

REVIEW

Belimumab in systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is one of the most challenging autoimmune disorders with a complex pathophysiology and diverse clinical presentation. Many drugs have been used to treat SLE with suboptimal results, especially in patients with moderate-to-severe disease. Belimumab is the first biological drug to be approved for the treatment of SLE in more than 50 years. This monoclonal antibody blocks B-cell activating factor, a cytokine important for B-cell differentiation and survival. In this review we focus on the activity of belimumab in patients with SLE and discuss the controversies of its use.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disorder with multisystem involvement.^{1 2} Its prevalence ranges from approximately 40–200 cases per 100 000 population³ and is expected to increase because of more accurate diagnosis and improved survival (10 year survival estimated 92%).^{1 4} SLE is significantly more common in women than in men (9:1), particularly in women after puberty and before menopause.^{1 5 6} For reasons not understood, it is also more frequent in certain ethnic groups including African-Americans and Hispanics.^{1 3 5}

DIAGNOSTIC CRITERIA AND CLINICAL COURSE

SLE may involve any of the vital organs. Not surprisingly, it has very diverse clinical manifestations ranging from fatigue and mild skin rash to end-stage renal failure. The diagnostic criteria also reflect this diversity. The Systemic Lupus International Collaborating Clinics (SLICC) group has recently published a set of classification criteria.^{1 7} This set includes 11 clinical criteria related to cutaneous, mucosal, serous, renal, neurological and haematological involvement, and 6 immunological criteria including the presence of antinuclear antibodies (ANA),

Key messages

- Systemic lupus erythematosus (SLE) is a heterogeneous disease largely dependent on the generation of auto-reactive antibodies by B cells.
- Belimumab is a monoclonal antibody against B-cell activating factor (BAFF) and the first biological drug to be approved for the treatment of SLE in more than 50 years.
- The BLISS-52 and 76 are phase III randomised trials that were conducted to evaluate belimumab efficacy and safety throughout 52 and 76 weeks of treatment respectively.
- BLISS-52 and 76 demonstrated that belimumab has a role as add-on therapy in adult patients with active, autoantibody-positive SLE with a high degree of disease activity, in those patients who principally have mucocutaneous and musculoskeletal involvement.
- Several on going trials attempt to understand the role of belimumab in specific settings (lupus nephritis, patients with African ancestry, paediatric patients and the impact on vaccine responses), as well as its long-term efficacy and tolerability.
- Many questions remain to be addressed such as the ideal combined therapy, its effectiveness compared to other drugs or its cost-effectiveness out of the clinical trials setting.

anti-double-stranded DNA (anti-dsDNA), anti-Smith (anti-Sm) and antiphospholipid antibodies, a direct Coombs' test (in the absence of haemolytic anaemia) and low levels of complement.^{1 7} SLE diagnostic criteria are met if a patient has four or more criteria (at least one clinical and one immunological) or a biopsy-proven nephritis compatible with lupus in the presence of ANA or anti-dsDNA.⁷

The clinical course of SLE is characterised by spontaneous or treatment-induced remissions and relapses. Disease activity is assessed by evaluating clinical manifestations, such as the number and type of skin lesions, or arthritis, together with laboratory and immunological tests, including complete blood

count, serum complement levels and titres of anti-dsDNA.⁸ However, several indices have been developed for more sensitive and accurate monitoring of disease. The 2008 EULAR (The European League Against Rheumatism) recommendations suggest that at least one of the following indices should be used to monitor disease activity: the SLE Disease Activity Index (SLEDAI), the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI, the British Isles Lupus Assessment Group (BILAG) index, the European Consensus Lupus Activity Measurement or the Systemic Lupus Activity Measure.⁸ In addition, the assessment of patients' health status can be performed with health-related quality of life measures, such as the 36-item short form health survey (SF-36),⁹ or the more lupus specific LupusQoL.¹⁰

