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Targeting B cells with biologics in SLE

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Abstract

Importance of the field—The use of biologics as immune modulators in several autoimmune diseases has provided new tools to the physician's therapeutic armamentarium and has led to improved patients' outcomes and quality of life. By producing autoantibodies, B cells in SLE are key players in the pathogenesis of the disease and in its clinical manifestations. Therefore, biologics that target B cells in SLE aims at reducing the activity of these cells for the induction of remissions and/or amelioration of disease activity, reduction of organ involvement, and limitation of the complications and side effects caused by immunosuppressive therapies.

Areas covered in this review—This review describes the past and current clinical trials with B cell-targeted biologics in SLE, to provide a historical perspective and the state-of-the-art on the topic.

What the reader will gain—We will review how the disappointment in the field from promising agents has been instrumental in providing valuable lessons leading to an improved design of new trials that are now giving encouraging results

Take home message—In systemic lupus erythematosus (SLE), the use of B cell-based biologics in clinical trials has shown both disappointment and promise

Keywords

Systemic Lupus Erythematosus; B Cells; Autoantibodies; Biologics; Clinical Trials

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the involvement of multiple organs and by the presence of dysregulated immune responses. These include immune aberrations associated with an impaired immune tolerance (partly related to the availability of self antigens secondary to abnormal apoptosis), abnormal patterns in the expression of pro-inflammatory and anti-inflammatory cytokines, hyperactivity of T helper and B cells, and hyperproduction of autoantibodies. Since autoantibodies can bind self-antigens and form immune complexes that can deposit in tissue (where they can activate complement, promoting local inflammation that can cause tissue damage), one of the therapeutic goals in the treatment of SLE is the blockade and/or the reduction in the levels of autoantibodies in patients. Consequently, one modality of intervention in the disease considers the depletion and/or the blockade of B cells that make antibodies that have a pathogenetic role in the disease manifestations and/or complications.

Clinically, the multi-organ involvement and the broad spectrum of manifestations in SLE patients represent a significant challenge for the physician, both in terms of diagnosis and management of the disease. Although the mortality and morbidity of SLE have significantly improved in the last decades due to the development of better tools for diagnosis, improved therapeutic protocols, and a better knowledge of the disease pathogenesis, fatal complications

from the disease do occur. The disease complexity and heterogeneity of clinical manifestations among patients can sometimes result in therapeutic unresponsiveness for certain patients. As a result, disease can progress and lead to the development of organ damage, sometimes with ill-fated consequences. Also, the frequent use of immunosuppressive agents in SLE may often cause undesired side effects, and favor the development of complications such as infection. Thus, the addition of new therapeutic agents is long awaited to possibly improve the management of the disease. In this context, biologics represent promising candidates.

The use of biologics has significantly impacted the therapy of several diseases, including systemic autoimmune conditions such as rheumatoid arthritis (RA). The success of TNF inhibitors in RA has somehow paved the way to the development and use of other biologics in other autoimmune conditions, including SLE.

2. Antibody-Based Therapies in SLE

One biologic therapy in SLE employs the use of monoclonal antibodies that target single specificities (generally present on the surface of selected immune cell subsets) without affecting other molecules. One advantage of this approach is the specificity in selecting only those cells that need to be targeted for depletion or functional blockade. Another practical advantage is represented by the possibility to easily produce large amounts of monoclonal antibodies through hybridoma techniques.

Mechanistically, the therapeutic effect of monoclonal antibodies *in vivo* can be ascribed to different activities that can be summarized as antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity, or induction of apoptosis.

Four types of monoclonal antibodies have been made available to the clinic: murine antibodies, chimeric (fusion proteins where the receptor that provides specificity is linked to an immunoglobulin) antibodies, humanized antibodies, and fully human antibodies. The two last types of antibodies have obvious reduced antigenicity in humans, possibly exhibit longer half-lives, and may thus carry lesser risk of limited therapeutic efficacy in the recipients.

While acknowledging the variety of the new therapeutic approaches in the treatment of SLE such as the use of biologics that interfere with co-stimulation or that promote immune tolerance, we focus in this review specifically on the biologics that directly target B cells.

