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[Intervention Review]

Immunosuppressive treatment for focal segmental glomerulosclerosis in adults

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ABSTRACT

Background

Corticosteroids remain the mainstay of treatment in idiopathic nephrotic syndrome, including focal and segmental glomerulosclerosis (FSGS). However, only about 20% of patients with FSGS experience a partial or complete remission of nephrotic syndrome despite treatment.

Objectives

To assess the effects of different immunomodulatory and immunosuppressive regimes in adults with FSGS.

Search methods

We searched MEDLINE, EMBASE and CENTRAL and handsearched congress reports of the American Society of Nephrology and the European Dialysis and Transplantation Association.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs which examined the effects of different doses, dose strategies and duration of treatment of steroids, alkylating agents, cyclosporin A and antimetabolites in the treatment of FSGS in adults, where included.

Data collection and analysis

At least two authors independently assessed abstracts and/or full text articles to determine which studies satisfied the inclusion criteria. Information was entered onto a separate data sheet for each identified study. Data relevant to outcomes (complete or partial remission of nephrotic syndrome, doubling of serum creatinine, adverse effects) from identified studies were included. Results were expressed as risk ratios (RR) with 95% confidence intervals (CI).

Main results

Four studies (108 participants) were included. Three studies investigated cyclosporin A (CSA) with or without prednisone versus prednisone or no treatment and one compared chlorambucil plus prednisone versus no treatment. Outcome data was only available for complete or partial remission and doubling of serum creatinine. There was a significant increase in the number of participants who obtained complete

or partial remission with CSA plus low dose prednisone versus prednisone alone (one study, 49 participants: RR 8.85, 95% CI 1.22 to 63.92). Pooled analyses were not performed due to the heterogeneity of the data.

Authors' conclusions

Adult patients treated with CSA at an initial dose of 3.5-5 mg/kg/d in two divided doses perhaps in combination with oral prednisolone 0.15 mg/kg/d are more likely to achieve a partial remission of the nephrotic syndrome compared with symptomatic treatment or prednisolone alone. However, there is a probability of deterioration of kidney function due to the nephrotoxic effect of CSA in the long term. For CSA, a larger controlled trial with longer follow-up should be performed to prove the benefit of this regimen not only on proteinuria but also on the preservation of kidney function. Present available data do not support the general use of alkylating substances for the treatment of FSGS in adults.

PLAIN LANGUAGE SUMMARY

Immunosuppressive treatment for focal segmental glomerulosclerosis in adults

Focal and segmental glomerulosclerosis (FSGS) is a rare disease whose cause is unknown and is a condition in which the glomeruli leak protein from the blood into the urine. It is described as focal because only some of the glomeruli become scarred (while others remain normal) and segmental as only part of an individual glomerulus is damaged. Over half of all persons with FSGS will develop chronic kidney failure within 10 years. Thus, immunosuppressive strategies are used to control proteinuria and prevent kidney failure. This systematic review identified four studies (108 participants) investigating immunosuppressive treatments for adults with biopsy-proven FSGS. Adult patients treated with cyclosporin A in combination with prednisone were more likely to achieve partial remission of nephrotic syndrome compared with prednisone alone, however this result is based on only one small study. No data was available on the progression to kidney failure or death.

BACKGROUND

Focal segmental glomerulosclerosis (FSGS) is a condition in which the glomeruli leak protein from the blood into the urine. It was described as a pattern of idiopathic nephrotic syndrome (INS) which is focal (i.e. only a minority of glomeruli are involved) and segmental in location. It develops initially in the juxtamedullary glomeruli and progresses to involve a greater number and portion of the glomerular tufts. It results in asymptomatic proteinuria (the glomeruli may be normal by light microscopy and immunofluorescence leading to the misdiagnosis of minimal change disease) in almost half of the cases, and symptoms of nephrotic syndrome in the rest. FSGS is frequently associated with microscopic haematuria, hypertension and a decline in renal function progressing towards end-stage kidney disease (ESKD). FSGS is a rare kidney disease but can appear at any age (Bohle 1986). In recent years the number of people suffering from FSGS has been increasing in frequency (Valeri 1996).

Currently, different opinions exist about the optimal treatment of FSGS. Corticosteroids remain the mainstay of treatment in INS, including FSGS. But the response of adults to corticosteroids is much lower when compared to children (Meyrier 1999). Treatment with prednisone of 0.5-2.0 mg/kg/d should continue for a total duration of six months before declaring the patient steroid resistant. Korbet 1994 found in his analysis to FSGS that the highest remission rates of over 30% were observed in cases treated for over five months, while the lowest rates (less than 20%) were in patients treated for less than two months. The current schedule for treating adults with lesions of FSGS is: prednisone 1 mg/kg/d for the first 8-12 weeks followed by 0.5 mg/kg/d (or at least 60 mg/d) for a further 6-8 weeks (Glassock 1993). Complete remission predicts a good long-term outcome. No relapses were found in those patients who achieved remission and none of them progressed to ESKD. Those patients not receiving any treatment, or failing to respond to treatment, had a high risk of developing chronic renal failure (CKD) (Burgess 1999). Corticosteroid resistance or steroid-dependency justify the trial of other therapeutic agents essentially cytotoxic therapy or cyclosporin A (CSA). The first trials with CSA for INS were reported in 1986 (Meyrier 1986). Steroid-dependent patients were more likely to experience a remission than steroid-resistant patients. Approximately 40% of patients with FSGS had sustained remission of INS while maintained on CSA. However, relapses were common when CSA treatment was stopped. The major concern in the treatment of FSGS with CSA is nephrotoxicity. The time period from beginning treatment until remission was analysed by the Collaborative Study Group of Sandimmun in Nephrotic Syndrome (Von Graffenried 1991). The maximum cumulative rate of complete remission was achieved at six months, indicating that pursuing CSA treatment for a longer period of time is of no benefit in terms of additional remissions, but is an unreasonable risk with respect to nephrotoxicity. The most commonly used cytotoxic agents have been cyclophosphamide and chlorambucil. Alkylating agents for the treatment of FSGS were mainly used in corticosteroid-resistance and corticosteroid dependent INS. Cyclophosphamide given at a dose of 2 mg/kg/d resulted in complete or partial remission in approximately 75% of cases (Korbet 1994, Schulman 1988). Most of those patients had been treated for eight weeks. But in cases of steroid-resistance, cyclophosphamide was much less effective, with less than 25% deriving sustained benefit from an 8-12 weeks course of therapy (Korbet 1994, Schulman 1988). Likewise, there were similar

results for treating FSGS with chlorambucil. Tune 1995 reported an excellent response in treating steroid-resistant children with chlorambucil 0.15-0.20 mg/kg/d for the same period of time. Of 32 children, 66% had a complete remission. Twenty patients suffering from idiopathic FSGS treated with prednisone/cyclophosphamide over two years did not show an increase in serum creatinine but did also not show a significant decline in proteinuria (Grcevska 2006). In another retrospective study comparing corticosteroids alone with a combination of prednisolone and azathioprine or CSA disclosed a more rapid decline of kidney failure in the prednisolone alone group. The administration of immunosuppressive agents was more often followed by remission of nephrotic syndrome (Goumenos 2006).

