versus placebo/no treatment at 48 months	2	152	Risk Ratio (IV, Random, 95% CI)	4.82 [1.98, 11.69]
9.7 Alkylating agents+steroids versus placebo/no treatment at 60 months	3	173	Risk Ratio (IV, Random, 95% CI)	2.64 [1.43, 4.90]
9.8 Alkylating agents+steroids versus placebo/no treatment at 72 months	1	93	Risk Ratio (IV, Random, 95% CI)	2.94 [1.16, 7.42]
9.9 Alkylating agents+steroids versus placebo/no treatment at 84 months	1	93	Risk Ratio (IV, Random, 95% CI)	2.94 [1.16, 7.42]
9.10 Alkylating agents+steroids versus placebo/ no treatment at 96 months	1	93	Risk Ratio (IV, Random, 95% CI)	2.94 [1.16, 7.42]
9.11 Alkylating agents+steroids versus placebo/ no treatment at 108 months	1	93	Risk Ratio (IV, Random, 95% CI)	2.94 [1.16, 7.42]
9.12 Alkylating agents+steroids versus placebo/ no treatment at 120 months	2	174	Risk Ratio (IV, Random, 95% CI)	4.17 [1.65, 10.53]
9.13 Alkylating agents+steroids versus ACEi/ ARB at final follow-up (9 months) (ITT analysis)	1	9	Risk Ratio (IV, Random, 95% CI)	6.0 [0.37, 98.16]

9.14 Alkylating agents+steroids versus ACEi/ARB at 9 months	1	9	Risk Ratio (IV, Random, 95% CI)	6.0 [0.37, 98.16]
9.15 Alkylating agents+steroids versus steroids (same dose) at final follow-up (12-54 months) (ITT analysis)	2	112	Risk Ratio (IV, Random, 95% CI)	1.52 [0.84, 2.75]
9.16 Alkylating agents+steroids versus steroids (same dose) at 12-15 months	2	112	Risk Ratio (IV, Random, 95% CI)	1.78 [0.84, 3.79]
9.17 Alkylating agents+steroids versus steroids (same dose) at 24 months	1	91	Risk Ratio (IV, Random, 95% CI)	2.94 [1.01, 8.55]
9.18 Alkylating agents+steroids versus steroids (same dose) at 36 months	1	84	Risk Ratio (IV, Random, 95% CI)	3.67 [1.32, 10.24]
9.19 Alkylating agents+steroids versus steroids (same dose) at 48 months	1	63	Risk Ratio (IV, Random, 95% CI)	1.11 [0.46, 2.69]
9.20 Alkylating agents+steroids versus steroids (low dose) at final follow-up (46 months) (ITT analysis)	1	90	Risk Ratio (IV, Random, 95% CI)	2.51 [1.61, 3.94]
9.21 Alkylating agents+steroids versus steroids (low dose) at 46 months	1	71	Risk Ratio (IV, Random, 95% CI)	2.14 [1.44, 3.18]
10 Partial remission	7		Risk Ratio (IV, Random, 95% CI)	Subtotals only
10.1 Alkylating agents+steroids versus placebo/no treatment/ACEi/ARB/steroids at final follow-up (9-120 months) (ITT analysis)	7	422	Risk Ratio (IV, Random, 95% CI)	0.94 [0.56, 1.57]
10.2 Alkylating agents+steroids versus placebo/no treatment at final follow-up (60-120 months) (ITT analysis)	3	211	Risk Ratio (IV, Random, 95% CI)	1.00 [0.50, 2.02]
10.3 Alkylating agents+steroids versus placebo/no treatment at 12 months	2	173	Risk Ratio (IV, Random, 95% CI)	3.26 [1.48, 7.20]
10.4 Alkylating agents+steroids versus placebo/no treatment at 24 months	2	172	Risk Ratio (IV, Random, 95% CI)	2.23 [1.22, 4.09]
10.5 Alkylating agents+steroids versus placebo/no treatment at 36 months	2	165	Risk Ratio (IV, Random, 95% CI)	1.61 [0.59, 4.41]
10.6 Alkylating agents+steroids versus placebo/no treatment at 48 months	2	152	Risk Ratio (IV, Random, 95% CI)	1.51 [0.76, 3.03]

10.7 Alkylating agents+steroids versus placebo/ no treatment at 60 months	3	173	Risk Ratio (IV, Random, 95% CI)	1.11 [0.50, 2.43]
10.8 Alkylating agents+steroids versus placebo/ no treatment at 72 months	1	93	Risk Ratio (IV, Random, 95% CI)	1.86 [0.97, 3.56]
10.9 Alkylating agents+steroids versus placebo/ no treatment at 84 months	1	93	Risk Ratio (IV, Random, 95% CI)	1.86 [0.97, 3.56]
10.10 Alkylating agents+steroids versus placebo/ no treatment at 96 months	1	93	Risk Ratio (IV, Random, 95% CI)	1.69 [0.91, 3.15]
10.11 Alkylating agents+steroids versus placebo/ no treatment at 108 months	1	93	Risk Ratio (IV, Random, 95% CI)	1.69 [0.91, 3.15]
10.12 Alkylating agents+steroids versus placebo/ no treatment at 120 months	2	174	Risk Ratio (IV, Random, 95% CI)	1.17 [0.54, 2.56]
10.13 Alkylating agents+steroids versus ACEi/ ARB at final follow-up (9 months) (ITT analysis)	1	9	Risk Ratio (IV, Random, 95% CI)	0.55 [0.22, 1.35]
10.14 Alkylating agents+steroids versus ACEi/ ARB at 9 months	1	9	Risk Ratio (IV, Random, 95% CI)	0.55 [0.22, 1.35]
10.15 Alkylating agents+steroids versus steroids (same dose) at final follow-up (12-54 months) (ITT analysis)	2	112	Risk Ratio (IV, Random, 95% CI)	1.57 [0.81, 3.06]
10.16 Alkylating agents+steroids versus steroids (same dose) at 12-15 months	2	112	Risk Ratio (IV, Random, 95% CI)	1.88 [0.80, 4.41]
10.17 Alkylating agents+steroids versus steroids (same dose) at 24 months	1	91	Risk Ratio (IV, Random, 95% CI)	1.26 [0.63, 2.52]
10.18 Alkylating agents+steroids versus steroids (same dose) at 36 months	1	84	Risk Ratio (IV, Random, 95% CI)	1.05 [0.55, 1.99]
10.19 Alkylating agents+steroids versus steroids (same dose) at 48 months	1	63	Risk Ratio (IV, Random, 95% CI)	1.94 [0.83, 4.52]
10.20 Alkylating agents+steroids versus steroids (low dose) at final follow-up (46 months) (ITT analysis)	1	90	Risk Ratio (IV, Random, 95% CI)	0.08 [0.00, 1.29]
10.21 Alkylating agents+steroids versus steroids (low dose) at 46 months	1	71	Risk Ratio (IV, Random, 95% CI)	0.06 [0.00, 1.09]
11 Final proteinuria	6		Mean Difference (IV, Random, 95% CI)	Subtotals only

11.1 Alkylating agents+steroids versus placebo/ no treatment/ACEi/ARB/ steroids at final follow-up (9-120 months)	6	279	Mean Difference (IV, Random, 95% CI)	-1.25 [-1.93, -0.57]
11.2 Alkylating agents+steroids versus placebo/ no treatment at final follow-up (60-120 months)	2	174	Mean Difference (IV, Random, 95% CI)	-2.06 [-3.69, -0.44]
11.3 Alkylating agents+steroids versus placebo/ no treatment at 6 months	1	81	Mean Difference (IV, Random, 95% CI)	-2.30 [-3.67, -0.93]
11.4 Alkylating agents+steroids versus placebo/ no treatment at 12 months	2	174	Mean Difference (IV, Random, 95% CI)	-2.17 [-3.10, -1.24]
11.5 Alkylating agents+steroids versus placebo/ no treatment at 18 months	1	81	Mean Difference (IV, Random, 95% CI)	-3.10 [-4.69, -1.51]
11.6 Alkylating agents+steroids versus placebo/ no treatment at 24 months	2	174	Mean Difference (IV, Random, 95% CI)	-2.37 [-2.97, -1.77]
11.7 Alkylating agents+steroids versus placebo/ no treatment at 48 months	1	93	Mean Difference (IV, Random, 95% CI)	-1.65 [-2.21, -1.09]
11.8 Alkylating agents+steroids versus placebo/ no treatment at 72 months	1	93	Mean Difference (IV, Random, 95% CI)	-1.9 [-2.36, -1.44]
11.9 Alkylating agents+steroids versus placebo/ no treatment at 96 months	1	93	Mean Difference (IV, Random, 95% CI)	-1.50 [-1.79, -1.21]
11.10 Alkylating agents+steroids versus placebo/ no treatment at 120 months	1	93	Mean Difference (IV, Random, 95% CI)	-1.4 [-1.64, -1.16]
11.11 Alkylating agents+steroids versus ACEi/ ARB at final follow-up (9 months)	1	9	Mean Difference (IV, Random, 95% CI)	-1.0 [-2.20, 0.20]
11.12 Alkylating agents+steroids versus ACEi/ ARB at 9 months	1	9	Mean Difference (IV, Random, 95% CI)	-1.0 [-2.20, 0.20]
11.13 Alkylating agents+steroids versus steroids (same dose) at final follow-up (9-120 months)	3	96	Mean Difference (IV, Random, 95% CI)	-0.52 [-1.40, 0.37]
11.14 Alkylating agents+steroids versus steroids (same dose) at 12-15 months	2	70	Mean Difference (IV, Random, 95% CI)	-0.68 [-2.21, 0.84]
11.15 Alkylating agents+steroids versus steroids (same dose) at 24-29 months	2	76	Mean Difference (IV, Random, 95% CI)	-0.13 [-2.53, 2.28]

11.16 Alkylating agents+steroids versus steroids (same dose) at 36 months	1	50	Mean Difference (IV, Random, 95% CI)	-1.60 [-2.77, -0.43]
11.17 Alkylating agents+steroids versus steroids (same dose) at 48 months	1	50	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.58, 0.38]
12 Temporary or permanent discontinuation or hospitalisation due to adverse events	8	448	Risk Ratio (IV, Random, 95% CI)	2.11 [0.77, 5.79]
12.1 Alkylating agents+steroids versus placebo/no treatment	3	211	Risk Ratio (IV, Random, 95% CI)	9.79 [1.28, 75.01]
12.2 Alkylating agents+steroids versus ACEi/ARB	1	9	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.3 Alkylating agents+steroids versus steroids (same dose)	3	138	Risk Ratio (IV, Random, 95% CI)	2.37 [0.45, 12.67]
12.4 Alkylating agents+steroids versus steroids (low dose)	1	90	Risk Ratio (IV, Random, 95% CI)	0.91 [0.26, 3.18]

Comparison 5. Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or ESKD (dialysis/transplantation) (ITT analysis)	3	147	Risk Ratio (IV, Random, 95% CI)	1.17 [0.15, 9.36]
1.1 At final follow-up (15 months)	1	20	Risk Ratio (IV, Random, 95% CI)	6.0 [0.87, 41.21]
1.2 At final follow-up (32-39 months)	2	127	Risk Ratio (IV, Random, 95% CI)	0.40 [0.08, 2.09]
2 Death (ITT analysis)	3	147	Risk Ratio (IV, Random, 95% CI)	3.0 [0.14, 65.90]
2.1 At final follow-up (15 months)	1	20	Risk Ratio (IV, Random, 95% CI)	3.0 [0.14, 65.90]
2.2 At final follow-up (32-39 months)	2	127	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 ESKD (dialysis/transplantation) (ITT analysis)	3	147	Risk Ratio (IV, Random, 95% CI)	1.09 [0.16, 7.72]
3.1 At final follow-up (15 months)	1	20	Risk Ratio (IV, Random, 95% CI)	5.0 [0.70, 35.50]
3.2 At final follow-up (32-39 months)	2	127	Risk Ratio (IV, Random, 95% CI)	0.40 [0.08, 2.09]
4 100% increase in serum creatinine	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only

