Belimumab in systemic lupus erythematosus: a perspective review

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Abstract: Belimumab (Benlysta®) is a fully humanized monoclonal antibody that inhibits B-lymphocyte stimulator (also known as B cell activating factor of the tumor necrosis factor family) and was approved by the US Food and Drug Administration and the European Medicines Evaluation Agency for treatment of autoantibody-positive systemic lupus erythematosus (SLE) in adults. This review discusses the key findings of the phase III trials, *post hoc* analyses, and real-world postmarketing use of belimumab in the routine care of SLE patients. It also highlights the safety profile of belimumab and gives insight into its potential use to treat childhood-onset SLE. It concludes with a discussion of the current clinical trials investigating belimumab in specific SLE disease states and a look to the future with novel targeted B-cell therapies.

Keywords: belimumab, lupus treatment, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a complex, multisystem autoimmune disease of unknown etiology with a heterogeneous range of clinical and serologic manifestations. It can affect multiple organ systems and its hallmark is the production of autoantibodies [Choi *et al.* 2012; D'Cruz *et al.* 2007; Rahman and Isenberg, 2008]. There are 11 criteria as specified by the American College of Rheumatology or the Systemic Lupus International Collaborating Clinics for classification of disease as SLE [Hochberg, 1997; Petri *et al.* 2012]. SLE predominantly affects women of child-bearing age, with a female-to-male ratio of 9:1 [Costenbader *et al.* 2007] and has higher prevalence in African Americans, Hispanics and Afro-Caribbeans compared with Caucasians worldwide [Symmons, 1995]. The course of disease is complicated by its unpredictability with periods of increased inflammatory disease activity, as well as the accrual of organ damage, and is often associated with significant morbidity and mortality [Choi *et al.* 2012; D'Cruz *et al.* 2007; Rahman and Isenberg, 2008].

The uniqueness of disease expression in each patient necessitates frequent follow up and laboratory assessments. Physicians currently manage SLE with multiple immunosuppressive medications that

improve disease control, some of which may also put patients at risk for potential severe side effects from broad immunosuppression [Askanase *et al.* 2009; Carneiro and Sato, 1999]. Moreover, patients may continue to develop disease flares despite what appears to be optimal treatment, requiring escalation of therapy including increased use of corticosteroids and possibly contributing to subsequent long-term damage [Urowitz *et al.* 2012]. Thus, there continues to be a need for more effective and safe options to treat SLE.

Over the past decade, better understanding of SLE immunopathogenesis, in particular, specific B-cell mechanisms, has allowed for a focus on targeted, rather than broad, immunosuppression [Nashi *et al.* 2010; Vincent *et al.* 2014; Kamal and Khamashta, 2014; Bluml *et al.* 2013]. In healthy individuals, B cells play an integral part in maintaining a functioning immune system by serving as antigen-presenting cells, secreting pro-inflammatory cytokines, and producing protective antibodies. However, in SLE, a large number of B cells cannot distinguish self-antigens from non self-antigens, resulting in the production of antibodies against self-antigens, and triggering an over-active inflammatory immune response [Nashi *et al.* 2010]. B lymphocyte stimulator (BlyS), also known as B cell activating factor of the tumor

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Table 1. Belimumab drug summary.

Drug name	Belimumab (Benlysta®)
Mechanism of action	Fully humanized monoclonal antibody inhibiting B-lymphocyte stimulator (also known as B cell activating factor of the tumor necrosis factor family) actions
Dosing	10 mg/kg intravenously once every 2 weeks for 6 weeks, then 10 mg/kg intravenously once every 4 weeks thereafter
Approvals	2011 US Food and Drug Administration 2011 European Medicines Evaluation Agency
Approved for	Autoantibody-positive systemic lupus erythematosus excluding patients with lupus nephritis and/or neuropsychiatric lupus over 18 years of age
Key studies	Phase III clinical trials (BLISS-52 and BLISS-76) Predictors of response (<i>post hoc</i> phase III trial analysis) Postmarketing experience with belimumab in routine lupus care 7 year follow up including adverse effects