OBJECTIVES

The aim of this review was to assess the effects of different immunomodulatory and immunosuppressive regimens in adults with FSGS.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) which examined the effects of different doses, dose strategies and duration of treatment of steroids, alkylating agents, CSA and antimetabolites in the treatment of FSGS in adults, where included.

Types of participants

Adult patients suffering from idiopathic biopsy-proven FSGS with NS. FSGS is defined as a diffuse kidney disease, usually in association with NS, which is distinguished from membranoproliferative glomerulonephritis (MPI-GN) with NS by;

1. additional, focal and segmental changes, which first appear in the juxtamedullary position, altering all structures of the capillary convoluta,
2. segmentally obliterated capillaries with accumulation of acellular matrix and hyaline deposits,
3. coarsely granular deposits of IgM and C3,
4. foot process fusion on electron microscopy,
5. and a relatively strong tendency to develop an interstitial fibrosis of the renal cortex.

Types of interventions

- Immunomodulatory/immunosuppressive treatments (corticosteroids, CSA, either alone or in combination).
- Cytotoxic therapies (cyclophosphamide, chlorambucil, either alone or in combination with corticosteroids).
- Antimetabolites (azathioprine, mycophenolate mofetil, either alone or in combination with corticosteroids).
- Plasmapheresis or immunoabsorption, either alone or in combination with immunomodulatory/immunosuppressive drug therapy.

Types of outcome measures

- Kidney function (rate of ESKD as defined by initiation of dialysis, transplantation, doubling of serum creatinine).
- Remission of NS (complete remission defined as proteinuria < 0.2 g/24 h; partial remission defined as proteinuria $\geq$ 0.2 g/24 h but < 2 g/24 h).
- Incidence of side effects of FSGS (rate of infections, rate of thromboembolic complications, rate of hospitalisation, mean hospitalisation time/patient-year).
- Incidence of adverse effects of therapy (death related to therapy, rate of infections, rate of drug-induced diabetes, rate of malignancy).

Search methods for identification of studies

Search was performed using the following databases (see [Appendix 1](#) for search terms used):

- MEDLINE 1966 to January 2007.
- EMBASE 1974 to January 2007.
- Pascal (French literature database) to July 2000.
- The Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library* issue 2, 2008).
- The Cochrane Renal Group's specialised register (May 2008).
- Hand-searching of abstract books of the American Society of Nephrology and the European Dialysis and Transplantation Association.
- All calculations will be performed on an intention to treat analysis and the Cochrane Collaboration Search strategy.
- If duplicated published trials were identified the most recent update of the trial will be included only

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts were screened and irrelevant studies discarded, although studies and reviews that might include relevant data or information on trials were retained initially. Basic information was entered into a separate data sheet for each identified study. At least two authors independently assessed abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. Disagreements were resolved by discussion.

Data extraction and management

Data were extracted by one author (FS) using a standardised form. Information were collected on the study methods including definitions of FSGS, type and duration of intervention and on the outcome specified above. Any discrepancies in data collection were resolved in consultation with the other reviewers.

Assessment of risk of bias in included studies

The quality of the included studies were assessed independently without blinding to authorship or journal of publication using the checklist shown below. Discrepancies were resolved by discussion. The quality items to be assessed were allocation concealment, blinding, intention-to-treat analysis and completeness of follow-up.

Allocation concealment

- Adequate (A)
- Unclear (B)
- Inadequate (C)

Blinding

Blinding of investigator, participant and outcome assessor.

Intention-to-treat analysis

- Yes
- No
- Not stated

Data synthesis

For dichotomous outcomes (ESKD, remission, side effects) the risk ratio (RR) with 95% confidence intervals (95% CI) were calculated and a summary point was to be estimated using the random effects model. Heterogeneity was analysed with an alpha of 0.1 used for statistical significance. No continuous outcomes were reported in the studies evaluated.

RESULTS

Description of studies

Results of the search

The systematic literature survey identified 34 studies addressing the question of immunosuppressive therapy in idiopathic FSGS in adult patients. However, only four ([Bhamik 2002](#); [Cattran 1999](#); [Imbasciati 1980](#); [Ponticelli 1993](#)) met our inclusion criteria. The other publications were either of retrospective design ([Banfi 1991](#); [Beaufils 1978](#); [Bolton 1977](#); [Chan 1991](#); [Crenshaw 1999](#); [Dudar 2004](#); [Mowry 1993](#); [Nagai 1994](#); [Pei 1987](#); [Ponticelli 1999](#); [Rydel 1995](#); [Emre 2001](#); [Goumenos 2006](#); [Grcevaska 2006](#)), case-series reports ([Bakir 1996](#); [Dantal 1998](#); [El-Reshaid 1995](#); [Ittel 1995](#); [Meyrier 1986](#); [Meyrier 1994](#)), cross-over designed trials ([Lee 1995](#); [Meyrier 1989](#); [Walker 1990](#); [Heering 2004](#); [Garin 1988](#)) or prospective but referring to the treatment of children ([Bagga 2003](#); [Gulati 2000](#); [Medizábal 2005](#); [Raafat 2004](#); [Xia 2003](#)).

Included studies

Four studies included 108 adult patients with biopsy-proven FSGS.

- Patients included in the largest trial were all nephrotic with a proteinuria of more or equal to 3.5 g/24 h and had a creatinine clearance higher or equal to 42 mL/min/1.73 m² ([Cattran 1999](#)). This trial was also the only placebo-controlled, RCT investigating the effect of CSA. CSA was administered in two divided doses at an initial daily dose of 3.5 mg/kg/d. Prednisone was given to all patients at a dose of 0.15 mg/kg/d. Five in the control group and 6 in the treatment group received another immunosuppressive regimen before entering the study. Follow-up was on average four years. Outcome measures were remission of nephrotic syndrome and ESKD. Complete remission of nephrotic syndrome was defined as a decline of proteinuria $\leq$ 0.3 g/24 h and stable kidney function. Partial remission was defined as a decline of proteinuria by 50% but at least $\leq$ 3.5 g/24 h with stable kidney function.

