Review of refractory lupus nephritis

Despite significant advances in the management of patients with lupus nephritis, a significant proportion of patients either do not respond to first-line immunosuppressive drugs, or relapse after having achieved initial remission. Various factors including ethnicity, gender, genetics, clinical features, serology and histology affect response to therapy and prognosis. The term 'refractory nephritis' is used for those patients who have no or partial response to first-line therapies, which include cyclophosphamide and mycophenolate mofetil. Alternative therapies that are currently available include the 'multitarget therapy' and various biologics that target B cells, T cells or different cytokines. Among these, multitarget therapy, which includes cyclosporine, mycophenolate mofetil and prednisolone, and the anti-CD20 antibody rituximab, alone or in combination with immunosuppressives, have demonstrated efficacy in treating refractory nephritis. In this review, we will discuss the definition of refractory nephritis and partial and complete responses, various factors associated with refractory nephritis, followed by an overview of the treatment of lupus nephritis, and finally on the various drugs currently available and potential new agents for the treatment of refractory nephritis.

KEYWORDS: belimumab ■ lupus nephritis ■ refractory ■ rituximab ■ triple therapy

Shabina Habibi

Department of Rheumatology, Nizam's Institute of Medical Sciences, Hyderabad, 500082, India
Tel.: +91 040 23489000
shabina.h@gmail.com

Systemic lupus erythematosus (SLE) is an extremely heterogeneous, multisystem, autoimmune disease, characterized by the presence of multiple autoantibodies and deposition of immune complexes in various tissues. Nephritis, which is the most frequent serious manifestation of the disease, can affect up to 60% of adults and 80–90% of children throughout the course of illness [1,2]. Untreated it has a dismal prognosis, with 5-year survival rates varying from 0 to 20%. The introduction of corticosteroids and then immunosuppressive therapies, namely cyclophosphamide (CYP) and, more recently, mycophenolate mofetil (MMF), which is less toxic than CYP with regard to gonadal toxicity, have improved prognosis, such that 5-year survival rates are approximately 95%, and at 10 years 90% [3]. Rates of end-stage renal failure (ESRF) have, however, remained static at 10–20% despite the effective therapies available [3]. Response to therapy is slow and often incomplete, with approximately 25–50% patients experiencing remission (both partial and complete) at 2 years, and the majority having a relapse after 5 years, despite continuous immunosuppressive therapy [4].

The term 'refractory nephritis' is used for those patients with none or partial response to first-line therapies, namely CYP or MMF. Response criteria for lupus nephritis clinical trials have been established by the ACR, on the basis of the effects of treatment on renal function, proteinuria and urinary sediments [5]. These have been endorsed by a European consensus statement in 2009 [6]. A complete response is defined as inactive urinary sediment, a decrease in proteinuria to ≤0.2 g/day and normal or stable renal function. A sustained response of 3–6 months is considered a remission, but cannot be judged to be complete remission in the absence of a biopsy. Partial response is a level of improvement defined as an inactive urinary sediment, proteinuria <0.5 g/day, with normal or stable renal function. Recently, the European League Against Rheumatism (EULAR)-European Dialysis and Transplant Association (EDTA) have published definitions of response in lupus nephritis [7]. Complete renal response is defined as urine protein:creatinine ratio <50 mg/mmol and normal or near normal (within 10% of normal glomerular filtration rate [GFR] if previously abnormal) GFR. Partial renal response is defined as >50% reduction in proteinuria to subnephrotic levels and normal or near normal GFR. This should be achieved preferably by 6 months and no later than 12 months following treatment initiation. Improvement is defined as any reduction in proteinuria and normalization or stabilization of GFR. Switching to an alternative agent is recommended for patients who do not improve within 3–4 months, or those

Future Medicine part of fsg

who do not achieve partial remission within 6–12 months or complete remission within 2 years [7].

Flare is an increase in disease activity, requiring more aggressive immunosuppressive therapy. A renal flare is indicated by an increase in proteinuria, serum creatinine, presence of active urine sediments or a decrease in creatinine clearance. It may be a proteinuric, nephritic or a severe nephritic flare. Nephritic flares are common, even in those patients who achieve complete response [8]. Patients with nephritic flares have a higher risk of developing doubling of serum creatinine and ESRD over the long term as compared with those with proteinuric flares [9].

Factors affecting prognosis

The prognosis of nephritis is unpredictable. Various demographic, clinical, histological and serologic factors affect the outcome (**Box 1**) [10]. Individual risk factors are extremely heterogeneous and vary in their overall impact. Those patients with the highest number of risk factors are likely to have more aggressive disease with a worse prognosis.

The incidence of nephritis is higher, and its severity greater, in African, Asian and Latin American individuals, as compared with Caucasians [11–13]. Patients of African–American ethnicity also have a less favorable response to CYP with greater flares, both nephritic and proteinuric, compared with Caucasians [14]. Male gender and juvenile-onset SLE have also been associated with a higher incidence and more severe nephritis [12,15–17]. Various other features such as nephrotic syndrome, azotemia, presence of antiphospholipid antibodies, high activity index and marked chronic changes on histopathology, class III, IV and combined class IV/V, have also indicated adverse prognosis in different studies.

Long-term follow-up of the Euro-Lupus trial concluded that early response to therapy at 6 months, defined as a decrease in serum creatinine and proteinuria <1 g/24 h, was the best predictor of good long-term renal outcome [18,19]. Overall 10-year survival rates and renal survival rates are better in patients who attain complete remission (95 and 94%, respectively) as compared to those who attain partial remission (76 and 45%, respectively) or no remission (45 and 19%, respectively) [20]. Similarly, failure to attain complete remission at 6 months predicts renal relapse and ESRD in the long term [21].

Box 1. Factors associated with adverse prognosis in lupus nephritis.

Demographic

- Black race, male gender, juvenile-onset disease

Clinical

- Hypertension, pregnancy, failure to achieve or a marked delay (>2 years) to achieve remission

Laboratory

- Azotemia, nephritic urinary sediment, nephrotic syndrome, presence of antiphospholipid antibodies, anemia, thrombocytopenia

Histologic

- Proliferative or mixed membranous and proliferative nephritis, high activity index, marked chronicity

Overview of the treatment of lupus nephritis

Treatment of lupus nephritis is a challenge despite recommendations published by the ACR and more recently the EULAR/EDTA, due to overall poor response to recommended treatment. It is divided into two phases: induction of remission and maintenance of remission. The recently published ACR guidelines for the management of lupus nephritis have recommended that all patients with clinical evidence of nephritis, who were previously untreated, undergo a renal biopsy to classify the glomerular disease by the ISN/RPS classification and evaluate for activity, chronicity, vascular and tubular lesions [22]. The EULAR/EDTA also recommend biopsy in patients with any sign of renal involvement, especially in those with reproducible proteinuria >0.5 g/24 h with glomerular hematuria and cellular casts [7].

