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Why Targeted Therapies are Necessary for Systemic Lupus Erythematosus

Laura Durcan, M.D.¹ and Michelle Petri, M.D. M.P.H.²

¹Division of Rheumatology, University of Washington, Seattle

²Division of Rheumatology, Johns Hopkins University, School of Medicine, Baltimore

Abstract

Systemic lupus erythematosus (SLE) continues to have important morbidity and accelerated mortality despite therapeutic advances. Targeted therapies offer the possibility of improved efficacy with fewer side-effects. Current management strategies rely heavily on non-specific immunosuppressive agents. Prednisone, in particular, is responsible for a considerable burden of later organ damage.

There are a multitude of diverse mechanisms of disease activity, immunogenic abnormalities and clinical manifestations to take into consideration in SLE. Many targeted agents with robust mechanistic pre-clinical data and promising early phase studies have ultimately been disappointing in phase III randomized controlled studies. Recent efforts have focused on B cell therapies, in particular given the success of belimumab in clinical trials, with limited success. We remain optimistic regarding other specific therapies being evaluated including interferon alpha blockade.

It is likely that in SLE, given the heterogeneity of the population involved, precision medicine is needed, rather than expecting that any single biologic will be universally effective.

Keywords

SLE; Treatment; Targeted therapy

Introduction

Systemic Lupus Erythematosus (SLE) has important morbidity and mortality. Death in SLE can attributed to the disease itself, to complications of therapies, or to long-term sequelae. In essence, there is a bimodal pattern associated with SLE mortality in most populations described(1). Early deaths are often attributable to active disease, infections and thromboses whilst later (yet still premature) mortality is frequently owing to cardiovascular causes and organ damage(2). The standardized mortality rate for SLE has been estimated at 2.4(3)–5.9(4), this is significantly higher in those with renal involvement(5), with substantial ethnic and geographic variation(6). The rate of damage accrual and premature death in this population remains unacceptably high despite medical advancements, antimalarials, antibiotics, angiotensin converting enzyme inhibitors, renal replacement therapy and immunosuppressive agents. Historically, the five-year survival rate in SLE was only 50%, whereas more recently, the 10-year survival is in excess of 90%(3, 7). Given the young age

of the population affected by this disease, improving this figure further is of critical importance, in particular given that much of the excess mortality demonstrated in recent cohorts has been attributed to treatment-effects and cardiovascular disease rather than uncontrolled inflammation.

This highlights the fact that current, non-specific, treatment approaches are limited by both short and long-term toxicity and in many cases contribute to morbidity and in some cases, mortality. However, due to the heterogeneous nature of SLE, in terms of clinical manifestations and mechanisms of disease, the development of specific, targeted therapies (which demonstrate efficacy in clinical trials) has been problematic. This review outlines the limitations of our current treatment regimens, the challenges encountered to date in the development of targeted therapies in SLE, and the unmet clinical need for effective targeted therapies in this serious autoimmune disease.

Corticosteroid therapy in SLE

Since their development by Hench *et al*(8), the administration of synthetic corticosteroids, of which prednisone is the most commonly prescribed, has been a cornerstone of the management of SLE. However, reliance on prednisone as a therapeutic strategy is strongly associated with the accrual of irreversible organ damage. Although capable of powerful immunosuppression, corticosteroid therapy, in particular when chronic, produces a wide spectrum of adverse effects. Corticosteroids exert potent anti-inflammatory and immunosuppressive effects by non-selectively reducing the expression of cytokines (IL-2, IL-6, TNF α and prostaglandins) and adhesion molecules, which inhibit leukocyte, fibroblast and endothelial cell function. This non-specific mechanism of action is in stark contrast to more recent drugs approved or in development for SLE in which cellular mechanisms have been targeted based on robust mechanistic data

Over-reliance on corticosteroids for immunosuppression in SLE leads to poor health outcomes. Previous work in the Hopkins Lupus Cohort has shown that patients who received higher maintenance prednisone doses (≥ 7.5 mg/day) during follow-up were more likely to develop organ damage, even after adjustment for disease activity and other variables. Thamer *et al* demonstrated that the risk of developing organ damage increased by 50% when patients were exposed to an average prednisone dose of >6 –12 mg/day versus those who had no, or low dose, exposure(9). Al Sawah and colleagues showed that daily prednisone doses of over 7.5 mg increased the risk of developing cataracts, osteoporotic fractures and cardiovascular damage. They estimated that an increase in mean prednisone dose of just 1 mg/day was associated with a 3.8% increased risk of cataracts and 4.2% increase in osteoporotic fractures(10). Using multivariate modeling, chronic prednisone use was one of the factors which predicted the accrual of organ damage in SLE(11).

