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

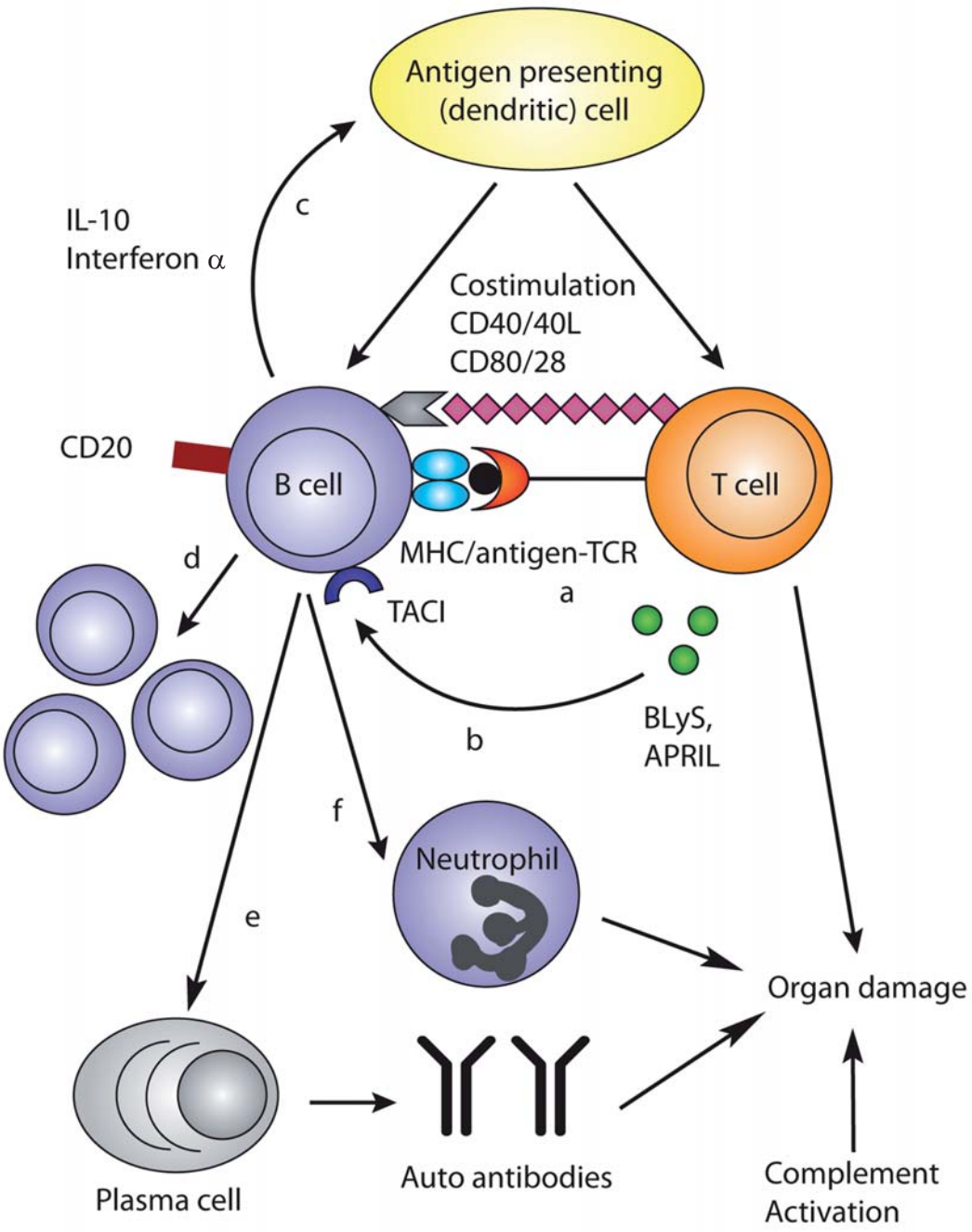

Figure 1. Emerging immunobiology of systemic lupus erythematosus. a) Auto-antigen stimulation of T cells by antigen presenting cells (APC) or B cells via MHC/antigen-T cell receptor interactions in conjunction with co-stimulation by CD80 (86)-CD28 or CD40-CD40L interactions; b) T cell secretion of cytokines 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

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

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 wider spread 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

