Targeting B cells to treat systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that can induce a variety of nonspecific constitutional symptoms such as fatigue, malaise, fever and weight loss, but also can involve various organs such as the skin, joints, heart, kidneys, nervous, hematologic and musculoskeletal systems. Lupus nephritis is the key predictor of poor outcome. Some of the SLE manifestations have an unpredictable clinical course and can be life-threatening. Genetics seem to play an important role in lupus severity as ethnicity predisposes people more to renal and neuropsychiatric damage than socioeconomic factors [1]. Furthermore, SLE manifestations are usually more severe in African and Asian patients than in those of European ancestry [1]. Compared with the general population, SLE patients have a three- to five-fold increased mortality [2].

The fundamental immunologic characteristic of SLE is a broad dysregulation of immune responses that includes hyperactivity of CD4+ helper T cells and B cells, leading to the formation of autoantibodies [3,4]. Antinuclear antibodies (ANAs), the hallmark autoantibodies in SLE, are directed against dsDNA and other nuclear components [5]. Although historically, the production of autoantibodies has been thought of as the only mechanism of B-cell-mediated effects, this notion is now archaic, as B cells have been found to exert a handful of other functions, such as the presentation of autoantigens to T cells, regulation of dendritic cell differentiation, maintenance of lymphoid organization, and secretion of cytokines that can affect inflammation and lymphopoiesis, and play other effector roles in immune responses [2,6]. B cells in SLE patients are hyperactive and display a variety of abnormalities; lupus B cells have increased calcium influx upon B-cell receptor engagement, reduced levels of Lyn kinase and increased CD45 in lipid rafts, and decreased expression of FcγRIIB on IgM CD27+ memory cells [7].

Despite the multitude of studies testing various therapies, there are only a few drugs that are approved for treatment of SLE [8]. The current treatments are nonspecific immunosuppressants that can induce multiple side effects including severe infections and ovarian failure. The rationale for developing B-cell-directed therapies for SLE is based on the aforementioned critical role of B cells in the pathogenesis of lupus. The aim is to develop novel focused drugs that will be devoid of the significant side effects of the broad-spectrum immunosuppressants. Better specificity and improved efficacy are the major characteristics expected of the new drugs, with the goal being amelioration of SLE disease activity and prevention of sequelae without significant side effects.

This article will highlight the newest treatments that target B cells in lupus (Figure 1). Despite the fact that some of the trials that target B cells have been disappointing, they have provided valuable information that can help improve the design of future trials.

Therapies directed to B-cell surface markers CD20 & CD22

Rituximab is the most commonly used monoclonal antibody for rapid B-cell depletion. It is a chimeric antibody directed against the B-cell-specific surface marker CD20, which is expressed on immature and mature B cells, but
not on early pre-B cells or plasma cells (Table 1). Rituximab depletes CD20+ B cells through antibody-dependent cell-mediated and complement-mediated cytotoxicity [9]. Rituximab has been approved for the treatment of non-Hodgkin’s B-cell lymphoma and, more recently, rheumatoid arthritis. In case reports and case series, rituximab has benefited SLE patients with refractory vasculitic ulcers, shrinking lung syndrome, refractory thrombotic thrombocytopenic purpura, bilateral retinal vasculitis and recurrent enteritis [10–14]. Although open-label trials also implied the efficacy of rituximab in SLE [15,16], two moderate-sized, randomized, placebo-controlled trials of rituximab in extrarenal and renal lupus (Exploratory Phase II/III SLE Evaluation of Rituximab [EXPLORER] and Lupus Nephritis Assessment with Rituximab [LUNAR] trials, respectively) disappointingly failed to meet their primary and secondary end points. The EXPLORER trial was a 52-week study that randomly assigned 257 SLE patients with moderate to severe disease activity in a 2:1 ratio to rituximab or placebo [17]. The patients were administered intravenous infusions as two 1000-mg doses on days 1, 15, 168 and 182, as well as daily prednisone (as per trial regimen) and their baseline immunosuppressive regimen, which could have included azathioprine, mycophenolate mofetil or methotrexate. Compared with placebo, slightly more patients in the rituximab group showed a major or partial clinical response, but the difference did not reach statistical significance (29.6 vs 28.4%). However, the decrease and increase in the levels of anti-dsDNA autoantibodies and complement, respectively, were significantly different between the rituximab- and the placebo-treated patients. Furthermore, patients with baseline thrombocytopenia had improved platelet counts when treated with rituximab [18]. It is also worthwhile noting that the subgroup analysis showed that the African–American and Hispanic patients, who comprised approximately a third of the study population, did have significant benefit from rituximab (33.8 vs 15.7%). In addition, an ad hoc analysis demonstrated that the subgroup of patients who received rituximab on background therapy with methotrexate had improved mean global British Isles Lupus Assessment Group (BILAG) scores compared with placebo. Serious adverse events occurred at a similar percentage of patients in both the rituximab and placebo groups (37.9 vs 36.4%).

