Targeted Therapies in Systemic Lupus Erythematosus: A State-of-the-Art Review

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Abstract
Systemic lupus erythematosus is a chronic multisystem autoimmune disease leading to substantial morbidity and mortality. In this disease, autoimmunity is triggered against universal cellular antigens. Dysfunction is found in both innate and adaptive immunity. While our previous therapies for lupus were nonspecific, a better understanding of the pathogenesis of lupus has led to an explosion of pharmaceutical research into targeted therapies. These new therapies hold great promise to improve treatment of this difficult disease and also provide insight into the dominant mechanisms of lupus immunopathogenesis.

Keywords: Systemic lupus erythematosus; Lupus; Clinical trial; Biological therapy; B cell; T cell

Introduction
Systemic lupus erythematosus is a chronic multisystem autoimmune disorder associated with significant morbidity and mortality. Traditionally, the cornerstone of SLE therapy has focused on anti-malarial or anti-metabolite medications in combination with corticosteroids. While effective in some patients, not all have an adequate response and treatment toxicity is often a limiting feature. In the past decade, our understanding of lupus pathogenesis has significantly increased. Specifically, the role of B lymphocytes, T lymphocytes, and various cytokines in the development and disease progression of SLE has been better elucidated. While uncertainties remain in the precise pathogenetic mechanisms of lupus, these discoveries have ushered in a new era of research into the development of targeted therapies to more effectively and safely treat these patients. This review will discuss our current understanding of lupus pathogenesis, highlight the results of key trials evaluating targeted therapies in SLE, and address ongoing and upcoming trials that will hopefully expand our knowledge of lupus management.

Lupus Pathogenesis
Lupus is a complex heterogeneous disease with as yet incompletely defined pathogenesis. It appears to occur in genetically predisposed patients who are triggered by environmental exposures to abnormally activate the immune system. Genome-wide association studies have revealed a number of genetic polymorphisms conferring a higher risk for SLE compared to healthy control patients [1-3]. However, the high-risk gene loci individually contribute only slight risk, some are not specific for SLE, and some are not present across all racial groups [4]. Prior to the onset of clinical manifestations, patients may be in a “pre-clinical” state in which pathogenic autoantibodies increase leading to subclinical disease.

Aberrant activation of the adaptive, and more recently, innate component of the immune system have been identified as important mechanisms of SLE pathogenesis. Among the adaptive immune responses, critical abnormalities in B cell function in lupus include production of autoantibodies, antigen presentation to autoreactive T cells, and production of pro-inflammatory cytokines and chemokines [5-7]. B lymphocyte stimulator (BLYS, also known as BAFF or B cell activating factor) is also overexpressed in lupus patients. BLYS plays an important role in B cell survival and differentiation [8-10]. In addition, mouse models of lupus have shown that BLYS overexpression can induce lupus nephritis [11]. Another B cell abnormality identified in SLE is impaired B cell tolerance leading to incomplete removal of autoreactive B cells [12,13].

T cell dysfunction has also been characterized in SLE. There is evidence for an increase in Th lymphocytes producing interleukin 17 (Th17) cells and decreased T regulatory (Treg) cells [14-16]. A recent study demonstrated that these alterations in T cell subsets, as well as increased memory B cells, are associated with an increase in circulating CD4+ T cell populations producing IL-21 [17]. In addition, diminished CD8+ T cell activity along with clonal expansion of follicular T helper (TFH) cells have been observed in SLE [18,19]. Mouse models of lupus have also demonstrated aberrant function of TFH cells that stimulate B cell differentiation in germinal centers [20]. Other T cell abnormalities include dysregulated mitochondrial function leading to increased oxidative stress [21]. There is also abnormal activation of mammalian target of rapamycin which plays a role in intracellular signaling of T (and B) cells [22].

