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REVIEW

New treatment options for lupus – a focus on belimumab

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Abstract: Belimumab is the first biologic approved for patients with systemic lupus erythematosus (SLE). Belimumab is the first of a new class of drug targeting B cell-stimulating factors or their receptors to reach the market. Its target, BLyS, also known as BAFF (B cell-activating factor from the tumor necrosis factor family), is a type II transmembrane protein that exists in both membrane-bound and soluble forms. Additionally to a robust rational from murine experiments conducted in lupus prone mice, BLyS circulating levels are increased in SLE patients. After the negative results of a Phase II trial, two Phase III trials met their primary endpoints. Some SLE patients are still refractory to the standard options of care or necessitate prolonged high-dose corticotherapy and/or long-term immunosuppressive regimens. However, some experts still feel that the effect of this biologic might not be clinically relevant and blame the use of the new systemic lupus response index as well as the discrepancies between both trials and the noninclusion of the severe form of the disease as nephritis. In this review, we aim to discuss the characteristics of belimumab, critically evaluate the different steps of its development, and consider its future place in the arsenal against SLE, taking into account the patients' perspectives.

Keywords: systemic lupus erythematosus, belimumab, treatment, monoclonal antibodies, adverse effects, BLyS

Introduction

Although biologics have largely revolutionized the management of patients with rheumatoid arthritis (RA) during the past decade,[1] belimumab, the first biologic for patients with systemic lupus erythematosus (SLE), developed by Human Genome Sciences Inc, (HGS, Rockville, MD) in collaboration with GlaxoSmithKline (Research Triangle Park, NC), was only approved in 2011 by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[2,3]

For many reasons, this approval was considered an important milestone for SLE, but also, more broadly, in the field of systemic autoimmune diseases. Firstly, this is the first approval for >50 years by the FDA of a drug for this indication, which explains the hopes raised among patients and physicians who had become accustomed to using mostly off-label drugs (Table 1). Secondly, belimumab is the first biologic to be directly derived from genomics to reach the market. It is the result of the "proof of principle" that has translated the data generated by the Human Genome Project into clinical practice.[4] Thirdly, belimumab is also the first drug to have a successful B cell-targeting strategy. It may rebalance the failure to obtain significant results in recent prospective trials using other B-cell depletive approaches,[5,6] and could pave

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Table 1 Drugs used to treat lupus with or without label

Drugs	FDA	EMA	AFSSAPS
Prednisone	✓	NA	✓
Prednisolone	✓	NA	✓
Methylprednisolone	✓	NA	✓
Aspirine	✓	NA	–
NSAIDs	–	NA	–
Chloroquine	–	NA	✓
Hydroxychloroquine	✓	NA	✓
Thalidomide	–	–	§
Azathioprine	–	NA	✓
Cyclophosphamide	–	NA	✓
Methotrexate	–	NA	–
Mycophenomate mofetil	–	–	–
Cyclosporine	–	NA	–
Rituximab	–	–	§
Belimumab	✓*	✓**	NA

Notes: ✓, approval; –, no approval; NA, no evaluation available; §, special authorizations: thalidomide for severe cutaneous lupus, rituximab for severe SLE refractory to immunosuppressants and/or plasmapheresis ("Protocole Thérapeutique Temporaire"). *Seropositive patients, with SLE refactory to standard regimen; **seropositive patients, with SLE refractory to standard regimen and positive anti-DNA antibodies and low complement levels.
Abbreviations: FDA, Food and Drug Administration; EMA, European Medicines Agency; AFFSAPS, Agence Française de Sécurité Sanitaire des Produits de Santé.

the way towards developing new targeted agents for this disease (Table 2).

However, many clinicians in the field do not share this enthusiasm,[7,8] and their pessimistic comments on this recently labeled drug may antagonize other physicians and patients. Indeed, from a scientific point of view, the most surprising aspect is probably that some physicians persist in supporting rituximab for SLE, although it has failed to meet its primary endpoints in two prospective Phase III trials.[5,6] This is in contrast to belimumab, which has provided positive results in two prospective Phase III trials that have included about 1700 SLE patients[9,10] and have followed FDA recommendations.[11]

In this review, we discuss the characteristics of belimumab, critically evaluate the different steps in its development, and assess its future place in the arsenal against SLE.

