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B Cell-Based Treatments in SLE: Past Experience and Current Directions

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Abstract
Purpose of Review B cells have been targeted recently by novel therapeutic approaches in patients with SLE. In this review, we discuss recent data that have emerged on this issue placing special emphasis in studies published during the last 5 years.
Recent Findings Despite the negative results stemming from double-blind placebo-controlled studies, B cell depletion with rituximab is indeed employed worldwide, particularly in standard treatment refractory lupus, with promising results. In addition, positive experience with the approved agent belimumab is steadily increasing. Both regimens have an acceptable safety profile.
Summary Identification of B cells as a therapeutic target in SLE has been so far rewarding, since one such treatment, belimumab, has been the only regulatory authority-approved medication in SLE for over half a century. Focusing specifically on autoreactive instead of non-specifically altering/depleting lupus, B cells may lead to more rational treatment modes.

Keywords Systemic lupus erythematosus · B cells · Rituximab · Belimumab · BLyS

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Introduction

B lymphocytes are a major component of the adaptive immune response. Generated in the bone marrow and following the successful completion of the incompletely understood process of negative selection, the mature circulating B cell pool is largely but by no means completely devoid of autoreactive B cells [1].

B cell stimulation following ligation of antigen to the B cell surface antigen receptor (BCR) may lead to the activation of multiple effector mechanisms. Memory B cells are generated, as well as short- and long-lived plasma cells that secrete antibodies. Memory B cells contribute to the immune response by requiring a lower threshold for reactivation on reencountering their cognate antigen and thereafter rapidly differentiating into plasma cells. Short-lived plasma cells provide a rapid antibody response that may be generated without T cell help. Long-lived plasma cells can be maintained for many years in the bone marrow and hence contribute to both immune memory and maintenance of normal immunoglobulin levels. In addition, T cell activation following interaction with B cells may activate other effector mechanisms besides those of B and plasma cells, such as release of inflammatory cytokines.

Hence, B cells may mediate autoimmune disease among others, by production of autoantibodies (autoAb) or immune complexes via plasma cells, by presenting antigen to T cells leading to T cell-mediated inflammation or by producing cytokines themselves. B cells in SLE are characteristically overactive and over-reactive. They produce dozens of autoAb leading to pathology directly or indirectly. Therefore, B cells have long been considered as a potential target of treatment in patients with SLE.

B Cell Depletion

Anti-CD20 mAb-Based Treatments

CD20 is a 33- to 37-kDa non-glycosylated phosphoprotein expressed on the surface of mature naïve circulating B cells. CD20 is selectively expressed on mature B cells but not on precursors such as stem cells or on the surface of their progeny, such as antibody-secreting plasma cells. Therefore, depletion of CD20+ B cells permits B cell regeneration via precursors and prevents, at least initially, immunoglobulin level reduction. Rituximab (RTX) has been the first chimeric anti-CD20 mAb to be used therapeutically to efficiently deplete B cells. B cell depletion with RTX generally decreases autoAb titers following long-term treatment in most patients; however, autoAb titer changes may only partially explain any clinical response.

The use of RTX in patients with SLE is currently off-label. It has been estimated the off-label administration of RTX in Europe was 0.5–1.5% of all patients with SLE [2]. RTX is currently administered in a small proportion of patients with SLE having treatment refractory high disease activity and/or a significant burden of SLE-related damage. An additional yet equally significant reason for administering RTX in patients with refractory SLE is corticosteroid sparing.

The GRAID registry [3] included 85 patients with SLE with a mean follow-up period of 10 months. Treatment with RTX led to a complete response in 37 patients (46.8%) and a partial response in 27 (34.2%). Infections were reported at a rate of 19.5 per 100 patient-years. Despite the restrictions of a retrospective study, the results support data of other registries suggesting a favorable benefit-risk ratio of RTX in patients refractory to standard treatment.