- Nineteen adult nephrotic patients with FSGS and normal kidney function (creatinine clearance > 80 mL/min) were randomised to receive either CSA or only supportive therapy (Ponticelli 1993). Initial CSA dose was 5 mg/kg/d in two divided doses. CSA was stopped after six months if no remission occurred. Median duration of follow-up was 18 months (3-24 months) for the treatment group and 24 months (12-24 months) for the control group. Outcome measures were remission of nephrotic syndrome and relapse of nephrotic syndrome.
- The third study randomised patients with proteinuria above 1 g/24 h and serum creatinine < 2 mg/dL to either IV methylprednisolone plus subsequent oral prednisolone combined with oral chlorambucil or to symptomatic treatment. Outcome measures were remission of proteinuria (defined by a proteinuria < 0.1 g/24 h), partial remission (defined by a decrease of proteinuria by 50% of baseline levels) and deterioration of kidney function (defined by a 50% increase of creatinine) (Imbasciati 1980). No time period of follow-up was given in this study.
- In the fourth study, 25 patients were included with biopsy-proven primary FSGS, therapy-resistant to oral prednisolone (Bhamik 2002). CSA was combined with oral prednisolone in an initial dose of 10-40 mg/d for 6 months. Patients in the control group received IV methylprednisolone in a dose of 250-750 mg/d for 7 days followed by weekly administration for at least 12 weeks. Outcome measures were complete remission, partial remission, ESKD within 3 years and decline of creatinine clearance.

Risk of bias in included studies

Allocation concealment

- All studies had adequate allocation concealment.

Blinding

- Cattran 1999 reported the study was single blind.
- Ponticelli 1993: The two treatments were very different and blinding of investigators or participants was not possible.

Intention-to-treat analysis

- Imbasciati 1980: Seventeen patients were enrolled. One participant from each group was excluded.
- Ponticelli 1993: Forty five patients were enrolled. Four dropped out within the first 45 days.

Effects of interventions

The systematic literature survey identified 34 studies addressing the question of immunosuppressive therapy in idiopathic FSGS in adult and/or paediatric patients. However, only four studies (Bhamik 2002; Cattran 1999; Imbasciati 1980; Ponticelli 1993) in 108 patients with biopsy-proven FSGS were included in our analyses. Three of these studies evaluated the effect of CSA (Bhamik 2002; Cattran 1999; Ponticelli 1993) and one study evaluated chlorambucil treatment (Imbasciati 1980). All except (Ponticelli 1993) treated the control patients with prednisolone. Most patients had slightly impaired kidney function and not all patients showed biochemical and clinical signs of nephrotic syndrome.

We have displayed the results in forest plots but have not pooled the results due to the differing treatment regimes and populations.

Remission of proteinuria

Complete remission of proteinuria

Analysis 1.1

1. *CSA + low dose prednisone versus prednisone*: There was no significant difference in the number of patients with complete remission of proteinuria between the two groups (RR 2.67, 95% CI 0.11 to 62.42).
2. *CSA + prednisolone versus methylprednisolone*: There was no significant difference in the number of patients with complete remission of proteinuria between the two groups (RR 2.31, 95% CI 0.55 to 9.74).
3. *Prednisolone + chlorambucil versus no treatment*: There was no significant difference in the number of patients with complete remission of proteinuria between the two groups (RR 1.75, 95% CI 0.20 to 15.41).
4. *CSA versus no treatment*: There was no significant difference in the number of patients with complete remission of proteinuria between the two groups (RR 4.55, 95% CI 0.25 to 83.70).

Partial remission of proteinuria

Analysis 1.2

1. *CSA + low dose prednisone versus prednisone*: There was a significant increase in the number of patients with partial remission in the CSA + low prednisone group (RR 7.96, 95% CI 1.09 to 58.15).
2. *CSA + prednisolone versus methylprednisolone*: There was no significant difference in the number of patients with partial remission of proteinuria between the two groups (RR 1.38, 95% CI 0.51 to 3.74).
3. *Prednisolone + chlorambucil versus no treatment*: There was no significant difference in the number of patients with partial remission of proteinuria between the two groups (RR 2.63, 95% CI 0.35 to 19.85).
4. *CSA versus no treatment*: There was no significant difference in the number of patients with partial remission of proteinuria between the two groups (RR 1.20, 95% CI 0.36 to 3.97).

Complete or partial remission of proteinuria (combined end-point)

Analysis 1.3

1. *CSA + low dose prednisone versus prednisone*: There was a significant increase in the number of patients with complete or partial remission in the CSA + low prednisone group (RR 8.85, 95% CI 1.22 to 63.92).
2. *CSA + prednisolone versus methylprednisolone*: There was no significant difference in the number of patients with partial remission of proteinuria between the two groups (RR 1.69, 95% CI 0.92 to 3.12).
3. *Prednisolone + chlorambucil versus no treatment*: There was no significant difference in the number of patients with partial remission of proteinuria between the two groups (RR 2.19, 95% CI 0.60 to 7.93).
4. *CSA versus no treatment*: There was no significant difference in the number of patients with partial remission of proteinuria between the two groups (RR 1.80, 95% CI 0.63 to 5.16).

Complete or partial remission of proteinuria - CSA versus any or no treatment

Analysis 1.4

Among the CSA studies ($n = 3$), the addition of CSA increased the number of patients with complete or partial remission of proteinuria, however this increase was not significant (RR 2.15, 95% CI 0.98 to 4.73).

Deterioration of kidney function

Only three studies reported data on kidney function (Cattran 1999; Imbasciati 1980; Ponticelli 1993).

Doubling of serum creatinine

Analysis 2.1

1. *CSA + low dose prednisone versus prednisone*: There was no significant difference in the number of patients with doubling of serum creatinine between the two groups (RR 1.18, 95% CI 0.72 to 1.94).
2. *Prednisolone + chlorambucil versus no treatment*: There was no significant difference in the number of patients with doubling of serum creatinine between the two groups (RR 0.30, 95% CI 0.01 to 6.29).
3. *CSA versus no treatment*: There was no significant difference in the number of patients with doubling of serum creatinine between the two groups (RR 0.60, 95% CI 0.25 to 1.46).

Adverse effects

1. *CSA + low dose prednisone versus prednisone*: Nausea and vomiting was reported in one patient after 12 months in the CSA + low dose prednisone group (Cattran 1999).
2. *CSA + prednisolone versus methylprednisolone*: Twenty-five percent of patients receiving methylprednisolone required hospitalisation due to therapy-related complications while this was not necessary in CSA treated patients (Bhamik 2002).
3. *Prednisolone + chlorambucil versus no treatment*: Adverse reactions were not reported in the study by Imbasciati 1980.
4. *CSA versus no treatment*: Infection, gum hyperplasia, hypertrichosis, transient gastric discomfort, paraesthesia, flushing, epicondylitis, tendinitis, headache and bronchospasm were reported for the patients receiving CSA while infection, cardiac arrhythmia, anaemia, headache and bronchospasm were reported in the control group (Ponticelli 1993).

Implication of health economics

No data could be retrieved from either included or excluded studies addressing the economical impact of treating or not treating idiopathic FSGS in adults.