Management issues for lupus

SLE is a chronic autoimmune disease involving multiple organs with a large diversity of possible clinical manifestations, including, among others, arthritis, pleuritis, pericarditis, stroke, seizure, nephritis, anemia, thrombocytopenia, photosensitivity, and rash.[12] The disease primarily affects women of child-bearing age, and has a prevalence of up to 1.5 million in the USA alone.[12] SLE evolution is characterized by inflammatory flare-ups that can ultimately cause permanent damage to multiple organ systems, which explains why it has one of the highest mortality rates among autoimmune diseases.[12,13]

Current treatment options to relieve symptoms and control the progression of SLE include antimalarial drugs (mainly hydroxychloroquine), steroidal and nonsteroidal anti-inflammatory agents, nonspecific immunosuppressive drugs, including methotrexate, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil (MMF), and biologics. However, only a few of these drugs have been approved (Table 1), hydroxychloroquine being the last drug

Table 2 Drugs targeting BLyS pathway under development for SLE

Company	Product/route of administration	Target	Status and ongoing or planned trials (www.clinicaltrials.gov)	Evaluation
Human Genome Sciences Inc/ GlaxoSmithKline	Benlysta belimumab LymphoStat-B intravenous	Human mAb targeting soluble BLyS (BAFF)	Approved by FDA and EMA NCT00724867 NCT00712933 NCT00583362 Phase III (long-term safety) NCT01345253 PhIII (Asia) NCT00732940 Phase II (Subcutaneous)	SRI
Eli Lilly	LY2127399 Subcutaneous	Human mAb targeting soluble and membrane-bound BLyS (BAFF)	NCT01196091 NCT01205438 Phase III	SRI
Merck KGaA/ Bristol-Myers Squibb	Atacicept (TACI-Ig) Subcutaneous	BLyS and APRIL (Soluble fusion protein containing the extracellular portion of TACI linked to Fc)	NCT00573157 Phase II/III* NCT00624338 Phase II/III NCT01440231 Phase II (dose response*)	Renal response BILAG SRI-50
Anthera Pharmaceuticals Inc/ Amgen	A-623 AMG 623 Blisibimod Subcutaneous	Peptide fusion protein that antagonizes soluble and membrane-bound BLyS (BAFF)	NCT01395745 Phase II NCT01162681 Phase II NCT01305746 Phase II (safety)	SRI SLE response**

Notes: *Dose of 5 to 115 mg/weekly because 150 mg dose judged unfavorable in renal Phase II/III trials; **SLE response is defined as the percentage of subjects with SLE response compared with baseline at the time of assessment (SRI included in secondary endpoints).
Abbreviations: BILAG, British Isles Lupus Assessment Group; SLE, systemic lupus erythematosus; SRI, SLE Response Index.

to be labeled by the FDA for SLE in the 1950s. In many countries, a "graduated" therapeutic escalation has been recommended.[14] Standard options of care (SOC) for mild to moderate SLE consist of nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarials, and corticosteroids, while life-threatening flare-ups, such as those affecting the kidneys or central nervous system (CNS), are treated with high-dose corticosteroids, and immunosuppressive agents such as cyclophosphamide and azathioprine, or MMF. Importantly, recent immunological and clinical research strongly supports the broad use of antimalarials for all SLE patients (including patients receiving immunosuppressants) to help prevent complications.[13,15,16]

In spite of this arsenal, some patients are still refractory to SOC or need prolonged high-dose corticotherapy and/or a long-term immunosuppressive regimen to maintain remission. In many cases, the drugs themselves cause irreversible damage, sometimes leading to death. Among other serious side effects, corticosteroids cause weight gain, hypertension, increased susceptibility to infection, osteoporosis, while immunosuppressants increase the risk of infections (including opportunist pathogens), malignancy, and infertility. Actually, avoiding this "collateral" damage is the strongest rationale for the development of biologics. Unfortunately for SLE patients, so far, available biologics have been either not recommended, such as tumor necrosis factor (TNF) blockers that can induce SLE[17], or have not gained approval in prospective evaluations, such as rituximab.[5,6] In this context, belimumab has just been labeled, but its place in the management of SLE is already a matter of debate, as evidenced, for example, by the discrepancies between the labeling given by the FDA and EMA (Table 1).

Pharmacology, mode of action, and pharmacokinetics of belimumab

To most immunologists, the physiopathology of SLE is so complex that the identification of a single factor/molecule that can mirror TNF-α for RA seemed until recently nearly impossible.[18] Nevertheless, the rationale for developing B-lymphocyte (BLy) inhibitors has been robust and has included successive in vitro, murine, and human investigations.

SLE is a systemic autoimmune disease characterized by autoantibody production against self-antigens (Ags). B-cell stimulatory factors that can promote the loss of B-cell tolerance and drive autoantibody production are exciting new candidates. In 1997, HGS discovered and rapidly identified the function of the B-lymphocyte stimulator (BLyS) protein.[19] BLyS, also known as BAFF (B-cell-activating factor from the TNF family), is a type II transmembrane protein that exists in both membrane-bound and soluble forms.[19] BLyS is expressed at the surface of a wide variety of immune cell types (monocytes, activated neutrophils, T cells, and dendritic cells), and its expression/secretion can be increased by various inflammatory cytokines.[20,21]