3. B-cell-Based Therapies in SLE

The central role of B cells in the pathogenesis of SLE is undisputed. B cells make autoantibodies, present self-antigens, secrete and respond to cytokines and chemokines, and can regulate the function of other immune cells [1-2]. Because of these characteristics, selected subsets of B cells have been targeted for depletion in SLE, as possible therapeutic means. Below we list the biologics used to this goal, with an overview of their action and activity in clinical trials.

3.1. Therapies that Target B Cell Surface Markers

3.1.1. CD20—CD20 is expressed on immature and mature B cells, but not on plasma cells. The function and natural ligand(s) of CD20 are currently unknown, although it has been suggested that this molecule might be involved in B cell activation by influencing Ca^{++} influx across the plasma membranes [3].

3.1.1.1. Ocrelizumab: Ocrelizumab is a humanized (90%) anti-CD20 monoclonal antibody that targets mature B cells. It was investigated in two phase III, randomized, double blind,

placebo-controlled, multicenter studies, one in patients with lupus nephritis (BELONG) (Study ID ClinicalTrials.gov Identifier: NCT00626197), and another study that evaluated two doses of ocrelizumab in patients with active SLE (BEGIN) (Study ID ClinicalTrials.gov Identifier: NCT00539838). These trials have recently been suspended due to the detection of serious and opportunistic infections [4].

3.1.1.2. Rituximab: Rituximab is a chimeric IgG1 monoclonal antibody that targets CD20. As such, it depletes immature, naïve, memory, and germinal center B cells, but spares pro-B cells, early pre-B cells and plasma cells [5]. It is made of murine light and heavy chain variable regions and a human constant region. The murine Fab domain binds CD20, and the human Fc domain can cause B cell lysis by ADCC and apoptosis [6]. Since rituximab does not reduce significantly the levels of circulating antibodies [7-8], it also does not decrease titers of circulating autoantibodies.

Rituximab was initially approved for the treatment of low-grade non-Hodgkin B-cell lymphomas. After its success in that context, the use of rituximab was tested in autoimmunity in RA, where it showed positive effects in combination therapy with methotrexate or cyclophosphamide [9].

In SLE, rituximab has shown efficacy in case series and in open studies [10-14]. Several clinical trials with rituximab have been done in SLE (ClinicalTrials.gov Identifier: NCT00036491; NCT00278538; NCT00282347; NCT00293072; NCT00556192; NCT00908986). Studies have also addressed the effects of hematopoietic stem cell transplant post-rituximab treatment in SLE patients (ClinicalTrials.gov Identifier: NCT00230035; NCT00726518) or the safety and efficacy of the use of rituximab in combination therapy (e.g. with cyclophosphamide or mycophenolate mofetil in lupus nephritis; EXPLORER and VOYAGER [a phase II/III extension study to evaluate safety of rituximab retreatment in subjects with moderate to severe SLE]) (ClinicalTrials.gov Identifier: NCT00137969; NCT00381810).

In patients with refractory SLE treated with rituximab and cyclophosphamide, improvement or clinical remission lasting for a mean of three years in a third of the patients has been observed [13-14]. Also, a phase I/II prospective open-label study that followed 24 patients with active lupus refractory to conventional immunosuppressant found that one fourth of the patients had B-cell return to baseline at 24 weeks, and one third developed human anti-chimeric antibody which correlated with poor B-cell depletion [15] - a concern related to the fact that this agent is not fully human. The maximum therapeutic effects of rituximab in SLE seemed to occur at or after twelve weeks, although B-cell depletion from peripheral blood was rapid and variable from two to eighteen months [7,16]. Apparently, this biologic might be effective in severe SLE refractory to conventional treatment and might possibly provide benefits to subgroups of SLE patients [7,17-18].