The LUNAR trial was a Phase III, randomized, double-blind, placebo-controlled, multicenter study in which 144 patients with active proliferative nephritis (class III/IV) were randomly assigned in a 1:1 ratio to rituximab or placebo, in the same dose and regimen that was administered in EXPLORER [19]. Background therapy of steroids and mycophenolate mofetil was permitted. Patients who took prednisone at a dose greater than 20 mg daily for more than
2 weeks prior to screening were excluded. The primary end point, assessed at 52 weeks, was the percentage of patients who achieved a complete or partial renal response. There were numerically more responders in the rituximab group than in the placebo group (57% vs 46%), but the difference did not reach statistical significance in the end points – complete or partial renal responses at week 52. Despite this, the rituximab group displayed a significantly greater improvement in the levels of anti-dsDNA and complement than the placebo group. The numbers of serious adverse events were similar between the treatment and placebo groups, except that the rituximab group had more neutropenia, leukopenia and hypotension.

The fact that EXPLORER and LUNAR studies did not reach their end points has provoked multiple discussions regarding their study designs, end points and background immunosuppressive therapies [20,21]. Concerns regarding glucocorticoids and other immunosuppressants masking rituximab’s effects have been expressed. In addition, some lupologists believe that the variability caused by SLE heterogeneity may have had a negative impact on the results of the rituximab studies and advocate that new clinical trials focus on patient subsets with specific organ system involvement and/or specific lupus autoantibody profile. Furthermore, additional research has shown that the following factors are closely connected to the therapeutic effect (or

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EXPLORER: Exploratory Phase II/III SLE Evaluation of Rituximab; LUNAR: Lupus Nephritis Assessment with Rituximab; SLE: Systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SRI: SLE responder index.
lack of) of rituximab: serum levels of the treatment antibody, FcγRIIIa genotype, phenotype of the circulating B cells and the B-cell subset emerging after the completion of treatment [22,23], indicating that the prediction of response is very complex and includes a high number of variables.

Studies with lupus prone mice have demonstrated that even without secreting antibodies, B cells significantly influenced the course of lupus [24,25]. These results suggest that therapies targeting B cells, but not affecting plasma cells and/or autoantibodies, might be an effective treatment for SLE. However, the lack of CD20 expression on the surface of plasma cells has not been excluded as a possible factor implicated in the failure of the randomized controlled trials (RCTs) with rituximab. Concerns regarding the lack of effect of rituximab on antibody secreting cells have led to the consideration of utilizing rituximab along with agents affecting antibody secretion. Nevertheless, combination treatments of rituximab and anti-B lymphocyte stimulator (BLyS) or anti-IL-10 monoclonal antibody therapies have not been explored.