Various abnormalities in the innate immune system are present in SLE as well. Pro-inflammatory cytokines are increased in lupus. Interferon-alpha (IFN-alpha) is primarily produced by plasmacytoid dendritic cells and immune complexes containing anti-double stranded DNA antibodies (anti-dsDNA) are strong promoters of IFN-alpha activity. In addition, elevated serum IFN-alpha activity as well as genetic polymorphisms impacting type 1 IFN activity, signaling, and production have been associated with SLE predisposition [23-27]. IL-6 is a cytokine predominantly produced by macrophages that has pleiotropic effects including the stimulation of acute phase proteins and fever. In mouse models of lupus there is evidence for an age-associated rise in serum IL-6 and aberrant expression of the IL-6 receptor [28-30].

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Exogenous IL-6 was also shown to increase autoantibody production and lead to more rapid progression of glomerulonephritis [31,32]. Patients with SLE have higher levels of IL-6 though not all studies have shown this to be associated with disease activity or anti-dsDNA levels [33-36].

Levels of IL-10, a cytokine that mainly acts as a negative feedback inhibitor for activated dendritic cells and macrophages, are also increased in SLE and are related to disease activity [37-44]. In addition, there is increased TNF-alpha expression and the degree appears to be associated with lupus disease activity, as well as renal disease activity in those with lupus nephritis [45-51]. Toll-like receptors (TLR) 7 and 9 on dendritic cells (and B cells) are aberrantly stimulated in response to corresponding RNA (for TLR7) and DNA (for TLR9) in lupus immune complexes [52]. While signaling via TLR7 appears to be pathogenic in SLE based on murine models, some evidence suggests that TLR9 signaling may be protective [53-56].

**B-cell Targeted Therapies: Rituximab and Belimumab**

Given the prominent role of B cells in the pathogenesis of lupus, it is not surprising that they have become an attractive target for potential targeted therapies. B-cell depletion has been studied as one potential therapeutic approach. Rituximab is a chimeric monoclonal antibody that selectively depletes CD20-positive B cells [57-59]. It is already an approved therapy for several conditions including non-Hodgkin’s lymphoma, rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis [60-63]. In addition, multiple open-label studies have demonstrated benefit with rituximab in SLE including its utility in severe refractory cases [64-66].

There have been two large randomized, double-blind, placebo-controlled, multicenter trials further evaluating the use of rituximab in SLE. Efficacy and Safety of Rituximab in Patients with Severe SLE (EXPLORER) studied 257 patients with moderately-to-severely active non-renal SLE [67]. Participants with ≥ 1 British Isles Lupus Assessment Group (BILAG) A score or ≥ 2 BILAG B scores were randomized at a 2:1 ratio to receive either rituximab (1000 mg) or placebo on days 1, 15, 168, and 182. All patients also received daily prednisone over 10 weeks (0.5-1 mg/kg). Patients were allowed to remain on their background immunosuppressive regimen (azathioprine 100-250 mg/day, mycophenolate mofetil 1-4 g/day, or methotrexate 7.5-27.5 mg/week).

The primary endpoints of the EXPLORER trial were the effect of rituximab versus placebo in reaching and maintaining a major clinical response (MCR), a partial clinical response (PCR), or no clinical response at week 52 using each of the 8 BILAG index organ system scores. MCR was defined as achieving BILAG C scores or better in all organs at week 24 without having a severe flare (1 new domain with a BILAG A score or 2 new domains with a BILAG B score) from study onset to week 24, and keeping this response without a moderate or severe flare (1 new domain with a BILAG A or B score) to week 52. The study failed to show a significant difference between the two groups for either the MCR (12.4% in the rituximab group versus 15.9% in the placebo group) or the PCR (17.2% in the rituximab group versus 12.5% in the placebo group). Of note, among African American and Hispanic patients in a pre-specified subgroup analysis those receiving rituximab were significantly more likely to have a major or partial clinical response (33.8% compared to 15.7% among placebo). The overall rate of treatment-emergent serious adverse events was similar between groups, though there were more grade 3 or 4 neutropenia events in the rituximab group.