PATHOGENESIS

The pathogenesis of SLE is not completely understood but it is believed to result from complex interactions between genetic susceptibility, environmental and hormonal factors, and disturbances in the innate as well as adaptive immune system.¹⁻² Several genetic and epigenetic phenomena have been implicated in the pathogenesis of SLE. Deficiencies in complement components are well known to predispose to the development of a lupus-like disease, and a number of single-nucleotide polymorphisms may also contribute to this risk, particularly loci such as TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10.¹¹⁻¹² Although these loci seem to account for only about 15% of the heritability of SLE,¹³ they will help to identify additional inflammatory pathways that may be used as therapeutic targets.¹

The development of SLE depends largely on the generation of autoreactive antibodies that lead to deregulated inflammatory responses and immune complex deposition responsible for the majority of target organ failure.⁵ It is believed that a priming event on this cascade follows an environmental trigger (eg, ultraviolet radiation or Epstein-Barr virus infection), probably linked to inherent abnormalities in the immune systems and ineffective clearance of apoptotic nuclear fragments.¹⁻⁵ These include dsDNA and single-stranded DNA, RNA binding nuclear antigens (Ro, La and Smith antigens) and other non-nuclear fragments, which are then processed by antigen presenting cells (APC).⁵ Self-antigens are presented to autoreactive T cells, which then trigger auto-B cells into producing anti-self antibodies and propagate the inflammatory response by acting as APC, contributing to the release of proinflammatory cytokines such as interferon α , interleukins (IL-6 and IL-17), B-cell activating factor (BAFF), tumour necrosis factor α and a proliferation-inducing ligand (APRIL).^{1-5, 14}

Several studies in mice models of SLE support this central role of B cells and autoreactive antibodies in SLE pathogenesis. A study using a knockout gene mutation

to prevent lupus mice developing B cells resulted in the absence of autoreactive antibody and clinical manifestations of disease.¹⁵ These mice also exhibited a significantly reduced number of activated T cells suggesting the importance of B-T cell interaction.¹⁶ When these animals were genetically manipulated to express surface immunoglobulins (not soluble antibodies), they demonstrated T-cell activation and developed nephritis, without renal antibody deposition, suggesting the existence of antibody-independent mechanisms of lupus nephritis.¹⁷

In addition, hormones, particularly oestrogen, also contribute to SLE pathogenesis through an unknown mechanism.¹⁻⁵ SLE is more frequent in women during childbearing period and the risk of relapse is increased in SLE females treated with hormone replacement therapy and, on occasion, during pregnancy.¹⁸ The X chromosome may also contribute independently for this increased prevalence of SLE in females. Studies using genetically modified mice (females XX or XO; males XY or XXY) suggest that the presence of two X chromosomes increases the severity of SLE.¹⁹ The reasons for it, however, are still to be clarified.

THE BAFF/APRIL AXIS

Improving our understanding of the pathogenesis of SLE is crucial to develop new drugs targeted at particular pathological mechanisms. It is hoped that this may increase efficacy and decrease side effects. The recognition of B cells as central in the pathogenesis of SLE led to the development of several drugs that block their activity, including antibodies to B-cell surface antigens, B-cell toleragens, blockers of co-stimulatory molecules and inhibitors of cytokines with direct effect on B cells.²⁰

The BAFF/APRIL axis has been extensively studied as these cytokines are vital to B-cell maturation and survival.²¹⁻²³ BAFF and APRIL act mainly through their soluble form (although BAFF also has a transmembrane form of unknown physiological relevance).²¹⁻²³ They are produced by a number of different cells, most importantly monocytes, neutrophils, macrophages, dendritic cells and T cells, and bind to three different receptors on B cells.²³ Both BAFF and APRIL bind to TACI (transmembrane activator and cyclophilin ligand interactor) and BCMA (B-cell maturation antigen), and BAFF additionally binds to BAFF-receptor (BAFF-R). BAFF binds strongly to BAFF-R and TACI, and APRIL binds strongly to BCMA and weakly to TACI (reviewed in ref. 23). According to the receptor expression patterns, BAFF may be more important for immature B-cell survival and APRIL for plasmablasts and plasma cells.²⁴⁻²⁵ BAFF-R expression is diminished, but still detectable, on germinal centre B cells whereas it is greatly reduced or absent on plasma cells.²⁴⁻²⁶

Although the exact role of BAFF/APRIL in autoimmune disorders is not completely understood, several

lines of evidence suggest they may make an important contribution. Data from animal studies demonstrated a link between BAFF overexpression and development of SLE. They showed an amelioration of clinical disease in SLE mice following either treatment with a BAFF antagonist or the genetic elimination of BAFF.^{27 28}

Furthermore, in human studies, serum concentration of these cytokines was elevated in a proportion of patients with SLE,²⁹ and a correlation between BAFF levels and disease activity has been reported.^{30–33}

These data suggest that some patients at least might benefit from BAFF/APRIL blocking therapies.

