Emerging treatments for lupus nephritis

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Abstract

Lupus nephritis is the most common organ threatening complication of systemic lupus erythematosus and is associated with a significantly decreased survival. Current standard therapies for lupus nephritis are complicated by high rates of toxicity and adverse events. After a long period of little change in our treatment of lupus nephritis, an improved understanding of its biology has lead to the development of many new treatments recently. Rational biologic targets for which experimental therapies exist include B and T cells and their interactions, complement and cytokines such as interleukins and tumor necrosis factor. In this article we review a selection of promising experimental therapies for the treatment of lupus nephritis.

Key words: systemic lupus erythematosus, lupus glomerulonephritis, rituximab, biologic therapy.

Introduction

Systemic lupus erythematosus (SLE) is the most common of the multi-system autoimmune disease. Systemic lupus erythematosus occurs with an incidence of between 2 and 7.4 cases/100,000/year in North America and Europe [1]. Up to 30% of patients with SLE will have renal involvement at some point [2]. Renal involvement has been classified by the International Society of Nephrology and the Renal Pathologist Society according to the presence and degree of endothelial immune deposits, endothelial proliferation, membranous lesions and scarring [3]. Proliferative lesions may lead to glomerulosclerosis, interstitial fibrosis and eventually to end-stage renal disease (ESRD) if disease activity is left unchecked. Lupus nephritis is also associated with an increased risk of all cause mortality [4]. Due to the serious consequences of lupus nephritis, effective therapies are required to spare patients renal function and preserve their quantity and quality of life. The evolving understanding of the immunologic basis of SLE has provided the rationale for many new therapies (Figure 1). This review will focus on the evidence of some novel therapies for SLE and lupus nephritis.

Current standards of care and the need for new treatments

There are currently no medications that have a specific indication for lupus nephritis. However, glucocorticoids and cyclophosphamide are almost universally accepted as the standard of care for patients with proliferative lupus nephritis. This practice is based predominantly on small randomized clinical trials performed 20 to 30 years ago [5-8]. Much of this practice is derived from the clinical observations that high dose glucocorticoids
resulted in a rapid attenuation of disease activity but relapses of disease were also common [9]. The addition of oral cyclophosphamide to glucocorticoids resulted in less progressive renal disease but had high rates of adverse events including infertility and possibly serious infections [10].

The search for less toxic treatment regimens began by changing from daily oral to intravenous pulses of cyclophosphamide resulting in lower total cumulative cyclophosphamide exposure. Treatment regimens then became sequential in nature with a period of high intensity induction treatment with

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**Figure 1.** Emerging immunobiology of systemic lupus erythematosus. a) Auto-antigen stimulation of T cells by antigen presenting cells (APC) or B cells via MHC/antigen-T cell receptor interactions in conjunction with co-stimulation by CD80 (86)-CD28 or CD40-CD40L interactions; b) T cell secretion of cytokines such as BLyS or APRIL which, via cell surface receptors like TACI, induce B cell maturation and differentiation to plasma cells; c) B cell secretion of cytokines such as interleukin-10 and interferon α induce differentiation of APC to monocytes; d) B cell clonal proliferation after exposure to autoantigens; e) B cell differentiation to autoantibody producing plasma cells; f) neutrophil activation and recruitment in peripheral tissues by B cell derived cytokines.
monthly cyclophosphamide and high dose glucocorticoids followed by a less intense period of the maintenance of remission with quarterly cyclophosphamide infusions and a reduction or discontinuation in glucocorticoids. This was followed by evidence that non-cyclophosphamide immunosuppressive medications such as azathioprine or mycophenolate mofetil, appear at least as efficacious as cyclophosphamide during the maintenance of remission [11]. Further studies sought to reduce toxicity by using low-dose cyclophosphamide infusions every two weeks for three months before beginning maintenance of remission therapy [12].