Both the 52 week-long EXPLORER (257 patients) and the LUNAR (144 patients) trials with rituximab (the first one in non-renal SLE and the second one in proliferative lupus nephritis patients) did not meet their primary endpoints of achieving a complete or partial response after 52 weeks [19-20]. In the EXPLORER trial [19], the proportion of patients who had a major clinical response defined as no severe flare up to week 24 and no moderate or severe flare to week 52 was similar between the rituximab group (12.4%) and the placebo group (15.9%), as well as the proportion who had a partial clinical response (17.2% versus 12.5%, respectively). In the LUNAR trial [20], there was not a statistically significant difference between rituximab-treated patients and controls, although at 52 weeks 57% of patients in the rituximab group had a renal response versus only 45.9% in the placebo group. Also the secondary endpoints were not met (for the EXPLORER trial: major or minor clinical response at week 52, the achievement of improved British Isles Lupus Assessment Group (BILAG) score at week 24, time to

moderate or severe flare over 52 weeks, change in Short Form (SF)-36 Health Survey from baseline at week 52, and a major clinical response with less than 10 mg daily prednisone from week 24 to 52; for the LUNAR trial: drop of urine protein-to-creatinine ratio from greater than 3 at baseline to less than 1 at week 52, time to first complete renal response, change from baseline in the SF-36 Physical Functioning score, and time-adjusted area under the curve minus baseline of the BILAG index global score). Interestingly, however, subgroup analyses in the EXPLORER trial showed that black and Hispanic patients treated with rituximab had a statistically significant improvement in the primary endpoints (but not in the secondary endpoints). Methotrexate-treated patients also did statistically significantly better with rituximab. In the LUNAR trial, non statistically significant data showed that in the subgroup of black patients, 70.0% of who received rituximab had a response compared with 45.0% of those who received placebo. For Hispanic patients, the response rates were 55.0% with rituximab and 47.8% with placebo.

Recently, the analysis of prospective data on rituximab treatment in a cohort of 136 SLE patients from the French Autoimmune and Rituximab Registry that were followed for about 18 months showed a significant reduction of SLEDAI score at six months and less severe infection than the EXPLORER study [21].

Notwithstanding these considerations, caution may be required in using rituximab for the risk of severe acute infection and the reactivation of latent infection, such as of JC virus, which causes progressive multi-focal leukoencephalopathy (PML) [22]. For example, deaths from PML in SLE patients treated with rituximab and PML after rituximab therapy in patients with hematologic malignancies under immunosuppressive drugs (e.g.: chemotherapy, stem cell transplant) have been reported [22-23], although it must be acknowledged that PML may be a concern for SLE patients independently of rituximab therapy.

3.1.1.3. TRU-015 and SBI-087: TRU-015 is a single chain polypeptide comprising one binding domain, one hinge domain and one effector domain. TRU-015 has potent ADCC activity and targets CD20 to deplete B cells. A randomized study assessing safety, pharmacokinetics and pharmacodynamics of TRU-015 added to standard therapy in patients with membranous lupus nephropathy (Study ID ClinicalTrials.gov Identifier: NCT00479622) has been terminated, mainly because of its similarity to the ongoing phase I clinical trial on safety, pharmacokinetics and pharmacodynamics of SBI-087 (another fully humanized anti-CD20 that temporarily depletes B cells) in SLE patients (ClinicalTrials.gov Identifier: NCT00714116) that showed good safety and tolerability in subjects with controlled SLE [24].

3.1.2. CD22—CD22 is an adhesion molecule that regulates B cell responses through the recruitment of key signaling molecules to the B cell receptor complex. CD22 has an important role in B cell development, survival and, interestingly, can exert both stimulatory and inhibitory effects on B-cell signaling [25]. Differently from CD20 - that is expressed from the pre-B-cell to the activated B-cell stage - CD22 is only expressed in mature B cells and disappears upon their differentiation into plasma cells [26].

3.1.2.1. Epratuzumab: Epratuzumab is a fully humanized, little immunogenic antibody to CD22. Epratuzumab negatively regulates hyperactive B cells by inhibiting B cell receptor signaling and by inducing the internalization of CD22 [27]. Epratuzumab also causes a 30-45% reduction of B cell numbers [28-29] but it does not affect significantly the titers of circulating autoantibodies [28,30]. The safety and pharmacokinetics of epratuzumab in SLE have been reported (ClinicalTrials.gov Identifier: NCT00383214; NCT00111306; NCT00113971), and a phase III clinical trial on the long-term use in SLE is ongoing (ClinicalTrials.gov Identifier: NCT00383513). A phase II trial addressing dose response and frequency

(ClinicalTrials.gov Identifier: NCT00624351) recently showed a relatively rapid reduction in disease activity in some patients with moderate to severe active disease [31].

