Notes on the kidney and its diseases for the neurologist

Michael S Zandi, Alasdair J Coles

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To save their patients from dialysis and transplantation, neurologists need simply remain alert to the possibility of renal failure, particularly in the context of systemic disease, diabetes, sepsis and drugs. Of the numerous territories shared by our respective specialities, we outline a pragmatic approach to the diagnosis and treatment of the vasculitides, underpinned by knowing which questions to ask, equally importantly when to ask them, and in the art of obtaining a tissue diagnosis. We consider the current evolving trial evidence that directs the usage of a growing arsenal of therapies in the induction and maintenance stages of vasculitis treatment, and extend this consideration to Lupus and Sjogren's.

KIDNEYS FAIL QUIETLY BUT DRUGS CAN PREVENT PROGRESSION

Remember just how ineloquent the kidney is compared with our organ. To save their patients from the miseries of dialysis and the difficulties of renal transplant life, neurologists should be alert to the possibility of renal failure, particularly in the context of systemic disease, sepsis and drugs. Whatever the situation, if there is a hint of undiagnosed kidney trouble, insist on urine dipstick and microscopy, shortly followed by a renal ultrasound. Then refer early to your local nephrologist. To be helpful, you could add a Bence Jones urinalysis and 24 h quantification of urinary protein and creatinine clearance. While awaiting the renal physician, obsess about the patient's blood pressure. Aggressive control of hypertension can slow down the rate of kidney failure, especially if you use angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists, which are reno-protective over and above their hypotensive effect.¹

Renal vigilance in diabetes

If ever there was a case for worrying about the kidneys, surely it is when seeing the diabetic about this or that neurological complication. If the patient is not plugged into a diabetic service, then refer them, first going through the mantra of dipstick, ultrasound and blood pressure. Diabetes is the leading cause of nephropathy and need for dialysis in the Western world, and is becoming increasingly prevalent (www.who.int). The reno-protective role of ACE inhibitors and angiotensin receptor blockers in diabetes is now well established,² with evidence emerging for a similar effect for peroxisome proliferator activated receptor gamma agonists.³ As far as preventing and treating neuropathy, the EURODIAB prospective

complications study group has shown raised triglyceride level, body mass index, smoking and hypertension as modifiable risk factors, independent of glycaemia.⁴ In addition, watch for the development of erythropoietin as a neuroprotective agent.⁵

Calcineurin inhibitors and renal transplantation

Every ward weary neurologist will have come across the many neurological syndromes associated with the calcineurin inhibitors, which are commonly used to prevent rejection of renal transplants. Ciclosporin and tacrolimus toxicity can cause headache, tremor and ataxia, as well as seizures.⁶ Grapefruit juice and other innocuous agents may provoke toxicity (table 1). Newer agents such as rapamycin (sirolimus) are thought to be less neurotoxic.⁷ A curious association of the use of calcineurin inhibitors is with posterior reversible encephalopathy syndrome, formerly known as reversible posterior leukoencephalopathy syndrome.⁸ This is probably similar pathogenically to hypertensive encephalopathy and has also been associated with renal disease and lupus. Patients can rapidly develop headaches, cortical blindness, altered mental state and seizures. It usually occurs shortly after transplantation and is by and large reversible. A characteristic feature is that the patient looks much better than their grossly abnormal MRI scans would suggest. Malignancies and Epstein-Barr virus related lymphoma develop in 5–10% of renal transplants, a median of 4 years later.⁹

FOCUS ON VASCULITIS

The diagnosis of vasculitis: biopsy, biopsy, biopsy

The problem with many neurologists' approach to vasculitis is the lack of diagnostic precision. Too often the term vasculitis is a soubriquet for "the immune system is somehow involved". For example, lupus causes many things but only very rarely a vasculitis. The pathological classification of the vasculitides, based on vessel wall size, is of little practical help.^{10 11} For the jobbing neurologist, a more utilitarian scheme is presented in fig 1. Roughly speaking, the process is:

- (1) *Could this be a vasculitis mimic?* Pause to consider endocarditis, hepatitis C, HIV, malignancy or drugs?