Although the above studies were universally small, they successfully demonstrated a reduced cyclophosphamide exposure can likely maintain therapeutic efficacy while reducing toxicity. All these regimens are still marked by several common shortcomings however. Shortcomings include: 1) primary treatment failures (the inability to adequately control disease activity initially) occur in up to 20% of patients with proliferative lupus nephritis [13]; 2) relapses of proliferative lupus nephritis occur in up to 10% of patients per year [14-17]; 3) although toxicity is diminished, the risks of cyclophosphamide and glucocorticoids still exceed tolerable limits for many patients and physicians. The last point is underscored by the rates of amenorrhea that range up to 41% that are particularly important in SLE due to the predominantly young, female population [18].

**Mycophenolate mofetil**

The search for regimens that maintain the efficacy of cyclophosphamide and glucocorticoids has lead to the investigation of mycophenolate mofetil and glucocorticoids in the last decade [19-21]. Several trials have had promising results of at least equal efficacy to cyclophosphamide based regimens with fewer infections and a lower incidence of amenorrhea, although it is associated with high rates of gastrointestinal toxicity [22]. Although there is some evidence to suggest mycophenolate mofetil may be more efficacious than cyclophosphamide in terms of inducing remission there is little evidence to suggest long term renal function or survival is impacted [23]. What little evidence there is based on small trials with few events and usually short follow-up. Therefore, although mycophenolate mofetil is the most developed alternative to cyclophosphamide and has the most randomized trial evidence to support its use, the bulk of this evidence is short term and focuses on the induction of remission rather than the prevention of relapses, the preservation of renal function, or survival.

The shortcomings in the current treatment of lupus nephritis have created a need for effective, long-term therapies with a low toxicity profile. This research agenda has been forwarded by the modern era of therapeutic monoclonal antibodies and targeted biologic therapies which seem ideally suited for the treatment of immunologic disease. This paper will review several of the candidate therapies currently undergoing investigation for use in lupus nephritis. Investigational therapies can be broadly categorized by their therapeutic targets and include those directed against B cells, T cells, cell signaling, and multi-target therapies (Table I).

**B cell therapies**

B cells have gained prominence in theories of the pathogenesis of SLE and lupus nephritis [24]. As such, B cell depleting therapies and B cell modulating therapies hold promise as valuable therapies in the treatment of lupus nephritis.

Monoclonal antibodies directed against the B cell have received a great deal of attention recently. Rituximab, a monoclonal antibody directed against the CD20 cell marker, was originally marketed for use in B cell lymphoma [25]. The observation that rituximab reduced rheumatoid arthritis symptoms in a number of patients lead to its use and subsequent licensing in rheumatoid arthritis and widespread off label investigations in other inflammatory conditions [26, 27]. Several prospective single limb studies were conducted in non-renal SLE and demonstrated effective disease control in patients with refractory disease [28-31]. Several studies included patients with lupus nephritis and at least two have been performed specifically in patients with lupus nephritis with encouraging results [32-37]. Induction of remission, predominantly in patients with relapsing disease, appears successful in between 50 and 100% of patients on the basis of stabilized or improved serum creatinine and proteinuria [38]. The majority of these therapies hold promise as valuable therapies in the treatment of lupus nephritis.

**Table I. Emerging therapeutic targets in SLE**

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<tr>
<th>Target</th>
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<tr>
<td>B cells</td>
<td>Anti-CD20 (rituximab, ocrelizumab, ofatumumab)</td>
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<td>Anti-CD22 (epratuzumab)</td>
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<td>Anti-BLYS (belimumab)</td>
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<td>Anti-TACI Ig (atacicept)</td>
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<td>Anti-DNA toleragen (abetimus sodium)</td>
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<td>T cells/T –</td>
<td>CTLA4-Ig (abatacept)</td>
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<td>B cell interactions</td>
<td>Anti-CD40L</td>
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<td>Complement activation</td>
<td>Anti-C5a (eculizumab)</td>
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<td>Anti-interferon α</td>
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patients are treated with rituximab for relapsing disease and relapses are still common after treatment with rituximab. There is no controlled data to suggest whether medium to long-term disease control and renal function are improved with rituximab compared to cyclophosphamide. Other considerations in interpreting the rituximab literature are that relapses were common (up to 60% of patients) even in these relatively short studies, concomitant therapies were varied, and publication bias may skew the body of literature towards positive studies [39].