The second large randomized, double-blind, placebo-controlled, multicenter trial was entitled Efficacy and Safety of Rituximab in Patients with Active Proliferative Lupus Nephritis (LUNAR). This study compared rituximab to placebo among 144 patients with class III or IV lupus nephritis [68]. Patients were randomized 1:1 to rituximab 1000 mg or placebo on days 1, 15, 168, and 182. In addition, all patients received mycophenolate mofetil and corticosteroids. The primary end point of renal response at week 52 was not significantly different between rituximab and placebo groups. However, those receiving rituximab did have significant decreases in serum complement C3, C4, and anti-dsDNA levels. The rate of adverse events was overall similar between both groups. An upcoming phase III, randomized, open-label European trial entitled Rituximab for Lupus Nephritis with Remission as a Goal (RING) will evaluate the percent of patients with lupus nephritis receiving rituximab compared to standard therapy alone who achieve remission at 104 weeks [69]. Despite the lack of benefit compared to placebo in the two published large randomized trials, rituximab has filtered into clinical practice due to the profusion of anecdotal data endorsing its use.

Another B cell target, inhibition of BlyS, has thus far proven to be the most successful therapeutic avenue for modern targeted therapies for SLE. Belimumab, a fully human immunoglobulin (Ig) G1-gamma monoclonal antibody, is a selective inhibitor of soluble BlyS. The initial phase III study was entitled Efficacy and Safety of Belimumab in Patients with Active Systemic Lupus Erythematosus: a Randomized Placebo-Controlled, Phase 3 Trial (BLISS-52) [70]. Seropositive SLE patients with active disease were randomized to receive belimumab 1 mg/kg or 10 mg/kg or placebo over 48 weeks. The study was conducted in multiple centers across Latin America, Asia-Pacific, and Eastern Europe. All three of the pre-defined primary endpoints for belimumab, collectively defined as the SLE responder index (SRI), were met at both doses. Belimumab responders were defined as those patients who had reduction in the SELENA-SLEDAI score by at least 4 points during 52 weeks, no new BILAG A organ domain score or more than 1 new B organ domain flare, and no increase in the Physician’s Global Assessment (PGA) score. Rates of adverse events (including serious or severe adverse events) were similar across all groups.

A second longer trial conducted mainly in North America and Europe was entitled A Phase III, Randomized, Placebo-Controlled Study of Belimumab, a Monoclonal Antibody That Inhibits B Lymphocyte Stimulator, in Patients with Systemic Lupus Erythematosus (BLISS-76) [71]. Seropositive SLE patients with active disease were again randomized to receive belimumab 1 mg/kg or 10 mg/kg or placebo, though this time for 72 weeks. The primary efficacy end point was again the SRI at week 52. In this study, only patients in the higher dose belimumab group (10 mg/kg) met the primary end point with a significantly increased SRI response at week 52 versus placebo. In addition, while SRI response rates were greater with belimumab compared to placebo at week 76 this difference was not statistically significant. However, the risk of severe lupus flares was reduced by belimumab at both doses compared to placebo and there were similar rates of adverse events across all groups.

On the basis of these phase III clinical trials the FDA approved belimumab (Benlysta) as the first new agent for the treatment of SLE in over 50 years. Several limitations in extrapolating the results of the aforementioned belimumab trials still need to be addressed. First, patients with severe active lupus nephritis or CNS lupus were excluded. Therefore, it is not known if belimumab would be effective in lupus patients with these complications. Nevertheless, approximately 15%...
of patients in these studies had lupus nephritis of lesser activity and a post-hoc analysis indicated belimumab was helpful in decreasing proteinuria and renal flares [72]. In addition, a phase III trial currently in the recruitment phase entitled Efficacy and Safety of Belimumab in Patients with Active Lupus Nephritis (BLISS-LN) will enhance our understanding in this area [73]. Interestingly, another post-hoc analysis from BLISS-52 and BLISS-72 demonstrated that African American patients in both trials had a decreased response to belimumab [74]. An upcoming phase III/IV trial entitled Efficacy and Safety of Belimumab in Black Race Patients with Systemic Lupus Erythematosus (EMBRACE) will further address this question [75]. Lastly, though based on existing data belimumab appears to have an acceptable long-term safety profile, the results of further follow-up studies are needed before this conclusion can be fully established (Table 1) [76-78].