Abbreviations: ACE, angiotensin converting enzyme; ANCA, antineutrophil cytoplasmic antibodies; BAFF, B cell activating factor or BlyS; IVlg, intravenous immunoglobulin; NPSLE, neuropsychiatric systemic lupus erythematosus; TNF, tumour necrosis factor

See end of article for authors' affiliations

Correspondence to: Alasdair Coles, Department of Clinical Neurosciences, University of Cambridge, Box 165, Addenbrooke's Hospital, Cambridge, UK; ajc1020@medschl.cam.ac.uk

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Table 1 Drugs that increase the levels of immunosuppressive agents and hence may precipitate neurotoxicity

Ciclosporin	Tacrolimus
Fluconazole	Fluconazole
Trimethoprim-sulfamethoxazole	Clotrimazole
Verapamil	Erythromycin
Methylprednisolone (high doses)	Danazol
Erythromycin	
Ciprofloxacin	
Norfloxacin	
Oral contraceptives	
Danazol	
Colchicine	
(Grapefruit juice/high fat diet)	

From EFM Wijdicks. *Neurologic complications in organ transplant recipients*. Oxford: Butterworth Heinemann, 1999. This is an incomplete list.

- (2) *Is the peripheral nervous system or CNS affected?* It is unusual for a vasculitis to affect both in the same patient. Focal deficits with headache, seizures or encephalopathy suggest a vasculitis. Spinal fluid and MRI brain scans may be non-specifically abnormal.¹² Angiograms are often unhelpful, but when characteristic, can save the patient from a tissue biopsy. Serial abrupt painful mononeuropathies suggest a vasculitic neuropathy. But a rampant vasculitis may summate to produce the picture of a symmetrical neuropathy. Vasculitic neuropathies are probably underdiagnosed in the elderly.¹³
- (3) *Is there systemic disease and/or is the patient positive for antineutrophil cytoplasmic antibodies (ANCA)?* Work on the assumption that some other organ is involved. Renal disease must not be missed; it is common, often silent

until severe, and can be fatal. Early identification allows for reno-protective strategies and an easy biopsy option.

- (4) *Which tissue should be biopsied?* Take a leaf from the nephrologists' book and hunt down a tissue diagnosis. With peripheral nerve involvement, encourage your surgeon to take a snip of muscle at the same time to improve diagnostic yield¹⁴; this is particularly easy if you sample the superficial peroneal nerve and underlying peroneus brevis muscle. For CNS disease, if there are no other options, go for a brain and meningeal biopsy, ideally of affected tissue or of the non-dominant frontal lobe or temporal pole (see fig 2). Although these biopsies have complications, so too does managing a cushingoid patient whose undiagnosed illness is no better 12 months and 15 g of cyclophosphamide later.

Treatment of ANCA positive vasculitis

First control the disease

This is the most dangerous phase in the management of vasculitis; you can expect a mortality of 5% in the first 3 months of treatment.¹⁵ Cyclophosphamide and steroids are still the work-horse for inducing remission. Oral cyclophosphamide 2 mg/kg/day (reduced by 25 mg for those over 60 years) and prednisolone 1 mg/kg/day, tapering to 0.25 mg/kg/day, should achieve remission in 90% or more of patients by 6 months (75% by 3 months). Female and black people are more resistant to remission induction.¹⁶ Monthly pulsed intravenous cyclophosphamide (0.75 g/m²) is probably as effective and possibly safer than oral dosing.¹⁷ MESNA can be given to reduce the risk of haemorrhagic cystitis (in three oral doses totalling 75% of the dose of cyclophosphamide for every dose of intravenous cyclophosphamide) although some units rely on vigorous hydration with each dose. A small study has

Working classification of vasculitides affecting the adult nervous system

Figure 1 Classification of the vasculitides. ANCA, antineutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PNS, peripheral nervous system; SLE, systemic lupus erythematosus.

Figure 2 Contrast enhancing meningeal disease, which proved to be due to Wegener's granulomatosis on biopsy, in a 50 year old woman with anterior uveitis and headaches.

shown that ovarian suppression with a gonadotrophin releasing hormone analogue may reduce the rates of premature ovarian failure in women given cyclophosphamide for lupus,¹⁸ following regimens common in cancer.