When cleaved from the membrane, BLyS becomes a soluble trimer that is a ligand for three receptors expressed primarily on B lymphocytes (Figure 1): BLyS receptor 3 (BR3 or BAFF-R), transmembrane activator-1, calcium modulator and cyclophilin ligand-interactor (TACI), and B-B-lymphocyte stimulator cell maturation antigen (BCMA). BLyS is the sole ligand for BR3, whereas TACI and BCMA can each bind with BLyS or another TNF family ligand known as a proliferation-inducing ligand (APRIL). These ligand–receptor interactions vary in affinity and BLyS binds more strongly to BR3 than to TACI or BCMA. In theory, APRIL can mediate effects similar to those of BLyS, but as the three BLyS family receptors vary in their expression patterns and levels across different B-cell subsets, its biologic action may be primarily on memory and plasma cells (Figure 1). In vitro, BLyS exhibits a strong costimulatory function on B-cell activation that leads to B-cell and plasma cell proliferation, differentiation, and survival, and to immunoglobulin G (IgG) class switching.[19]

Interestingly, results from murine models have indicated that increased expression of BLyS may lead to systemic autoimmune disease in mouse models and constitutes one of the first clues for a potential role for BLyS in human autoimmune disease. First, BLyS-transgenic mice developed severe B-cell hyperplasia and autoimmune lupus-like disease, characterized by the presence of autoantibodies against nuclear Ags and immune complex deposits in the kidneys.[22,23] Secondly, in two murine models of human SLE (MRL/Mp-*lpr*/*lpr* and NZB/W F1 mice), there were increased serum levels of BLyS that correlated with autoimmune kidney damage, and treatment with soluble BLyS receptors significantly improved survival of these lupus mice.[24]

In SLE patients, two cross-sectional studies have shown that serum levels of BLyS were significantly increased in a third of patients,[25,26] and were associated with IgG levels and antidouble-stranded DNA (anti-dsDNA) titers. Of note, this increase was not specific to SLE, as high circulating BLyS levels were also observed in patients with RA, Sjögren, and antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis.[27–29] Although patients with positive antinuclear antibodies (ANA), but no other American College of Rheumatology (ACR) criteria for lupus, had marginally