There are a multitude of adverse musculoskeletal side effects associated with prednisone therapy. Osteoporosis, by densitometry, and fragility fractures have been associated with SLE(12) and in particular with prednisone therapy(13) . This is the most commonly reported item on the American College of Rheumatology/ Systemic Lupus International Collaborating Clinics damage index (ACR/SLICC SDI)(14). Patients with SLE also have a

significantly higher risk of vertebral fractures than controls, and the majority of these fractures occur in pre-menopausal women(13, 15, 16). Zonana-Nacach *et al*(17) found that cumulative corticosteroid dose was most strongly associated with osteoporotic fractures, with a 2.5-fold increased risk for each decade of prednisone at 10 mg/day or more (which persisted with adjustment for age, gender, ethnicity, and exposure to high-dose and pulse therapy). Prednisone is a major modifiable risk factor for osteoporosis and fracture in this population.

Avascular necrosis also needs to be taken into consideration in SLE, where again, both the disease itself and prednisone therapy are risk factors. In the evaluation of damage attributable to chronic corticosteroid use, the most significant association of high-dose prednisone was with avascular necrosis(17). This disabling condition has been described primarily in SLE patients who have been exposed to corticosteroids (although some reports exist of avascular necrosis in steroid naive individuals(18, 19)). Other potential disease related risk factors include vasculitis, Raynaud's phenomenon, elevated triglycerides and the presence of antiphospholipid antibodies(20, 21). Given the young age of most SLE patients, a condition which commonly necessitates total joint replacement (often involving multiple joints) is particularly problematic with the potential need for re-do procedures and complicated orthopedic interventions. Thus, modifying prescribing practices to minimize this complication is important.

In terms of the accelerated cardiovascular mortality associated with SLE, there is a substantial body of evidence directly linking chronic prednisone use with cardiovascular events(22). This risk appears to be independent of the changes seen in cardiovascular risk factors such as blood pressure and glucose with steroid therapy. In the Hopkins Lupus Cohort, the risk of a cardiovascular event has been estimated at 2.66 that of Framingham controls with a dose dependent increase in cardiovascular events in those taking corticosteroids. In fact, those taking 20mg prednisone or more, were shown to have a 5-fold increase in cardiovascular events(22). This association, between glucocorticoid use and cardiovascular incidents, is not unique to SLE and has been demonstrated in other chronic diseases(23).

Attention should also be given to the increased risk of infection demonstrated with corticosteroid therapy. Patients with SLE are known to have impaired innate and adaptive immune responses and infections are amongst the most important causes of morbidity and mortality(24). Evaluation of hospitalizations in the Hopkins Lupus Cohort demonstrated that bacterial infections were responsible for 15% of hospital admissions in this population(25). Ruiz- Irastorza *et al*(26) demonstrated, in a nested case-control study, that each increase of 10 mg per day of prednisone increased by 11-fold the risk of serious infection. Interestingly, in this study, treatment with anti-malarials, showed a strong inverse association with major infections and treatment with 'any' immunosuppressive drug did not associate with major infections(26). In the rheumatoid arthritis literature, corticosteroid therapy has also been found to be a strong predictor of infection(27).

In SLE, premature cataracts are common and are considered in the SLICC/ACR damage index(14). Globally, cataract is the most common cause of blindness and in SLE, cataract is

the second most frequently reported damage item (exceeded only by osteoporotic fractures) (14). Both the cumulative and the highest dose of prednisone prescribed associate with cataract formation, in SLE. Patients with a cumulative prednisone dose of 10 mg or more for 10 years or more have been shown to have a threefold increased risk of developing cataracts(28).

Other considerations include the adverse endocrine and metabolic effects of corticosteroids. There is a dose- and time-dependent relationship between corticosteroid dosing and serum glucose(29). Hypertension, dyslipidemia, increased adiposity and reduced muscle mass have all been associated with chronic corticosteroid use.

