Is B Cell-Targeted Therapy Effective in Systemic Lupus Erythematosus?

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ABSTRACT: In the past decade we have witnessed a dramatic change in the management of autoimmune diseases, such as rheumatoid arthritis, due to the development of new biologic drugs designed to target key mediators in the autoimmune process. However, the development of similar target-specific drugs for the management of SLE has not been as successful. The B cell has long been considered central to the pathogenesis of SLE and has been regarded as an important target for biologic drugs. Several B cell-targeted drugs have been developed and although the mechanisms seem promising, most of the studies published to date have failed to achieve their primary endpoints, leading to an ongoing debate regarding the role of B cell therapy in SLE. The present report discusses the pros and cons of B cell-targeted therapy in SLE, reviews the clinical studies, and offers possible explanations for the discrepancies between randomized control studies and real-life experience.

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Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease affecting predominantly young women of childbearing age. Disease manifestations range from a mild disease involving one or two systems to a multisystem, severe and sometimes life-threatening disease. In managing this condition the chief goals are to control active disease, achieve remission, and prevent irreversible organ damage while avoiding drug-induced side effects.

The only drugs approved by the Food and Drug Administration (FDA) for SLE since 1955 are hydroxychloroquine and corticosteroids, although multiple immunosuppressant drugs – methotrexate, azathioprine, mycophenolate mofetil (MMF), cyclosporine and cyclophosphamide (CYC) – have been used over the years to control the severe manifestations. These drugs lead to generalized immunosuppression, with multiple adverse effects including predisposition to infection, malignancy and infertility. Moreover, they are not universally effective, with partial or no response in many cases. In view of this poor benefit-risk profile, new drugs have recently been developed to target specific immune cells or cytokines thought to be central to the disease pathogenesis with the aim of achieving better control of the disease with fewer side effects.

B cells have a central role in the pathogenesis of SLE and exert multiple effects. B cells not only produce pathogenic autoantibodies but have additional pivotal roles in the autoimmune process: they act as antigen-presenting cells, provide co-stimulatory signals for T cell activation and differentiation, secrete and respond to cytokines, link innate and acquired immunity by Toll-like receptors, affect follicular dendritic cell differentiation, and help shape the architecture of peripheral lymphoid organs. Alteration of these B cell functions may lead to breach of tolerance and autoimmune disease. Loss of B cell tolerance occurs very early in SLE, as shown by Arbuckle et al. [1] who looked at serum samples from the U.S. Defense Serum Repository and found that autoantibodies are typically present many years before the onset of SLE while patients are still asymptomatic. Subsets of B cells are altered in SLE with an increase in transitional B cells, memory cells and plasma cells and an increase in a subset of autoreactive B cells (9G4+) in blood and peripheral lymphoid organs. Autoreactive B cells lead to development of autoreactive memory B cells and plasma cells.

B cells seem to play an important role in the pathogenesis of SLE, but no B cell-depleting therapy in RCTs has achieved a satisfactory therapeutic effect in this disease

Indeed belimumab, the first FDA-approved drug for the treatment of SLE in more than 50 years, is a B cell-targeted therapy. There is currently an ongoing debate regarding the role of B cell-targeted therapy in SLE due to the modest effect of belimumab in two large phase III randomized control trials (RCT) in contrast to the seemingly dramatic effect of B cell depletion therapy with rituximab in open-label studies, while rituximab failed to show a significant effect in two randomized control studies.

This review will discuss the pros and cons of B cell-targeted therapy in SLE, review the clinical studies and reports,

and offer possible explanations for the discrepancies between studies and real-life experience.

MECHANISMS OF B CELL TARGETING

Several mechanisms of B cell targeting have been studied to date, including inactivation of autoreactive B cells via tolerance induction, B cell depletion using monoclonal antibodies that bind B cell surface antigens, blockade of B cell survival factors, and blockade of co-stimulatory signals.

Although the mechanisms of action of these drugs are promising, all these drugs except for belimumab have failed to show clinical benefit [2]. This might be due to the complex effects and counter-effects of the multiple arms of the immune system and/or to flaws in study design, which will be discussed.

