CLINICAL INVESTIGATION

Updating the clinical evidence on belimumab role modulating B-cell response and treatment of systemic lupus erythematosus

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Treatment of patients with systemic lupus erythematosus (SLE) is still a challenge for many physicians and often associated with a range of adverse side effects. Based on the evidence of the central role of B cells in SLE pathogenesis, several new drugs have been developed. Inhibition of BAFF/APRIL system has appeared as one of the key factors in modulating B-cell response in patients with SLE. In 2011, belimumab was approved by the European and American regulatory agencies for the treatment of SLE patients. Four years later, consistent clinical experience has been accumulated. This article aims to review the mechanisms behind this system and the evidence provided by up-to-date trials on the safety, efficacy and effectiveness of belimumab in SLE patients.

Keywords: B-cells inhibitor • BAFF • belimumab • bliss • BlyS • lupus • monoclonal antibody • OBSErve • systemic lupus erythematosus • TNF

Background

Systemic lupus erythematosus (SLE) is a multisystem and heterogeneous autoimmune disease with an estimated incidence of 5–50 cases per 100,000 people with a notably variation between countries, population and genders [1]. Moreover, its prevalence seems to increase probably due to an earlier identification of milder cases and improved survival [2]. Its onset usually affects women of childbearing age with a frequency six- to ten-times higher than men [3]. Although the cause of this disease remains unknown, scientific work carried out over the past years has provided significant progress on its etiopathogenesis. Inflammation in response to immunocomplex precipitation in several tissues and organ damage are the causes of many lupus manifestations. Loss of tolerance to nuclear antigens by autoreactive B cells seems to be a hallmark in the pathogenesis of SLE because these cells are the ones, which after maturing to plasma cells, finally secrete these antibodies. Thus, based on their ability to present antigen, secrete inflammatory cytokines and produce autoantibodies, B cells seem to be at the center of SLE pathogenesis. Currently, standard-of-care for SLE typically begins with the combination of hydroxychloroquine, corticosteroids and nonsteroidal anti-inflammatory drugs to control mucocutaneous and articular involvement, although immunosuppressive drugs are added when the disease is not clinically under control or it affects major organs, such as the kidney or the CNS. However, current therapy is associated with risks, adverse effects and complications that limit its use, that is, opportunistic infections, osteoporosis, diabetes, cataracts and Cushing syndrome. Thus, these observations encouraged many scientists to search for new, better-tolerated and more effective therapies. In this sense, several treatment strategies have been developed that directly or indirectly affect B cells. Rituximab, a monoclonal antibody against CD20, when used off-label, as a last resort treatment when SLE patients do not respond to standard therapy empirically shows efficacy. Unfortunately, rituximab did not succeed in proving its efficacy in clinical trials [4] and, thus, it is not approved for use in SLE patients.

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The BAFF/APRIL system takes part in B-cell activation and regulation by the innate immune system [5]. B lymphocyte stimulator (BLyS), also known as B-cell-activating factor (BAFF), has proven to be a key factor in the selection and survival of naive autoreactive B cells [6]. In 2011, belimumab, a new monoclonal antibody targeting human BLyS/BAFF, was approved by the American and European drug regulatory agencies for the treatment of adults with SLE after two randomized controlled trials proved its efficacy. *Post hoc* analysis of data from patients treated with belimumab suggested that mechanisms other than B-cell depletion are affected during response.

The aim of this review article is to summarize the evidence-based information on the clinical usefulness of belimumab in the treatment of patients with SLE.

BAFF/APRIL pathway

The BAFF/APRIL system is formed by two type II transmembrane proteins from the TNF receptor superfamily that role as ligands (BAFF and APRIL) and three main receptors: BAFF-R or BR3 (BAFF receptor), BCMA (B-cell maturation antigen) and TACI (transmembrane activator and cyclophilin ligand interactor). Type II membrane proteins can act either as a membrane-bound protein or as a proteolytically processed soluble cytokines in an autocrine, paracrine or endocrine manner. BAFF is processed from the membrane form to soluble forms while APRIL acts, with rare exceptions, in a soluble form [5]. Although still under discussion, membrane-bound BAFF seems not to play any role in B-cell biology and seems unable to trigger a signal on B cells [7]. Both ligands are mainly synthesized primary by monocytes, activated neutrophils and dendritic cells [8]. However, lymphoid cells, including B cells and activated T cells, can also produce BAFF and APRIL [5]. Secretion of BAFF is upregulated in myeloid cells by several cytokines, including IFN-γ, IFN-α, TGF-β and estrogens.

