

Treatment of SLE and Secondary Sjogren's Syndrome with Belimumab

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Received date: August 26, 2016; Accepted date: October 05, 2016; Published date: October 12, 2016

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Abstract

Belimumab neutralizes the soluble form of B-cell activating factor and is FDA-approved for treating Systemic Lupus Erythematosus (SLE). In this retrospective analysis 16 female SLE patients had been treated with belimumab according to FDA guidelines along with any immunosuppressive drugs or antimalarial drugs they had previously been prescribed, in addition to prednisone. Thirteen of 16 patients presented with serologic evidence of positive anti-nuclear antibody titer while several other SLE patients also had clinical evidence of secondary Sjogren's Syndrome (2°SS), the latter supported by sicca symptoms and positive anti-Sjogren's-syndrome-related antigen A antibody titer. Changes in the SLE symptoms after belimumab therapy was assessed by the recipient's responses on the Short Form-36 questionnaire. Ten of the 16 SLE patients reported a decrease in arthralgias or in symptoms of arthritis while fatigue was reduced in 9/16 patients. However, SLE patients with sicca symptoms failed to show any change in the Short Form-36 score after treatment with belimumab. In conclusion, although the results in this small cohort study supported the use of belimumab as an adjunctive therapy for SLE, sicca symptoms associated with 2°SS did not appear to respond to belimumab.

Keywords: Arthritis; Autoantibodies; Belimumab; Sjogren's Syndrome; Sicca; SLE

Introduction

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune inflammatory disease characterized primarily by the production of autoantibodies produced via dysfunctional B-cell activity [1]. As reviewed by Rahman and Isenberg [2], the prevalence of SLE ranges from about 40 cases/100,000 persons among Northern Europeans to more than 200/100,000 persons among African-Americans. Furthermore, in the US, the total number of SLE patients is greater than 250,000.

Importantly, the life expectancy of lupus patients has continually increased so that the approximate 4-year survival rate of lupus patients has increased from 50% in the 1950s to a 15-year survival rate of 80% today [2]. As indicated above, the prevalence rates for SLE are higher in African-American females compared to white females [3,4]. However, the clinical course of SLE tends to more severe in men than in women.

Even though overall survival and life expectancy has recently improved, SLE remains an autoimmune disease associated with significant morbidity and mortality due to an increase in relative risk for organ damage, heart disease and other cardiovascular complications, infection and frequent clinical flares which require the administration of high-dose corticosteroids. In addition to conventional first-line therapies with non-steroidal anti-inflammatory drugs, corticosteroids, antimalarial drugs, cytotoxic and/or immunosuppressive drugs, belimumab was approved in Europe and also by the United States Federal Drug Administration (USFDA) in March 2011 as an adjuvant therapy for SLE. The FDA recommended

that belimumab be employed at a dosage of 10 mg/kg in seropositive active SLE patients [5].

Although SLE remains a disease of unknown etiology it was postulated that SLE patients inherit or acquire defects in B-cell tolerance to nuclear antigens as a result of genetic susceptibility factors and/or by exposure to neo-antigens following infection which results in a deregulation of interferon-mediated signaling [6]. In addition, it is now well-accepted that hyperactivation of B-cells plays a central role in SLE disease progression. Thus, following a breach in central tolerance, autoreactive B-cells stimulate humoral and cell-mediated immune responses through a variety of mechanisms, including, production of autoantibodies, deposition of immune complexes in various tissues most notably the kidney, heightened cytokine production and T-cell activation. Importantly, uncontrolled overly activated B-cells amplify the tissue-specific autoimmune responses [7].

B-cell Activation Factor (BAFF) also known as B-Lymphocyte Stimulator (BLyS) is a member of the tumor necrosis factor family [8]. BLyS was shown to promote B-cell proliferation, maturation and survival [9,10] and most critically, serum levels of BLyS were found to be elevated in patients with autoimmune diseases, including SLE [11]. Additionally, a close association between the plasma levels of BLyS and SLE disease activity has been reported [12]. This finding led to the view that neutralizing BAFF/BLyS activity would improve the clinical symptoms of SLE. In that regard, belimumab is a human IgG1 λ monoclonal antibody that was shown to neutralize soluble BLyS resulting in reduced B-cell survival and impaired B-cell differentiation without directly causing B-cell death [13,14].

