Anti-BLyS Treatment of 36 Israeli Systemic Lupus Erythematosus Patients

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ABSTRACT: **Background:** Anti-BLyS treatment with the human belimumab monoclonal antibody was shown to be a safe and effective therapeutic modality in lupus patients with active disease (i.e., without significant neurological/renal involvement) despite standard treatment.

Objectives: To evaluate the "real-life" safety and efficacy of belimumab added to standard therapy in patents with active lupus in five Israeli medical centers.

Methods: We conducted a retrospective open-labeled study of 36 lupus patients who received belimumab monthly for at least 1 year in addition to standard treatment. Laboratory tests (C3/C4, anti-dsDNA autoantibodies, chemistry, urinalysis and complete blood count) were done every 3–4 months. Adverse events were obtained from patients' medical records. Efficacy assessment by the treating physicians was defined as excellent, good/partial, or no response.

Results: The study group comprised 36 lupus patients (8 males, 28 females) with a mean age of 41.6 ± 12.2 years. Belimumab was given for a mean period of 2.3 ± 1.7 years (range 1–7). None of the patients discontinued belimumab due to adverse events. Four patients (11.1%) had an infection related to belimumab. Only 5 patients (13.9%) stopped taking belimumab due to lack of efficacy. The response was excellent in 25 patients (69.5%) and good/partial in the other 6 (16.6%). Concomitantly, serological response (reduction of C3/C4 and anti-dsDNA autoantibodies) was also observed. Moreover, following belimumab treatment, there was a significant reduction in the usage of corticosteroids (from 100% to 27.7%) and immunosuppressive agents (from 83.3% to 8.3%).

Conclusions: Belimumab, in addition to standard therapy, is a safe and effective treatment for active lupus patients.

IMAJ 2017; 19: 44–48

KEY WORDS: systemic lupus erythematosus (SLE), belimumab, safety, efficacy, steroid sparing

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting almost any organ of the body [1]. The disease appears in both genders at any age but is more common in young females [2]. The precise etiology of SLE has not yet been defined, though genetic, hormonal and environmental factors were all shown to play a role in the pathogenesis of lupus [3]. SLE is characterized by disturbances in both the innate and adaptive immune systems with dysregulation of pro-inflammatory and suppressive cytokines, complement, T and B cells [4]. The hallmark of SLE is abnormal (stimulatory) B cell function with hypergammaglobulinemia and the production of autoantibodies [5]. Thus, antinuclear antibodies (ANA) can be detected in the sera of almost all lupus patients, whereas anti-dsDNA and anti-Sm autoantibodies can be detected in the sera of 80–85% and 20–30% of SLE patients, respectively [6].

B lymphocyte stimulator (BLyS), also designated B cell activating factor (BAFF), is a 250 amino acid protein that belongs to the tumor necrosis factor (TNF)-ligand superfamily [7]. It is produced and secreted mainly by monocytes and activated T cells. The three BLyS receptors, BLyS receptor 3 (BR3, also known as BAFF-R), transmembrane activator-1 and calcium modulator and cyclophilin ligand-interactor (TACI), and B cell maturation antigen (BCMA), are expressed on B cells [7]. BLyS plays a major role in the stimulation, proliferation and maturation of B cells to plasma cells which produce immunoglobulins [7].

As was shown in lupus-prone mice studies [8], high BLyS levels were reported in sera obtained from 40–50% of SLE patients [9]. However, the correlation between sera BLyS levels and disease activity in lupus patients has not been established [10-12]. It was suggested that high mRNA BLyS levels in monocytes of SLE patients correlate to disease activity better than BLyS sera levels [13]. Recently, we were able to determine high BLyS levels in 80.5% of sera obtained from 41 Israeli lupus patients [14]. Although BLyS levels fluctuated over time in the sera of our patients, no significant correlation to disease activity or to anti-dsDNA autoantibody levels was observed [14].

Despite recent improvement in survival, SLE remains associated with significant mortality and morbidity (including lupus flares) due to infections, renal disease, central nervous system (CNS) disease and heart disease [1]. The current standard treatment for SLE does not provide complete response in all lupus patients [1-3]. Moreover, those medications, especially corticosteroids, can cause significant morbidity such as osteoporosis, osteonecrosis, metabolic diseases (e.g., hyperlipidemia, hyperglycemia), infections, weight gain and mood disorders [15]. Thus, a new effective and safe treatment modality for SLE is needed.