necrosis factor family (BAFF), can bind to three different receptors that are critical for B-cell maturation and survival [Vincent *et al.* 2014, Baker *et al.* 2003]. BlyS/BAFF and type I interferons act synergistically in the pathogenesis of SLE through Toll-like receptor-dependent and -independent mechanisms. Mouse models of SLE demonstrate overproduction of BlyS/BAFF and elevated numbers of mature B cells and autoantibodies [Mackay *et al.* 1999]. Moreover, defective signals for apoptosis in B cells have been observed in these mice which overexpress BlyS/BAFF, impairing tolerance, and allowing B cells that recognize self-antigen to survive [Figgett *et al.* 2013].

Patients with SLE, in comparison with serum from healthy individuals and patients with rheumatoid arthritis, have higher serum concentrations of BlyS/BAFF [Zhang *et al.* 2001]. Interestingly, there was a study suggesting that BlyS/BAFF serum levels were higher in African-American SLE patients than in Caucasian SLE patients, though the difference did not reach significance [Ritterhouse *et al.* 2011]. There have also been studies demonstrating an association between serum BlyS/BAFF levels and SLE disease activity [Petri *et al.* 2008], making BlyS/BAFF an attractive target for treatment of SLE.

Induction and maintenance of disease remission in SLE is as important as prevention of chronic end-organ damage and drug-related morbidity. This review provides an overview of the efficacy and safety of belimumab from the phase III trials and their *post hoc* analyses. The current clinical real-world experience with belimumab use in

SLE patients and the impact of belimumab on the quality of life of SLE patients is also discussed, along with a review of the use of belimumab in childhood-onset SLE (defined as diagnosis of SLE made prior their 18th birthday, cSLE) to date. A discussion of the current clinical trials investigating the use of belimumab in specific SLE disease states and the development of new B-cell targeted therapies conclude this review.

Clinical efficacy of belimumab

Belimumab is a fully humanized, monoclonal antibody against BlyS/BAFF. Postmarketing studies estimate that approximately 5% of all SLE patients are on treatment with belimumab (Table 1) [Yazdany *et al.* 2013; Askanase *et al.* 2014]. The protocol for the phase III clinical trials was adjusted based on the data from phase II trials. SLE patients with moderately active disease (SLE disease activity indices ≥ 6) and who were autoantibody-positive showed improvement in disease control in response to belimumab treatment when compared with all SLE patients treated with belimumab. In addition, given the heterogeneity of SLE and the possible confounding by changes in concomitant medications, the phase III studies allowed for medication changes only for the first 6 months of belimumab therapy. In order to better define clinical efficacy of belimumab, a novel outcome measure, SLE Responder Index (SRI), was developed and defined as a combination of changes in validated measures of disease activity: the SLE disease activity index (SLEDAI); British Isles Lupus Assessment Group index; and the physician's global assessment.

Two multicenter, randomized, placebo-controlled clinical trials were then conducted in separate geographic sites to assess the efficacy of belimumab in addition to standard of care therapy in patients with active SLE [Navarra *et al.* 2011; Furie *et al.* 2011]. Patients on placebo were also receiving standard of care SLE therapy. Inclusion criteria were a diagnosis of SLE as defined by American College of Rheumatology criteria, seropositivity prior to enrollment in the trial, and a SLEDAI ≥ 6 . Patients were randomized to receive intravenous infusions of belimumab at 1 mg/kg, 10 mg/kg, or placebo at enrollment, at 2 and 4 weeks later, and every 4 weeks thereafter. BLISS-52 enrolled 867 patients from Eastern Europe, Asia and Latin America who received belimumab or placebo as randomized above, plus standard of care therapy for 52 weeks. BLISS-76 included 819 patients from Europe and North America, who also received belimumab or placebo as above, plus standard of care therapy for 76 weeks. Both studies met the primary efficacy endpoint with a statistically significant improvement in patients receiving 10 mg/kg belimumab over placebo at 52 weeks. In BLISS-52, there were 58% patients in the 10 mg/kg belimumab group who met the SRI response criteria compared with 44% in the placebo group; in BLISS-76 there were 43% patients in the 10 mg/kg belimumab group who responded compared with 33% in the placebo group. However, there was no significant difference in response at 76 weeks between the groups on belimumab and the placebo group.