From a safety perspective, rituximab appears well tolerated with few serious adverse events even with repeated dosing [40]. There is little information currently available regarding the occurrence of infections in SLE patients treated with rituximab but concerns have been raised over the occurrence of serious, rare infections such as PML [41] and there is emerging data to suggest bacterial infections are not uncommon in patients receiving rituximab for refractory disease [42].

Two randomized control trials were designed to investigate rituximab’s efficacy and safety in SLE, one in non-renal SLE (EXPLORER, clinicaltrials.gov number NCT00137969) and one in lupus nephritis (LUNAR, clinicaltrials.gov number NCT00282347). Disappointingly, preliminary results from EXPLORER, comparing rituximab with prednisone alone for mild to moderate SLE, were negative. Whether this is predominantly due trial design issues or a failure of the drug remains to be seen with the full publication of the trial results. The results of LUNAR are not yet complete.

Other B cell targeted therapies are on the horizon as a new generation of monoclonal antibodies become available. Ocrelizumab, a fully humanized anti-CD20 molecule, is under investigation for SLE also in a non-renal SLE population and lupus nephritis population. It is hoped that a fully humanized molecule may improve long term efficacy of the drug due to a lower incidence of the development of blocking antibodies. Due to the negative results of EXPLORER, further non-renal SLE investigations appear unlikely.

Epratuzumab, a fully humanized monoclonal antibody against CD22, another B cell restricted transmembrane protein, is also under investigation. In vitro studies suggest epratuzumab preferentially inhibit B cell proliferation in patients with SLE compared to normal patients [43]. A small, open-label, single-centre study of patients with SLE demonstrated a reduction in disease manifestations measured by the British Isles Lupus Assessment Group score including renal subscores in 3 out of 4 patients with renal involvement at baseline [44]. A randomized trial of 210 patients comparing epratuzumab to placebo in patients with active disease is underway (clinicaltrials.gov number NCT00624351).

B lymphocytic stimulator (BlyS) plays an essential role in the activation and development of B cells. Human studies suggest BlyS is overexpressed in patients with SLE and may be pathogenic [45]. Belimumab is a fully human IgG1 monoclonal antibody that neutralizes BlyS and has been used in early studies in patients with SLE. In patients with SLE, the administration of belimumab is well tolerated and associated with a moderate reduction in circulating B cells [46, 47]. However, improvements in SLE disease activity with belimumab have been variable in these small studies. The full results of Phase III studies have yet to be reported. There is no reliable evidence of the effects of belimumab in lupus nephritis. Amgen 623, a fusion protein that acts as an anti-B cell activating factor (BAFF), also targets B cell maturation and proliferation and is undergoing early clinical testing.

The proinflammatory cytokine, IL-6 also known as B lymphocyte stimulating factor 2, is elevated in murine models of SLE and in humans with SLE [48-50]. IL-6 is involved in the differentiation of B cells into anti-body producing cells, and T cells to effector cells. In murine models, the blockade of IL-6 reduces disease activity [51]. Early studies of a monoclonal antibody directed against the IL-6 receptor (tocilizumab) in rheumatoid arthritis suggest blockade of IL-6 in humans is well tolerated although mild disturbances of hepatic enzymes, leucopenia, and diarrhea have been observed and infection rates were slightly higher in tocilizumab treated patients than in patients treated with conventional disease modifying drugs (7.6 vs. 4.1%) [52-55]. Studies in patients with SLE are expected.

Atacicept, a novel recombinant fusion protein that blocks the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), is also under investigation for use in SLE [56]. TACI is a receptor for BlyS and other B cell stimulating molecules such as APRIL. After encouraging early development results, a phase II/III trial in lupus nephritis was launched using atacicept in addition to mycophenolate mofetil and steroids (clinicaltrials.gov identifier NCT00573157). This trial was terminated due to an excess of severe infections in the atacicept limb but a trial in generalized SLE continues.

