Future prospects in the treatment of lupus nephritis: proliferative lupus nephritis

Rebecca Fischer-Betz & Matthias Schneider†

†Author for correspondence
Heinrich-Heine University,
Clinic of Endocrinology,
Diabetology & Rheumatology, M corinstr. 5,
40225 Düsseldorf, Germany
Tel.: +49 211 811 7817;
Fax: +49 211 811 6455;
schneider@rheumanet.org

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Lupus nephritis is a common manifestation of systemic lupus erythematosus, and a predictor of an adverse outcome in this disease. With respect to long-term renal outcome, cyclophosphamide pulses plus steroids are the standard therapy for lupus nephritis. During the last decade, the first international, multicenter, randomized controlled trials were conducted to evaluate new substances for the treatment of lupus nephritis. The testing of other immunosuppressive drugs, anticytokine therapies, modulation of cell–cell interactions, (anti)cytokine therapies and lupus erythematosus-specific immunomodulation is currently underway. On the basis of experiences from other indications, mycophenolate and rituximab are currently the most promising drugs, concluding 30 years without any new licensed lupus drugs. Other approaches appear to use more specific interventions, but it may be that the evaluation of anticytokine interventions or lupus erythematosus-specific immunomodulation requires new biomarkers that enable a sensitive analysis of the different processes (e.g., immunoresponse, inflammation and scarring) that are involved in the pathophysiology of nephritis.

The heterogeneous clinical picture of systemic lupus erythematosus (SLE) is mainly drawn from its major organ involvements. Lupus nephritis is a common manifestation of SLE and a predictor of an adverse outcome in SLE [1,2]; for example, 10-year survival is reduced in patients who presented with nephropathy [2]. This review is focused on the actual status and developments in the management of proliferative lupus nephritis. Optimal therapy for lupus nephritis should aim at enhancing efficacy, reducing toxicities and preventing relapses.

Standard care
The European League Against Rheumatism recommendations for the management of SLE include evidence-based standard care for proliferative lupus nephritis [3].

As in all organ manifestations, the early detection of developing lupus nephritis is the first important step towards adequate treatment. As clinical signs of lupus nephritis, such as edema or hypertension, may appear late in the course of the disease, urine analyses at every routine check of a lupus patient are mandatory. In the case of erythrocyturia and/or a positive screening for proteinuria, urinary dysmorphic erythrocytes, 24 h proteinuria (or urine protein above urine creatinine), urinary casts and a creatinine clearance should be determined.

If there are no contraindications, renal biopsies should be weighed in any new urine pathologies to confirm the diagnosis using International Society of Nephrology/Renal Pathology Society classification or assigning activity or chronicity scores. Active lupus nephritis is an absolute indication of immunosuppressive treatment and chronicity is a sign of irreversible damage.

Immunosuppressive therapies for proliferative nephritis were evaluated in several randomized, controlled trials and their results are summarized in a recent Cochrane Review [4]. With respect to long-term renal outcome, cyclophosphamide (CY) pulses plus steroids are the standard therapy for lupus nephritis. Premature ovarian failure, which is dose and age dependent, and infections remain considerable problems of this strategy. Gonadal protection, using a synthetic gonadotropin-releasing hormone-analog, less intensive regimens of CY [5] and sequential therapy with a short course of intravenous CY followed by azathioprine [6], have been advocated. The duration of immunosuppressive therapies and follow-up medications are mostly decided by the individual situation based on the experience of the treating physician. There is a trend towards splitting therapy into induction and maintenance regimes, although the optimal sequence of the various immunosuppressive drugs still has to be defined.

There is, in addition, a place for nonimmunosuppressive medications, such as statins, angiotensin-converting enzyme inhibitors and aspirin [3].
As suggested by American College of Rheumatology (ACR) response criteria for clinical trials, proteinuria, erythrocyturia and creatinine are major determinants of clinical response in lupus nephritis [7]. Results from several studies and trials indicate that improvements in proteinuria and reductions in serum creatinine correlate with a favorable outcome in therapy of lupus nephritis [7,8]. A third of patients with lupus nephritis suffer from renal flaring after remission. Predictors of renal flare are increases in anti-double stranded (ds)DNA titers and consumption of C3 [9]. Studies from the NIH have demonstrated the importance of duration of follow-up in accurately assessing the efficacy of a given treatment regimen, with important differences in hard renal outcomes, such as end-stage renal disease, requiring at least 5 years of follow-up before they become apparent [10].