Current therapies in SLE

A heavy reliance on corticosteroid therapy in SLE reflects established practices, which are difficult to challenge and change, but also the fact that current therapies are not without their limitations. Corticosteroids work fast and for most organ manifestations. There remain a multitude of deficiencies in current treatment strategies. These are outlined in Table 1.

Mortality rates may have been impacted upon over time but other pertinent outcome measures, renal and cardiovascular, are unchanged by therapeutic advances. Cardiovascular disease is responsible for a considerable proportion of the excess mortality attributable to SLE. This has remained unchanged over the past 50 years(30). A lack of impact on the rate of progression to end stage renal disease with modern therapies is also a point of concern. In lupus nephritis, renal response rates, amongst patients receiving standard treatment, approach 50–80% at 12 months and many of these responses are only partial(31, 32). A metaanalysis (in press, Tektonidou *et al*, A+R) evaluated 187 articles, reporting on 18,309 patients. The pooled 5-year risk of developing end stage kidney failure decreased from 16% in the early 1970's to around 11% in the mid-1990's and since then has plateaued. Patients with class IV lupus nephritis had the greatest risk of requiring renal replacement therapy, with a 15-year risk of 44%. This is a huge population of patients who fail current management strategies without an appreciable improvement in outcomes in recent years. In the development of future therapies, consideration needs to be given to these pertinent outcome measures, although the long follow up required to do this in a meaningful manner is a challenge.

Hydroxychloroquine is an essential tool in the medical management of SLE with multiple disease-specific and longitudinal benefits(33–39). The mechanism of action of this anti-malarial drug includes many molecular pathways. Hydroxychloroquine is thought to work in part by increasing lysosomal pH in antigen presenting cells, reducing toll-like receptor signaling resulting in decreased activation of dendritic cells and through the reduction of interferon production(40), amongst other mechanisms(41). In addition to disease specific benefits in SLE, hydroxychloroquine has been shown to have lipid lower properties(42, 43), anti-thrombotic effects(41) and hypoglycemic actions(44). Hydroxychloroquine is a safe, non-immunosuppressive therapy with good tolerability. However, there are increasing concerns regarding retinopathy, in particular in light of new screening methods, which are thought to have increased sensitivity(45). Current American Academy of Ophthalmology

guidelines advise monitoring beyond the dilated retinal examination and automated visual field testing, in an attempt to identify toxicity early and include one or more of the following: spectral domain optical coherence tomography, multifocal electroretinogram, and fundus autofluorescence(46). The sensitivity and specificity of these tests are not yet known for hydroxychloroquine related retinal toxicity. There is a high rate of baseline abnormalities, in particular in those who are elderly or have comorbid disease, which make any abnormalities challenging to interpret. Another issue is that SLE itself associates with the presence of retinal abnormalities, adding further to the complexity of deciphering these tests. There are limitations to the immunomodulating properties of hydroxychloroquine. It is insufficient monotherapy in the management of many disease manifestations. Despite evidence that withdrawal of therapy results in increased disease activity(33), hydroxychloroquine, in the placebo group of a clinical trial, was unhelpful in the prevention of severe flares(47). Thus, there are inherent limitations with our most important background medication.

Mycophenolate mofetil, a pro-drug of mycophenolic acid, is an inhibitor of inosine monophosphate dehydrogenase, which is the rate-limiting enzyme in de novo synthesis of guanosine nucleotides. Mycophenolate mofetil has become first line therapy in the management of lupus nephritis. It has similar efficacy to cyclophosphamide without the same toxicity profile(31). Mycophenolate mofetil is a slow therapy, with response rates only in the region of 50% at one year. At 24 weeks, Ginzler *et al* demonstrated complete remission in only 16/56 (26.7%) of patients(31). In a meta-analysis, the pooled complete response rate in clinical trials was 36% with mycophenolate mofetil, 55% achieved partial response and subsequent relapses were described in 27%(48). These data indicate that a significant proportion of patients with lupus nephritis do not respond, or respond slowly, to first line therapy. This is one of the reasons why patients with lupus nephritis continue to progress to the development of renal damage and in many cases, end-stage renal disease. A further limiting factor with mycophenolate mofetil, in particular given the demographics of SLE patients, is that it is a teratogen. With maternal exposure to mycophenolate a high number of fetal losses and a specific pattern of birth defects consisting of cleft lip, external auditory canal atresia, trachea-esophageal atresia and other anomalies have been reported(49).