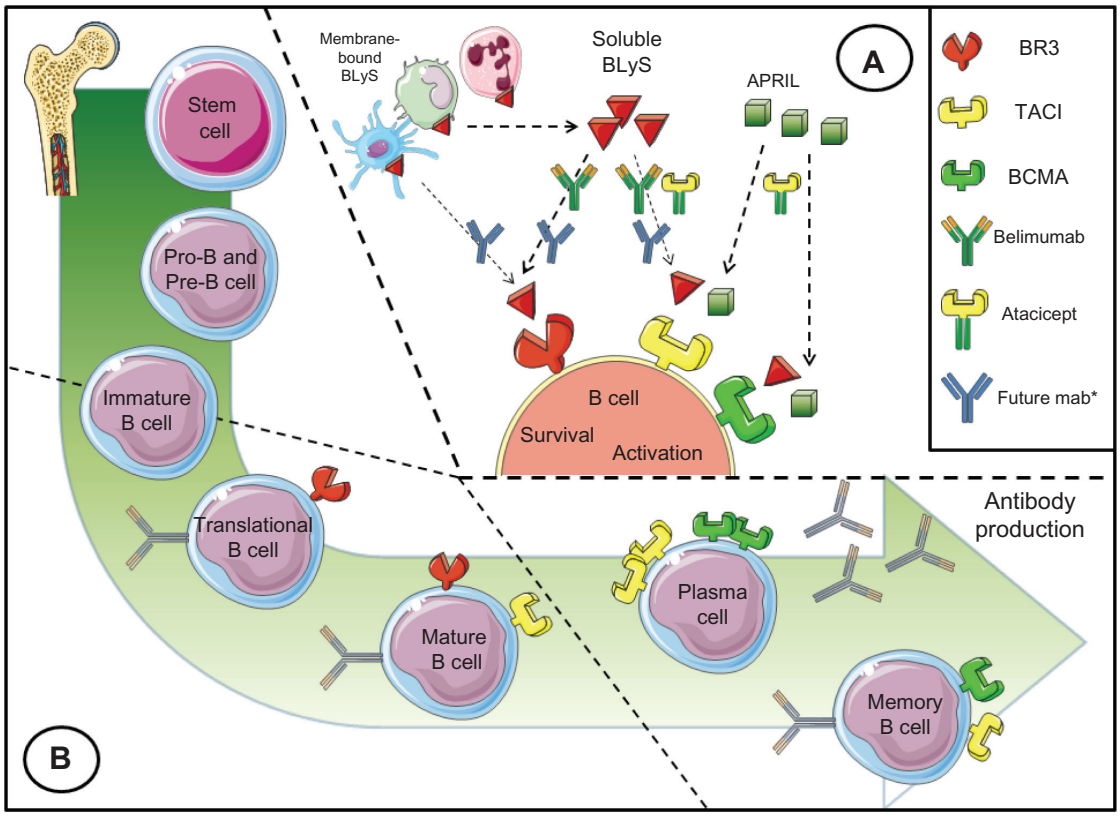

Figure 1 BLyS, its receptors and "anti-BLyS" biologics. (**A**) BLyS exists in both membrane-bound form (at the surface of a wide variety of cell types as monocytes, activated neutrophils, T cells, and dendritic cells) and, after cleavage, soluble form, that is a ligand for three receptors on B lymphocytes: BLyS receptor 3 (BR3), transmembrane activator-1 and calcium modulator and cyclophilin ligand–interactor (TACI), and B cell maturation antigen (BCMA). BLyS is the sole ligand for BR3, whereas TACI and BCMA each can bind either BLyS or another ligand known as a proliferation-inducing ligand (APRIL). Belimumab blocks only soluble BLyS, whereas atacicept also blocks APRIL and other drugs (see Table 2*) also aim at membrane-bound BLyS. (**B**) The three BLyS family receptors vary in their expression patterns and levels across different B cell subsets, explaining why belimumab has little biologic action on memory and plasma cells.

elevated BLyS levels, those with positive ANA and several criteria for lupus had higher levels. However, in these studies, BLyS levels were not correlated with SLE activity when evaluated with the SLE Disease Activity Index (SLEDAI).[25,26]

To explain this lack of correlation, let us keep in mind that some pieces of the BLyS puzzle remain unanswered in humans (Figure 1). First, a 60-mer form of soluble BLyS (BLyS-60) has been observed in mice[30] and in vitro evidence suggests that BLyS-60 binds to TACI with 100-fold greater affinity than the canonical trimeric BLyS.[31] However, the existence of a soluble BLyS-60 remains to be determined in humans. Secondly, BLyS–APRIL heterotrimers have also been characterized, but their function in vivo is unclear.[32] Third, BLyS can be expressed as a membrane-bound protein by immune and also nonhematopoietic cells (osteoclasts and synovial fibroblasts).[33] Finally, some have recently emphasized the contribution of BCMA in the production of autoantibodies,[34] while others have reported an inverse correlation between APRIL and both BLyS levels and disease activity in SLE patients, suggesting a protective role for APRIL.[35] In addition, a trial that tested atacicept (Figure 1) in another autoimmune condition, multiple sclerosis, was recently stopped because of an unexpected pro-inflammatory effect:[36] this illustrates the limitations in our comprehension of this complex pathway.

The interpretation of BLyS levels is difficult in some specific settings. On the one hand, some have suggested that glomerulonephritis may increase BLyS excretion in the urine, thereby resulting in paradoxically lower plasma BLyS levels in patients with very active disease.[37] On the other hand, the influence of certain drugs on BlyS/B-cell biology are also probably underestimated: as an example, rituximab-induced B-cell depletion is followed by an increase in BLyS level, which then returns to near-baseline levels when B cells are repopulated in ANCA vasculitis, RA, and SLE patients.[38,39] Finally, in a longitudinal study, using multivariate analysis with complex adjustments, Petri et al found that the level of BLyS at one patient's visit was positively correlated with the increase in SELENA–SLEDAI (SS) score at the

following visit,[37] thus providing the missing link between in vitro/murine and human data.

Belimumab (Benlysta®; HGS) is a fully human IgG1λ recombinant monoclonal antibody directed against BLyS. Specific binding of belimumab with soluble BLyS prevents its interaction with its three receptors and indirectly decreases B-cell survival and production of autoantibodies.[40] Although TACI and BCMA also bind to APRIL, BLyS is BR3's only ligand and the interaction of BLyS and BR3 is necessary for survival of naïve B cells and mature primary B cells. This enables belimumab to have a greater effect on early B cells, such as naïve B cells, and a lesser effect on memory and plasma B cells (Figure 1).

Belimumab is the first of a new class of drugs to target B-cell stimulating factors or their receptors (Table 2). Importantly, in contrast to other drugs under development (Table 2), belimumab does not neutralize membrane-bound BLyS (Figure 1). Belimumab is administered intravenously from single-use vials containing 120 or 400 mg of lyophilized powder that is reconstituted to obtain 10 mg/kg of belimumab administered over 1 hour. The first three doses are administered every 2 weeks and then treatment is repeated every 4 weeks. A Phase I dose-ranging randomized controlled trial on 70 SLE patients demonstrated in vivo safety and provided pharmacokinetic data.[40] The half-life of belimumab is 19–20 days, its volume of distribution is small (69–112 mL/kg), and clearance is slow (7 mL/day/kg). No significant pharmacokinetic change is seen with concomitant use of belimumab and NSAIDs, antimalarials, corticosteroids, methotrexate, azathioprine, or MMF; however, there are no available data concerning previous or ongoing administration of other biologics such as rituximab.