DISCUSSION

FSGS is a rare and heterogeneous disease resulting in nephrotic range proteinuria and progressive kidney failure. First manifestation is usually between the second and third decade (Kincaid-Smith 1978). ESKD occurs in about half of the patients with proteinuria between 3.5-14 g/24 h within 10 years. All patients with

proteinuria > 14 g/24 h became dialysis-dependent within six years (Velosa 1983). A complete or partial remission was achieved despite treatment in only 19% of all patients (Korbet 1994).

A wide range of treatment protocols for idiopathic FSGS have been published over the years. However, most of these studies concern case-series and retrospective patient evaluations. Only four RCTs (three full publications and one abstract publication) were identified. Three studies investigated the use of CSA, with or without low-dose prednisolone (Bhamik 2002, Cattran 1999, Ponticelli 1993). One study evaluated the effect of an alkylating regimen in combination with chlorambucil and methylprednisolone and oral prednisone (Imbasciati 1980). Pooled meta-analysis of data was not applicable because of different immunosuppressive regimens and slightly different inclusion criteria. However, there was a trend for controlling proteinuria with all regimens but no effect was found regarding preservation of kidney function. This might be due to the overall short duration of follow-up and the small number of patients. Another explanation could be the nephrotoxic effect of CSA outweighs the benefit on urinary protein excretion.

AUTHORS' CONCLUSIONS

Implications for practice

Adult patients treated with CSA at an initial dose of 3.5-5 mg/kg/d in two divided doses perhaps in combination with oral prednisolone 0.15 mg/kg/d are more likely to achieve a partial remission of the nephrotic syndrome compared with symptomatic treatment or prednisolone alone. However, there is a probability of deterioration of kidney function due to the nephrotoxic effect of CSA in the long term. Alkylating substances (e.g. chlorambucil) also have a positive effect on proteinuria but side-effects should be carefully weighted against the lesser toxicity. Data from RCTs in adult FSGS do not support the general use of alkylating substances for this disease at present.

Implications for research

- The number of patients treated in controlled trials is very small and most evidence for the treatment of FSGS in adult patients is based on un-controlled clinical observations. For the use of CSA, a larger RCT with a longer follow-up should be performed to prove the benefit of this regimen not only on proteinuria but also on preservation of kidney function.
- Since there is evidence that alkylating substances have a positive effect on proteinuria and may not be nephrotoxic, a RCT testing CSA versus cyclophosphamide may be warranted.
- Recent research work emphasizes the importance of histological subtypes in FSGS for the response to treatment (Thomas 2006).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bhamik 2002

Methods

Design: Open RCT

Bhamik 2002 (Continued)

Participants	<ol style="list-style-type: none"> 1. Inclusion criteria: biopsy proven primary FSGS, therapy-resistant to oral prednisolone. 2. Country: India. 3. Number: 25 patients. 4. Age: 3 to 49 years.
Interventions	<p>Treatment group CSA plus oral prednisolone 10-40 mg/d for 6 months.</p> <p>Control group Methylprednisolone 250-750 mg IV daily for 7 days followed by weekly administration for at least 12 weeks.</p>
Outcomes	<ol style="list-style-type: none"> 1. Number with CR, PR with stable SCr. 2. ESKD within 3 years. 3. Decline in CrCl.
Notes	<ol style="list-style-type: none"> 1. Previous prednisolone dose 2 mg/kg/d for 8 weeks. 2. ESKD: 1/13 in the treatment group and 4/12 in the control group.
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Low risk A - Adequate

Cattran 1999

Methods	Design: Placebo-controlled RCT Blinding: Single-blind
Participants	<ol style="list-style-type: none"> 1. Inclusion criteria: Biopsy-proven FSGS, proteinuria ≥ 3.5 g/d or ≥ 50 mg/kg, CrCl ≥ 42 mL/min/1.73 m², BP $\leq 135/90$ mm Hg, dietary protein intake ≤ 0.8 g/kg. 2. Country: Canada/USA. 3. Age: 18-70 years. 4. Number: Treatment group (26), control group (23).
Interventions	<p>Treatment group CSA 3.5 mg/kg/d in 2 divided doses and low-dose prednisone at 0.15 mg/kg/d (maximum daily dose 15mg).</p> <p>Control group Placebo in 2 divided doses and prednisone at 0.15 mg/kg/d (maximum daily dose of 15 mg). Duration: 26 weeks, then tapered.</p>
Outcomes	<ol style="list-style-type: none"> 1. Number with CR: proteinuria ≤ 0.3 g/d + stable kidney function. 2. Number with PR: 50% reduction of initial PU and ≤ 3.5 g/d with stable kidney function. 3. Number with ESKD: CrCl < 12 mL/min, start of dialysis or transplantation or study closure.
Notes	<ol style="list-style-type: none"> 1. Prior to therapy both, placebo and treatment group received prednisone for a mean duration of 13 weeks (treatment group, mean dose 120 mg/kg) and 14 weeks (control group, mean dose 100 mg/kg). 2. 11 patients (control group (5), treatment group (6)) received a course of a cytotoxic agent (cyclophosphamide (9), azathioprine (2)) in a dose range of 1-3 mg/kg for a mean of 2 months. 3. All patients were followed for an average of 200 weeks.

Cattran 1999 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Imbasciati 1980

Methods	Design: Open RCT Duration: 6 months
Participants	1. Inclusion criteria: Biopsy-proven FSGS, proteinuria > 1 g/d, SCr < 2 mg/dL. 2. Country: Italy. 3. Number: Treatment group (8), control group (7).
Interventions	Treatment group IV methylprednisolone/oral prednisolone plus chlorambucil. Control group No specific treatment.
Outcomes	1. Number with CR: proteinuria < 100 mg/d. 2. Number with PR: persistent proteinuria but < 50% of baseline value and worsening kidney function.
Notes	1. Reported results are defined as "preliminary". 2. No length of follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ponticelli 1993

Methods	Design: Open prospective RCT
Participants	1. Inclusion criteria: Adults with biopsy-proven FSGS, nephrotic syndrome and CrCl > 80 mL/min/1.73 m ² . 2. Country: Italy 3. Age: 20.1- 57.7 years. 4. Number: Treatment group (10), control group (9).
Interventions	Treatment group 1. CSA orally at the initial dose of 5 mg/kg/d divided in 2 doses. 2. After sixth months CSA was stopped in those who had not obtained either complete or partial remission. For those who responded the dose was reduced by 25% every 2 months, so that CSA was stopped by the end of one year. 3. CrCl: 99.89 ± 35.99 mL/min/1.73 m ² . 4. Proteinuria: 167.15 ± 55.84 mg/m ² /h. Control group

Immunosuppressive treatment for focal segmental glomerulosclerosis in adults (Review)

Ponticelli 1993 (Continued)

1. Supportive treatment only, (excluding corticosteroid and immunosuppressive agents), erythromycin, cotrimoxazole, aminoglycosides, ACEi, NSAIDs, and/or anti-epileptic drugs.
2. Duration: For non-responders 6 months and for responders 6 months then tapered off until end of year.
3. CrCl: 99.42 ± 29.36 mL/min/1.73 m².
4. Proteinuria: 196.16 ± 159.66 mg/m²/h.