Data from an Italian multicenter RTX Registry confirmed the efficacy and safety of RTX in 145 SLE patients refractory to standard treatment in clinical practice setting [4]. After the first course of RTX, a favorable response was observed in 85.5%; more specifically, a complete response was recorded in 45.5% of this cohort. Among patients retreated, a response was observed in 84.4% and a complete response in 57.8% of cases. The mean follow-up was 27 months. No severe infusion reactions or deaths were recorded. Hickman et al. supported the efficacy and safety of RTX in 15 patients with SLE [5]. Twelve patients responded by 6 months and six avoided major flares for more than 1 year. A significant steroid-sparing effect was achieved; however, an increased risk of serious infection was seen in two patients among those receiving more than four courses of RTX. Another retrospective observational study was conducted in Colombia [6]. Eighteen patients were included and at that time disease was active with a median Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of 12.5. The mean follow-up in this study was 38 months. At the end of follow-up, SLEDAI score was 0 in 14 patients, 2 in 3 patients, and 4 in 1 patient. The median relapse rate before treatment with RTX was 3 per year decreasing to 0 at the end of follow-up. All patients achieved a remission at the end of the study.

RTX can be considered as an additional potent therapeutic treatment option for patients with SLE and Sjögren's syndrome presenting with refractory thrombocytopenia according to the results of an observational study of 21 patients [7]. The overall response rate to RTX treatment was 80.95% (complete response in 52.38% and a partial response in 28.57%). Significant increases of platelet counts were achieved as early as 1 month after the first RTX infusion. Even though relapses did occur during the first 9 months of treatment, a favorable response was generally maintained for 10 months on average. In this study, two patients died of severe pneumonia and another developed lymphoma, the latter being strikingly unusual.

Repeated cycles of B cell depletion that induce longer B cell depletion are associated with better clinical outcomes according to a retrospective analysis of clinical and serological features of 98 patients with SLE treated with RTX over a 12-year period [8]. Lymphopenia was a factor correlated with longer times to repopulate; however, it was not clear if lymphopenia was due to RTX or to the combined effects of SLE itself plus RTX therapy. In another study, RTX was given to 97 patients with highly active SLE despite treatment with corticosteroids and immunosuppressants. B cell depletion was reported in 78% of the patients shortly after RTX therapy initiation. During the 3.5 years of follow-up, the beneficial effects of RTX were seen in 82% of the retreated patients. Exacerbations were observed in 24.7% of the patients [9]. Focusing again on patients with severe SLE manifestations refractory to standard treatment another retrospective analysis evaluated clinical outcomes and safety of RTX treatment in 115 patients seen over 14 years that received a total of 224 infusions [10•]. A complete response was reported in 40% and a partial response in 27% while 80.4% of them remained free of adverse events.

Efficacy and safety of long-term RTX has also been supported by our own ongoing study regarding renal as well as extra-renal manifestations of SLE in 30 patients refractory to standard treatment [11].

RTX in Lupus Nephritis

According to both the ACR the EULAR/ERA-EDTA recommendations for the management of lupus nephritis, RTX can be administered as an alternative therapeutic regimen in patients who failed to respond to mycophenolate mofetil (MMF) and/or cyclophosphamide (CYC) [12, 13]. Some of the studies supporting this can be found below.

An observational study compared the efficacy on renal and extra-renal manifestations as well as the toxicity of induction

therapy with RTX alone vs. CYC pulses and vs. MMF in 54 patients with active lupus nephritis [14]. At 12 months, complete remission was achieved in 70.6% of patients on RTX, in 52.9% on MMF, and in 65% on CYC. One should note that patients treated with RTX had more severe disease with more negative renal prognostic factors. Another multi-system SLE open-label phase II trial was conducted in Japan [15]. Twenty-six out of a total of 34 SLE patients (76.5%) responded to RTX at week 53; of these, 16 (47.1%) achieved a complete remission and 10 (29.4%) achieved partial remission. In 17 patients having renal involvement, the median value of urine protein/creatinine ratio decreased from 2.2 at baseline to 0.4 at week 53. RTX was reportedly well tolerated; all adverse events were mild-to-moderate in severity.