Efficacy studies, including any comparative studies

The following logical step in the development of belimumab was to conduct a Phase II double-blind randomized controlled trial on 449 SLE patients assigned to either belimumab (1, 4, or 10 mg/kg) or a placebo, administered intravenously on days 0, 14, and 28, and then every 28 days for 52 weeks.[41] All subjects also received the SOC, with a stable regimen of steroids, antimalarials, or immunosuppressants for 60 days prior to the first belimumab dose. Unfortunately, there were no significant differences between the treated and placebo groups regarding efficacy endpoints (percentage of change in the SS score at 24 weeks and the time to first SLE flare-up), and no dose response was observed in this trial. However, some secondary results were considered interesting. First, the time until a first flare-up was longer with belimumab (154 days in the combined belimumab group compared to 104 days with the placebo, $P = 0.036$). This suggests that the drug could have a postponed effect, which is not visible at 24 weeks: indeed, a significant decrease in the mean physician's global assessment (PGA) score at 52 weeks was noted (31% with belimumab compared to 14% with the placebo, $P = 0.0019$).

Secondly, post-hoc analysis of the subgroup of patients with serologically active disease (ANA >1:80 and/or anti-dsDNA >30 IU/mL) yielded significantly better responses at 52 weeks in belimumab- versus placebo-treated patients by SS score and PGA. This subset of patients exhibited higher disease activity (especially with regards to biologic markers) at baseline compared to ANA-negative patients. Finally, the large and poorly controlled use of corticosteroids was identified as a potential cause for the negative results in Phase II studies. In addition, in two later negative Phase II/III studies that tested rituximab in SLE patients, corticosteroids were blamed for masking the effect of the biologic therapy.[5,6] All these points have led to major modifications in the design of Phase III trials for belimumab.

The most important measures were the restriction of inclusion to seropositive patients, and the introduction of a novel tool to assess changes in disease activity, which was used as the primary endpoint: the Systemic Lupus Erythematosus Responder Index (SRI). In this compound index, SS scores were utilized to define global improvement, British Isles Lupus Assessment Group (BILAG) domain scores to ensure no significant worsening in previously unaffected systems, and PGA to ensure that improvement in disease activity was not achieved to the detriment of the patient's overall condition. From reanalysis of Phase II data, the SRI was defined as a ≥4 point reduction in SS score compared to baseline, plus no worsening (increase <0.3 points from baseline) in PGA score, plus absence of any new BILAG organ domain score of A or two new BILAG scores of B at week 52 compared to baseline. BILAG scores A and B, respectively, indicated a severe and moderate flare-up in any of the eight organ domains of the index.[42]

Two multicenter Phase III trials, BLISS-52 and BLISS-76, have been simultaneously conducted. In both trials, seropositive patients were randomized to one of three treatment groups: 10 mg/kg belimumab, 1 mg/kg belimumab, or a placebo. SOC therapy was given to all enrolled patients in addition to respective treatment. Intravenous belimumab was administered on days 0, 14, and 28, then every 28 days thereafter for the duration of the study. In the BLISS-52 trial,[9] which enrolled

865 seropositive patients, SRI rates were observed to be significantly higher in the belimumab-1 and 10-mg/kg group than with the placebo group at the end of week 52 (Table 3), whereas no significant difference was found between belimumab and the placebo with respect to adverse effects. In the BLISS76 trial,[10] 819 seropositive patients were observed for 76 weeks. The patients' response rates, to be measured by SRI at weeks 52 and 76, were the primary and major secondary endpoints, respectively. No significant SRI improvement was seen with belimumab at 1 mg/kg compared to the placebo. However, the improvement was significantly higher in the 10-mg/kg belimumab group than the placebo by week 52, but could not be sustained later and the difference by week 76 was not statistically significant (Table 3). The results of these two studies, compatible with the June 2010 FDA guidelines,[11] led to approval of belimumab in March 2011,[2] but deserve additional comments to explain the skepticism of some reports.[7,8]

First, some have criticized the use of a novel (and automatically poorly validated) composite endpoint to evaluate disease activity that was designed by HGS, namely SRI. The goal of devising a composite endpoint was to ensure that belimumab did not improve some manifestations at the expense of others. Whereas SS captures only the presence or absence of symptoms at a given point in time, BILAG captures improvement or worsening within eight organ systems. However, although the BILAG was the preferred index for measuring disease reduction,[11] the FDA had previously approved the choice of SRI. Nevertheless, it is important to note that choosing particular combinations of these parameters is not negligible. The different sensitivity of SS and BILAG might possibly provide totally different results with the same combination of parameters when used in a different way. This has been recently reported in an ongoing trial that compared SRI and BILAG-based Combined Lupus Assessment.[43]

The FDA and other experts have been concerned that only part of the scale was being used due to the exclusion of severe renal and CNS disease, and that a 4-point difference in scores might not be clinically meaningful using a reduced scale, especially as an ACR committee had concluded that a decrease of 7 points in SS was clinically meaningful.[44]