Outcomes	<ol style="list-style-type: none"> 1. Number with CR: Proteinuria ≤ 0.2 g/d on 3 non-consecutive days. 2. Number with PR: Proteinuria ≤ 3.5 g/d on 3 non-consecutive days. 3. Number with relapse of nephrotic syndrome: Patients who attained CR or PR but with the reappearance of proteinuria > 3.5 g/d for at least 2 weeks.
Notes	Median duration of follow-up: 18 months (3-24) for treatment group and 24 months (12-24) for control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

ACEi - angiotensin converting enzyme inhibitor; BP - blood pressure; CrCl - creatinine clearance; CR - serum creatinine reduction; CSA - cyclosporin A; ESKD - end-stage kidney disease; FSGS - focal segmental glomerulosclerosis; NSAIDs - nonsteroidal anti-inflammatory drugs; PR - protein reduction; SCr - serum creatinine

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bagga 2003	Design: Prospective clinical trial in children.
Bakir 1996	Design: Case-series.
Banfi 1991	Design: Retrospective case-control study.
Beaufils 1978	Design: Retrospective case-control study.
Bolton 1977	Design: Retrospective study.
Chan 1991	Design: Retrospective case-control study.
Crenshaw 1999	Design: Retrospective case-control study.
Dantal 1998	Design: Case-report.
Dudar 2004	Design: Retrospective study.
El-Reshaid 1995	Design: Case-series.
Emre 2001	Design: Prospective clinical trial in children, Not a RCT.
Garin 1988	Design: Cross-over RCT in children, median age 12 years (3-18).
Goumenos 2006	Design: Retrospective cohort study.

Study	Reason for exclusion
Grcevaska 2006	Design: Retrospective cohort study.
Gulati 2000	Design: Prospective study in children, not a RCT.
Heering 2004	Design: RCT. Patients: 57 nephrotic adults with FSGS, mean age 47 ± 15 years. Interventions: Group 1 (n = 34) prednisolone + aspirin, group 2 (n = 23) prednisolone + chlorambucil. Duration: 6-12 weeks, follow-up 4 years. Outcome measures: CR, PR, ESKD, creatinine, cholesterol, proteinuria. Results: group 1: CR 8/34, PR 13/34, ESKF 4/34; group 2: CR 4/23, PR 11/23, ESKD 5/23.
Ittel 1995	Design: Case-series.
Lee 1995	Design: Multicentre, prospective interventional study, not a RCT.
Lieberman 1996	Design: Randomised double-blind placebo controlled trial. Patients: Children aged 6 months to 21 years.
Medizábal 2005	Design: Prospective clinical trial, not a RCT.
Meyrier 1986	Design: Case-series.
Meyrier 1989	Design: Prospective interventional study, not a RCT.
Meyrier 1994	Design: Case-series.
Mowry 1993	Design: Retrospective case-control study.
Nagai 1994	Design: Retrospective case-control study.
Pei 1987	Design: Retrospective case-control study.
Ponticelli 1999	Design: Retrospective case-control study.
Raafat 2004	Design: Prospective clinical trial, not a RCT.
Rydel 1995	Design: Retrospective clinicopathological study.
Tarshish 1996	Design: RCT in children.
Walker 1990	Design: Randomised cross-over study in adults and children. Patients: An unknown number of patients received CSA and warfarin, and in the other group an unknown number of patients received warfarin alone.
Xia 2003	Design: Prospective clinical trial in children

Characteristics of ongoing studies *[ordered by study ID]*

Chan 2003

Trial name or title	A prospective randomized open-label study to compare mycophenolate mofetil and corticosteroid with conventional immunosuppressive treatment on proteinuria in idiopathic membranous nephropathy (MN) and focal segmental glomerulosclerosis (FSGS)
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Chan 2003 (Continued)

Methods	Treatment, randomized, open label, active control, parallel assignment, safety/efficacy study
Participants	Age: 18 to 65 years Gender: Both Inclusion criteria Abnormal urine protein excretion and biopsy-proven idiopathic membranous nephropathy or focal segmental glomerulosclerosis.
Interventions	Control: Prednisolone Treatment: Prednisolone and mycophenolate mofetil
Outcomes	Primary outcome <ul style="list-style-type: none">Proteinuria Secondary outcome <ul style="list-style-type: none">Adverse effects
Starting date	November 2006
Contact information	Daniel TM Chan Tel: (852) 28554542 Email: dtmchan@hkucc.hku.hk
Notes	

Friedman 2004

Trial name or title	Focal segmental glomerulosclerosis clinical trial (FSGS-CT)
Methods	Treatment, randomized, open label, active control, parallel assignment, efficacy study
Participants	Age: 2 to 40 years Gender: Both Inclusion criteria <ul style="list-style-type: none">Age 2-40 years at onset of signs or symptoms of FSGSAge $\leq$ 40 years at time of randomization (randomization date before 41st birthday)Estimated GFR $\geq$ 40 mL/min/1.73 m² at most recent measure prior to randomization<ul style="list-style-type: none">For participants < age 18 years: Schwartz formulaFor participants $\geq$ age 18 years: Cockcroft-Gault formulaUp/c > 1.0 g protein/g creatinine on first am void at time of randomizationBiopsy confirmed as primary FSGS (including all subtypes) by study pathologist. A minimum of 1 glomerulus demonstrating segmental sclerosis on light microscopy will be required to confirm the diagnosis.Steroid resistance: The participant must have demonstrated steroid resistance (defined as a failure to achieve a sustained Up/c $\leq$ 1.0) based on at least one treatment course with high dose steroids prior to randomization which satisfies both of the following conditions:<ul style="list-style-type: none">minimal treatment duration of 4 weeksminimum cumulative dose of 56 mg/kg or 1680 mg of prednisone or its equivalent. In addition, the participant must not have had a complete remission of proteinuria (Up/c < 0.2 or dipstick urine protein 0/trace) subsequent to the latest qualifying 4-week course demonstrating steroid resistance.

Friedman 2004 (Continued)

- Willingness to follow the clinical trial protocol, including medications, and baseline and follow-up visits and procedures.
- Participants may be taking ACEI, ARB, Vitamin E, or lipid lowering therapy.