Human BAFF is a 285-amino acid transmembrane protein member expressed on the membrane surface that belongs to the TNF ligand superfamily. It is coded in the distal arm of human chromosome 13 (13q34) [6]. BAFF is cleaved by furin protease releasing a biologically active 17-kDa soluble molecule [6]. Two main isoforms of this protein are expressed pending on posttranscriptional splicing [9]. Full-length BAFF mRNA codes for the biologically active full-length protein while alternative splicing codes for a protein without a small peptide (ΔBAFF). ΔBAFF attaches to full-length isoforms forming biologically inactive heterotrimers, thus antagonizing its BAFF effect [9,10]. However, the pathways that normally regulate BAFF expression are not known.

The other ligand of BAFF/APRIL system is APRIL, a 250-amino acid member of the TNF ligand superfamily. APRIL is not expressed as cellular membrane protein; instead, it is processed within the cell and released in its soluble, biologically active form. APRIL is coded on chromosome 17 [6]. APRIL costimulates B cells, induces Ig class switching and promotes plasma cell survival. However, APRIL knockout mice are phenotypically normal or with only selective circulating IgA or IgA response deficiency due to mucosa offense [11,12].

There are three BAFF receptors on the BAFF/APRIL system: BCMA, TACI and the BR3·or BAFF-R [5]. APRIL and BAFF can both bind to BCMA and TACI, whereas BAFF is the single ligand for BAFF-R [5]. However, the biological effect of BAFF is depended on the receptor it binds to.

Binding of the ligands to their respective receptors induces oligomerization and a complex intracellular cascade signaling events downstream. These include translocation and activation of both classical and alternative NF-κB pathways, probably by release of its constitutive inhibition by TNF receptor-associated factor 3 (TRAF3) in B cells [13,14]. Finally, this cascade leads to B cell longer survival, maturation of immature B cells to mature B cells and to Ig class switching and Ig production. Mature, activated B cells differentiate into plasmablast or memory B cells and, then, cease expressing BAFF receptors. Not surprising, BAFF seems not to play any role on the persistence of memory B cells [15]. Indeed, no effects on antibody response to previous vaccination have been detected after 1 year of treatment with BAFF antagonists [16]. Thus, immature B cells are, in general, more dependent on BAFF for survival than mature B cells. Some studies have suggested that autoreactive B cells have a greater dependency on BAFF for their survival than nonautoreactive B cells. Yet, other authors propose that this relation may be more a function of their immaturity rather than their autoreactivity [7].

Simultaneously, however, BAFF preferentially promotes IL-10 producing regulatory cells (B_{regs}) from marginal zone B-populations rather than from newly formed follicular B cells [17]. Moreover, BAFF can costimulate proliferation of T cells and cytokine production capable of switching toward a T-helper response and away from the Th2 response and promotes Th17 cell response [16].

BAFF/APRIL pathway in SLE

Increased B-cell activity is probably related to high levels of cytokines and growth factors. Several reports have suggested a central role of BAFF in the pathogenesis of SLE, both in mice and in humans [18–20]. Mice

