

Subcutaneous formulation of belimumab in treatment of systemic lupus erythematosus: a critical review with focus on safety and satisfaction

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Abstract: Belimumab is a novel add-on therapy that has been approved for patients with active and antibody-mediated systemic lupus erythematosus. It is a monoclonal antibody that decreases the activation of B-cells and consequently decreases antibodies' production. Recently, the US Food and Drug Administration approved subcutaneous belimumab for patients who have received training on using it. Subcutaneous belimumab can be administered using either a prefilled syringe or an auto-injector device. Weekly subcutaneous belimumab seems to be as effective as monthly intravenous belimumab with a similar safety margin. In this article, we reviewed the literature on subcutaneous belimumab focusing on safety and patients' experiences and satisfaction. Overall, subcutaneous belimumab appears to be preferred over intravenous belimumab for a number of reasons. However, more studies are still required to prove these findings.

Keywords: belimumab, subcutaneous, safety, self-injection, patient satisfaction, adherence, auto-injector

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease associated with variable clinical presentations. Its prevalence in the US is estimated to be up to 150 patients per 100,000.¹ The disease typically runs a relapsing course and can result in multiple co-morbidities.² Mortality may occur early in the course of the disease. Causes of mortality and morbidity include severe organ damage, infections as a result of suppressed immune system, and cardiovascular events secondary to accelerated atherosclerosis.³ The precise etiology of SLE is not known and is postulated to be secondary to genetic, environmental, immune, and/or hormonal factors. However, despite the unclear etiology, it is known that most of the disease manifestations are mediated by the formation of different autoantibodies and antigen-antibody complexes.⁴⁻⁸ This abundance of autoantibodies in SLE is reflective of a significant role of B-cell-mediated pathogenesis.⁹

Earlier guidelines for SLE treatment recommended the use of antimalarial medications, nonsteroidal anti-inflammatory drugs, and corticosteroids.^{10,11} Later, immunosuppressant medications were recommended for specific systems' involvement, severe disease, and as corticosteroid sparing agents.¹²⁻¹⁴ Since 1998, hydroxychloroquine has been the only medication approved by the US Food and Drug Administration (FDA) for the treatment of SLE.^{15,16} In 2011, the FDA approved the use of belimumab for treatment of patients with antibody-positive active SLE without active lupus nephritis or central nervous system (CNS) involvement. In July 2017, the FDA approved the use

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of the subcutaneous (SC) form of belimumab by patients who received user training from their health care providers.¹⁷

In this review, we used different combinations of keywords “Belimumab”, “Subcutaneous”, “Preference”, “Safety”, and “Efficacy” in PubMed, Cochrane, and Google Scholar to find studies and articles that discussed efficacy, safety, and patient preference of SC belimumab.

Belimumab

BAFF protein, known as B-cell lymphocyte stimulator, is a TNF that binds to different receptors in the B-cell resulting in proliferation, differentiation, and secretion of antibodies.^{18,19} Elevated levels of BAFF have been found in patients with SLE and have been linked to disease flares.^{20–23} Belimumab is a human monoclonal IgG1 antibody that binds to BAFF protein resulting in a significant decrease in the number and activation of B-cells with a sequential decrease in autoantibodies’ production.^{24,25} Clinical trials have demonstrated that belimumab resulted in significant reduction of anti-dsDNA (double-stranded DNA) antibody, improvement of complement levels, and resolution of hypergammaglobulinemia.^{26–29}

SC belimumab

After the successful use of intravenous (IV) belimumab in the treatment of SLE,^{30–35} the need for more convenient routes of administration, especially SC injection, has emerged.³⁶ Phase I studies demonstrated an acceptable bioavailability with different doses of SC belimumab. Moreover, weekly SC belimumab dosed at 200 mg achieved blood levels and bioavailability similar to those achieved by a monthly 10 mg/kg IV belimumab dose, regardless of the site of injection or body size. SC belimumab achieved maximum serum concentration within 3.9–5.9 days with a half-life of 18.2 days.^{37–39} Phase II studies indicated an acceptable safety profile of SC belimumab similar to the IV form.^{40–42}

In a 52-week double-blinded, randomized controlled Phase III study (BLISS-SC), SC belimumab added to standard of care showed significantly higher efficacy, using SLE response index (SRI-4), time to severe flare, and corticosteroid dose reduction, compared to standard of care plus placebo.⁴³ Similar to IV belimumab, its efficacy was higher in a difficult-to-treat group of patients with positive anti-dsDNA and low complement level.⁴⁴ Moreover, in a 24-week open-label extension study that included 662 patients, SC belimumab continued to show the same efficacy.⁴⁵ Efficacy of SC belimumab was not different from IV belimumab when both were indirectly compared.⁴⁶ It is important to

remember that only SLE patients with moderate to severe disease (score of ≥ 8 on the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index) were included in all previously mentioned studies.^{32,33,35,43}

Forms of SC belimumab

Currently, SC belimumab can be administered via either auto-injector or prefilled syringes. Both devices contain a single dose of 1 mL of preservative-free liquid solution (polysorbate 80, L-arginine hydrochloride, L-histidine, L-histidine monohydrochloride, and sodium chloride) in which 200 mg of belimumab is dissolved. Both devices come with a fixed 27-gage, half inch needle and are latex free.