4.1 At final follow-up (15-32 months) (ITT analysis)	2	52	Risk Ratio (IV, Random, 95% CI)	0.82 [0.02, 41.02]
4.2 At 6 months	1	18	Risk Ratio (IV, Random, 95% CI)	5.0 [0.27, 91.52]
4.3 At 12 months	1	17	Risk Ratio (IV, Random, 95% CI)	12.22 [0.78, 191.46]
4.4 At 32 months	1	32	Risk Ratio (IV, Random, 95% CI)	0.11 [0.02, 0.78]
5 50% increase in serum creatinine	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1 At final follow-up (15-39 months) (ITT analysis)	3	147	Risk Ratio (IV, Random, 95% CI)	0.85 [0.13, 5.39]
5.2 At 6 months	1	18	Risk Ratio (IV, Random, 95% CI)	11.00 [0.70, 173.66]
5.3 At 12 months	1	17	Risk Ratio (IV, Random, 95% CI)	6.75 [1.02, 44.71]
5.4 At 32-39 months	2	127	Risk Ratio (IV, Random, 95% CI)	0.46 [0.02, 8.67]
6 Final serum creatinine	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 At final follow-up (12-39 months)	3	128	Mean Difference (IV, Random, 95% CI)	-18.67 [-134.94, 97.60]
6.2 At 6 months	2	48	Mean Difference (IV, Random, 95% CI)	50.17 [-74.60, 174.93]
6.3 At 12 months	2	41	Mean Difference (IV, Random, 95% CI)	17.46 [-156.11, 191.03]
6.4 At 32-39 months	2	114	Mean Difference (IV, Random, 95% CI)	-50.62 [-174.05, 72.81]
7 Complete or partial remission	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7.1 At final follow-up (15-39 months) (ITT analysis)	3	147	Risk Ratio (IV, Random, 95% CI)	1.64 [0.72, 3.76]
7.2 At 12 months	1	18	Risk Ratio (IV, Random, 95% CI)	0.75 [0.23, 2.44]
7.3 At 32-39 months	2	119	Risk Ratio (IV, Random, 95% CI)	2.12 [0.48, 9.31]
8 Complete remission	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.1 At final follow-up (15-39 months) (ITT analysis)	3	147	Risk Ratio (IV, Random, 95% CI)	2.22 [0.76, 6.47]
8.2 At 12 months	1	18	Risk Ratio (IV, Random, 95% CI)	2.0 [0.22, 18.33]
8.3 At 32-39 months	2	119	Risk Ratio (IV, Random, 95% CI)	2.52 [0.38, 16.81]
9 Partial remission	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.1 At final follow-up (15-39 months) (ITT analysis)	3	147	Risk Ratio (IV, Random, 95% CI)	1.16 [0.58, 2.31]
9.2 At 12 months	1	18	Risk Ratio (IV, Random, 95% CI)	0.33 [0.04, 2.63]
9.3 At 32-39 months	2	119	Risk Ratio (IV, Random, 95% CI)	1.26 [0.58, 2.74]
10 Final proteinuria	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 At final follow-up (32-39 months)	2	118	Mean Difference (IV, Random, 95% CI)	-2.74 [-7.71, 2.23]
10.2 At 6 months	1	31	Mean Difference (IV, Random, 95% CI)	-3.5 [-5.77, -1.23]
10.3 At 12 months	1	27	Mean Difference (IV, Random, 95% CI)	-4.8 [-7.66, -1.94]
10.4 At 32-39 months	2	118	Mean Difference (IV, Random, 95% CI)	-2.74 [-7.71, 2.23]
11 Temporary or permanent discontinuation or hospitalisation due to adverse events	3	147	Risk Ratio (IV, Random, 95% CI)	0.48 [0.26, 0.90]

Comparison 6. Cyclosporine (CSA) versus other treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or ESKD (dialysis/transplantation) (ITT analysis)	6	202	Risk Ratio (IV, Random, 95% CI)	1.00 [0.47, 2.15]
1.1 CSA versus placebo/no treatment at final follow-up (12-21 months)	2	38	Risk Ratio (IV, Random, 95% CI)	1.04 [0.15, 7.21]
1.2 CSA+steroids versus placebo/no treatment at final follow-up (60 months)	1	33	Risk Ratio (IV, Random, 95% CI)	1.5 [0.18, 12.80]
1.3 CSA+steroids versus ACEi/ARB at final follow-up (9 months)	1	10	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 CSA+steroids versus steroids at final follow-up (18 months)	1	51	Risk Ratio (IV, Random, 95% CI)	4.14 [0.21, 82.11]
1.5 CSA+steroids versus alkylating agents+steroids at final follow-up (9-60 months)	2	47	Risk Ratio (IV, Random, 95% CI)	0.97 [0.25, 3.75]
1.6 CSA+steroids versus azathioprine+steroids at final follow-up (36 months)	1	23	Risk Ratio (IV, Random, 95% CI)	0.42 [0.02, 9.43]
2 Death (ITT analysis)	6	202	Risk Ratio (IV, Random, 95% CI)	1.28 [0.35, 4.66]
2.1 CSA versus placebo/no treatment at final follow-up (12-21 months)	2	38	Risk Ratio (IV, Random, 95% CI)	2.7 [0.13, 58.24]
2.2 CSA+steroids versus placebo/no treatment at final follow-up (60 months)	1	33	Risk Ratio (IV, Random, 95% CI)	1.57 [0.07, 35.57]
2.3 CSA+steroids versus ACEi/ARB at final follow-up (9 months)	1	10	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 CSA+steroids versus steroids at final follow-up (18 months)	1	51	Risk Ratio (IV, Random, 95% CI)	2.48 [0.11, 58.20]
2.5 CSA+steroids versus alkylating agents+steroids at final follow-up (9-60 months)	2	47	Risk Ratio (IV, Random, 95% CI)	0.73 [0.11, 4.63]
2.6 CSA+steroids versus azathioprine+steroids at final follow-up (36 months)	1	23	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 ESKD (dialysis/transplantation) (ITT analysis)	6	202	Risk Ratio (IV, Random, 95% CI)	0.96 [0.37, 2.53]
3.1 CSA versus placebo/no treatment at final follow-up (12-21 months)	2	38	Risk Ratio (IV, Random, 95% CI)	0.84 [0.06, 11.76]

3.2 CSA+steroids versus placebo/no treatment at final follow-up (60 months)	1	33	Risk Ratio (IV, Random, 95% CI)	1.0 [0.10, 9.86]
3.3 CSA+steroids versus ACEi/ARB at final follow-up (9 months)	1	10	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 CSA+steroids versus steroids at final follow-up (18 months)	1	51	Risk Ratio (IV, Random, 95% CI)	2.48 [0.11, 58.20]
3.5 CSA+steroids versus alkylating agents+steroids at final follow-up (9-60 months)	2	47	Risk Ratio (IV, Random, 95% CI)	1.45 [0.14, 14.69]
3.6 CSA+steroids versus azathioprine+steroids at final follow-up (36 months)	1	23	Risk Ratio (IV, Random, 95% CI)	0.42 [0.02, 9.43]
4 100% increase in serum creatinine	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1 CSA versus other treatments at final follow-up (18-60 months) (ITT analysis)	2	122	Risk Ratio (IV, Random, 95% CI)	0.86 [0.39, 1.87]
4.2 CSA+steroids versus placebo/no treatment at final follow-up (60 months) (ITT analysis)	1	33	Risk Ratio (IV, Random, 95% CI)	0.67 [0.18, 2.47]
4.3 CSA+steroids versus placebo/no treatment at 60 months	1	33	Risk Ratio (IV, Random, 95% CI)	0.67 [0.18, 2.47]
4.4 CSA+steroids versus steroids at final follow-up (18 months) (ITT analysis)	1	51	Risk Ratio (IV, Random, 95% CI)	1.64 [0.33, 8.18]
4.5 CSA+steroids versus steroids at 18 months	1	51	Risk Ratio (IV, Random, 95% CI)	1.64 [0.33, 8.18]
4.6 CSA+steroids versus alkylating agents+steroids at final follow-up (60 months) (ITT analysis)	1	38	Risk Ratio (IV, Random, 95% CI)	0.73 [0.21, 2.48]
4.7 CSA+steroids versus alkylating agents+steroids at 60 months	1	38	Risk Ratio (IV, Random, 95% CI)	0.73 [0.21, 2.48]
5 50% increase in serum creatinine	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1 CSA versus other treatments at final follow-up (18-36 months) (ITT analysis)	2	74	Risk Ratio (IV, Random, 95% CI)	1.00 [0.34, 2.96]
5.2 CSA+steroids versus steroids at final follow-up (18 months) (ITT analysis)	1	51	Risk Ratio (IV, Random, 95% CI)	1.64 [0.33, 8.18]
5.3 CSA+steroids versus steroids at 18 months	1	51	Risk Ratio (IV, Random, 95% CI)	1.64 [0.33, 8.18]

5.4 CSA+steroids versus azathioprine+steroids at final follow-up (36 months) (ITT analysis)	1	23	Risk Ratio (IV, Random, 95% CI)	0.65 [0.15, 2.87]
5.5 CSA+steroids versus azathioprine+steroids at 36 months	1	23	Risk Ratio (IV, Random, 95% CI)	0.65 [0.15, 2.87]
6 Final serum creatinine	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 CSA versus other treatments at final follow-up (12-36 months)	3	95	Mean Difference (IV, Random, 95% CI)	16.86 [-17.84, 51.55]
6.2 CSA versus placebo/no treatment at 12 months	1	21	Mean Difference (IV, Random, 95% CI)	11.5 [-50.19, 73.19]
6.3 CSA+steroids versus steroids at 6 months	1	51	Mean Difference (IV, Random, 95% CI)	35.36 [17.46, 53.26]
6.4 CSA+steroids versus steroids at 12 months	1	51	Mean Difference (IV, Random, 95% CI)	35.36 [8.19, 62.53]
6.5 CSA+steroids versus steroids at 18 months	1	51	Mean Difference (IV, Random, 95% CI)	26.52 [-16.66, 69.70]
6.6 CSA+steroids versus azathioprine+steroids at 6 months	1	23	Mean Difference (IV, Random, 95% CI)	-17.60 [-69.68, 34.48]
6.7 CSA+steroids versus azathioprine+steroids at 12 months	1	23	Mean Difference (IV, Random, 95% CI)	-48.3 [-135.75, 39.15]
6.8 CSA+steroids versus azathioprine+steroids at 18 months	1	23	Mean Difference (IV, Random, 95% CI)	-49.30 [-122.84, 24.24]
6.9 CSA+steroids versus azathioprine+steroids at 24 months	1	23	Mean Difference (IV, Random, 95% CI)	-61.0 [-186.67, 64.67]
6.10 CSA+steroids versus azathioprine+steroids at 30 months	1	23	Mean Difference (IV, Random, 95% CI)	-96.60 [-234.88, 41.68]
6.11 CSA+steroids versus azathioprine+steroids at 36 months	1	23	Mean Difference (IV, Random, 95% CI)	-102.5 [-280.28, 75.28]
7 Final GFR [mL/min/1.73 m ²]	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 CSA versus other treatments at final follow-up (9-36 months)	4	71	Mean Difference (IV, Random, 95% CI)	9.13 [-2.95, 21.21]
7.2 CSA versus placebo/no treatment at 6 months	1	16	Mean Difference (IV, Random, 95% CI)	12.26 [-7.88, 32.40]
7.3 CSA versus placebo/no treatment at 12 months	2	36	Mean Difference (IV, Random, 95% CI)	6.42 [-9.48, 22.33]
7.4 CSA versus placebo/no treatment at 24 months	1	8	Mean Difference (IV, Random, 95% CI)	7.81 [-27.36, 42.98]
7.5 CSA+steroids versus ACEi/ARB at 9 months	1	10	Mean Difference (IV, Random, 95% CI)	9.20 [-19.01, 37.41]

7.6 CSA+steroids versus alkylating agents+steroids at 9 months	1	9	Mean Difference (IV, Random, 95% CI)	9.30 [-18.44, 37.04]
7.7 CSA+steroids versus azathioprine+steroids at 6 months	1	23	Mean Difference (IV, Random, 95% CI)	17.5 [-3.34, 38.34]
7.8 CSA+steroids versus azathioprine+steroids at 12 months	1	23	Mean Difference (IV, Random, 95% CI)	17.70 [-6.07, 41.47]
7.9 CSA+steroids versus azathioprine+steroids at 18 months	1	23	Mean Difference (IV, Random, 95% CI)	21.60 [-2.40, 45.60]
7.10 CSA+steroids versus azathioprine+steroids at 24 months	1	23	Mean Difference (IV, Random, 95% CI)	21.90 [-1.66, 45.46]
7.11 CSA+steroids versus azathioprine+steroids at 30 months	1	23	Mean Difference (IV, Random, 95% CI)	25.40 [-0.04, 50.84]
7.12 CSA+steroids versus azathioprine+steroids at 36 months	1	23	Mean Difference (IV, Random, 95% CI)	23.20 [-1.98, 48.38]
8 Complete or partial remission	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.1 CSA versus other treatments at final follow-up (9-60 months) (ITT analysis)	5	185	Risk Ratio (IV, Random, 95% CI)	1.03 [0.73, 1.44]
8.2 CSA versus placebo/no treatment at final follow-up (21 months) (ITT analysis)	1	21	Risk Ratio (IV, Random, 95% CI)	0.55 [0.13, 2.38]
8.3 CSA versus placebo/no treatment at 12 months	1	21	Risk Ratio (IV, Random, 95% CI)	0.55 [0.13, 2.38]
8.4 CSA+steroids versus placebo/no treatment at final follow-up (60 months) (ITT analysis)	1	33	Risk Ratio (IV, Random, 95% CI)	0.94 [0.59, 1.49]
8.5 CSA+steroids versus placebo/no treatment at 60 months	1	33	Risk Ratio (IV, Random, 95% CI)	0.94 [0.59, 1.49]
8.6 CSA+steroids versus ACEi/ARB at final follow-up (9 months) (ITT analysis)	1	10	Risk Ratio (IV, Random, 95% CI)	0.64 [0.31, 1.30]
8.7 CSA+steroids versus ACEi/ARB at 9 months	1	10	Risk Ratio (IV, Random, 95% CI)	0.64 [0.31, 1.30]
8.8 CSA+steroids versus steroids at final follow-up (18 months) (ITT analysis)	1	51	Risk Ratio (IV, Random, 95% CI)	3.01 [0.95, 9.52]
8.9 CSA+steroids versus steroids at 6 months	1	51	Risk Ratio (IV, Random, 95% CI)	3.45 [1.54, 7.71]
8.10 CSA+steroids versus steroids at 12 months	1	51	Risk Ratio (IV, Random, 95% CI)	3.56 [1.15, 10.99]
8.11 CSA+steroids versus steroids at 18 months	1	51	Risk Ratio (IV, Random, 95% CI)	3.01 [0.95, 9.52]