The analysis of prospective data from the nationwide French Autoimmunity and Rituximab (AIR) registry showed good clinical efficacy of rituximab in the treatment of SLE patients [26]. The AIR patients (n = 136) had articular, cutaneous, hematologic and renal manifestations of SLE. More than half of the patients were treated with two doses of 1 g rituximab, and less than half were treated with four doses of 375 mg/m² rituximab. Rituximab was added to a stable background regimen of immunosuppressive agents, and the mean prednisone dosage was 30 mg/day. In the entire cohort, the mean follow-up duration was 18.6 months from the last rituximab infusion. The mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score decreased significantly at 6 months. The rate of severe infections was less than that reported in the EXPLORER study. However, the AIR registry does not meet the rigor of a randomized clinical trial; the data are observational and reflect anecdotal experience, and therefore do not allow for reliable conclusions. In any case, the AIR registry data are positive and the two major RCTs with rituximab have reported negative findings, reopening the debate on clinical benefit of B-cell depletion in SLE.

Of the serious adverse events associated with this treatment, it is noteworthy to mention that two SLE patients who received rituximab later on developed progressive multifocal leukoencephalopathy. One of the patients was treated with steroids and cyclophosphamide prior to the two rounds of rituximab 375 mg/m²/week for 4 weeks [27]. It is uncertain whether rituximab itself led to the development of progressive multifocal leukoencephalopathy, since it has been indicated that severe immunosuppression and SLE alone may be associated with a predisposition to progressive multifocal leukoencephalopathy [28].

The experience with anti-CD20 therapies other than rituximab is rather scarce, and includes ocrelizumab and SBI-087. Ocrelizumab, a humanized monoclonal antibody against CD20, underwent a Phase III clinical trial (BEGIN) for active extra-renal SLE [10] and Phase III trial (BELONG) for class III or IV lupus nephritis [29,102], but the latter study was terminated due to serious and opportunistic infections. The reasons for the increased infection rates with ocrelizumab, but not rituximab, are not clear. SBI-087 is a novel therapeutic agent that targets CD20; it is a humanized small modular immunopharmaceutical that consists of single-chain variable regions (V_L and V_H) that bind CD20 [50]. These single chains are fused by a human IgG1 hinge domain to the constant regions of human IgG1 heavy domains (CH2 and CH3). In an open-label study, this anti-CD20 fusion protein was administered at doses of 0.5 mg/kg intravenous, 25 mg subcutaneous or 75 mg subcutaneous to 18 patients with controlled SLE, and was generally well tolerated [31]. SBI-087 is currently in a Phase I trial for SLE [103]. This study plans to enroll 24 ANA+ patients with SLE to assess safety and tolerability as primary outcome measures, and pharmacokinetics and pharmacodynamics as secondary end points.

Epratuzumab is a humanized monoclonal antibody against the B-cell surface antigen CD22. CD22 is expressed on a subset of mature B cells, but disappears when B cells differentiate into plasma cells. This molecule is involved in B-cell receptor (BCR) signaling and can exert both stimulatory or inhibitory effects on the BCR signal transduction [32,33].

Epratuzumab downregulates hyperactive B cells by inhibiting BCR signaling and by inducing rapid internalization of CD22 [54]. In addition, epratuzumab causes approximately 40% reduction in the B cells in peripheral blood. The results of the initial Phase III RCTs, SL0003 and SL0004, suggested clinically meaningful efficacy of epratuzumab in SLE patients at week 12, but both trials were terminated early due to problems with manufacturing the medication.

More recently, a dose-ranging Phase Ib study with epratuzumab, EMBLEM™, was completed. As reported at EULAR 2010, epratuzumab
demonstrated clinically meaningful improvements in patients with moderate-to-severe SLE. Statistically significant response rates to epratuzumab were seen in the 600 mg/week group and in the combined group of all patients who received a cumulative dose of 2400 mg during the 12-week treatment. Compared with placebo, epratuzumab 600 mg/week provided greater BILAG improvement in all affected body systems, but the efficacy was especially prominent in cardiorespiratory and neuropsychiatric systems [38]. Two Phase III studies of epratuzumab for the treatment of patients with moderate and severe lupus will be initiated in the second half of 2010.