Table 3 Efficacy results of belimumab in BLISS-52 and BLISS-76 Phase III trials

	BLISS-52 (study C1057)			BLISS-76 (study C1056)		
	Placebo (n = 287)	Benlysta 1 mg/kg (n = 288)	Benlysta 10 mg/kg (n = 290)	Placebo (n = 275)	Benlysta 1 mg/kg (n = 271)	Benlysta 10 mg/kg (n = 273)
Primary endpoint						
SRI	125 (44%)	148 (51%)	167 (58%)	93 (34%)	110 (41%)	118 (43%)
Difference vs placebo		8%	14%		7%	9%
OR [95% CI] vs placebo		1.55 [1.10, 2.19]	1.83 [1.3, 2.59]		1.34 [0.94, 1.91]	1.52 [1.07, 2.15]
P-value		0.0129	0.0006		0.1041	0.0207
Subcomponents						
4-point reduction in	132 (46%)	153 (53%)	169 (58%)	98 (36%)	116 (43%)	128 (47%)
OR [95% CI] vs placebo		1.51 [1.07, 2.14]	1.71 [1.21, 2.41]		1.36 [0.96, 1.93]	1.63 [1.15, 2.32]
P-value		0.0189	0.0024		0.0869	0.0062
No worsening in PGA	199 (69%)	227 (79%)	231 (80%)	173 (63%)	197 (73%)	189 (69%)
OR [95% CI] vs placebo		1.68 [1.15, 2.47]	1.74 [1.18, 2.55]		1.60 [1.11, 2.30]	1.32 [0.92, 1.90]
P-value		0.0078	0.0048		0.012	0.1258
No new BILAG	210 (73%)	226 (79%)	236 (81%)	179 (65%)	203 (75%)	189 (69%)
OR [95% CI] vs placebo		1.38 [0.93, 2.04]	1.62 [1.09, 2.42]		1.63 [1.12, 2.37]	1.20 [0.84, 1.73]
P-value		0.1064	0.0181		0.0108	0.3193
Secondary endpoints on efficacy						
SLE Flares over 52 W						
Median Time to first SELENA-SLEDAI Flare (days)	84	126	119	82	85	84
OR [95% CI] vs placebo*		0.75 [0.62–0.90]	0.76 [0.63–0.91]		0.89 [0.74–1.08]	0.93 [0.78–1.13]
P-value		0.0026	0.0036		0.2324	0.4796
SRI W76	–	–	–	89 (32%)	106 (39%)	105 (39%)
Difference vs placebo		–	–		7%	6%
OR [95% CI] vs placebo		–	–		1.3 [0.9–1.9]	1.3 [0.9–1.9]
P-value		–	–		0.10	0.13

Note: *Median time to first flare was not available in the original paper,[10] and corresponding hazard ratios were taken from the FDA official document.[2]
Abbreviations: BILAG, British Isles Lupus Assessment Group; CI, confidence interval; OR, Odds Ratio; PGA, physician's global assessment; SRI, SLE Response Index; W, week.

But post hoc sensitivity analyses showed that patients receiving belimumab had a significantly greater rate of SRI response when higher SS thresholds of 5, 6, and 7 were used.[45]

In addition, although the designs of the two Phase III trials were identical (except that patients in the BLISS-52 trial were treated for 48 weeks, and those in BLISS-76 continued treatment until 72 weeks), discrepancies exist between their results, which may be explained in part by some of the difference in the selected patients (Table 4), which leads to questions about the generalizability of these results. As an example, the less favorable results in the BLISS-76 trial could suggest decreased efficacy of belimumab in patients with late established SLE, as the mean disease duration of enrolled patients was longer in the BLISS-76 trial, and BLISS 52 included almost no black patients, who have been shown to be unresponsive to belimumab in these studies.

Also, the management of other therapies was of concern. No new immunosuppressants were permitted after randomization, and no increases in dose of immunosuppressants or antimalarials was allowed after week 16. Increases of steroids were limited after week 24. Thus, because these trials evaluated efficacy at 52 weeks (instead of the 24-week evaluation period in the Phase II trial), this seemed to evaluate the capacity of belimumab to maintain the response obtained after initial changes in SOC. Also, patients who required changes to background medications that were not permitted by the protocol were scored as treatment failures, which happened more often in the placebo group, and might have exaggerated the effect of belimumab. However, this point was also addressed by further sensitivity analyses.[2]

Table 4 Difference in patients' characteristics between the belimumab Phase III trials