Post hoc exploratory analyses in BLISS-52 and BLISS-76 showed that treatment with belimumab added to standard of care therapy significantly reduced the rate of disease flares, allowed for lower prednisone doses, and decreased serologic activity compared with the placebo group who were only on standard of care therapy [van Vollenhoven *et al.* 2012]. Moreover, it was suggested that patients who had greater disease activity, lower complement levels and higher anti double-strand DNA (anti-dsDNA) levels, and who were on prednisone at the time of enrollment may have greater therapeutic benefit with the addition of belimumab [van Vollenhoven *et al.* 2012]. Newer data show there is also improvement in the patient-reported quality of life and fatigue after initiation of belimumab compared with placebo [Furie *et al.* 2014].

There were 267 patients with lupus nephritis in the phase III trials. A subgroup analysis of these

patients suggested that belimumab in combination with mycophenolate mofetil may result in improvement of renal disease [Dooley *et al.* 2013]. In patients with active lupus nephritis, those who were seropositive and on treatment with belimumab were more likely to improve than those who were seronegative and/or on placebo, with normalized laboratory derangements, and improved proteinuria at 52 weeks after initiation of belimumab.

There were 54 pregnancies in combined data from the phase II and III trials [Ginzler *et al.* 2014; Wallace *et al.* 2013], 21 of which resulted in live births and 13 in fetal loss. Two of the live births in patients on belimumab had congenital abnormalities: one had a chromosomal abnormality also present in the mother and the other had a cerebral malformation of the cerebellum and fourth ventricle. Approximately 33% of SLE patients on belimumab had anticardiolipin antibodies. These patients had a higher rate of fetal loss.

Real-world use

Since the results of the phase III trials, three post-marketing studies show arthritis and mucocutaneous disease as common indications for the initiation of belimumab therapy [Yazdany *et al.* 2013; Askanase *et al.* 2014; Hui-Yuen *et al.* 2014]. Data on 195 patients show response to belimumab at 3 and 6 months post-initiation to be consistent with those reported in the phase III trials, with 48% of patients responding clinically by 3 months and 58% of patients by 6 months [Hui-Yuen *et al.* 2014]. A similar observational study of 384 SLE patients over 12 months revealed sustained efficacy of belimumab after 12 months of use and allowed for tapering of corticosteroid dose [Collins *et al.* 2013]. However, six patients were also started on corticosteroids during the study. Clinical response was noted in 47% of SLE patients by 6 months and 30% at 12 months. Safety was not assessed in this study.

Yazdany and colleagues followed 68 SLE patients enrolled in the Lupus Clinical Trials Consortium national patient registry who were being treated with belimumab [Yazdany *et al.* 2013]. The most common indications for starting belimumab were arthritis and mucocutaneous disease. There were 48% of patients who were seropositive at initiation of belimumab. At 6 months, 85% of patients continued on belimumab with small decreases in disease activity scores, and corticosteroid dosing.

At 12 months, 65% of patients remained on belimumab with similar disease activity scores, and no change in corticosteroid use or dosing. These data suggest that belimumab in addition to standard of care therapy resulted in improvement in disease activity up to 12 months after initiation and are consistent with the phase III trials.

Another study of 18 patients treated with belimumab in addition to standard of care therapy had a follow up of 9 months [Andreoli *et al.* 2014]. At the initiation of belimumab, 83% of patients were seropositive. A significant decrease in disease activity as measured by SLEDAI score was noted as early as 3 months after initiation of belimumab therapy and sustained at 9 months. Laboratory improvement and decreased autoantibody levels was also noted as early as 3 months after starting treatment. These data demonstrate a significant decrease in the amount of corticosteroid use 9 months after initiation of belimumab, suggesting a role for belimumab as a steroid-sparing agent.