Therapies that block costimulation
Costimulation plays a role in T-cell activation, and also in the multistep process of antibody production. One of the costimulatory pathways involves the CD28 and cytotoxic T lymphocyte antigen 4 (CTLA4) receptors on T cells and their coligands B7.1 and B7.2 on antigen-presenting cells, including B cells. CTLA4 binds the B7 molecules with greater affinity than CD28 and delivers an inhibitory signal to the activated T cell.

Abatacept, a CTLA4 Ig fusion protein, acts as a blocker of costimulation. An exploratory, Phase Ib trial randomized 175 SLE patients with polyarthritis, discoid lesions, pleuritis and/or pericarditis in a 2:1 ratio to abatacept (10 mg/kg) or placebo [36]. Therapy was given in addition to prednisone 30 mg/day for a month, which was then tapered. The primary end point was the proportion of patients with new BILAG A/B score flare in any organ system after the beginning of the steroid taper. This study did not meet its primary or secondary end points. A Phase II study (Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis [ACCESS]) sponsored by the National Institute of Allergy and Infectious Diseases is currently recruiting patients with active proliferative lupus nephritis to determine whether abatacept in combination with cyclophosphamide is more effective than cyclophosphamide alone [41]. The primary outcome measure is the proportion of patients who achieve a complete response at 24 weeks.

Closely related to CD28 is a molecule called inducible co-stimulator [37]. Inducible co-stimulator interacts with B7-related protein-1, which is expressed on B cells. B7-related protein-1 costimulates T cells [38]. AMG 557 is a fully human monoclonal antibody that binds to B7-related protein-1. A Phase I study is currently enrolling SLE patients to compare AMG 557 with placebo [105].

Therapies that block B-cell-stimulating cytokines
The cytokine BlyS, which is also known as B-cell-activating factor or BAFF, belongs to the tumor necrosis family. BlyS is an essential factor in the differentiation, homeostasis, selection and survival of B cells [39]. SLE patients have elevated circulating BlyS levels and rising BlyS concentrations can predict increases in SLE disease activity [40]. In the Phase I trial, belimumab, a recombinant, fully human monoclonal antibody that binds to soluble human BlyS, was found to be biologically active in vivo in patients with mild-to-moderate SLE [41]. The Phase II study randomized 449 SLE patients with a SELENA-SLEDAI score of at least four to receive 1, 4 or 10 mg/kg of belimumab or placebo on days 0, 14 and 28, and then every 28 days in addition to standard of care therapy [42]. This trial did not meet its co-primary efficacy end points of changes in SELENA-SLEDAI score or time to first flare during 52 weeks of treatment. The inclusion criteria for this study required SLE patients to have a history of autoantibodies such as ANAs or anti-dsDNA, but they were not mandated to be positive at screening. Thus, at baseline, only 71.3% of these patients had an ANA titer of 1:80 or greater and 50% had anti-dsDNA antibodies. The subset of seronegative patients included in the study could have confounded the evaluation of belimumab’s effect on the reduction of SLE disease activity [43]. When serologically active patients (ANAs ≥1:80 by HEP-2 cell immunofluorescence and/or anti-dsDNA antibodies ≥30 IU/ml) were retrospectively evaluated, the belimumab group had a statistically larger percentage of responders than the placebo group at 52 and 56 weeks. Two large anti-BlyS Phase III trials (BLISS-52 and -76) treated 865 and 819 patients, respectively, and reported favorable clinical responses compared with placebo. The primary efficacy end point in both trials was the SLE responder index, defined as improvement in four or more points in SELENA-SLEDAI score without clinically significant worsening in the physician’s global assessment and BILAG. BLISS-52 randomized seropositive SLE patients to belimumab 1 or 10 mg/kg or placebo on days 0, 14 and 28 and then every 28 days for 48 weeks on top of standard of care therapy [44]. Belimumab
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significantly reduced SLE disease activity, flare rates and use of prednisone. BLISS-76, a Phase III, 76-week study, also evaluated belimumab 1 mg/kg or 10 mg/kg against placebo [106]. The study enrolled 275 patients in the placebo arm, 271 patients in the belimumab 1 mg/kg arm, and 273 patients in the belimumab 10 mg/kg arm. Only patients with positive serology (ANA and anti-DNA antibodies) were included in the study. At week 52, the response rates for placebo, belimumab 1 and 10 mg/kg were 33.6%, 40.6% and 43.2%, respectively. Compared with placebo, only the 10 mg/kg dose showed significantly improved SLE responder index.