• INDUCTION OF TOLERANCE

To date, induction of tolerance has been attempted with two drugs, abetimus and edratide, but they have not achieved their primary endpoints in their respective clinical studies. Abetimus is composed of four identical strands of dsDNA, covalently linked to a small molecule platform that cross-links B cell receptors (BCRs) leading to anergy or deletion of autoreactive B cells. The drug rapidly reduces anti-double-stranded DNA (anti-dsDNA) antibody levels by formation and clearance of drug-antibody complexes. In view of the important role of anti-dsDNA antibodies in the pathogenesis of lupus nephritis, abetimus was studied as a possible agent to prevent renal flares. However, two pivotal trials (phase II and III, n=317) with a large number of lupus nephritis patients did not demonstrate a significant prolongation in time until renal flare. There were no significant side effects [3]. Edratide is a designed peptide (hCDR1) based on the sequence of the complementarity-determining region (CDR)1 of a human anti-DNA monoclonal antibody that bears the major idiotype 16/6Id. hCDR1 was shown to ameliorate the serological and clinical manifestations of induced or spontaneously developed lupus in mice. The beneficial effects of hCDR1 were associated with the down-regulation of pathogenic cytokines: interleukin-1beta (IL-1β), interferon-gamma (IFNγ) and IL-10, and the up-regulation of the immunosuppressive cytokine transforming growth factor-beta (TGFβ). Treatment with hCDR1 significantly reduced production of the B cell stimulator (BLyS) in lupus-prone mice, reduced T cell apoptosis and induced CD4+CD25+Foxp3+ regulatory cells [4]. However, a phase II randomized, double-blind, placebo-controlled, multiple-dose study to assess the efficacy and safety of edratide in SLE did not meet its primary endpoint.

• B CELL DEPLETION

► Rituximab

B cell depletion with rituximab (RTX) is currently approved for the treatment of rheumatoid arthritis and antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis [5-7]. Given the central role of B cells in SLE, B cell depletion seems an attractive mechanism for the management of SLE as well. Indeed, open-label uncontrolled studies have reported a beneficial effect of RTX in more than 400 patients worldwide. The majority of patients were refractory to multiple immunosuppressants including CYC. The major manifestations treated successfully with RTX include nephritis, severe thrombocytopenia and hemolytic anemia, severe central nervous system (CNS) manifestations, and severe skin disease. A retrospective 7 year analysis of the first 50 patients with refractory SLE who were treated at University College London reported the 6 month clinical outcome as well as the long-term safety profile [8]. Of the 45 patients available for follow-up at 6 months, 19 (42%) achieved remission, and 21 (47%) reached partial remission after one cycle of RTX. B cell depletion resulted in a decrease in median global BILAG scores from 12 to 5 ($P < 0.0001$) and median anti-dsDNA antibody titers from 106 to 42 IU/ml ($P < 0.0001$), and an increase in the median C3 level from 0.81 to 0.95 mg/L ($P < 0.02$) at 6 months. Five serious adverse events were observed. The authors concluded that RTX is an effective treatment for patients with active SLE whose disease has failed to respond to standard immunosuppressive therapy. Two European registries reported similar results. The French AutoImmunity and Rituximab registry described 136 patients with SLE who were treated with RTX. Overall response, according to the SELENA-SLEDAI score was observed in 71% of the patients.. Efficacy did not differ significantly between patients receiving RTX monotherapy and those receiving concomitant immunosuppressive agents who had higher baseline disease activity. Among responders, 41% experienced a relapse of disease, with a response in 91% after retreatment with RTX [9]. A pooled analysis of the efficacy of RTX from European cohorts diagnosed with biopsy-proven lupus nephropathy (LN) who were treated with RTX yielded 164 patients. RTX was administered in combination with corticosteroids (99%) and immunosuppressive agents in 124 patients (76%) (cyclophosphamide in 58 and mycophenolate in 55). At 6 and 12 months, respectively, response rates were 27% and 30% for complete response (CR), 40% and 37% for partial response (PR) and 33% for no response. Significant improvement in 24 hour proteinuria ($P = 0.006$), serum albumin ($P < 0.001$) and protein/creatinine ratio ($P < 0.001$) at 12 months was observed. The authors concluded that RTX may be an effective option for

Although RCTs designed to assess the efficacy of rituximab in SLE have failed to achieve their primary endpoints, rituximab use has been included in the ACR and EULAR guidelines for the management of patients with refractory lupus nephritis (class III/IV) who have not responded to mycophenolate mofetil and cyclophosphamide

patients with LN, especially those refractory to standard treatment or who experience a new flare after intensive immunosuppressive treatment [10].