Exclusion criteria

- Secondary FSGS
- Prior therapy with sirolimus, CSA, tacrolimus, MMF, or azathioprin (Imuran)
- Treated with cytoxan, chlorambucil, levamisole, methotrexate, or nitrogen mustard in the last 30 days
- Lactation, pregnancy, or refusal of birth control in women of child bearing potential
- Participation in another therapeutic trial concurrently or 30 days prior to randomization
- Active/serious infection (including, but not limited to Hepatitis B, C, or HIV)
- Malignancy
- Blood pressure > 140/95 or > 95th percentile for age/height.
- Participant is receiving 4 or more antihypertensive agents for the primary purpose of controlling blood pressure.
- Participants with previously diagnosed diabetes mellitus type I or II: the diagnosis of DM I or II will be based on local criteria for participants with an established diagnosis. If hyperglycemia is detected during the screening period, the WHO criteria for the diagnosis of DM I and II will be used.
- Clinical evidence of cirrhosis or chronic active liver disease
- Abnormal laboratory values at the time of study entry:
 - * Absolute neutrophil count (ANC) < 2000/mm³, or
 - * Hematocrit (HCT) < 28%
- History of significant gastrointestinal disorder, e.g, severe chronic diarrhea (> 5 watery stools per day) or active peptic ulcer disease.
- Organ transplantation
- Obesity (based on estimated dry weight at onset of disease prior to steroid therapy) defined as
 - * BMI > 97th percentile for age if aged 2-20 years
 - * BMI > 40 kg/m² for age > 21 years
- Allergy to study medications
- Inability to consent/assent

Note: Participants with conditions meeting exclusion criteria at a particular evaluation for eligibility may be re-evaluated at a later time to determine if the conditions have changed so that all entry criteria are met. In particular, if blood pressure > 140/95 or > 95th percentile for age/height while the participant is on less than three antihypertensive agents, the participant may be re-evaluated for eligibility after adding other antihypertensive agents so long as the total number of agents does not exceed three

Interventions
Control: Cyclosporin

Participants assigned to this group will initiate treatment with CSA, 5-6 mg/kg/d with a 250 mg/d maximum starting dose, divided into two daily doses. The CSA dose will be adjusted based on drug levels determined at specified study visits in order to achieve a 12-hour trough concentration in the therapeutic range of 100-250 ng/mL.

Treatment: MMF and Dexamethasone

MMF: 25-36 mg/kg/d with a maximum dose of 2 g/d divided into two daily doses. The dose range reflects the use of fixed size (250 mg) capsules and application of defined daily doses to specific weight ranges. In younger children or those participants who are unable to swallow capsules, a liquid formulation will be used to provide 36 mg/kg/d to a maximum of 2 g/d. The starting MMF dose will be 0.5-0.67 of the full dose for 2 weeks before advancing to the full dose for the duration of the 12-month treatment period.

Dexamethasone: 0.9 mg/kg/dose, with a maximum dose of 40 mg

Friedman 2004 (Continued)

Outcomes

Primary outcomes

- The primary outcome is a 6-level ordinal variable defined based on the achievement of remission from proteinuria during the first 52 weeks after randomization [time frame: first 52 weeks after randomization].

Secondary outcomes

- The main secondary outcome is a 5-level ordinal variable defined based on the persistence of remissions after immunosuppressive agents are withdrawn [time frame: based on the participant's level of proteinuria during the period from week 52 through week 78 following withdrawal of CSA or MMF/Pulse steroids].

Starting date	November 2004
Contact information	Aaron Friedman, MD Tel: +1 401 4445648 Email: AFriedman@Lifespan.org Jennifer Gassman, PhD Tel: +1 216 4449938 Email: fsgs_dcc@bio.ri.ccf.org
Notes	

Liu 2006

Trial name or title	Tacrolimus treatment of patients with idiopathic focal segmental glomerulosclerosis
Methods	Treatment, randomized, open label, active control, parallel assignment, safety/efficacy study
Participants	Age: 15 to 50 years Gender: Both Accepts healthy volunteers Inclusion criteria <ul style="list-style-type: none"> • Age 14-50 years at onset of signs or symptoms of FSGS • Biopsy proven FSGS • Estimated glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m², • Urine protein > 3.5 g/24 h • Biopsy confirmed primary FSGS (including all subtypes) • Willingness to follow the clinical trial protocol, including medications, and baseline and follow-up visits and procedures. Exclusion Criteria: <ul style="list-style-type: none"> • Secondary FSGS • Prior therapy with sirolimus, CSA, MMF, or azathioprin, cytoxan, chlorambucil, levamisole, methotrexate, or nitrogen mustard in the last 90 days • Active/serious infection • Malignancy • Previously diagnosed diabetes mellitus type 1 or 2 • Clinical evidence of cirrhosis or chronic active liver disease • History of significant gastrointestinal disorder • Allergy to study medications, and Inability to consent/assent.

Liu 2006 (Continued)

Interventions	Tracrolimus versus steroids
Outcomes	<p>Primary outcome measures:</p> <ul style="list-style-type: none"> To assess the efficacy of tacrolimus treatment idiopathic focal segmental glomerulosclerosis [time frame:18 months]. <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> To investigate the safety and tolerability of tacrolimus vs steroids in treatment idiopathic focal segmental glomerulosclerosis [time frame: 18 months].
Starting date	March 2006
Contact information	Shijun Li, M.D. Tel: +86 25 80860469 email: lsj8855@yahoo.com.cn
Notes	

NIDDK 2003

Trial name or title	Pulse dexamethasone over 48 weeks for podocyte disease
Methods	<p>Approximately 70 participants, including adults and children older than age 2, will be enrolled in this study. They will receive 48 doses of oral dexamethasone over a period of 48 weeks. One group will take two daily doses every 2 weeks; the other group will take four daily doses every 4 weeks. Doctors will monitor participants before, during, and after the steroid treatment with extensive exams and testing. At the completion of the study, researchers will evaluate the safety and efficacy of the drug treatment</p>
Participants	<p>Age: 2 years and older Gender: Both</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> Adults and children greater than 2.0 years of age are eligible. We will exclude children less than 2.0 years of age in light of the higher risk of steroid therapy in this age group and the higher likelihood genetic or syndromic FSGS, which is less likely to respond to steroids. Diagnosis:A) Biopsy-proven MCD and its variants, including IgM nephropathy and MCD with mesangial hypertrophy.B) Biopsy-proven FSGS, including idiopathic FSGS and collapsing FSGS. We will exclude patients with HIV-associated FSGS, as the risks of steroids are increased in these patients. We will exclude hyperfiltration FSGS associated with morbid obesity (BMI greater than 40 kg/m²), sickle cell anemia, reflux nephropathy, chronic tubular injury, congenital renal anomalies, and reduced nephron mass; the rationale is that these FSGS variants are considered refractory to steroids. Proteinuria: patients must have nephrotic range proteinuria. Baseline tests will be obtained when patients have been off all immunosuppressive therapy for greater than or equal to 1 month. Renal function: estimated GFR must be greater than or equal to 40 mL/min/1.73 m² at the time of study entry; In children weighing less than 40 kg, GFR will be estimated by the Schwartz formula and expressed as GFR/1.73 m²: GFR equal to [0.7 (males) or 0.57 (females) X height (cm)]/serum creatinine. Angiotensin antagonists: Patients must be receiving angiotensin antagonist therapy, at any dose approved by the FDA. Nephrotic range proteinuria will be defined as urine protein greater than or equal to 3.5 g/1.73 m²/d (adults) and greater than 50 mg/kg (children less than 40 kg)

NIDDK 2003 (Continued)

while receiving maximally tolerated dose of angiotensin antagonist therapy for at least 4 weeks prior to study entry.