Belimumab (Benlysta®, GSK, United Kingdom) is an anti-BLyS human IgG1λ monoclonal antibody that binds and inhibits soluble human BLyS [16,17]. In a phase II study, lupus patients with moderately active disease showed improved disease activity after one year of belimumab treatment (combined with standard treatment) as compared to standard treatment alone [18]. The two phase III studies (BLISS-52 and BLISS-76) [18,19] met their primary endpoints of a significant higher response rate, at week 52, in patients treated with belimumab (compared to placebo) in addition to standard treatment. The belimumab-treated lupus patients revealed significantly fewer lupus flares, greater reduction of daily corticosteroid dosage and higher rates of normalization of complement (C3) and anti-dsDNA autoantibody levels compared to the placebo-treated patients [19-21]. It should be noted that although the above differences were statistically significant, the therapeutic effects of belimumab, on top of standard treatment, were modest [21]. As shown in the phase II study, the safety profile of belimumab was good, similar to that of the placebo [18].

Recently, belimumab was approved in Israel for treatment of lupus patients with active (not renal/CNS) disease when treatment with hydrochloroquine or immunosuppressive agents did not yield a satisfactory response [15]. We present here the results of belimumab (an open-label study) treatment in 36 lupus patients in 5 medical centers in Israel.

PATIENTS AND METHODS

All patients were diagnosed with SLE according to at least four American College of Rheumatology (ACR) classification criteria [22]. Belimumab treatment was initiated according to the Israeli "health basket," which included patients with active lupus disease, without severe active CNS/renal disease, despite hydrochloroquine or immunosuppressive therapy. Belimumab was given, intravenously, at a dosage of 10 mg/kg on days 0, 14 and 28 and every 28 days thereafter. All patients were treated with belimumab for at least one year. Belimumab was given in addition to standard therapy that included one or more (combination) of the following: corticosteroids, hydrochloroquine and immunosuppressive agents [azathioprine, mycophenolate mofetil (MMF), or cyclophosphamide]. Data on the patients' past and current medical history, medications (daily dosage) and laboratory tests (including complete blood count, chemistry, urine analysis, ANA, anti-dsDNA, C3, C4) were collected from the medical records. Patients were evaluated monthly (at the time of belimumab injection). Laboratory tests were done every 3–4 months (or more often according to the physician's judgment).

SAFETY ASSESSMENT

Patients were monitored for safety by the treating physicians throughout the study period, and adverse events (including possible events) were recorded.

EFFICACY MEASUREMENTS

Disease response was assessed by the Physicians Global Assessment (PGA) [23]. Response was defined as excellent, good/partial, or no response. No response was defined in case of active disease or new disease manifestations requiring change or increase of standard lupus treatment despite belimumab treatment. Dosage of one or more of the lupus standard medications was reduced or discontinued according to the treating physician's medical judgment. Serological response was defined as normalization of complements levels (C3, C4) and/or anti-dsDNA autoantibodies.

STATISTICAL ANALYSIS

Data are presented as mean ± SD. Mann-Whitney, unpaired Student's *t*-test and chi-square tests were used for statistical analysis. A value of $P \leq 0.05$ was considered statistically significant.

RESULTS

Thirty-six lupus patients were included in our retrospective open-labeled belimumab study. Patients were recruited from five Israeli medical centers around the country: Sheba (Tel Hashomer), Rambam and Bnei-Zion (Haifa), Hadassah (Jerusalem) and Kaplan (Rehovot). All patients fulfilled at least four ACR classification criteria [22]. Table 1 summarizes the prevalence of the ACR classification criteria in our patients along the entire period of their disease. All patients had high titers of ANA in their sera. The relatively low rate of neurological and renal involvement in our cohort probably reflects the fact that patients with active renal or neurological diseases were not eligible for belimumab treatment. Eight patients (22%) were males and 28 were females (78%). The mean age of the patients at the time of the study was 41.6 ± 12.2 years (range 22–69). The patients were diagnosed with lupus 15.7 ± 9.6 years (range 3–40) prior to the initiation of belimumab treatment.