AMG 623 is a peptide-Fc fusion protein, which binds both cell surface-expressed BlyS and soluble BlyS. AMG 623 was administered subcutaneously or intravenously against placebo to 54 and 63 SLE patients in Phase Ia and Ib studies, respectively [48]. A dose-independent decrease in the percentage of naive B cells was detectable, and the safety profile was comparable between the AMG 623 and placebo groups. Further studies are needed to evaluate therapeutic effects of AMG 623 on lupus disease activity and to elucidate whether AMG 623’s ability to bind both surface and soluble BlyS will translate into better efficacy than the efficacy of belimumab, which binds only soluble BlyS.

B-cell-activating factor mediates its effects through three different receptors: BAFF receptor, B-cell maturation antigen and transmembrane activator and calcium modulator and cyclophilin-ligand interactor (TACI). Related to BAFF is another member of the TNF ligand superfamily called a proliferation-inducing ligand (APRIL; also known as TNF ligand superfamily called a proliferation-inducing cyclophilin-ligand interactor (TACI). Related to BAFF is another member of the TNF ligand superfamily called a proliferation-inducing ligand (APRIL; also known as TNF ligand superfamily member 13A, TALL-1 and TRDL-1). APRIL functions as a soluble factor and binds to B-cell maturation antigen and TACI, but does not bind to the BAFF receptor. APRIL is involved in T-cell-independent type II antigen responses [46] and activation of B cells [47]. In addition, APRIL can complex with BlyS into heterotrimers, which can promote survival, selection and differentiation of B cells into plasma cells [48]. Circulating levels of APRIL/BlyS heterotrimers are frequently increased in patients with SLE [49]. Atacicept (TACI-Ig) is a recombinant fusion protein that binds both BAFF and APRIL, and inhibits their effects on B cells [50]. A Phase Ib trial included 47 patients with mild-to-moderate SLE who were treated with subcutaneous atacicept or placebo in a 3:1 ratio [51]. Atacicept administration was associated with dose-dependent reductions in the immunoglobulin levels and in the mature and total B cell numbers. Mild injection site reactions were observed more frequently in the atacicept-treated patients than the placebo-treated patients. Another Phase Ib study randomized 24 patients with mild-to-moderate SLE (5:1) to receive intravenous atacicept, single or multiple doses, or placebo and followed them for 6 weeks [50]. Treatment with atacicept resulted in a reduction of B cells in the peripheral blood (40% from baseline in the single dose group and 55% reduction from baseline in the multiple dose group) and immunoglobulin levels, and again only mild injection site reactions were reported. Despite this favorable safety profile of atacicept monotherapy, a Phase II trial using atacicept in combination with mycophenolate mofetil for active lupus nephritis was halted because of increased serious infection rates [52]. Nonetheless, a Phase II/III study (APRIL SLE) is actively recruiting SLE patients who recently experienced a flare. The study will compare the effects of atacicept 75 or 150 mg subcutaneously versus placebo over a period of 52 weeks [107]. The primary outcome measure will assess the proportion of patients with a new flare as defined by a BILAG score of A or B.