Table I. Emerging therapeutic targets in SLE

Target	Investigational agent
B cells	Anti-CD20 (rituximab, ocrelizumab, ofatumumab) Anti-CD22 (epratuzumab) Anti-BLyS (belimumab) Anti-BAFF (Amgen 623) Anti-TACI Ig (atacicept) Anti-DNA toleragen (abetimus sodium)
T cells/T – B cell interactions	CTLA4-Ig (abatacept) Anti-CD40L
Complement activation	Anti-C5a (eculizumab)
Cell signalling	Anti-TNF (infliximab) Anti-IL-10 Anti-interferon α

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 to 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 IgG1λ 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 cyclophylin 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 inhibory 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 (ruplizumab) 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 antinuclear 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

1. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus 2006; 15: 308-18.
2. Alarcon GS, Bastian HM, Beasley TM, et al. Systemic lupus erythematosus in a multi-ethnic cohort (LUMINA) XXXII: [corrected] contributions of admixture and socioeconomic status to renal involvement. Lupus 2006; 15: 26-31.

3. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004; 15: 241-50.
4. Abu-Shakra M, Urowitz MB, Gladman DD, Gough J. Mortality studies in systemic lupus erythematosus. Results from a single center. II. Predictor variables for mortality. J Rheumatol 1995; 22: 1265-70.
5. Austin HA III, Klippel JH, Balow JE, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med 1986; 314: 614-9.
6. Boumpas DT, Austin HA, III, Vaughn EM, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet 1992; 340: 741-5.
7. Donadio JV Jr, Holley KE, Ferguson RH, Ilstrup DM. Treatment of diffuse proliferative lupus nephritis with prednisone and combined prednisone and cyclophosphamide. N Engl J Med 1978; 299: 1151-5.
8. Gourley MF, Austin HA III, Scott D, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med 1996; 125: 549-57.
9. 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 a cohort of 145 patients participating in randomized controlled studies. Arthritis Rheum 2002; 46: 995-1002.
10. Flanc RS, Roberts MA, Strippoli GF, Chadban SJ, Kerr PG, Atkins RC. Treatment of diffuse proliferative lupus nephritis: a meta-analysis of randomized controlled trials. Am J Kidney Dis 2004; 43: 197-208.
11. Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med 2004; 350: 971-80.
12. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002; 46: 2121-31.
13. Illei GG, Austin HA, Crane M, et al. Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. Ann Intern Med 2001; 135: 248-57.
14. Alarcon-Segovia D, Tumlin JA, Furie RA, et al. 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 2003; 48: 442-54.
15. 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 a cohort of 145 patients participating in randomized controlled studies. Arthritis Rheum 2002; 46: 995-1002.
16. 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 2004; 50: 2559-68.
17. Moroni G, Quaglini S, Maccario M, Banfi G, Ponticelli C. "Nephritic flares" are predictors of bad long-term renal outcome in lupus nephritis. Kidney Int 1996; 50: 2047-53.
18. Gourley MF, Austin HA, III, Scott D, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med 1996; 125: 549-57.
19. Chan TM, Li FK, Tang CS, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med 2004; 343: 1156-62.
20. Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med 2004; 350: 971-80.
21. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med 2005; 353: 2219-28.
22. Walsh M, James M, Jayne D, Tonelli M, Manns BJ, Hemmelgarn BR. Mycophenolate mofetil for induction therapy of lupus nephritis: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2007; 2: 968-75.
23. Walsh M, James M, Jayne D, Tonelli M, Manns BJ, Hemmelgarn BR. Mycophenolate mofetil for induction therapy of lupus nephritis: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2007; 2: 968-75.
24. Anolik JH. B cell biology and dysfunction in SLE. Bull NYU Hosp Jt Dis 2007; 65: 182-6.
25. Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998; 92: 1927-32.
26. Protheroe A, Edwards JC, Simmons A, Maclennan K, Selby P. Remission of inflammatory arthropathy in association with anti-CD20 therapy for non-Hodgkin's lymphoma. Rheumatology (Oxford) 1999; 38: 1150-2.
27. Gorman C, Leandro M, Isenberg D. B cell depletion in autoimmune disease. Arthritis Res Ther 2003; 5 Suppl 4: S17-21.
28. Gottenberg JE, Guillevin L, Lambotte O, et al; Club Rheumatismes et Inflammation (CRI). Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis 2005; 64: 913-20.
29. Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA. An open study of B lymphocyte depletion in systemic lupus erythematosus. Arthr Rheumat 2002; 46: 2673-7.
30. Looney RJ, Anolik JH, Campbell D, et al. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. Arthr Rheumat 2004; 50: 2580-9.
31. Smith KG, Jones RB, Burns SM, Jayne DR. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. Arthr Rheumat 2006; 54: 2970-82.
32. Gottenberg JE, Guillevin L, Lambotte O, et al.' Club Rheumatismes et Inflammation (CRI). Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis 2005; 64: 913-20.
33. Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA. An open study of B lymphocyte depletion in systemic lupus erythematosus. Arthr Rheum 2002; 46: 2673-7.
34. Looney RJ, Anolik JH, Campbell D, et al. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. Arthr Rheum 2004; 50: 2580-9.
35. Sfikakis PP, Boletis JN, Lionaki S, et al. Remission of proliferative lupus nephritis following B cell depletion therapy is preceded by down-regulation of the T cell costimulatory molecule CD40 ligand: an open-label trial. Arthr Rheumat 2005; 52: 501-13.
36. Smith KG, Jones RB, Burns SM, Jayne DR. Long-term comparison of rituximab treatment for refractory systemic

lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. Arthrs Rheum 2006; 54: 2970-82.
37. Vigna-Perez M, Hernandez-Castro B, Paredes-Saharopulos O, Portales-Perez D, Baranda L, bud-Mendoza C. Clinical and immunological effects of Rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study. Arthrs Res Therapy 2006; 8: R83.
38. Walsh M, Jayne D. Rituximab in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis and systemic lupus erythematosus: past, present and future. Kidney Int 2007; 72: 676-82.
39. Walsh M, Jayne D. Rituximab in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis and systemic lupus erythematosus: past, present and future. Kidney Int 2007; 72: 676-82.
40. Walsh M, Jayne D. Rituximab in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis and systemic lupus erythematosus: past, present and future. Kidney Int 2007; 72: 676-82.
41. Rituximab Information: FDA alert. U. S. Food and Drug Administration Website. 2006.
42. Catapano F, Walsh M, Jayne D. Tolerance and safety of rituximab in vasculitis and SLE. J Am Soc Nephrol 2008; 19: 782B.
43. Jacobi AM, Goldenberg DM, Hiepe F, Radbruch A, Burmester GR, Dorner T. Differential effects of epratuzumab on peripheral blood B cells of patients with systemic lupus erythematosus versus normal controls. Ann Rheum Dis 2008; 67: 450-7.
44. Dorner 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 2006; 8: R74.
45. Stohl W, Metyas S, Tan SM, et al. B lymphocyte stimulator overexpression in patients with systemic lupus erythematosus: longitudinal observations. Arthritis Rheum 2003; 48: 3475-86.
46. Baker KP, Edwards BM, Main SH, et al. Generation and characterization of LymphoStat-B, a human monoclonal antibody that antagonizes the bioactivities of B lymphocyte stimulator. Arthritis Rheum 2003; 48: 3253-65.
47. Furie R, Stohl W, Ginzler EM, et al. Biologic activity and safety of belimumab, a neutralizing anti-B-lymphocyte stimulator (BLyS) monoclonal antibody: a phase I trial in patients with systemic lupus erythematosus. Arthritis Res Ther 2008; 10: R109.
48. Finck BK, Chan B, Wofsy D. Interleukin 6 promotes murine lupus in NZB/NZW F1 mice. J Clin Invest 1994; 94: 585-91.
49. Mihara M, Takagi N, Takeda Y, Ohsugi Y. IL-6 receptor blockage inhibits the onset of autoimmune kidney disease in NZB/W F1 mice. Clin Exp Immunol 1998; 112: 397-402.
50. Tackey E, Lipsky PE, Illei GG. Rationale for interleukin-6 blockade in systemic lupus erythematosus. Lupus 2004; 13: 339-43.
51. Mihara M, Takagi N, Takeda Y, Ohsugi Y. IL-6 receptor blockage inhibits the onset of autoimmune kidney disease in NZB/W F1 mice. Clin Exp Immunol 1998; 112: 397-402.
52. Choy EH, Isenberg DA, Garrood T, et al. Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial. Arthritis Rheum 2002; 46: 3143-50.
53. Nishimoto N, Yoshizaki K, Maeda K, et al. Toxicity, pharmacokinetics, and dose-finding study of repetitive treatment with the humanized anti-interleukin 6 receptor antibody MRA in rheumatoid arthritis. Phase I/II clinical study. J Rheumatol 2003; 30: 1426-35.
54. Nishimoto N, Yoshizaki K, Miyasaka N, et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum 2004; 50: 1761-9.
55. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis 2007; 66: 1162-7.
56. Dall'Era M, Chakravarty E, Wallace D, et al. Reduced B lymphocyte and immunoglobulin levels after atacicept treatment in patients with systemic lupus erythematosus: results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating trial. Arthritis Rheum 2007; 56: 4142-50.
57. Furie RA, Cash JM, Cronin ME, et al. Treatment of systemic lupus erythematosus with LJP 394. J Rheumatol 2001; 28: 257-65.
58. Weisman MH, Bluestein HG, Berner CM, de Haan HA. Reduction in circulating dsDNA antibody titer after administration of LJP 394. J Rheumatol 1997; 24: 314-8.
59. Cardiel MH, Tumlin JA, Furie RA, Wallace DJ, Joh T, Linnik MD. Abetimus sodium for renal flare in systemic lupus erythematosus: results of a randomized, controlled phase III trial. Arthritis Rheum 2008; 58: 2470-80.
60. Cunnane G, Chan OT, Cassafer G, et al. Prevention of renal damage in murine lupus nephritis by CTLA-4Ig and cyclophosphamide. Arthritis Rheum 2004; 50: 1539-48.
61. Daikh DI, Wofsy D. Cutting edge: reversal of murine lupus nephritis with CTLA4Ig and cyclophosphamide. J Immunol 2001; 166: 2913-6.
62. Boumpas DT, Furie R, Manzi S, et al. A short course of BG9588 (anti-CD40 ligand antibody) improves serologic activity and decreases hematuria in patients with proliferative lupus glomerulonephritis. Arthritis Rheum 2003; 48: 719-27.
63. Kalunian KC, Davis JC Jr, Merrill JT, Totoritis MC, Wofsy D. Treatment of systemic lupus erythematosus by inhibition of T cell costimulation with anti-CD154: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002; 46: 3251-8.
64. Llorente L, Richaud-Patin Y, Wijdenes J, et al. Spontaneous production of interleukin-10 by B lymphocytes and monocytes in systemic lupus erythematosus. Eur Cytokine Netw 1993; 4: 421-7.
65. Llorente L, Richaud-Patin Y, Fior R, et al. In vivo production of interleukin-10 by non-T cells in rheumatoid arthritis, Sjogren's syndrome, and systemic lupus erythematosus. A potential mechanism of B lymphocyte hyperactivity and autoimmunity. Arthritis Rheum 1994; 37: 1647-55.
66. Gonzalez-Amaro R, Portales-Perez D, Baranda L, et al. Role of IL-10 in the abnormalities of early cell activation events of lymphocytes from patients with systemic lupus erythematosus. J Autoimmun 1998; 11: 395-402.
67. Ishida H, Muchamuel T, Sakaguchi S, Andrade S, Menon S, Howard M. Continuous administration of anti-interleukin 10 antibodies delays onset of autoimmunity in NZB/W F1 mice. J Exp Med 1994; 179: 305-10.
68. Llorente L, Richaud-Patin Y, Garcia-Padilla C, et al. Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic lupus erythematosus. Arthritis Rheum 2000; 43: 1790-800.