When looking at the immunological effects of RTX, clinical response correlates with B cell depletion, is not dependent on serologic response, and may precede decline in autoantibody levels. This observation suggests a beneficial effect on autoantibody-independent functions of B cells. Patients who are serologic responders enjoy a more prolonged clinical response (> 3 years vs. 6 months). RTX reduces anti-dsDNA and antinucleosome antibodies by 30–40% but does not reduce anti-Ro or protective antibodies. Response to treatment is better in extractable nuclear antigen antibody (ENA)-negative patients. These observations suggest that short-lived plasma cells (rapidly proliferating B cell clones) produce anti-dsDNA, anticardiolipin and antinucleosome antibodies which are affected by RTX, as compared to long-lived plasma cells which produce anti-Ro, anti-RNP and protective antibodies and are not affected by B cell depletion with RTX. B cell depletion has the potential to partially restore tolerance. In patients who respond well to RTX and maintain prolonged clinical remission there is a progressive disappearance of lupus-specific antibodies (anti-dsDNA antibodies, 9G4 antibodies), repopulation with an increased number of naïve B cells, and a dramatic and prolonged expansion of transitional B cells – "resetting" the immune system and possibly reinstituting tolerance [11].

Belimumab is the only B cell-targeted therapy found in RCTs to be effective for SLE, leading to an ongoing debate on the role of this treatment as well as on the importance of study design of RCTs in lupus

Despite these promising reports, the two large randomized controlled studies designed to assess the efficacy of RTX in non-renal lupus (EXPLORER) [12] and lupus nephritis (LUNAR) [13] did not achieve their respective primary endpoints. The EXPLORER was a phase II/III RCT and included 257 patients with moderately to severely active extrarenal SLE (≥ 1 BILAG A in > 50% of patients or ≥ 2 BILAG B) despite ongoing immunosuppression. All patients received high dose prednisone on entry (more than 60% received an average dose of 45.9 ± 16.4 mg/day). In addition, the primary endpoints were stringent. A major clinical response required achieving BILAG C in all systems at week 24 without a moderate or severe flare by week 52, and a partial response was defined as a BILAG C in all systems at week 24 and maintaining this for 16 weeks, BILAG B in only one system by week 24 without a new BILAG A or B by week 52.

No differences were observed between placebo and RTX in the primary and secondary efficacy endpoints. However, a beneficial effect of RTX on the primary endpoint was observed in the preplanned subgroup analysis of African Americans and Hispanics. This trial enrolled patients with active SLE and used aggressive background treatment, which could have masked the beneficial effect of the addition of RTX to standard of care therapy. In addition, the definitions of a response were stringent and differed from what might be expected in a real-life setting. A quantifiable immunological effect was seen with the reduction in anti-dsDNA and anticardiolipin antibodies and CD8 memory T cells. An enhanced effect on anti-dsDNA was seen in anti-dsDNA-positive and ENA-negative patients, as well as an increase in complement (in all with anti-dsDNA at baseline) and an increase in platelets in patients with initial low levels [14-16].

The LUNAR trial enrolled 144 patients with active lupus nephritis (class III or IV). All patients were treated with high dose steroids and mycophenolate mofetil and were randomized 1:1 to receive RTX or placebo. The overall (complete and partial) renal response rates were 45.8% among the 72 patients receiving placebo and 56.9% among the 72 patients receiving RTX ($P = 0.18$). The primary endpoint (superior response rate with RTX) was not achieved; however, there were more responders in the RTX group at 12 months (56.9% vs. 45.8%), increased improvement in proteinuria (32% vs .9%), and fewer patients required rescue treatment with CYC (0% vs. 8%). A possible true benefit may have been missed due to the small sample size. In addition, a longer follow-up may have demonstrated a more beneficial effect since the time to true proteinuria remission is 2 years [17]. Similar to the EXPLORER trial, effective background therapy with steroids and MMF was used in both arms. MMF and steroids are effective in a large percentage of patients with LN and their use may have masked the beneficial effect of RTX treatment.

