Biologics in SLE: The Current Status

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Abstract
Systemic lupus erythematosus (SLE) can be a severe and potentially life-threatening disease that often represents a therapeutic challenge because of its heterogeneous organ manifestations. Only glucocorticoids, hydroxychloroquine, mycophenolate mofetil, azathioprine, cyclophosphamide, and very recently belimumab have been approved for SLE therapy. Dependence on glucocorticoids and resistance to the approved therapeutic agents, as well as substantial toxicity, are frequent. B-cells abnormalities leading to autoantibody production play a central role in Systemic Lupus Erythematosus (SLE) pathogenesis. The targets of these biological therapies are directed toward the B cell depletion, interference in the co-stimulation signals and the blockade of cytokines. Biologic agents targeting specific pathways (i.e. T-B lymphocyte interaction, cytokines and complement) have been also proposed as new tools for SLE treatment. B-cell targeted therapies, including anti-B lymphocyte stimulator (BlyS) and anti-CD20 monoclonal antibodies are at forefront of new SLE treatment. Results from randomized trials in systemic lupus erythematosus (SLE) have been very disappointing, with lack of efficacy for some drugs and development of severe side-effects such as infections for others. Fortunately, as more and more trials of biologics in the treatment of lupus are being performed, the first promising results have been achieved. Today, belimumab is expected to become the first approved drug for use in lupus in several decades. In this review we will focus on biological drugs whose potential efficacy have been evaluated in open-label and randomized clinical trials. Biologics provide encouraging results that represent a possible option in the treatment of refractory lupus.

Thus we review recent clinical trials in patients with systemic lupus erythematosus (SLE), with emphasis on outcomes and on mechanisms by which the biological agents suppress autoimmunity.

Introduction
Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organs. It causes damage by deposition of autoantibodies and immune complexes or by vascular occlusion (antiphospholipid antibodies). SLE is more common in women, African Americans, Asians, and Hispanics. SLE is caused by a complex interplay of genes, sex hormones, the immune system and the environment. Autoantibodies are seen in at least 95% of SLE patients. These may have specificities for nuclear (antinuclear antibodies [ANA]), cytoplasmic, or cell surface proteins. Anti–double-stranded deoxyribonucleic acid (anti-dsDNA) and anti-Smith (anti-Sm) antibodies are unique to SLE and thus serve as diagnostic markers. Increase in anti-dsDNA antibody titers and reductions in C3 levels have been found to be predictors of SLE flares. The American College of Rheumatology (ACR) criteria for SLE requires at least 4 of the 11 different organ system involvement.

Biological therapy has been proven to be effective in inflammatory diseases such as rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease. But the efficacy of biological therapy in SLE is still controversial. The goal of our present study is to review the recent literature on the effectiveness of various biological therapies in SLE. Immunosuppressive therapies including corticosteroids, hydroxychloroquine, azathioprine, cyclophosphamide and mycophenolate mofetil have been utilized for the treatment of moderate-to-severe SLE; however, a significant proportion of patients fail to achieve remission or experience relapses during maintenance therapy. Thus, the need for improved therapies for SLE is great because most patients do not have good disease control, even though survival has improved dramatically over the past few decades.

Disease Activity Measures
In recent years, many indices of SLE disease activity have been developed and validated. These include the British Isles Lupus Assessment Group (BILAG), the Systemic Lupus Activity Measure (SLAM), the SLE Disease Activity Index (SLEDAI) and the modified Safety of Estrogen in Lupus Erythematosus National Assessment (SLENA). The BILAG index consists of organ-specific domains, whereas the SLAM and SLEDAI measure global disease activity.

Targets of Therapy
B lymphocytes play a central role in the pathogenesis of SLE. Pathogenic autoantibodies produced by hyper-reactive B cells lead to tissue damage via immune complex formation, complement activation and direct effects on cells. B cells also contribute to immune dysregulation by producing cytokines, presenting antigens and regulating T-cell functions. Over the last few years, multiple open-label studies documented the beneficial effects of targeting B cells in refractory SLE. T cells have important regulatory and effector functions, both of which are abnormal in patients with SLE. Elevated levels of certain cytokines/chemokines /growth factors made by monocytes/macrophages and endothelial cells also drive lupus disease activity and organ damage. These include B-cell activating factor (BAFF)/B lymphocyte stimulator, tumor necrosis factor (TNF) alpha, INF-a, IFNγ, interleukin (IL)-12, IL-6, IL-10 and MCP-1. Appropriate targets for therapeutic modulation include T/B lymphocyte signaling, inhibition of T-cell activation and B-cell activation and/or maturation, TNF-alpha inhibition and antibodies to IFN, Interleukins and anti-CD40L and CTLA4lg. Table 1 summarizes the targets of therapy.
### Table 1: Target of Therapy