Other B-cell Targeted Therapies

Several other B-cell targeting agents have been investigated as possible treatments for SLE. Atacicept is a soluble, fully human, recombinant fusion protein that inhibits both BLYS and APRIL, unlike belimumab which selectively blocks BLYS activity. The largest atacicept trial to date was entitled Atacicept in Combination with MMF and Corticosteroids in Lupus Nephritis (APRIL-LN), a randomized, double-blind, placebo-controlled, phase II/III study [79]. Patients received either atacicept or placebo in addition to concurrent high-dose corticosteroids and mycophenolate mofetil started at study onset. However, the trial was prematurely terminated after only 6 patients enrolled due to serious infections and reductions in serum IgG. There is an ongoing trial of non-renal lupus patients entitled Atacicept Phase II/III in Generalized Systemic Lupus Erythematosus (APRIL SLE) that will evaluate whether atacicept can reduce the frequency of flares [80].

Abetimus is a B cell tolerogenic DNA-oligomeric construct that is comprised of approximately 97% dsDNA. The presumed mechanism of action is a rapid decrease in anti-dsDNA antibody levels through clearance of drug-antibody complexes and development of tolerance among anti-dsDNA-specific B cells [81]. While an initial phase II/III trial of abetimus in SLE patients with a history of renal disease did not show benefit in the prospective analysis, a retrospective analysis revealed that patients receiving abetimus had significantly improved clinical outcomes compared to placebo including decreased SLE and renal flares [82]. However, a subsequent phase III double-blind, placebo-controlled trial in patients with lupus nephritis failed to show an improvement in the primary outcome of time to renal flare [83]. As a result, no subsequent trials have been performed using abetimus in lupus patients.

Ocrelizumab, a humanized anti-CD20 monoclonal antibody, has also been evaluated in SLE. A phase III trial entitled A Study to Evaluate Two Doses of Ocrelizumab in Patients with Active Systemic Lupus Erythematosus (BEGIN) enrolled patients with moderate-to-severe non-renal SLE [84]. The trial was discontinued prematurely after the study investigators concluded ocrelizumab was unlikely to have efficacy based on findings from the rituximab trials. Nevertheless, a phase III trial entitled A Study to Evaluate Ocrelizumab in Patients with Nephritis Due to Systemic Lupus Erythematosus (BELONG) is ongoing to determine whether ocrelizumab will be beneficial in patients with SLE nephritis class III or IV lupus nephritis [85].

B-cell depletion using CD22 as a target has also been studied as a potential therapy in SLE. Epratuzumab is a humanized monoclonal antibody against CD22. Unlike anti-CD20 medications such as rituximab and ocrelizumab, epratuzumab affects B cell activity without fully depleting peripheral B cell stores. In an initial pilot study of patients with moderate SLE, disease activity as measured by total BILAG scores was reduced by ≥ 50% in all 14 patients (including at 6 weeks in 77% of patients) [86]. B cells were on average depleted by 35% at 18 weeks and levels remained low at 6 months after completion of therapy. The phase II trial was entitled Epratuzumab Demonstrates Clinically Meaningful Improvements in Patients with Moderate to Severe Systemic Lupus Erythematosus (EMBLEM) [87]. In this study, total BILAG scores were significantly reduced by epratuzumab compared to placebo. Furthermore, the degree of B cell depletion in patients receiving epratuzumab was similar to that seen in the previous trial. Epratuzumab was overall well-tolerated in both studies. On the basis of the promising data from EMBLEM, a phase III multicenter trial entitled Study of Epratuzumab Versus Placebo in Subjects with Moderate to Severe General Systemic Lupus Erythematosus (EMBODY 1) is currently in the recruitment phase [88]. Whether epratuzumab will be of benefit in patients with lupus nephritis is not known and warrants further investigation.