- f. Prior immunosuppressive therapy: For children with MCD, we require a minimum of 4 weeks and a maximum of 10 weeks of daily steroid therapy at a dose of greater than or equal to 60 mg/m² with proteinuria persisting in the nephrotic range (excluding steroid-sensitive, steroid-dependent and frequently relapsing MCD). For children with FSGS and adults with MCD and FSGS, we require no minimum and a maximum of 8 weeks of daily or alternate day steroids at a dose of greater than 0.5 mg/kg with proteinuria persisting in the nephrotic range. Patients with prior immunosuppressive therapy other than steroids are eligible.
- g. If hypertensive, adequate blood pressure control (target BP less than 125/75 mm Hg at greater than 75% of measurements in adults).
- h. Women with reproductive potential who are sexually active must maintain an effective birth control regimen (oral contraceptive, intrauterine device, or barrier method plus spermicide) and must have a negative urine HCG test prior to beginning therapy.
- i. Patients must either have a negative PPD test within 3 months of study entry while off immunosuppressive therapy or, if they have a history of positive PPD, they must have appropriate evaluation to exclude untreated tuberculosis (with the advice of an Infectious Disease consultant).

Exclusion criteria

1. Patients with diabetes mellitus type 1 will be excluded, as these patients typically have brittle diabetic control that increases the risk of steroid treatment. Patients with diabetes mellitus type 2 will be included they manifest good glycemic control (glycosylated hemoglobin less than 7.5%), if they have lack proliferative retinopathy (the presence of proliferative retinopathy would place them at high risk for vision loss if steroids worsened glycemic control) and if they have had a renal biopsy within 6 months of study entry that shows no evidence for diabetic nephropathy.
2. Poorly controlled hypertension (greater than 25% of values greater than 125/75).
3. Evidence of significant chronic or occult infection. Specifically, subjects must not have evidence of active hepatitis B or hepatitis C infection, or HIV-1 infection, or untreated mycobacterial infection. Minor infections, such as skin or nail fungal infections or other infections with the advice of an Infectious Disease consultant, will not be the basis for exclusion.
4. Immunosuppressive medication other than glucocorticoids, whether for podocyte disease or another indication, must have been discontinued greater than 8 weeks prior to study entry. This does not apply to topical immunosuppressant medication.
5. Pregnancy.
6. Existence of any other condition that would complicate the implementation or interpretation of the study.

Interventions	Patients will receive 48 doses of oral dexamethasone over a period of 48 weeks. Patients will be randomized to one of two arms: 2 daily doses every 2 weeks or 4 daily doses every 4 weeks
Outcomes	Primary outcome <ul style="list-style-type: none">To determine if intermittent oral dexamethasone administered over 48 weeks can induce complete remission. Secondary outcome <ul style="list-style-type: none">Part of a long term effort to define the most effective mode of administering pulse dexamethasone
Starting date	July 2003
Contact information	http://clinicalstudies.info.nih.gov/detail/A_2003-DK-0226.html
Notes	

Trachtman 2005

Trial name or title	Pilot studies of novel therapies to treat resistant focal segmental glomerulosclerosis (FSGS)
Methods	<p>Treatment, randomized, open label, active control, parallel assignment, safety study</p> <ol style="list-style-type: none"> To assess the safety and tolerability of two novel drugs - a TNF-α antagonist and a PPARγ agonist - in patients with resistant FSGS. To conduct a pharmacokinetic (PK) assessment of the selected agents to enable selection of medication regimens for investigation in a randomized Phase II study.
Participants	<p>Age: 2 to 40 years Gender: Both</p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> Aged 2-42 years at onset of proteinuria Aged ≤ 42 years at time of randomization (randomization date before 43rd birthday) Estimated glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m² at most recent measurement prior to randomization <ol style="list-style-type: none"> For patients < age 18 years: Schwartz formula For patients ≥ 18 years: Cockcroft-Gault formula Up/c > 1.0 g/g creatinine on first morning void at time of randomization Biopsy confirmed as primary FSGS (including all subtypes) by study pathologist. Steroid resistance: During the last treatment course with high dose steroids prior to randomization, the patient must have demonstrated steroid resistance defined below and not have had a complete remission of proteinuria (Up/c < 0.2 or dipstick urine protein negative/trace) subsequently. The course of steroid treatment that defines resistance must be the same or equivalent to at least 4 weeks of every day dosing with a minimum cumulative dose of 56 mg/kg or 1680 mg of prednisone or its equivalent. May be taking angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocking agent (ARB), vitamin E, or lipid lowering therapy Willingness to comply with clinical trial protocol, medications, and follow-up visits, etc. Screen failure in FSGS-CT based on prior treatment with excluded medication Treatment failure in FSGS-CT based on failure to achieve remission after 26 weeks or 52 weeks of test therapy, i.e., cyclosporine or mycophenolate mofetil (MMF) + oral dexamethasone pulses <p>Exclusion Criteria</p> <ol style="list-style-type: none"> Secondary FSGS Treated with cyclophosphamide, chlorambucil, levamisole, methotrexate, nitrogen mustard, or other immunosuppressive medications in the 30 days prior to randomization Lactation, pregnancy, or refusal of birth control in women of child bearing potential Participation in another therapeutic trial concurrently or for 30 days prior to randomization Active/serious infection (including, but not limited to hepatitis B or C, HIV) Malignancy Systemic lupus erythematosus (SLE) or multiple sclerosis Hepatic disease defined as serum AST/ALT > 2.5X the upper limit of normal Patients with blood pressure > 140/95 or > 95th percentile for age/height while receiving maximal doses of 3 or more antihypertensive agents. Diabetes mellitus (DM) type I or II. Hematocrit < 30% Organ transplantation Obesity (based on estimated dry weight at disease onset prior to steroid therapy) defined as: <ol style="list-style-type: none"> Body mass index (BMI) > 97th percentile for age if aged 2-20 years BMI > 40 kg/m² if aged ≥ 21 years Allergy to study medications

Trachtman 2005 (Continued)

	15. Inability to consent/assent
Interventions	Control: Active comparator Treatment: Rosiglitazone (Avandia) oral drug administration Control: Active comparator Treatment: Adalimumab (Humira) injection of drug biweekly
Outcomes	Primary outcome <ul style="list-style-type: none"> Safety and tolerance of medications [Time frame: 16 week treatment period] Secondary outcome <ul style="list-style-type: none"> Reduction in proteinuria [Time frame: 16 week treatment period]
Starting date	September 2005
Contact information	http://www.fsgstrial.org/
Notes	