3.2. Therapies that Target Soluble Mediators for B cells

3.2.1. B-lymphocytic Stimulator (BLyS)—B-lymphocyte stimulator (BLyS, also known as B cell activating factor BAFF, TALL-1, THANK, zTNF4) is a member of the TNF family that is essential for the development, homeostasis, proliferation, survival and differentiation of B cells into mature plasma cells. Expressed as transmembrane protein on monocytes, dendritic cells and activated T cells, or released as a soluble molecule, BLyS binds to its receptors expressed on activated B cells. There are three receptors for BLyS: B-cell-activating factor receptor (BAFF-R, BR3), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), and B cell maturation antigen (BCMA). These receptors are present mainly on mature B cells, with TACI being expressed predominantly on CD27⁺ memory B cells and BCMA on plasma blasts, plasma cells, and tonsillar germinal center B cells, and BAFF-R on all peripheral B cells (in which it promotes cell survival, similarly to BCMA that also inhibits apoptosis). The stimulation of all three receptors increases nuclear factor- κ B (NF- κ B), which promotes cell differentiation and proliferation.

BLyS hyperproduction associates with autoimmune diseases including murine SLE [32], and its serum levels are elevated in lupus patients and correlate with autoantibody titers [33-34]. Of interest, the levels of serum BLyS increase after B cell depletion therapy with rituximab [35-37].

3.2.1.1. Belimumab (Benlysta): Belimumab is a fully human IgG1 that specifically binds to BLyS, inhibiting BLyS's stimulation of B cell development and restoring apoptosis in autoantibody-secreting B cells. After phase I trials that showed tolerability, immunogenicity, and pharmacology of belimumab in mild to moderate SLE patients (ClinicalTrials.gov Identifier: NCT00657007), phase II studies failed to meet their endpoints (ClinicalTrials.gov Identifier: NCT00071487). However, as these studies showed an improvement in SLE disease activity measures and serological improvement in serologically active patients [38], to further address the long term efficacy and safety of belimumab in SLE patients, two phase III double-blind, placebo controlled, multi-center superiority trials were initiated in seropositive patients (ClinicalTrials.gov Identifier: NCT00424476; NCT00410384). The two studies, which represent the largest clinical trial programs ever conducted in SLE, had similar design but a difference of duration therapy and location/recruitment sites: 52 weeks with 865 patients at 90 clinical sites in Asia, South America and Eastern Europe for “BLISS-52”, and 76 weeks with 826 patients at 133 clinical sites in North America and Europe for “BLISS-76”. The primary efficacy endpoint were based on the new SLE Responder Index, which takes into account a reduction from baseline of SELENA SLEDAI and BILAG scores and the physician global assessment, these parameters being analyzed on intention-to-treat (ITT) adjusted for baseline stratification factors including the SELENA SLEDAI score, proteinuria and race. In each of the two trials, patients were randomized to two doses of belimumab (1mg/kg and 10 mg/kg) and received the biologic agent i.v. on day 0, 14, 28, and then every 28 day for the entire duration of the study, together with standard care therapy. Overall, a statistically significant improvement versus the placebo group was observed in both trials at the 52 weeks time point. There was a delay of the time to first flare, a reduction of disease activity, reduced need for steroid use, and reduced fatigue and better quality of life for the SLE patients treated with belimumab [39]. The results at 76 weeks from the BLISS-76 study showed higher response rates compared with placebo plus standard of care; however, this secondary endpoint did not reach statistical significance [40].

3.2.1.2. A-623: A-623 is a fusion polypeptide consisting of a BLyS binding domain fused to the N-terminus of the Fc region of a human antibody. A-623 binds to BLyS and inhibits the interaction of BLyS with its receptors. Based on the positive results in phase Ia and Ib clinical studies, a phase IIb clinical study using subcutaneous administration of A-623 or placebo plus standard of care is currently enrolling serologically active lupus patients.

