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Belimumab in systemic lupus erythematosus (SLE): evidence-to-date and clinical usefulness

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***Abstract*:** Systemic lupus erythematosus (SLE) is a complex autoimmune rheumatic disease with multiple presentations, whose management presents many challenges. Many disease modifying or immunosuppressive drugs have been used with limited success, especially in patients with more severe disease activity. Belimumab is the first drug to be approved specifically for the treatment of SLE in more than 50 years. By blocking the B-cell activating factor, it interferes in B-cell differentiation and survival. Here we consider the results of the clinical trials that led to its approval, as well as the post-hoc analyses, follow-up studies and the current trials.

Keywords: belimumab, biologic therapy, immunosuppressive agents, systemic lupus erythematosus

Introduction

In 2016, the National Institute for Health and Care Excellence (NICE) approved the use of belimumab for the treatment of autoantibody-positive systemic lupus erythematosus (SLE) [NICE, 2016]. It is timely to review the prospects for belimumab in the UK and worldwide.

In 2011, belimumab became the first drug in over 50 years to be approved by the Federal Drug Administration (FDA) in the USA for the treatment of SLE. It is available in the USA for autoantibody positive lupus patients with active, skin or joint disease who have inadequate response to standard therapy. It is not, however, approved for the treatment of renal disease or severe central nervous system (CNS) involvement in SLE [US FDA, 2012].

It interesting to consider what the two clinical trials that led to its approval actually found [Furie *et al.* 2011; Navarra *et al.* 2011]. We will also review the follow-up studies.

Clinical trials

Belimumab is a recombinant, fully human IgG1λ mAb, which binds to soluble B-lymphocyte stimulator (BAFF) [Baker *et al.* 2003]. Given that BAFF inhibits B-cell apoptosis, stimulates the differentiation of B cells into immunoglobulin producing cells [Do *et al.* 2000] and BAFF serum levels correlate with disease activity [Petri *et al.* 2008], it was hypothesized that it might be a target in SLE treatment.

A phase I trial of belimumab in 70 SLE patients with stable disease for 2 months indicated an abnormal rate of adverse events, but there was a significant reduction in percentages of CD20+ B cells and anti-dsDNA autoantibody titres after one or two doses of belimumab, without any changes in disease activity [Furie *et al.* 2008]. A 52-week phase II trial included 449 SLE patients with active disease. Belimumab was administered to 336 and placebo to 113 patients. The inclusion criteria required a Safety of Oestrogen in Lupus Erythematosus National Assessment SLE Disease Activity Index (SELENA-SLEDAI) score ⩾4, history of measurable antibodies (not necessarily present at screening) and a stable therapeutic regimen for ⩾60 days. Patients with active lupus nephritis or CNS disease were excluded. Patients were randomized to receive 1, 4, or 10 mg/kg of belimumab or placebo on days 0, 14, 28, and subsequently every 28 days for 52 weeks plus standard of care [Wallace *et al.* 2009].

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The primary clinical endpoints (change in SELENA–SLEDAI score at week 24 and time to first flare) were not met, as the mean percent changes in SELENA–SLEDAI were -19.5% for the belimumab groups *versus* -17.2% for the placebo group at 24 weeks, and -27.2% *versus* -20.6% at 52 weeks. Similarly, there were no differences between the four groups in the rate of flares (mild/moderate or severe) or time to first flare over 52 weeks, but time to first flare starting at week 24 through week 52 showed a median time of 154 days in the belimumab groups and 108 days in the placebo group ($p = 0.0361$), suggesting that belimumab might stabilize the disease. However, almost 30% of the patients were antinuclear antibody (ANA) negative, which lead to concerns about the veracity of the diagnosis. But we have reported that in a 10-year period 17% of strongly ANA positive lupus patients become ANA negative [Acosta-Mérida *et al.* 2013]. A subgroup analysis in the Belimumab study demonstrated that serologically active patients ANA $\geqslant$1:80 or levels of anti-dsDNA autoantibody $\geqslant$30 IU/ml) treated with belimumab had a significantly greater reduction in SELENA–SLEDAI scores from baseline to week 52 [Wallace *et al.* 2009].

Based on the phase II trial results, a new SLE responder index (SRI) was developed for use in clinical trials. This tries to capture an improvement in disease activity without worsening of the overall condition or the development of significant disease activity in new organ systems. A responder is defined as a $\geqslant$4-point reduction in SELENA–SLEDAI score, no new British Isles Lupus Assessment Group (BILAG) A or no $>$1 new BILAG B domain score and no deterioration from baseline in the Physician's Global Assessment (PGA) by $\geqslant$0.3 points [Furie *et al.* 2009].

