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EFFICACY OF BELIMUMAB ON RENAL OUTCOMES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A SYSTEMATIC REVIEW

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Abstract

Both BLISS-52 and BLISS-76 international phase III trials in Systemic Lupus Erythematosus (SLE) met their primary outcomes; however, they were not designed to assess the efficacy of belimumab for the treatment of lupus nephritis (LN). LN is a frequent cause of SLE-associated morbidity and mortality, and emerging evidence suggests a potential therapeutic role for agents that target B lymphocyte stimulator (BLyS).

We conducted a systematic review to identify data on the effect of belimumab on LN.

A total of 2004 patients with SLE were identified from 11 studies. Three hundred and twenty-six patients had LN at baseline and 234 (71.8%) of those received belimumab. Thirteen patients out of 234 (5.5%) received belimumab for active LN. Due to the heterogeneous definitions of treatment response, clinical presentation and renal involvement, it was not possible to compare results using a single outcome parameter. However, the majority of these studies defined clinical response in terms of rates of renal flare, renal remission, and/or renal organ disease improvement. One hundred twenty nine (55.1%) of the 234 patients with LN at baseline showed an improvement in renal parameters after treatment with belimumab. In patients with baseline proteinuria >0.2g/24h, (n=687), those receiving belimumab had a median reduction in proteinuria during follow-up as high as 38%. When focusing on patients with proteinuria ≥1g/24h (n= 228), 70.7% of those treated with belimumab (n=157) achieved a renal response.

In the pooled population of patients receiving belimumab, we found an overall annual renal flare rate of 1.7% [24/1448, mean observation time 1.1 years (0,5-3)].

Despite the limitations of the studies included in this analysis, available data are promising and provide preliminary support for targeting BlyS to induce or maintain a renal response. Further trials should examine whether belimumab (alone or following rituximab) represents an additional therapeutic option in the treatment of LN.
INTRODUCTION

Belimumab is a human immunoglobulin-G1λ monoclonal antibody that inhibits B-cell differentiation and survival by inhibiting the biologic activity of soluble B-lymphocyte stimulator (BLyS). Two international phase III trials, BLISS-52 and BLISS-76, showed a similar safety profile and a significantly higher rate of response as measured by the Systemic Lupus Erythematous Responder Index (SRI) in antibody positive Systemic Lupus Erythematosus (SLE) patients treated with belimumab versus placebo in combination with background immunosuppressives. (Arthritis Rheum 2011; 63: 3918–3930; Lancet 2011; 377: 721–731.).

Lupus nephritis (LN) is a frequent cause of SLE-associated morbidity and mortality. Renal involvement occurs in 40%–70% of patients, and 10-20% progress to end-stage renal disease (Arch Int Med 2000; 160: 3136–1340; Medicine 2006; 85: 147–156; Arthritis Rheum 2006; 54: 2550–2557; Arthritis Care Res 2012; 64:797–808.).

Notably, the BLISS trials were not designed to specifically assess the effect of belimumab on the treatment of LN. (Arthritis Rheum 2011; 63: 3918–3930; Lancet 2011; 377: 721–731.). Patients with proteinuria>6 g/24 h or serum creatinine >2.5 mg/dl, and those who required hemodialysis or high-dose prednisone within 90 days of study initiation were excluded from these trials.


We conducted a systematic review to identify published data on the effect of belimumab on renal parameters in SLE patients with LN. We included in our analysis a) patients with active
biopsy proven LN receiving belimumab; b) patients with previous LN but no sign of renal activity when treatment with belimumab was started; c) patients with signs of renal activity when treatment with belimumab was started but no histological confirmation of LN; d) patients with no previous history of LN who developed signs of renal activity when receiving treatment with belimumab.

METHODS

Information sources and search strategy

A detailed literature search was developed a priori.