Two Phase 3, randomized, double-blind, placebo-controlled trials with belimumab, namely, BLISS-52 and BLISS-76, met the primary endpoint for significant clinical improvement in SLE measured by the Systemic Responder Index (SRI) at week 52 when compared with

standard therapy alone in patients with seropositive SLE [14,15]. Other studies have shown that belimumab promoted the normalization of serologic activity in SLE, reduced severe lupus flares, decreased concurrent prednisone dose, decreased proteinuria while also improving the score on the Health Status Questionnaire Short Form-36 (SF-36) [16,17]. SF-36 is a self-reporting questionnaire which is frequently employed to assess the response of patients with autoimmune diseases to various clinical therapies.

The overall objective of this small retrospective cohort study was to assess the serologic and clinical outcomes associated with belimumab therapy in patients with active SLE as determined by both clinical and serologic measurements. We also determined the clinical efficacy of belimumab in patients who also presented with clinical and serologic evidence of secondary Sjogren's Syndrome (2°SS), a condition which has been shown to be often associated with SLE [18].

Results

Clinical cohort

This study was performed in a single rheumatology clinic at the Chagrin-Highlands Medical Center, (Orange Village, Ohio), an outpatient facility of University Hospitals Cleveland Medical Center (Cleveland, Ohio). The study employed a retrospective cohort which included 16 patients with clinically-confirmed active SLE who were begun on belimumab infusion therapy (10 mg/kg every 4 weeks) from March, 2011 to July, 2015. Because the number of studied patients exceeded 3, the study design and implementation protocol had to be approved by the University Hospitals Cleveland Medical Center Institutional Review Board (Protocol Title: "Benlysta Experience in the Division of Rheumatology at University Hospitals Cleveland", Protocol #09-15-26; Reference #050869).

Clinical evaluation

The records of 16 female patients were reviewed for clinical evidence of SLE; 9/16 (56.3%) patients were Caucasian and 7/16 (43.7%) were African-American. The mean age of these patients was 44.4 years. The diagnosis of SLE was confirmed on the basis of clinical symptoms, including, photosensitivity, malar rash, oral ulcers, alopecia and arthritis.

ANA testing

ANA screening and determination of ANA titers was obtained using the BioPlex™ 2200 ANA Screen (Bio-Rad, Berkeley, CA) method which is a multiplex flow immunoassay resembling traditional enzyme immunoassay. In addition, the appearance of ANA positive cells was evaluated using the human epithelial cell line, Hep-2 and immunofluorescence staining (Inova Diagnostics, San Diego, CA). Of the 16 SLE patients in this cohort, 15 were tested for ANA and 12/15 (75%) were found to have a positive ANA titer (cut-off for positive; dilution, <1:40) (Table 1). ANA- positivity on Hep-2 cells was characterized as either homogenous, speckled or mixed (Table 1). Neither nucleolar nor centromere patterns were detected. Although 3 patients had a "negative" ANA screen (Table 1) they were nevertheless diagnosed with SLE on the basis of their clinical presentation as defined above.

In the ANA-positive group, 4/16 (25%) patients were positive for anti-double-stranded DNA (anti-ds-DNA) and 3/16 (18.8 %) had low

serum levels of complement C3 or C4. Importantly, 4/16 (25%) of the SLE patients were also positive for the anti-Sjogren's-Syndrome-related antigen A (anti-SSA/anti-Rho) antibody (Table 1). As indicated above, all of the SLE patients presented with arthralgias and/or arthritis whereas 12/16 (75%) showed clinical evidence of fatigue. Of note, sicca symptoms were present in 6/16 (37.5%) of these SLE patients (Table 1). However, in the group with sicca symptoms there was no evidence of elevated anti-SSA/anti-Rho or anti-Sjogren's-Syndrome-related antigen B (anti-SSB/anti-La) antibody titers.

Patient No.	ANA: + or -; (Titer) ³	ANA Appearance ⁴
1	Not Available ⁵	Not Available ³
2 ⁷	Positive (1:160)	Homogeneous
3	Negative (<1:40) ⁶	Negative ⁶
4 ^{1,2}	Positive (1:80)	Homogeneous
5	Positive (1:320)	Mixed
6 ^{1,2}	Positive (1:40)	Homogeneous
7 ^{1,2}	Negative (<1:40) ⁶	Negative ⁶
8 ⁷	Positive (1:160)	Speckled
9 ^{1,2}	Positive (1:160)	Speckled
10 ⁷	Positive (1:320)	Speckled
11	Negative (<1:40) ⁶	Negative ⁶
12	Positive (1:40)	Speckled
13 ^{1,2}	Positive (1:320)	Mixed
14	Positive (1:40)	Speckled
15 ⁷	Positive (1:320)	Speckled
16 ^{1,2}	Positive (1:640)	Speckled