In patients with proliferative nephritis, CYP, administered either as the modified NIH regime or the Euro-Lupus regime, or MMF, are used for inducing remission [22]. A recent meta-analysis considered both these drugs to be of equivalent efficacy [23]. In certain situations, for example, African–American and Hispanic individuals and in certain patients to avoid premature ovarian failure, MMF is preferred as the first choice for induction of remission [14,24]. The Euro-Lupus regime of low dose CYP pulse therapy has demonstrated the same efficacy as the NIH regime over 10 years, with better safety [19]. This trial included predominantly Caucasian and not blacks or Hispanic individuals. Thus the recent ACR guidelines recommend this low-dose therapy only for patients of western or southern European backgrounds [22].

Either azathioprine or MMF is used as maintenance therapy once remission is achieved [22]. The maintenance phase of the ALMS trial showed superior efficacy of MMF to maintain remission [25]. The MAINTAIN nephritis trial on the other hand showed equivalent efficacy and safety [26]. The ALMS trial included patients of

diverse ethnicity and different geographic regions, treated with either high-dose CYP (modified NIH protocol) or MMF in the induction phase, whereas the MAINTAIN trial was an extension of the Euro-Lupus trial, which predominantly included Caucasians with active nephritis who were treated with low-dose CYP (Euro-Lupus regime) for induction of remission.

Adjunctive therapy includes hydroxychloroquine, which decreases flare rate and there is significantly lesser damage accrual, including renal damage in patients on hydroxychloroquine [27–29]. For patients with proteinuria, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are required. These agents reduce the intraglomerular pressure and delay doubling of serum creatinine and progression to end-stage renal disease [25]. Control of hypertension with target values <130/80 mmHg, and hyperlipidemia in patients with LDL cholesterol >100 mg/dl with statins is also essential [101,102].

Treatment of refractory lupus nephritis

There is no international consensus on the definition of refractory lupus nephritis. According to NIH criteria refractory patients are those who show no response to treatment and those in whom proteinuria does not decrease to less than half of pretreatment value or to <3 g/day and who have persistent active urinary casts or deterioration in serum creatinine level [30]. According to the EULAR consensus statement, nonresponders or patients with treatment failure are those who do not achieve even a partial response [6]. Switching to an alternative agent is recommended in patients who fail to improve within 3–4 months, do not achieve partial response after 6–12 months or complete response after 2 years [7]. Switching to another first-line drug, for example, MMF if the patient received CYP, and vice versa may be attempted [22,31]. Additionally, alternative treatments as given below may also be considered.

Calcineurin inhibitors

Cyclosporine (CsA) is a prodrug, which after binding to its cytoplasmic receptor cyclophyllin, subsequently binds to calcineurin, and interferes with IL-2 production, which causes T-cell activation and thus it dampens T-cell cytokine production. It also causes cell arrest in G0–G1 phase of the cell cycle, thus decreasing T-cell proliferation [32]. It also stabilizes the actin skeleton of the podocytes and decreases proteinuria [33]. Tacrolimus binds to a different receptor, FK-binding protein-12, which then interacts with calcineurin, inhibiting IL-2 production. These drugs have been successfully used to treat refractory nephritis.

An initial trial of 18 patients with proliferative nephritis, refractory to conventional therapy, when administered CsA at 5 mg/kg/day, demonstrated reduction in proteinuria, improvement in renal function and decrease in the dose of corticosteroids [34]. A trial that compared cyclosporine with CYP as induction and maintenance in patients with active proliferative nephritis demonstrated comparable efficacy of both the drugs [35]. A multicenter randomized controlled trial of 75 patients with diffuse proliferative nephritis, compared the efficacy of CsA versus azathioprine as maintenance therapy after induction of remission with 3 months of prednisolone and oral CYP [36]. Treatment was continued for 4 years. The flare rates were comparable (7 in CsA group versus 8 in the azathioprine group), and there was no difference in the proteinuria and blood pressure levels, with both the drugs being well tolerated. Significantly higher number of patients in the CsA group had undetectable proteinuria (42 vs 15%). Another trial of ten patients randomized to receive prednisolone or CsA for 1 year showed that proteinuria decreased significantly in patients receiving CsA (i.e., from 2.5 g/day to 0.14 g/day) [37]. Hence CsA is an effective option for patients with refractory nephritis, especially to decrease proteinuria and the cumulative corticosteroid dose.

A study compared multitarget therapy (MT) comprising tacrolimus, MMF and prednisolone with intravenous (iv.) CYP in patients with biopsy proven combined class V and IV LN for 6, or 9 months if complete remission was not achieved [38]. Enrolled patients (n = 40) had preserved renal function, proteinuria 4.4 ± 2.0 g/day and 70% had previously been treated with MMF or CYP. Rates of complete remission were higher both at 6 and 9 months with MT (50 and 65%, respectively) as compared with iv. CYP (5 and 15%, respectively). Rates of partial remission at 6 months were similar in both groups (40%). At 9 months partial remission was observed in 30% in the MT group and 40% in the iv. CYP group. Adverse events were more frequent in the iv. CYP group, but new onset of hypertension was seen in the MT group. This study highlighted the role of MT in the treatment of mixed class IV and V LN, which responds less well to conventional immunosuppressives and has a poor prognosis.

In another study of seven LN patients refractory to MMF, it was shown that when tacrolimus was added (dual therapy), one patient

achieved complete response, three attained partial response and one had a reduction in proteinuria [39]. However, toxicity limited the use of tacrolimus in five patients (diabetic ketoacidosis in one, proteinuria in two and muscle pain in two patients), but there was no severe nephrotoxicity.

The study concluded that MT is a good option in refractory cases, but patients must be monitored for possible side effects.

A recent study of 70 patients with proliferative and membranous nephritis, who were treated with MMF, of whom 23 failed treatment and 17 received tacrolimus in combination with MMF [40]. Twelve out of 17 (70%) responded (six complete remission and six partial remission), four of whom relapsed at 19 ± 6 months. The study concluded that combination with tacrolimus is a safe and effective option for MMF-resistant patients.

Hence tacrolimus, either as monotherapy or as multitarget therapy is an option in patients refractory to CYP or MMF or both.

Table 1 summarizes the results of various trials with calcineurin inhibitors in refractory lupus nephritis.

Leflunomide

Leflunomide, which is currently used as a disease-modifying drug in patients with rheumatoid arthritis, has demonstrated efficacy in patients with lupus nephritis refractory or intolerant to standard drugs [41]. Nineteen patients with lupus nephritis, of whom 12 were refractory to CYP, were given a loading dose of leflunomide of 100 mg/day for 3 days followed by 20 mg/day for a mean of 52 weeks. Thirteen out of 17 (76%) patients achieved a response. Complete response was observed in five out of 17 (29%) and partial response in eight out of 17 (47%) patients.

Another Chinese study of 51 nephritis patients, 15 of whom had relapsing disease demonstrated total response in 60% and complete remission in 6.7% of the patients when treated with leflunomide [42].