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### Targeting B Cells

#### Rituximab

Rituximab (RTX) is a chimeric monoclonal antibody that binds CD20, a protein expressed on B cells at all stages of development (except plasma cells). Two randomized double-blind, placebo-controlled trials (EXPLORER and LUNAR)\(^\text{18-19}\) were designed to objectively assess the efficacy and safety of RTX. Quite unexpectedly, both trials were negative. Efficacy and Safety of RTX in patients with severe SLE (EXPLORER) recruited 257 non-renal SLE patients.\(^\text{18-19}\) They received intravenous placebo or RTX 1gm in addition to an immunosuppressant. MCR (major clinical response) was 15.9 versus 12.4% and PCR (partial clinical response) was 12.5 versus 17.2% for placebo and RTX groups, respectively. The RTX group showed significant improvement in anti-dsDNA and complement levels.\(^\text{18-19}\) The main flaws in this trial were that the majority of patients had mucocutaneous and musculoskeletal involvement which represent relatively milder forms of SLE, both groups received high doses of corticosteroids, therapeutic doses of immunosuppressants and the total follow-up duration was only 52 weeks. Prior open-label studies have shown maximal clinical benefit to be evident even after 18 months.\(^\text{20}\) Some patients after RTX, reconstitute with naive B cells, which are more receptive to tolerance induction.\(^\text{21}\) One would not want to re-deplete these patients by RTX re-treatment.

The LUNAR (The Efficacy and Safety of Rituximab in class III or IV lupus nephritis) trial, compared RTX therapy versus placebo, when added to background of steroids and mycophenolate mofetil.\(^\text{20}\) A total of 144 patients were randomized to receive placebo or RTX.

The results did not show any significant difference in the two treatment arms in any primary or secondary outcomes. In contrast multiple open-label studies continue to report the efficacy of RTX in patients with severe refractory SLE and catastrophic antiphospholipid syndrome.\(^\text{8,15}\) The majority of patients receiving RTX in these studies have failed multiple prior immunosuppressants and have multisystem severe life or organ-threatening disease. A recent review\(^\text{22}\) evaluated the use of RTX in 188 SLE patients from 35 studies, reporting efficacy rates approaching 90 percent. Similarly high response rates were reported in a meeting by multiple experts using RTX in SLE in ongoing studies at tertiary referral centers. Although RTX cannot be considered first-line therapy for mild-to-moderate SLE, the benefit in severe refractory disease may justify its use in such cases. Low-dose rituximab therapy is even effective in treating severe thrombocytopenia in SLE patients who do not respond to vigorous glucocorticoid plus immunosuppressants.\(^\text{23}\)

The safety of B-cell depletion in SLE was raised after reports of progressive multifocal leukoencephalopathy was seen in SLE patients treated with RTX. Although EXPLORER and LUNAR did not report any significant increase in serious adverse effects in the RTX-treated group. However, higher rates of neutropenia and herpes infections were reported at 72 weeks follow-up of patients in EXPLORER.\(^\text{24}\)

#### Epratuzumab

Epratuzumab is a monoclonal antibody directed against the B-cell-specific molecule CD22. Results from a open-label, single-center study of 14 patients with moderately active SLE (composite BILAG scores of 6-12) were sufficiently promising to support further drug development. It has been used to treat patients with SLE with mild to moderate mucocutaneous and musculoskeletal symptoms. The dosage is 360 mg/m\(^2\), IV, every 2 weeks, for 4 doses, with good outcome and safety profile. Positive results from the phase IIB EMBLEM trial of epratuzumab have been noted with the overall responder rate index was 43.2 for the 74 patients on a total of 2,400 mg of epratuzumab vs. 21.1 for those on placebo. Especially impressive were the epratuzumab-induced reductions in neuropsychiatric and cardiorespiratory symptoms of SLE, which are often particularly resistant to conventional therapies.