Then maintain remission

Traditionally, cyclophosphamide (1.5 mg/kg) and prednisolone (as low as possible) were used together for at least 1 year to maintain remission. There is a relapse rate of about 10% a year with this protocol (more with Wegener's and less with microscopic polyangiitis) and 50% will relapse when cyclophosphamide is weaned. The presence of anti-PR3 antibodies and pulmonary involvement are associated with higher relapse rates.¹⁶ However, an important recent multicentre trial showed that the introduction of azathioprine (2 mg/kg/day) after induction of remission is just as efficacious and possibly less toxic than continued cyclophosphamide.¹⁵ Methotrexate (used cautiously up to 0.3 mg/kg/week following the NPSA guidelines (<http://www.npsa.nhs.uk/health/display?contentId=5085>))

may also be useful in limited disease, but relapse rates may be higher.¹⁹

There were high expectations that the addition of etanercept, a soluble tumour necrosis factor (TNF) receptor that mops up TNF, to standard treatment would reduce relapse rates. But these hopes were dashed in a trial of 180 patients with Wegener's, followed for 2 years. Etanercept had no useful efficacy but was associated with six solid malignancies, with none occurring in the control group.²⁰ The most telling finding of a trial of mycophenolate mofetil to induce or maintain remission was that 28/51 patients came off the drug, predominantly because it was ineffective! Of those patients in remission on mycophenolate, a relapse rate of 50% by 14 months is unacceptably high²¹ (see table 2).

Treatment of a relapse

During the early phase of induction treatment, a brief pulse of corticosteroids may be sufficient to treat a relapse while cyclophosphamide begins to bite. Later, in the azathioprine maintenance phase, options for the treatment of a relapse are more steroids, intravenous immunoglobulin (IVIg) or a return to a cyclophosphamide induction regimen. IVIg, which contains anti-ANCA antibodies, is particularly useful in treating flares of vasculitic neuropathies.²² It should be used cautiously in those with renal disease, as it is may be nephrotoxic, perhaps because of the high osmotic load of sucrose containing preparation.²³

WHAT IS NEW IN LUPUS?

The calling card of lupus is the failure, caused in part by genetic susceptibility and the hormonal milieu, to delete pathogenic autoantibodies through B and T cell overactivity, interferon α overexpression by dendritic cells, failure to clear apoptotic debris, faulty inhibitory receptors and a defective complement system.²⁴ A multisystem disorder par excellence, it is a useful model of autoimmunity, with common renal and neurological involvement.

Lupus is not a vasculitis. Leaving aside strokes due to the antiphospholipid syndrome secondarily associated with lupus, CNS manifestations of lupus arise from diffuse dysfunction without structural imaging lesions. "Neuropsychiatric lupus" (NPSLE) consists most frequently of a subcortical cognitive deficit, with impaired verbal fluency and low mood, with normal imaging.^{25, 26} Newly defined antibodies against the NR-2 N-methyl-D-aspartate receptors concentrated in the

Table 2 Recent trials of immunotherapies

Agent	Design	Result	Induction of remission or maintenance	Reference
SLE				
MMF	n = 59 nephritis WHO III or above	MMF as effective as CTX in maintaining remission once induced with CTX	Maintenance	Contreras ⁴²
MMF	n = 140, non-inferiority open label	MMF more effective than CTX in inducing remission	Induction	Ginzler <i>et al</i> ⁸⁰
AZA	n = 32, equivalence	No difference between pulsed CTX with MP, and oral CTX induction followed by Pred and AZA	Induction	Yee ⁴³ (see also Contreras ⁴²)
ANCA associated vasculitis				
AZA	n = 144, equivalence	AZA is as effective, and probably safer, in maintaining remission than CTX	Maintenance	Jayne ¹⁵
Infliximab (anti-TNF α)	Two groups. prospective open label n = 16 acute, n = 16 persistent.	88% achieved remission, but 20% severe infection. (CTX and Pred given in conjunction)	Induction	Booth ⁴⁴
Etanercept (competitive inhibitor)	n = 180, placebo (+CTX/Pred) controlled	Ineffective at maintaining remission in Wegener's.	Maintenance	WGET ²⁰
Sjögren's IFN- α	n = 3 case reports	Reduction of symptoms and antibody titres		Yamada ³⁵

ANCA, antineutrophil cytoplasmic antibodies; AZA, azathioprine; CTX, cyclophosphamide; IFN- α , interferon α ; MMF, mycophenolate mofetil; MP, methylprednisolone; Pred, prednisolone; TNF α , tumour necrosis factor α .