Two phase III trials were designed: BLISS-52 and BLISS-76 were conducted. The BLISS-52 trial recruited 865 patients from South America, Asia and Eastern Europe [Navarra *et al.* 2011]. BLISS-76 assessed 819 patients from North America, Europe and Israel [Furie *et al.* 2011], leading to two different ethnic origin distributions. They had a similar design. The inclusion criteria were SLE patients aged $\geqslant$18 years, SELENA–SLEDAI $\geqslant$6 and stable treatment regimen for at least 30 days. Both trials included only serologically active SLE patients [Furie *et al.* 2011; Navarra *et al.* 2011]. The exclusion criteria were severe active lupus nephritis or CNS involvement; pregnancy; previous treatment with any B-lymphocyte-targeted drug, intravenous cyclophosphamide in the previous 6 months, and IVIg or prednisone $>$100 mg/day within 3 months [Furie *et al.* 2011; Navarra *et al.* 2011]. The patients were randomized in a 1:1:1 ratio to receive 1 mg/kg belimumab, 10 mg/kg belimumab, or placebo intravenously on days 0, 14, and 28 and then every 28 days until 48 weeks in the BLISS-52 trial [Navarra *et al.* 2011] and for 72 weeks in the BLISS-76 trial [Furie *et al.* 2011]. The standard of care regimen and limitations on steroid use are described elsewhere. [Furie *et al.* 2011].

The primary endpoint in both trials was the SRI response rate at week 52 [Furie *et al.* 2011; Navarra *et al.* 2011]. The secondary endpoints were the percentage of patients with a four-point reduction from baseline in SELENA–SLEDAI score at week 52, change in PGA score at week 24, change in Short Form 36 version 2 (SF36) at week 24 and percentage of patients in which the mean prednisone dose was decreased 25% from baseline to 7.5 mg/day or less during weeks 40–52 [Furie *et al.* 2011; Navarra *et al.* 2011]. In the BLISS-76 trial, SRI response rate at week 76 was also a secondary endpoint [Furie *et al.* 2011].

In the BLISS-52 trial, belimumab resulted in a significantly higher response rate [1 mg/kg: 148 (51%); $p = 0.0129$ and 10 mg/kg: 167 (58%); $p = 0.0006$] compared to placebo [125 (44%)] at week 52 as assessed by SRI. This revealed a dose response pattern, as belimumab 10 mg/kg had a significantly greater response than placebo in all three SRI components, though belimumab 1 mg/kg showed a greater response than placebo in SELENA–SLEDAI and PGA [Navarra *et al.* 2011].

In the BLISS-76 trial, there were more SRI responders in the 10 mg/kg belimumab group than in the placebo group (43.2% *versus* 33.5%; $p = 0.017$) at 52 weeks. However, the percentage of SRI responders in the 1 mg/kg belimumab group (40.6%), while numerically greater than that in the placebo group, was not statistically significant ($p = 0.089$). Similarly, at week 76 the SRI response rates were numerically greater in the belimumab groups than in the placebo group, but not significant [Furie *et al.* 2011].

Significantly greater and sustained reductions were noted in anti-dsDNA antibody levels in the

belimumab groups in both trials when compared to placebo [Furie *et al.* 2011; Navarra *et al.* 2011],

In the BLISS-52 trial, the patients with baseline prednisone doses >7.5 mg/day showed that sustained dose reduction (≥12 weeks until week 52) was more likely with belimumab 1 mg/kg and 10 mg/kg than with placebo [Navarra *et al.* 2011]. In the BLISS-72 trial, more patients in the belimumab groups were able to reduce corticosteroids by 25% and to 7.5 mg/day between weeks 40 and 52 compared with patients receiving placebo, but this was not significant [Furie *et al.* 2011].

The rates of adverse effects were similar between all three groups in both trials [Furie *et al.* 2011; Navarra *et al.* 2011].

Post-hoc *analyses*

Several studies pooled the data from both phase III trials in *post-hoc* analyses to detect the treatment effects in more detail, but the BLISS trials were not powered to assess these parameters. One of the studies compared the changes in different measures at 52 weeks between SRI responders ($n = 761$) and nonresponders ($n = 923$). Responders were more likely to have higher disease activity, less serological activity (based on anti-dsDNA titre, $p < 0.001$; percentage of patients with C3 or C4 levels less than the lower limits of normal, $p < 0.001$ and $p < 0.0001$, respectively), and to have received a corticosteroid dose >7.5 mg/d ($p < 0.01$), but not an immunosuppressant ($p < 0.0001$) [Furie *et al.* 2014]. More responders than nonresponders achieved a ≥4 point reduction in SELENA–SLEDAI score (3.8% of nonresponders *versus* 100% of responders; $p < 0.001$), while a reduction of ≥7 occurred in 40.3% of responders *versus* 1.3% of nonresponders [Furie *et al.* 2014].

Another study assessed which factors were related to a greater response to belimumab. In the univariate analysis, patients with a higher baseline disease activity (SELENA–SLEDAI ≥10, low complement levels, raised anti-dsDNA autoantibody levels or treatment with corticosteroids) had a greater response *versus* standard therapy alone, especially the belimumab 10 mg/kg group. In the multivariate analysis, the serologically active subgroup was more difficult to treat with standard therapy (SRI rate of 32% *versus* 39% in the overall population and 44% in the SELENA–SLEDAI ≥10 subgroup) and belimumab treatment led to significantly greater SRI response rates when compared to placebo at 52 weeks (SRI rate 31.7% with placebo; 41.5% with belimumab 1 mg/kg ($p = 0.002$); and 51.5% with belimumab 10 mg/kg ($p < 0.001$)), even when complement and anti-dsDNA autoantibodies changes were excluded from the SRI (28.9% with placebo; 38.7% with belimumab 1 mg/kg ($p = 0.001$) and 46.2% with belimumab 10 mg/kg ($p < 0.001$)) [Van Vollenhoven *et al.* 2012].

More patients treated with belimumab showed a four-point or greater reduction in the SELENA–SLEDAI score at week 52 when compared to placebo (40.7% with placebo; 48.1% with belimumab 1 mg/kg ($p = 0.006$); 52.6% with belimumab 10 mg/kg ($p < 0.001$)) and the proportions with no new BILAG A or no more than one new B score at week 52 were 76.7% ($p = 0.005$) and 75.5% ($p = 0.02$) with belimumab 1 and 10 mg/kg, respectively, *versus* 69.4% in the placebo group. At 52 weeks, there was a significantly higher number of patients in both belimumab groups with improvement in the musculoskeletal and mucocutaneous BILAG domains. Similarly, significantly more patients in the belimumab groups had improvements in the musculoskeletal (1 mg/kg), mucocutaneous (10 mg/kg) and immunological (1 and 10 mg/kg) domains, as assessed by SELENA-SLEDAI. The changes in adjusted mean SELENA–SLEDAI scores over 52 weeks were significantly greater with belimumab 1 and 10 mg/kg for the musculoskeletal and immunological domains over 52 weeks and for the immunological domain from weeks 24 to 52. When removing the contribution of these three organ domains or both the musculoskeletal and mucocutaneous domains to SELENA–SLEDAI, the treatment effect with belimumab remained. There were significantly fewer patients treated with belimumab than placebo who had worsening in the SELENA–SLEDAI immunological, haematological and renal domains, or BILAG haematological domain ($p < 0.05$) when these specific organ domains were not involved at baseline [Manzi *et al.* 2012].

Although the BLISS trials were not designed to assess the effects of belimumab in renal disease, one *post-hoc* analysis assessed whether the patients with stable renal involvement had any additional benefit from belimumab. At week 52, a higher proportion of patients with SELENA–SLEDAI renal involvement at baseline and treated with belimumab had renal improvement, including reductions in haematuria and

proteinuria. Of 267 patients with SELENA–SLEDAI renal involvement, a greater percentage of the subset of serologically active patients (n =182) had renal organ system and item improvements with belimumab 10 mg/kg *versus* standard therapy alone, but it was not statistically significant. Similarly, in patients with renal involvement who were treated with mycophenolate mofetil (MMF) at baseline, there was a SELENA–SLEDAI renal improvement: 27.8% in the placebo group, 52.6% in belimumab 1 mg/kg, 63.2% in belimumab 10 mg/kg which was statistically significant ($p = 0.03$). There was also a BILAG renal improvement (20.0%, 32.4%, and 30.6% in the placebo, and belimumab 1 and 10 mg/kg groups, respectively), but this was not statistically significant [Dooley *et al.* 2013].