genetically deficient in BAFF lack mature B cells and are immunodeficient, whereas mice that overproduce BAFF have high numbers of mature B cells and antibodies, including autoantibodies, and develop an autoimmune disease similar to SLE in humans [18]. Selective APRIL block can delay the development of diseases in lupus prone mice [21]; however, the evidence of BAFF role in SLE is conclusive, the evidence of any APRIL role in SLE is scanty. APRIL seems to be highly, if not completely, dispensable for development of full-blown SLE in New Zealand-mixed mice (NZM) and may actually play a protective, rather than pathogenic role [7]. Furthermore, a Phase III clinical trial of a chimeric recombinant fusion protein that combined TACI with immunoglobulin constant region capable of blocking BAFF, APRIL and BAFF-APRIL has been linked to hipogammaglobulinemia, increased risk of infections and early deaths when used in high doses [22]. At least 50% of people with SLE (as well as patients with Sjögren's syndrome or rheumatoid arthritis) have elevated plasma levels of soluble BAFF; however, this rate may be higher if the capacity of steroids in reducing BAFF levels is considered [16,23]. Furthermore, some authors have found a positive association between high levels of BAFF and high anti-dsDNA levels and disease activity measured by the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [24,25]. However, this association between BAFF levels and SLE activity was not found by other authors [26]. These observations, together with evidence that BAFF blockade decreased symptoms of SLE in mouse models, promoted BAFF as a potential therapeutic target for the treatment of patients with SLE. Interestingly, some studies have measured cytokines levels in SLE subsets showing an increase of BAFF in SLE patients with CNS or renal manifestations [27].

Belimumab

Belimumab is a 147-kDa human recombinant monoclonal antibody that binds to soluble BLyS/BAFF, without affecting other TNF family members, thus inhibiting its binding to its three receptors, especially in naive B cells. Therefore, administration of belimumab depletes native and activated B cells and plasma cells but an increase is seen in memory B and in helper and cytotoxic T cells [9]. Although these changes are seen as soon as in 8 weeks, they did not predict clinical response.

Belimumab is produced by recombinant DNA technology in a mammalian cell expression system [28]. Due to the nature of the molecule, traditional pharmacokinetic studies exploring the absorption, distribution, metabolism and elimination (ADME) of belimumab have not been performed [29]. The recommended dose regimen is 10 mg/kg once on days 0, 14, and 28, and at 4-week intervals thereafter and discontinuation should be considered if there is no improvement in disease control after 6 months of treatment [29]. Systemic clearance has been shown to rise with increasing weight. making an adjustment of belimumab dose by weight necessary [30,31]. No dose adjustment is required for age, gender or race. It is administered by intravenous infusion over 1 h [31]. Maximum concentration is reached immediately after infusion. Intravenous drugs sometimes should be administered by a qualified healthcare professional trained to give infusion therapy and maybe able to manage potential infusion reactions. Thus, subcutaneous-administered belimumab efficacy is under evaluation in SLE patients. Indeed, clinical studies have shown that a fixed dose of 200 mg weekly reaches the same average steady-state serum concentration of belimumab than 10 mg/kg intravenously every 4 weeks [32]. This dose is thus currently being evaluated in a Phase III randomized controlled trials for its use in clinical practice [33].

As a macromolecule, belimumab distributes to plasma and intracellular compartments with limited distribution to other tissues. The estimated population half-life of belimumab is 19.4 days like other IgG1 monoclonal antibodies [30,31]. Although no formal studies have been conducted to examine the effects of hepatic or renal impairment on belimumab pharmacokinetics, as a protein, belimumab is expected to be metabolized through degradation to small peptides by widely distributed proteolytic enzymes. Accordingly, renal elimination may have no role on its half-life, although some plasma concentration variability has been described in patients with an increased clearance and proteinuria higher than 2 g/day [31]. There is limited information on the true occurrence of specific and nonspecific antidrug antibodies in the patients receiving belimumab; however, the development of such antibodies has been described in some cases [34]. However, detected antibodies do not seem to alter belimumab concentration effectiveness nor safety.

Effectiveness & safety of belimumab in SLE

Efficacy

The first randomized clinical trial (RCT) on belimumab efficacy was the Phase II trial [35]. Although a treatment effect was not demonstrated in this trial for any of the primary or secondary end points evaluated, *post hoc* analysis suggested an effect in the subgroup of patients with positive autoantibodies. Thus, only positive autoantibodies patients were studied in pivotal trials. Two Phase III large randomized, double-

blind, placebo-controlled trials named BLISS-52 [36] and BLISS-76 [37] were the first studies to confirm the superiority efficacy of belimumab over placebo both added to standard of care. Both trials had the same design but treatment was continued through week 76 in the BLISS-76 study, while it was stopped at week 52 in BLISS-52 [36,37]. These trials were the pivotal studies that paved the way to belimumab approval by the regulatory agencies as an add-on therapy to standard of care in adults with active, antinuclear antibody-positive SLE with high degree of diseases activity (e.g., positive anti-dsDNA and low complement).