Table 3 Some newer experimental treatments—a rapidly evolving list

Drug name	Construction	Target	Effect	Possible future indication	Reference
Rituximab (Mabthera)	Chimeric (murine/human)	CD20	B depletion with minimal effect on immunoglobulins or ANCA	RA, ANCA associated vasculitis. Lupus (no large randomised trials yet)	Edwards ⁴⁶
Epratuzumab	Humanised	CD22 (internalisation)	Non-depleting	Sjögren's and lupus, ?in combination with depleting drugs?	Dorner ⁴⁷
Alemtuzumab (Campath-1H)	Humanised	CD52 (T and B cells)	Sustained T depletion	Behcet's	Lockwood ⁴⁸
Abatacept (Orencia) (CTLA-4Ig)	Recombinant fusion protein	B7(CD80,86): CD28 B, T costimulation		Rheumatoid arthritis, lupus	Genovese ⁴⁹
TACI-Ig	Murine, experimental	BAFF blockade	Reduce B proliferation	Lupus, ?in combination	Ramanujam ⁵⁰
Belimumab, lymphostat B antiCD40L	Human	Anti-BAFF	Reduce B proliferation	Sjögren's	Ding ⁵¹
		CD40-CD40L	Costimulatory blockade	Lupus. Abandoned due to thrombosis	Nakamura ⁵²
Anti-IL6 (tocilizumab/MRA)	Humanised	IL-6	Targets the proinflammatory cytokine	RA, Crohn's, juvenile arthritis, ?lupus	Maini ⁵³
CDK/GSK-3 inhibitors	Small molecule		Multifactorial, including cell cycle arrest in proliferating cells (early trials in IgA nephropathy)	Proliferative renal disease	Soos (DNP 2006) ⁵⁴
Gene therapy			To restore normal T cell phenotypes	Lupus, global.	Kyrtaris ⁵⁵
Stem cell transplant				Lupus, global	Tyndall ⁵⁶

ANCA, antineutrophil cytoplasmic antibodies; Ig, immunoglobulin; IL, interleukin; RA, rheumatoid arthritis.

hippocampus may be responsible for this, with anti-ribosomal P seen with frank psychosis and seizures,^{27–28} the other major manifestations of NPSLE.

The big news in the treatment of lupus is mycophenolate mofetil. Mycophenolate mofetil and steroids have been shown to be more effective, and safer, at inducing remission than cyclophosphamide in two trials totalling 182 patients with lupus nephritis.^{29–30} There is no reason to think that mycophenolate mofetil will have any different effect on NPSLE but that has not yet been proved. A controlled trial has shown no additional benefit of plasma exchange to standard therapy in lupus nephritis.³¹ The role of B cell depleting or co-stimulatory blocking antibodies awaits trial.

WHAT IS NEW IN SJÖGREN'S?

Mice that are transgenic for the BAFF (B cell activating factor or BLYS) develop an illness similar to Sjögren's as they age. In addition, in humans with the real disease, serum BAFF is elevated. The thinking is that BAFF over expression leads to

excessive survival signals to autoreactive B cells.³² This may also explain the significantly increased incidence of B cell lymphoma in patients with primary Sjögren's.³³ A comprehensive case series of Sjögren's neuropathy suggests that autonomic involvement is common and that the sensory ataxic, painful and perhaps trigeminal neuropathies are not vasculitic, whereas multiple mononeuropathy and multiple cranial neuropathy are.³⁴ We await news on the effects of B cell depletion in Sjögren's, which can be very resistant to standard immunotherapy. In just three patients, interferon α was reported to be beneficial for the neuropathy associated with Sjögren's.³⁵

THE BIOLOGICAL REVOLUTION

The new biological therapies (table 3) hold much promise,³⁶ although there are very few long term data, randomised controlled trials are few, and in them severe disease is often excluded. There have also been some nasty surprises with biologicals. For instance, the anti-TNF drugs have worsened multiple sclerosis^{37–38} and, in an unreported single case, Behcet's

Figure 3 A 59-year-old woman with Behcet's syndrome and a spastic paraparesis who developed worsening leg weakness 2 weeks after starting Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody 3 mg/kg).