Key words and subject terms used in the search included: (“belimumab”[All Fields] AND ("lupus erythematosus, systemic”[MeSH Terms] OR "lupus”[All Fields] AND "erythematosus”[All Fields] AND "systemic”[All Fields]) OR "systemic lupus erythematosus”[All Fields] OR ("systemic”[All Fields] AND "lupus”[All Fields] AND "erythematosus”[All Fields])) OR ("lupus nephritis”[MeSH Terms] OR ("lupus”[All Fields] AND "nephritis”[All Fields]) OR "lupus nephritis”[All Fields]))).

The search strategy was applied to Ovid MEDLINE, In-Process and Other Non-Indexed Citation and Ovid Medline from 2000 to present. Abstracts from EULAR and ACR/ARHP Annual Meetings (2011-2015) were screened and included in the analysis if they met the inclusion criteria and did not replicate studies published elsewhere.

Studies that met the inclusion criteria were systematically analyzed by two independent reviewers (SS and MR). Disagreements were resolved by consensus; if consensus could not be achieved, a third party (MJC) provided an assessment of eligibility. As the data on eligibility were dichotomous (eligible: yes / no), inter-rater agreement at both the title and abstract review and the full article review stages was determined by calculation of Cohen’s kappa coefficient (k=0.91)[13].
**Inclusion Criteria**

**Types of studies**

We searched the literature for case reports, case series, clinical trials and prospective and retrospective observational studies in SLE patients with LN receiving belimumab. Only studies reporting the effect of belimumab on renal parameters were included.

**Types of participants**

We included all patients with SLE who had LN receiving belimumab for treatment. There were no restrictions with regards to age, race/ethnicity, gender, or concomitant treatment. When possible, patients were stratified in the categories a, b, c and d as detailed above.

**Types of outcome measures**

Due to heterogeneous definitions of treatment response, clinical presentation and renal involvement in SLE, outcome measures were considered as per each study definition. Overall, the effect of belimumab on renal outcomes was analyzed in term of rates of renal flare, renal remission, renal organ disease improvement [assessed by Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI), Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), British Isles Lupus Assessment Group (BILAG), and/or Systemic Lupus Activity Measure (SLAM) Index]. Serum creatinine, urinalysis, 24h proteinuria, and serologic markers of active disease (anti-DNA antibodies and C3 and C4 levels) were recorded or computed when available.

**Exclusion criteria**

We excluded studies if (1) the effect of belimumab on renal parameters was not quantifiable; (2) if they were reviews of the literature with no primary data; (3) if they described the renal outcome in patients prior to belimumab treatment or in non-belimumab treated patients.
When several publications involving the same group of patients were found, only the most recent and comprehensive paper was included, unless the publication was derived from another patient cohort.

**Results**

Search Results

The systematic search (performed on 1st July, 2016) retrieved 375 titles, of which 344 studies did not meet the inclusion criteria. Most of the excluded articles were review articles or did not report renal outcomes. Of the remaining 31 articles, 12 duplicate publications were excluded, leaving a total of 19 articles for further analysis. A proportion of missing data was obtained from the corresponding authors when not reported in the original studies. A total of 11 articles were eligible for the final analysis.

A total of 2004 patients with SLE were identified. Three hundred and twenty-six patients had LN at baseline and 234 (71.8%) of those received belimumab. Thirteen patients out of 234 (5.5%) received belimumab for active LN, 7 of those with biopsy proven LN and for whom detailed characteristics were available are described separately in our analysis. Studies design and characteristics are summarized in Table 1.

**Efficacy of belimumab on renal parameters in SLE patients**

Due to the heterogeneous definitions of treatment response, clinical presentation and renal involvement in the included studies, it was not possible to compare results using a single outcome parameter. However, the majority of these studies defined clinical response in term of rates of renal flare, renal remission, and/or renal organ disease improvement [assessed by SELENA-SLEDAI, SLEDAI-2K, BILAG, and/or SLAM indexes].