SC belimumab should be stored at a temperature of 2°C–8°C (36–46°F). It should be allowed to warm at room temperature for 30 minutes before administration. SC tissue of both thighs and the abdomen (except for 2 cm around the umbilicus) are recommended as injection sites.⁴⁷

Safety of SC belimumab

In the 52-week BLISS-SC study, safety results in the belimumab group (556 patients) were comparable to the safety results in the placebo group (280 patients). Total adverse events were reported in 84% vs 80% in the placebo and the belimumab groups, respectively. Most common adverse events reported were infections. Serious adverse events were, surprisingly, reported more in the placebo group (15.7% vs 10.8%). As expected, treatment-related adverse events were higher in the belimumab group (31% vs 26%). Study discontinuation, due to adverse events, was more in the placebo group (8.9% vs 7.2%). Herpes zoster was reported more in the placebo group (4.6% vs 3.2%). There were three (0.5%) deaths in the belimumab group that resulted from bacterial sepsis, urosepsis, and CNS tuberculosis, and two (0.7%) deaths in the placebo group that were secondary to cardiac arrest and SLE-related thrombocytopenia.

Although local site injection reactions were reported more in the belimumab group, post-injection hypersensitivity reactions were reported more in the placebo group. It was noted that the adverse events, in general, were higher in patients with higher body weight in both groups but this finding was not explained. Depression was reported more in the placebo group (3.6% vs 2.7%). Suicidal ideation, with no execution/fatality, was reported in 0.4% of the belimumab patients.⁴³

Safety results continued to be similar in the group of patients with positive anti-dsDNA and low complement level. Total and treatment-related adverse events rates were similar

to previously mentioned results. However, serious adverse events were higher in both treatment and placebo groups compared to the previously mentioned study, and continued to be higher in the placebo group (23.1% vs 13.3%).⁴⁴

Even after a 24-week extension of treatment, SC belimumab continued to be well tolerated and showed similar adverse events rates with lower treatment discontinuation rate.⁴⁵ SC belimumab resulted in less adverse events than IV belimumab; however, this was not statistically significant.⁴⁶

Patient satisfaction with SC belimumab using the auto-injector device

A two-part survey study evaluated the satisfaction of rheumatologists (N=88) and patients with SLE receiving treatment with and without belimumab (total N=513). It concluded that patient satisfaction was mainly driven by their ability to function on a daily basis while physician satisfaction with treatment was driven primarily by different clinical outcomes. Patients and physicians strongly agreed that improvement of fatigue was a significant component of satisfaction with treatment. The authors suggested that belimumab could be considered in patients who report dissatisfaction with their standard of care.

More than half of the patients who received belimumab preferred to self-administer their injectable medications at home and considered the convenience and flexibility of treatment administration vital drivers for satisfaction. This preference was higher among patients who were employed.³⁶

Another study that included 548 patients with SLE evaluated their preference for SC injection via an online survey. SC injection was the most preferred choice (41.2%) followed by IV infusions (36.9%). Surprisingly, 21.9% of the patients were not able to decide. Most patients in the latter group were the ones who did not have any previous experience with biological therapy. Older patients were more resistant to trying new SC injections. Patients who preferred SC injections emphasized the importance of not losing working days, avoiding going to the hospital, and being autonomous and comfortable at home. Those who expressed their preference for IV infusions emphasized the importance of feeling safe and the presence of qualified staff during therapy administration.

Despite the good number of study participants, it had some limitations as it relied only on patients who were able to use the internet and on their own interpretation of the questions and their knowledge.⁴⁸

We found only one study that assessed the patients' experiences after using the auto-injector device for SC belimumab.⁴⁹ Forty-three patients who received IV belimumab and SC belimumab via prefilled syringes were switched to SC belimumab via auto-injector device and were followed-up for 2 months. The authors used a questionnaire and a semi-structured telephone interview at the beginning and the end of the eight weeks. Approximately 88% of the patients were very satisfied, and 12% were satisfied with the training they received for using the auto-injector device. By the end of the study, 83% of the patients felt extremely confident using the auto-injector device correctly. Approximately 70% of the patients were very satisfied, 26% were satisfied, and 5% were somewhat satisfied with using the auto-injector device.

The most common reported advantages of the auto-injector were convenience (71%), easy and quick administration (57%), and self-administration (24%). By the end of the study, patients endorsed more advantages: shorter administration time (38%), ease of incorporation into their daily routine (19%), and ability to administer at home (19%). On the other hand, 62% of the patients reported disadvantages including: injection-related discomfort, pain, stinging, nausea, and lack of control of injection speed. Pain was rated as mild in 83% of the patients, while 7% rated it as intermediate, and 10% rated it as severe. Other disadvantages included inconvenience which was explained by the need to store the medication in the refrigerator and the need to wait 30 minutes to achieve room temperature before using it.

Overall, 76% of the patients preferred the use of an auto-injector for SC belimumab over IV belimumab. Patients who preferred the IV form reported better control of their symptoms. In the same context, 52% reported no change in the severity of symptoms, while 24% reported improvement in symptoms that they thought was related to maintaining consistent levels of the medication with SC belimumab.

It is worth noting that the results from all previously mentioned studies could be biased as they relied on the memory recall of the patients included. Also, in such studies, patients may show higher compliance rates and their perspectives may be influenced by the fact that they are using new medication.

Conclusion

The majority of patients may prefer to use SC injections due to different reasons. Working status is a significant variable that may determine patients' preference to use SC injections. Health care staff should provide sufficient training on SC

injections' administration and discuss their side effects and complications.

Data about SC belimumab were obtained from a limited number of studies. SC belimumab appears to be as effective as, and also as safe as, if not more so, than IV belimumab. SC belimumab is more convenient, time-saving, easier to use, and easier to incorporate into patients' daily routines. These advantages were appreciated more by patients who were employed. Disadvantages of SC belimumab include discomfort and pain at the injection site, storage in the refrigerator, and the need to wait for the injector to warm-up prior to use.

Further head-to-head studies comparing IV belimumab, SC belimumab using auto-injector and prefilled syringes in a larger sample size and with a longer follow-up duration are still needed to confirm the results of these preliminary data.

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Disclosure

The authors report no conflicts of interest in this work.

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