Five key points

- (1) *Kidneys fail quietly.* The neurologist should pay attention to urine dipstick results and, if concerned, request urine microscopy, renal ultrasound and quantification of creatinine and protein clearance, before referring to the nephrologist.
- (2) *Obsess about blood pressure.* ACE inhibitors, or angiotensin II receptor antagonists, are more reno-protective than drugs with similar hypotensive effects.
- (3) *Ask four questions to classify vasculitis.* Could this be a vasculitis mimic? Is the peripheral nervous system or CNS affected? Is there systemic disease and/or is the ANCA positive? And then, above all, which tissue should be biopsied?
- (4) *To treat ANCA associated vasculitis,* induce remission with pulsed intravenous cyclophosphamide and corticosteroids, then maintain remission with steroids and azathioprine or methotrexate. Consider IVIg for the treatment of a relapse, especially of the vasculitic neuropathies, that has not responded to corticosteroids.
- (5) *To treat lupus.* Mycophenolate mofetil and steroids can induce, and maintain, remission in lupus renal disease, more safely than cyclophosphamide. Probably the same is true for neuropsychiatric lupus, which is associated with antibodies against NR-2 N-methyl-D-aspartate receptors.

disease (fig 3). A class of drugs to watch, without doubt, is rituximab and the other B lymphocyte depleting monoclonal antibodies. Licensed for the treatment of B cell lymphomas, it has quickly carved a niche for itself in the treatment of diseases that have been regarded as B cell diseases, such as lupus, and others that have not, such as rheumatoid arthritis. However, 60% of patients with lupus or vasculitis will relapse within 2 years.³⁹ Furthermore, antiglobulin antibodies may limit efficacy.⁴⁰ Also, rituximab treatment may not be as innocuous as first hoped; in December 2006, the FDA issued an alert (<http://www.fda.gov/medwatch/safety/2006/safety06.htm#rituxan>) about the use of rituximab in lupus following the death of two patients with progressive multifocal leukoencephalopathy out of an estimated 8000 patients with systemic lupus erythematosus treated with rituximab worldwide. This news not only needs to temper enthusiasm for prescribing the drug and inform patients considering it, but units administering B cell depleting antibodies need to develop protocols for ensuring that patients developing neurological symptoms are assessed promptly with progressive multifocal leukoencephalopathy in mind (much as has been done following reports of progressive multifocal leukoencephalopathy after natalizumab treatment of multiple sclerosis⁴¹).

Authors' affiliations

Michael S Zandi, Alasdair J Coles, Department of Clinical Neurosciences, University of Cambridge, Box 165, Addenbrooke's Hospital, Cambridge, UK
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REFERENCES