New therapeutic options

For more than 30 years there have been no new drugs licensed for lupus. During the last decade, the first international, multicenter, randomized controlled trials were conducted to evaluate new substances in lupus. Owing to the relative homogeneity given by WHO classification, lupus nephritis was often the primary target of these trials. Unfortunately, two of the first substances, anti-C40-ligand antibodies and LJP 394, a construct to bind dsDNA antibodies, failed to be certified owing to side-effects or lack of efficacy. However, these trials helped to shape the design of randomized controlled trials in lupus, a process that will continue until the first successfully finalized trial.

The actual therapeutic developments can be separated into:

- Other immunosuppressive drugs
- Anticellular therapy
- Cell-cell interaction
- (Anti)cytokine therapy
- Lupus erythematosus-specific immunomodulation

Other immunosuppressive drugs: mycophenolate mofetil

Mycophenolate mofetil (MMF), which inhibits purine synthesis and has antiproliferative effects on lymphocytes, is used in solid-organ transplantation and has been evaluated in five short-to-medium-term randomized controlled trials [11]. Data from these trials indicate at least similar efficacy and a more favorable toxicity profile compared with pulse CY for both induction and maintenance therapy. For example, in maintenance of proliferative lupus nephritis, the event-free survival rate for the composite end point of death or chronic renal failure was higher in the MMF group compared with the CY group, and the cumulative probability of hospitalization was lower in the MMF group. Sustained amenorrhea was rare in the MMF-treated patients. Additional, long-term trials are required to further evaluate the efficacy of MMF in lupus nephritis.

Anticellular therapies

Cells have surface proteins to interact with cytokines and other cells. These can be addressed with antibodies in the form of anticellular therapies that may alter the function of the addressed cells or even induce cell death. Such treatments were first developed for CD4 cells and used in rheumatoid arthritis; at present target surface structures are identified for various cell types. B cells are the most commonly addressed targets in lupus because they appear to have a major role in the pathology: they produce antibodies, are responsible for antigen presentation, activate antigen-presenting cells involved in T-cell activation, anergy or differentiation, produce cytokines and regulate lymphoid organisation. The anti-B-cell therapies, rituximab, ocrelizumab, epratuzumab and belimumab, are currently in Phase II/III trials for the management of lupus nephritis. The primary advantage of these cell-specific interventions seems to be their specificity, promising less toxicity. However, theoretically-based advantage has to be carefully proven in clinical trials evaluating clinical efficacy of these interventions, as well as their long-term safety.

Rituximab

Most available data are for rituximab, an anti-CD20 chimeric antibody licensed for the treatment of lymphoma that acts by removing CD20-positive B lymphocytes [2]. A review of the literature by Sfikakis considered data on the use of rituximab in 90 patients from different trials; most were refractory to conventional immunosuppression and approximately 50% were treated for proliferative lupus nephritis [12]. Although the results are likely to be biased by the tendency of researchers to publish positive results, they were encouraging overall, with 80% of patients achieving clinically meaningful decreases in global lupus disease activity and an 80% rate of clinical remission among the reported patients treated for active
globulins and hypogammaglobulinaemia are not rheumatologic and nonrheumatologic conditions.

A recent pilot study of rituximab added to immunosuppressant therapy in 22 patients with active SLE and renal involvement refractory to conventional immunosuppressive therapy found a significant reduction in disease activity in 90% of patients at days 60 and 90 of rituximab therapy, and significant reductions in proteinuria in some cases as early as day 15 but in other patients at 60 or 90 days [13]. Long-term data are missing.

As these first data are promising and results of controlled trials with rituximab – or better still, a human or humanized antibody, such as epratuzumab – are keenly awaited, the safety of this intervention has to be carefully explored, although rituximab is now licensed in rheumatoid arthritis as well. At the end of 2006, a US FDA Alert was sent out following the death of two lupus patients (off-label) treated with rituximab. The cause of death was a viral infection of the brain termed progressive multifocal leukoencephalopathy (PML), which is caused by reactivated JC virus. A reactivation is mostly seen in immunocompromized patients, a situation that is obviously provoked by the anti-B-cell action of rituximab, as indicated by some other PML reports in rituximab-treated patients suffering from lymphoma.

These findings, as well as other experiences, teach us that not only may efficacy differ in different indications, but also that side-effects may vary in lupus patients in comparison to other rheumatologic and nonrheumatologic conditions.

Epratuzumab
Epratuzumab is an anti-CD22 humanized antibody that is undergoing Phase III trials in patients with SLE designated with the fast-track label by the FDA. It is another type of anti-B-cell therapy explored in non-Hodgkin's lymphoma. First oncology data indicate that CD22 targeting may add to anti-CD20 therapy. CD22 is expressed in the cytoplasm of pro- and early pre-B cells and on the surface of mature B cells; anti-CD22 causes internalization of the surface protein and only mild depletion of circulating B cells, which may offer advantages in safety.