T-cell Targeted Therapies

Various potential T cell therapeutic targets have also been studied in SLE. Abatacept binds to the B7 (CD80/86) molecule on the surface of antigen-presenting cells and B lymphocytes to inhibit co-stimulation of T cells. In a phase Ib randomized, double-blind, placebo-controlled trial among patients with active non-renal SLE (using BILAG A or B score) who were allowed to continue on a background of corticosteroids, there was no response to abatacept compared to placebo at 1 year [89]. Specifically, the primary end point of the proportion of patients with a new SLE flare was not met. Of concern, the rate of serious adverse events was significantly higher in the abatacept cohort. Abatacept has also been evaluated in patients with active lupus nephritis. An initial phase II/III multicenter, randomized, double-blind, placebo-controlled trial was discontinued early on owing to lack of efficacy of abatacept [90]. There is one ongoing phase II trial entitled Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis (ACCESS) evaluating whether the addition of abatacept to the Euro-lupus regimen is a more effective induction treatment approach for lupus nephritis [91]. Furthermore, an upcoming phase III trial will compare abatacept to placebo (in addition to a background of mycophenolate mofetil and prednisone up to 60 mg/day) in active class III or IV lupus nephritis [92]. These two trials will provide important data regarding the effectiveness of abatacept in this subset of SLE patients.

Mitochondrial abnormalities in T cells of SLE patients leading to oxidative stress have also been the subject of clinical investigation. Rapamycin regulates mitochondrial transmembrane potential and calcium flow. An initial phase I pilot study of 9 patients with refractory SLE showed rapamycin was both safe and effective in reducing disease activity [93]. A phase II clinical trial investigating rapamycin in patients with SLE is currently in the recruitment phase [94]. N-acetylcysteine is a precursor of glutathione that inhibits mTOR activity in T lymphocytes. In a recent randomized, double-blind, placebo-controlled, phase I/II pilot study, N-acetylcysteine resulted in decreased disease activity in patients with SLE receiving the 2.4 and 4.8 g daily doses (but not the 1.2 g daily dose) [95]. N-acetylcysteine was well-tolerated overall, though 33% of those receiving the 4.8 g daily dose experienced reversible nausea. Notably, patients were clinically stable (including no active nephritis) and not on any biologic therapies for their SLE.
Other potential T cell targets that have been studied in SLE are spleen tyrosine kinase and CD40 ligand blockade. Spleen tyrosine kinase (Syk) acts downstream of mTOR. R788, an orally bioavailable Syk inhibitor, has been effective in treating nephritis and skin disease in mouse models of lupus [96,97]. Blockade of the CD40 ligand in a lupus murine model with anti-CD40 ligand antibody resulted in reduced disease severity and greater survival [98]. In addition, BG9588, a humanized anti-CD40 ligand antibody decreased anti-dsDNA antibodies, increased C3 levels, and decreased hematuria in a pilot study of 18 patients with active proliferative lupus nephritis [99]. However, the study was prematurely terminated due to thromboembolic events (two myocardial infarctions) and no further clinical trials involving CD40 ligand blockade have been undertaken. Two oral quinoline-3-carboxamide small molecules have also drawn interest as possible therapies in SLE. Laquinimod alters the T helper cell response in favor of Th2 over Th1 cells leading to suppression of pro-inflammatory cytokines and promotion of several anti-inflammatory cytokines [100]. It is the subject of two ongoing phase IIa randomized, double-blind, placebo-controlled trials in SLE, one involving patients with active lupus arthritis and the other consisting of patients with active proliferative or membranous lupus nephritis [101,102]. Paquinimod, the other oral quinoline-3-carboxamide small molecule, was recently evaluated in a phase Ib double-blind, placebo-controlled, dose-ranging study of patients with mildly active SLE [103]. The tolerability of paquinomid was the primary aim of this study and it was well tolerated at doses of up to 3 mg/day. However, there were