Long-term damage attributable to steroids necessitates the employment of steroid-avoiding protocols. Encouraging results were provided by a prospective observational single-center cohort study by Condon et al. [16•]. Fifty patients with lupus nephritis were treated with two doses of RTX (1 g) and methylprednisolone (500 mg) on days 1 and 15 and maintenance treatment with MMF alone, without oral steroids. By 52 weeks, complete response and partial response had been achieved in in 52 and 34%, respectively. Adverse events were infrequent. In this study, the number of patients enrolled (n = 50) even though sizable was rather small in order to extract firm conclusions. Even more, 44% of patients had pure membranous instead of classic proliferative (class IV and/or class III) nephritis. In addition, patients with rapidly progressive glomerulonephritis, as well as other serious lupus manifestations (severe CNS disease), were excluded. Finally, in this single-center trial, there was no control group; therefore, the authors employed results from other, previously published studies evaluating what is now called "standard treatment" in order to compare the results they obtained. Porter et al. reported the outcomes of the RITUXILUP regimen over ≥ 5 years, analyzing data from 42/50 of the initial cohort [17]. A remission, preservation of renal function, and minimal oral steroid use were seen in the great majority of patients over a prolonged period. Relapses were not uncommon and retreatment without oral steroids was generally successful; relapses did not predict poor outcomes, but no response at all, or not achievement of partial response at 6 months did. In contrast to the above, Davies et al. reported a disappointing effect of RTX in crescentic lupus nephritis [18]. It was thought that because there was already evidence of significant renal impairment, RTX treatment did not prevent end-stage renal disease and dialysis.

RTX in Pediatric Lupus

The beneficial effects of RTX were illustrated in an observational study including 50 children with SLE [19]. B cell depletion was thought to contribute to decreased disease activity and steroid burden, although data regarding extra-renal SLE manifestations were inadequate. Efficacy and safety of RTX compared to standard induction therapies have been also evaluated in children with active lupus nephritis by Basu et al. [20]. Complete remission with RTX was seen in 76.5% of cases vs. 41.7% with MMF and 46.7% with CYC. Flare-free post-treatment periods were significantly longer with RTX compared to MMF and CYC (100% for RTX vs. 83% for MMF and 53% for CYC). All treatment arms suffered from minor adverse events; serious adverse events were seen in the CYC group only.

A pilot study [21] demonstrated that systematically administered courses of RTX and CYC over an 18-month period provided sustained relief for patients with childhood onset SLE which was maintained over a 60-month period, minimizing the need for corticosteroids without adding excessive toxicity.

An additional study included 16 children with refractory SLE treated with CYC and RTX [22]. The data showed beneficial therapeutic and steroid-sparing effects of RTX as an adjunctive treatment for both renal and extra-renal manifestations. Although RTX was well tolerated in most patients, it was thought to be associated with various adverse events.

RTX improves disease activity in children with lupus and serious adverse events are infrequent, according to the results of the UK JSLE Cohort Study database [23]. Sixty-three patients received 104 courses of intravenous RTX over a 10-year period. The global BILAG score improved numerically but did not change significantly [pre-RTX = 4.5 (2.0–9.0), post-RTX = 3.0 (2.0–5.0); p = 0.16]. Oral corticosteroid dosages were significantly reduced. Adverse events occurred in 19 (18%) of all courses.

Other RTX-Related Effects in Patients with SLE

RTX may improve the lipid profile of patients with SLE refractory to standard treatment, proposedly by reducing inflammatory activity as demonstrated in a retrospective multicenter, national cohort in Spain [24]. Seventy-nine patients were assessed during 149.3 patient-years. Prior to the treatment, 69% had dyslipidemia. Triglycerides more specifically were reduced at short- and long-term follow-up after RTX treatment.