#### Belimumab

It is the first and the only biologic agent approved for the treatment of SLE. The B-lymphocyte stimulator (BlyS) is important for the survival of B cells. Animal and human data have shown overexpression of BlyS in SLE\(^\text{25}\) and higher BlyS levels correlated with SLE disease activity.\(^\text{26}\) Belimumab is a fully human monoclonal antibody that binds to BlyS and inhibits its biological activity. Efficacy, tolerability and safety of three different doses of belimumab in SLE were evaluated in a multicenter phase 2 study.\(^\text{27}\) A total of 449 patients were randomized to receive 1, 4 or 10 mg/kg of belimumab or placebo. There was no significant difference in either outcome in the combined belimumab group versus placebo. In the subgroup of serologically active patients [positive antinuclear (ANA) and/or anti-dsDNA antibody], belimumab did lead to a significantly better response over placebo. Belimumab treatment led to a significant reduction in B-cell counts, immunoglobulin levels and anti-dsDNA levels. Complement levels rose in patients with baseline low levels of complement.\(^\text{27}\) The limitations of this study were the use of immunosuppressants and inclusion of seronegative (negative ANA and/or anti-dsDNA antibody) patients (28%). This trial was later continued as an open-label extension study.\(^\text{28}\) Four year safety and efficacy data for 237 patients have recently been reported. Serologically active
patients showed sustained improvement in all flares and severe flares over time. Belimumab was further evaluated in two large randomized, double-blind, placebo-controlled, multicenter phase 3 trials, BLISS-52 and BLISS-76. Including 865 and 826 seropositive (ANA and/or anti-dsDNA) patients, respectively. In each of these trials, patients were randomized to receive 10 mg/kg belimumab, 1 mg/kg belimumab, or placebo. Patients were dosed intravenously on days 0, 14, and 28, then every 28 days thereafter for the duration of the study. The primary efficacy endpoint was the SLE responder index at week 52 (defined as at least four-point reduction in SELENA-SLEDAI, no new BILAG A score and no worsening of disease activity by physician global assessment). Belimumab achieved significantly better results than placebo in both studies. In BLISS-52, response rates were 51.7% for belimumab 1 mg/kg and 57.6% for 10 mg/kg belimumab, compared with 43.6% for placebo. In BLISS-76, response rates were 43.2% for 10 mg/kg belimumab, 40.6% for 1 mg/kg belimumab, and 33.8% for placebo. In addition, belimumab significantly delayed time to first SLE disease flare versus placebo and lead to significant reduction in steroid doses in BLISS-52. Belimumab was well tolerated, with rates of overall adverse events, serious adverse events, infections and fatalities comparable between belimumab and placebo groups.

**Anti TNF Therapy**

**Atacicept**

Targeting BLYS could be of potential therapeutic benefit to SLE patients given the B-cell hyperactivity and elevated serum levels of BLYS. Atacicept is a recombinant fusion protein consisting of TACI (transmembrane activator and calcium modulator ligand interactor) conjugated to the Fc portion of Ig which inhibits B cell stimulation by binding to BLYS and proliferation inducing ligand. The biologic effects of atacicept in SLE patients with mild-to-moderate disease activity were evaluated in a small phase 1b double-blind, placebo-controlled, dose-escalating trial. Dose-dependent reductions up to 60% of baseline values were seen in mature and total B-cell populations, whereas T cells, monocytes, and natural killer cells were unaffected. Dose-dependent reductions in Ig levels were observed. There were no statistical differences in the frequency or types of adverse events between the placebo- and atacicept-treated groups.

**Anticytokine Therapy**

**Anti TNF Therapy**

Two large randomized trials were designed to evaluate the efficacy and safety of TNF inhibitors (infliximab, etanercept) in SLE but both were terminated prematurely. At the same time, TNF inhibitor use in RA can lead to formation of autoantibodies. Recently, a few cases of severe SLE were reported after use of TNF inhibitors for treatment of RA and other inflammatory arthritis. In view of these findings, it is unlikely that TNF inhibition will be used routinely in SLE treatment.