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Key Clinical Trials (*denotes ongoing or upcoming trial)</th>
<th>Primary Endpoint Met</th>
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<td>B cells</td>
<td>Rituximab</td>
<td>Chimeric monoclonal anti-CD20 antibody</td>
<td>Phase III (EXPLOER) [67]: SLE</td>
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<td>Abetimus</td>
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<td>Phase III [82]: lupus nephritis</td>
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<td>T cells</td>
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<td>Phase IIa [102]: lupus nephritis</td>
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Table 1: Summary of targeted agents investigated for the treatment of SLE.
a total of eight serious adverse events in the 4.5 and 6 mg/day dose groups. Whether paquinomod at lower (safer) doses will demonstrate efficacy in SLE remains to be seen (Table 1).

**Anti-Cytokine Targeted Therapies**

Given the role of pro-inflammatory cytokines in both the innate and adaptive immune pathogenesis of lupus, a number of anti-cytokine therapies have been the focus of research to more selectively and efficaciously manage patients with SLE. Anti-IFN-alpha-therapy is one such area of interest. Sifalimumab is a fully human IgG1K monoclonal antibody that binds strongly to IFN-alpha and inhibits IFN-alpha signaling through its receptor, IFNAR. In a phase I randomized, double-blind, multicenter trial (with an open-label extension component), patients with moderately active SLE received either escalating doses of sifalimumab or placebo [104]. Sifalimumab resulted in dose-dependent inhibition of type I IFN-induced mRNA. Rates of adverse events were similar between the two groups, most were mild, and no grade 3 or 4 adverse events were deemed treatment-related. Though assessment of safety was the primary aim of this study, there was a trend toward improved disease activity among patients receiving sifalimumab compared to placebo. There is an ongoing phase II open-label study assessing the long-term safety of sifalimumab in SLE (as well as in patients with active dermatomyositis or polymyositis) [105]. In addition, a phase Ib, randomized, placebo-controlled, dose-ranging study is actively recruiting participants to evaluate the efficacy and safety of sifalimumab in moderate-severe SLE [106].

Rontalizumab, a humanized IgG1 monoclonal antibody that inhibits IFN, was just recently evaluated for the first time in patients with SLE. In a phase I randomized, placebo-controlled, double-blind, dose-escalation study of subjects with mildly active SLE, those receiving rontalizumab experienced a rapid decrease in expression of messenger RNA levels of IFN-regulated genes (IRGs) in the 3 mg/kg and 10 mg/kg cohorts [107]. In addition, rontalizumab was overall well-tolerated and no adverse events led to study drug discontinuation. The results from a phase II trial entitled Efficacy and Safety of Rontalizumab (Anti-Interferon Alpha) in SLE Subjects with Restricted Immunosuppressant Use (ROSE) were recently presented in abstract form at the 2012 ACR/ARHP annual meeting [108]. Study participants had moderate-to-severe SLE and baseline immunosuppressive regimens were discontinued upon randomization except for steroids which were tapered to ≤ 10 mg/day by week 8. Though response rates as measured by BILAG and the SRI were similar between the rontalizumab and placebo arms, rontalizumab was associated with a decrease in both lupus flares and steroid burden at week 24 in a pre-specified biomarker defined group of patients. In addition, there was a similar incidence of adverse events among patients receiving rontalizumab compared to placebo, most commonly urinary tract infections, upper respiratory infections, headache, and nausea.