There was a lower rate of renal flares in patients receiving belimumab. In the subgroup of patients receiving MMF at baseline, the rates of renal flares during the 52 weeks were 4.9%, 4.9%, and 1.5% with placebo, and belimumab 1 and 10 mg/kg, respectively (not statistical significant) [Dooley *et al.* 2013]

Significantly more pooled patients treated with belimumab converted to seronegative for anti-dsDNA (both doses of belimumab), anti-Sm (10 mg/kg), anti-ribosomal P (10 mg/kg), and IgG anti-cardiolipin (both doses) autoantibodies by week 52. By week 8, there was a significantly lower anti-dsDNA autoantibody level in both belimumab groups compared to placebo ($p < 0.001$). In patients with low complement levels at baseline, significant and sustained increases were observed with belimumab by week 4 compared to placebo (in the 1 mg/kg group: $p < 0.05$; in the 10 mg/kg group: $p < 0.001$). Plasma cells decreased in a dose dependent manner with belimumab [Furie *et al.* 2014], which is clinically relevant as it has been shown that the number and frequency of CD27(high) plasma cells correlate with SLE disease activity and with anti-dsDNA autoantibodies titer [Jacobi *et al.* 2003]. In contrast, seroconversion to anti-dsDNA positivity was infrequent and occurred significantly more often in patients receiving placebo than in those receiving 10 mg/kg of belimumab ($p = 0.02$) [Stohl *et al.* 2012]. When comparing SRI responders with nonresponders, median anti-dsDNA autoantibody levels were lower in SRI responders than in nonresponders at week 52 (−34.2% *versus* −26.1%; $p = 0.01$), normalization of anti-dsDNA levels occurred in more responders (14.4% *versus* 10.8%; $p = 0.10$) and when hypocomplementemia was present at baseline, a greater median per cent increase was observed in responders [C3: 14.5% *versus* 9.0% ($p = 0.001$); C4: 40.0% *versus* 28.6% ($p = 0.003$)] [Furie *et al.* 2014].

In terms of health-related quality of life scores, one of the analyses found significantly greater improvements in physical component summary (PCS), SF-36 vitality domain, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scores in both belimumab groups at week 52 [Strand *et al.* 2014]. For SRI responders, mean improvements in SF-36 PCS and mental component summary (MCS) scores were greater when compared to nonresponders at week 52 (4.9 *versus* 2.6 and 4.4 *versus* 1.7, respectively; $p < 0.001$) and exceeded minimum clinically important differences (MCID), defined as a 2.5 points difference from baseline; a higher percentage of responders also showed improvements ⩾MCID, both in PCS (59% *versus* 49%) and in MCS (56% *versus* 44%). Sustainable improvement in SF-36 scores throughout the trial were not observed [Furie *et al.* 2014].

A total of 86% of the pooled patients received corticosteroid therapy and the mean dose (prednisone equivalent) was 12.5 mg/day. While the overall exposure to all corticosteroids increased on average in all treatment groups from baseline to 52 weeks, the overall mean cumulative change in corticosteroid dose was 531 mg in the belimumab 10 mg/kg group *versus* 916 mg in the placebo group ($p < 0.0001$) and the mean overall change in daily corticosteroid dose was 1.5 mg with belimumab 10 mg/kg and 2.5 mg with placebo ($p < 0.0001$). Similarly, only 22.6% of patients treated with belimumab 10 mg/kg had an increase in corticosteroids over 52 weeks *versus* 35.0% of patients on placebo. A total of 37% of patients had a decrease in corticosteroid dose while on belimumab 10 mg/kg *versus* 29.7% of patients on placebo [Van Vollenhoven *et al.* 2016]. When comparing SRI responders with nonresponders at week 52, of the patients treated with prednisone >7.5 mg/day at baseline (62% of responders; 55% of nonresponders), it was observed that more responders than nonresponders had dose reductions ⩾25% to <7.5 mg/day (25.5% *versus* 16.4%; $p < 0.001$). There were fewer responders who had their prednisone dose increased to >7.5 mg/day at week 52 from

⩽7.5 mg/day at baseline (4.1% *versus* 21.3%; $p < 0.001$) [Furie *et al.* 2014].

Safety Considerations in the BLISS trials

The safety profile was analysed on the pooled data on patients from the phase II and III trials ($n = 1458$). The most common cause of withdrawal was adverse events, which did not vary significantly between the three groups. These included renal disorders (1.2%, 0.9%, 0%, and 1.2% with placebo, and belimumab 1, 4, and 10 mg/kg, respectively), infections (1.2%, 0.7%, 0.9%, and 0.6%), neurologic disorders (0.6%, 0.7%, 0%, and 1.0%), and skin disorders (0.9%, 0.4%, 0.9%, and 0.7%). The rate of serious infections was also similar across treatment groups [Wallace *et al.* 2013].

In the BLISS-76 trial, patients were assessed for changes in pre-existing antigen-specific antibodies and response to vaccination during the study. Despite the small number of patients, no difference was found in antitetanus toxoid IgG levels between the placebo, belimumab 1 mg/kg and 10 mg/kg groups. There was an increase in antibody levels to the tested antigens after antipneumococcal vaccination was administered, in both placebo and belimumab groups, but these were not consistent. Even healthy subjects may not mount a response to all serotypes. In total, 89 patients received influenza vaccine during the study and the antibodies to all antigens increased in all groups [Chatham *et al.* 2012].