¹SLE patients presenting clinically with 2°SS; ²SLE/2°SS patients with evidence of sicca symptoms; Sicca symptoms in patient no. 13 improved with belimumab therapy, but sicca symptoms in patients 4, 6, 7, 9 and 16 did not improve; ³The ANA titer was determined by the BioPlex™ 2200 ANA Screen system. The cut-off dilution for a "positive" ANA was 1:40 or greater; ⁴The appearance of the ANA-positive reactive product on Hep2 cells was examined by immunofluorescence microscopy; ⁵Although the ANA titer from this patient could not be obtained, the patient was noted to have an elevated anti-ds DNA titer; ⁶Patients No. 3, 7 and 11 with a "negative" ANA were diagnosed with SLE on the basis of clinical symptoms including photosensitivity, malar rash, oral ulcers, alopecia and arthritis. Patient No. 7 had sicca symptoms; ⁷Patients No. 2, 8, 10, and 15 had positive anti-SSA/anti-Ro antibody titer determined by the BioPlex™ 2200 ANA Screen system. The defined cut-off dilution for a positive anti-SSA/anti-Ro titer was >1.0.

Table 1: Anti-Nuclear Antibody (ANA) Titers and ANA Cell Patterns in the SLE Patient Cohort.

Treatment with belimumab

Belimumab was added to an immunosuppressive or antimalarial drug regimen along with prednisone. In the SF-36 analysis, 10/16 (62.5%) patients reported improvement in arthralgias or symptoms of arthritis whereas fatigue was improved in 9/16 (56.3%) of these patients. However, 5/6 patients (83.3%) who had evidence of sicca symptoms showed no improvement in the SF-36 score after treatment with belimumab. Notably, in this group only 4/16 (25%) patients

continued to show evidence of a positive anti-SSA antibody titer. However, in these 4 patients 3 of them continued to show evidence of anti-SSA antibody, but none of these patients had sicca symptoms. Importantly, all of the SLE patients had normal renal function, which had been assessed by measuring blood urea nitrogen and creatinine levels prior to, and during therapy with belimumab. Of note, 3/16 patients (18.7%) patients reported a reoccurrence of fatigue, arthralgia or arthritis after about 3 months when belimumab therapy could not be continued due to patient withdrawal, alcohol use or issues with coverage by medical insurance. Importantly, only 3/16 patients (18.7%) developed significant side-effects on belimumab therapy which included, severe headache, yeast infection and flares in symptoms of irritable bowel syndrome.

Discussion

Belimumab has been shown to improve the clinical symptoms associated with SLE [17] and testing of belimumab in patients with primary Sjogren's Syndrome has also been reported [19]. However, a review of the PubMed database as the results of this study was being prepared for publication did not disclose the extent to which belimumab was used to treat patients with SLE and associated 2°SS. With reference to the association between SLE and 2°SS as demonstrated in this clinical study, Hernández-Molina et al. [20] had previously shown that 18.5% of SLE patients, all female, developed 2°SS which they termed Sjogren's syndrome/SLE. The presence of anti-SSA/anti-Ro antibody was identified as a predictor for developing Sjogren's Syndrome in recent-onset SLE, whereas the absence of anti-SSA/anti-Rho antibody, anti-SSB/anti-La antibody and rheumatoid factor identified SLE patients at the lowest risk for developing Sjogren's syndrome. Thus, the results of our small 16 patient cohort study appears to be the first in which SLE patients with concomitant serologic evidence of 2°SS were treated with belimumab. In that regard, the results supported using belimumab as an adjunctive therapy for the treatment of SLE as evidenced by a clinical improvement in arthralgias and/or arthritis as well as less fatigue in the SLE patients who were also receiving standard SLE therapy. Importantly, the ability to predict the development of 2°SS in our SLE patients was supported by our finding of elevated anti-SSA antibody titers and, in addition, the presence or absence of sicca symptoms. We also noted that the sicca symptoms in this SLE cohort failed to respond to belimumab therapy. However, a longitudinal study will now be required for the further investigation of the association between therapy with belimumab and the resolution of sicca symptoms. It was also important to note that no serious adverse events occurred in the SLE patients treated with belimumab.

Three limitations in this study were 1) its small cohort size 2) performance at a single outpatient Rheumatology clinic, and 3) no male patients in this SLE cohort. Therefore, no conclusions can be drawn regarding how treatment with belimumab might alter the clinical symptoms or progression of SLE or 2°SS in male SLE patients.

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