BELIMUMAB

Belimumab is a monoclonal antibody against BAFF, and is currently the only approved biological for the treatment of SLE.³⁴

An initial human study with belimumab (a phase I randomised trial in patients with SLE with mild-to-moderate disease) revealed promising results. The drug was well tolerated and reduced the levels of peripheral B lymphocytes (CD20+ B cells).³⁵

Subsequently, Wallace *et al* conducted a 52-week, phase II trial, in which 449 patients with SLE were randomised to receive placebo or 1, 4 or 10 mg/kg of belimumab. Results showed that the drug was well tolerated and biologically active, as 63–71% of patients experienced a depletion of naïve, activated and plasmacytoid CD20+ B cells, and a decrease in anti-dsDNA titres ($p \leq 0.0017$). However, no difference was seen in SELENA-SLEDAI score at week 24 or in the median time to the first flare over 52 weeks, thus this study did not meet primary end points perhaps because approximately 30% of the patients involved in the trial were ANA negative. However, subgroup analyses revealed that patients who were serologically active at baseline had a significant improvement in SELENA-SLEDAI and SF-36 scores at week 52 of belimumab treatment.³⁶

Based on this post hoc analysis, SLE Responder Index (SRI) was developed.³⁷ It utilises new outcome criteria based on three components: the SLEDAI, which monitors the overall improvement of disease activity, the BILAG, which documents that no domain of the disease worsened, and a physician's global assessment, which provides confirmation by clinicians and ensures that improvements in disease activity are not achieved at the expense of the patient's overall condition.³⁸

Subsequently, in 2011, two large phase III randomised studies, referred to as the BLISS-52 and BLISS-76 trials, showed some, though far from comprehensive, encouraging results.^{38 39}

The BLISS-52 trial (NCT00424476) was conducted in Latin America, Asia-Pacific and Eastern Europe, and included 865 patients with SLE with moderate-to-severe disease (≥ 6 on SELENA-SLEDAI score), and positive ANA and/or anti-dsDNA. Patients were randomised to receive intravenous belimumab 1 (n=289) or 10 mg/kg

(n=290) or placebo (n=288) with standard of care (SOC). The primary efficacy end point defined was an improvement in the SRI at week 52. When assessed for the SRI at week 52, significantly more patients showed a response in the belimumab 1 (51%) and 10 mg/kg (58%) groups than in the placebo group (44%; $p=0.0129$ and $p=0.0006$, respectively for 1 and 10 mg/kg group vs placebo). Generally, belimumab-treated patients showed a higher response rate. Belimumab remained well tolerated, reduced disease activity, improved serological activity, prevented flares and reduced corticosteroid use.³⁸

The BLISS-76 study (NCT00410384), had a very similar design and was conducted in 819 patients from North/Central America and Europe who were randomised to receive intravenous belimumab 1 (n=271) or 10 mg/kg (n=273) or placebo (n=275) with SOC. Forty-three per cent of patients with SLE in the 10 mg/kg belimumab group were SRI responders compared with 33.5% in the placebo group at week 52, although at week 76 there was no significant difference between the treatment arms.³⁹ The primary end point was not achieved with the 1 mg/kg group in this trial. Similar to the previous randomised controlled trial (RCT), belimumab-treated patients showed a significantly improved SRI response rate, reduced disease activity and severe flares. However, the effects on fatigue and quality of life were of modest, often short-lived, benefit.