The data relating to pregnancy are sparse. In the phase II and III clinical trials, there were 54 pregnancies on belimumab, of which 21 resulted in live births, 13 ended in foetal loss, 10 were electively terminated, 6 were ongoing, and 4 had an unknown outcome. Two live births on belimumab had congenital abnormalities. Six pregnancies occurred on placebo and 3 ended in foetal loss and three were electively terminated [Wallace *et al.* 2013].

In the pooled data of the phase II and III clinical trials, during the blinded period, there were 14 deaths (3 on placebo, 5 on belimumab 1 mg/kg, none on 4 mg/kg, and 6 on 10 mg/kg), with a mortality rate of 0.43 (95% CI: 0.09– 1.27; 692 patient-years) with placebo and 0.73 (95% CI: 0.36–1.30; 1,516 patient-years) with belimumab (1, 4, and 10 mg/kg dosages combined) [Wallace *et al.* 2013].

Long-term follow-up

Clinical efficacy

The initial post-marketing experience was described in small observational studies. One study included 115 patients who received belimumab for at least 3 months, of whom 79 received it for at least 6 months. The other study included 68 patients who had received one previous belimumab infusion. The most common clinical manifestations in these two studies were arthritis (73.5% and 52%, respectively), mucocutaneous involvement (51.0% and 19%), and serositis (17.2% and 8%). Clinical response was defined by a ⩾50% reduction in the investigator's impression in addition to no worsening in other organ systems in the first study. Less than half of the patients responded in either or both arthritis and rash at 3 months and <60% clinically responded in arthritis, rash and/or nephritis at 6 months. Belimumab was discontinued in 13.2% of patients for various reasons. In the second study, PGA, SELENA–SLEDAI score and prednisone dose were compared between baseline, 6 and 12 months of follow-up. PGA and SELENA–SLEDAI score decreased during those 12 months, from 1.35 to 0.78 and from 4.40 to 2.30, respectively. However, during this period, 18 patients discontinued the treatment and the corticosteroid dosage remained stable (17.8 mg/day at baseline and 16.0 mg/day at 12 months) [Askanase *et al.* 2014]. These results are not impressive.

Another observational noncontrolled study (the OBSErve study) reviewed patients who had received ⩾8 infusions of belimumab in a clinical setting (excluding those who took part in clinical trials) to evaluate clinical response at the end of each 6-month period for 24 months [Collins *et al.* 2016]. As previously reported [Askanase *et al.* 2014], the primary outcome was a physician's impression of change, defined by a physician described response of 20%, 50%, and 80% improvement for each 6-month period. Of 501 patients, 112 were lost to follow-up and 112 discontinued treatment, due to patient request ($n = 45$), lack of medication efficacy ($n = 33$) and adverse effects ($n = 14$), usually sepsis or depression. At baseline, 2.2% of patients had mild, 77.6% moderate and 20.2% severe disease and the mean SELENA–SLEDAI score ($n = 122$) was 12.4 [Collins *et al.* 2016]. The most commonly involved organ systems were musculoskeletal (76.9%), mucocutaneous (63.5%), constitutional (56.7%), immunological (54.0%)

and haematological (35.3%). At month 6, the percentage of patients with moderate and severe disease reduced to 47.7% and 2.4%, respectively, and at month 24 to 33.1% and 1.9%. Simultaneously, the mean SELENA–SLEDAI score showed a persistent reduction to 5.9 at month 6 and the percentage of anti-dsDNA-antibody positive patients also decreased (69.1% at baseline; 63.0% at month 6, 50.9% at month 12 and 48.6% at month 24) [Collins *et al.* 2016]. As this was a noncontrolled study, caution against an overoptimistic reaction is needed, given the natural tendency of SLE patients' disease activity to 'wax and wane'.

Patients who completed the phase II clinical trial could receive belimumab 10 mg/kg in an open-label continuation study, which included 296 patients and whose data relating to a total of 7 years of follow-up has already been published. By year 2, 57% of patients achieved an SRI response, which increased to 65% by year 7. In the first year, the SRI response was similar between seronegative and seropositive patients (44% *versus* 46%, respectively), becoming slightly lower in the second year when compared with seropositive patients (48% *versus* 57%, respectively). In years 3 to 7, the rate of SRI responders became similar again between both groups [Ginzler *et al.* 2014].