Several explanations for the discrepancies between real-life experience with RTX in SLE and the results of RCTs have been suggested [16]. The majority of patients in uncontrolled studies had severe and sometimes life-threatening disease, refractory to immunosuppressants which were usually not continued, while in the RCTs life-threatening cases were excluded and all cases received background immunosuppression. The endpoints in RCTs are stringent and any changes in corticosteroid or immunosuppressive doses would be considered non-responders, while in real life dose adjustments are common. In addition, RCTs used high dose steroids which may mask a beneficial effect, whereas in the real-life setting concomitant use of high dose steroids is uncommon. The possible synergistic effect of a combination of CYC and RTX as used in real-life refractory cases has not been assessed in RCTs. RCTs set predefined endpoints and do not assess long-term benefits, which may be especially relevant when assessing the effects on lupus nephritis.

Indeed, despite the fact that RTX was not shown to be efficacious in lupus nephritis in RCTs, the recent guidelines of both the EULAR and the ACR for the management of LN have recommended the use of RTX in patients with LN refractory to MMF and to CYC based on the real-life experience reports in

refractory cases [18,19]. One could argue that RTX indeed may have a role in refractory cases but not in early cases, such as those enrolled in the RCTs. This argument was recently challenged as well by the promising reports of the beneficial effect of RTX treatment early on in LN, employing a regimen with minimal steroids and MMF [20]. Lightstone and team [20] report the results of their study on the first 50 patients in the rituxilup cohort where patients with LN received two doses of RTX 1000 mg (given 2 weeks apart) accompanied by two doses of intravenous methylprednisolone 500 mg and MMF with no additional steroids. Renal remission was defined as serum creatinine not higher than 15% above baseline; complete remission (CR) was defined as urine protein:creatinine ratio (PCR) < 50 mg/mmol, partial remission (PR) if PCR > 50 mg/mmol but non-nephrotic and > 50% reduction. Ninety percent of patients (45/50) achieved complete or partial remission (CR 72%, persistent PR 18%) [21]. Moreover, Moroni et al. [22] recently reported the first attempt to compare RTX to MMF or CYC as a regimen for remission induction in LN. Although this was a small study of 54 patients, complete remission was achieved in 70.6% of patients on RTX, in 52.9% on MMF, and in 65% on CYC. Partial remission was reached in 29.4% on RTX, 41.2% on MMF, and 25% on CYC. The authors conclude that RTX seemed to be at least as effective as MMF and CYC pulses in inducing remission, especially when considering that patients treated with RTX had more negative renal prognostic factors in this study.

► Ocrelizumab

Evaluation of another anti-CD20 antibody, ocrelizumab, a humanized rather than a chimeric anti-CD20 antibody, in two phase III studies – the BEGIN and the BELONG that were similar to the EXPLORER and LUNAR – were stopped prematurely due to an increase in infections [16,23].

► Epratuzumab

Epratuzumab is a monoclonal antibody that targets CD22, a B cell-specific surface antigen involved in B cell signaling. The mechanism of action is still not fully defined but data indicate that it selectively modifies B cell activation and function [24]. The first two international randomized controlled trials (ALLEVIATE 1 and 2) evaluating epratuzumab in patients with moderately to severely active SLE were discontinued prematurely because of interruption in drug supply [25]. The results of the EMBLEM study, a phase IIb trial to assess the efficacy and safety of epratuzumab in patients with moderate to severe SLE, were published recently. Epratuzumab led to a modest decrease of about 30% in B cells, without a change in immunoglobulin levels [24]. In this study the proportion of responders was higher in all epratuzumab groups compared with placebo, but the overall treatment effect was not statistically significant [24]. Multicenter phase III studies with epratuzumab in patients with SLE are currently ongoing.