The long-term efficacy and safety of belimumab was evaluated in 296 SLE patients who enrolled in the phase II continuation study that lasted 7 years [Ginzler *et al.* 2014]. Of the 177 patients who remained in the study, 135 had positive serology at enrollment. These patients had decreased number and severity of disease flares, and steady improvement in disease activity over 7 years. There were also sustained decreases in autoantibody levels and corticosteroid dosing, indicating sustained efficacy of belimumab over time.

Use of belimumab in cSLE

We have reported on the use of belimumab in 39 patients with cSLE, diagnosed with SLE prior to their 18th birthday, out of a cohort of 195 patients who had not participated in the belimumab phase III trials. The mean age at initiation of belimumab was 29 years of age, with 4 patients who were under 18 years of age at time of start of belimumab therapy [Hui-Yuen *et al.* 2014]. The main reasons for initiation of belimumab were inability to taper steroids, arthritis, rash and worsening serologic activity. After 6 months, a greater proportion of cSLE patients responded clinically to belimumab (65%) compared with 45% of adult SLE patients. In addition, 48% of cSLE patients on belimumab had more than 25% improvement in complement and/or anti-dsDNA antibody

levels. Moreover, 48% of cSLE patients had at least a 25% decrease in their dose of corticosteroids 6 months after initiation of belimumab, which is higher than that reported in the phase III clinical trials (19%) [Navarra *et al.* 2011; Furie *et al.* 2011]. Interestingly, 35% of cSLE patients were able to discontinue steroids, suggesting a more important role for belimumab as a steroid-sparing agent in cSLE.

Adverse events

Two studies have focused on the safety profile of belimumab. One was a continuation of the phase II trial to 7 years, the other pooled data from the phase II and phase III trials [Ginzler *et al.* 2014; Wallace *et al.* 2013]. Ginzler and colleagues noted that the rates of severe adverse events, including serious infection, were stable or decreased during 7 years of treatment with belimumab [Ginzler *et al.* 2014]. Wallace and colleagues analyzed the pooled data from phase II and III trials, and found that the serious adverse event rate was 18% in SLE patients on treatment with belimumab compared with 16.6% in those receiving placebo [Wallace *et al.* 2013].

The most common adverse effect reported while on belimumab therapy was infection, both in the clinical trials and postmarketing experiences [Wallace *et al.* 2013; Askanase *et al.* 2014]. Similarly, the most common reason for discontinuation of therapy was lack of response to belimumab. The rate of adverse events ranged from 6 to 38% [Ginzler *et al.* 2014; Wallace *et al.* 2013; Andreoli *et al.* 2014] and included infusion reactions, hypersensitivity, headache, nausea and fatigue, in addition to infections as mentioned above. Over 16% of patients were reported to have a psychiatric adverse event while on belimumab by Wallace and colleagues [Wallace *et al.* 2013], which is higher than the reported rates with standard SLE therapy alone. Over half of those experienced insomnia or anxiety; however, there were 6% of the patients who experienced severe depression and 0.1% reported suicidal ideation while on belimumab. There was a two-fold greater likelihood in patients on belimumab of developing a psychiatric disorder if the patient had a history of existing psychiatric disease. Moreover, there have been two reported cases of progressive multifocal leukoencephalopathy in patients on treatment with belimumab [Fredericks *et al.* 2014]. While treatment was discontinued in both patients, one of the patients was concomitantly on belimumab,

mycophenolate mofetil and low-dose corticosteroids at the time of neurologic deterioration and ultimately died [Fredericks *et al.* 2014].

Malignancies were described in 11 patients in the first 4 years of the phase II continuation trial; this figure decreased to 6 in years 5–6 and 4 in year 7 [Ginzler *et al.* 2014]. The most common malignancies throughout the continuation trial were skin cancers (nonmelanomatous, squamous cell carcinoma and basal cell carcinomas). Mortality due to the use of belimumab was most commonly attributed to severe infection [Ginzler *et al.* 2014] and also included suicide, cardiac disease and malignancy. The mortality rate observed in patients on open-label belimumab is 0.4/100 patient-years, which is below the mortality rate for SLE patients as a whole (1.63/100 patient-years) [Bernatsky *et al.* 2006].