**Tocilizumab**

**(Interleukin-6 Receptor Inhibitor)**

Interleukin-6 (IL-6) is a key proinflammatory cytokine. In murine models, IL-6 increases auto-antibody production and progression of glomerulonephritis. Urinary IL-6 excretion is increased in patients with active SLE nephritis, decreasing after treatment. A phase I dose finding study evaluated in 16 patients with moderately active disease (SELENA-SLEDAI score between 3 and 10 or active glomerulonephritis) received tocilizumab at (2, 4, and 8 mg/kg), twice weekly for 12 weeks. Tocilizumab led to reduction in inflammatory markers and auto-antibody levels. Disease activity decreased significantly (SELENA-SLEDAI from 9.5 at baseline to 5.5 at 20 weeks). Almost all patients developed dose-related neutropenia and high rates of infections were recorded. These preliminary data are insufficient to consider the use of tocilizumab in SLE until further studies are completed.

**Anti IL-10 Antibody**

Several studies have confirmed the presence of increased levels of IL-10 in patients with SLE. Whereas IL-10 promotes the proliferation of B cells, it is also capable of reducing proinflammatory responses. Despite the uncertainty of effects of antagonizing IL-10 in human SLE, a small study in 6 SLE patients was performed with 20 mg intravenous murine anti-IL-10 (B-N10) was administered daily for 21 days with a follow-up period of 6 months. Cutaneous lesions and joint symptoms improved in all patients, and improvement was sustained for 6 months. SLEDAI scores were reduced from a mean of 8.83 on day 1 to 1.33 at month 6. The requirement for prednisone was significantly reduced by month 6.

**Induction of Tolerance**

**Abetimus**

It is an intravenously administered tetrameric oligonucleotide conjugate that safely reduces anti-dsDNA antibodies. Given the importance of anti-dsDNA antibodies in the pathogenesis of lupus nephritis, the Phase II and III trials were designed to evaluate whether treatment with abetimus sodium could prolong the time to renal flare in cohorts of patients at high risk of nephritic flares. Administration of abetimus to patients with SLE has uniformly been associated with reductions in circulating anti-dsDNA antibodies. However, two pivotal trials with large numbers of lupus nephritis patients failed to demonstrate statistically significant prolongations in time to renal flare. An event-driven randomized placebo-controlled trial was abruptly terminated after an interim data safety monitoring board determined that achievement of a successful study outcome was futile.

**Blockade of T Cell Co-Stimulation**

**Abatacept**

Abatacept is a fully human recombinant fusion protein that selectively modulates T-cell activation by blocking co-stimulation via the B7:CD28 pathway. This results in decreased T-cell activation, proliferation, cytokine secretion and subsequent autoantibody production without depletion of T or B cells. Animal data suggest a beneficial role of T-cell co-stimulation blockade with CTLA-4 immunoglobulin, in murine SLE models. Abatacept has been tested in non-renal lupus and in lupus nephritis, respectively. In the clinical trial on non-renal lupus, 175 patients with SLE were randomized in a 2:1 ratio to receive either monthly infusions of 10 mg/kg abatacept or placebo along with prednisone. The proportion of patients with BILAG A and B flares, respectively, after 12 months was 79.7% for abatacept versus 82.5% for placebo and thus showed no significant differences. Abatacept, however appeared to be superior to placebo in reducing fatigue symptoms and improving quality of life according to the short form 36 (SF-36) health survey. In a subsequent analysis abatacept treatment was associated with a lower number of BILAG A flares in the arthritis group. Serious adverse events were higher in the abatacept group (19.8%) compared with placebo (6.8%).

Two large randomized multicenter placebo-controlled trial currently ongoing to evaluate the use of abatacept in
SLE nephritis in combination with mycophenolate mofetil or cyclophosphamide. Their results, when available, will help to further define the role of co-stimulation blockade in SLE treatment.

Future Targets

BG9588 and IDEC-131 (Anti CD-40 Ligand Antibodies)

Anti-CD40 ligand antibodies interfere with the interactions between CD40 on B cells and its T-cell-based ligand, CD40L, thus resulting in inhibition of T-cell costimulation. In a phase 2, double-blind, placebo-controlled, multicenter, dose-ranging study of 85 patients with mild to moderately active, at week 20, SLEDAI scores improved from the baseline values in all groups; however, differences between treatment groups and placebo were not statistically significant. The types and frequencies of adverse events were similar between the IDEC-131 and placebo groups. A second development program with an anti-CD40L antibody, known as BG9588, was terminated prematurely because of thrombotic complications. Results of an open-label trial in patients with proliferative lupus nephritis revealed a reduction in proteinuria in anti-dsDNA antibody, an increase in serum C3 concentrations and hematuria disappeared in all 5 patients with significant hematuria at baseline. Huang et al had the opportunity to evaluate the immunologic effects of BG9588 therapy in 5 patients. Despite the limitations of this study, there was sufficient evidence that BG9588 was bioactive.