Almost all patients (35/36, 97%) were treated with hydroxychloroquine (Plaquenilâ, Sanofi-Aventis, France) and all of them (36/36) were treated with corticosteroids (≥ 10 mg prednisone

Table 1. Prevalence of ACR classification criteria [22] from the time of SLE diagnosis in 36 lupus patients

ACR criteria	Patients (%)
Arthritis	95
Photosensitivity	72
Discoid lupus (DLE)	68
Hematological*	66
Mucosal ulcers	55
Malar rash	52
Serositis	40
Neurological**	13
Renal***	12
Immunological (anti-dsDNA, anti-Sm, APLA)	89
ANA	100

Patients were diagnosed with SLE according to at least four ACR (American College of Rheumatology) classification criteria [22]

All 36 patients demonstrated high titers of anti-nuclear antibodies (ANA) in their sera. *Hematological: hemolytic anemia, leukopenia (white blood cell count ‹ 4000/µl), lymphopenia (‹ 1500/µl), or low platelet count (‹ 100,000/µl) in the absence of the offending drug

**Neurological: seizures or psychosis in the past, not at the time of belimumab initiation

***Renal: › 0.5 g per day protein in urine or active urine sediment with cellular casts in the past, not at the time of belimumab initiation

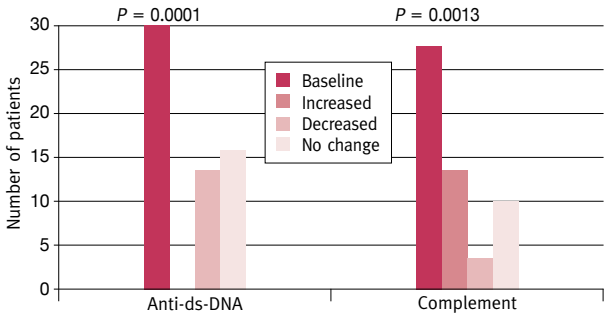
daily) at the initiation of the study. Thirty patients (83.3%) were also treated with another immunosuppressive agent (22 with azathioprine, 7 with methotrexate and 1 with MMF). Prior to the initiation of belimumab treatment, five patients were treated with cyclophosphamide and another patient with MMF (past treatment). Seven patients (19.4%) exhibited severe corticosteroid adverse events (5 with severe osteoporosis and 2 with cataract) before starting belimumab treatment. The decision to initiate belimumab was made by the treating physicians at the different medical centers. Only patients who were treated with belimumab were included in our retrospective study; thus, there is no comparison with other lupus patients who were treated by different therapeutic modalities.

At the beginning of the study, ANA were observed in the sera of all our patients, anti-dsDNA autoantibodies in 30 (83.3%), and low complement levels (C3 and or C4) in 77.7%.

The main indications for the initiation of belimumab treatment, in addition to the standard treatment (as described above), were arthritis, mucocutaneus manifestations, fever, and hematological cytopenias (mainly thrombocytopenia). Belimumab was given intravenously as described above. The mean duration of belimumab treatment in the present study was 2.3 ± 1.7 years (range 1–7). At the end of the study, 31 patients (86.1%) are still on belimumab treatment; 5 (13.9%) had stopped belimumab due to lack of sufficient efficacy.

During the period of the study (2.3 ± 1.7 years), our patients received more than 1100 intravenous belimumab injections.

Figure 1. Serological improvement following belimumab treatment. At baseline, prior to the initiation of belimumab, 30 patients (83.3%) had high anti-dsDNA autoantibodies and 28 patients (77.7%) had low complement (C3/C4) levels. At the end of the study, anti-dsDNA was not detected in 48% of the patients with initial high autoantibodies levels. In none of the patients were raised titers (or new appearance) of anti-dsDNA autoantibodies observed ($P = 0.0001$). Complement (C3/C4) levels normalized (increased) in 50% of the patients who had low levels at the initiation of the study ($P = 0.0013$) but declined in 13% of the patients during the study