• BLOCKADE OF B CELL SURVIVAL FACTORS

► Belimumab

While the use of RTX has not been approved for the treatment of SLE, another B cell-targeted therapy, belimumab, is the first drug approved for the treatment of SLE in 50 years. Belimumab is a human immunoglobulin (Ig)-G1λ monoclonal antibody that binds soluble B lymphocyte stimulator (BLyS) and inhibits its biologic activities. Elevated BLyS levels correlate with increased SLE disease activity. Belimumab was approved by the FDA in 2011 for the treatment of active SLE (not including severe lupus nephritis or CNS disease) refractory to standard therapy. The efficacy of belimumab was demonstrated in two large RCTs (BLISS 52, BLISS 76) with more than 800 patients in each study. Pooled data showed a beneficial effect in 50.6% of belimumab-treated patients versus 46.2% ($P < 0.0001$) in the placebo arm [26,27]. The large number of participants allowed sufficient power to demonstrate a modest beneficial effect. In addition, the use of a novel composite endpoint, the SLE responder Index (SRI), has allowed the detection of reduction in disease activity without worsening in other organ systems.

These study design issues might explain why RTX, a relatively potent drug with a marked biologic effect and dramatic clinical effects in uncontrolled studies, has not achieved the primary endpoint in RCTs, while belimumab has overcome the hurdles of FDA approval with statistically significant effects in well-designed trials. There are, however, several questions that remain to be clarified regarding the use of belimumab in real-life patients with SLE [28], including the clinical relevance of the modest differences as compared to the placebo arm as well as the possible role of belimumab in the treatment of refractory severe disease and renal or central nervous system lupus. The cost-benefit ratio should be addressed as well.

► Atacicept

Atacicept (TACI-IgG) is a humanized fusion protein that binds BLys and APRIL (a proliferation-inducing ligand) and might be more effective than belimumab in the management of lupus. A phase II/III trial of atacicept in LN was terminated after the enrollment of six patients due to an unexpected decline in serum IgG and the occurrence of serious infections; however, in retrospect these complications may have been due to concomitant treatment with MMF [29]. Results of an RCT of subcutaneous atacicept 75 mg or 150 mg, or placebo twice weekly for 4 weeks, then weekly for 48 weeks in patients with moderate to severe SLE, were recently published. There was no difference between atacicept 75 mg and placebo for flare rate or time to first flare (as defined by BILAG A or B). Analysis of atacicept 150 mg suggested benefit [30].

THE FUTURE OF B CELL-TARGETED THERAPIES IN SLE

Following the failure of RCTs to demonstrate a beneficial effect of B cell depletion with RTX in non-renal lupus and LN,

many questions have been raised regarding this mechanism of intervention:

- Are we depleting both pathogenic and protective B cells, hence not showing benefit?
- RTX depletes short-lived plasma cells but does not affect pathogenic long-lived plasma cells. Could interventions directed against the plasma cell be more effective?
- Could RTX be an effective approach in early SLE and not only in refractory cases?
- Is combination treatment of RTX with CYC synergistic and necessary for a significant beneficial effect?
- Have RCTs failed to show a beneficial effect with RTX due to flaws in study design?

Several points should be addressed in future study designs:

- A large number of patients should be recruited to achieve sufficient statistical power
- A sufficiently long follow-up is needed to detect a beneficial effect: in LN trials a follow-up of at least 2 years is required to detect proteinuria remission and at least 5 years are required to discern differences in maintenance therapies
- Background therapies including corticosteroids and concomitant immunosuppressants need to be at the lowest dose possible to avoid the masking of a beneficial effect. A good example would be the two well-designed RCTs of RTX in the treatment of ANCA-associated vasculitis, where RTX was compared to CYC without additional background immunosuppression and a well-outlined protocol for corticosteroid dose and tapering was used in both arms [6,7]
- Clinically meaningful endpoints are needed to better define response in this heterogenous disease.

Although the use of biologics for the management of patients with SLE has lagged behind the dramatic change in the management of rheumatoid arthritis, significant advances have been made. Better designed future studies, better understanding of immunological disturbances in individual SLE patients at different times in the course of disease, and better definition of protective and pathogenic mechanisms of different B cell populations with possible targeting of selective populations may aid in the development of effective B cell-targeted therapies for the treatment of SLE.

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