Tacrolimus, a calcineurin inhibitor, has recently been shown to be additive to mycophenolate mofetil(50, 51), and in other studies, a viable alternative for induction therapy(52, 53). Azathioprine, on the other hand associated with more flares in renal disease than mycophenolate mofetil(54), although it remains a crucial tool in the management of nephritis in pregnancy.

Despite advances in therapy, a large proportion of patients go on to develop end stage kidney disease(55, 56). There are many factors, which predict poor outcomes in lupus nephritis, including adherence, ethnicity, education and gender(57–59). There are treatment failures to consider and in those who go on to develop end stage kidney disease, a dramatic reduction in life expectancy(5). For patients who fail, or have an inadequate response to these therapies we still use cyclophosphamide(60), an alkylating agent with substantial toxicities. Thus, for

reasons of toxicity and efficacy it is essential that improved therapies are developed. Targeted therapies offer hope, but the science has lagged behind.

SLE is heterogenous in terms of clinical manifestations, serological abnormalities and immunologic mechanisms of disease. This diversity makes it difficult to compare any SLE population in a general way and means that all global measures of disease activity are inherently limited. It is also probable that the different subsets of SLE, with serological and organ specific clustering, require different therapeutic approaches. This is likely to be the first step in the development of precise and personalized medicine in SLE.

Figure 1, reproduced with permission from Davidson *et al*(61), demonstrates the many mechanisms which contribute to the dysregulated immune response in SLE in self-sustaining and amplifying pathways. These include aberrant interferon production, excessive B cell activating factor allowing for autoreactive B cells, the engagement of toll-like receptors and cytokine production (many are implicated) with switching and reactivation of memory B cells. This complex network of cellular interactions mean that there are numerous potential mechanisms to target in SLE, but also, in each individual, that disease activity may be contributed to by different pathways of immune activation.

Targeted therapies against B cells

There are a number of targeted therapies, which have been developed and trialed in SLE to date with limited success. These will be discussed in greater detail elsewhere in this publication. Rituximab, a chimeric monoclonal antibody specifically targeting CD20 on B-cells, resulting in the depletion of mature B-cells and B-cell precursors, is one such agent. B-cells are central to the pathogenesis of SLE and therefore have always been considered an attractive therapeutic target. In support of the rationale for these therapies, B-cell depletion has been used successfully to treat other autoimmune diseases, such as rheumatoid arthritis and anti-neutrophil cytoplasmic antibody-associated vasculitis.

‘Lupus Nephritis Assessment with Rituximab’ (LUNAR), a phase III randomised controlled trial, evaluated the efficacy and safety of rituximab (in addition to prednisone and mycophenolate mofetil) in 144 patients with active proliferative lupus nephritis. The primary and secondary efficacy end points were not significantly different between the placebo and the drug group, although rituximab therapy did associate with a numerically higher (not significantly significant) response rate than placebo (57% versus 46% for complete and partial renal responses combined)(62). Rituximab has also been evaluated for the treatment of non-renal disease. The ‘Exploratory Phase II/III SLE Evaluation of Rituximab’ (EXPLORER) study evaluated patients with moderate to severely active non-renal SLE and noted no difference between those who received rituximab and the placebo group(63). Further, there was no reduction in flares demonstrated with rituximab therapy(64). To date, despite robust mechanistic data, innumerable case reports and promising open label studies reporting efficacy(65), this agent has been disappointing in clinical trials.

Another B-cell therapy, discouraging in clinical trial, is ocrelizumab. Which is a recombinant humanized monoclonal antibody, and also targets and depletes CD20 positive B-cells. This was not found to be effective in lupus nephritis(66). These targeted, anti CD20 B-cell therapies in SLE have been mechanistically promising and backed by a large volume of published literature, but ultimately no differences have been demonstrated in clinical trials.

Epratuzumab targets CD22 on mature B-cell lineages and appears to modify B cell activation and function. This was studied in 'EMBLEM', which was a 12-week, multi-center, phase IIb randomized controlled trial, designed to assess the efficacy and safety in patients with moderate to severe SLE. There were some improvements in disease activity demonstrated which did not meet statistical significance. This study was followed by EMBODY I and II, which were phase III, multicenter, randomized, double-blind, placebo-controlled studies involving 1,579 adults in which epratuzumab was ultimately shown to be no better than placebo.