The long-term (up to 7 years) use of RTX with respect to its steroid-saving capacity and clinical effectiveness has been emphasized by Gracia-Tello et al. [20]. However, limitations of this observational study included the small number of patients, heterogeneity in the maintenance treatment, and necessitation to retreat some patients during the follow-up period. In addition to the above, RTX is emerging as a potential weapon in SLE-associated antiphospholipid syndrome [25, 26].

RTX has been administered successfully in a patient with SLE and recurrent diffuse alveolar hemorrhage [27].

Successful RTX treatment of refractory hemophagocytic lymphohistiocytosis and autoimmune hemolytic anemia associated with SLE has also been reported [28]; this is in agreement with our own unpublished experience. RTX is reportedly highly effective in patients with the so-called rhupus syndrome (lupus and rheumatoid-like arthritis) refractory to conventional therapy [29].

Other CD20-Targeting mAbs

Ofatumumab, a fully humanized monoclonal anti-CD20 antibody, was administered as an alternative B cell depletion treatment in four patients with lupus nephritis with a good initial response to RTX but who had developed side effects [30]. A reduction of proteinuria, but not total normalization, was observed in all four cases and treatment was well tolerated in three patients. Such preliminary findings have been confirmed by Basu in non-lupus-related RTX-resistant nephrotic syndrome [31].

Ocrelizumab is another fully humanized anti-CD20 mAb. The CD20 epitopes binding ocrelizumab and RTX are overlapping. In patients with active lupus nephritis, overall renal response rates with ocrelizumab were numerically but not statistically significantly superior to those with placebo [32]. Patients receiving ocrelizumab had a higher incidence of infections (serious or opportunistic) compared with those receiving placebo plus standard of care; thus, the study was discontinued.

Obinutuzumab is a new-generation glyco-engineered type II anti-CD20 mAb that is at least twofold more efficient than RTX at inducing cytotoxicity and B cell depletion. There is an ongoing randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of obinutuzumab in patients with class III or IV lupus nephritis.

Anti-CD22 mAb

Epratuzumab is a humanized mAb binding to the glycoprotein CD22 of the cell surface of mature B cells. CD22 plays an inhibitory role in BCR-initiated B cell activation. Both ALLEVIATE studies evaluating efficacy and safety of epratuzumab were interrupted prematurely due to discontinuation of the drug supply [33]. Nevertheless, the initial efficacy and safety profile of epratuzumab supports its continued development for SLE therapy. Most endpoints in these analyses [34] did not achieve statistical significance, but primary efficacy and safety results were not disappointing. Open-label epratuzumab treatment was well tolerated for up to 2 years and was associated with sustained improvements in disease activity along with a reduction of corticosteroid dosages [35]. However, this was an under-controlled study because no comparisons were available with patients receiving standard SLE therapy alone. Encouraging results were also demonstrated in a randomized study in Japanese patients [36]. On the contrary, in another study including patients with moderate or severe SLE, treatment with epratuzumab plus standard therapy was not superior to the placebo plus standard therapy group [37]. A placebo-controlled phase IIb trial was conducted aiming to identify the efficacy and safety of epratuzumab in SLE patients with moderate or severe disease; the overall response rate was not significant [38].

Inhibition of B Cell Survival

Belimumab

The cytokine B cell activating factor (BAFF)/B cell stimulator (BLyS) modulates B cell survival and maturation and is a member of the tumor necrosis factor superfamily. It is produced and secreted by dendritic cells, neutrophils, macrophages, and monocytes. BLyS is present in soluble as well as in membrane-bound form, the soluble form being biologically active. Three types of BLyS receptors are expressed on the B cells: BLyS receptor 3 (BR3 or BAFF3), transmembrane activator and calcium modulator and cyclophylin ligand interactor (TACI), and B cell maturation antigen (BCMA). The interaction of BLyS with BR3 is the strongest. Such BLyS-BR3 interaction promotes the survival of B cells (including the autoreactive B cell population) by preventing their negative selection and apoptosis. The levels of BLyS (found elevated in patients with active lupus) correlate positively with the anti-dsDNA antibody titers. Belimumab, the only drug that has been approved for patients with SLE through randomized controlled trials, is a fully human IgG1λ recombinant mAb directed against BLyS. Specific binding of belimumab with soluble BLyS prevents the interaction of BLyS with its three receptors and finally decreases B cell survival and hence production of autoAb.