The primary end point was not achieved with the 1 mg/kg group in this trial. Combining the data from both trials (n=1684) revealed that belimumab-treated patients had a greater improvement in IgG levels, with a median reduction of 13.8% and 15.3% for 1 and 10 mg/kg belimumab, respectively, versus 2.5% for placebo group ($p < 0.001$). In addition, it increased C3 (median increase of 14.7–17% vs 2.2% in placebo; $p < 0.001$) and C4 (median increase of 37.5–50% vs 12.9 in placebo; $p < 0.001$) levels and reduced autoantibody levels with a significantly higher number of patients converting from seropositive to seronegative for anti-dsDNA (change of –36.6% and –40.8% for 1 and 10 mg/kg belimumab, respectively, vs –10.2% for placebo group; $p < 0.001$), anti-Sm (–39.1% and –51.2% vs –28.8%, $p < 0.01$), antiribosomal p (–35.7% and –54.0% vs –8.2%, $p < 0.01$) and IgG anticardiolipin (–30.8% and –32.1% vs –22.7%, $p < 0.05$) autoantibodies.

In the BLISS-76 cohort, the effect of belimumab on lymphocytes revealed a significant reduction on median levels of CD19+ and CD20+ B cells (median % change of –54.8% to –55.7%; $p < 0.001$) and preservation of B-cell and T-cell populations. In addition, a significant reduction in naïve (CD20+CD27–; from –73.4% to –76.3% vs –3.4% in placebo group, $p < 0.05$) and activated (CD20+CD69+; from –43.2% to –49.1% vs –25.2%, $p < 0.001$) B cells were observed in belimumab-treated patients, an effect also seen in plasmacytoid cells (CD20+CD138+; –56% vs –35.1%, $p < 0.01$). Memory cells, however, transiently increased and gradually returned to baseline levels

over the 76 weeks. This partial B-cell depletion with persistence of memory B cells is both a limitation, because these cells give rise to progeny that can secrete undesirable autoantibodies, and an advantage, because protective antibodies against influenza, pneumococcus and tetanus are maintained, and can be successfully induced, with revaccination.^{32 40 41}

The 10 mg/kg belimumab-treated group had a significant improvement in disease activity, particularly in the mucocutaneous ($p < 0.05$) and musculoskeletal ($p < 0.05$) systems; some improvement in vasculitis and central nervous system (CNS) was also observed but these trials were not designed to look at these aspects.⁴² Post hoc analysis of patients with SLE with renal involvement on mycophenolate mofetil or serologically active at baseline showed a higher improvement after belimumab treatment, with better results on renal flare rates, renal remission, proteinuria reduction and renal organ disease improvement, though few reached statistical significance (which is not surprising, as patients with highly active renal disease were excluded).⁴³

In summary, a better response to belimumab treatment was associated with higher baseline disease activity (SELENA-SLEDAI ≥ 10), anti-dsDNA positivity, low complement levels or corticosteroid treatment at baseline.⁴⁴ In addition, early normalisation of C3 or anti-dsDNA antibody values were predictors of a reduced risk of severe flares.^{40 42} Interestingly, the baseline levels of serum BAFF were not a predictor of clinical response.

Results from phases II and III RCT both showed that the rate of serious infections and cancers was similar between belimumab and placebo.⁴⁵ Interestingly, the 7-year open-label study showed a stable rate of adverse events and infections among belimumab-treated patients, and, in some cases, they might even have decreased over time.⁴⁵ However, the advantage for the serologically active patients was lost over long-term follow-up.

Since March 2011, intravenous belimumab has been licensed and approved by the US Food and Drug Administration and the European Medicines Evaluation Agency as an add-on therapy in adults with active, ANA or anti-dsDNA-positive SLE with a high degree of disease activity in the skin and/or musculoskeletal systems that remains moderately to severely active despite optimised standard immunosuppression. In the approved regimen, belimumab is administered at 10 mg/kg every 2 weeks for the first three doses, and then given every 4 weeks.⁴⁶

However, it is important to remember that patients with severe lupus kidney disease or active CNS lupus are excluded from belimumab treatment, as those manifestations were excluded in BLISS-52 and BLISS-76 studies.^{38 39}