Intravenous immunoglobulin

In a small randomized trial, iv. immunoglobulin (400 mg/kg monthly for 18 months) was as effective as iv. CYP pulse (1 g/m^2 every 2 months for 6 months and then every quarterly for 1 year) as maintenance therapy in patients with proliferative nephritis [43]. Although there are reviews on the efficacy of this drug, controlled trials are required [44,45]. Adverse reactions have been reported in up to 20% of infusions, most of which are minor and transient, such as headache and transfusion-related reactions [46]. Potential serious reactions that can occur in 2–6% of patients include hemolysis, thrombotic complications, aseptic meningitis and acute renal failure [47].

Biologic agents

Various biologics have been tried in uncontrolled studies in patients with relapsed or refractory lupus nephritis (Table 2). However, the small number of patients, short follow-up and different regimes used warrant caution when interpreting these studies. Biologics that target B cells, T cells or cytokines and complement components have been tried. Among the various biologics, there is much greater experience with B-cell directed therapies, especially rituximab.

B-cell directed therapies

B cells are central in the pathogenesis of lupus nephritis. These produce pathogenic autoantibodies, act as antigen presenting cells for autoreactive T cells, provide costimulatory support for T-cell activation and produce a

Table 1. Trials with calcineurin inhibitors in refractory lupus nephritis.

Study (year)	Patients (n)	Drug	Effectiveness	Ref.
Favre *et al.* (1989)	18	CsA 5 mg/kg/day	Reduction in proteinuria, improvement in renal function and decrease in the dose of corticosteroids	[34]
Zavada *et al.* (2010)	40	CsA vs CYP for induction	Comparable efficacy of both drugs	[35]
Moroni *et al.* (2006)	75	CsA vs azathioprine for maintenance	No difference in the proteinuria and blood pressure Comparable flare rates	[36]
Balletta *et al.* (1992)	10	CsA vs prednisolone	Proteinuria decreased significantly in patients receiving CsA	[37]
Bao *et al.* (2008)	40	MT vs intravenous CYP	Higher rates of complete remission with MT at 6 and 9 months	[38]
Lanata *et al.* (2010)	7	Tacrolimus added to MMF	Five responded	[39]

CsA: Cyclosporine; CYP: Cyclophosphamide; MMF: Mycophenolate mofetil; MT: Multitarget therapy.

variety of cytokines such as IL-6 and TNF-α [48]. Biologics act by depleting B cells, inhibiting their activation and reducing B-cell and plasma cell survival.

B-cell depletion

Rituximab is a chimeric mouse–human monoclonal antibody directed against the B-cell surface molecule CD20. This molecule is absent on the pre-B cells and plasma cells. Thus it causes depletion of the peripheral B cells, without affecting regeneration of these cells or the production of immunoglobulins [49,50]. It depletes B cells by antibody-dependent, cell-mediated cytotoxicity (ADCC), apoptosis and complement-mediated cell lysis [51]. A number of case reports and case series have reported efficacy of this drug in refractory patients [52–59]. However, the LUNAR trial, which was a randomized double-blind placebo-controlled trial comparing rituximab with placebo in addition to MMF and prednisolone in 144 patients (approximately half were refractory to conventional therapy) with class III or IV nephritis, did not demonstrate a superior response with rituximab [60]. Rates of partial and complete responses were 57 and 46% in patients treated with rituximab versus placebo, respectively. There was, however, an 11% difference in the absolute renal response at the end of 1 year. Additionally, eight placebo-treated patients and no patient who was given rituximab required CYP rescue therapy. A complete response with respect to proteinuria was also higher in patients who received rituximab (32 vs 9%). This reduction in proteinuria persisted through 78 weeks, raising the possibility that a longer duration of observation may be necessary to understand the impact of rituximab. When renal response according to race and ethnicity was taken into account, the difference in the treatment responses between the two groups in black individuals was 25%. The failure to achieve the primary outcome by rituximab may be explained by the fact that the trial included a heterogeneous population with respect to ethnicity, unlike the case series, which predominantly comprised white individuals, and these patients did not have very active disease, and were also concomitantly receiving other immunosuppressants, namely MMF, which may have masked any beneficial effect of rituximab.

In a recently published systematic analysis of published reports on the efficacy of rituximab in patients with refractory nephritis, 300 patients followed-up for 60 weeks reported complete and partial response rates in 87, 76, 67 and 76% of patients with class III, IV, V and mixed class, respectively [61]. The analysis concluded that rituximab effectively induces remission in those patients in whom standard therapies fail.

In a systematic review of published reports on the use of rituximab between 2002 and 2007, in 188 SLE patients of which 103 had nephritis, the overall rate of renal response was 91% [57]. The response rates were 82, 98 and 100% in class III, IV and V nephritis, respectively.

Another Mexican study of 52 treatment refractory SLE patients, 13 of whom had nephritis, 38.4% each had complete and partial renal responses [62]. The drug also allowed a reduction in prednisolone dose in the majority of patients.

A French study assessed the long-term efficacy and safety (>12 months) of rituximab in 20 patients with severe proliferative (n = 15) and membranous nephritis (n = 5) [63]. Twelve patients received rituximab for refractory, and six for relapsing nephritis. After a median follow-up of 22 months, seven and five patients had complete and partial renal remission, respectively. Among the patients with class IV nephritis, 66% responded, with five achieving complete and five achieving partial remission. Two out of five patients with class V nephritis had complete remission. The injections were overall well tolerated.

Studies have also demonstrated the effectiveness of rituximab in improving the histological class. A study involving seven female patients with

Table 2. Biologics for refractory lupus nephritis.

Drug	Target
Biologics targeting B cells	
B-cell depletion:	
Rituximab (chimeric mAb)	CD20
Ocrelizumab (humanized mAb)	CD20
Epratuzumab (humanized mAb)	CD22
B-cell survival factors:	
Belimumab (human mAb)	BLyS/BAFF
Aticacept (TACI–Ig fusion protein)	BAFF/APRIL
Tolerizing B cells:	
Abetimus (synthetic toleragen)	dsDNA, BCR
Biologics targeting T cells	
Blocking costimulation:	
Abatacept (murine CTLA-4 Ig)	CD28/B7
Ruplizumab	CD40L
Tolarizumab	CD40L
Cytokine & complement inhibitors	
Sifalimumab	IFN-α
Tocilizumab	IL-6R
Eculizumab	Complement-5

BCR: B-cell receptor; mAb: Monoclonal antibody.

CYP-resistant proliferative nephritis who were treated with rituximab, repeat renal biopsies during follow-up demonstrated improvement in the majority of patients, and a decrease in the activity index was noted (from 6 to 3) [58]. Clinical improvement as indicated by a decrease in SLEDAI, decreases in anti-dsDNA antibodies and decrease in anti-c1q antibodies was seen. Another report of two patients with CYP refractory proliferative nephritis, who were given four infusions of rituximab and two additional CYP pulses, a reduction in activity was noted on repeat biopsy [59]. One patient was subsequently maintained on low-dose prednisolone alone. Rituximab is thus an option in patients refractory to first-line immunosuppressants, namely CYP and MMF. It can be given as an add-on therapy to MMF or CYP, or as monotherapy [7].