In postmarketing studies, the discontinuation rate ranged between 11 and 26.5%, and there were 6–18.6% of patients who experienced adverse events, consistent with phase II and III data as described above. In 18 Italian patients on belimumab, there was a higher proportion who experienced infections while on belimumab (38%) compared with the phase III trials.

In cSLE patients, there were three patients who developed or had worsening of lupus nephritis [Hui-Yuen *et al.* 2014]. There was also one cSLE patient who developed seizures while on belimumab, but no patients developed psychiatric adverse events. There have been no reports of malignancies or death in cSLE patients on belimumab to date.

Overall, the safety profile of belimumab appears to be acceptable, with low incidence of serious infections, death and malignancies in both the phase III trials and long-term follow-up data [Ginzler *et al.* 2014; Wallace *et al.* 2013]. However, the severe neuropsychiatric effects (severe depression, suicidal ideation) and occurrence of 2 cases of progressive multifocal leukoencephalopathy over 7 years of treatment with belimumab should be carefully considered in the decision to start belimumab, especially in patients with a prior history of psychiatric disorder.

Future directions

The precise role of belimumab in the management of moderate to severe SLE remains to be

fully elucidated. To date, data from the phase III trials and postmarketing surveillance studies demonstrate an acceptable safety profile, with low incidence of severe infections, malignancies and death [Ginzler *et al.* 2014; Wallace *et al.* 2013]. There are several ongoing clinical trials investigating its use, among others, in patients with active lupus nephritis, African-American SLE patients and cSLE patients.

In addition, it is as yet unclear whether belimumab is beneficial in treating neuropsychiatric lupus and lupus nephritis. There is an ongoing belimumab trial investigating its use in the management of severe lupus nephritis. We are hopeful this trial will provide information to determine whether belimumab would be beneficial in severe, active lupus nephritis. Belimumab is not recommended to treat neuropsychiatric lupus as those patients were not included in the clinical trials. There is a 2-fold greater likelihood of developing a psychiatric disorder if a patient has a history of existing psychiatric disease upon initiation of therapy with belimumab and 2 reported cases of progressive multifocal leukoencephalopathy over 7 years of belimumab treatment.

Currently, studies are underway to determine if belimumab would be an effective treatment for other diseases, including Sjogren's syndrome and atherosclerosis [De Vita *et al.* 2014; Tsiantoulas *et al.* 2015].

Conclusion

There is no question that B cells play an essential role in the pathogenesis of SLE. In addition, it has been demonstrated that SLE patients have elevated serum levels of BlyS/BAFF compared with other autoimmune diseases, making its inhibition by belimumab a logical choice as an addition to the existing SLE armamentarium. Moreover, belimumab has been shown in clinical trials to be effective through favorable improvement of disease activity and serologic abnormalities in SLE patients.

The precise profile of the SLE patient who would derive the most benefit from belimumab treatment remains to be defined. To date, belimumab has been shown to be effective in autoantibody positive adult SLE patients with moderately active disease (SLEDAI score ≥ 6) whose clinical manifestations are predominantly mucocutaneous and/or musculoskeletal. Emerging data confirm

that cSLE patients with similar characteristics also respond favorably to belimumab. In particular, emerging data suggest a potential role for belimumab as a steroid-sparing agent given that many patients are able to taper and even discontinue their existing corticosteroid use after initiation of belimumab.

Overall, the safety profile of belimumab appears to be acceptable, with continuation study data confirming the low incidence of malignancies, infection and death observed in the clinical trials. However, it is as yet unclear what duration of belimumab use would be most beneficial in controlling disease activity. Given that belimumab has been shown to reduce the incidence and severity of flares, it is acceptable to continue belimumab therapy unless there is development of adverse events or contraindications to its continued use. Data from postmarketing experiences support the use of belimumab safely in addition to standard of care therapies. We eagerly look forward to the results of further registry studies and randomized controlled clinical trials to further delineate long-term effects of belimumab and define its role in the SLE armamentarium.

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Conflict of interest statement

A.D.A. serves as a consultant for GSK. The other authors declare no conflicts of interest in preparing this article.

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