Table 1 shows the overall response according to applied outcome measures for each included study. The use of belimumab in active biopsy proven LN is separately detailed in Tables 2 and
3. One hundred twenty nine (55.1%) of the 234 patients with LN at baseline treated with belimumab between 2013 and 2016 showed an improvement in renal parameters assessed either by SELENA-SLEDAI, SLEDAI-2K, BILAG, and/or SLAM indexes. In the patients with baseline proteinuria >0.2g/24h, (n=687), those receiving belimumab had a median reduction in proteinuria during the follow-up of 38% (range 0-100). For patients with proteinuria ≥1g/24h (n: 228), 70.7 % of those treated with belimumab (n:157) achieved a renal remission (defined as per each study definition).

When directly comparing patients with LN from RTCs receiving belimumab (mean proteinuria 1.8±1.4 g/24h, serum creatinine 77.3±30.1 µmol/l, anti-DNA positive in 82.9%) with placebo (mean proteinuria 1.8±1.7 g/24h, serum creatinine 74.8±23.9 µmol/l, anti-DNA positive in 81.5%), we observed a higher percentage of renal remission (68.1% Vs. 58.7%, Chi square value= 4.9814, p=0.025) and a shorter time to renal remission (median time 139.5 Vs. 167 days) in the treatment groups.

In the pooled population of patients receiving belimumab, we found an overall annual renal flare rate of 1.7% [24/1448, mean observation time 1.1 years (0.5-3)]. When directly comparing patients with LN from RTCs receiving belimumab with placebo, we observed a lower rate of renal flare in the treatment groups (1.95% Vs. 3%, chi-square value = 1.8742, p=0.17), even though it failed to reach a statistical significance.

Due to heterogeneity in data availability, it was not possible to stratify patients in groups a, b, c and d as planned. Similarly, the differences between studies make it impossible to evaluate the renal response to belimumab according to lupus nephritis diseases severity.

**Efficacy of belimumab in patients with biopsy proven active LN**

We found 7 patients with active biopsy proven LN who received belimumab with an overall rate of therapeutic response of 100% (median follow-up, 18 months, range 12-36).
There were 6 (86%) women and 1 (14%) man, with a mean age of 29 (range 19-42) years. The renal characteristics of these patients at the time of belimumab are detailed in Tables 2 and 3. In brief, when histopathological results were specified, they included type III LN in 1 patient (14%), type IV in 4 patients (57%) and type V in 1 patient (14%). In 5 cases, belimumab was started due to lack of response to conventional immunosuppression (REF), as detailed in Table 2. In two cases, it was used to achieve (REF) or maintain (REF) complete remission after treatment with rituximab. In one case, belimumab was used throughout pregnancy to treat active LN (REF). Six patients (all but the case of the woman who received belimumab throughout pregnancy) were concomitantly treated with mycophenolate mofetil (MMF) and belimumab with good safety and efficacy outcomes.

**Excluded studies**

Among the studies excluded from our analysis, three are worthy of some consideration. To begin with, Parodis at al. (Parodis I, Sjöwall C, Jönsen A, Zickert A, Frodlund M, Ramsköld D, Bengtsson AA, Gunnarsson I. Decreased Disease Activity and Corticosteroid Usage and Improved Quality of Life during Belimumab Treatment in Patients with Systemic Lupus Erythematosus – a Prospective Real-Life Observational Study [abstract]. Arthritis Rheumatol. 2015; 67 (suppl 10).) described a cohort of 52 SLE patients treated with belimumab who experienced a reduction of disease activity and steroid use. In their real-life observational study, belimumab treatment decreased disease activity, reduced steroid use and improved pain, fatigue and well-being over time. There was no progression of organ damage during follow-up. However, despite 5 patients receiving belimumab for renal involvement, it was not possible to separately study renal outcomes. In one patient, belimumab was discontinued for the occurrence of biopsy-proven class III LN.