Phase 3 trials	BLISS-52 (C1057)	BLISS-76 (C1056)
Disease duration (year), mean	5.3	7.5
BILAG 1A/2B, %	58	64
SELENA-SLEDAI	9.8	9.7
Renal, %	20	11
Musculoskeletal, %	59	73
Cutaneous, %	82	82
Immunology, %	85	74
ANA positive, %	95	92
Anti-DNA positive, %	75	64
Low C4, %	59	53
SLICC/ACR damage index	0.57	0.99
Antimalarials, %	67	63
Corticosteroids, %	96	76
Prednisone >7.5 mg/day, %	69	46
Immunosuppressant, %	42	56
Geographic regions, %	Latin America 50 Asia 38 Eastern Europe 11 Australia 2	USA/Canada 53 Western Europe/ Israel 25 Eastern Europe 11 Latin America 11
Ethnicity, %		
Caucasian	27	70
Asian	38	3
Black/African American	4	14
Alaskan Native/ American Indian	32	13

Abbreviations: ANA, antinuclear antibodies; BILAG, British Isles Lupus Assessment Group; C4, complement fraction C4; SLICC, Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index.

Finally, the clinical relevance of this new therapy has been questioned. The trials enrolled a total of 1684 patients who were positive for autoantibodies and had SS scores ≥6. The most commonly involved organ systems were musculoskeletal (60%), mucocutaneous (59%), hematologic (16%), renal (11%), general (11%), and vasculitis (9%): there were no data from patients who had involvement of organ systems associated with mortality (CNS or proliferative nephritis). Even if mucocutaneous and musculoskeletal symptoms are debilitating and reduce quality of life (Qol), they are not generally lethal. This questions the relevance of the effect of belimumab, which seemed overall to be mild: this was either because there was little effect in the whole population or only a significant effect in a subset of patients. The latter hypothesis seems probable. First, the effect did not seem to concern specific subsets, as black patients given belimumab did even worse than those given a placebo in the Phase III trials. Black patients, who account for about 25% of lupus patients in the USA, tend to have more severe disease than the general lupus population. Of note, the BLISS-52 trial included no patients from the USA and had only 4% of patients with an African heritage, whereas the BLISS-76 trail had 14% black patients, though still far from the 25% expected in the USA. Thus, the negative results in the BLISS-76 trial at week 76 seem to be attributable to a lack of power due to exclusions, which implies that the huge sample size was probably one of the key factors to reach significance. In addition, required post-hoc analyses have been conducted and led EMA to restrict the label approved for belimumab to patients who are biologically active (positive anti-DNA and low complement levels), which is in contrast to the FDA recommendation.[2,3]

The mild and unsustained effect of belimumab, as well as the inability to clearly define which patients may benefit from belimumab, enables us to focus on the safety issues of

this new drug and to evaluate its benefit/risk ratio, especially as this drug is intended for patients with no life-threatening form of SLE.

Safety and tolerability

As with any other newly approved molecule, the long-term safety of the drug needs to be monitored since the results of any trial cannot fully predict a drug's safety profile in real-life practice (Table 2). Apart from the limited follow up of the three prospective trials, we also have data from open follow-up periods of >5 years.[46,47] Besides infusion reactions, such as urticaria, and hematologic reactions, such as neutropenia and thrombocytopenia, which have been reported in some patients, few serious adverse events have been reported during the clinical trials. However, serious infections and suicides, due to severe depression, have been reported more frequently with belimumab than with placebo (0.8% vs 0.4%). Six malignancies occurred (one in a placebo patient, three on 1 mg/kg, and two on 10 mg/kg). More deaths were reported with belimumab at 1 and 10 mg/kg than with a placebo (0.7% and 0.9% vs 0.4%). There were four deaths related to infection (one in the placebo group, three in the belimumab groups), and infection may have contributed to two more deaths in the belimumab arms.

To know whether belimumab's marginal efficacy is strong enough to justify individually the potential risks suggested by the small increases in a few serious adverse effects found in these trials, FDA calculated the death rate per 100 patient-years in the belimumab groups to be almost double that in the placebo group (0.79 vs 0.43; 95% confidence intervals [CI]: 0.49–10.08). According to statistical experts, 11 patients needed to be treated to achieve one SRI response, based on the BLISS-76 trial, and seven needed to be treated based on the BLISS-52 trial, whereas, in pooled analysis of both trials, 342 was the number needed to harm, or the number who would need to be treated before one death occurred. Thus, one death should be expected for every 30 or 50 patients who achieve an effect as the primary endpoint. However, against this pessimistic evaluation, the benefit/ratio of initiating belimumab treatment should obviously not solely take into account the risk due to this biologic, but instead include the risk in the calculation if patients that do not receive belimumab remain dependent on other treatments, especially long-term corticosteroids and their morbidity–mortality and impact on QoL. Of course, these safety concerns require a strict long-term follow-up, especially to detect rare side effects or side effects that may be more prevalent in patients outside of trials, who often exhibit more comorbidities.