Rituximab has an overall acceptable tolerability and safety profile. Reported adverse effects are usually mild and either self-limited or responsive to conventional therapy. There are, however, reports of progressive multifocal leukoencephalopathy developing in patients who were administered the drug, and the US FDA has issued a warning with regard to this complication [64,65]. It is usually administered at doses recommended for lymphoma (375 mg/m^2 BSA weekly for four doses) or in rheumatoid arthritis (two 1000 mg doses separated by 2 weeks).

Ocrelizumab is a fully human monoclonal antibody directed against the CD20 molecule on the B cells. This molecule has been occasionally used in patients with severe refractory lupus nephritis [66]. However, a Phase III trial (BELONG trial) was prematurely discontinued due to severe infections [103].

Epratuzumab is a humanized monoclonal antibody that targets the CD22 molecule on the surface of B cells, and is present from the pre-B-cell stage to mature cells, but is absent on the plasma cells. It induces depletion of naive and transitional B cells, and also inhibits B-cell activation and proliferation [67,68].

In an initial open-label trial on 14 patients with moderately active SLE, significant efficacy of epratuzumab was demonstrated, as evidenced by reduction in BILAG scores by at least 50% in 77% of the patients by 18 weeks [67]. Tolerability of the drug was satisfactory. However, none of the patients had renal involvement. Preliminary results from Phase III trials showed that patients given epratuzumab had sustained improvement in BILAG scores, significant improvement in quality of life and less corticosteroid use compared with those given placebo [69,70].

B-cell survival factors

Among the various cytokines and growth factors essential for B-lymphocyte survival and maturation, the B-lymphocyte stimulator protein, also called B-cell activation factor (BAFF), and a proliferation-inducing ligand (APRIL), is the most important. It is a member of the TNF ligand superfamily and binds to three different receptors: transmembrane activator and calcium-modulating cytophilin ligand interactor (TACI), the B-cell maturation antigen (BCMA) and the BAFF receptor (BAFF-R).

Belimumab is a human monoclonal IgG1 antibody that binds to and inhibits soluble B-lymphocyte stimulator protein. It has been found to be superior compared with placebo in two Phase III placebo-controlled trials; BLISS-52 and BLISS-76 [71,72]. These trials compared two doses of belimumab, 1 mg/kg and 10 mg/kg versus placebo, in addition to standard therapy in more than 1500 serologically positive SLE patients, using the SLE responder index as the primary end point. There was a statistically significant positive result for the primary end point with belimumab 10 mg/kg and standard of care as compared with placebo, as well as a decrease in the anti-dsDNA antibody levels and increase in serum complement levels. Overall, the drug was well tolerated and was safe. However, these trials excluded patients with CNS involvement and severe nephritis. The drug was recently approved (2011) by the FDA to treat antibody-positive SLE, in combination with standard therapies. The trial results as well as the FDA approval have raised hopes that it may be the long-awaited therapy for SLE, including for severe CNS and renal manifestations.

Aticacept is a decoy recombinant fusion protein comprising the extracellular domain of the TACI receptor and Fc region of human IgG1. TACI binds both BAFF and APRIL, thereby affecting memory cells, plasma cells and immunoglobulin production [73]. In an early phase trial involving 24 patients with SLE, the drug demonstrated some effect with good overall tolerability [74]. A Phase II trial was prematurely terminated due to concerns of severe infections. Currently it is under investigation.

Tolerizing B cells

Abetimus sodium (LJP 394) is a tetrameric oligonucleotide that binds to circulating anti-dsDNA, forming soluble drug–antibody immune complexes, which are rapidly eliminated. A more prolonged effect is related to tolerizing anti-dsDNA-specific B cells. A randomized

placebo-controlled Phase III trial involving 317 SLE patients with a history of renal flare and anti-dsDNA antibodies >15I U/ml, using 100 mg/week of abetimus for 22 months did not meet its primary end point, in other words, prolong the time to renal flare [75]. There was, however, 25% fewer renal flares in the abetimus group as compared with the placebo group. In addition, abetimus treatment decreased anti-dsDNA antibody and increased complement levels. Significantly more patients in the abetimus group had a decrease of ≥50% proteinuria. Those patients who had impaired renal function at baseline had a trend towards reduced rates of renal and SLE flares. The drug was well tolerated overall. Another placebo-controlled trial involving 230 patients with SLE revealed that there was no difference in time to renal flare among patients receiving abetimus compared with placebo [76]. The drug, however, prolonged the time needed to add high-dose corticosteroids or immunosuppressants, and 41% required fewer treatments with immunosuppressants. In addition, patients with worse renal function (creatinine >1.5 mg/dl) had 50% lesser flares.

T-cell directed therapies

T cells are also involved in the pathogenesis of lupus nephritis. Antibodies in patients with SLE are class switched (IgG isotype) and have undergone somatic hypermutation. Both these indicate that the autoreactive B cells have received input from cognate T cells. T cells in addition directly infiltrate the renal parenchyma causing damage by direct cytotoxicity, and facilitating the recruitment and activation of macrophages.

Blocking costimulation

Optimal activation of T cells requires, in addition to antigen presentation in the context of the major histocompatibility complex proteins, a second signal by costimulatory molecules on the surface of T cells and antigen-presenting cells, the most important of which is CD28 on the T cells and B7 (CD80/86) on the antigen-presenting cells. Cytotoxic T-lymphocyte activation-4 (CTLA-4), which is expressed on activated T cells, binds to B7 with a higher affinity than CD28 generating inhibitory signaling to the T cells.

Abatacept is a recombinant fusion protein comprising the extracellular domain of human CTLA-4 fused to the Fc portion of IgG1. It binds to CD80/86 with high affinity, preventing T-cell activation. It has been found to be effective in preventing the progress of nephritis, prolonging survival, inducing remission and preventing damage when used in combination with CYP in mice models of lupus nephritis [77–79].

A trial (ACCESS) using the combination of abatacept with CYP (ELNT regime) in patients with nephritis is ongoing [104].

Another important costimulation molecule is the CD40 on B cells, which interacts with CD40L (C154) on the surface of T cells. Targeting this pathway reduces the activation of autoreactive T cells. Ruplizumab and tolarizumab are monoclonal antibodies against CD40L. Results from preliminary trials revealed good clinical responses [80]. However, owing to an increase in the incidence of thromboembolic complications, these trials were prematurely terminated. Additional studies will be needed to assess the long-term effects of these drugs.

Cytokine & complement inhibitors

A variety of cytokines secreted by the T and B cells are responsible for much of the damage in lupus nephritis, which makes them potential therapeutic targets.

Gene expression profiling of the peripheral blood mononuclear cells from patients with SLE has revealed an IFN-α signature, which correlates with disease activity [81,82]. A Phase I study of sifalimumab, a monoclonal antibody against IFN-α demonstrated an inhibition of IFN-α mRNA and improvement of disease activity [83]. Phase II trials are currently ongoing.