Other agents with specific mechanisms, relating to B cells, have been evaluated and, in the case of belimumab, approved for use in SLE. Belimumab is a fully humanized monoclonal antibody that specifically binds to soluble trimeric B cell activating factor (BAFF), preventing its interaction with receptors, leading to a reduction in the numbers of peripheral naive, transitional and activated B cells. Two large, phase III, multi-center, prospective, randomized, controlled trials have compared belimumab with placebo in patients with SLE, receiving standard therapies(67, 68). Post-hoc analyses demonstrated that this medication is best utilized in those with high disease activity despite standard therapy, low complement levels, antibodies to double stranded DNA and corticosteroid use(69). In those with renal involvement, 267 patients with renal involvement were included in the belimumab studies and pooled subgroup analysis demonstrated greater improvement in those who received belimumab in addition to standard therapy than in the placebo groups(70). A phase IV randomized clinical trial on lupus nephritis is underway.

Another targeted agent, tabalumab, a human IgG4 monoclonal antibody which binds to and neutralizes membrane and soluble BAFF, was evaluated in the Illuminate study(71). This drug elicited changes in anti-dsDNA titers, complement levels, B-cell populations and immunoglobulin levels. However, the clinical efficacy endpoints showed only modest efficacy. Blisibimod is a human peptibody, which also selectively targets BAFF, and has been evaluated in a phase II clinical trial(72). A post-hoc analysis of higher doses, showed improvement in disease activity and associated serological improvements. A phase III study is being undertaken.

Other specific therapeutic targets

The interferons have long been implicated in SLE pathogenesis and disease activity(73). Promising phase II results were presented for anifrolumab, which is an anti interferon alpha receptor monoclonal antibody (74). At six months 34% (up to 54.6% at 12 months) of the study group met the primary end point compared to 17% in the placebo group.

The sera of patients with SLE have been shown to contain elevated levels of various cytokines. This led to the assessments of agents which block these proinflammatory pathways including antibodies to interleukin 6 (IL-6). Tocilizumab is a humanized monoclonal antibody against the alpha chain of the IL-6 receptor and is currently in use for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis and Castleman's disease. IL-6 is strongly implicated in lupus nephritis(75, 76). This was therefore considered to be an agent of considerable interest and was studied in an open-label phase I dose escalation study(77), in which disease activity was shown to improve (although the numbers were small). The improvements seen were predominantly articular, making this a potentially interesting agent in the management of lupus arthritis. However, the benefits were considered hampered by the high frequency of dose-related neutropenia.

There is also hope for drug development in SLE with T-cell therapies although these are for the most part unexplored avenues. Abatacept, a selective T cell costimulation modulator, has been evaluated in lupus nephritis(78). This study did not meet its primary end point. However, treatment did associate with serological improvements and a greater reduction in urinary protein to creatinine ratio compared to placebo(78). The failure of this study to meet the designed end-point prompted significant discussion on what outcomes should be considered in randomized controlled studies and also on entry criteria. If other criteria for response were applied to this population, (such as the ACR criteria, or those used in LUNAR) then the rates of complete response demonstrated with abatacept were promising(79). This was then followed by the randomized, double-blind phase II add-on trial, 'Abatacept and Cyclophosphamide Combination Efficacy and Safety Study' (ACCESS)(80). Patients received either abatacept or placebo in conjunction with the Euro-Lupus regimen of cyclophosphamide, followed by maintenance azathioprine. The primary efficacy end-point was achieved by approximately a third of participants in both the treatment and placebo arms. A large multicenter international trial of abatacept with mycophenolate mofetil is presently underway which will may determine the utility of this approach. Other possible therapies of the future include spleentynosine kinase inhibitors(81), janus kinase inhibitors(82), rapamycin(83) and N-acetylcysteine(84).

Conclusion

The utility of current, untargeted SLE treatment strategies is limited by short and long-term toxicities and by inefficacy. Recent therapies have failed to impact upon longitudinal outcomes, in particular cardiovascular and renal measures, whilst in the shorter term, available treatments are frequently hindered by slow responses and inefficacy.