3.2.2. Briobacept (BR3-Fc)—Briobacept is a homodimeric recombinant fusion glycoprotein of the extracellular ligand-binding portion of BAFF-R and the Fc portion of an IgG1. It blocks circulating BLyS, thus inhibiting B cell activation and promoting B cell apoptosis. Preclinical studies showed effectiveness of briobacept in reducing B cells *in vivo* [41], which was confirmed by the finding of a 55% reduction in peripheral B cells in clinical trials in RA patients. While preliminary, these data suggest possible therapeutic activities of briobacept in SLE.

3.2.3. A Proliferation-Inducing Ligand (APRIL)—APRIL, also known as TALL-2, TRDL-1 and TNFSF13A, is another member of the TNF-ligand superfamily that, unlike BLyS, only functions as a soluble factor. APRIL binds to BCMA and TACI, but not to BAFF-R. Although APRIL alone has little effects on B cells, together with BLyS can form circulating BLyS/APRIL heterotrimers (BAHTS) with BLyS-like activity [42].

3.2.4. Atacicept—Atacicept is a recombinant fusion protein made of the extracellular portion of TACI fused to the Fc of a human IgG. It blocks the activation of TACI by APRIL and BLyS. The efficacy and safety of atacicept in combination with mycophenolate mofetil to treat lupus nephritis has been evaluated in a randomized, double-blind, placebo-controlled phase II/III trial with primary outcome measures an improvement in renal response to treatment at 52 weeks (ClinicalTrials.gov Identifier: NCT00573157). Another phase II/III trial in generalized SLE that evaluates the use and effective dose of atacicept compared to placebo in reducing numbers of flares in SLE patients is ongoing (ClinicalTrials.gov Identifier: NCT00624338).

5. Expert Opinion

In certain autoimmune diseases, the use of biologics is providing an enormous contribution to disease stabilization and the prevention of complications. Compared to the use of biologics in RA, the use of biologics in SLE has been slower, likely due to the differences in the pathogenesis of the two diseases and the inter-individual variety of manifestations and therapeutic needs in SLE patients.

Despite the relative novelty in the use of biologics in SLE, the field is showing promise, and new investigations are fueled by the encouraging results from recent clinical trials. The hope is to possibly find new drugs that can be partly devoid of the significant side effects that characterize the use of immunosuppressive drugs - widely used in the disease management - while providing effectiveness in inducing disease remission or in reducing disease activity. More specificity of action, a targeted use, and improved efficacy, are the major goals expected for new drugs that might be approved for the treatment of SLE in a near future.

Another consideration is that the critical evaluation of the failures of past clinical trials has been somehow instrumental in improving the design of newer trials. One example is the selection of seropositive SLE patients in the benlysta phase III trials after the negative results of the phase II studies.

Additional aspects improving trial design have included and will include the use of better instruments for the measurement of outcomes, better selection of endpoints, pre-identification of possible responders and subsetting of patients with common characteristics, choice of

disease status and duration at enrollment, organ involvement, concomitant therapy, and possibly even consideration on the genetic backgrounds. Timing of response, bioavailability and duration of effects, in addition to best dosing to avoid side effects, should be the additional parameters to take into account. Statistical power has also frequently been a problem due to the clinical diversity of SLE patients, and trials with large numbers of patients may be required to obtain meaningful information. Ultimately, the goal is to find new targeted effective therapies in SLE that may allow a better clinical management, a more favorable prognosis, and an improved quality of life for SLE patients.

Highlights box

- B cells are major targets in the design of new approaches for a better management and therapy of SLE because they produce pathogenic autoantibodies that are implicated in the development of tissue and organ damage.
- Several surface markers expressed by B cells at different stages of their differentiation have been targeted in clinical trials for the modulation of B cell activity in the disease.
- The blockade of B-lymphocyte stimulator (BLyS) in recent clinical trials seems at present to be the most effective novel B cell-targeted approach capable to reduce clinical disease activity in certain subgroups of SLE patients.

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