In these trials, all patients were required to meet the American College of Rheumatology (ACR) criteria for the classification of SLE, had to have seropositive autoantibodies (ANA titer ≥80 and/or anti-dsDNA antibodies ≥30 IU/ml) with an active disease defined as SELENA–SLEDAI score ≥6 and to be on stable therapy for ≥30 days at screening. Patients with active lupus nephritis or CNS manifestations were excluded from these two trials. Further excluded were those patients who received other B-cell-targeted therapies anytime, other biologics within 1 year or cyclophosphamide within prior 6 months among others. BLISS-52 included 865 Latin American, Asian and east European patients, while BLISS-76 enrolled 819 patients from North America, Central America and Europe. Patients were randomly assigned to receive belimumab 10 mg/kg, belimumab 1 mg/kg or placebo despite their current therapy. The primary end point was defined by the so-called SLE Responder Index (SRI) rate at week 52 [36]. The SRI is a composite end point resulting from the combination of three validated tools for estimating SLE disease activity: the SELENA–SLEDAI, physician global assessment (PGA) and British Isles Lupus Assessment Group index (BILAG) [38]. An improvement of disease activity was set to a reduction of four points or more on SELENA–SLEDAI index according to previous reports, no worsening in PGA and no new BILAG A organ domain score or two new BILAG B organ domain scores compared with baseline at the time of assessment. Treatment was administered intravenously on days 0, 14 and 28, and every 28 days thereafter through week 48 in BLISS-52 and week 72 in BLISS-76. Each trial recruited at least 810 patients with more than 270 subjects per group to provide at least 90% power at a 5% significance and to detect an 14% absolute improvement in response rate in the 10 mg/kg belimumab group (or both drug-receiving groups) using the most conservative estimate for the standard deviation in the population (50%).

In the BLISS-76 study, 630 (77%) patients completed 52 weeks of treatment. The addition of belimumab 10 mg/kg leads to an increased 9.4% of responders compared with placebo when adjusted by baseline SELENA–SLEDAI (≤9 vs ≥10), proteinuria (<2 g/24 h vs ≥2 g/24 h) and race (African descent or indigenous American descent vs other), while 1 mg/kg belimumab arm increase did not reach statistically significant superiority over placebo (Table 1). However, durability of treatment effect was not maintained at the week 76 time-point as assessed by the SRI response rate. Interestingly, this achievement was attributable to a significant improvement on disease score measured by SELENA–SLEDAI score with no difference in other components of the primary end point. The results from the rest of the secondary end points were suggestive of improvements in belimumab treatment groups but statistically significance was not reached since multiplicity correction was not planned in the protocol nor implemented in the analysis [39].

In the BLISS-52 study, a 14.0% increased response rate was found in patients treated with 10 mg/kg belimumab versus placebo at week 52, while a 7.8% was found in the 1 mg/kg belimumab dose arm when compared with placebo (Table 2). However, its benefit did not appear before 16–24 weeks but was stable through week 52. When the different components of SRI were analyzed separately, both 1 and 10 mg/kg belimumab doses showed improved results over placebo for SELENA–SLEDAI and PGA components, while only the 10 mg/kg belimumab arm was able to show an increase on the frequency of patients with 'no new BILAG 1A/2B domain score' (Tables 3 & 4)

To clarify to which extend the benefit observed mainly in SELENA–SLEDAI index would translate to a clinical benefit, a new analysis was performed in which patients with improvement only in immunological parameters were set as nonresponders with results consistently showing that difference between groups was not only due to laboratory changes [29].