The overproduction of IL-10 and -6 in SLE-inspired studies to determine if blockade of these cytokines can have therapeutic benefit [53]. B cells have been shown to produce IL-6 [84]. In SLE patients, IL-6 also appears to activate B cells, and thus plays a role in the production of anti-DNA antibodies. In particular, IL-6 contributes to the generation of the IgG anti-DNA antibodies, which are known for their pathogenic potential [54]. In an open-label Phase I pilot study with tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, 16 SLE patients with moderately active lupus were given this therapy in doses of 2, 4 or 8 mg/kg intravenously every 2 weeks for a total of seven infusions in addition to prednisone [56]. At the end of 14 weeks, there was a significant improvement in modified SELENA-SLEDAI and Systemic Lupus Activity Measure (SLAM) scores. Although the primary adverse event was dose-related neutropenia, these results seem promising and can lead to future controlled trials of tocilizumab in SLE patients.

IL-10 plays a critical role in immunoglobulin production [57] and SLE patients have increased serum levels of IL-10 [58]. An open pilot study of six SLE patients who received daily infusions of B-N10, an anti-IL-10 monoclonal antibody, for 21 days showed that blocking IL-10 may have beneficial therapeutic effect in SLE. After 6 months, five patients were clinically inactive,
as measured by Mexican (MEX)-SLEDAI scores of less than three [59]. The only adverse event was chills during an infusion on day 16. However, there are no ongoing trials with this treatment.

**Conclusion**

Systemic lupus erythematosus is considered a prototypical autoimmune disease. Autoantibodies, the trademark of SLE, are produced by hyperactive B cells that recognize a plethora of nuclear antigens such as DNA, Ro, La, Sm and ribosomal P protein. The production of pathogenic autoantibodies is not the only mechanism by which autoreactive B cells induce and perpetuate inflammation in SLE. B cells also secrete proinflammatory cytokines, increase costimulation and activate autoreactive T cells. Furthermore, lupus B cells are characterized by a variety of abnormalities including increased calcium influx upon BCR engagement, reduced levels of Lyn kinase in lipid rafts and decreased expression of FcγRIIB in IgM CD27+ memory cells. The array of autoreactive B-cell functions implicated in the pathogenesis of SLE has led to the emergence of B-cell-directed therapeutic approaches for lupus.

Over the past decade, the growing interest in B cells evolved after open-label studies produced promising results. The RCTs have inspired even more curiosity, despite the fact that the majority of them did not reach their end points. It has been suggested that in the rituximab and abatacept RCTs, the heterogeneous nature of SLE created a challenge for successful results since one organ system may improve while another worsens.

Many of the lupus researchers believe that the failure of EXPLORER and LUNAR studies with rituximab was more attributable to flaws in the study design than to the ineffectiveness of the drug [51]. Multiple factors related to the end points, patient population and background anti-inflammatory therapy have been considered as possible contributors to the failure of these studies. The use of high doses of oral glucocorticoids and other immunosuppressants such as mycophenolate mofetil has been heavily scrutinized since these background therapies may already have been aggressive enough to treat active SLE without rituximab. The heterogeneity of the disease relating to genetic differences among lupus patients, differences in disease activity, specific organ system involvement, particular symptoms and duration of the symptoms, and the presence or absence of serological parameters have also been considered as factors that could have affected the results of these studies.

The serological status of patients is another important parameter that needs to be considered in lupus trials. In the Phase II studies of belimumab, a large number of seronegative SLE patients were included, which may have skewed the results. However, the recent Phase III study with belimumab that included only ANA+ patients met its primary end point and, thus far, is the only bright spot among the clinical lupus trials in recent years. By the end of 2010, we may witness the approval of belimumab as a new drug for SLE. The prospect of a new lupus drug heralds an exciting time for rheumatologists and holds the promise for development of novel B-cell-directed therapies for patients with SLE. Well-designed clinical trials focused on specific clearly defined SLE subsets are needed to better understand the therapeutic potential of B-cell depleting and anticytokine therapies in lupus.