Based on favourable results of the previous RCT with belimumab, several trials in SLE are currently active and will evaluate: vaccine responses (a phase IV randomised, open-label study is currently recruiting patients to assess the impact of belimumab on immune response to both

pneumococcal vaccine and tetanus toxoid in adults with active SLE disease (ClinicalTrials.gov Identifier: NCT01597492)⁴⁷); lupus nephritis (the BLISS-LN phase III randomised ongoing study will evaluate the efficacy and safety of belimumab in adults with active lupus nephritis (NCT01639339)⁴⁸); African ancestry (the EMBRACE study is a phase III/IV randomised study started in 2013 that will evaluate efficacy and safety of belimumab in adult patients of black race (NCT01632241)⁴⁹); paediatric subjects (PLUTO study (NCT01649765) is a phase II randomised study to evaluate pharmacokinetics, safety and efficacy of intravenous belimumab in patients aged 5–17 years with active SLE (SELENA-SLEDAI score ≥ 8)⁵⁰). Belimumab failed to demonstrate a positive effect among African-American patients with SLE, which may raise a concern about the responsiveness of the drug across racial groups.

In addition, several ongoing RCTs are currently recruiting (NCT01705977,⁵¹ NCT02119156,⁵² NCT01345253,⁵³ NCT01597622,⁵⁴ NCT00724867,⁵⁵ NCT00712933,⁵⁶ NCT00583362⁵⁷ and the BLISS-SC study NCT01484496)⁵⁸ and are helping to evaluate the long-term safety and efficacy of belimumab in patients with SLE. The BASE (NCT01705977)⁵¹ and SABLE studies (NCT01729455),⁵⁹ currently recruiting, will be helpful in assessing adverse events in patients with SLE treated with belimumab over a period of 52 weeks and 5 years, respectively. In addition, the Belimumab Pregnancy Registry is a prospective cohort study currently collecting data on pregnancies and pregnancy outcomes (on a voluntary basis) in women with SLE who have received commercially supplied belimumab within the 4 months prior to and/or during pregnancy (NCT01532310).⁶⁰ The registry will also evaluate the outcome of infants.

There are currently no clinical studies focusing on the safety and efficacy of belimumab in patients with SLE with CNS involvement, so it is not recommended in this situation.^{38 39}

Although belimumab has generated much enthusiasm there are still many questions to answer. Besides the lack of evidence of efficacy of belimumab in patients with SLE with renal and CNS involvement, as previously discussed, we still do not know about the comparative effectiveness of belimumab as there are no data comparing it directly with other therapies. It is also not known whether it is better to add an antimalarial agent, steroids or an immunosuppressive agent to belimumab. The best combined therapy has not yet been established. Even the combination of belimumab with rituximab is a hypothesis. Rituximab is an anti-CD20 drug that leads to B-cell depletion.² It has had promising results in small open-label uncontrolled studies, but these results could not be confirmed in large RCTs.^{61 62} Recently, Carter *et al.*⁶³ reported that following rituximab treatment, those patients with rising BAFF levels were more likely to flare. The results suggest that rituximab followed by belimumab may be very effective in some patients.

The cost of belimumab is also a significant worry. One year of treatment with belimumab is estimated to cost more than 20 times the treatment with a conventional non-biological drug.³² The clinical outcome of this investment can take several months to be seen (6–12 months are necessary to establish a non-responder), so long-term cost-effective studies will be helpful to clarify the usefulness of this drug.^{32 33}

One final consideration concerns long-term treatment with belimumab and its potential adverse effects. Although it has been well tolerated to date, it is not known whether it will have additional unexpected side effects over very lengthy periods of use or if patients will develop antibelimumab antibodies that might reduce the efficacy of the drug.

CONCLUDING REMARKS

Belimumab is an approved biological drug for the treatment of patients with persistently active SLE with skin and/or joint disease that do not respond to standard therapies. Although many questions related to this drug remain unanswered, data from clinical trials are somewhat encouraging. Belimumab has shown modest efficacy in SLE treatment without significant side effects. It would be very helpful to determine whether some subgroups of patients in particular will benefit from its use and whether it might work better in combination with another therapy. The relative success of belimumab should encourage studies of other molecules that act on the BAFF/APRIL axis.

Competing interests None.

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