8.12 CSA+steroids versus alkylating agents+steroids at final follow-up (9-60 months) (ITT analysis)	2	47	Risk Ratio (IV, Random, 95% CI)	1.01 [0.46, 2.22]
8.13 CSA+steroids versus alkylating agents+steroids at 9 months	1	9	Risk Ratio (IV, Random, 95% CI)	0.65 [0.31, 1.35]
8.14 CSA+steroids versus alkylating agents+steroids at 60 months	1	38	Risk Ratio (IV, Random, 95% CI)	1.45 [0.84, 2.53]
8.15 CSA+steroids versus azathioprine+steroids at final follow-up (36 months) (ITT analysis)	1	23	Risk Ratio (IV, Random, 95% CI)	1.3 [0.68, 2.48]
8.16 CSA+steroids versus azathioprine+steroids at 6 months	1	23	Risk Ratio (IV, Random, 95% CI)	0.59 [0.30, 1.15]
8.17 CSA+steroids versus azathioprine+steroids at 12 months	1	23	Risk Ratio (IV, Random, 95% CI)	0.54 [0.29, 1.03]
8.18 CSA+steroids versus azathioprine+steroids at 18 months	1	23	Risk Ratio (IV, Random, 95% CI)	0.87 [0.61, 1.23]
8.19 CSA+steroids versus azathioprine+steroids at 24 months	1	23	Risk Ratio (IV, Random, 95% CI)	0.87 [0.61, 1.23]
8.20 CSA+steroids versus azathioprine+steroids at 30 months	1	23	Risk Ratio (IV, Random, 95% CI)	1.3 [0.77, 2.21]
8.21 CSA+steroids versus azathioprine+steroids at 36 months	1	23	Risk Ratio (IV, Random, 95% CI)	1.3 [0.68, 2.48]
9 Complete remission	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.1 CSA versus other treatments at final follow-up (9-60 months) (ITT analysis)	5	185	Risk Ratio (IV, Random, 95% CI)	1.03 [0.52, 2.03]
9.2 CSA versus placebo/no treatment at final follow-up (21 months) (ITT analysis)	1	21	Risk Ratio (IV, Random, 95% CI)	0.36 [0.02, 8.03]
9.3 CSA versus placebo/no treatment at 12 months	1	21	Risk Ratio (IV, Random, 95% CI)	0.36 [0.02, 8.03]
9.4 CSA+steroids versus placebo/no treatment at final follow-up (60 months) (ITT analysis)	1	33	Risk Ratio (IV, Random, 95% CI)	1.25 [0.29, 5.44]
9.5 CSA+steroids versus placebo/no treatment at 60 months	1	33	Risk Ratio (IV, Random, 95% CI)	1.25 [0.29, 5.44]
9.6 CSA+steroids versus ACEi/ARB at final follow-up (9 months) (ITT analysis)	1	10	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

9.7 CSA+steroids versus ACEi/ARB at 9 months	1	10	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.8 CSA+steroids versus steroids at final follow-up (18 months) (ITT analysis)	1	51	Risk Ratio (IV, Random, 95% CI)	1.64 [0.16, 16.99]
9.9 CSA+steroids versus steroids at 6 months	1	51	Risk Ratio (IV, Random, 95% CI)	1.64 [0.16, 16.99]
9.10 CSA+steroids versus steroids at 12 months	1	51	Risk Ratio (IV, Random, 95% CI)	1.64 [0.16, 16.99]
9.11 CSA+steroids versus steroids at 18 months	1	51	Risk Ratio (IV, Random, 95% CI)	1.64 [0.16, 16.99]
9.12 CSA+steroids versus alkylating agents+steroids at final follow-up (9-60 months) (ITT analysis)	2	47	Risk Ratio (IV, Random, 95% CI)	0.74 [0.27, 2.01]
9.13 CSA+steroids versus alkylating agents+steroids at 9 months	1	9	Risk Ratio (IV, Random, 95% CI)	0.4 [0.05, 2.98]
9.14 CSA+steroids versus alkylating agents+steroids at 60 months	1	38	Risk Ratio (IV, Random, 95% CI)	0.91 [0.29, 2.86]
9.15 CSA+steroids versus azathioprine+steroids at final follow-up (36 months) (ITT analysis)	1	23	Risk Ratio (IV, Random, 95% CI)	1.95 [0.40, 9.54]
9.16 CSA+steroids versus azathioprine+steroids at 6 months	1	23	Risk Ratio (IV, Random, 95% CI)	0.42 [0.02, 9.43]
9.17 CSA+steroids versus azathioprine+steroids at 12 months	1	23	Risk Ratio (IV, Random, 95% CI)	3.82 [0.17, 84.90]
9.18 CSA+steroids versus azathioprine+steroids at 18 months	1	23	Risk Ratio (IV, Random, 95% CI)	2.60 [0.59, 11.46]
9.19 CSA+steroids versus azathioprine+steroids at 24 months	1	23	Risk Ratio (IV, Random, 95% CI)	1.3 [0.43, 3.96]
9.20 CSA+steroids versus azathioprine+steroids at 30 months	1	23	Risk Ratio (IV, Random, 95% CI)	2.60 [0.59, 11.46]
9.21 CSA+steroids versus azathioprine+steroids at 36 months	1	23	Risk Ratio (IV, Random, 95% CI)	1.95 [0.40, 9.54]
10 Partial remission	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
10.1 CSA versus other treatments at final follow-up (9-60 months) (ITT analysis)	5	185	Risk Ratio (IV, Random, 95% CI)	0.84 [0.54, 1.31]
10.2 CSA versus placebo/no treatment at final follow-up (21 months) (ITT analysis)	1	21	Risk Ratio (IV, Random, 95% CI)	0.73 [0.15, 3.53]

10.3 CSA versus placebo/no treatment at 12 months	1	21	Risk Ratio (IV, Random, 95% CI)	0.73 [0.15, 3.53]
10.4 CSA+steroids versus placebo/no treatment at final follow-up (60 months) (ITT analysis)	1	33	Risk Ratio (IV, Random, 95% CI)	0.83 [0.41, 1.69]
10.5 CSA+steroids versus placebo/no treatment at 60 months	1	33	Risk Ratio (IV, Random, 95% CI)	0.83 [0.41, 1.69]
10.6 CSA+steroids versus ACEi/ARB at final follow-up (9 months) (ITT analysis)	1	10	Risk Ratio (IV, Random, 95% CI)	0.64 [0.31, 1.30]
10.7 CSA+steroids versus ACEi/ARB at 9 months	1	10	Risk Ratio (IV, Random, 95% CI)	0.64 [0.31, 1.30]
10.8 CSA+steroids versus steroids at final follow-up (18 months) (ITT analysis)	1	51	Risk Ratio (IV, Random, 95% CI)	3.70 [0.89, 15.44]
10.9 CSA+steroids versus steroids at 6 months	1	51	Risk Ratio (IV, Random, 95% CI)	3.90 [1.54, 9.85]
10.10 CSA+steroids versus steroids at 12 months	1	51	Risk Ratio (IV, Random, 95% CI)	4.52 [1.11, 18.36]
10.11 CSA+steroids versus steroids at 18 months	1	51	Risk Ratio (IV, Random, 95% CI)	3.70 [0.89, 15.44]
10.12 CSA+steroids versus alkylating agents+steroids at final follow-up (9-60 months) (ITT analysis)	2	47	Risk Ratio (IV, Random, 95% CI)	0.47 [0.12, 1.89]
10.13 CSA+steroids versus alkylating agents+steroids at 9 months	1	9	Risk Ratio (IV, Random, 95% CI)	0.8 [0.19, 3.42]
10.14 CSA+steroids versus alkylating agents+steroids at 60 months	1	38	Risk Ratio (IV, Random, 95% CI)	0.18 [0.02, 1.48]
10.15 CSA+steroids versus azathioprine+steroids at final follow-up (36 months) (ITT analysis)	1	23	Risk Ratio (IV, Random, 95% CI)	1.04 [0.37, 2.90]
10.16 CSA+steroids versus azathioprine+steroids at 6 months	1	23	Risk Ratio (IV, Random, 95% CI)	0.65 [0.33, 1.29]
10.17 CSA+steroids versus azathioprine+steroids at 12 months	1	23	Risk Ratio (IV, Random, 95% CI)	0.43 [0.20, 0.94]
10.18 CSA+steroids versus azathioprine+steroids at 18 months	1	23	Risk Ratio (IV, Random, 95% CI)	0.52 [0.23, 1.18]
10.19 CSA+steroids versus azathioprine+steroids at 24 months	1	23	Risk Ratio (IV, Random, 95% CI)	0.65 [0.27, 1.56]

10.20 CSA+steroids versus azathioprine+steroids at 30 months	1	23	Risk Ratio (IV, Random, 95% CI)	0.87 [0.33, 2.26]
10.21 CSA+steroids versus azathioprine+steroids at 36 months	1	23	Risk Ratio (IV, Random, 95% CI)	1.04 [0.37, 2.90]
11 Final proteinuria	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 CSA versus other treatments at final follow-up (9-36 months)	5	131	Mean Difference (IV, Random, 95% CI)	0.61 [-0.87, 2.09]
11.2 CSA versus placebo/no treatment at 12 months	2	38	Mean Difference (IV, Random, 95% CI)	0.94 [-6.70, 8.58]
11.3 CSA versus placebo/no treatment at 21 months	1	17	Mean Difference (IV, Random, 95% CI)	-4.70 [-9.04, -0.36]
11.4 CSA+steroids versus ACEi/ARB at 9 months	1	10	Mean Difference (IV, Random, 95% CI)	0.40 [-1.10, 1.90]
11.5 CSA+steroids versus steroids at 6 months	1	51	Mean Difference (IV, Random, 95% CI)	-2.8 [-6.54, 0.94]
11.6 CSA+steroids versus steroids at 12 months	1	51	Mean Difference (IV, Random, 95% CI)	0.40 [-2.08, 2.88]
11.7 CSA+steroids versus steroids at 18 months	1	51	Mean Difference (IV, Random, 95% CI)	0.5 [-2.49, 3.49]
11.8 CSA+steroids versus alkylating agents+steroids at 9 months	1	9	Mean Difference (IV, Random, 95% CI)	1.4 [-0.37, 3.17]
11.9 CSA+steroids versus azathioprine+steroids at 6 months	1	23	Mean Difference (IV, Random, 95% CI)	2.50 [-0.05, 5.05]
11.10 CSA+steroids versus azathioprine+steroids at 12 months	1	23	Mean Difference (IV, Random, 95% CI)	4.80 [0.33, 9.27]
11.11 CSA+steroids versus azathioprine+steroids at 18 months	1	23	Mean Difference (IV, Random, 95% CI)	3.40 [1.00, 7.80]
11.12 CSA+steroids versus azathioprine+steroids at 24 months	1	23	Mean Difference (IV, Random, 95% CI)	2.4 [-0.91, 5.71]
11.13 CSA+steroids versus azathioprine+steroids at 30 months	1	23	Mean Difference (IV, Random, 95% CI)	1.80 [-1.67, 5.27]
11.14 CSA+steroids versus azathioprine+steroids at 36 months	1	23	Mean Difference (IV, Random, 95% CI)	1.00 [-2.02, 4.02]
12 Temporary or permanent discontinuation or hospitalisation due to adverse events	6	202	Risk Ratio (IV, Random, 95% CI)	1.18 [0.06, 23.79]
12.1 CSA versus placebo/no treatment	2	38	Risk Ratio (IV, Random, 95% CI)	5.45 [0.29, 101.55]
12.2 CSA+steroids versus placebo/no treatment	1	33	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

12.3 CSA+steroids versus ACEi/ARB	1	10	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.4 CSA+steroids versus steroids	1	51	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.5 CSA+steroids versus alkylating agents+steroids	2	47	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.6 CSA+steroids versus azathioprine+steroids	1	23	Risk Ratio (IV, Random, 95% CI)	0.25 [0.01, 4.78]