**Future perspective**

Despite multiple studies exploring the pathogenesis of SLE, researchers have been unable to exploit this knowledge to develop new therapies for lupus for more than 40 years. In that same vein, the majority of recent randomized clinical trials with B-cell-directed therapies have also yielded negative results. However, many lessons can be learnt from the failed clinical studies. Flaws in trial designs, end points and/or the background immunosuppressive therapies have been considered as the possible reasons for the poor success of these trials. Patient stratification based on characteristics such as genetic factors, specific organ involvement, disease stage, autoantibody patterns or approximate severity scores may also help develop focused clinical trials with a better chance for success. Within the coming decade, clinical trials involving B-cell-depleting and cytokine-blocking therapies are expected to result in novel treatments for SLE patients whose disease manifestations are refractory to the current standard of care management.

**Financial & competing interests disclosure**

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

- Over the past decade B cells have become a major therapeutic target in lupus. Open-label studies, randomized controlled trials and registries on B-cell-directed treatments have provided inconsistent data.
- Complete B-cell depletion with the chimeric anti-CD20 monoclonal antibody rituximab in systemic lupus erythematosus (SLE) did not meet the primary and secondary end points in the Exploratory Phase III/III SLE Evaluation of Rituximab (EXPLORER) and Lupus Nephritis Assessment with Rituximab (LUNAR) trials, but the French registry Autoimmunity and Rituximab (AIR) showed good clinical efficacy of rituximab in lupus. Reopening the debate on clinical benefit of anti-CD20 therapy in SLE. Studies with epratuzumab, a humanized anti-CD22 monoclonal antibody, demonstrated clinically meaningful improvements in patients with SLE.
- A clinical trial evaluating the costimulation blocker abatacept in extrarenal lupus did not meet its primary end point, but another trial is currently recruiting patients to investigate the effects of abatacept in lupus nephritis.
- B-cell-stimulating cytokines have also been targeted. Belimumab, a monoclonal antibody directed to a B-cell stimulator, decreased lupus activity as measured by SLE responder index, and may soon receive US FDA approval to treat SLE. Atacicept, a transmembrane activator and calcium modulator and cyclophilin-ligand interactor immunoglobulin, which targets cytokines B-lymphocyte stimulator and APRIL, has been shown to reduce immunoglobulin levels and B-cell numbers, and currently there is an ongoing trial with atacicept recruiting SLE patients with disease flares. IL-6 and -10 are also therapeutic targets in SLE. An open-label Phase I pilot study with tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, demonstrated beneficial therapeutic effects in lupus patients with moderately active disease.
- Although some of the randomized controlled trials with B-cell-directed therapies have yielded disappointing results, they have provided valuable information. Applying the lessons learnt from these trials can help design better clinical studies in SLE.

Bibliography

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


A set of candidate biomarkers for lymphocyte monitoring in rituximab-treated patients with autoimmune disease is described.


Effects of a novel subcutaneous anti-CD20 treatment on B cells in SLE patients with controlled disease are described.


A Phase Ib study with the anti-CD22 monoclonal antibody epratuzumab provided benefits in SLE patients with moderate-to-severe disease.


The primary and secondary end points were not met in the Phase Ib study with abatacept, but improvements in several exploratory measures suggest some efficacy in SLE patients with non-life-threatening disease.


In a Phase III clinical trial, belimumab demonstrated therapeutic effect in SLE patients with active disease.


**In a Phase I study, SLE patients show promising clinical and serologic responses to tocilizumab.


** Websites


103 Clinical Trials http://clinicaltrials.gov/ct2/show/NCT00714116?term=SBI-087+AND+lupus&rank=1

104 Clinical Trials http://clinicaltrials.gov/ct2/show/NCT00774852?term=abatacept+AND+cyclophosphamide+AND+lupus&rank=1

105 Clinical Trials http://clinicaltrials.gov/ct2/show/NCT007774943?term=AMG+557&rank=1