One further observational study with 195 patients on belimumab reported that 52% of patients showed an improvement in the clinical manifestations that had led to initiation of belimumab at 3 months, more specifically 61% of patients with arthritis, 43% of patients with rash, and 78% of patients with renal manifestations. At 6 months, of 120 patients 51% showed clinical response (46% of patients with arthritis, 52% of patients with rash, and 57% of patients with renal manifestations). Interestingly, black patients had a higher clinical response rate at 3 months compared to nonblack patients (82% *versus* 45%, $p = 0.0001$), and at 6 months 67% out of 21 black patients responded to belimumab [Hui-Yuen *et al.* 2015].

In the OBSErve study, of 251 patients with a $\geq$20% improvement in disease in the first 6 months, 99.2% reported no disease flare at months 12, 18 and 24, and of 134 patients with a $\geq$50% improvement, 99.3% reported no worsening of disease later. Moreover, of 27 patients with SELENA–SLEDAI $\geq$6 at baseline that reduced to $<$6 at month 6, none had an increase in SELENA–SLEDAI of $>$3 up to month 24 [Collins *et al.* 2016]. In patients who completed 7 years of treatment, the rate of any flares and severe flares declined from year 2 to 7, from 70.9% and 4.9% to 44.7% and 1.9%, respectively. The rate of flares was similar in the seronegative and seropositive patients [Ginzler *et al.* 2014]. However, patients were evaluated every 16 weeks, which might underestimate the occurrence of flares. Three clinical case reports described severe flares a year after discontinuation of belimumab in patients who had clinical improved during treatment, involving previously unaffected organs [Furer *et al.* 2016].

Damage in the pooled patients from the two open-label continuation studies based on BLISS-52 and BLISS-76, at years 5 to 6 was evaluated. The mean change in Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) from baseline to years 5 to 6 was 0.2, while 343 out of 403 patients showed no change in SDI score, 46 had an SDI increase of 1, 13 had an increase of 2, and 1 had an increase of 3. Despite the absence of a control group, belimumab seemed to be associated with low rates of damage accrual [Bruce *et al.* 2016].

Corticosteroid usage decreased by 33% at year 2 to 60% at year 7 and the percentage of patient using corticosteroids declined from 73.9% at year 2 to 65.2% at year 7 [Ginzler *et al.* 2014]. In the OBSErve study, 386 out of 501 patients received steroids at baseline (mean daily dose of 19.9 mg). At month 6, 76.9% were on a reduced dose, 11.9% had no change, 9.1% stopped steroids and 2.1% had a dose increase. The mean dose reduced to 8.4 mg/day. This trend continued from month 6 to month 24, with a mean dose of 6.1 mg/day. A gradual decrease in the proportion of patients on $>$7.5 mg/day was also observed (67.5% at baseline to 30.9% at month 6, 21.2% at month 12, 21.6% at month 18 and 18.4% at month 24) [Collins *et al.* 2016]. Another observational study did not show a significant decrease in the mean daily dosage at 6 months (from 12.2 mg/day to 9.3 mg/day) [Hui-Yuen *et al.* 2015].

Safety in long term follow-up

No new concerns have emerged about adverse effects and mortality. In the 7-year open-label continuation study, the most common adverse effects were mild-moderate infections in years 5

to 7, particularly upper respiratory tract infections. The serious adverse effects which affected ⩾5 patients in any year were cellulitis, transient ischemic attack and pneumonia. Rates tended to decrease over time and the rate of serious and/or severe infections peaked during the first year [Ginzler *et al.* 2014]. Another study showed that >95% of patients had an adverse effect, with almost a third experiencing a severe adverse effect, but the incidence also decreased during the study from 10.8% (study year 0 to 1) to 5.6% (study year 5 to 6) [Bruce *et al.* 2016]. The most common adverse effects were infections/infestations (28.3%) and gastrointestinal disorders (13.9%). Opportunistic infection was seen in 23 (2.3%) patients and herpes zoster infection in 87 patients (8.7%) [Bruce *et al.* 2016].

Malignancies occurred at a similar rate to that expected in the general SLE population: 0.34/100 patient-years (95% CI: 0.09–0.88) during the 4-year period (excluding nonmelanoma skin cancer) [Merrill *et al.* 2012] and of 0.7/100 patient-years (95% CI: 0.4–1.27) during the 7-year period (including nonmelanoma skin cancer). Seven nonmelanoma skin cancers were reported on the 4-year period and four on the 5 to 7-year period [Ginzler *et al.* 2014].

The most common causes of discontinuation for clinical reasons over 7 years were malignancies (9), infections (7), skin disorders (6), respiratory pathologies (5), and decreased IgG/hypogammaglobinaemia (4) [Ginzler *et al.* 2014].