69. Ramos-Casals M, Brito-Zeron P, Munoz S, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. Medicine (Baltimore) 2007; 86: 242-51.
70. Aringer M, Graninger WB, Steiner G, Smolen JS. Safety and efficacy of tumor necrosis factor alpha blockade in systemic lupus erythematosus: an open-label study. Arthritis Rheum 2004; 50: 3161-9.
71. Aringer M, Steiner G, Graninger WB, Hofler E, Steiner CW, Smolen JS. Effects of short-term infliximab therapy on autoantibodies in systemic lupus erythematosus. Arthritis Rheum 2007; 56: 274-9.
72. Wang Y, Hu Q, Madri JA, Rollins SA, Chodera A, Matis LA. Amelioration of lupus-like autoimmune disease in NZB/WF1 mice after treatment with a blocking monoclonal antibody specific for complement component C5. Proc Natl Acad Sci U S A 1996; 93: 8563-8.
73. Kaplan M. Eculizumab (Alexion). Curr Opin Investig Drugs 2002; 3: 1017-23.
74. Furie R, Matis L, Rollins S. A Single Dose, Placebo-Controlled Double-Blind, Phase I Study of Humanized Anti-C5 Antibody h5G1.1 in Patients with Systemic Erythematosus. Annual Scientific Meeting of the American College of Rheumatology. 2000.