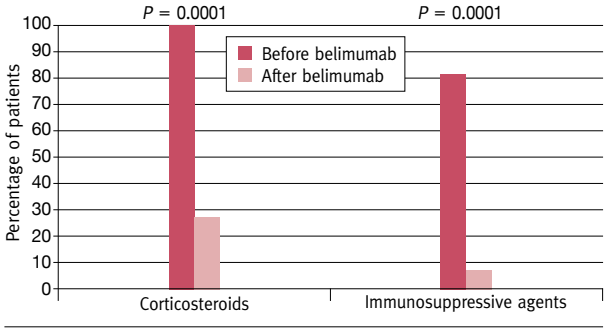


Belimumab was well tolerated without significant adverse events. Two patients (5.5%) reported slight headache following belimumab injections; 4 patients (11.1%) demonstrated infections (3 with herpes zoster, 1 with pneumonia) which were probably related to belimumab treatment. There were no drop-outs from the study and no patient had stopped belimumab because of adverse events or inconvenience of the intravenous injections.

At the end of the study, 25 patients (69.4%) demonstrated excellent response with complete clinical remission. Six other patients (16.6%) improved with belimumab treatment, demonstrating partial clinical remission. These 31 patients are still treated with monthly injections of belimumab. In 5 patients (13.9%) a sufficient clinical response was not observed. Thus, despite belimumab and standard treatment, those patients had lupus flares characterized by either worsening of their original mucocutaneous and joint disease or by the appearance of new lupus manifestations (pneumonitis in one patient and pericarditis in another). Belimumab was discontinued in those five patients. The significantly high response rate ($P = 0.0001$ between responders and non-responders) was observed regardless of the gender of the patients or their serological status (C3, C4 or anti-dsDNA autoantibody levels prior to belimumab treatment).

Along with the good clinical response, belimumab treatment led to significant improvement of lupus-related serological parameters. Thus, in half of the patients normalization (from baseline prior to belimumab treatment) of anti-dsDNA autoantibodies (48%) and complement (C3, C4) levels (50%) were observed following belimumab treatment [Figure 1]: $P = 0.0001$ between patients with decreased vs. increased anti-

Figure 2. Discontinuation of corticosteroids and immunosuppressive agents following belimumab treatment. At baseline, prior to the initiation of belimumab, all 36 patients were treated with corticosteroids (≥ 10 mg prednisone/day) and 30 patients (83.3%) were also treated with methotrexate, azathioprine, or mycophenolate mofetil (MMF). At the end of the study, only 10 patients (27.7%) were still treated with corticosteroids and 3 patients (8.3%) with immunosuppressive agents (P = 0.0001 for the reduction of both corticosteroids and immunosuppressive agents)



dsDNA autoantibody levels and P = 0.0013 between patients with increased vs. decreased complement (C3/C4) levels.

Concomitantly with the serological and clinical responses following the addition of belimumab to the standard treatment in active lupus patients, a significant reduction in the rate of patients treated with corticosteroids and immunosuppressive agents was also seen. All 36 patients entering our retrospective study (100%) were taking corticosteroids (≥ 10 mg daily prednisone) and 30 (83.3%) were treated with immunosuppressive agents at baseline (prior to belimumab treatment). The proportion of patients taking corticosteroids or any immunosuppressive agent declined significantly following the addition of belimumab. Thus, at the end of the study, only 10 patients (27.7%) were treated with any dosage of corticosteroids (P = 0.0001) and 3 patients (8.3%) were still on immunosuppressive agents (P = 0.0001) [Figure 2].

DISCUSSION

Our retrospective open-labeled study demonstrated that belimumab is a safe and efficient treatment modality, in addition to standard therapy, in patients with active lupus disease (despite standard treatment). There were no discontinuations due to belimumab adverse events. Only 5 patients (13.9%) discontinued belimumab due to insufficient clinical response. Along with the good clinical response following belimumab treatment, serological response (normalization of C3/C4 and anti-dsDNA autoantibodies) with a significant rate of withdrawal of corticosteroids and immunosuppressive agents was also observed.