- 1 Maschio G, Alberti D, Janin G, *et al.* Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med* 1996;**334**:939–45.
- 2 Lewis EJ, Hunsicker LG, Clarke WR, *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**:851–60.
- 3 Sarafidis PA, Bakris GL. Protection of the kidney by thiazolidinediones: An assessment from bench to bedside. *Kidney Int* 2006;**70**:1223–33.
- 4 Tesfaye S, Chaturvedi N, Eaton SE, *et al.* Vascular risk factors and diabetic neuropathy. *N Engl J Med* 2005;**352**:341–50.
- 5 Lipton SA. Erythropoietin for neurologic protection and diabetic neuropathy. *N Engl J Med* 2004;**350**:2516–17.
- 6 Guarino M, Ito-Leon J, Decruyenaere J, *et al.* EFNS guidelines on management of neurological problems in liver transplantation. *Eur J Neurol* 2006;**13**:2–9.
- 7 Marambaou BV, Wijdsick EF. Sirolimus may not cause neurotoxicity in kidney and liver transplant recipients. *Neurology* 2004;**63**:1958–9.
- 8 Hinchey J, Chaves C, Appignani B, *et al.* A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996;**334**:494–500.
- 9 Baccarani U, Adani GL, Montanaro D, *et al.* De novo malignancies after kidney and liver transplantations: experience on 582 consecutive cases. *Transplant Proc* 2006;**38**:1135–7.
- 10 Jennette JC, Falk RJ, Andrasz K, *et al.* Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994;**37**:187–92.
- 11 Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997;**337**:1512–23.
- 12 Cikes N. Central nervous system involvement in systemic connective tissue diseases. *Clin Neurol Neurosurg* 2006;**108**:311–17.
- 13 Chia L, Fernandez A, Lacroix C, *et al.* Contribution of nerve biopsy findings to the diagnosis of disabling neuropathy in the elderly. A retrospective review of 100 consecutive patients. *Brain* 1996;**119**(Pt 4):1091–8.
- 14 Vital C, Vital A, Canron MH, *et al.* Combined nerve and muscle biopsy in the diagnosis of vasculitic neuropathy. A 16-year retrospective study of 202 cases. *J Peripher Nerv Syst* 2006;**11**:20–9.
- 15 Jayne D, Rasmussen N, Andrasz K, *et al.* A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003;**349**:36–44.
- 16 Hogan SL, Falk RJ, Chin H, *et al.* Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann Intern Med* 2005;**143**:621–31.
- 17 Haubitz M, Schellong S, Gobel U, *et al.* Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. *Arthritis Rheum* 1998;**41**:1835–44.
- 18 Somers EC, Marder W, Christman GM, *et al.* Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. *Arthritis Rheum* 2005;**52**:2761–7.
- 19 de Groot K, Rasmussen N, Bacon PA, *et al.* Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005;**52**:2461–9.
- 20 Tanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005;**352**:351–61.
- 21 Koukoulaki M, Jayne DR. Mycophenolate mofetil in anti-neutrophil cytoplasmic antibodies-associated systemic vasculitis. *Nephron Clin Pract* 2005;**102**:c100–7.
- 22 Jayne DR, Chapel H, Adu D, *et al.* Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *QJM* 2000;**93**:433–9.
- 23 Orbach H, Tishler M, Shoenfeld Y. Intravenous immunoglobulin and the kidney – a two-edged sword. *Semin Arthritis Rheum* 2004;**34**:593–601.
- 24 Diamond B. Systemic lupus erythematosus and Sjögren syndrome. *Curr Opin Rheumatol* 2006;**18**:449–50.
- 25 Brey RL, Holliday SL, Saklad AR, *et al.* Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. *Neurology* 2002;**58**:1214–20.
- 26 Leritz E, Brandt J, Minor M, *et al.* "Subcortical" cognitive impairment in patients with systemic lupus erythematosus. *J Int Neuropsychol Soc* 2000;**6**:821–5.
- 27 DeGiorgio LA, Konstantinov KN, Lee SC, *et al.* A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. *Nat Med* 2001;**7**:1189–93.
- 28 Reichlin M. Ribosomal P antibodies and CNS lupus. *Lupus* 2003;**12**:916–18.
- 29 Chan TM, Li FK, Tang CS, *et al.* Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *N Engl J Med* 2000;**343**:1156–62.
- 30 Ginzler EM, Dooley MA, Aranow C, *et al.* Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005;**353**:2219–28.
- 31 Lewis EJ, Hunsicker LG, Lan SP, *et al.* A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. *N Engl J Med* 1992;**326**:1373–9.
- 32 Groom J, Kallied SL, Cutler AH, *et al.* Association of BAFF/BlyS overexpression and altered B cell differentiation with Sjögren's syndrome. *J Clin Invest* 2002;**109**:59–68.
- 33 Theander E, Henriksson G, Ljungberg O, *et al.* Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors. *Ann Rheum Dis* 2006;**65**:796–803.
- 34 Mori K, Iijima M, Koike H, *et al.* The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. *Brain* 2005;**128**:2518–34.
- 35 Yamada S, Mori K, Matsuo K, *et al.* Interferon alpha treatment for Sjögren's syndrome associated neuropathy. *J Neurol Neurosurg Psychiatry* 2005;**76**:576–8.
- 36 Chan AT, Flossmann O, Mukhtyar C, *et al.* The role of biologic therapies in the management of systemic vasculitis. *Autoimmun Rev* 2006;**5**:273–8.
- 37 The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. *Neurology* 1999;**53**:457–65.