Comparison 7. Cyclosporine (CSA) (1.5 mg/kg, twice/d) versus CSA (3.0 mg/kg, once/d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete remission at 12 months	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Final proteinuria at 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 8. Tacrolimus (TAC) versus other treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or ESKD (dialysis/transplantation) (ITT analysis)	2	121	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.20]
1.1 TAC versus placebo/no treatment at final follow-up (30 months)	1	48	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.20]
1.2 TAC+steroids versus alkylating agents+steroids at final follow-up (12 months)	1	73	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Death (ITT analysis)	2	121	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.20]
2.1 TAC versus placebo/no treatment at final follow-up (30 months)	1	48	Risk Ratio (IV, Random, 95% CI)	0.31 [0.01, 7.20]
2.2 TAC+steroids versus alkylating agents+steroids at final follow-up (12 months)	1	73	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 ESKD (dialysis/transplantation) (ITT analysis)	2	121	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.1 TAC versus placebo/no treatment at final follow-up (30 months)	1	48	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 TAC+steroids versus alkylating agents+steroids at final follow-up (12 months)	1	73	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

4 50% increase in serum creatinine	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1 TAC versus other treatments at final follow-up (12-30 months) (ITT analysis)	2	121	Risk Ratio (IV, Random, 95% CI)	0.15 [0.02, 1.18]
4.2 TAC versus placebo/no treatment at final follow-up (30 months) (ITT analysis)	1	48	Risk Ratio (IV, Random, 95% CI)	0.15 [0.02, 1.18]
4.3 TAC versus placebo/no treatment at 6 months	1	48	Risk Ratio (IV, Random, 95% CI)	0.10 [0.01, 1.81]
4.4 TAC versus placebo/no treatment at 12 months	1	48	Risk Ratio (IV, Random, 95% CI)	0.15 [0.02, 1.18]
4.5 TAC versus placebo/no treatment at 18 months	1	48	Risk Ratio (IV, Random, 95% CI)	0.15 [0.02, 1.18]
4.6 TAC versus placebo/no treatment at 30 months	1	48	Risk Ratio (IV, Random, 95% CI)	0.15 [0.02, 1.18]
4.7 TAC+steroids versus alkylating agents+steroids at final follow-up (12 months) (ITT analysis)	1	73	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.8 TAC+steroids versus alkylating agents+steroids at 6 months	1	73	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.9 TAC+steroids versus alkylating agents+steroids at 12 months	1	60	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Final GFR [mL/min/1.73 m ²]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 TAC versus other treatments at final follow-up (12 months)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 TAC+steroids versus alkylating agents+steroids at 12 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Complete or partial remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.1 TAC versus other treatments at final follow-up (12-30 months) (ITT analysis)	2	121	Risk Ratio (IV, Random, 95% CI)	1.19 [0.91, 1.55]
6.2 TAC versus placebo/no treatment at final follow-up (30 months) (ITT analysis)	1	48	Risk Ratio (IV, Random, 95% CI)	1.31 [0.60, 2.87]
6.3 TAC versus placebo/no treatment at 6 months	1	48	Risk Ratio (IV, Random, 95% CI)	4.29 [1.41, 13.04]
6.4 TAC versus placebo/no treatment at 12 months	1	48	Risk Ratio (IV, Random, 95% CI)	3.31 [1.47, 7.47]
6.5 TAC versus placebo/no treatment at 18 months	1	48	Risk Ratio (IV, Random, 95% CI)	2.91 [1.41, 6.00]
6.6 TAC versus placebo/no treatment at 30 months	1	48	Risk Ratio (IV, Random, 95% CI)	1.31 [0.60, 2.87]
6.7 TAC+steroids versus alkylating agents+steroids at final follow-up (12 months) (ITT analysis)	1	73	Risk Ratio (IV, Random, 95% CI)	1.18 [0.89, 1.56]

6.8 TAC+steroids versus alkylating agents+steroids at 6 months	1	73	Risk Ratio (IV, Random, 95% CI)	1.31 [0.99, 1.73]
6.9 TAC+steroids versus alkylating agents+steroids at 12 months	1	60	Risk Ratio (IV, Random, 95% CI)	1.10 [0.92, 1.32]
7 Complete remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7.1 TAC versus other treatments at final follow-up (12-30 months) (ITT analysis)	2	121	Risk Ratio (IV, Random, 95% CI)	0.91 [0.47, 1.74]
7.2 TAC versus placebo/no treatment at final follow-up (30 months) (ITT analysis)	1	48	Risk Ratio (IV, Random, 95% CI)	0.55 [0.15, 2.06]
7.3 TAC versus placebo/no treatment at 6 months	1	48	Risk Ratio (IV, Random, 95% CI)	1.38 [0.25, 7.53]
7.4 TAC versus placebo/no treatment at 12 months	1	48	Risk Ratio (IV, Random, 95% CI)	1.38 [0.45, 4.28]
7.5 TAC versus placebo/no treatment at 18 months	1	48	Risk Ratio (IV, Random, 95% CI)	2.45 [0.74, 8.15]
7.6 TAC versus placebo/no treatment at 30 months	1	48	Risk Ratio (IV, Random, 95% CI)	0.55 [0.15, 2.06]
7.7 TAC+steroids versus alkylating agents+steroids at final follow-up (6 months) (ITT analysis)	1	73	Risk Ratio (IV, Random, 95% CI)	1.07 [0.50, 2.26]
7.8 TAC+steroids versus alkylating agents+steroids at 6 months	1	73	Risk Ratio (IV, Random, 95% CI)	1.07 [0.50, 2.26]
8 Partial remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.1 TAC versus other treatments at final follow-up (12-30 months) (ITT analysis)	2	121	Risk Ratio (IV, Random, 95% CI)	1.60 [0.99, 2.59]
8.2 TAC versus placebo/no treatment at final follow-up (30 months) (ITT analysis)	1	48	Risk Ratio (IV, Random, 95% CI)	3.22 [0.74, 13.95]
8.3 TAC versus placebo/no treatment at 6 months	1	48	Risk Ratio (IV, Random, 95% CI)	10.12 [1.42, 72.37]
8.4 TAC versus placebo/no treatment at 12 months	1	48	Risk Ratio (IV, Random, 95% CI)	11.04 [1.56, 78.36]
8.5 TAC versus placebo/no treatment at 18 months	1	48	Risk Ratio (IV, Random, 95% CI)	3.37 [1.07, 10.59]
8.6 TAC versus placebo/no treatment at 30 months	1	48	Risk Ratio (IV, Random, 95% CI)	3.22 [0.74, 13.95]
8.7 TAC+steroids versus alkylating agents+steroids at final follow-up (6 months) (ITT analysis)	1	73	Risk Ratio (IV, Random, 95% CI)	1.48 [0.89, 2.45]
8.8 TAC+steroids versus alkylating agents+steroids at 6 months	1	73	Risk Ratio (IV, Random, 95% CI)	1.48 [0.89, 2.45]
9 Final proteinuria	3		Mean Difference (IV, Random, 95% CI)	Subtotals only

9.1 TAC versus other treatment at final follow-up (9-18 months)	3	132	Mean Difference (IV, Random, 95% CI)	-1.06 [-1.66, -0.47]
9.2 TAC versus placebo/no treatment at final follow-up (18 months)	1	48	Mean Difference (IV, Random, 95% CI)	-1.30 [-3.75, 1.15]
9.3 TAC versus placebo/no treatment at 12 months	1	48	Mean Difference (IV, Random, 95% CI)	-2.50 [-4.70, -0.30]
9.4 TAC versus placebo/no treatment at 18 months	1	48	Mean Difference (IV, Random, 95% CI)	-1.30 [-3.75, 1.15]
9.5 TAC+steroids versus alkylating agents+steroids at final follow-up (9-12 months)	2	84	Mean Difference (IV, Random, 95% CI)	-1.03 [-1.69, -0.37]
9.6 TAC+steroids versus alkylating agents+steroids at 6 months	1	60	Mean Difference (IV, Random, 95% CI)	-1.25 [-2.23, -0.27]
9.7 TAC+steroids versus alkylating agents+steroids at 9 months	1	24	Mean Difference (IV, Random, 95% CI)	-1.2 [-1.87, -0.53]
9.8 TAC+steroids versus alkylating agents+steroids at 12 months	1	60	Mean Difference (IV, Random, 95% CI)	-0.36 [-1.80, 1.08]
10 Temporary or permanent discontinuation or hospitalisation due to adverse events	2	121	Risk Ratio (IV, Random, 95% CI)	1.74 [0.47, 6.45]
10.1 TAC versus placebo/no treatment	1	48	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 TAC+steroids versus alkylating agents+steroids	1	73	Risk Ratio (IV, Random, 95% CI)	1.74 [0.47, 6.45]

Comparison 9. Mycophenolate mofetil (MMF) versus other treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or ESKD (dialysis/transplantation) (ITT analysis)	3	77	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.1 MMF versus placebo/no treatment at final follow-up (12 months)	1	36	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 MMF+steroids versus alkylating agents+steroids at final follow-up (15-17 months)	2	41	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Death (ITT analysis)	3	77	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.1 MMF versus placebo/no treatment at final follow-up (12 months)	1	36	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

2.2 MMF+steroids versus alkylating agents+steroids at final follow-up (15-17 months)	2	41	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 ESKD (dialysis/transplantation) (ITT analysis)	3	77	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.1 MMF versus placebo/no treatment at final follow-up (12 months)	1	36	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 MMF+steroids versus alkylating agents+steroids at final follow-up (15-17 months)	2	41	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 100% increase in serum creatinine	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4.1 MMF versus other treatments at final follow-up (12 months) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 MMF versus placebo/no treatment at final follow-up (12 months) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 MMF versus placebo/no treatment at 12 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 50% increase in serum creatinine	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5.1 MMF versus other treatments at final follow-up (12 months) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 MMF versus placebo/no treatment at final follow-up (12 months) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 MMF versus placebo/no treatment at 12 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Final GFR [mL/min/1.73 m²]	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 MMF versus other treatments+steroids at final follow-up (12-17 months)	2	51	Mean Difference (IV, Random, 95% CI)	7.12 [-2.16, 16.41]
6.2 MMF versus placebo/no treatment at 6 months	1	35	Mean Difference (IV, Random, 95% CI)	12.17 [-4.10, 28.44]
6.3 MMF versus placebo/no treatment at 12 months	1	32	Mean Difference (IV, Random, 95% CI)	12.37 [-4.93, 29.67]
6.4 MMF+steroids versus alkylating agents+steroids at 17 months	1	19	Mean Difference (IV, Random, 95% CI)	5.0 [-6.00, 16.00]
7 Complete or partial remission	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7.1 MMF versus other treatments at final follow-up (12-24 months) (ITT analysis)	3	77	Risk Ratio (IV, Random, 95% CI)	0.88 [0.58, 1.35]
7.2 MMF versus placebo/no treatment at final follow-up (12 months) (ITT analysis)	1	36	Risk Ratio (IV, Random, 95% CI)	0.89 [0.39, 2.03]
7.3 MMF versus placebo/no treatment at 6 months	1	35	Risk Ratio (IV, Random, 95% CI)	1.57 [0.44, 5.60]

7.4 MMF versus placebo/no treatment at 12 months	1	32	Risk Ratio (IV, Random, 95% CI)	1.13 [0.52, 2.48]
7.5 MMF+steroids versus alkylating agents+steroids at final follow-up (17-24 months) (ITT analysis)	2	41	Risk Ratio (IV, Random, 95% CI)	0.88 [0.53, 1.44]
7.6 MMF+steroids versus alkylating agents+steroids at 15-17 months	2	38	Risk Ratio (IV, Random, 95% CI)	0.98 [0.63, 1.54]
7.7 MMF+steroids versus alkylating agents+steroids at 24 months	1	19	Risk Ratio (IV, Random, 95% CI)	0.73 [0.31, 1.69]
8 Complete remission	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.1 MMF versus other treatments at final follow-up (12-24 months) (ITT analysis)	3	77	Risk Ratio (IV, Random, 95% CI)	0.99 [0.35, 2.82]
8.2 MMF versus placebo/no treatment at final follow-up (12 months) (ITT analysis)	1	36	Risk Ratio (IV, Random, 95% CI)	0.45 [0.04, 4.50]
8.3 MMF versus placebo/no treatment at 6 months	1	35	Risk Ratio (IV, Random, 95% CI)	2.84 [0.12, 65.34]
8.4 MMF versus placebo/no treatment at 12 months	1	32	Risk Ratio (IV, Random, 95% CI)	0.57 [0.06, 5.64]
8.5 MMF+steroids versus alkylating agents+steroids at final follow-up (17-24 months) (ITT analysis)	2	41	Risk Ratio (IV, Random, 95% CI)	1.16 [0.29, 4.69]
8.6 MMF+steroids versus alkylating agents+steroids at 15-17 months	2	38	Risk Ratio (IV, Random, 95% CI)	1.20 [0.22, 6.65]
8.7 MMF+steroids versus alkylating agents+steroids at 24 months	1	19	Risk Ratio (IV, Random, 95% CI)	0.48 [0.10, 2.26]
9 Partial remission	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.1 MMF versus other treatments at final follow-up (12-24 months) (ITT analysis)	3	77	Risk Ratio (IV, Random, 95% CI)	0.83 [0.41, 1.70]
9.2 MMF versus placebo/no treatment at final follow-up (12 months) (ITT analysis)	1	36	Risk Ratio (IV, Random, 95% CI)	1.07 [0.40, 2.89]
9.3 MMF versus placebo/no treatment at 6 months	1	35	Risk Ratio (IV, Random, 95% CI)	1.26 [0.33, 4.82]
9.4 MMF versus placebo/no treatment at 12 months	1	32	Risk Ratio (IV, Random, 95% CI)	1.36 [0.52, 3.56]
9.5 MMF+steroids versus alkylating agents+steroids at final follow-up (17-24 months) (ITT analysis)	2	41	Risk Ratio (IV, Random, 95% CI)	0.64 [0.19, 2.08]
9.6 MMF+steroids versus alkylating agents+steroids at 15-17 months	2	38	Risk Ratio (IV, Random, 95% CI)	0.66 [0.24, 1.84]

9.7 MMF+steroids versus alkylating agents+steroids at 24 months	1	19	Risk Ratio (IV, Random, 95% CI)	1.09 [0.23, 5.09]
10 Final proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.1 MMF versus other treatments+steroids at final follow-up (15 months)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 MMF+steroids versus alkylating agents+steroids at 15 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 Temporary or permanent discontinuation or hospitalisation due to adverse events	3	77	Risk Ratio (IV, Random, 95% CI)	0.81 [0.12, 5.29]
11.1 MMF versus placebo/no treatment	1	36	Risk Ratio (IV, Random, 95% CI)	8.10 [0.47, 140.24]
11.2 MMF+steroids versus alkylating agents+steroids	2	41	Risk Ratio (IV, Random, 95% CI)	0.35 [0.08, 1.59]

Comparison 10. Mycophenolate mofetil (MMF)+cyclosporine (CSA) versus CSA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete or partial remission	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.1 At final follow-up (12 months) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 At 6 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 At 12 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Complete remission	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.1 At final follow-up (12 months) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 At 6 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 At 12 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Partial remission	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3.1 At final follow-up (12 months) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 At 6 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 At 12 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 11. Adrenocorticotrophic hormone (ACTH) versus other treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or ESKD (dialysis/transplantation) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.1 ACTH versus alkylating agents+steroids at final follow-up (22 months)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Death (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.1 ACTH versus alkylating agents+steroids at final follow-up (22 months)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 ESKD (dialysis/transplantation) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3.1 ACTH versus alkylating agents+steroids at final follow-up (22 months)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 100% increase in serum creatinine	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4.1 ACTH versus alkylating agents+steroids at 22 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 50% increase in serum creatinine	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5.1 ACTH versus alkylating agents+steroids at 22 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Final serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 ACTH versus alkylating agents+steroids at 22 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Complete or partial remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
7.1 ACTH versus other treatments at final follow-up (21-22 months) (ITT analysis)	2	62	Risk Ratio (IV, Random, 95% CI)	2.55 [0.45, 14.55]
7.2 ACTH versus placebo/no treatment at final follow-up (21 months) (ITT analysis)	1	30	Risk Ratio (IV, Random, 95% CI)	7.00 [1.91, 25.62]
7.3 ACTH versus placebo/no treatment at 9 months	1	30	Risk Ratio (IV, Random, 95% CI)	10.33 [2.25, 47.53]
7.4 ACTH versus placebo/no treatment at 21 months	1	30	Risk Ratio (IV, Random, 95% CI)	7.00 [1.91, 25.62]
7.5 ACTH versus alkylating agents+steroids at final follow-up (22 months) (ITT analysis)	1	32	Risk Ratio (IV, Random, 95% CI)	1.17 [0.83, 1.64]
7.6 ACTH versus alkylating agents+steroids at 6 months	1	32	Risk Ratio (IV, Random, 95% CI)	1.22 [0.71, 2.11]
7.7 ACTH versus alkylating agents+steroids at 12 months	1	32	Risk Ratio (IV, Random, 95% CI)	1.3 [0.83, 2.03]
7.8 ACTH versus alkylating agents+steroids at 18 months	1	22	Risk Ratio (IV, Random, 95% CI)	1.21 [0.88, 1.66]

7.9 ACTH versus alkylating agents+steroids at 24 months	1	18	Risk Ratio (IV, Random, 95% CI)	1.12 [0.83, 1.50]
8 Complete remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
8.1 ACTH versus other treatments at final follow-up (21-22 months) (ITT analysis)	2	62	Risk Ratio (IV, Random, 95% CI)	3.81 [0.75, 19.27]
8.2 ACTH versus placebo/no treatment at final follow-up (22 months) (ITT analysis)	1	30	Risk Ratio (IV, Random, 95% CI)	11.00 [1.62, 74.88]
8.3 ACTH versus placebo/no treatment at 9 months	1	30	Risk Ratio (IV, Random, 95% CI)	21.0 [1.34, 328.86]
8.4 ACTH versus placebo/no treatment at 21 months	1	30	Risk Ratio (IV, Random, 95% CI)	11.00 [1.62, 74.88]
8.5 ACTH versus alkylating agents+steroids at final follow-up (22 months) (ITT analysis)	1	32	Risk Ratio (IV, Random, 95% CI)	2.0 [0.75, 5.33]
8.6 ACTH versus alkylating agents+steroids at 6 months	1	32	Risk Ratio (IV, Random, 95% CI)	3.0 [0.35, 25.87]
8.7 ACTH versus alkylating agents+steroids at 12 months	1	32	Risk Ratio (IV, Random, 95% CI)	4.0 [1.00, 15.99]
8.8 ACTH versus alkylating agents+steroids at 18 months	1	22	Risk Ratio (IV, Random, 95% CI)	3.5 [0.92, 13.24]
8.9 ACTH versus alkylating agents+steroids at 24 months	1	18	Risk Ratio (IV, Random, 95% CI)	2.0 [0.71, 5.62]
9 Partial remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.1 ACTH versus other treatments at final follow-up (21-22 months) (ITT analysis)	2	62	Risk Ratio (IV, Random, 95% CI)	1.03 [0.33, 3.25]
9.2 ACTH versus placebo/no treatment at final follow-up (22 months) (ITT analysis)	1	30	Risk Ratio (IV, Random, 95% CI)	3.0 [0.35, 25.68]
9.3 ACTH versus placebo/no treatment at 9 months	1	30	Risk Ratio (IV, Random, 95% CI)	5.0 [0.66, 37.85]
9.4 ACTH versus placebo/no treatment at 21 months	1	30	Risk Ratio (IV, Random, 95% CI)	3.0 [0.35, 25.68]
9.5 ACTH versus alkylating agents+steroids at final follow-up (22 months) (ITT analysis)	1	32	Risk Ratio (IV, Random, 95% CI)	0.75 [0.34, 1.67]
9.6 ACTH versus alkylating agents+steroids at 6 months	1	32	Risk Ratio (IV, Random, 95% CI)	1.0 [0.50, 2.00]
9.7 ACTH versus alkylating agents+steroids at 12 months	1	32	Risk Ratio (IV, Random, 95% CI)	0.63 [0.26, 1.50]
9.8 ACTH versus alkylating agents+steroids at 18 months	1	22	Risk Ratio (IV, Random, 95% CI)	0.57 [0.23, 1.41]
9.9 ACTH versus alkylating agents+steroids at 24 months	1	18	Risk Ratio (IV, Random, 95% CI)	0.6 [0.20, 1.79]
10 Final proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.1 ACTH versus alkylating agents+steroids at 22 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

11 Temporary or permanent discontinuation or hospitalisation due to adverse events	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
11.1 ACTH versus alkylating agents+steroids	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 12. Azathioprine versus other treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or ESKD (dialysis/transplantation) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.1 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Death (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.1 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 ESKD (dialysis/transplantation) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3.1 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 100% increase in serum creatinine	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4.1 Azathioprine versus placebo/no treatment at final follow-up (12 months) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Azathioprine versus placebo/no treatment at 12 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 50% increase in serum creatinine	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5.1 Azathioprine versus placebo/no treatment at final follow-up (12 months) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Azathioprine versus placebo/no treatment at 12 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Final serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Azathioprine versus placebo/no treatment at 12 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Final GFR [mL/min/1.73 m ²]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

7.1 Azathioprine versus placebo/no treatment at 12 months	1	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Complete or partial remission	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
8.1 Azathioprine versus placebo/no treatment at 12 months	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9 Complete remission	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
9.1 Azathioprine versus placebo/no treatment at 12 months	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10 Partial remission	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
10.1 Azathioprine versus placebo/no treatment at 12 months	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 Final proteinuria	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
11.1 Azathioprine versus placebo/no treatment at 12 months	1	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12 Temporary or permanent discontinuation or hospitalisation due to adverse events	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
12.1 Azathioprine versus placebo/no treatment	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 13. Mizoribine versus other treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% increase in serum creatinine	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.1 Mizoribine versus placebo/no treatment at final follow-up (6 months) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Mizoribine versus placebo/no treatment at 6 months	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Complete or partial remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1 Mizoribine versus placebo/no treatment at final follow-up (6-24 months) (ITT analysis)	2	114	Risk Ratio (IV, Random, 95% CI)	2.24 [1.14, 4.38]
2.2 Mizoribine versus placebo/no treatment at 6 months	2	106	Risk Ratio (IV, Random, 95% CI)	1.68 [0.71, 3.98]
2.3 Mizoribine versus placebo/no treatment at 12 months	1	19	Risk Ratio (IV, Random, 95% CI)	1.45 [0.35, 6.09]
2.4 Mizoribine versus placebo/no treatment at 18 months	1	18	Risk Ratio (IV, Random, 95% CI)	4.45 [0.69, 28.87]

2.5 Mizoribine versus placebo/ no treatment at 24 months	1	17	Risk Ratio (IV, Random, 95% CI)	3.27 [0.51, 21.21]
3 Complete remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1 Mizoribine versus placebo/ no treatment at final follow-up (6-24 months) (ITT analysis)	2	114	Risk Ratio (IV, Random, 95% CI)	4.08 [0.73, 22.81]
3.2 Mizoribine versus placebo/ no treatment at 6 months	2	106	Risk Ratio (IV, Random, 95% CI)	3.57 [0.42, 30.62]
3.3 Mizoribine versus placebo/ no treatment at 12 months	1	19	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Mizoribine versus placebo/ no treatment at 18 months	1	18	Risk Ratio (IV, Random, 95% CI)	2.0 [0.09, 43.22]
3.5 Mizoribine versus placebo/ no treatment at 24 months	1	17	Risk Ratio (IV, Random, 95% CI)	4.08 [0.25, 68.01]
4 Partial remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1 Mizoribine versus placebo/ no treatment at final follow-up (6-24 months) (ITT analysis)	2	114	Risk Ratio (IV, Random, 95% CI)	1.89 [0.90, 3.97]
4.2 Mizoribine versus placebo/ no treatment at 6 months	2	106	Risk Ratio (IV, Random, 95% CI)	1.62 [0.79, 3.32]
4.3 Mizoribine versus placebo/ no treatment at 12 months	1	19	Risk Ratio (IV, Random, 95% CI)	1.45 [0.35, 6.09]
4.4 Mizoribine versus placebo/ no treatment at 18 months	1	18	Risk Ratio (IV, Random, 95% CI)	3.82 [0.58, 25.35]
4.5 Mizoribine versus placebo/ no treatment at 24 months	1	17	Risk Ratio (IV, Random, 95% CI)	1.64 [0.21, 12.49]
5 Temporary or permanent discontinuation or hospitalisation due to adverse events	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5.1 Mizoribine versus placebo/ no treatment	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 14. Tripterygium wilfordii versus other treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or ESKD (dialysis/transplantation) (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.1 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at final follow-up (12 months)	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Death (ITT analysis)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

2.1 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at final follow-up (12 months)	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 ESKD (dialysis/transplantation) (ITT analysis)	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
3.1 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at final follow-up (12 months)	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 100% increase in serum creatinine (ITT analysis)	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
4.1 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at final follow-up (12 months)	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 50% increase in serum creatinine	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
5.1 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at final follow-up (12 months) (ITT analysis)	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at 12 months	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Complete or partial remission	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
6.1 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at final follow-up (12 months) (ITT analysis)	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at 6 months	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at 12 months	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Complete remission	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
7.1 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at final follow-up (12 months) (ITT analysis)	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at 6 months	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

7.3 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at 12 months	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Partial remission	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
8.1 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at final follow-up (12 months) (ITT analysis)	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at 6 months	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Tripterygium wilfordii+steroids versus Tripterygium wilfordii at 12 months	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9 Temporary or permanent discontinuation or hospitalisation due to adverse events	1	Risk Ratio (IV, Random, 95% CI)	Totals not selected
9.1 Tripterygium wilfordii+steroids versus Tripterygium wilfordii	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 15. Early versus late immunosuppressive treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or ESKD (dialysis/transplantation)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Death	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 ESKD (dialysis/transplantation)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Final serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Final GFR [mL/min/1.73 m ²]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Complete or partial remission	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Complete remission	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8 Partial remission	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
9 Final proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Temporary or permanent discontinuation or hospitalisation due to adverse events	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, Outcome 1 Death or ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 1 Death or ESKD (dialysis/transplantation) (ITT analysis)

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Analysis 1.2. Comparison 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, Outcome 2 Death (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 2 Death (ITT analysis)

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Analysis 1.3. Comparison 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, Outcome 3 ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 3 ESKD (dialysis/transplantation) (ITT analysis)

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Analysis 1.4. Comparison 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, Outcome 4 100% increase in serum creatinine (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 4 100% increase in serum creatinine (ITT analysis)

(Continued ...)

Analysis 1.5. Comparison 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, Outcome 5 50% increase in serum creatinine (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 5 50% increase in serum creatinine (ITT analysis)

(Continued ...)

Analysis 1.6. Comparison 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, Outcome 6 Final serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 6 Final serum creatinine

Analysis 1.7. Comparison 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, Outcome 7 Final GFR [mL/min/1.73 m²].

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 7 Final GFR [mL/min/1.73 m²]

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Analysis 1.8. Comparison 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, Outcome 8 Complete or partial remission (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 8 Complete or partial remission (ITT analysis)

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Analysis 1.9. Comparison 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, Outcome 9 Complete remission (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 9 Complete remission (ITT analysis)

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Analysis 1.10. Comparison 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, Outcome 10 Partial remission (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 10 Partial remission (ITT analysis)

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Analysis 1.1.1. Comparison 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, Outcome 11 Final proteinuria.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 11 Final proteinuria

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Analysis 1.12. Comparison 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments, Outcome 12 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 1 Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 12 Temporary or permanent discontinuation or hospitalisation due to adverse events

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Analysis 2.1. Comparison 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments, Outcome 1 Death or ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 1 Death or ESKD (dialysis/transplantation) (ITT analysis)

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Study or subgroup	Steroids n/N	Control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Total events: 16 (Steroids), 22 (Control)					
Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 2.67$, $df = 2$ ($P = 0.26$); $I^2 = 25\%$					
Test for overall effect: $Z = 0.72$ ($P = 0.47$)					
Test for subgroup differences: $\chi^2 = 2.61$, $df = 1$ ($P = 0.11$), $I^2 = 62\%$					

Analysis 2.2. Comparison 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments, Outcome 2 Death (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 2 Death (ITT analysis)

Study or subgroup	Steroids n/N	Control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 At final follow-up (24 months)					
Coggins 1979	0/34	2/38		23.9 %	0.22 [0.01, 4.48]
Subtotal (95% CI)	34	38		23.9 %	0.22 [0.01, 4.48]
Total events: 0 (Steroids), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.98$ ($P = 0.33$)					
2 At final follow-up (48 months)					
Cameron 1990	1/52	4/51		39.0 %	0.25 [0.03, 2.12]
Cattran 1989	3/64	1/56		37.1 %	2.63 [0.28, 24.52]
Subtotal (95% CI)	116	107		76.1 %	0.79 [0.08, 8.04]
Total events: 4 (Steroids), 5 (Control)					
Heterogeneity: $\tau^2 = 1.55$; $\chi^2 = 2.24$, $df = 1$ ($P = 0.13$); $I^2 = 55\%$					
Test for overall effect: $Z = 0.20$ ($P = 0.84$)					
Total (95% CI)	150	145		100.0 %	0.58 [0.11, 2.97]
Total events: 4 (Steroids), 7 (Control)					
Heterogeneity: $\tau^2 = 0.58$; $\chi^2 = 2.75$, $df = 2$ ($P = 0.25$); $I^2 = 27\%$					
Test for overall effect: $Z = 0.66$ ($P = 0.51$)					
Test for subgroup differences: $\chi^2 = 0.42$, $df = 1$ ($P = 0.51$), $I^2 = 0.0\%$					

Analysis 2.3. Comparison 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments, Outcome 3 ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 3 ESKD (dialysis/transplantation) (ITT analysis)

Analysis 2.4. Comparison 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments, Outcome 4 100% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 4 100% increase in serum creatinine

Analysis 2.5. Comparison 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments, Outcome 5 50% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 5 50% increase in serum creatinine

Analysis 2.6. Comparison 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments, Outcome 6 Final serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 6 Final serum creatinine

Analysis 2.7. Comparison 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments, Outcome 7 Final GFR [mL/min/1.73 m²].

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 7 Final GFR [mL/min/1.73 m²]

Analysis 2.8. Comparison 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments, Outcome 8 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 8 Complete or partial remission

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Analysis 2.9. Comparison 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments, Outcome 9 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 9 Complete remission

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Analysis 2.10. Comparison 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments, Outcome 10 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 10 Partial remission

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Analysis 2.11. Comparison 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments, Outcome 11 Final proteinuria.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 11 Final proteinuria

Analysis 2.12. Comparison 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments, Outcome 12 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 2 Steroids versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 12 Temporary or permanent discontinuation or hospitalisation due to adverse events

Analysis 3.1. Comparison 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments, Outcome 1 Death or ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 1 Death or ESKD (dialysis/transplantation) (ITT analysis)

Analysis 3.2. Comparison 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments, Outcome 2 Death (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 2 Death (ITT analysis)

Analysis 3.3. Comparison 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments, Outcome 3 ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 3 ESKD (dialysis/transplantation) (ITT analysis)

Analysis 3.4. Comparison 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments, Outcome 4 100% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 4 100% increase in serum creatinine

Analysis 3.5. Comparison 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments, Outcome 5 50% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 5 50% increase in serum creatinine

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Analysis 3.6. Comparison 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments, Outcome 6 Final serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 6 Final serum creatinine

Analysis 3.7. Comparison 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments, Outcome 7 Final GFR [mL/min/1.73 m²].

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 7 Final GFR [mL/min/1.73 m²]

Analysis 3.8. Comparison 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments, Outcome 8 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 8 Complete or partial remission

Analysis 3.9. Comparison 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments, Outcome 9 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 9 Complete remission

Analysis 3.10. Comparison 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments, Outcome 10 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 10 Partial remission

Analysis 3.11. Comparison 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments, Outcome 11 Final proteinuria.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 11 Final proteinuria

Analysis 3.12. Comparison 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments, Outcome 12 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 3 Cyclophosphamide (CPA) versus placebo/no treatment/non-immunosuppressive treatments

Outcome: 12 Temporary or permanent discontinuation or hospitalisation due to adverse events

Analysis 4.1. Comparison 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids, Outcome 1 Death or ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome: 1 Death or ESKD (dialysis/transplantation) (ITT analysis)

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Analysis 4.2. Comparison 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids, Outcome 2 Death (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome: 2 Death (ITT analysis)

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Analysis 4.3. Comparison 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids, Outcome 3 ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome: 3 ESKD (dialysis/transplantation) (ITT analysis)

Analysis 4.4. Comparison 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids, Outcome 4 100% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome: 4 100% increase in serum creatinine

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Analysis 4.5. Comparison 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids, Outcome 5 50% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome: 5 50% increase in serum creatinine

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Analysis 4.6. Comparison 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids, Outcome 6 Final serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome: 6 Final serum creatinine

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Analysis 4.7. Comparison 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids, Outcome 7 Final GFR [mL/min/1.73 m²].

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome: 7 Final GFR [mL/min/1.73 m²]

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Analysis 4.8. Comparison 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids, Outcome 8 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome: 8 Complete or partial remission

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Analysis 4.9. Comparison 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids, Outcome 9 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome: 9 Complete remission

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Analysis 4.10. Comparison 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids, Outcome 10 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome: 10 Partial remission

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Analysis 4.11. Comparison 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids, Outcome 11 Final proteinuria.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome: 11 Final proteinuria

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Analysis 4.12. Comparison 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids, Outcome 12 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 4 Alkylating agents+steroids versus placebo/no treatment/non-immunosuppressive treatments/steroids

Outcome: 12 Temporary or permanent discontinuation or hospitalisation due to adverse events

Analysis 5.1. Comparison 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids, Outcome 1 Death or ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids

Outcome: 1 Death or ESKD (dialysis/transplantation) (ITT analysis)

Analysis 5.2. Comparison 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids, Outcome 2 Death (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids

Outcome: 2 Death (ITT analysis)

Analysis 5.3. Comparison 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids, Outcome 3 ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids

Outcome: 3 ESKD (dialysis/transplantation) (ITT analysis)

Analysis 5.4. Comparison 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids, Outcome 4 100% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids

Outcome: 4 100% increase in serum creatinine

Analysis 5.5. Comparison 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids, Outcome 5 50% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids

Outcome: 5 50% increase in serum creatinine

Analysis 5.6. Comparison 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids, Outcome 6 Final serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids

Outcome: 6 Final serum creatinine

Analysis 5.7. Comparison 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids, Outcome 7 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids

Outcome: 7 Complete or partial remission

Analysis 5.8. Comparison 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids, Outcome 8 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids

Outcome: 8 Complete remission

Analysis 5.9. Comparison 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids, Outcome 9 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids

Outcome: 9 Partial remission

Analysis 5.10. Comparison 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids, Outcome 10 Final proteinuria.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids

Outcome: 10 Final proteinuria

Analysis 5.11. Comparison 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids, Outcome 11 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 5 Cyclophosphamide (CPA)+steroids versus chlorambucil+steroids

Outcome: 11 Temporary or permanent discontinuation or hospitalisation due to adverse events

Analysis 6.1. Comparison 6 Cyclosporine (CSA) versus other treatments, Outcome 1 Death or ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 6 Cyclosporine (CSA) versus other treatments

Outcome: 1 Death or ESKD (dialysis/transplantation) (ITT analysis)

(Continued ...)

Analysis 6.2. Comparison 6 Cyclosporine (CSA) versus other treatments, Outcome 2 Death (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 6 Cyclosporine (CSA) versus other treatments

Outcome: 2 Death (ITT analysis)

(Continued . . .)

Analysis 6.3. Comparison 6 Cyclosporine (CSA) versus other treatments, Outcome 3 ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 6 Cyclosporine (CSA) versus other treatments

Outcome: 3 ESKD (dialysis/transplantation) (ITT analysis)

(Continued ...)

Analysis 6.4. Comparison 6 Cyclosporine (CSA) versus other treatments, Outcome 4 100% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 6 Cyclosporine (CSA) versus other treatments

Outcome: 4 100% increase in serum creatinine

(Continued . . .)

Analysis 6.5. Comparison 6 Cyclosporine (CSA) versus other treatments, Outcome 5 50% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 6 Cyclosporine (CSA) versus other treatments

Outcome: 5 50% increase in serum creatinine

Analysis 6.6. Comparison 6 Cyclosporine (CSA) versus other treatments, Outcome 6 Final serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 6 Cyclosporine (CSA) versus other treatments

Outcome: 6 Final serum creatinine

(Continued ...)

(... Continued)

Analysis 6.7. Comparison 6 Cyclosporine (CSA) versus other treatments, Outcome 7 Final GFR [mL/min/1.73 m²].

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 6 Cyclosporine (CSA) versus other treatments

Outcome: 7 Final GFR [mL/min/1.73 m²]

(Continued ...)

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Analysis 6.8. Comparison 6 Cyclosporine (CSA) versus other treatments, Outcome 8 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 6 Cyclosporine (CSA) versus other treatments

Outcome: 8 Complete or partial remission

Analysis 6.9. Comparison 6 Cyclosporine (CSA) versus other treatments, Outcome 9 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 6 Cyclosporine (CSA) versus other treatments

Outcome: 9 Complete remission

Analysis 6.10. Comparison 6 Cyclosporine (CSA) versus other treatments, Outcome 10 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 6 Cyclosporine (CSA) versus other treatments

Outcome: 10 Partial remission

(Continued ...)

Analysis 6.11. Comparison 6 Cyclosporine (CSA) versus other treatments, Outcome 11 Final proteinuria.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 6 Cyclosporine (CSA) versus other treatments

Outcome: 11 Final proteinuria

(Continued ...)

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Analysis 6.12. Comparison 6 Cyclosporine (CSA) versus other treatments, Outcome 12 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 6 Cyclosporine (CSA) versus other treatments

Outcome: 12 Temporary or permanent discontinuation or hospitalisation due to adverse events

(Continued ...)

