Letter to Editor Rheumatology
www.lettertoeditor.org

An international open-access and peer-reviewed online journal

Letter

Lett Ed Rheumatol
doi:10.2399/ler.13.0001

Belimumab in the treatment of lupus: is the target really the group which is difficult to cure in daily practice?

Omer Nuri Pamuk, MD

Division of Rheumatology, Department of Internal Medicine, Trakya University Medical Faculty, Edirne, Turkey

Abstract

The approval of a drug for the treatment of SLE has been exciting and led to expectations in both SLE patients and physicians treating them. Nevertheless, when belimumab-SLE studies are scrutinized, it is seen that treatment goals in the severe lupus group, in spite of some improvement in a group of patients, with which rheumatologists face the most difficulties during daily practice are not met.

Key words: Systemic lupus erythematosus, belimumab.

***Correspondence:**
Omer Nuri Pamuk, MD
Eski Yildiz Cad. Park Apt.
No:24, Daire:18
Besiktas, İstanbul, Turkey
Tel: +90 284 235 27 30
e-mail: omernpamuk@yahoo.com

Dear Editor,

The approval of belimumab by FDA for the treatment of SLE, after a period of almost 50 years, is regarded as an important progress. However, SLE is a heterogenous disease to a large extent and belimumab-SLE studies should be analyzed in detail, criticized, and the groups for which the drug is effective should be known. We want to share our criticisms about BLISS-76[1] study in which belimumab was administered to SLE patients for 76 weeks and its efficacy and safety were investigated. In addition, we will present our criticisms about the concurrent BLISS-52[2] study with similar design. In the initial phase II study in which belimumab was used in SLE, its SLE disease activity or flare reducing effects were not found significant.[3] The subgroup analysis of the study revealed that serologically active SLE patients had better response with belimumab. Later, the administration of belimumab to only seropositive SLE patients for a 52-week period in the phase III study (BLISS-52) led to significant improvement in SLE responder index (SRI). SRI response was simply defined as ≥4 points reduction in the SELENA-SLEDAI score, no new BILAG A organ domain score, no more than 1 increase in BILAG B score, and no more than 0.3 or more increase in the physician's general evaluation score of the patient and disease activation.[1,2] In BLISS-76, the duration of treatment was prolonged to 76 weeks, it was investigated whether there has been loss of efficacy and safety data was presented. Another difference between BLISS-76 versus BLISS-52 was that the former was conducted in North America and Europe, whereas the latter was conducted in Asia, South America and East Europe.

The most important question mark about BLISS-76 –similar to BLISS-52– seems to be the exclusion criteria. The study includes active, severe SLE patients who improved with belimumab; however, the serious problem is that SLE patients with active lupus nephritis and neurologic involvement were not included into the study. Severe cases were excluded initially: this decreases the drug's target population and it becomes evaluable only in patients with low-intermediate disease activity. One possibility which comes to mind might be that the primary aim of the investigators was to obtain approval for the drug in SLE –at least in a subgroup of patients. As known, despite excluding

Citation: Pamuk ON. Belimumab in the treatment of lupus: is the target really the group which is difficult to cure in daily practice? Lett Ed Rheumatol 2013;1:e130001. doi:10.2399/ler.13.0001

Received: September 5, 2012; **Accepted:** December 29, 2012; **Published:** January 24, 2013

Conflicts of Interest: The author has declared that no conflicts of interests exist.

patients with severe neurologic and renal involvement, rituximab studies which had targeted moderately-to-severely active lupus patients ended in disappointment.[4] The investigators –knowing this– formed SRI response criteria, similar to ACR response criteria in rheumatoid arthritis. This is important to catch up minimum differences in order to prove the efficacy of the drug; but, it does not compensate for the lack of an effective treatment in patients who are difficult to treat.

Another concern about the study is that SRI response which is significantly higher in the belimumab arm at 52 weeks, loses its significance (in favor of belimumab) at 76 weeks. The primary end-point at the start of study was defined as 52 weeks; but, considering factors like safety, tolerability it was extended to 76 weeks. The authors suggest that the loss of efficacy until 76 weeks could be because of the more liberal use of high dose steroids in especially the placebo arm after 52 weeks and could be associated with high withdrawal rates. As a result, in a study with a predefined target to report primary outcome in 52 weeks, but presenting data at 76 weeks because of misconception of design causes confusion. The proven efficacy of belimumab at 52 weeks might have masked its efficacy at 76 weeks. In order to mask this, in spite of loss of efficacy after 52 weeks, the authors falsely present data in a positive way like "The SRI response rates were numerically greater with 10 mg/kg belimumab (38.5%) (p=0.13) and 1 mg/kg belimumab (39.1%) (p=0.11) than with placebo (32.4%)".

Another noteworthy point is the high rate of patients who did not complete the study. The withdrawal rates for all groups at 52 weeks is about 25%, and it's similar around 30% in all groups at 76 weeks. Causes of withdrawal do not seem to differ among the groups; however, a high number of patients defined in the power analysis at the beginning of the study could not complete the study. In order to solve this problem, "last observation carried forward" method was used for patients who completed the study.

As a result, it is exciting to have a new drug being approved in SLE for physicians treating lupus patients. However, it is of utmost importance to know in which patient group the drug is effective and to understand the long-term side effects. That means more data is needed on this issue. The current data proves that –in spite of some progress- new treatment modalities are urgently awaited for SLE patients, especially for those with severe disease activity.

References

1. Furie R, Petri M, Zamani O, et al. BLISS-76 Study Group. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011; 63:3918-30.
2. Navarra SV, Guzmán RM, Gallacher AE, et al. BLISS-52 Study Group. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011;377(9767):721-31.
3. Wallace DJ, Stohl W, Furie RA, et al. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Rheum* 2009;61:1168-78.
4. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum* 2010; 62:222-33.
5. Furie RA, Looney JR, Rovin B, et al. Group LS. Efficacy and safety of rituximab in patients with proliferative lupus nephritis: results from the randomized, double-blind phase III LUNAR study. *Ann Rheum Dis* 2010;69(Suppl 3):549.