Several pooled analyses from the BLISS trials have been performed to detect the treatment effects in more detail. The clinically meaningful improvements in health-related quality of life of patients treated with belimumab and standard therapy are consistent with the reductions in disease activity observed in BLISS-52 and BLISS-76 trials [39]. Additionally, safety data that were pooled and analyzed from one phase 2 and two phase 3 double-blind, placebo-controlled support the conclusion that belimumab was generally well tolerated [40].

According to the results of a pooled analysis from phase III belimumab trials, more patients in the belimumab group had reductions in oral corticosteroid dosages and fewer had increases compared with the placebo groups [41].

The SRI response in patients with active, autoAb-positive SLE was associated with improvements in clinical, laboratory, and patient-reported outcome measures, indicating that the SRI response was associated with a global benefit [42].

More responders than non-responders achieved a ≥ 4-point reduction in their SELENA-SLEDAI scores (3.8% of non-responders vs. 100% of responders; $p < 0.001$), while a reduction of ≥ 7 occurred in 40.3% of responders vs. 1.3% of non-responders.

Data from BLISS-52 and BLISS-76 were pooled post hoc in an effort to identify patients at increased risk of flares [43]. A univariate logistic regression analysis model was employed to identify factors predictive of high circulating BLyS (≥ 2 ng/mL), a factor already known to be correlated with an increased risk of flares. Monitoring factors including positive anti-Smith, low C3, anti-dsDNA ≥ 80 IU/mL, immunosuppressive regimen, proteinuria, elevated CRP, and low total lymphocyte count could identify patients with BLyS ≥ 2 ng/mL who have an increased risk of flare. Such patients are thought to potentially benefit more with belimumab. Pooled data were examined from two open-label studies that enrolled patients who had completed the BLISS-52 or BLISS-76 studies [44]. Patients with SLE treated with a long-term belimumab regimen plus standard of care had a low incidence of organ damage accrual, including those patients of high-risk with pre-existing organ damage. A serious limitation of this study was the lack of a placebo group.

A post hoc analysis from the BLISS trials examined the efficacy and safety of belimumab (at 10 mg/kg) administered with standard SLE care in the following treatment groups: steroids only, antimalarials only, antimalarials plus immunosuppressants, and steroids plus antimalarials plus immunosuppressants [45]. For all groups, at week 52, a numerically greater SRI response was observed with belimumab compared with placebo. The benefit was greatest for the antimalarials plus steroids group, whereas the antimalarials-only group had the smallest benefit from the addition of belimumab. However, the number of patients in the antimalarials-only group was small limiting perhaps the value of this conclusion.

An observational cohort study was conducted in US clinical practices and included patients who had received ≥ 8 infusions of belimumab in everyday practice in order to evaluate clinical responses at the end of each 6-month period for a total of 24 months [46]. At baseline, 77.6% of patients had moderate and 20.2% had severe disease. At month 6, the percentages of patients with moderate and severe disease activity were reduced to 47.7 and 2.4%, respectively, and at month 24 to 33.1 and 1.9%, respectively.

An open-label continuation study included patients who had completed the double-blind, placebo-controlled, 52-week study of belimumab and an additional 24-week extension of belimumab infusions. The previously established disease control and safety profile were maintained in patients with active SLE receiving belimumab plus standard treatment for up to 7 years [47]. Severe flares occurred in 19% with placebo and 17% with belimumab during the first year, with the annual rate declining to 2–9% during the following 6 years.