Later, van Vollenhoven *et al.* [40] used data from the pivotal studies to identify the factors predictive of response in belimumab-treated patients included in the trials. *Post hoc* analysis of the RCT's showed that belimumab had an increased benefit in patients with a SELENA–SLEDAI ≥10, low complement, anti-dsDNA above 30 IU/ml and higher baseline corticosteroid use. This subgroup of patients showed a response index of 51.5% compared with 31.7% in the placebo group ($p < 0.001$). Patients with higher SELENA–SLEDAI showed a response index of 63.2% compared with 44.3% in the placebo group ($p < 0.001$), thus representing an increase of 20% in the response rate. In addition, a statistical analysis was done removing anti-dsDNA and complement from the model showing the positive results were not due to lab changes.

Table 1. Baseline demographic and clinical characteristics of patients in BLISS-76.

Parameters	Placebo	10 mg/kg
Age (SD)	40 (11.9)	40 (11.1)
Women	252 (91.6%)	259 (94.9%)
SELENA–SLEDAI (SD)	9.8 (4.0)	9.5 (3.6)
SELENA–SLEDAI score ≥10	140 (50.9%)	136 (49.8%)
BILAG 1A or 2B	187 (68.0%)	160 (58.6%)
Prednisone	212 (77.1%)	200 (73.3%)
>7.5 mg/day at baseline	126 (45.8%)	120 (44.0%)
Immunosuppressive drugs	154 (56.0%)	148 (54.2%)
Anti-dsDNA ≥30 IU/ml	174 (63.3%)	179 (65.6%)

BILAG: Bristish Isles Lupus Activity Group; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Patients with major organ involvement were excluded from the pivotal trials due to concerns on the with regards to the rapid treatment changes these patient may require. Thus, belimumab efficacy is mainly established for mucocutaneous and musculoskeletal involvement. However, lupus nephritis is a frequent cause of SLE-associated morbidity affecting up to 30% of patients with SLE [41] Thus, whether belimumab could be useful in patients with severe manifestations of SLE-like active lupus nephritis or CNS diseases is unknown [36,37]. However, *post hoc* analysis of the data from pivotal trials showed that patients with proteinuria included in BLISS trials showed an improvement in their proteinuria and in the SLEDAI measurements [42]. This evidence led the company to start an ongoing RCT to evaluate the efficacy of belimumab as an add-on therapy during both the induction and maintenance periods in patients with lupus nephritis [43], which will clarify the role of belimumab in these patients.

B-cell repopulation kinetics appear to be closely associated to BAFF levels following rituximab therapy. BAFF levels have been related to B-cell count after a B-cell depleting therapy [25]. This observation raised the hypothesis of a possible advantage on the combination of belimumab to rituximab therapy [44] and, thus, boost the launching of an ongoing open Phase II trial to prove the safety of this combination in lupus nephritis [45] that may add a potential powerful tool to the SLE treatment armamentarium. However, some concern is arise regarding this combinations because rituximab seems to influence the relation between BAFF and B cells.

Unfortunately, limited data are available on belimumab efficacy and safety in special populations such as pediatric, pregnant and lactating patients because they were excluded from pivotal trials and, when a pregnancy occurred, treatment was discontinued [36,37]. However, identified pregnant women were followed until delivery and outcomes were analyzed neither showing a higher frequency of fetal loses nor a higher index of congenital anomalies, although there are only 66 pregnant women have been identified so far [46]. Thus, belimumab should not be used during preg-

Table 2. Baseline demographic and clinical characteristics of patients in BLISS-52.

Parameters	Placebo	10 mg/kg
Age (SD)	36.2 (11.8)	35.4 (10.8)
Women	270 (94%)	280 (97%)
SELENA–SLEDAI (standard deviation)	9.7 (3.6)	10.0 (3.0)
SELENA–SLEDAI score ≥10	158 (55%)	160 (55%)
BILAG 1A or 2B	166 (58%)	172 (59%)
Prednisone	276 (96%)	278 (96%)
>7.5 mg/day at baseline	192 (67%)	204 (70%)
Immunosuppressive drugs	122 (43%)	123 (42%)
Anti-dsDNA ≥30 IU/ml	205 (71%)	218 (75%)

BILAG: Bristish Isles Lupus Activity Group; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Table 3. BLISS-76: response at week 52 (adjusted).