- 38 **Van Oosten BW**, Barkhof F, Truyen L, *et al.* Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. *Neurology* 1996;**47**:1531–4.
- 39 **Smith KG**, Jones RB, Burns SM, *et al.* Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. *Arthritis Rheum* 2006;**54**:2970–82.
- 40 **Mirick GR**, Bradt BM, Denardo SJ, *et al.* A review of human anti-globulin antibody (HAGA, HAMA, HACA, HAHA) responses to monoclonal antibodies. Not four letter words. *Q J Nucl Med Mol Imaging* 2004;**48**:251–7.
- 41 **Yousry TA**, Major EO, Ryschkewitsch C, *et al.* Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 2006;**354**:924–33.
- 42 **Contreras G**, Pardo V, Leclercq B, *et al.* Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 2004;**350**:971–80.
- 43 **Yee CS**, Gordon C, Dostal C, *et al.* EULAR randomised controlled trial of pulse cyclophosphamide and methylprednisolone versus continuous cyclophosphamide and prednisolone followed by azathioprine and prednisolone in lupus nephritis. *Ann Rheum Dis* 2004;**63**:525–9.
- 44 **Booth A**, Harper L, Hammad T, *et al.* Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol* 2004;**15**:717–21.
- 45 **Seo P**, Min YI, Holbrook JT, *et al.* Damage caused by Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGTE). *Arthritis Rheum* 2005;**52**:2168–78.
- 46 **Edwards JC**, Szczepanski L, Szechinski J, *et al.* Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;**350**:2572–81.
- 47 **Dorner T**, Kaufmann J, Wegener WA, *et al.* Initial clinical trial of epratuzumab (humanized anti-CD22 antibody) for immunotherapy of systemic lupus erythematosus. *Arthritis Res Ther* 2006;**8**:R74.
- 48 **Lockwood CM**, Hale G, Waldman H, *et al.* Remission induction in Behcet's disease following lymphocyte depletion by the anti-CD52 antibody CAMPATH 1-H. *Rheumatology (Oxford)* 2003;**42**:1539–44.
- 49 **Genovese MC**, Becker JC, Schiff M, *et al.* Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005;**353**:1114–23.
- 50 **Ramanujam M**, Wang X, Huang W, *et al.* Mechanism of action of transmembrane activator and calcium modulator ligand interactor-Ig in murine systemic lupus erythematosus. *J Immunol* 2004;**173**:3524–34.
- 51 **Ding C**, Jones G. Belimumab Human Genome Sciences/Cambridge Antibody Technology/GlaxoSmithKline. *Curr Opin Investig Drugs* 2006;**7**:464–72.
- 52 **Nakamura M**, Tanaka Y, Satoh T, *et al.* Autoantibody to CD40 ligand in systemic lupus erythematosus: association with thrombocytopenia but not thromboembolism. *Rheumatology (Oxford)* 2006;**45**:150–6.
- 53 **Maini RN**, Taylor PC, Szechinski J, *et al.* Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006;**54**:2817–29.
- 54 **Soos TJ**, Meijer L, Nelson PJ. CDK/GSK-3 inhibitors as a new approach for the treatment of proliferative renal diseases. *Drug News Perspect* 2006;**19**:325–8.
- 55 **Kyrtaris VC**, Sfrikakis PP, Juang YT, *et al.* Gene therapy in systemic lupus erythematosus. *Curr Gene Ther* 2005;**5**:677–84.
- 56 **Tyndall A**, Saccardi R. Haematopoietic stem cell transplantation in the treatment of severe autoimmune disease: results from phase I/II studies, prospective randomized trials and future directions. *Clin Exp Immunol* 2005;**141**:1–9.

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