A further study evaluated the use and efficacy of belimumab in academic practices [48]. Of the 120 patients receiving belimumab for at least 6 months, 51% responded clinically and 67% had ≥ 25% improvement of selected laboratory parameters. Belimumab was administered in 18 Italian patients with active SLE on top of their current treatment [49]. There was a significant reduction in the SLEDAI-2K score after 3 months of treatment followed by a significant decrease in steroid intake at 9 months of treatment. The short-term follow-up is a downside in making firm conclusions. A prospective study included 67 patients with active SLE treated with belimumab in addition to background therapy [50]. Belimumab was particularly effective in musculoskeletal, mucocutaneous, and renal manifestations. Flare rates were lower at 1 and 2 years following belimumab initiation when compared to the periods before treatment. Limitations of the study are the lack of a control group and the different duration of belimumab treatment in different patients.

The OBSErve Germany was the first observational study of belimumab as an add-on treatment, retrospectively collecting data from 102 SLE patients, 6 months before and following belimumab initiation [51]. After 6 months of belimumab treatment, 78% of patients had an improvement in overall disease activity. A notable dose reduction was seen for concomitant oral corticosteroids. Similarly, 48 patients with active SLE were evaluated after 1 year of continuous treatment with belimumab that was administered along with standard of care [52]. The mean SLEDAI score decreased from 12 ± 3.0 to 2.5 ± 2.5, and the daily steroid dose from 30 ± 12.5 to 7.5 ± 5.0 mg.

Another retrospective open-labeled study of 36 lupus patients who received belimumab monthly for at least 1 year in addition to standard treatment was conducted [53]. The response was excellent in 25 patients (69.5%) and good/partial in 6 (16.6%). Moreover, there was a significant reduction in the usage of corticosteroids (from 100 to 27.7% of patients) and immunosuppressive agents (from 83.3 to 8.3% of patients). A multicenter, retrospective study in Canada included a total of 52 patients with SLE [54]. Following 6 months of belimumab treatment, 80.8, 57.7, and 17.3% of patients had an overall clinical improvement of ≥ 20, ≥ 50, and ≥ 80%, respectively. Among patients still receiving oral glucocorticoids at 6 months of belimumab therapy, the glucocorticoid dose was decreased in 59.1%, remained the same in 22.7%, and was increased in 6.8% of patients. The major limitation of this analysis was that the quantification of clinical response was not standardized. In addition, there was no control group.

Belimumab is currently available and approved in a subcutaneous form. Intravenous and subcutaneous exposure of belimumab after 4 weeks of SC dosing yielded overlapping belimumab concentrations [55]. According to the results of a Bayesian network meta-analysis, the SRI response rate at

week 52 was significantly higher in the belimumab 10 mg/kg group, in the belimumab 1 mg/kg group, and the belimumab 200 mg SC group compared to the responses seen in the placebo group [56]. Furthermore, belimumab 200 mg SC and belimumab 10 mg/kg had the highest probability of being the best treatment for achieving the SRI response, followed by belimumab 1 mg/kg and placebo.

A phase III randomized, double-blind, placebo-controlled study investigated the safety and efficacy of belimumab 200 mg SC plus standard therapy in patients with SLE [57]. At week 52, 61.4% were SRI4 responders compared with 48.4% for placebo. The SRI4 response was greater in the belimumab group as compared to the placebo group as early as week 16 and such differences were sustained up to week 52. The risk of any flare was 60.6% in the belimumab group and 68.6% in the placebo group. Regarding changes in corticosteroid dosages, 18.2% of patients receiving belimumab reduced the daily dose by ≥ 25% to ≤ 7.5 mg/day during weeks 40–52 compared to 11.9% of patients in the placebo group but this was not statistically significant. Severe adverse events were reported for 10.8 and 15.7% of patients in the belimumab and the placebo group, respectively. However, similarly to all previous trials of belimumab, factors such as the exclusion of patients with active nephritis or active CNS disease and the small numbers of some subgroups diminish the possibility of drawing firm conclusions.