IL-6 is a proinflammatory cytokine that causes T-cell proliferation, and in mice models increases antibody production and progression of glomerulonephritis [84]. A Phase I dose escalation study on 16 SLE patients using tocilizumab,

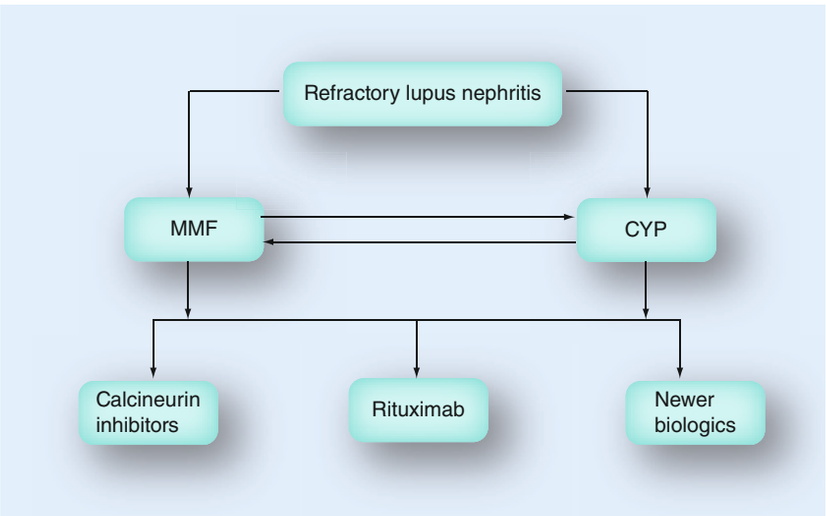

Figure 1. Flowchart guiding the management of patients with refractory lupus nephritis.
CYP: Cyclophosphamide; MMF: Mycophenolate mofetil.

a monoclonal antibody to IL-6 receptor, demonstrated significant improvement in disease activity in eight out of 15 evaluable patients [85]. Levels of anti-dsDNA antibodies decreased by 47%. However, neutropenia developed in all patients and high rates of infections were noted. Further studies are needed to establish the optimal dosing regimen and efficacy.

Treatment of patients with rheumatoid arthritis with anti-TNF-α therapies leads to the development of ANA and anti-dsDNA antibodies, and a lupus-like syndrome in some. Two large randomized controlled trials of infliximab and etanercept in SLE were prematurely terminated [105,106]. However, in a series of eight patients with refractory nephritis who received three infusions of infliximab, a decrease in urine protein was observed in six, and improvement in SLEDAI noted in five patients [86]. Another series evaluated the long-term efficacy and safety in 13 patients with SLE [87]. Of the nine patients with nephritis, six had long-term responses, although rates of serious adverse events, particularly infections, were high. This drug may be considered an option in refractory nephritis, with careful monitoring for adverse effects.

The complement system is involved in the pathogenesis of SLE, and its activation causes tissue inflammation. Eculizumab, an anti-C5 monoclonal antibody that inhibits complement activation, is in early stages of clinical trials in SLE [88].

Among the various immunosuppressive agents and biologics discussed, currently available agents include calcineurin inhibitors, leflunomide, intravenous immunoglobulin, rituximab, belimumab, abatacept, infliximab, adalimumab and tocilizumab. The other agents discussed are novel, not yet available drugs in various stages of development. Figure 1 demonstrates a flowchart guiding the management of patients with refractory lupus nephritis.

Conclusion

Refractory nephritis develops in a considerable number of patients with SLE. Multiple therapeutic options are currently available, notably multitarget therapy with tacrolimus, and rituximab. The recently published EULAR guidelines recommend the use of rituximab, either as monotherapy or as add-on therapy in patients with refractory nephritis. Newer agents, in particular biologics, hold considerable promise. However, the place of any drug must be considered among the existing therapies and it is important to gain more evidence with regard to the patients, situations and combinations in which these drugs can be used. Long-term safety, tolerability and cost–effectiveness, in particular, are of significant importance.

Future perspective

In the next 5–10 years, we will see a better design of clinical trials especially with regard to the patient population and outcome measures regarding the use of various biologics for refractory lupus nephritis. This will be especially true in the cases of rituximab and belimumab,

Executive summary

Refractory nephritis

- Refractory nephritis refers to those cases with no or partial response to first-line therapies, namely cyclophosphamide (CYP) and mycophenolate mofetil (MMF).
- Despite continuous immunosuppressive therapy, the majority of patients develop a relapse of nephritis after 5 years.

Prognostic factors

- Various demographic, genetic, clinical, histological and serologic factors affect the outcome.

Treatment options in refractory nephritis

- In case of refractory nephritis, switching to another first-line drug, for example, MMF if the patient received CYP and *vice versa*, may be attempted.
- Alternatively, adding another drug may be considered.

Calcineurin inhibitors

- Calcineurin inhibitors, cyclosporine and tacrolimus have demonstrated in case series and randomized controlled trials to be effective in refractory nephritis, decreasing proteinuria and corticosteroid dose. Multitarget therapy using tacroilimus, prednisolone and MMF has demonstrated improved rates of partial and complete remission. Patients, however, must be monitored for potential side effects.

Biologics

- Various biologics targeting B cells, T cells and cytokines have been tried in refractory disease.
- Rituximab, in particular, has been found to be effective in refractory nephritis based on evidence from uncontrolled studies and this drug has been recommended either as monotherapy or add-on therapy to MMF or CYP.

which hold considerable promise. Additional potential targets for therapeutic intervention will be identified through improved understanding of disease etiopathogenesis. Combinations that have the maximum efficacy and safety will be identified. More large-scale registries will be available to understand the, as yet, unknown side effects. Collaborative efforts between developing nations and the West will be a major step forward. The use of biomarkers will help tailor treatment of patients with nephritis, and better reflect activity and severity of disease. Finally, genomics will help to better predict which patients will respond or develop side effects with a particular drug, thus optimizing therapy to suit patients.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
▪ of interest
▪▪ of considerable interest

1 Brunner HI, Gladman DD, Ibañez D, Urowitz MD, Silverman ED. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. *Arthritis Rheum.* 58(2), 556–562 (2008).

2 Borchers AT, Keen CL, Shoenfeld Y, Gershwin ME. Surviving the butterfly and the wolf: mortality trends in systemic lupus erythematosus. *Autoimmun. Rev.* 3(6), 423–453 (2004).

3 Cervera R, Khamashta MA, Font J *et al.* European Working Party on Systemic Lupus Erythematosus. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine (Baltimore)* 82(5), 299–308 (2003).

4 Smith RM, Clatworthy MR, Jayne DR. Biological therapy for lupus nephritis-tribulations and trials. *Nat. Rev. Rheumatol.* 6(9), 547–552 (2010).

5 Renal Disease Subcommittee of the American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria. The American College of Rheumatology response criteria for proliferative and membranous renal disease in systemic lupus erythematosus clinical trials. *Arthritis Rheum.* 54(2), 421–432 (2006).

▪▪ **First to provide recommendations of the end points, the minimal clinically significant changes in these end points and covariates that should be reported in clinical trials of proliferative and membranous lupus nephritis.**

6 Gordon C, Jayne D, Pusey C *et al.* European consensus statement on the terminology used in the management of lupus glomerulonephritis. *Lupus* 18(3), 257–263 (2009).

▪ **Reports consensus statements on classifications, treatment options and definitions of various outcomes in patients with lupus nephritis.**

7 Bertsias GK, Tektonidou M, Amoura Z *et al.* Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann. Rheum. Dis.* 71(11), 1771–1782 (2012).

8 Illei GG, Takada K, Parkin D *et al.* Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: long-term followup of cohort of 145 patients participating in randomized controlled studies. *Arthritis Rheum.* 46(4), 995–1002 (2002).

9 Mok CC, Ying KY, Tang S *et al.* Predictors and outcome of renal flares after successful cyclophosphamide treatment for diffuse proliferative lupus glomerulonephritis. *Arthritis Rheum.* 50(8), 2559–2568 (2004).

10 Mok CC. Prognostic factors in lupus nephritis. *Lupus* 14(1), 39–44 (2005).

11 Alarcón GS, Friedman AW, Straaton KV *et al.* Systemic lupus erythematosus in three ethnic groups: III. A comparison of characteristics early in the natural history of the LUMINA cohort. LUpus in MInority populations: NAture vs. Nurture. *Lupus* 8(3), 197–209 (1999).

12 Pons-Estel BA, Catoggio LJ, Cardiel MH *et al.*; Grupo Latinoamericano de Estudio del Lupus. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among 'Hispanics'. *Medicine (Baltimore)* 83(1), 1–17 (2004).

13 Alarcón GS, McGwin G Jr, Petri M, Reveille JD, Ramsey-Goldman R, Kimberly RP; PROFILE Study Group. Baseline characteristics of a multiethnic lupus cohort: PROFILE. *Lupus* 11(2), 95–101 (2002).

14 Isenberg D, Appel GB, Contreras G *et al.* Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. *Rheumatology (Oxford)* 49(1), 128–140 (2010).

▪▪ **Excellent study highlighting better responses to mycophenolate mofetil as compared to cyclophosphamide among black and Hispanic individuals.**

15 Font J, Cervera R, Espinosa G *et al.* Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. *Ann. Rheum. Dis.* 57(8), 456–459 (1998).

16 Tucker LB, Uribe AG, Fernández M *et al.* Adolescent onset of lupus results in more aggressive disease and worse outcomes: results of a nested matched case–control study within LUMINA, a multiethnic US cohort (LUMINA LVII). *Lupus* 17(4), 314–322 (2008).

17 Brunner HI, Gladman DD, Ibañez D, Urowitz MD, Silverman ED. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. *Arthritis Rheum.* 58(2), 556–562 (2008).

▪ **Compares the clinical features with disease activity, along with medications required and damaged accrued, of an inception cohort of children and adults with systemic lupus erythematosus (SLE).**

18 Houssiau FA, Vasconcelos C, D'Cruz D *et al.* Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. *Arthritis Rheum.* 50(12), 3934–3940 (2004).

19 Houssiau FA, Vasconcelos C, D'Cruz D *et al.* The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann. Rheum. Dis.* 69(1), 61–64 (2010).

▪▪ **Landmark trial comparing low-dose versus high-dose cyclophosphamide in patients with proliferative nephritis demonstrating**

equivalent efficacy and better safety of the low-dose regimen in the long term.

20 Chen YE, Korbet SM, Katz RS, Schwartz MM, Lewis EJ; Collaborative Study Group. Value of a complete or partial remission in severe lupus nephritis. *Clin. J. Am. Soc. Nephrol.* 3(1), 46–53 (2008).

21 So MW, Koo BS, Kim YG, Lee CK, Yoo B. Predictive value of remission status after 6 months induction therapy in patients with proliferative lupus nephritis: a retrospective analysis. *Clin. Rheumatol.* 30(11), 1399–1405 (2011).

22 Hahn BH, McMahon MA, Wilkinson A *et al.* American College of Rheumatology. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res. (Hoboken)* 64(6), 797–808 (2012).

▪▪ **Most recent recommendations by the ACR on management of the different classes of lupus nephritis.**

23 Touma Z, Gladman DD, Urowitz MB, Beyene J, Uleryk EM, Shah PS. Mycophenolate mofetil for induction treatment of lupus nephritis: a systematic review and metaanalysis. *J. Rheumatol.* 38(1), 69–78 (2011).

24 Dooley MA, Hogan S, Jennette C, Falk R. Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. Glomerular Disease Collaborative Network. *Kidney Int.* 51(4), 1188–1195 (1997).

25 Dooley MA, Jayne D, Ginzler EM *et al.* ALMS Group. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N. Engl. J. Med.* 365(20), 1886–1895 (2011).

▪▪ **Landmark trial in lupus nephritis that demonstrated superiority of mycophenolate mofetil over azathioprine for remission maintenance in patients with nephritis.**

26 Houssiau FA, D'Cruz D, Sangle S *et al.* MAINTAIN Nephritis Trial Group. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. *Ann. Rheum. Dis.* 69(12), 2083–2089 (2010).

27 A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. *N. Engl. J. Med.* 324(3), 150–154 (1991).

▪ **Randomized study that demonstrated increased rates of flare of disease and shorter time to flare in patients with quiescent lupus when hydroxychloroquine was withdrawn.**

28 Fessler BJ, Alarcón GS, McGwin G Jr *et al.* LUMINA Study Group. Systemic lupus erythematosus in three ethnic groups: XVI. Association of hydroxychloroquine use with reduced risk of damage accrual. *Arthritis Rheum.* 52(5), 1473–1480 (2005).

29 Pons-Estel GJ, Alarcón GS, McGwin G Jr *et al.* Lumina Study Group. Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort. *Arthritis Rheum.* 61(6), 830–839 (2009).

30 Boumpas DT, Balow JE. Outcome criteria for lupus nephritis trials: a critical overview. *Lupus* 7(9), 622–629 (1998).

31 Houssiau FA, Ginzler EM. Current treatment of lupus nephritis. *Lupus* 17(5), 426–430 (2008).

32 Moroni G, Doria A, Ponticelli C. Cyclosporine (CsA) in lupus nephritis: assessing the evidence. *Nephrol. Dial. Transplant.* 24(1), 15–20 (2009).

33 Faul C, Donnelly M, Merscher-Gomez S *et al.* The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat. Med.* 14(9), 931–938 (2008).

34 Favre H, Miescher PA, Huang YP, Chatelanat F, Mihatsch MJ. Ciclosporin in the treatment of lupus nephritis. *Am. J. Nephrol.* 9(Suppl. 1), 57–60 (1989).

35 Zavada J, Pesickova S, Rysava R *et al.* Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the Cyclofa-Lune study. *Lupus* 19(11), 1281–1289 (2010).

36 Moroni G, Doria A, Mosca M *et al.* A randomized pilot trial comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over four years. *Clin. J. Am. Soc. Nephrol.* 1(5), 925–932 (2006).

37 Balletta M, Sabella D, Magri P *et al.* Ciclosporin plus steroids versus steroids alone in the treatment of lupus nephritis. *Contrib. Nephrol.* 99, 129–130 (1992).

38 Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V+IV lupus nephritis with multitarget therapy. *J. Am. Soc. Nephrol.* 19(10), 2001–2010 (2008).

39 Lanata CM, Mahmood T, Fine DM, Petri M. Combination therapy of mycophenolate mofetil and tacrolimus in lupus nephritis. *Lupus* 19(8), 935–940 (2010).

40 Cortés-Hernández J, Torres-Salido MT, Medrano AS, Tarrés MV, Ordi-Ros J. Long-term outcomes – mycophenolate mofetil treatment for lupus nephritis with addition of tacrolimus for resistant cases. *Nephrol. Dial. Transplant.* 25(12), 3939–3948 (2012).

41 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. *Ann. Rheum. Dis.* 65(3), 417–418 (2006).

42 Cui TG, Hou FF, Ni ZH *et al.* Treatment of proliferative lupus nephritis with leflunomide and steroid: a prospective multi-center controlled clinical trial. *Zhonghua Nei Ke Za Zhi* 44(9), 672–676 (2005).

43 Boletis JN, Ioannidis JP, Boki KA, Moutsopoulos HM. Intravenous immunoglobulin compared with cyclophosphamide for proliferative lupus nephritis. *Lancet* 354(9178), 569–570 (1999).

44 Zandman-Goddard G, Levy Y, Shoenfeld Y. Intravenous immunoglobulin therapy and systemic lupus erythematosus. *Clin. Rev. Allergy Immunol.* 29(3), 219–228.

45 Zandman-Goddard G, Blank M, Shoenfeld Y. Intravenous immunoglobulins in systemic lupus erythematosus: from the bench to the bedside. *Lupus* 18(10), 884–888 (2009).

46 Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus. Med. Rev.* 17(4), 241–251 (2003).

47 Orange JS, Hossny EM, Weiler CR *et al.* Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J. Allergy Clin. Immunol.* 117(Suppl. 4), S525–53 (2006).

48 Diamanti AP, Rosado MM, Carsetti R, Valesini G. B cells in SLE: different biological drugs for different pathogenic mechanisms. *Autoimmun. Rev.* 7(2), 143–148 (2007).

49 Thatayatikom A, White AJ. Rituximab: a promising therapy in systemic lupus erythematosus. *Autoimmun. Rev.* 5(1), 18–24 (2006).

50 Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA. An open study of B lymphocyte depletion in systemic lupus erythematosus. *Arthritis Rheum.* 46(10), 2673–2677 (2002).

51 Reff ME, Carner K, Chambers KS *et al.* Depletion of B cells *in vivo* by a chimeric mouse human monoclonal antibody to CD20. *Blood* 83(2), 435–445 (1994).

52 Trachana M, Koutsonikoli A, Farmaki E, Printza N, Tzimouli V, Papachristou F. Safety and efficacy of rituximab in refractory pediatric systemic lupus erythematosus nephritis: a single-center experience of northern Greece. *Rheumatol. Int.* doi:10.1007/s00296-011-2239-6 (2011) (Epub ahead of print).

53 Pinto LF, Velásquez CJ, Prieto C, Mestra L, Forero E, Márquez JD. Rituximab induces a rapid and sustained remission in Colombian patients with severe and refractory systemic lupus erythematosus. *Lupus* 20(11), 1219–1226 (2011).

54 Roccatello D, Sciascia S, Rossi D *et al.* Intensive short-term treatment with rituximab, cyclophosphamide and methylprednisolone pulses induces remission in severe cases of SLE with nephritis and avoids further immunosuppressive maintenance therapy. *Nephrol. Dial. Transplant.* 26(12), 3987–3992 (2011).

55 Terrier B, Amoura Z, Ravaud P *et al.* Club Rhumatismes et Inflammation. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. *Arthritis Rheum.* 62(8), 2458–2466 (2010).

56 Pepper R, Griffith M, Kirwan C *et al.* Rituximab is an effective treatment for lupus nephritis and allows a reduction in maintenance steroids. *Nephrol. Dial. Transplant.* 24(12), 3717–3723 (2009).

57 Ramos-Casals M, Soto MJ, Cuadrado MJ, Khamashta MA. Rituximab in systemic lupus erythematosus: a systematic review of off-label use in 188 cases. *Lupus* 18(9), 767–776 (2009).

58 Gunnarsson I, Sundelin B, Jónsdóttir T, Jacobson SH, Henriksson EW, van Vollenhoven RF. Histopathologic and clinical outcome of rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis. *Arthritis Rheum.* 56(4), 1263–1272 (2007).

59 van Vollenhoven RF, Gunnarsson I, Welin-Henriksson E *et al.* Biopsy-verified response of severe lupus nephritis to treatment with rituximab (anti-CD20 monoclonal antibody) plus cyclophosphamide after biopsy-documented failure to respond to cyclophosphamide alone. *Scand. J. Rheumatol.* 33(6), 423–427 (2004).

60 Rovin BH, Furie R, Latinis K *et al.* LUNAR Investigator Group. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum.* 64(4), 1215–1226 (2012).

▪▪ **First randomized controlled trial of rituximab for lupus nephritis.**

61 Weidenbusch M, Römmele C, Schröttle A, Anders HJ. Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis. *Nephrol. Dial. Transplant.* doi:10.1093/ndt/gfs285 (2012) (Epub ahead of print).

62 Garcia-Carrasco M, Mendoza-Pinto C, Sandoval-Cruz M *et al.* Anti-CD20 therapy in patients with refractory systemic lupus erythematosus: a longitudinal analysis of 52 Hispanic patients. *Lupus* 19(2), 213–219 (2010).

63 Melander C, Sallée M, Trolliet P *et al.* Rituximab in severe lupus nephritis: early B-cell depletion affects long-term renal outcome. *Clin. J. Am. Soc. Nephrol.* 4(3), 579–587 (2009).

64 Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy associated with immunosuppressive therapy in rheumatic diseases: evolving role of biologic therapies. *Arthritis Rheum.* 64(9), 3043–3051 (2012).

65 Calabrese LH, Molloy ES, Huang D, Ransohoff RM. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. *Arthritis Rheum.* 56(7), 2116–2128 (2007).

66 Faria RM, Isenberg DA. Three different B-cell depletion (anti-CD20 monoclonal antibodies) treatments for severe resistant systemic lupus erythematosus. *Lupus* 19(10), 1256–1257 (2010).