In 2014, Zeron reported the data from the BIOGEAS-SEMI registry including real-life Spanish patients with refractory SLE (P. Brito Zeron, L. Caminal-Montero, A. Chamorro et al. blocking
the human b lymphocyte stimulator molecule (blys) using a monoclonal antibody (belimumab) in systemic lupus erythematosus: first results in real-life Spanish patients with refractory disease (biogeas-semi registry)Ann Rheum Dis 2014;73(Suppl2): 985). Although one patient had refractory LN, there were not enough details to include that case in our study. Similarly, Shum and colleagues reported early data supporting the use of belimumab across all ethnic groups and found an efficacy profile similar to that reported in the Phase III trials as assessed at three months. They presented data on 83 patients treated with belimumab from ten academic SLE clinical practices. Although 7.2% of the patients treated with belimumab had renal involvement (4 membranous and 2 proliferative LN), it was not possible to include those cases because conclusions were not stratified for organ manifestations (Shum, Katrina M., Buyon, Jill P., Belmont, H. Michael, Franks, Andrew G., Furie, Richard, Kamen, Diane L., et al; Favorable Response to Belimumab At Three Months. [abstract]. Arthritis Rheum 2012;64 Suppl 10 :1417 DOI: 10.1002/art.39149).

Discussion

Renal involvement is a common cause of morbidity in SLE (Arch Int Med 2000; 160: 3136–1340, Medicine 2006; 85: 147–156, Arthritis Rheum 2006; 54: 2550–2557). The current management of LN includes steroids and non-specific immunosuppressive agents such as cyclophosphamide, MMF and azathioprine, but there is increasing use of targeted biologic therapy for refractory disease, most commonly rituximab (Arthritis Care Res 2012; 64:797–808). The BLISS trials excluded patients with severe, active LN, and the effect of belimumab therapy on renal involvement was not a pre-specified endpoint of those studies (Arthritis Rheum 2008; 58: 2453–2459.; Arthritis Rheum 2011;63: 3918–3930.). This systematic review was conducted to describe published data about the potential effect of belimumab on renal parameters in SLE patients with LN.
We observed that more than half of patients (55.1%) with LN at baseline treated with belimumab between 2013 and 2016 showed an improvement in renal parameters (assessed by SELENA-SLEDAI, SLEDAI-2K, BILAG, and/or SLAM indexes). In the analyzed randomized trials, adding belimumab to standard of care improved the rate of renal remission of 10% when compared to placebo groups.

Interestingly, we found that among the subgroup of patients with proteinuria \( \geq 1 \text{g}/24\text{h} \) receiving belimumab, about 70% achieved a renal remission. These results are in line with Manzi et al., who showed that in patients with proteinuria greater than 1 g/24 h, the percent improvements from baseline were significantly greater with belimumab at weeks 24, 28, 32, 40, 44 and 48 than with placebo (all \( p<0.05 \)). Similarly, Dooley et al. observed that proteinuria \( \geq 2\text{g}/24\text{h} \) developed less frequently in patients treated with belimumab compared to placebo. Conversely, Coster and Sjowall reported one patient with severe non-renal SLE who developed LN while being treated with belimumab (REF).