Belimumab has been successfully used for the treatment of recalcitrant cutaneous lupus [58]. There are only case reports supporting the beneficial effect of belimumab in lupus nephritis [59, 60]. In contrast, Sjöwall et al. described a patient with SLE who developed proliferative lupus nephritis under treatment with belimumab [61]. In addition, we have recently reported two patients in which lupus nephritis developed shortly after initiation of treatment with belimumab; it is of note that both patients improved promptly and fast, simply by belimumab withdrawal, practically before the initiation of standard treatment for their lupus nephritis [62•].

It has been previously documented that B cell depletion leads to a sharp homeostatic rise in the titers of circulating BLys. Therefore, some have proposed a sequential form of treatment with RTX followed by belimumab, to block the post-RTX BLyS rise and hence avoid a rapid reconstitution of the autoreactive B cell pool. To this end, case reports [63–65] suggest that sequential treatment with RTX followed by belimumab could represent a promising strategy for lupus nephritis by interfering with the rebound increases in BLyS. This potentially interesting strategy is being formally investigated in two ongoing trials called Synergetic B cell Immodulation in SLE and Rituximab Plus Cyclophosphamide followed by Belimumab for the Treatment of Lupus Nephritis.

Other BLyS Targeting Agents

Blisibimod is a fully human construct consisting of four high-affinity binding domains of BAFFR fused with an IgG1 Fc fragment; the construct binds both soluble and membrane BLyS. According to the results of a randomized, double-blind phase 1a and phase 1b trials [66], blisibimod changed the constituency of the B cell pool. A limitation of these studies is that participating patients had mild or even inactive disease so the evaluation of clinical response of "nearly-healthy" individuals does not seem meaningful. The REARL-SC study enrolling 547 patients with active lupus did not meet the primary endpoint, the SRI-5 response, at week 24, but did meet it at week 20 (for patients treated with the higher blisibimod dose) [67]. A separate analysis of the REARL-SC study revealed that fatigue also improved, particularly in those patients receiving the highest dose of blisibimod [68].

Tabalumab is another human monoclonal IgG4 antibody that also neutralizes both soluble and membrane BLyS. According to the results of ILLUMINATE 1 study, key clinical efficacy endpoints did not achieve statistical significance [69]. Furthermore, in ILLUMINATE-2 [70] enrolling 1124 patients with moderately to severely active SLE, although tabalumab failed to meet three secondary endpoints (corticosteroid sparing, time-to-first severe flare, and the change from baseline in fatigue), it did meet the primary endpoint, which was the SRI-5 response in the dosage of 120 mg q2w (38.4 vs. 27.7%, for tabalumab vs. placebo, respectively, $p = 0.002$). It is of note that the less frequent dosing scheme (120 mg q4w) was only borderline non-significant ($p = 0.051$). The same regimen demonstrated efficacy in a subgroup analysis of the ILLUMINATE-1 study [71]. According to the results of two phase III studies [72], tabalumab did not significantly affect renal parameters such as urine protein/creatinine ratio, serum creatinine concentration, or renal flare rates over 1 year. Tabalumab treatment decreased significantly circulating B cells and concentrations of serum IgG. However, the effect of tabalumab vs. placebo recorded in ILLUMINATE-2 study was small despite its statistical significance. This along with the failure to meet secondary endpoints led to the suspension of further development of tabalumab. It was rather unusual for the study design though that patients with any change in dosages of concomitant medications (e.g., antimalarials, immunosuppressants) were classified as "non-responders" even though this change would be a (desirable) decrease.