During the 7 years of belimumab treatment, seven deaths were reported (incidence rate of 0.4/100 patient-years). Five deaths occurred during the first 4 years and two occurred in year 7 [Ginzler *et al.* 2014]. In a study with pooled data from BLISS-52 and BLISS-76, 11 deaths were recorded during the 6-year study period and three additional deaths occurred after study exit. Causes of death included pneumonia, septic shock, pancreatitis, thrombocytopenia, cardiogenic shock, pulmonary haemorrhage, hypertensive heart disease, polypharmacy toxicity, stroke, intracranial haemorrhage and cardiac arrest [Bruce *et al.* 2016].

Cost effectiveness

One-year of belimumab treatment is up to 20 times more expensive compared to immunosuppressive therapies [Hahn, 2013], but studies in some European countries have shown belimumab to be cost-effective in those medical settings [Specchia *et al.* 2014; Díaz-Cerezo *et al.* 2015; Pierotti *et al.* 2015]. An Italian study showed an Incremental Cost-Effectiveness Ratio (ICER) value per life year gained of €22,990 and an incremental cost per Quality Adjusted Life Year (QALY) of €32,859 based on a belimumab price which includes a confidential patient access scheme (PAS) [Pierotti *et al.* 2015].

In the UK, GlaxoSmithKline developed a model to evaluate cost-effectiveness in this particular setting, which includes patient characteristics, disease activity, medication (corticosteroid use), risk of organ damage development and mortality. Data were gathered from the Johns Hopkins cohort, BLISS trials and other data from the literature. In this model, the incremental costs were £51,925, the incremental QALYs 0.806 and the ICER £64,410 per QALY gained. However, when this model is applied to a maximum treatment of 6 years (which is thought to be long enough to guarantee a reduction in long-term morbidity), it resulted in a lower ICER of £47,342 per QALY gained. A significant proportion of patients will probably need treatment for >6 years. Despite doubts about the economic modelling in the UK and a list price of £121.50 for a 120-mg vial and £405 for a 400-mg vial (the company agreed a PAS, providing a simple discount which is confidential), NICE finally decided to approve its use in restricted circumstances [NICE, 2016].

Clinical pearls

Belimumab has been approved in the UK as an option in SLE patients with serologically active disease and a SELENA–SLEDAI score ⩾10, as this constitutes a clinically relevant group of patients. The recommended dosage is 10 mg/kg on days 0, 14, 28, and subsequently every 28 days. Treatment should only be continued beyond 24 weeks if there is an improvement in the SELENA–SLEDAI score of at least four points [NICE, 2016], but an American study has showed that >50% of patients take it for >6 months [Hill *et al.* 2015]. Due to doubts regarding the use of SELENA–SLEDAI in clinical practice, it was decided not to use a more restricted SELENA–SLEDAI score improvement of >6. In the UK, it was also determined that evidence regarding Belimumab will be collected through the BILAG registry [NICE, 2016].

Table 1. Pros and cons of belimumab treatment.

Pros	Cons
Moderate efficacy in serologically active patients with skin and joint involvement [Furie *et al.* 2011; Navarra *et al.* 2011] Improvement in immunological markers [Stohl *et al.* 2012] No safety issues or increased mortality [Ginzler *et al.* 2014; Bruce *et al.* 2016]	Lack of data about benefit in CNS, renal, lung and heart involvement Slow onset of action [Hui-Yuen *et al.* 2015] Lack of data regarding safety in pregnancy [Wallace *et al.* 2013] Contradictory data on corticosteroid dose sparing [Hui-Yuen *et al.* 2015, Collins *et al.* 2016] No data on combination therapies

CNS, central nervous system.

However, there are still many unanswered questions as far as length of treatment is concerned. Some experts hypothesize that it might be stopped sometime after sustained response is achieved or on-demand, similarly to other treatments used in SLE. As previously discussed, belimumab seems to reduce the rate of flares over time [Ginzler *et al.* 2014], but there are a few reports of severe flares after discontinuation [Furer *et al.* 2016].

What does the future hold?

Several randomized control trials of belimumab are recruiting or ongoing at the moment. As the two original trials excluded patients with active lupus nephritis, the effect of belimumab in these patients is unknown. A phase III clinical trial is evaluating its efficacy and safety in this subset (NCT01639339). Due to the differences between the BLISS trials, there are two randomized controlled trials assessing clinical response and safety in black (NCT01632241) and East Asian (NCT01345253) patients. A multicentre study in a paediatric population is also ongoing (NCT01649765).