We found an overall renal flare rate of 1.7% in patients treated with belimumab in a mean follow-up of 1 year. In the SLICC inception cohort, Hanly and colleagues reported a cumulative frequency of LN of 19.1% during follow-up (mean 4.6 \( \pm 3.4 \) years) in SLE patients receiving current standard of care therapies. Their observation was very similar to incidence of LN reported in studies from North America, Europe and the Middle East (Rovin BH, Stillman I. Kidney. In: Lahita R, ed. Systemic Lupus Erythematosus, 5th ed. San Diego, CA, USA: Academic Press, 2011: 769–814.). Despite these encouraging preliminary findings regarding the potential use of belimumab in preventing renal flare, the role of belimumab as maintenance therapy for LN has not been determined in an adequately powered RCT and the heterogeneity among the analyzed studies make it impossible to evaluate the renal response to belimumab according to LN diseases severity. A future challenge is to evaluate annual renal flare rates in patients with different levels of renal involvement treated with belimumab.
The efficacy of belimumab as induction treatment in patients with active biopsy proven LN is mainly supported by case reports. Despite limited evidence, preliminary observations are promising, but further study is required. In 2 cases, belimumab was used to achieve (REF) or maintain (REF) complete remission after treatment with rituximab. Ongoing studies are aiming to understand and define the use of synergic approaches for B cell immunomodulation. The CALIBRATE trial is currently investigating the safety and efficacy of rituximab plus IV CYC followed by maintenance therapy with belimumab in patients with refractory lupus nephritis (CALIBRATE trial, ClinicalTrials.gov Identifier: NCT02260934). Similarly, the SYNBIoSe trial (ClinicalTrials.gov Identifier: NCT02284984) is investigating the effect combining rituximab and belimumab on SLE pathogenic autoantibodies.

Interestingly, we observed that concomitant use of belimumab with MMF may be associated with the most favorable renal outcomes. In the previously mentioned pooled analysis of BLISS 52 and BLISS 76, the mean proportion of patients with renal involvement at baseline who were also receiving MMF was 18.7% (21% as assessed by SELENA-SLEDAI renal involvement, 16% with BILAG renal A/B scores, 16% with BILAG renal C or D scores, and 22% with proteinuria >0.5 g/24 h). By week 52, a significant renal improvement as assessed by SELENA-SLEDAI was observed in 27.8%, 52.6%, and 63.2% of patients randomized to placebo, and belimumab 1 and 10- mg/kg, respectively. Improvements in hematuria and proteinuria were observed in patients receiving MMF with involvement of those items at baseline.

The strength of our study relies on the very strict inclusion criteria. Most importantly, only studies reporting renal outcomes in patients treated with belimumab were included. Conversely, there are a number of reasons to be cautious about the interpretation of the present analysis. It is not yet possible to make definite recommendations for the off-label use of belimumab in LN. The global analysis of all cases with active LN reported to date suggests
that the use of belimumab is effective and relatively safe and should be considered to maintain remission or as a second-line therapy in patients with refractory SLE without other options. The high rate of efficacy found in this systematic review may be partially explained by the fact that most published reports include cases with a favorable response while, in contrast, cases without such a response may not have been reported. However, the fact that data from both the RCTs and observational studies are concordant justifies further study of the drug for LN. Properly designed randomized clinical trials should confirm these observations in order to establish the correct dose, the length of therapy, and the appropriate use of concomitant medications.

Secondly, none of the included studies was specifically designed to assess the additional role of belimumab in inducing renal remission in patients with LN. Only a small proportion (6%) of the total sample size of patients treated with belimumab had a diagnosis of active biopsy proven LN at baseline. Similarly, the level of renal involvement (e.g. proteinuria) was very heterogeneous in the included cohorts, with a surprisingly low prevalence in some studies (Parodis et al 2013). Most importantly, we were not able to stratify patients according to renal histology, disease severity, or treatment status.

Thirdly, the differences between studies make it impossible to evaluate the renal response to belimumab according to the clinical characteristics of renal disease activity.

In conclusion, we believe that available published data support the continued investigation of belimumab for the treatment of LN. Current studies provide preliminary support for targeting the BlyS pathway in patients with LN. Future trials will address the question of whether belimumab (alone or in combination with rituximab) represents an additional therapeutic option in the treatment of LN.
LEGENDS:

Table 1: Available evidence including patients with SLE and renal involvement treated with belimumab

Table 2: Available evidence including patients with SLE and active biopsy proven LN treated with belimumab

Table 3: Demographic, clinical, serological and histological characteristics of SLE patients with biopsy proven LN treated with belimumab