Atacicept is a recombinant fusion protein consisting of the extracellular domain of the TACI receptor bound to a human IgG1 Fc fragment. It blocks both BLyS and APRIL cytokines, adding thus plasma cells to the frame, since APRIL affects plasma cells principally. In a

double-blind, placebo-controlled study, SLE patients were randomized to atacicept 75 or 150 mg [73]. Primary and secondary efficacy measures were the proportion of patients who had experienced at least one flare and time-to-first-flare, respectively. There was no difference between atacicept 75 mg and placebo for flare rates or time-to-first-flare, but analysis of atacicept 150 mg suggested a beneficial effect. Although the results with the higher dose were encouraging, one should keep in mind the possible infection risk resulting in two deaths in that group. A post hoc analysis demonstrated a dose-response relationship between atacicept concentrations, reduced Ig levels, and reduced flare rates and suggest that baseline biomarkers such as high levels of BLyS and APRIL may help to identify patients are most likely to benefit from atacicept therapy [74].

Conclusions

Experience gained over the last few years has brought us additional weapons in fighting recalcitrant SLE. Because lupus B cells not only produce autoAb, some of which can have pathogenic contributions in tissue injury, but also produce cytokines and also are efficient antigen cells, they have been considered as targets for treatment (Table 1). The first agent employed has been rituximab, a treatment that brought revolution to the treatment of hematological malignancies of B cell origin. Two different double-blind, placebo-controlled, randomized studies evaluating efficacy and safety of RTX in the treatment of lupus nephritis were completed with negative results. However, these two studies have been heavily criticized for their design, an issue that is beyond the scope of this review. Nevertheless, clinicians dealing with difficult-to-treat patients with lupus have been using RTX not only in renal but also in non-renal lupus with quite encouraging results. Ourselves and others feel that following the administration of standard of care treatment, should one need to enhance the therapeutic regimen, the addition of RTX is an acceptable and commonly rewarding choice. Scientific organizations now formally recommend treatment with RTX in standard treatment refractory lupus nephritis, and several studies suggest that non-renal manifestations such as arthritis and hematological abnormalities in particular are highly sensitive to RTX administration. However, the dosing scheme has not been formatted yet and the need for retreatment or not remains questionable, the answers being based on the experience of the treating physician and the manifestations of each individual patient. Even though treatment with RTX is considered safe, infections can always be an issue and the possibility of hypogammaglobulinemia should be kept in mind, even in patients with SLE that have hypergammaglobulinemia in the majority.

Belimumab is increasingly used on top of standard treatment, in patients with refractory SLE, but has not been formally tested in patients with severe lupus nephritis and CNS involvement. Even though some clinicians feel that the improvement obtained with belimumab is less than expected, one should keep in mind is that this improvement does occur in refractory patients already receiving optimized still maximal standard of care. The unmet needs of patients with refractory lupus nephritis have pushed into formally testing belimumab into this setting, with results expected soon. The availability of SC belimumab is thought to increase our experience with this novel and safe agent.

Both RTX and belimumab however are B cell depleters and anti-BLyS agents, respectively, and despite their efficacy, they remain B cell non-specific. The reasonable target of treatment in SLE could be autoreactive B cells specifically and not anti-B cell treatments non-specifically. Previous efforts to this point have not proved to be rewarding, but we suggest that this should not become an obstacle to current and future trends towards this direction.

Table 1 Current and under development agents targeting B cells in SLE

Agent	Mechanism of action	Efficacy in lupus nephritis	Disease activity improvement
Rituximab[a]	Anti-CD20 mAb	Encouraging	Encouraging
Ofatumumab	Anti-CD20 mAb	Encouraging	NA
Ocrelizumab	Anti-CD20 mAb	Study terminated	Study terminated
Obinutuzumab[a]	Anti-CD20 mAb	NA	NA
Epratuzumab	Anti-CD22 mAb	NA	Questionable
Belimumab[a]	Anti-BLyS mAb	NA	+
Blisibimod	BLyS blocker	NA	Encouraging
Tabalumab	Anti-BLys mAb	–	+
Atacicept	BLyS & APRIL blocker	NA	+

NA no available data

[a] Commercially available

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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