Parameters	Placebo	1 mg/kg	10 mg/kg
SRI response rate:	93 (33.8%)	110 (40.6%)	118 (43.2%)
– Difference vs placebo		7%	9%
– OR vs placebo (95% CI)		1.34 (0.94–1.91)	1.52 (1.06–2.15)
– p-value		0.0996	0.0215
Components			
SELENA–SLEDAI ≥4 point reduction:	97 (35.3%)	116 (42.8%)	127 (46.5%)
– OR vs placebo (95% CI)		1.36 (0.96–1.93)	1.63 (1.15–2.32)
– p-value		0.0869	0.1258
No worsening in PGA:	173 (62.9%)	197 (72.7%)	189 (69.2%)
– OR vs placebo (95% CI)		1.60 (1.11–2.30)	1.32 (0.92–1.90)
– p-value		0.0120	0.1258
No new 1A/2B BILAG domain scores:	179 (65.1%)	203 (74.9%)	189 (69.2%)
– OR vs placebo (95% CI)		1.63 (1.12–2.37)	1.20 (0.84–1.73)
– p-value		0.0108	0.3193

Odds radio (95% CI) and p-values are from logistic regression where categorical variables SRI, baseline SELENA–SLEDAI (≤9 vs ≥10), baseline proteinuria (<2 g/24 h vs ≥2 g/24 h) and race (African descent or indigenous American descent vs other) were included.
BILAG: Bristish Isles Lupus Activity Group; PGA: Physician global assessment; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SRI: SLE responder index.

nancy until further research elucidates its safety during this period.

A difference in response rate according to race was pointed out when analysis of subgroups was undertaken. An exploratory analysis of the data from black patients included in the Phase III trials reported a lower utility of belimumab in this subgroup, while a better response rate was observed in Phase II study, although conclusions are difficult to draw because of the small size of these sets. In order to address this issue, a new international clinical trial is being undergone in order to evaluate its clinical utility in black race patients [47], which should clarify this shadow.

Fatigue is considered by some patients the most debilitating aspect of the disease and has an important impact on their lives. *Post hoc* analysis of data obtained during BLISS trials, even when individually not powered to detect significant differences in health-related quality of life (HRQOL), showed some additional benefit of belimumab. It was found to improve patients quality of life at week 52 measured by fatigue scores. Moreover, belimumab group showed an improvement of the mean Short Form 36 health survey (SF-36) mental component scores (MCS) and physical component summary (PCS) scores improved significantly. However, most treating physicians are reluctant to administer such a complex and expensive drug for this symptom.

Due to an apparent loss of efficacy by the 76th week in BLISS-76 trial, some concern was raised regarding a possible loss of efficacy of belimumab over time. However, the 7-year open-label continuation of the Phase II study [48] that included a total follow-up of 1746 patient-years, to whom belimumab had been added to standard therapy, showed a response rate at week 52 measured by SRI of 46% in autoantibody-positive patients versus 26% in the placebo group. By the end of the second year, belimumab group had a response rate of 57% and it was up to 65% by the 7th year. Additionally, patients showed an annual declining rate up to 2–9% during years 2–7. Moreover, patients with positive anti-dsDNA at baseline treated with belimumab had a progressive decline of 40–60% over 2–7 years and reduction of 50% on corticosteroid dose during 5–7 years, without an increase in adverse events [48]. However, the open-label design must stress to avoid taking conclusions.

Lately, observational studies have been carried out showing usefulness of belimumab in real clinical practice, although they have not yet been published in peer-reviewed journals. The OBSErve study was a retrospective, multicenter, medical chart review study conducted initially in the USA and later in several European countries [49–51]. The data were obtained from community-based rheumatology practices where more than ten SLE patients were treated. All adult SLE patients in their practices who received belimumab (10 mg/kg) were included. Activity of the disease was evaluated over a 6-month period, as was the healthcare resource utilization.