All patients who entered the study had active lupus disease prior to the initiation of belimumab treatment. Indeed, 100% of our patients were treated with corticosteroids and 83.3% of them were also treated with another immunosuppressive agent. The standard treatment was continued as needed along with belimumab. Changes (discontinuations, dose reduction) of corticosteroid treatment were implemented according to the patient's clinical state and the physician's medical judgment. At the end of the study (mean years of belimumab treatment 2.3 ± 1.7), 25 patients (69.4%) demonstrated excellent response with complete lupus remission and another 6 (16.6%) demonstrated partial clinical response. It should be noted that five of the six patients who demonstrated partial clinical response were treated with belimumab for a relatively short time (about 1 year). Although the lack of a placebo-treated group of patients may influence our results, the response rate in our real-life retrospective study is impressive and even higher than that reported in the phase II/III study [18-20] or the 7 years continuous belimumab study [24].

As shown in previous belimumab studies [21], we were also able to demonstrate significant serological improvement following belimumab treatment. Normalization of complement (C3, C4) levels and decrease in anti-dsDNA autoantibody levels were observed in 50% and 48% of our patients, respectively [Figure 1]. Normalization of the above serological tests is important since these biomarkers have been shown to associate with increased risk of lupus renal disease and severe lupus flares [5].

Prolonged treatment with corticosteroids as well as with other immunosuppressive agents are associated with significant adverse events and morbidity [3,25]. Thus, discontinuation of those drugs, especially corticosteroid-sparing, is likely to be beneficial for lupus patients [15]. Indeed, corticosteroid use in our patients decreased significantly (from 100% to 27.7%) following the initiation of belimumab treatment. Similarly, the proportion of patients who were treated with another immunosuppressive agent (e.g., azathioprine, methotrexate, or MMF) also decreased significantly (from 83.3% to 8.3%) following the addition of belimumab to standard lupus treatment [Figure 2]. Our results are in agreement with previous belimumab studies [16] which also reported corticosteroid-sparing following belimumab treatment.

Our safety results are consistent with the previous belimumab studies [18-20], which reported a similar adverse events rate in the belimumab- and placebo-treated groups of patients. A recent long-term (7 years) study of belimumab treatment in lupus patients [24] also demonstrated the safety profile of belimumab treatment in lupus patients.

Although the phase II belimumab trial reported a better response rate in patients with low complement and high anti-dsDNA autoantibodies [18], later studies, especially the 7 years longitudinal study [24], reported a similar good response in both "high and low autoantibodies titers" groups of lupus patients. As reported by the later study [24], we also did not find a significant difference in clinical response to belimumab

treatment related to the titer (low or high) of the autoantibodies observed in the sera of lupus patients. Indeed, the serological status of the patients is neither an indication nor a contraindication for the initiation of belimumab in lupus patients.

Our study has some limitations. First, it was a retrospective open-label study of a relatively small number of patients. Second, although the mean follow-up period (belimumab treatment period) was longer (2.3 ± 1.7 years, range 1–7) in our patients than in the phase II/III belimumab studies [18-20], at least one study previously reported the efficacy of belimumab treatment in lupus patients over a period of 7 years [24]. Nevertheless, our results are important since our study represents a real-life experience using belimumab to treat 36 lupus patients (males and females) over more than 2 years. The fact that belimumab has to be administered intravenously, every month, is somewhat inconvenient (for both patients and physicians). This may limit its usage as a long-term treatment modality. Indeed, the efficacy and safety of self-subcutaneous belimumab injections are currently under investigation. The low rate (13.9%) of belimumab discontinuations in our study is most probably due to the high safety and efficacy profile of the drug. The fact that every treating physician was responsible for a relatively small number of belimumab-treated patients (2–5 patients) also contributed to the persistence of a high percentage of patients on belimumab treatment along the study period (mean 2 ± 1.7 years).

To conclude, as was previously shown in large perspective placebo-controlled studies, our results demonstrate clinical and serological responses with a good safety profile and significant immunosuppressive agents (including corticosteroids) sparing in active lupus patients treated with belimumab in addition to standard therapy, for more than 2 years (range 1–7).

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"The measure of a man's real character is what he would do if he knew he would never be found out"

Thomas Babington Macaulay (1800-1859), British historian, politician and writer. His books on British history have been hailed as literary masterpieces