Eculizumab

Eculizumab, a humanized antibody that recognizes the human complement protein C5, blocks C5b cleavage and thereby prevents the generation of the proinflammatory complement components C5a and C5b-9. Eculizumab has been studied in early clinical trials of patients with SLE, rheumatoid arthritis and dermatomyositis. Furie et al reported the safety, tolerability, pharmacokinetics, and pharmacodynamics of a single administration of eculizumab (0.1, 0.75, 2, 4, and 8 mg/kg) or placebo in 24 patients with SLE; single doses of 4 and 8 mg/kg resulted in reductions of subjects’ CH50 by 80% or greater for 5 and 10 days, respectively.

N-Acetyl Cysteine

Mitochondrial dysfunction leads to increased production of reactive oxygen metabolites. This leads to depletion of ATP and reduced glutathione, predisposing cells to necrotic death which is highly proinflammatory. Administration of N-acetyl cysteine (NAC), which serves as a precursor of glutathione, improves outcome in murine lupus. A phase 1/2 trial is underway to assess the safety and efficacy of NAC treatment in SLE.

Rapamycin

Aberrant activation of mTOR (mammalian target of rapamycin) is yet another important recognized mechanism mTOR has multiple regulatory functions in T and B-cell intracellular signaling. Rapamycin interacts with mTOR by influencing gene transcription and multiple cellular metabolic pathways. A small pilot study of nine refractory SLE patients documented efficacy and safety of rapamycin in SLE. A phase 2 clinical trial of nine refractory SLE patients documented efficacy and safety of rapamycin in SLE. A phase 2 clinical trial is underway to assess the efficacy of rapamycin for the treatment of SLE.

Spleen Tyrosine Kinase (Syk)

Spleen tyrosine kinase (Syk) is involved in the development of cells of the immune system, including T and B cells. It acts downstream of mTOR and has been noted to have an important role in the aberrant function of T cells in patients with SLE. R788, an orally bioavailable Syk inhibitor, prevented development of renal disease and treated established nephritis and skin disease in murine lupus. In humans, Syk inhibition has been shown to be of benefit.

Sifalimumab

An anti-IFNα monoclonal antibody, were assessed in a phase I, multicentre, randomised, double-blind, dose-escalation study with an open-label extension in adults with moderately active SLE. Subjects received one intravenous dose of sifalimumab (n=33 blinded phase, 0.3, 1, 3, 10 or 30 mg/kg; n=17 open-label, 1, 3, 10 or 30 mg/kg) or placebo (n=17). Each phase lasted for 84 days. Adverse events (AEs) were similar between groups. Exploratory analyses showed consistent trends toward improvement in disease activity in sifalimumab treated versus placebo-treated subjects. A lower proportion of sifalimumab-treated subjects required new or increased immunosuppressive treatments (12% vs. 41%; p=0.03) and had fewer SLEDAI flares (3% vs. 29%); had a safety profile that supports further clinical development. This trial demonstrated that overexpression of type IFN signature in SLE is at least partly driven by IFNα, and IFNα inhibition may be associated with clinical benefit in SLE.

Autologous Stem Cell Transplantation

In patients with severe SLE refractory to conventional immunosuppressive treatments, AHSCT can achieve sustained clinical remissions (ranging from 50% to 70% disease-free survival at 5 years) associated with qualitative immunological changes not seen with other forms of treatment. However, this clinical benefit is associated with an increase in short-term mortality in most studies.

Conclusion

The pathogenesis of SLE involves aberrancy in multiple components of the immune system including B cells, T cells, cytokines and growth factors. Therapeutic agents targeting these mediators selectively have been tested for the treatment of SLE. Despite the enthusiasm in the field of biologic therapies, the majority of these new modalities have fallen short of expectations. Despite the enthusiasm in the field of biologic therapies, the majority of these new modalities have fallen short of expectations for various reasons. Only belimumab has recently met its primary outcome in two phase 3 trials. Biological therapy holds much promise in SLE and as we learn more about the disease and apply the lessons learned from recent trials, we will be in a strong position to further accelerate drug development in SLE.

References


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