The first OBSErve study was in the USA [49] and included 501 adult SLE patients who had received belimumab (10 mg/kg) as part of routine care, followed over 6 months after their first dose. The primary clinical outcome measure was the overall clinical response, reported as change from baseline in SLE disease manifestations, 6 months after belimumab initiation based on physician subjective assessment. After 6 months of belimumab treatment, the overall physician impression of clinical response was that 88% of the patients showed a 20% improvement, 49% of the patients showed more than 50% and 11% an improvement of more than 80% from baseline. Only 1% of the patients were reported to have no differences from their pretreatment activity.

The OBSErve study in Germany included 106 patients and showed a clinically assessed improvement of more than 20% in 78% of cases, more than 50% in 42% of cases and more than 80% in 9% of patients. Physicians assessed more than 50% improvement for arthritis in 56% of patients, high anti-dsDNA 21% of patients, fatigue in 25% of patients low complement in 51% of the patients.

The OBSErve study performed in Spain showed a decrease in SELENA–SLEDAI in 88% of the patients after 6 months of belimumab therapy, decreasing the mean SELENA–SLEDAI score from 10.1 to 4.5 ($p < 0.0001$) [50]. An improvement of more than 50% was observed in SLE manifestations, such as arthritis (69%), low complement (47%), high anti-dsDNA levels (48%) and fatigue (60%).

In the USA, 80% of patients received corticosteroids at baseline and 9% were able to discontinue with a further 13% being on a their lowest dose 6 months after initiation belimumab and almost all patients (86%) were able to successfully decrease the dose. The average reduction in corticosteroid dose was 11.5 mg prednisone. In Germany, the OBSErve study showed a mean reduction in corticosteroid dose of 5.8 mg/day from 13.6 to 7.8 mg/day and this reduction was of 6.8 mg/day in Spain. Of the 62 patients who received a high corticosteroid dose (>7.5 mg/day) at initiation, 48% were below this threshold or had discontinued corticosteroids after 6 months of belimumab treatment in Spain.

Safety

Belimumab is generally well tolerated and not associated to a high rate of adverse events compared with placebo. Integrated data from the three RCTs and data from preclinical trials showed its safety without any increase of infection rate. During the Phase II study, tolerability of belimumab was assessed by examining withdrawals due to lack of efficacy or adverse events. During the trials, belimumab was not associated with an increased likelihood of withdrawal whatever the cause or the dose. Moreover, safety results from Phase III studies revealed that belimumab was not at 1 mg/kg nor at 10 mg/kg associated with a higher number of adverse events, serious adverse events, severe adverse events, deaths, malignancies, infections or

Table 4. BLISS-52: response at week 52 (adjusted).

Parameters	Placebo	1 mg/kg	10 mg/kg
SRI response rate:	125 (44%)	148 (51%)	167 (58%)
– Difference vs placebo		7%	9%
– OR vs placebo (95% CI)		1.34 (0.94–1.91)	1.52 (1.06–2.15)
– p-value		0.0996	0.0215
Components			
SELENA–SLEDAI ≥4 point reduction:	132 (46%)	153 (53%)	169 (58%)
– OR vs placebo (95% CI)		1.51 (1.07–2.14)	1.71 (1.21–2.41)
– p-value		0.0189	0.0024
No new 1A/2B BILAG domain scores:	210 (73%)	226 (78%)	236 (81%)
– OR vs placebo (95% CI)		1.38 (0.93–2.04)	1.62 (1.09–2.42)
– p-value		0.1064	0.0181
No worsening in PGA:	199 (69%)	227 (79%)	231 (80%)
– OR vs placebo (95% CI)		1.68 (1.15–2.47)	1.78 (1.18–2.55)
– p-value		0.0078	0.0048

Odds radio (95% CI) and p-values are from logistic regression where categorical variables SRI, baseline SELENA–SLEDAI (≤9 vs ≥10), baseline proteinuria (<2 g/24 h vs ≥2 g/24 h) and race (African descent or indigenous American descent vs other) were included.
SRI: SLE responder index; PGA: Physician global assessment; OR: Odds ratio; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Table 5. Adverse events during the study BLISS-76.

Parameters	Placebo	10 mg/kg
Adverse events:		
– ≥1	253 (92)	253 (92.7%)
– ≥1 serious	54 (19.6)	61 (22.3)
– ≥1 severe	52 (18.9)	54 (19.8%)
Infections	190 (69.1%)	202 (74.0%)
Infuse reactions	27 (9.8%)	37 (13.6%)
Malignant diseases	1 (0.4%)	2 (0.7%)
Death	0	1 (0.4%)

infusion reactions (Tables 5 & 6). The most frequent adverse events (more than 10% of patients) were headaches, upper respiratory tract infection, arthralgia, nausea, urinary tract infection, diarrhea, fatigue and fever.

The rate of infections originated from B-cell depletion was not significantly higher with belimumab as compared with placebo. Infusion reactions were reported in 13.6% of the belimumab-treated patients (9.8% in the placebo) [36,37]. A slight increase in the number of patients that develop neuropsychiatric disorders for belimumab group compared with placebo was reported. However, a small proportion of patients in the treatment group reported medical history of neuropsychiatric disorders, which may account for the greater predisposition to develop clinical symptoms. Nevertheless, a definitive conclusion could not be made from the limited data. Similarly to rituximab, premedication with paracetamol and dyphenydramine has been advocated to prevent infusion reactions. However, currently there is no evidence that any of these agents can prevent them. Although, no case of progressive multifocal leukoencephalopathy has been reported so far in patients taking belimumab; however, risk assessment will need a complementary postmarketing surveillance with a prolonged follow-up.

Table 6. Adverse events during the study BLISS-52.

Parameters	Placebo	10 mg/kg
Adverse events:		
– ≥1	263 (92.0%)	266 (92.0%)
– ≥1 serious	36 (13.0%)	41 (14%)
– ≥1 severe	34 (12%)	33 (11.0%)
Infections	183 (64.0%)	194 (67.0%)
Infuse reactions	49 (17.0%)	48 (17%)
Malignant diseases	0	0
Death	3 (1.0%)	4 (1.0%)

Conclusion

In light of the experience gained first from the clinical trials and later from its clinical use brought together in the OBSErve registries, belimumab seems to perform very good with a low risk of adverse effects. However, the role of belimumab in patients with severe manifestations of SLE remains to be elucidated. Hopefully, the ongoing trials will add some information on the benefit of adding belimumab in patients with lupus nephritis; however, no comparative trial is planned with current treatment of lupus nephritis and such would probably add valuable information. Additionally, there is no ongoing study to assess the effectiveness of belimumab on other severe manifestations of SLE such as CNS involvement.

Moreover, the safety of belimumab in special clinical conditions, i.e., pregnancy and childhood, remains to be elucidated. Although no risk increase seems to arise from the cases included in the ongoing registry, a formal analysis has not been published so far. Additionally, very few information has been provided on pediatric patients and, to the best of our knowledge, no formal analysis in this possible target subpopulation is planned.

Therefore, future studies on the effect of belimumab on special populations such as pediatric patients and pregnant women are needed as well as in patients with severe organ manifestations such as CNS involvement.

Belimumab, combined with standard of care therapy when administered according to the trial schedule, has proven its efficacy in RCT's and observational studies, reducing SLE disease activity as assessed by the composite end point (SRI), especially in patients with clinically and immunologically active SLE, with a good safety profile and tolerance. Its use should be based on the data from clinical trials, since there are no guidelines form the American College of Rheumatology (ACR) nor from the European League against Rheumatism (EULAR) to assist physician's decision-making when facing SLE patients with this drug [44]. Ongoing research will help us to elucidate better the position of this still new drug in our armamentarium of SLE therapeutics.

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Executive summary

- B-cell-activating factor (BAFF)/APRIL system is made by two ligands (BAFF and APRIL) and three main receptors: BAFF-R or BR3, BCMA and TACI.
- BAFF/APRIL axis seems to be implied in systemic lupus erythematosus pathogenesis.
- Belimumab is a human monoclonal antibody synthesized by recombinant DNA technology.
- Belimumab is administered intravenous and metabolized in the liver as a protein.
- Belimumab was approved by the regulatory agencies after two randomized clinical trials proved its superiority over placebo as an add-on therapy.

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