Chronic prednisone therapy associates with an unacceptable side-effect profile and is responsible for a significant proportion of the morbidity associated with SLE. Hydroxychloroquine remains the cornerstone of the medical management of SLE but issues surrounding retinopathy and ocular screening can limit therapy. It is also insufficient as monotherapy in the management of many disease manifestations. Current immunosuppressive agents are a considerable improvement when compared to cyclophosphamide, in terms of side effects and toxicity, but are limited by a lack of efficacy in a substantial proportion of patients, slow response rates and teratogenicity.

These challenges in the management of SLE mean that the development of more specific and targeted approaches is a clinical necessity. There have been considerable disappointments in the development of targeted treatment strategies to date and so far, only one agent (belimumab) has been shown to be effective in phase III clinical trials. Therapies targeting CD20 and CD22 B-cells have yielded negative results. However, agents which target soluble mediators inhibiting B-cell growth and function, including belimumab, have shown more promise. Other specific therapies, including T cell co-stimulation modulation and interferon and interleukin 6 blockade have shown promise in pre-clinical and early phase studies but are yet to be successful in phase III randomized controlled trials.

Given the clinical and serological heterogeneity of any SLE population, it is probable that not only are targeted approaches required, but that we also need to consider that no one single therapeutic intervention is going to be effective in all patients. Thus it is likely that more specific and individualistic approaches will be necessary given the multitude of possible therapeutic targets and the myriad of pro-inflammatory disease mechanisms, which are active in SLE. It is also likely that drug development will need to mirror the development of biomarkers, to help predict therapeutic responses and identify culpable pathogenic pathways on an individual basis.

For reasons of clinical and mechanistic diversity, there are challenges in the development of specific therapies in SLE. However, there is a need for targeted and individualised approaches to therapy as a matter of clinical priority.

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Figure 1.

Dysregulated immune responses in SLE. Interferon alpha, released by plasmacytoid dendritic cells in response to exogenous antigens, contributes to disease initiation by priming the adaptive immune system, thereby providing T-cell help for autoreactive B cells (loop1). Alternatively, excessive B cell activating factor is sufficient to initiate disease without T cell help by promoting activation and class-switching of autoreactive B cells (loop 2). IgG autoantibodies that recognize nucleic acids are internalized via Fc receptor or B cell antigen receptor into toll like receptor expressing dendritic cells or B cells respectively. Toll like receptor engagement in plasmacytoid dendritic cells amplifies the production of type I interferon, whereas toll like receptor engagement in B cells increases B cell receptor

signalling and antibody production. Therefore, once long-lived plasma cells that secrete autoreactive IgG are present, perpetuation of the autoreactive response might continue in a Tcell dependent manner (loop 2).

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Table 1

The Limitations of Current Therapies in SLE

Current Therapy	Limitation
Hydroxychloroquine	Retinopathy(45)
	Failure to control flares(47, 85) (although withdrawal did result in flare(33))
	Insufficient mono-therapy for many SLE manifestations
	Slow response
Prednisone	Innumerable short and long term toxicities
	General
	• Cardiovascular morbidity and mortality(22)
	• Diabetes
	• Hypertension
	• Dyslipidemia
	• Obesity/ Cushing's
	• Infections
	• Psychosis/ depression/ sleep disturbance
	• Gastric ulceration/ gastritis
	Musculoskeletal
	• Osteoporosis and fracture
	• Avascular necrosis
	• Decreased muscle mass/ weakness
	Ocular
	• Cataract
	• Glaucoma
	• Central serous retinopathy
	Cutaneous
	• Striae/ impaired healing
	• Acne/ hirsutism
	Pregnancy complications
Mycophenolate	Teratogenicity(49)
	Slow therapy(31)
	Significant failure rates(31, 48, 51)
	Incomplete response to therapy is common(48)
Azathioprine	Slow therapy
	More renal flares than mycophenolate(54)
Tacrolimus	Similar (suboptimal) response rates to mycophenolate(52, 53)
	Nephrotoxicity (acute and chronic)/ electrolyte disorders
	Hypertension
	Tremor
Cyclophosphamide	Short term

Current Therapy	Limitation
	• Neutropenia
	• Infections
	• Teratogenicity
	• Nausea/ Vomiting
	• Alopecia
	Longer term
	• Infertility
	• Bladder cancer
	• Hematologic malignancy
Belimumab	Response in selected patients(69)
	Not yet evaluated in specific organ involvement