Patient-focused perspectives such as QoL, patient satisfaction/acceptability, adherence, and uptake

From a patient's perspective, the efficacy of a drug is not the only important issue. Unfortunately, results from the secondary endpoints generally did not support the primary analysis. Week 76 response rate, a secondary endpoint in BLISS-76, was not significant (Table 3). Numerically, more patients in the belimumab arms in both trials were able to reduce their steroid use by ≥25% to ≤7.5 mg/day, a secondary endpoint. But the results were inconsistent for the other steroid-related secondary endpoint.[2,3] Especially, in the BLISS-76 trial, fewer patients given 1 mg/kg belimumab needed to increase their steroid dose compared to the placebo group, but the 10-mg/kg arm needed similar steroid doses to the placebo group.[2] Also, patients with a severe form of SLE, a seronegative form, or black SLE patients were not concerned by the presented results, as attested by the label attributed by the FDA and the nonbiologically active SLE patients outlined by EMA.[2,3]

Finally, from careful examination of the data available so far, it is clear that the decision to approve belimumab was probably influenced by the lack of hope in this field, an influence that is practically impossible to avoid in severe diseases. This was recently illustrated by the withdrawal of accelerated approval for bevacizumab (Avastin; Genentech/Roche, South San Francisco, CA) for metastatic breast cancer by the FDA:[48] we fully agree that physicians and researchers have the obligation to "give hope – but not false hope". To paraphrase the recent words of Dr Sekeres,[48] and of course setting aside the issue of the cost of belimumab, what kind of conversation would I have with such a patient if I were trying to convince her to take a treatment like belimumab? "Well, I can offer you a drug that will not make you live longer (belimumab was not evaluated for severe and potentially lethal forms), won't make you feel better (no clear results on quality of life or steroid sparing), and may have rare but life-threatening side effects (long-term evaluation is needed to conclude), but, considering that you are not black and that your lupus is biologically active, with a monthly infusion, it will keep your lupus from worsening for several months (negative 76 week results)." Hope? Or false hope?

The modality of administration is also an important issue with regards to patient adherence. Indeed, nonsevere patients

are mostly managed as outpatients and because they have to come to a hospital monthly this factor probably also has a negative impact on QoL and/or adherence in some patients. However, a Phase II study on belimumab administered subcutaneously is ongoing (Table 2).

A few important issues should be evaluated before the initiation of belimumab to SLE patients refractory to SOC. First, a significant proportion of so-called refractory SLE patients are likely to have insufficient drug exposure due to either poor observance or inter-individual variability to drug metabolism, the primary source of treatment failure. Thus, adherence to treatment needs to be assessed using, among other ways, unscheduled measurement of drug blood levels, as proposed by Arnaud and colleagues,[49] to avoid unnecessary therapeutic intensification. Also, physicians could ideally enroll patients with persistent nonobservance in a therapeutic education program dedicated to SLE, to maximize their general adherence to treatment. Finally, due to its good tolerance profile and efficacy, there is a consensus for giving antimalarials to all SLE patients,[14] which was not the case for a third of patients in the BLISS trial (Table 4). Conversely, in cases of real intolerance or a contraindication to antimalarials, belimumab could be an interesting option instead of switching to long-term immunosuppressive treatments.

Conclusion: belimumab's place in therapy

Despite the need for huge trials and unique trial endpoints to demonstrate the drug's modest efficacy, belimumab could be useful in some carefully selected patients, and the approval of belimumab for SLE seems to be only the beginning of a long path to defining its role in real life.

In the meantime, we can already distinguish different patients/situations. First, for patients with severe flare-ups (nephritis or CNS), belimumab should not be used because there are no data available concerning these patients and because the slow onset of belimumab might not be compatible with the rapid control needed for a severe flare-up. Secondly, for patients with mild flare-ups, if they fulfill the approval terms (seropositive in the USA or seropositive with presence of anti-DNA and low complement in Europe), belimumab might be initiated in patients refractory to SOC. Nevertheless, due to the mild effect, especially on steroid sparing and some unavoidable reported serious side effects, black patients should not receive belimumab until additional data are available and only nonblack patients with real refractory disease (meaning with biologically active or high steroid dose, and good exposure/adherence to SOC, including ideally antimalarials) might be proposed for this new biotherapy. In cases of intolerance/contraindication to antimalarials, belimumab could also be a useful alternative. Initiation should be monitored across a registry, as proposed for other biologics,[50] to better characterize tolerance profiles in the long term.

Finally, physicians taking care of SLE patients are well aware that there is an urgent need to individualize therapy in such a heterogeneous disease. Efforts should be made to improve identification of patients who might respond to anti-BLyS. New tools available to fully assess the immune response of SLE patients across time should be evaluated to monitor treatment and also to predict drug responders.[51,52] Now that the era of biologics in SLE has come, questions about identification of appropriate lupus patients with active disease, trial endpoints, and the subgrouping of lupus patients remain, and independent efforts are needed to prevent the approval of a new biologic that relies on the use of its own "tailored" index.[11,43]

Disclosure

The authors report no conflicts of interest in this work.

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