Analysis 7.1. Comparison 7 Cyclosporine (CSA) (1.5 mg/kg, twice/d) versus CSA (3.0 mg/kg, once/d), Outcome 1 Complete remission at 12 months.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 7 Cyclosporine (CSA) (1.5 mg/kg, twice/d) versus CSA (3.0 mg/kg, once/d)

Outcome: 1 Complete remission at 12 months

Analysis 7.2. Comparison 7 Cyclosporine (CSA) (1.5 mg/kg, twice/d) versus CSA (3.0 mg/kg, once/d), Outcome 2 Final proteinuria at 12 months.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 7 Cyclosporine (CSA) (1.5 mg/kg, twice/d) versus CSA (3.0 mg/kg, once/d)

Outcome: 2 Final proteinuria at 12 months

Analysis 8.1. Comparison 8 Tacrolimus (TAC) versus other treatments, Outcome 1 Death or ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 8 Tacrolimus (TAC) versus other treatments

Outcome: 1 Death or ESKD (dialysis/transplantation) (ITT analysis)

Analysis 8.2. Comparison 8 Tacrolimus (TAC) versus other treatments, Outcome 2 Death (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 8 Tacrolimus (TAC) versus other treatments

Outcome: 2 Death (ITT analysis)

Analysis 8.3. Comparison 8 Tacrolimus (TAC) versus other treatments, Outcome 3 ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 8 Tacrolimus (TAC) versus other treatments

Outcome: 3 ESKD (dialysis/transplantation) (ITT analysis)

Study or subgroup	TAC n/N	Other n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 TAC versus placebo/no treatment at final follow-up (30 months)					
Praga 2007	0/25	0/23			Not estimable
Subtotal (95% CI)	25	23			Not estimable
Total events: 0 (TAC), 0 (Other)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 TAC+steroids versus alkylating agents+steroids at final follow-up (12 months)					
Chen 2010a	0/39	0/34			Not estimable
Subtotal (95% CI)	39	34			Not estimable
Total events: 0 (TAC), 0 (Other)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	64	57			Not estimable
Total events: 0 (TAC), 0 (Other)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: $\chi^2 = 0.0$, $df = 1$ ($P = 0.0$), $I^2 = 0.0\%$					

0.002 0.1 1 10 500

Favours TAC Favours other

Analysis 8.4. Comparison 8 Tacrolimus (TAC) versus other treatments, Outcome 4 50% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 8 Tacrolimus (TAC) versus other treatments

Outcome: 4 50% increase in serum creatinine

(Continued ...)

Analysis 8.5. Comparison 8 Tacrolimus (TAC) versus other treatments, Outcome 5 Final GFR [mL/min/1.73 m²].

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 8 Tacrolimus (TAC) versus other treatments

Outcome: 5 Final GFR [mL/min/1.73 m²]

Analysis 8.6. Comparison 8 Tacrolimus (TAC) versus other treatments, Outcome 6 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 8 Tacrolimus (TAC) versus other treatments

Outcome: 6 Complete or partial remission

(Continued ...)

Analysis 8.7. Comparison 8 Tacrolimus (TAC) versus other treatments, Outcome 7 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 8 Tacrolimus (TAC) versus other treatments

Outcome: 7 Complete remission

(Continued ...)

Analysis 8.8. Comparison 8 Tacrolimus (TAC) versus other treatments, Outcome 8 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 8 Tacrolimus (TAC) versus other treatments

Outcome: 8 Partial remission

(Continued ...)

Analysis 8.9. Comparison 8 Tacrolimus (TAC) versus other treatments, Outcome 9 Final proteinuria.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 8 Tacrolimus (TAC) versus other treatments

Outcome: 9 Final proteinuria

(Continued ...)

(... Continued)

Analysis 8.10. Comparison 8 Tacrolimus (TAC) versus other treatments, Outcome 10 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 8 Tacrolimus (TAC) versus other treatments

Outcome: 10 Temporary or permanent discontinuation or hospitalisation due to adverse events

Analysis 9.1. Comparison 9 Mycophenolate mofetil (MMF) versus other treatments, Outcome 1 Death or ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 9 Mycophenolate mofetil (MMF) versus other treatments

Outcome: 1 Death or ESKD (dialysis/transplantation) (ITT analysis)

Study or subgroup	MMF n/N	Other n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 MMF versus placebo/no treatment at final follow-up (12 months)					
Dussol 2008	0/19	0/17			Not estimable
Subtotal (95% CI)	19	17			Not estimable
Total events: 0 (MMF), 0 (Other)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 MMF+steroids versus alkylating agents+steroids at final follow-up (15-17 months)					
Chan 2007	0/11	0/9			Not estimable
Senthil Nayagam 2008	0/11	0/10			Not estimable
Subtotal (95% CI)	22	19			Not estimable
Total events: 0 (MMF), 0 (Other)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	41	36			Not estimable
Total events: 0 (MMF), 0 (Other)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: $\text{Chi}^2 = 0.0$, $\text{df} = 1$ ($P = 0.0$), $I^2 = 0.0\%$

Analysis 9.2. Comparison 9 Mycophenolate mofetil (MMF) versus other treatments, Outcome 2 Death (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 9 Mycophenolate mofetil (MMF) versus other treatments

Outcome: 2 Death (ITT analysis)

Study or subgroup	MMF n/N	Other n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 MMF versus placebo/no treatment at final follow-up (12 months)					
Dussol 2008	0/19	0/17			Not estimable
Subtotal (95% CI)	19	17			Not estimable
Total events: 0 (MMF), 0 (Other)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 MMF+steroids versus alkylating agents+steroids at final follow-up (15-17 months)					
Chan 2007	0/11	0/9			Not estimable
Senthil Nayagam 2008	0/11	0/10			Not estimable
Subtotal (95% CI)	22	19			Not estimable
Total events: 0 (MMF), 0 (Other)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	41	36			Not estimable
Total events: 0 (MMF), 0 (Other)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: $\text{Chi}^2 = 0.0$, $\text{df} = 1$ ($P = 0.0$), $I^2 = 0.0\%$					
			0.002 0.1 1 10 500 Favours MMF Favours other		

Analysis 9.3. Comparison 9 Mycophenolate mofetil (MMF) versus other treatments, Outcome 3 ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 9 Mycophenolate mofetil (MMF) versus other treatments

Outcome: 3 ESKD (dialysis/transplantation) (ITT analysis)

Study or subgroup	MMF n/N	Other n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 MMF versus placebo/no treatment at final follow-up (12 months)					
Dussol 2008	0/19	0/17			Not estimable
Subtotal (95% CI)	19	17			Not estimable
Total events: 0 (MMF), 0 (Other)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 MMF+steroids versus alkylating agents+steroids at final follow-up (15-17 months)					
Chan 2007	0/11	0/9			Not estimable
Senthil Nayagam 2008	0/11	0/10			Not estimable
Subtotal (95% CI)	22	19			Not estimable
Total events: 0 (MMF), 0 (Other)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	41	36			Not estimable
Total events: 0 (MMF), 0 (Other)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: $\text{Chi}^2 = 0.0$, $\text{df} = 1$ ($P = 0.0$), $I^2 = 0.0\%$

Analysis 9.4. Comparison 9 Mycophenolate mofetil (MMF) versus other treatments, Outcome 4 100% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 9 Mycophenolate mofetil (MMF) versus other treatments

Outcome: 4 100% increase in serum creatinine

Study or subgroup	MMF n/N	Other n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
1 MMF versus other treatments at final follow-up (12 months) (ITT analysis)				
Dussol 2008	0/19	0/17		Not estimable
2 MMF versus placebo/no treatment at final follow-up (12 months) (ITT analysis)				
Dussol 2008	0/19	0/17		Not estimable
3 MMF versus placebo/no treatment at 12 months				
Dussol 2008	0/19	0/17		Not estimable

0.002	0.1	1	10	500
Favours MMF			Favours other	

Analysis 9.5. Comparison 9 Mycophenolate mofetil (MMF) versus other treatments, Outcome 5 50% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 9 Mycophenolate mofetil (MMF) versus other treatments

Outcome: 5 50% increase in serum creatinine

Study or subgroup	MMF n/N	Other n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
1 MMF versus other treatments at final follow-up (12 months) (ITT analysis)				
Dussol 2008	0/19	0/17		Not estimable
2 MMF versus placebo/no treatment at final follow-up (12 months) (ITT analysis)				
Dussol 2008	0/19	0/17		Not estimable
3 MMF versus placebo/no treatment at 12 months				
Dussol 2008	0/19	0/17		Not estimable

0.002	0.1	1	10	500
Favours MMF			Favours other	

Analysis 9.6. Comparison 9 Mycophenolate mofetil (MMF) versus other treatments, Outcome 6 Final GFR [mL/min/1.73 m²].

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 9 Mycophenolate mofetil (MMF) versus other treatments

Outcome: 6 Final GFR [mL/min/1.73 m²]

Analysis 9.7. Comparison 9 Mycophenolate mofetil (MMF) versus other treatments, Outcome 7 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 9 Mycophenolate mofetil (MMF) versus other treatments

Outcome: 7 Complete or partial remission

(Continued ...)

Analysis 9.8. Comparison 9 Mycophenolate mofetil (MMF) versus other treatments, Outcome 8 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 9 Mycophenolate mofetil (MMF) versus other treatments

Outcome: 8 Complete remission

(Continued ...)

Analysis 9.9. Comparison 9 Mycophenolate mofetil (MMF) versus other treatments, Outcome 9 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 9 Mycophenolate mofetil (MMF) versus other treatments

Outcome: 9 Partial remission

Analysis 9.10. Comparison 9 Mycophenolate mofetil (MMF) versus other treatments, Outcome 10 Final proteinuria.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 9 Mycophenolate mofetil (MMF) versus other treatments

Outcome: 10 Final proteinuria

Analysis 9.11. Comparison 9 Mycophenolate mofetil (MMF) versus other treatments, Outcome 11 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 9 Mycophenolate mofetil (MMF) versus other treatments

Outcome: 11 Temporary or permanent discontinuation or hospitalisation due to adverse events

Analysis 10.1. Comparison 10 Mycophenolate mofetil (MMF)+cyclosporine (CSA) versus CSA, Outcome 1 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 10 Mycophenolate mofetil (MMF)+cyclosporine (CSA) versus CSA

Outcome: 1 Complete or partial remission

Analysis 10.2. Comparison 10 Mycophenolate mofetil (MMF)+cyclosporine (CSA) versus CSA, Outcome 2 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 10 Mycophenolate mofetil (MMF)+cyclosporine (CSA) versus CSA

Outcome: 2 Complete remission

Analysis 10.3. Comparison 10 Mycophenolate mofetil (MMF)+cyclosporine (CSA) versus CSA, Outcome 3 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 10 Mycophenolate mofetil (MMF)+cyclosporine (CSA) versus CSA

Outcome: 3 Partial remission

Analysis 11.1. Comparison 11 Adrenocorticotrophic hormone (ACTH) versus other treatments, Outcome 1 Death or ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 11 Adrenocorticotrophic hormone (ACTH) versus other treatments

Outcome: 1 Death or ESKD (dialysis/transplantation) (ITT analysis)

Analysis 11.2. Comparison 11 Adrenocorticotrophic hormone (ACTH) versus other treatments, Outcome 2 Death (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 11 Adrenocorticotrophic hormone (ACTH) versus other treatments

Outcome: 2 Death (ITT analysis)

Analysis 11.3. Comparison 11 Adrenocorticotrophic hormone (ACTH) versus other treatments, Outcome 3 ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 11 Adrenocorticotrophic hormone (ACTH) versus other treatments

Outcome: 3 ESKD (dialysis/transplantation) (ITT analysis)

Analysis 11.4. Comparison 11 Adrenocorticotrophic hormone (ACTH) versus other treatments, Outcome 4 100% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 11 Adrenocorticotrophic hormone (ACTH) versus other treatments

Outcome: 4 100% increase in serum creatinine

Analysis 11.5. Comparison 11 Adrenocorticotrophic hormone (ACTH) versus other treatments, Outcome 5 50% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 11 Adrenocorticotrophic hormone (ACTH) versus other treatments

Outcome: 5 50% increase in serum creatinine

Analysis 11.6. Comparison 11 Adrenocorticotrophic hormone (ACTH) versus other treatments, Outcome 6 Final serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 11 Adrenocorticotrophic hormone (ACTH) versus other treatments

Outcome: 6 Final serum creatinine

Analysis 11.7. Comparison 11 Adrenocorticotrophic hormone (ACTH) versus other treatments, Outcome 7 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 11 Adrenocorticotrophic hormone (ACTH) versus other treatments

Outcome: 7 Complete or partial remission

(Continued ...)

Analysis 11.8. Comparison 11 Adrenocorticotrophic hormone (ACTH) versus other treatments, Outcome 8 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 11 Adrenocorticotrophic hormone (ACTH) versus other treatments

Outcome: 8 Complete remission

(Continued ...)

Analysis 11.9. Comparison 11 Adrenocorticotrophic hormone (ACTH) versus other treatments, Outcome 9 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 11 Adrenocorticotrophic hormone (ACTH) versus other treatments

Outcome: 9 Partial remission

(Continued ...)