DATA AND ANALYSES

Comparison 1. Remission of proteinuria

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete remission	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 CSA + low dose prednisone versus prednisone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 CSA + prednisolone versus methylprednisolone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Prednisolone + chlorambucil versus no treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 CSA versus no treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Partial remission	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 CSA + low dose prednisone versus prednisone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 CSA + prednisolone versus methylprednisolone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Prednisolone + chlorambucil versus no treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 CSA versus no treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Complete or partial remission (combined end-point)	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 CSA + low dose prednisone versus prednisone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 CSA + prednisolone versus methylprednisolone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Prednisolone + chlorambucil versus no treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 CSA versus no treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Complete or partial remission - CSA versus any or no treatment	3	93	Risk Ratio (M-H, Random, 95% CI)	2.15 [0.98, 4.73]

Analysis 1.1. Comparison 1 Remission of proteinuria, Outcome 1 Complete remission.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.1.1 CSA + low dose prednisone versus prednisone				
Cattran 1999	1/26	0/23		2.67[0.11,62.42]
1.1.2 CSA + prednisolone versus methylprednisolone				
Bhamik 2002	5/13	2/12		2.31[0.55,9.74]
1.1.3 Prednisolone + chlorambucil versus no treatment				
Imbasciati 1980	2/8	1/7		1.75[0.2,15.41]
1.1.4 CSA versus no treatment				
Ponticelli 1993	2/10	0/9		4.55[0.25,83.7]
			Favours control 0.02 0.1 1 10 50 Favours treatment	

Analysis 1.2. Comparison 1 Remission of proteinuria, Outcome 2 Partial remission.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.2.1 CSA + low dose prednisone versus prednisone				
Cattran 1999	9/26	1/23		7.96[1.09,58.15]
1.2.2 CSA + prednisolone versus methylprednisolone				
Bhamik 2002	6/13	4/12		1.38[0.51,3.74]
			Favours control 0.01 0.1 1 10 100 Favours treatment

Analysis 1.3. Comparison 1 Remission of proteinuria, Outcome 3 Complete or partial remission (combined end-point).

Analysis 1.4. Comparison 1 Remission of proteinuria, Outcome 4 Complete or partial remission - CSA versus any or no treatment.

Comparison 2. Deterioration of kidney function

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Doubling of serum creatinine	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 CSA + low dose prednisone versus prednisone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Prednisolone + chlorambucil versus no treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 CSA versus no treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Deterioration of kidney function, Outcome 1 Doubling of serum creatinine.

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
MEDLINE (silver platter)	#1 RANDOMIZED-CONTROLLED-TRIAL in PT #2 CONTROLLED-CLINICAL-TRIAL in PT #3 RANDOMIZED-CONTROLLED-TRIALS #4 RANDOM-ALLOCATION #5 DOUBLE-BLIND-METHOD #6 SINGLE-BLIND-METHOD #7 #1 or #2 or #3 or #4 or #5 or #6 #8 TG=ANIMAL not (TG=HUMAN and TG=ANIMAL) #9 #7 not #8 #10 CLINICAL-TRIAL in PT #11 explode CLINICAL-TRIALS #12 (clin* near trial*) in TI #13 (clin* near trial*) in AB #14 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*) #15 (#14 in TI) or (#14 in AB)

(Continued)

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#16 PLACEBOS
#17 placebo* in TI
#18 placebo* in AB
#19 random* in TI
#20 random* in AB
#21 RESEARCH-DESIGN
#22 #10 or #11 or #12 or #13 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23 TG=ANIMAL not (TG=HUMAN and TG=ANIMAL)
#24 #22 not #23
#25 #24 not #9
#26 TG=COMPARATIVE-STUDY
#27 explode EVALUATION-STUDIES
#28 FOLLOW-UP-STUDIES
#29 PROSPECTIVE-STUDIES
#30 control* or prospectiv* or volunteer*
#31 (#30 in TI) or (#30 in AB)
#32 #26 or #27 or #28 or #29 or #31
#33 TG=ANIMAL not (TG=HUMAN and TG=ANIMAL)
#34 #32 not #33
#35 #34 not (#9 or #25)
#36 #9 or #25 or #35
#37 glomerulosclerosis
#38 glomerulonephritis
#39 nephritis
#40 focal
#41 segmental
#42 (#37 or #38 or #39) and #40
#43 (#37 or #38 or #39) and #41
#44 #42 or #43
#45 #36 and #44
```

EMBASE

```
C= 1 18606361 SELECT ME66;EM74
C= 2 18606361 SELECT ME66;EM74
C= 17 18606361 SELECT ME66;EM74
S= 19.00 2933 FIND CT D GLOMERULOSCLEROSIS, FOCAL
20.01 776 DUPLICATE CANDIDATES IN S= 18.00 (OUTPUT ONLY)
20.02 388 DUPLICATES REMOVED FROM S= 18.00 (OUTPUT ONLY)
21.00 1503 UNIQUE IN S= 18.00
22.00 1470475 FIND CONTROLLED?
23.00 454162 FIND RANDOM?
24.00 1668210 FIND 22 TO 23
25.00 72 FIND 21 AND 24
27.00 13174 FIND CT D META-ANALYSIS
28.00 98233 FIND CT D DOUBLE-BLIND?
29.00 7859 FIND CT D SINGLE-BLIND?
30.00 1686720 FIND 22;23;27;28;29
31.00 265 FIND 19 AND 30
32.00 12764689 PPS=HUMAN
33.00 213 FIND 31 AND 32
ME66: 68 Abstracts
EM74: 145
```

CENTRAL

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#1 MeSH descriptor Glomerulosclerosis, Focal, this term only
#2 ((focal and glomerulo*) or (focal and neph*)):ab,ti,kw
#3 ((segmental and glomerulo*) or (segmental and neph*)):ab,ti,kw
#4 FSGS:ab,ti
#5 (#1 OR #2 OR #3 OR #4)
```

WHAT'S NEW

Date	Event	Description
13 May 2009	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2001

Review first published: Issue 3, 2008

Date	Event	Description
27 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Norbert Braun: Design of review, literature survey, supervision of review process, writing the systematic review.
- Frank Schmutzler: Literature survey, data extraction, data analysis, writing the systematic review.
- Annalisa Perna: Literature survey, data extraction, critical reading of review.
- Catalina Lange: Literature survey, review of data and manuscript.
- Giuseppe Remuzzi: Critical reading and commenting of the review.
- Narelle Willis: Literature survey, finalising the review.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- University Hospital Tübingen, Sektion Nieren- und Hochdruckkrankheiten, Germany.
- HELIOS Kliniken Schwerin, Germany.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Chlorambucil [therapeutic use]; Cyclosporine [therapeutic use]; Glomerulosclerosis, Focal Segmental [*drug therapy]; Immunosuppressive Agents [*therapeutic use]; Prednisone [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans