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# B cells in SLE: Different biological drugs for different pathogenic mechanisms

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**Abstract**

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by a complex multi-factorial pathogenesis and a great clinical polymorphism. SLE is considered to be a B cell disease in which autoantibodies are the major players. Recently, the central role of B cells has been confirmed and it has been shown that that the relative frequency of B cells subsets is altered in SLE patients. Conventional immunosuppressive therapies such as azathioprine, cyclophosphamide or methotrexate, reduce disease activity and improves the patient's general health conditions. These treatments have possible side effects; in fact they could compromise liver function, fertility and innate and adaptive immune responses. Moreover, for unknown reasons a small group of SLE patients is refractory to immunosuppressive therapy. In these cases finding an effective treatment becomes a challenge. The progress in therapeutic antibody technology has led to the production of a wide array of humanized monoclonal antibodies, targeting specific cell types or pathways, initiating a new era in the treatment of autoimmune disorders. In contrast to general immuno-suppression, the availability of drugs interfering with specific pathogenetic pathways gives the possibility to choose therapies tailored to each disease in each patient.


*Keywords:* SLE; B cells; Autoantibodies; Biologic drugs

**Contents**



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## 1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease of unknown aetiology characterized by the presence of several autoantibodies and by the anatomical and functional damage of multiple organs. B cells play a central role in the pathogenesis of SLE.

Little is known about the frequency of the different B cell subsets in the peripheral blood of SLE patients and whether alteration of these subsets might relate to disease onset and progression.

Standard therapeutic strategies, commonly using corticosteroids and immunosuppressive drugs such as azathioprine (AZA), cyclophosphamide (CyC) or methotrexate (MTX), aim at the reduction of disease activity and improvement of the patient's general conditions.

Recently, the advances in antibody technology and identification of factors and pathways initiating and maintaining autoimmune disorders allowed the generation of a variety of novel molecules: humanized monoclonal antibodies, fusion proteins with antagonistic function and peptibodies, the "so called" biologic drugs. These molecules are designed to target different B cell subsets and/or signalling pathways involved in B-cell activation and in the inflammatory cascade, thus hopefully sparing patients from the side effects due to generalised immunosuppression (Table 1).

## 2. Altered B cell subset in SLE

The main function of B cells is to produce antibodies normally specific for pathogens (non-self) and in autoimmune diseases for self-antigens. Antibodies directed against several cellular molecules and structures are a hallmark of SLE, which is therefore considered a B-cell disease. An additional important role for B cells has been recently demonstrated in a mouse model for SLE. It has been shown that the disease does not develop in mice lacking B cells, but still occurs in animals with an intact B-cell compartment, but unable to secrete antibodies [1,2]. Thus, B cells may have an antibody-independent role in the pathogenesis of SLE, supposedly related to their antigen presenting function or cytokine production.

Over the last few years many studies have reported alterations of the relative frequency of peripheral blood B cell subsets in SLE patients. How these alterations relate to the disease is still a matter of debate [3,4].

In the absence of therapy and independently from disease activity, SLE patients may have a strong lymphopenia or, viceversa, normal or even increased lymphocyte counts.

In the peripheral blood it is possible to identify four different populations of B cells: mature-naive, IgM memory, switched memory and transitional B cells [5]. This last subset, corresponding to recent bone marrow emigrants, is increased in most of the patients [6] and our own results. Circulating plasma cells are virtually undetectable in healthy controls, but can be found in patients with active disease.

B lymphocyte stimulator (BLyS) protein (also known as BAFF, TALL-1, THANK, TNFSF13B, and zTNF4) is a member of the tumour necrosis factor (TNF) ligand superfamily. It binds with high affinity to BAFF-R expressed by all B-cell subsets. BAFF and its receptors were initially described in the mouse. It was demonstrated that the BAFF pathway is important in B cells development, survival and function [7]. BAFF over expression leads to the expansion of immature transitional type II B cells (T2) in the spleen, polyclonal hypergammaglobulinemia with increased numbers of

Table 1
Predominant B cell abnormalities in SLE and relative biological drugs

| B cell abnormalities | Pathogenic mechanism | Biologic therapy | Molecular target | Current status |
|---|---|---|---|---|
| Loss of tolerance, hyperactivity | Generation of autoreactive B cells | Anti BLyS | BLyS | Phase II |
| | | AMG 623 | BLyS | Phase I |
| | | Anti-BR3 | BLyS | Phase I |
| | | TACI-Ig | BLyS/APRIL | Phase II/III |
| | | Anti CD20 | CD20 | Phase III |
| | | Anti CD22 | CD22 | Phase III |
| Autoantibody | Immune complex Citolysis of antigen-positive cells | Tolerogens (LJP394) | Anti-DNA antibodies | Phase III |
| Autoantigen presentation to T cells | Activated autoreactive T cells | CTLA4Ig | CD28/B7 | Phase I |
| | | Anti CD40L | CD40/CD40L | Preclinical |
| Increased cytokine production | Cytokine mediated persistent inflammation and B cell activation | Anti IL6R | IL6 | Preclinical |
| | | Anti IL10 | IL10 | Phase I |
| | | Anti IFNα | Type I interferon | Preclinical |

plasma cells and increased levels of several autoantibodies (including anti-double-stranded DNA). Aged transgenic mice present with a lupus-like disease with circulating immune complexes and kidney Ig deposition [8]. On the basis of these observations it has been proposed that BAFF plays a role not only in the survival of immature T2 B cells [9], but also in the pathogenesis of SLE. Several studies have measured the concentration of BAFF in human autoimmune diseases and found increased BAFF in not only SLE, but also in Rheumatoid Arthritis, Multiple Sclerosis and Sjogren syndrome [10]. Because SLE patients have an increase frequency of transitional B cells and plasma cells, it has been supposed that BAFF might be a good therapeutical target in this disease; actually a fully human anti-human BAFF monoclonal antibody that neutralizes the activity of BAFF protein (Belimumab, Lympho-Stat-B) was used in a phase clinical I trial in SLE patients ($n=70$). Patients were randomized to receive 1, 4, 10, or 20 mg/kg versus placebo with a single intravenous (IV) dose or 2 infusions 21 days apart. This treatment was well tolerated, but showed modest clinical effects: peripheral blood $CD20^{pos}$ B-cell counts dropped by 12–47% without any change in anti-dsDNA antibody concentration or disease activity [11,12]. In the meantime other molecules were generated to target the BAFF pathway and are strong candidates to be used in clinical trials for SLE, for example, the fusion proteins TACI–Ig and BR3–Fc and the "peptibody" AMG623 all functioning as BAFF antagonists [13]. Importantly, TACI (that probably acts as a negative regulator of B cell) binds also a BAFF related ligand called APRIL, increased in some autoimmune disorders [14]. The role that each of these molecules might play in disease is not fully understood. Because TACI–Ig [15] is able to neutralize both BAFF and APRIL, the use of this molecule might have a higher clinical efficiency than the anti-BAFF Belimumab alone.

## 3. Lack of B cell tolerance/altered B cell selection

In the last years a developing awareness of the central role of B-lymphocytes in SLE has brought to the hypothesis that the disease may be caused by failure of tolerance induction. The induction of tolerance is necessary to purge the peripheral repertoire of dangerous specificities, that arise by the random rearrangement of heavy and light chain immunoglobulin genes and by the unrestrained assembly of their products. The elimination of these specificities occurs by negative selection, a phenomenon has is thought to occur during the early phases of B cell development in the bone marrow and in the periphery when transitional B cells differentiate in mature/memory. Negative selection occurs by the forced replacement of the light chain (editing) [16] or by the induction of cell death (clonal deletion) [17]. Generation of auto-reactive B cells in SLE can be a consequence of a failure of negative selection in the bone marrow. Thus, several attempts have been done with the idea of removing all autoreactive cells and their precursors and "resetting" the system. Hematopoietic stem cell transplantation has been recognised as a potential treatment in SLE patients that failed to respond to conventional therapy. After a series of unsuccessful allogenic transplantations [18], autologous donor cells reconstitution has been implemented. Although, with different modalities of BM ablation, the latter has given encouraging clinical results, but further studies are needed to support its use as a common therapeutic approach for SLE [19].

Another strategy is the induction of a massive B cell depletion by directly targeting surface molecules only expressed by B cells. One candidate target is the CD20 molecule. CD20 is a 33- to 37-kDa non-glycosylated tetraspan phosphoprotein calcium-channel that is expressed in all B cells, with the exception of pro-B in the BM and plasma cells. Rituximab (RTX) is an anti-CD20 humanized mAb that causes B cell depletion by at least three mechanisms: antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity and apoptosis. Rituximab was successfully used in non-Hodgkin B cell lymphoma before its introduction in the therapy of autoimmune disorders.

The first data showing the efficacy of RTX treatment in patients with SLE comes from open label trials published by Looney at al in 2002 [20]. In this Phase I/II trial 18 patients with clinically active non-organ-involving SLE were treated with a low (100 mg/m2), medium (375 mg/m2) and full dosage (4 weekly doses of 375 mg/m2). All patients showed a significant peripheral B cell depletion that correlated with the reduction of disease activity, but without significant changes in anti-dsDNA antibody levels [21]. Moreover, several groups have treated patients with lupus nephritis refractory to CyC, with a combination of CyC and RTX obtaining very promising results. In one of these studies, renal biopsy performed before and after the therapy, revealed an improvement in 5/5 cases of active nephritis. Also, Sfikakis and colleagues documented a successful renal response in 8/10 (5/10 complete remission) patients with proliferative lupus nephritis [22]. Efficacy of RTX therapy in SLE patients with compromised central nervous system has also been evaluated. Its use as monotherapy or in combination with CyC resulted in clinical improvement in 72% of 22

patients. In the remaining 28% the disease progressed or remained stable [23].

CD22 is a 135-kDa B-lymphocyte restricted type-I transmembrane sialoglycoprotein of the immunoglobulin (Ig) superfamily. It is first detectable at low levels in immature B cells, its strongly expressed on mature B cells and absent in plasma cells. In mouse, lack of CD22 expression has been shown to decrease the threshold of BCR reactivity and thus potentially increase BCR dependent B cell activation and antibody production. CD22, therefore, appeared to be a good candidate as a target of therapy in B-cell dependent autoimmune disorders. Epratuzumab (hLL2) is a humanized IgG1 monoclonal antibody against CD22 antigen that has been recently tested in an open-label, pilot study of 14 active SLE patients. Epratuzumab showed to be safe and effective. It gave very promising results: the majority of patients treated during phaseI/II trial experienced a 50% improvement in the BILAG (British Isles Lupus Assessment Group) score and a phase III lupus trial is ongoing [24].

## 4. T-B cell crosstalk and SLE

In humans, high-affinity antibodies are generated through an extensive process of hypermutation and affinity maturation that takes place in specialised structures called germinal centers (GC). GC are composed of follicular dendritic cells, B and T cells that come together in response to foreign antigens and results on the generation of high affinity class-switched memory B cells and plasma cells [25]. In autoimmune disorders the GC develops against self-antigens and generates memory B-cells expressing an autoreactive BCR repertoire. As this repertoire is probably already established at the time when the disease is diagnosed, targeting the germinal center in SLE has been taken with certain scepticism. However, as we still don't know whether GC are required for the continuous supply of auto-reactive plasma cells, antibodies targeting co-stimulatory signalling pathways able to interfere with T-B cell interactions have been launched in SLE clinical trials [26].

B cells, binding through CD40 to CD154 (CD40L) on T cells receive one of the most important co-stimulatory signals resulting in activation, proliferation, and Ig class switching in the germinal centre environment. Anti-CD40L monoclonal antibody (Biogen Hu5c9 antibody) has been used in two designed studies on SLE patients with and without renal involvement. Despite the encouraging results, improvement of renal function and reduction in circulating autoantibodies, the trial had to be abandoned because all patients suffered of life threatening thrombotic episodes. These vascular side effects were most probably due to the binding of the Biogen Hu5c9 antibody to platelets leading to massive aggregation [27–29].

Another co-stimulatory axis is composed of CD28, expressed by T cells, and B7 ligands on activated B cells. The interaction results in T cell activation, proliferation and up-regulation of. CTLA-4 (cytotoxic T-lymphocyte-associated protein 4). CTLA4 binds to B7 with higher affinity than CD28 and switches-off the activation signals delivered through the T-cell receptor.

CTLA4Ig is a recombinant fusion protein composed of an extracellular domain of CTLA and a constant region human immunoglobulin (Abatacept, Orencia; Bristol-Myers Squibb). Abatacept has been used with success in rheumatoid arthritis (RA) [30] and psoriasis and is currently being tested, associated with CyC, in a preliminary trial in SLE patients.

## 5. Cytokine therapy

Recently, it became apparent that the cytokine milieu is important in triggering and sustaining autoimmune disorders. In fact, in SLE patients levels of circulating type I interferon (IFN-α), IL-6 and IL-10 are increased. The exacerbated production of these inflammatory cytokines is the result of the abnormal activation of plasmacytoid dendritic cells [31]. IFN-α can be involved in the pathogenesis of lupus in multiple ways [32]. It triggers the maturation of myeloid dendritic cells thereby enhancing the adaptive immune response, and, in combination with CD40, induces plasmablast differentiation. IL-6 is thought to be indispensable for the final differentiation of plasmablasts to plasma cells [33,34]. Waiting for an approved IFN-blocking therapy, anti-IL-6 antibodies have been used in mouse models in which induced experimental nephritis could be delayed by IL-6 blockade. An anti-IL6R monoclonal antibody (Tocilizumab) has been approved for use in a human phase I clinical trial. The role of IL-10 in SLE pathogenesis is not very clear [35]. IL-10 is considered a regulatory/tolerogenic cytokine, because it inhibits monocyte and dendritic cell pro-inflammatory function and promotes the differentiation of regulatory T cells (Treg). In B cells it induces activation, differentiation and antibody production. In SLE patients the concentration of IL-10 correlates with disease activity. Ronnelid et al have showed that immune complexes isolated from SLE patients are able to induce IL-10 production in PBMC from healthy donors suggesting the involvement of IL-10 in the vicious cycle that maintain B cell hyperactivity and antibody secretion [36].

A murine anti-IL-10 monoclonal antibody has been used in a pilot trial involving 6 SLE patients. After three weeks of daily treatment 5/6 patients showed skin and joint improvement and at 6 months disease activity was strongly reduced (as measured with SLEDAI score). At the end of the follow-up all patients had developed antibodies against the murine MoAb but no significant side effects were reported [37].

## 6. Targeting autoantibodies

In SLE, like in several other autoimmune diseases, autoantibodies may be detectable in the serum many years before the onset of the clinical manifestations. It has been hypothesized that the first clinical symptoms appear either when the concentration of autoantibodies exceeds a certain threshold or when highly pathogenic specificities are produced. We know that not all autoantibodies are equal. In the mouse autoantibodies such as anti-Ro, anti-b2-glycoprotein I, anti-erythrocytes and anti-platelets have shown to be pathogenic once passively transferred through the placenta or injected in adult animals. Autoantibodies in immune complexes are responsible for the general activation of the inflammatory cascade not only via complement but also stimulating Toll-like receptors pathway.

Tolerogens by definition are synthetic agents that deplete or inactivate autoreactive B cells by binding to- and cross-linking autoantibodies. The tolerogen, LJP394, is a scaffold of a polyethylene glycol platform with attached DNA that selectively clears DNA-reactive autoantibodies in SLE. They form soluble complexes with the autoantibodies without activating the complement cascade, thus preventing renal damage. LJP394 (Abetimus sodium, Riquent) was introduced in 1994 in human trials. The successful results obtained in some of the first 13 trials were confirmed with an enlarged phase III study. The treatment with Abetimus of SLE patients with lupus nephritis and elevated dsDNA antibodies resulted in sustained and significant decrease in anti-dsDNA antibody levels, reduced incidence of renal flares and improvement of health-related quality of life. In a group of lupus nephritis patients the reduction in anti-dsDNA levels was transient and no significant clinical benefits were observed [38].

## 7. Conclusions and perspectives

Therapy for lupus disease could be greatly improved by the use of 'biologic' drugs in combination with the traditional immunosuppressants, specially in patients refractory to monotherapy. Few studies have given encouraging result, but larger clinical trials are needed in order to have a clear picture of the balance benefits/risks. Although biologic drugs represent an enormous step forward in the treatment of autoimmune disorders, we are still far from being able to target only auto-aggressive B-cells. As consequence the risk of infection is always present and has to be considered before any therapy.

Humanized antibodies became very fashionable and wildly used, but one should keep in mind that these molecules have two serious drawbacks. First, chimeric antibodies contain a foreign component and such can be immunogenic [39]. Second, the potential pathogenic B cells that do not express the receptors or express it at low levels are not affected by the antibody treatment.

### Take-home messages

- B cells have a pivotal role in SLE. Animal models and human studies recently identified multiple abnormalities in the B cell physiology (altered frequency of B cell subsets, break of B cell tolerance and hyperreactivity) in SLE, providing the rationale to introduce B cell targeted biologic drugs in therapeutical regimens.
- The safety and efficacy of Rituximab, Epratuzumab, Riquent and TACI–Ig usage in SLE has been demonstrated during the first clinical trials. Many other molecules are included in pre-clinical studies, after the successful results obtained in mouse models and primate.
- Despite the encouraging results obtained with biologic drugs, a category of SLE patients remain unresponsive to all treatments. For these patients we can envisage a combined regimen including either immunosuppression and biologic drugs or a combination of biologic drugs targeting distinct branches of B cell physiology.

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