LJP-394 (abetimus sodium) is a construct of four dsDNA epitopes attached to a nonimmunogenic polyethylene glycol platform [57, 58]. The mechanism of action of abetimus is thought to involve rapid reduction of anti-dsDNA antibody levels mediated by formation and clearance of drug-antibody complexes and a prolonged effect related to inducing tolerance in anti-dsDNA presenting B cells. Several randomized control trials have been performed...
to evaluate the efficacy of LJP-394 to reduce flares of disease. The results of one major trial found no benefit to LJP-394 over placebo in the primary analysis but suggested that benefit was limited to patients with high affinity antibodies to LJP-394 [2]. A second major trial of patients with high affinity anti-dsDNA antibodies was not able to confirm this finding, however [59]. At present, a much larger trial of LJP-394 attempting to enroll over 700 patients is underway (clinicaltrials.gov NCT00089804).

**T cells**

Inhibition of T cell costimulation, and therefore T cell activation, mediated by cytotoxic T lymphocyte associated antigen-4 (CTLA-4) is a potential treatment for patients with lupus nephritis. CTLA-4 is an inhibitor of second signal T cell activation by down regulating B7/CD28 interactions. Abatacept, a recombinant fusion protein developed to take advantage of the inhibitory nature of CTLA-4 on T cells, has demonstrated in vivo suppression of T and B cell costimulation and promising results in combination with cyclophosphamide in NZB/W mouse models of SLE [60, 61]. This agent, as an adjunct to low dose intravenous cyclophosphamide is currently undergoing phase II testing in lupus nephritis (clinicaltrials.gov identifier NCT00774852).

Co-stimulation via the T cell CD40 – B cell CD40 ligand interaction has also been targeted in the treatment of SLE. The CD40-CD40L interaction results in B cell proliferation and differentiation which leads to the production of antibodies and activating cytokines. Interfering with this interaction therefore reduces T cell mediated antibody production. This mechanism may be of importance in SLE because plasma CD40L levels are increased as is glomerular expression of CD40 and CD40L. Clinical trials of anti-CD40L (rupilizumab) have been disappointing. One small study in patients with lupus nephritis found a significant reduction in proteinuria [62] but this was not substantiated in a second trial of patients with mild to moderate disease [63]. Additionally, concerns over an excess of thrombotic events, presumably due to the presence of CD40L on endothelial cells, has halted development of this agent in lupus nephritis.

**Cell signaling**

Patients with SLE have been noted to have several abnormalities in levels of interleukins, interferons, and other cell signaling molecules. Interleukin-10 was noted to be increased in SLE patients and to correlate with disease activity [64-66]. These abnormal levels may result in T cell dysfunction and dysregulation of T cell dependent B cell functions. Anti-interleukin 10 antibody administration in murine models of lupus improved survival [67].

A study of six patients treated with an anti-interleukin-10 antibody experienced a marked decrease in circulating interleukin-10 and a concomitant reduction in disease activity [68].

Tumor necrosis factor (TNF) α has been a therapeutic target in several autoimmune diseases. TNF-α blockade in SLE, however, has been uncertain due to the observation that anti-TNF-α drugs have been associated with an increased development of antimicrobial antibodies, anti-dsDNA antibodies, and lupus-like syndromes [69]. Preliminary results in humans suggest anti-TNF-α therapy, including some patients with lupus nephritis, may reduce proteinuria, arthritis, and overall disease activity despite the development of auto-antibodies [70, 71].

**Complement**

Complement activation is an essential step in the development of tissue damage in SLE. C5 is a component of the final common pathway of complement activation and therefore a potential target in SLE. The administration of anti-C5 antibodies in murine models of SLE significantly delayed the onset of proteinuria and improved survival [72]. Eculizumab, a fully humanized monoclonal antibody that blocks the generation of the terminal components of C5a and C5-9 [73]. A preliminary study of anti-C5 antibody suggests it is well tolerated although there was little change in clinical parameters [74].

**Conclusions**

There are a very limited number of effective therapies currently accepted in the treatment of lupus nephritis. With an improved understanding of the immunology driving SLE and lupus nephritis, new therapies are becoming available. This review has only touched on the numerous potential therapies being pursued in lupus nephritis. Although single-limb studies and pilot randomized trials are providing encouraging results for many of these designer treatments, caution must be advised in their interpretation. While there are many exciting prospects for the treatment of lupus nephritis, adequately powered, high quality randomized control trials showing unequivocal benefits over standard therapies are required before any of these treatments should be considered for widespread use.

**References**


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