Another cytokine target for SLE therapy has been IL-6. Tocilizumab is a humanized monoclonal antibody against the alpha chain of the IL-6 receptor. It prevents IL-6 from binding to both membrane-bound and soluble IL-6 receptor [109]. Tocilizumab has already become an accepted therapeutic option in the management of rheumatoid arthritis based on the favorable results from several randomized clinical trials [110-113]. Tocilizumab has been evaluated in a phase I pilot open-label, dose-escalation study of 16 patients with mild-to-moderate SLE disease activity [114]. Patients were given one of three tocilizumab regimens intravenously every other week for 12 weeks (7 infusions): 2 mg/kg (4 pts), 4 mg/kg (6 pts), or 8 mg/kg (6 pts). Tocilizumab resulted in improved arthritis in all 7 patients with joint symptoms at baseline. In addition, disease activity improved in 8 of 15 evaluable patients using a decrease ≥ 4 points on the modified SLEDAI disease activity index. While dose-related neutropenia was noted in this study and two-thirds of enrolled patients experienced infections, most adverse events were mild and tocilizumab was overall well-tolerated. This study included only 5 patients with chronic renal disease and none had significantly active nephritis. Therefore, the impact of tocilizumab on outcomes in patients with active lupus nephritis will require further study. In addition, validation of the clinical improvement seen in this trial for patients with extra-renal SLE will need to be demonstrated in larger studies.

Anti-IL-10 therapy has also been investigated in SLE. In a small phase I pilot study, 6 patients with active steroid-dependent disease received B-N10, a murine anti-IL-10 monoclonal antibody, at 20 mg/kg for 21 consecutive days and were followed for 6 months [115]. All patients had improvement in cutaneous and musculoskeletal manifestations of lupus, and 5 out of 6 patients had clinically inactive disease at the end of the follow-up period. In addition, only one relatively mild adverse event was reported. Nevertheless, all patients developed antibodies against the study drug. There have been no subsequent studies of anti-IL-10 therapy in SLE.

Despite the remarkable success of anti-TNF-alpha targeted agents in the treatment of rheumatoid arthritis and the seronegative spondylarthropathies, the findings in SLE patients have led to significant trepidation toward their use for this indication. There have been two open-label pilot studies in SLE of infliximab, a chimeric monoclonal antibody against TNF-alpha [116,117]. Both studies included patients with moderately active lupus who were permitted to remain on background immunosuppression regimens. Infliximab led to decreased SLE disease activity in both trials. However, there are now well-established case reports of drug-induced lupus secondary to TNF-alpha inhibitors and concerning rates of serious adverse events in longer-term follow-up of SLE patients treated with these medications [118-120]. Likely due to these developments, two larger randomized trials involving TNF alpha inhibitors in patients with lupus nephritis (one study each using infliximab and etanercept) were both aborted prior to study completion [121,122]. Further interest regarding the use of TNF-alpha blockade in SLE is therefore unlikely (Table 1).

**Conclusion**

Lupus pathogenesis remains incompletely understood and the heterogeneous nature of disease has made clinical investigation more difficult compared to other rheumatologic diseases. In addition, the lack of consistency in disease activity indices employed in clinical trials has made direct comparison of targeted therapies in SLE more challenging. There is also a need for more specific biomarkers that can better reflect lupus disease activity. Nevertheless, important advances in our understanding of SLE in the past ten years have led to a renaissance of research activity to identify novel targeted agents to more effectively and safely treat patients with lupus. Numerous B-cell, T-cell, and anti-cytokine targets have been studied. Though a number of these possible therapeutic targets have met with failure or mixed results, others have shown promise in early trials and belimumab has become the first approved therapy for SLE in over half a century. It is highly likely that the approach to lupus management will undergo significant changes in the coming years and it is hoped that further targeted therapies will meet with success in the near future.
References


44. Liu TF, Jones BM (1998) Impaired production of IL-12 in system lupus erythematosus. II. IL-12 production in vitro is correlated negatively with serum IL-10, positively with serum IFN-gamma and negatively with disease activity in SLE. Cytokine 10: 148-153.


68. ClinicalTrials.gov. RING - Rituximab for lupus nephritis with remission as a goal (NCT01639339).


77. ClinicalTrials.gov. A continuation trial for subjects with lupus who completed protocol HGS1008-C1058 in the United States (NCT00724867).


104. ClinicalTrials.gov. A study to evaluate the long-term safety of MED-I in adult subjects with systemic lupus erythematosus or myositis (NCT00797654).


120. ClinicalTrials.gov. TNF blockade with remicade in active lupus nephritis WHO class V (TRIAL) (NCT00368264).


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