The first data on epratuzumab use in patients with lupus were published at the Annual Meeting of the ACR in 2004 [14]. Epratuzumab 360 mg/m^2 every 2 weeks for four doses was given to 14 patients with moderately active SLE [5]. At the time of reporting, 11 patients had completed treatment. A greater than 50% decrease in global disease activity from baseline was achieved in eight out of 11 (73%) patients. Three patients reported mild adverse events, such as sleepiness, which was attributed to premedication, herpes zoster infection, which was responsive to antivirals, and otitis media, which was responsive to antibiotics.

Belimumab
B-cell activation by T cells or dendritic cells can also be controlled, thereby holding up the B-cell activation factor (also known as B lymphocyte stimulator [BLyS])-related system. Belimumab is a human monoclonal antibody that specifically recognizes and inhibits the biological activity of soluble BLyS; in primates belimumab decreases tissue and peripheral blood B-lymphocytes. The importance of BLyS expression in the pathophysiology of lupus is still under discussion. First data in lupus are available from a prospective, randomized, double-blind, placebo-controlled Phase II trial in 449 patients [15]. Belimumab was safe and well tolerated. Reduction in dsDNA antibodies, complement increase and a reduction in flares in different subsets of patients are promising. Belimumab met the FDA approved combined end point (>3 point improvement in SLE disease activity index, British Isles Lupus Assessment Group [BILAG] A or B and physician's global assessment improvement) and is now in its pivotal trial.

In lupus, similar approaches have started with atacicept, a soluble fusion protein of the extracellular protein of transmembrane activator and calcium-modulating ligand interactor (TACI) receptor and Fc protein of human immunoglobulin (Ig). TACI has been shown to bind to BLyS and a proliferation-inducing ligand (APRIL). APRIL is a member of the tumor necrosis factor (TNF) ligand superfamily and is related to, but distinct from, BLyS. APRIL and BLyS can form heterotrimers that may exhibit effects on B cells that are not found with APRIL monomers. Initial results from 49 patients show a clear reduction of B cells, no greater safety problems and some clinical response in the few active patients [16].

Cell–cell interactions
Direct cell–cell interactions, such as the second signaling required to activate T cells, are also promising targets of inhibitory interventions.
In lupus, the first approach to target the second signal was performed using anti-CD40L antibodies. In one of the first international multicenter trials in lupus, interfering with the CD40L–CD40 interaction caused heart attacks and thrombosis at the beginning of the study, which was therefore stopped. Such occasions as this typify the situation with respect to data and trials in patients with lupus, for whom information from other diseases cannot be transferred directly. The same antibody was safely used in thrombocytopenia, another antibody against CD 40L did not exhibit similar side effects, but was not very efficient [17]. Thus, one promising approach targeting the second signal is on hold, with the question of efficacy not completely answered.

Interest is now focused on interacting with B7-1/B7-2 and CD28, another important second signaling. The fusion protein CTLA4Ig (Abatacept®) binds to B7-1/B7-2 on antigen-presenting cells, thereby inhibiting their binding to the costimulatory molecule CD28 on T cells. Abatacept was first licensed in rheumatoid arthritis and is in ongoing Phase IIIB trials for moderate-to-severe SLE. Data from rheumatoid arthritis show that it is safe, but no clinical data are yet available in patients with SLE [18].

(Anti)cytokine antibodies

The destructive process of rheumatoid arthritis can be controlled with anticytokine antibodies, most of which involve TNF-α blockade. Although animal models confirm that TNF plays a role in the inflammatory reaction in the kidney, rheumatologists have generally been reluctant to use anti-TNF-α drugs in patients with lupus because some patients with rheumatoid arthritis treated with infliximab - a chimeric anti-TNF antibody - develop antinuclear antibodies or even a lupus-like disease. Aringer and colleagues conducted an open-label study of infliximab (4 × 300 mg infusions) in addition to baseline immunosuppressive agents in six patients with low-to-moderately active SLE [19]. In four patients who had lupus nephritis, proteinuria was significantly decreased within one week of initiation of infliximab and was diminished by ≥60% within 8 weeks, remaining at low levels for more than 6 months after the last infusion of infliximab. This drug appears to act by addressing the secondary inflammation rather than the autoimmune response itself, a separate aspect in treating lupus nephritis that is addressed by the corticosteroids in actual therapeutic regimes. A trial with TNF-α blockade in patients with membranous nephritis is underway.

Other anti-inflammatory approaches are also in the pipeline. The anti-interleukin (IL)6 humanized antibody tocilizumab was used bi-weekly (2 mg/kg followed by 8 mg/kg) in a trial of 14 lupus patients [20]. The results demonstrated decreases in acute-phase reactant, activated B cells, memory B cells, activated CD4 and CD8 cells and IgG3 and 4, as well as increases in naïve B and T cells. Some response to treatment was observed, but the trial was tested on safety aspects rather than clinical efficacy and in patients with mild-to-moderate disease.

In a similar line are substances inhibiting neutrophils and macrophages. Indeed, Bao and colleagues demonstrated that, in mice, blockade of the receptor for complement 5A (C5A) with a CSA receptor antagonist prevented progressive impairments in renal function and reduced the infiltration of neutrophils and macrophages into the kidneys compared with saline [21].

Interference with monocyte chemoattractant protein (MCP)-1, another chemokine target, reduces macrophage infiltration and thus inflammation and, therefore, improves outcomes [22]. Interestingly, interference with protein kinase CK2, which is a gene mostly expressed in glomerular nephritis, also reduces inflammation and levels of MCP-1 and TNF-α and, very importantly, the reduction in inflammation is accompanied by reduced production of collagen type IV, fibronectin and fibrosis-inducing transforming growth factor (TGF)-α [23]. Thus, addressing inflammation might also prevent the production and development of fibrosis and scars in the kidney, which is important for the long-term outcome.

SLE-specific immunomodulation

Depletion and inhibition of T or B cells are still global approaches. The ideal is to directly target the specific immune dysregulation in SLE. Several potential agents are at various stages of investigation.

Edratide (TV-4710) is a CDR-1-based peptide from 16/6id that has demonstrated down-regulation of autoantibody T-cell responses. In mice models (Balb/C; NZB×NZWF1) it has been demonstrated to reduce proteinuria, reduce deposition of immune complexes in the kidney and improve survival [24]. Furthermore, investigation of the effects of edratide on...
Peripheral blood cells in patients with SLE demonstrated decreases in IL-2, interferon-γ and TNF-α and increases in TGF-β [25].

Linnik and colleagues modeled the relative risk of renal flare from baseline with data from studies that used the dsDNA-based bioconjugate LJP 394 in patients with systemic lupus nephritis and a history of lupus nephritis [26]. The Cox model used predicted that a point estimate of a 50% reduction in anti-dsDNA antibody levels would be associated with a 52–53% reduction in the risk of renal flare compared with no change in antibody levels. These data confirm the potential therapeutic importance of aiming to reduce anti-dsDNA antibody levels. LJP 394 is a synthetic biologic composed of four double-stranded oligonucleotides attached to a central branched platform. LJP 394 induces tolerance in B cells directed against dsDNA by cross-linking surface antibodies. The first randomized controlled trials with LJP 394 did not show any clinical importance in preventing renal flare. The interim analyses of an ongoing trial indicate a significant reduction of dsDNA antibody titers by up to 46% after 8 weeks.

Another approach to reduce anti-dsDNA antibodies was the use of a fusion protein in which anti-CR1 monoclonal antibodies are combined with dsDNA [27]. The intention is that the fusion protein will physiologically remove dsDNA antibodies through the CR1 receptor. Data from a Phase I trial in lupus indicate that the dsDNA antibodies can be fixed to the erythrocyte surface, but the fusion protein has to be improved further before further trials are undertaken.

It may also be possible to interfere with the reaction between dsDNA antibodies by introducing nucleosomal peptides that induce tolerance in patients. Tolerization with nucleosomal peptides in mouse models has been shown to diminish autoantibody levels and increase survival of mice with lupus nephritis by delaying nephritis [28]. Similar results can be achieved with peptides using the reactivity between other dsDNA antibodies and basement proteins. The application of peptides of laminin, a basement membrane protein that is over-expressed in lupus nephritis, could prevent deposition of the immune complex and, thus, control the activity of nephritis [29]. All current work in this area, however, is in animals.

As demonstrated with acetylcholinesterase inhibitors, nonimmunosuppressive drugs may be beneficial in the management of patients with lupus nephritis. Most noteworthy of these are the statins, which have effects on endothelial cells and B cells, as well as reducing levels of dsDNA antibodies and proteinuria and regaining normal control of kidney function [30].

Conclusion
Despite the lack of a new licensed drug over the past 30 years, physicians have been able to improve the survival of their lupus patients simply through the implementation of new strategies. Guidelines for the management of lupus nephritis have been developed on the basis of evidence, and actual treatment can be improved by following these recommendations [3].

The new immunosuppressive medications offer alternatives for patients who do not respond to standard therapies, hopefully their believed better benefit–risk ratio is persisting in greater cohorts with longer follow-up. However, real options and hopes are on the horizon with the new substances that are based on pathophysiologically-aimed interventions. The first successfully finished randomized controlled trials using one of the above mentioned anticytokine or anti-cellular strategies will open the window for fresh air in the treatment of lupus, as was the case with the first anti-TNF-α trials in rheumatoid arthritis.

After licensing, the optimal placing of these and other new drugs will be challenging. Rituximab, or a related anti-B-cell therapy with the advantage of experiences in lymphoma treatment, may be the next step, at first, for refractory lupus nephritis. As there is a need for less toxic drugs in the treatment of lupus nephritis, anti-B-cell therapies should be evaluated without cyclophosphamide and with less corticosteroids.

New approaches should always be considered in the battle to prevent damage, and the use of lupus-specific immunomodulators in early lupus may already support the tight disease control that is required to prevent organ-specific damage.

Future perspective
In the next few years, the ability to diagnose, treat and measure the outcome of lupus therapy will be improved. As there are several new therapeutic options already in the pipeline, the next important step in the management of lupus nephritis is expected to come from new drugs. Data from some of the few already closed trials indicate that a more differentiated analysis of the clinical status may be mandatory to identify the real therapeutic potential of the new drugs. Currently ongoing trials are designed with subgroups of similar patients by using severity instruments,
such as BILAG, or by the same organ involved. However, this raises the question of whether selecting similar lupus patients will lead to similar responses to the new interventions. From all that is known about lupus, every patient is unique and so is the response. Probably, pre-defined individualized aims are more helpful to evaluate the potential of the new substances.

The actual outcome parameters are probably not sensitive enough to detect the benefits of the more specific interventions that are in the pipeline. On the basis of creatinine doubling or end-stage renal disease, the differences between the different strategies in the NIH trial became obvious after 5 years. Therefore, most important for the development of new therapeutic strategies of lupus nephritis will be the detection of biomarkers that allow a sensitive analysis of the different processes (e.g., immunoresponse, inflammation and scarring) that are involved in the pathophysiology of nephritis. Biomarkers such as endothelial cell growth factor, TGF-α or chemokines will hopefully facilitate the evaluation of the new therapeutic approaches in lupus nephritis. As long as a cure for lupus nephritis is still outside the therapeutic potential, more sensitive and specific surrogate markers of outcome are mandatory.

### Executive summary

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<th>Standard care of proliferative lupus nephritis</th>
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<tr>
<td>- Urine analyses at every routine check of a lupus patient are mandatory for early detection of lupus nephritis.</td>
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<td>- Cyclophosphamide pulses plus steroids are the standard therapy for lupus nephritis.</td>
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<td>- Actual therapeutic developments can be separated into other immunosuppressive drugs, anticytokine therapy and lupus erythematosus-specific immunomodulation.</td>
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<td>- Mycophenolate mofetil has been evaluated in short-to-medium-term randomized controlled trials. Data indicate that it has at least similar efficacy and a favorable toxicity profile compared with cyclophosphamide pulses for both induction and maintenance therapy.</td>
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<td>- Experiences in smaller cohorts indicate some benefit of rituximab in lupus patients resistant to standard immune suppression; controlled trials are required for B-cell-directed interventions.</td>
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<td>- Other therapeutic strategies are in an exploratory state.</td>
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<td>- There is an urgent need for a differentiated analysis of the clinical status of lupus nephritis for biomarkers that allow a sensitive analysis of the different pathophysiological processes (e.g., immunoresponse, inflammation and scarring) in lupus nephritis and for more sensitive and specific surrogate markers of outcome.</td>
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### Bibliography

Papers of special note have been highlighted as either of interest (+) or of considerable interest (++). to readers.

3. Great overview of important clinical manifestations in lupus.
Future prospects in the treatment of lupus nephritis – REVIEW


Affiliations

• Rebecca Fischer-Betz
  Heinrich-Heine University, Clinic of Endocrinology, Diabetology & Rheumatology, M oonstr. 5, 40225 Düsseldorf, Germany
  Tel.: +49 211 811 7817;
  Fax: +49 211 811 6455;
  rebecca.fischer@med.uni-duesseldorf.de

• M atthias Schröder, Professor
  Heinrich-Heine University, Clinic of Endocrinology, Diabetology & Rheumatology, M oonstr. 5, 40225 Düsseldorf, Germany
  Tel.: +49 211 811 7817;
  Fax: +49 211 811 6455;
  schraeder@rheumanet.org