67 Dörner T, Kaufmann J, Wegener WA, Teoh N, Goldenberg DM, Burmester GR. Initial clinical trial of epratuzumab (humanized anti-CD22 antibody) for immunotherapy of systemic lupus erythematosus. *Arthritis Res. Ther.* 8(3), R74 (2006).

68 Jacobi AM, Goldenberg DM, Hiepe F, Radbruch A, Burmester GR, Dörner T. Differential effects of epratuzumab on peripheral blood B cells of patients with systemic lupus erythematosus versus normal controls. *Ann. Rheum. Dis.* 67(4), 450–457 (2008).

69 Petri M, Hobbs K, Gordon C *et al.* (RCTS) of epratuzumab (anti-CD22 mAb targeting B-cells) reveal clinically meaningful improvements in patients with moderate/severe SLE flares. *Ann. Rheum. Dis.* 67(Suppl. II), 53 (2008).

70 Wallace D, Hobbs K, Houssiau F *et al.* (anti-CD22 mAb targeting B-cells) reveal clinically meaningful reductions in corticosteroid use with favorable safety profile in moderate and severe flaring SLE patients. *Ann. Rheum. Dis.* 67(Suppl. II), 212 (2008).

71 Navarra SV, Guzmán RM, Gallacher AE *et al.* BLISS-52 Study Group. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, Phase 3 trial. *Lancet* 377(9767), 721–731 (2011).

▪▪ **Randomized controlled trial of belimumab in patients with SLE where a modified outcome measure, the SLE Responder Index was used. The trial demonstrated the efficacy of belimumab, leading to its approval by the US FDA.**

72 Furie R, Petri M, Zamani O *et al.* BLISS-76 Study Group. A Phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum.* 63(12), 3918–3930 (2011).

73 Ramanujam M, Wang X, Huang W *et al.* Similarities and differences between selective and nonselective BAFF blockade in murine SLE. *J. Clin. Invest.* 116(3), 724–734 (2006).

74 Pena-Rossi C, Nasonov E, Stanislav M *et al.* An exploratory dose-escalating study investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous atacicept in patients with systemic lupus erythematosus. *Lupus* 18(6), 547–555 (2009).

75 Cardiel MH, Tumlin JA, Furie RA, Wallace DJ, Joh T, Linnik MD; LJP 394-390-09 Investigator Consortium. Abetimus sodium for renal flare in systemic lupus erythematosus: results of a randomized, controlled Phase III trial. *Arthritis Rheum.* 58(8), 2470–2480 (2008).

76 Alarcón-Segovia D, Tumlin JA, Furie RA *et al.* LJP 394 Investigator Consortium. LJP 394 for the prevention of renal flare in patients with systemic lupus erythematosus: results from a randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* 48(2), 442–454 (2003).

77 Daikh DI, Wofsy D. Cutting edge: reversal of murine lupus nephritis with CTLA4Ig and cyclophosphamide. *J. Immunol.* 166(5), 2913–2916 (2001).

78 Schiffer L, Sinha J, Wang X *et al.* Short term administration of costimulatory blockade and cyclophosphamide induces remission of systemic lupus erythematosus nephritis in NZB/W F1 mice by a mechanism downstream of renal immune complex deposition. *J. Immunol.* 171(1), 489–497 (2003).

79 Cunnane G, Chan OT, Cassafer G *et al.* Prevention of renal damage in murine lupus nephritis by CTLA-4Ig and cyclophosphamide. *Arthritis Rheum.* 50(5), 1539–1548 (2004).

80 Boumpas DT, Furie R, Manzi S *et al.* BG9588 Lupus Nephritis Trial Group. A short course of BG9588 (anti-CD40 ligand antibody) improves serologic activity and decreases hematuria in patients with proliferative lupus glomerulonephritis. *Arthritis Rheum.* 48(3), 719–727 (2003).

81 Baechler EC, Batliwalla FM, Karypis G *et al.* Interferon-inducible gene expression signature

in peripheral blood cells of patients with severe Lupus. *Proc. Natl Acad. Sci. USA* 100(5), 2610–2615 (2003).

82 Bennett L, Palucka AK, Arce E *et al.* Interferon and granulopoiesis signatures in systemic lupus erythematosus *Blood J. Exp. Med.* 197(6), 711–723 (2003).

83 Merrill JT, Wallace DJ, Petri M *et al.* Lupus Interferon Skin Activity (LISA) Study Investigators. Safety profile and clinical activity of sifalimumab, a fully human anti-interferon αmonoclonal antibody, in systemic lupus erythematosus: a Phase I, multicentre, double-blind randomized study. *Ann. Rheum. Dis.* 70(11), 1905–1913 (2011).

84 Liang B, Gardner DB, Griswold DE, Bugelski PJ, Song XY. Anti-interleukin-6 monoclonal antibody inhibits autoimmune responses in a murine model of systemic lupus erythematosus. *Immunology* 119(3), 296–305 (2006).

85 Illei GG, Shirota Y, Yarboro CH *et al.* Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label Phase I dosage-escalation study. *Arthritis Rheum.* 62(2), 542–552 (2010).

86 Matsumura R, Umemiya K, Sugiyama T *et al.* Study Group on Nephrology at the National Hospital Organization of Japan. Anti-tumor necrosis factor therapy in patients with difficult-to-treat lupus nephritis: a prospective series of nine patients. *Clin. Exp. Rheumatol.* 27(3), 416–421 (2009).

87 Aringer M, Houssiau F, Gordon C *et al.* Adverse events and efficacy of TNF-alpha blockade with infliximab in patients with systemic lupus erythematosus: long-term follow-up of 13 patients. *Rheumatology (Oxford)* 48(11), 1451–1454 (2009).

88 Rother RP, Mojcik CF, McCroskery EW. Inhibition of terminal complement: a novel therapeutic approach for the treatment of systemic lupus erythematosus. *Lupus* 13(5), 328–334 (2004).

Websites

101 Mann JF, Bakris GL. Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults (2011). www.uptodate.com/contents/antihypertensivetherapy-and-progression-of-nondiabetic-chronic-kidneydisease-in-adults?source_see_link

102 Rosenson RS. ATP III guidelines for treatment of high blood cholesterol (2011). www.uptodate.com/contents/atp-iii-guidelines-for-treatment-of-high-blood-cholesterol

103 US National Library of Medicine. A study to evaluate ocrelizumab in patients with nephritis due to systemic lupus erythematosus (BELONG). http://clinicaltrials.gov/ct2/show/NCT00626197 (2010)

104 US National Library of Medicine. Abatacept and cyclophosphamide combination therapy for lupus nephritis (ACCESS). http://clinicaltrials.gov/ct2/show/NCT00774852

105 ClinicalTrials.gov. TNF blockade with remicade in active lupus nephritis WHO class V (TRIAL) (NCT00368264). http://clinicaltrialsgov/ct2/show/NCT00368264

106 ClinicalTrials.gov. Etanercept for the treatment of lupus nephritis (NCT00447265). http://clinicaltrialsgov/ct2/show/NCT00447265