Belimumab might also have a role when used together with Rituximab (RTX), as BAFF seems to drive disease flare following RTX in patients with elevated anti-dsDNA titres and low B-cell numbers and sequential RTX may promote ever increasing levels of BAFF [Carter *et al.* 2013]. A trial (BEAT–LUPUS) will determine whether belimumab can successfully be used following B-cell depletion with RTX to prevent further SLE flares in this subgroup of patients [Arthritis Research UK, 2015]. Two open-label studies are currently recruiting: one comparing a combination of rituximab and cyclophosphamide with a combination of rituximab and cyclophosphamide followed by belimumab in the treatment of lupus nephritis (NCT02260934); the other investigating the possibility of combining RTX and belimumab (NCT02284984). A phase III trial to evaluate efficacy and safety of subcutaneous belimumab has just been completed (NCT01484496).

In order to evaluate the effect of belimumab suspension for 6 months followed by its reintroduction, an open-label nonrandomized study has also been commenced (NCT02119156).

The BASE (NCT01705977) and the SABLE (NCT01729455) studies are evaluating long-term safety, especially serious events. A Pregnancy Register (NCT01532310) is assessing women who received belimumab within the 4 months prior to and/or during pregnancy. One study has recently been completed, considering the effect of belimumab in vaccine responses (NCT01597492).

Conclusion

Belimumab is approved for treating patients with active, autoantibody positive SLE with a SELENA–SLEDAI $\geqslant$10, who do not respond to conventional therapies. The data from the clinical trials, *post-hoc* analyses and long term follow-up studies are reasonably reassuring and are reviewed in Table 1 and figure 1. Belimumab seems to have some modest benefit in improving disease activity without an increase in significant adverse effects. However, it does not induce rapid clinical benefit and we know very little about its effectiveness in treating patients with renal, CNS, heart or lung disease. Many unanswered questions about the subgroups of patients who might benefit the most or the possible combinations with other therapies remain.

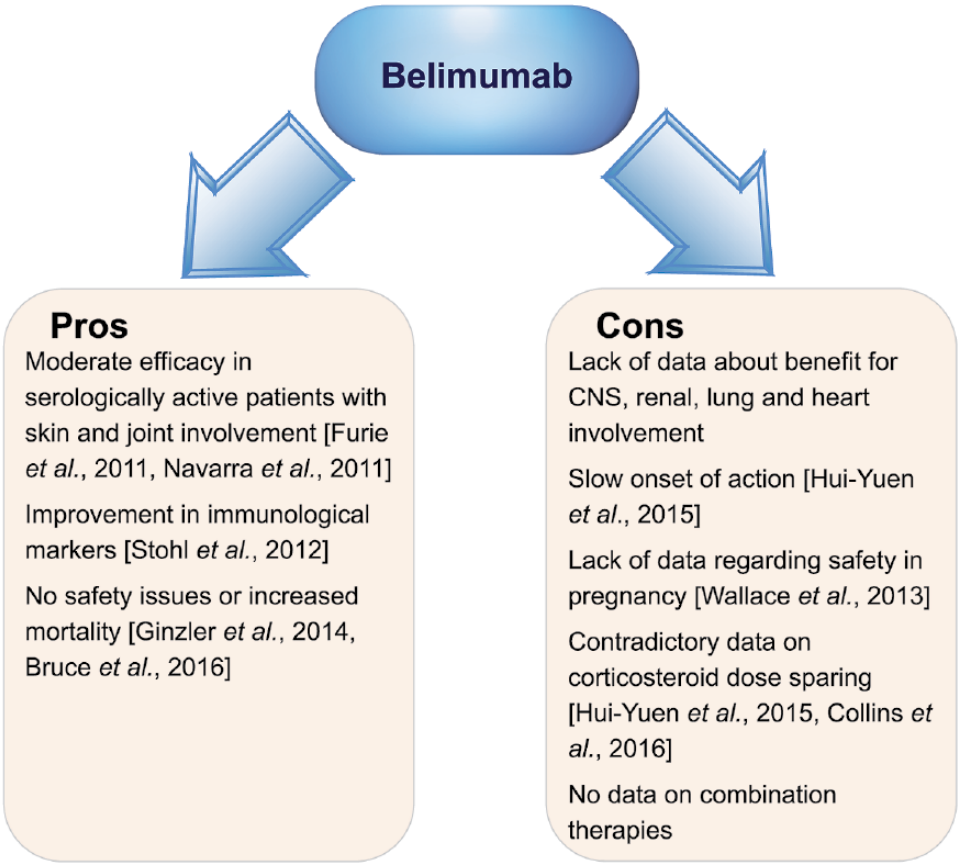

Figure 1. Pros and cons of belimumab treatment.
CNS, central nervous system.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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