Analysis 11.10. Comparison 11 Adrenocorticotrophic hormone (ACTH) versus other treatments, Outcome 10 Final proteinuria.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 11 Adrenocorticotrophic hormone (ACTH) versus other treatments

Outcome: 10 Final proteinuria

Analysis 11.11. Comparison 11 Adrenocorticotrophic hormone (ACTH) versus other treatments, Outcome 11 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 11 Adrenocorticotrophic hormone (ACTH) versus other treatments

Outcome: 11 Temporary or permanent discontinuation or hospitalisation due to adverse events

Analysis 12.1. Comparison 12 Azathioprine versus other treatments, Outcome 1 Death or ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 12 Azathioprine versus other treatments

Outcome: 1 Death or ESKD (dialysis/transplantation) (ITT analysis)

Analysis 12.2. Comparison 12 Azathioprine versus other treatments, Outcome 2 Death (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 12 Azathioprine versus other treatments

Outcome: 2 Death (ITT analysis)

Analysis 12.3. Comparison 12 Azathioprine versus other treatments, Outcome 3 ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 12 Azathioprine versus other treatments

Outcome: 3 ESKD (dialysis/transplantation) (ITT analysis)

Analysis 12.4. Comparison 12 Azathioprine versus other treatments, Outcome 4 100% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 12 Azathioprine versus other treatments

Outcome: 4 100% increase in serum creatinine

Analysis 12.5. Comparison 12 Azathioprine versus other treatments, Outcome 5 50% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 12 Azathioprine versus other treatments

Outcome: 5 50% increase in serum creatinine

Analysis 12.6. Comparison 12 Azathioprine versus other treatments, Outcome 6 Final serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 12 Azathioprine versus other treatments

Outcome: 6 Final serum creatinine

Analysis 12.7. Comparison 12 Azathioprine versus other treatments, Outcome 7 Final GFR [mL/min/1.73 m²].

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 12 Azathioprine versus other treatments

Outcome: 7 Final GFR [mL/min/1.73 m²]

Analysis 12.8. Comparison 12 Azathioprine versus other treatments, Outcome 8 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 12 Azathioprine versus other treatments

Outcome: 8 Complete or partial remission

Analysis 12.9. Comparison 12 Azathioprine versus other treatments, Outcome 9 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 12 Azathioprine versus other treatments

Outcome: 9 Complete remission

Analysis 12.10. Comparison 12 Azathioprine versus other treatments, Outcome 10 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 12 Azathioprine versus other treatments

Outcome: 10 Partial remission

Analysis 12.11. Comparison 12 Azathioprine versus other treatments, Outcome 11 Final proteinuria.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 12 Azathioprine versus other treatments

Outcome: 11 Final proteinuria

Analysis 12.12. Comparison 12 Azathioprine versus other treatments, Outcome 12 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 12 Azathioprine versus other treatments

Outcome: 12 Temporary or permanent discontinuation or hospitalisation due to adverse events

Analysis 13.1. Comparison 13 Mizoribine versus other treatments, Outcome 1 50% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 13 Mizoribine versus other treatments

Outcome: 1 50% increase in serum creatinine

Analysis 13.2. Comparison 13 Mizoribine versus other treatments, Outcome 2 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 13 Mizoribine versus other treatments

Outcome: 2 Complete or partial remission

Analysis 13.3. Comparison 13 Mizoribine versus other treatments, Outcome 3 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 13 Mizoribine versus other treatments

Outcome: 3 Complete remission

Analysis 13.4. Comparison 13 Mizoribine versus other treatments, Outcome 4 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 13 Mizoribine versus other treatments

Outcome: 4 Partial remission

Analysis 13.5. Comparison 13 Mizoribine versus other treatments, Outcome 5 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 13 Mizoribine versus other treatments

Outcome: 5 Temporary or permanent discontinuation or hospitalisation due to adverse events

Analysis 14.1. Comparison 14 Tripterygium wilfordii versus other treatments, Outcome 1 Death or ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 14 Tripterygium wilfordii versus other treatments

Outcome: 1 Death or ESKD (dialysis/transplantation) (ITT analysis)

Analysis 14.2. Comparison 14 Tripterygium wilfordii versus other treatments, Outcome 2 Death (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 14 Tripterygium wilfordii versus other treatments

Outcome: 2 Death (ITT analysis)

Analysis 14.3. Comparison 14 Tripterygium wilfordii versus other treatments, Outcome 3 ESKD (dialysis/transplantation) (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 14 Tripterygium wilfordii versus other treatments

Outcome: 3 ESKD (dialysis/transplantation) (ITT analysis)

Analysis 14.4. Comparison 14 Tripterygium wilfordii versus other treatments, Outcome 4 100% increase in serum creatinine (ITT analysis).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 14 Tripterygium wilfordii versus other treatments

Outcome: 4 100% increase in serum creatinine (ITT analysis)

Analysis 14.5. Comparison 14 Tripterygium wilfordii versus other treatments, Outcome 5 50% increase in serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 14 Tripterygium wilfordii versus other treatments

Outcome: 5 50% increase in serum creatinine

Analysis 14.6. Comparison 14 Tripterygium wilfordii versus other treatments, Outcome 6 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 14 Tripterygium wilfordii versus other treatments

Outcome: 6 Complete or partial remission

Analysis 14.7. Comparison 14 Tripterygium wilfordii versus other treatments, Outcome 7 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 14 Tripterygium wilfordii versus other treatments

Outcome: 7 Complete remission

Analysis 14.8. Comparison 14 Tripterygium wilfordii versus other treatments, Outcome 8 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 14 Tripterygium wilfordii versus other treatments

Outcome: 8 Partial remission

Analysis 14.9. Comparison 14 Tripterygium wilfordii versus other treatments, Outcome 9 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 14 Tripterygium wilfordii versus other treatments

Outcome: 9 Temporary or permanent discontinuation or hospitalisation due to adverse events

Analysis 15.1. Comparison 15 Early versus late immunosuppressive treatments, Outcome 1 Death or ESKD (dialysis/transplantation).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 15 Early versus late immunosuppressive treatments

Outcome: 1 Death or ESKD (dialysis/transplantation)

Analysis 15.2. Comparison 15 Early versus late immunosuppressive treatments, Outcome 2 Death.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 15 Early versus late immunosuppressive treatments

Outcome: 2 Death

Analysis 15.3. Comparison 15 Early versus late immunosuppressive treatments, Outcome 3 ESKD (dialysis/transplantation).

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 15 Early versus late immunosuppressive treatments

Outcome: 3 ESKD (dialysis/transplantation)

Analysis 15.4. Comparison 15 Early versus late immunosuppressive treatments, Outcome 4 Final serum creatinine.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 15 Early versus late immunosuppressive treatments

Outcome: 4 Final serum creatinine

Analysis 15.5. Comparison 15 Early versus late immunosuppressive treatments, Outcome 5 Final GFR [mL/min/1.73 m²].

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 15 Early versus late immunosuppressive treatments

Outcome: 5 Final GFR [mL/min/1.73 m²]

Analysis 15.6. Comparison 15 Early versus late immunosuppressive treatments, Outcome 6 Complete or partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 15 Early versus late immunosuppressive treatments

Outcome: 6 Complete or partial remission

Analysis 15.7. Comparison 15 Early versus late immunosuppressive treatments, Outcome 7 Complete remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 15 Early versus late immunosuppressive treatments

Outcome: 7 Complete remission

Analysis 15.8. Comparison 15 Early versus late immunosuppressive treatments, Outcome 8 Partial remission.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 15 Early versus late immunosuppressive treatments

Outcome: 8 Partial remission

Analysis 15.9. Comparison 15 Early versus late immunosuppressive treatments, Outcome 9 Final proteinuria.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 15 Early versus late immunosuppressive treatments

Outcome: 9 Final proteinuria

Analysis 15.10. Comparison 15 Early versus late immunosuppressive treatments, Outcome 10 Temporary or permanent discontinuation or hospitalisation due to adverse events.

Review: Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome

Comparison: 15 Early versus late immunosuppressive treatments

Outcome: 10 Temporary or permanent discontinuation or hospitalisation due to adverse events

ADDITIONAL TABLES

Table 1. Studies not included in the meta-analyses

Study ID	Reported results
Austin 1996a	Eleven of 15 patients with initial GFR < 60 mL/min showed an average 86% (median 67%) increase in GFR at 1 year. Treatment group, gender, severity of initial urinary protein, and degree of glomerular sclerosis or interstitial fibrosis did not predict change in GFR for all patients or those with GFR < 60 mL/min. Initial urinary protein averaged 12 g/d (median 10, range 2.1 to 36 g/d, 1 patient had initial urinary protein < 3.5 g/d). Urinary protein decreased > 50% in 14 patients, including 11/20 patients with initial urinary protein > 8 g/d. Only 6 patients had urinary protein < 2 g/d at 1 year. Treatment group, gender, initial GFR, glomerular sclerosis and interstitial fibrosis did not predict percent change in urinary protein or remission of urinary protein for all patients or those with initial urinary protein > 8 g/d. After one-year follow-up there was no evidence that cyclophosphamide plus prednisone was more effective than prednisone alone
Dyadyk 2001	After 12 to 48 months, cyclophosphamide group had a higher rate of proteinuria reduction (43.8% versus 6.3%, $P < 0.001$) and a lower level of SCr (186 $\mu\text{mol/L}$ versus 236 $\mu\text{mol/L}$, $P < 0.05$) than azathioprine group
Stegeman 1994	The interim analysis of the study failed to demonstrate the superiority of ACEi over placebo. No appropriate detailed data could be identified

ACEi - angiotensin-converting enzyme inhibitor; GFR - glomerular filtration rate; SCr - serum creatinine

APPENDICES

Appendix 1. Electronic search strategies

Databases	Search terms
CENTRAL	<ol style="list-style-type: none"> 1. MeSH descriptor Glomerulonephritis, Membranous, this term only in MeSH products 2. (membranous NEAR/2 glomerulo*):ti,ab,kw 3. (membranous NEAR/2 nephropathy):ti,ab,kw 4. (extramembranous next glomerulo*):ti,ab,kw 5. mgn:ti,ab,kw 14 6. imn:ti,ab,kw 56 7. (#1 OR #2 OR #3 OR #4 OR #5 OR #6
MEDLINE	<ol style="list-style-type: none"> 1. Glomerulonephritis, Membranous/ 2. (membranous adj2 glomerulo\$).tw. 3. (membranous adj2 nephropathy).tw. 4. extramembranous glomerulopathy.tw. 5. mgn.tw. 6. imn.tw. 7. or/1-6
EMBASE	<ol style="list-style-type: none"> 1. Membranous Glomerulonephritis/ 2. (membranous adj2 glomerulo\$).tw. 3. (membranous adj2 nephropathy).tw. 4. extramembranous glomerulopathy.tw. 5. mgn.tw. 6. imn.tw. 7. or/1-6

NOTE: Search strategies used in the original review can be found in [Schieppati 2004](#)

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	<i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)
	<i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention

(Continued)

	<i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<p><i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)</p> <p><i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure</p> <p><i>Unclear:</i> Randomisation stated but no information on method used is available</p>
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	<p><i>Low risk of bias:</i> No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken</p> <p><i>High risk of bias:</i> No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	<p><i>Low risk of bias:</i> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken</p> <p><i>High risk of bias:</i> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>

(Continued)

<p>Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data</p>	<p><i>Low risk of bias:</i> No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods</p> <p><i>High risk of bias:</i> Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
<p>Selective reporting Reporting bias due to selective outcome reporting</p>	<p><i>Low risk of bias:</i> The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)</p> <p><i>High risk of bias:</i> Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>

(Continued)

Other bias Bias due to problems not covered elsewhere in the table	<i>Low risk of bias:</i> The study appears to be free of other sources of bias.
	<i>High risk of bias:</i> Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	<i>Unclear:</i> Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

WHAT'S NEW

Date	Event	Description
19 November 2014	Amended	Minor edit to study names and number of reports of studies excluded and awaiting classification

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 4, 2004

Date	Event	Description
30 June 2014	New citation required and conclusions have changed	The conclusion has been changed in this update
30 June 2014	New search has been performed	New search undertaken, new studies identified and included
9 October 2008	Amended	Converted to new review format.
30 April 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

- Protocol: AS, AP, GR
- Search strategy: AP, GAG
- Study selection: AP, JZ
- Quality assessment: AP, JZ
- Data extraction and data entry: AP, GAG
- Resolution of disagreements: AS
- Final manuscript: AS, AP
- Final manuscript review: GR, AS, NB
- Update: YC, AP, GC, XC

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Division of Nephrology, State Key Discipline and State Key Laboratory of Kidney Diseases (2011DAV00088), Chinese People's Liberation Army (PLA) General Hospital (301 Hospital), Chinese PLA Medical Academy, Fuxing Road 28, Haidian District, Beijing 100853, China.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [therapeutic use]; Alkylating Agents [therapeutic use]; Cyclosporine [therapeutic use]; Drug Therapy, Combination [methods]; Glomerulonephritis, Membranous [*drug therapy; mortality]; Immunosuppression [adverse effects; methods]; Immunosuppressive Agents [*therapeutic use]; Nephrotic Syndrome [*complications; drug therapy]; Proteinuria [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans