Journal of Advances in Medicine and Medical Research

Volume 35, Issue 20, Page 312-320, 2023; Article no.JAMMR.105855
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Belimumab Treatment for Lupus Nephritis: A Narrative Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2023/v35i205202

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/105855

Systematic Review Article

Received: 01/07/2023
Accepted: 04/09/2023
Published: 07/09/2023

ABSTRACT

Background: Lupus nephritis (LN) is a common complication in Systemic lupus erythematosus (SLE) patients. Treatment of lupus nephritis ranges from initial management with lifestyle changes and medications like corticosteroids for mild cases to the most intensive approach involving high-dose immunosuppressive therapy and potentially kidney transplantation for severe cases. A monoclonal antibody, called belimumab, that targets the B-lymphocyte stimulator (BLyS) has shown promise as a treatment for LN. This narrative review endeavors to provide a comprehensive overview of how belimumab functions, its efficacy, and its safety considerations when utilized in the treatment of lupus nephritis.
Methodology: A literature review was conducted on various databases, including PubMed, Medline, Science Direct, and Google Scholar, using the following terms: "lupus nephritis", "safety", "efficacy" and "belimumab". All articles considered relevant were included. No limitations were imposed on the publication date**.**

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Results: Improvements in clinical response and a decrease in glucocorticoid dosage were observed in patients with lupus nephritis treated with belimumab, according to our narrative review. Additionally, significantly higher rates of renal response were proven with the combination of belimumab and standard therapy. Trials showed similar safety profiles for belimumab added to standard therapy versus standard therapy alone.
Conclusion: By focusing on B-cell dysregulation and lowering autoimmune response, belimumab provides a promising treatment approach for lupus nephritis. Its potential as an additional treatment for LN is supported by its effectiveness in enhancing renal responsiveness and overall disease activity as well as by its positive safety profile.

Keywords: Systemic lupus erythematosus; lupus nephritis; belimumab; efficacy; safety.

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune illness that is characterized by generalized inflammation, and organ damage that can be severe. Though the exact pathology is still debated, SLE has been linked to both genetic and environmental factors [1]. Another part that is believed to be involved in SLE is B-cells, the dysregulation of the cells is thought to handle the autoimmune response present in SLE [1,2]. A common complication of SLE is lupus nephritis (LN) correlated with 40-70% of patients with ongoing SLE [3]. If LN is still untreated, around 10-20% of patients continue to develop end-stage renal failure within 10 years of the diagnosis of lupus nephritis [4]. This highlights the importance of prompt treatment and the profound consequences of the delayed diagnosis of LN [4,5]. It was displayed that the onset of low-grade proteinuria in SLE patients was a good predictor for more upcoming severe proteinuria that later develops into lupus nephritis [6]. The main goal of the treatment of lupus nephritis is to reduce LN flares, which are associated with an unfavorable outcome for treatment response and overall patient survival [7]. Lupus nephritis can be addressed through various treatment avenues, and one such option is belimumab. In 2011, under the trade name Benlysta, Belimumab was FDA-approved for the treatment of active, autoantibody-positive, systemic lupus erythematosus (SLE), and in 2020, it gained FDA approval for adult patients with active lupus nephritis who were receiving standard therapy. Within this framework, we offer a comprehensive overview of this medication, which obtained FDA approval over ten years ago. In this narrative review, we are highlighting the efficacy and safety of the drug belimumab in the treatment of lupus nephritis.

2. METHODOLOGY

Conducting a narrative review of the existing literature involved exploration across the following five databases: PubMed, Medline, Science Direct, and Google Scholar, following search terms: "lupus nephritis," "safety," "efficacy," and "belimumab." The publication date was not subject to any restrictions and no exclusion or inclusion criteria were applied.

3. DISCUSSION

Multiple studies conducted throughout the years consistently demonstrate that belimumab therapy holds an advantage over standard treatments in the context of managing lupus nephritis. Belimumab belongs to a class of drugs known as monoclonal antibodies. It is a fully human recombinant monoclonal antibody and is used in the treatment of systemic lupus erythematosus (SLE) and lupus nephritis (LN) [8].

It can be administered intravenously or subcutaneously. For lupus nephritis, belimumab can be given as an intravenous infusion of 10 mg/kg over 1 hour [9]. The first 3 doses should be administered with a 2-week gap between each dose and then repeated every 4 weeks. Alternatively, it can be administered subcutaneously as a 400 mg dose with a 1-week gap between each dose, thereafter, a maintenance dose of 200 mg should be administered weekly [8,10]. It has a half-life of 19-20 days that remains constant regardless of the concentration of the drug, this means that it follows linear pharmacokinetics. Belimumab has a slow clearance rate of 7 mL/day/kg and a low volume of distribution of 69-112 mL/kg [9]. It can be used in combination with rituximab for the effective treatment of LN [11]. Additionally, belimumab can be effectively combined with low-dose mycophenolate mofetil as induction therapy in LN [12].

The mechanism of action of belimumab includes targeting the soluble form of a protein/cytokine known as B-lymphocyte stimulator (BLyS). This protein is also known as B-cell activating factor

(BAFF), and it plays a significant role in B-cell development, survival, and function [8]. BLyS is a tumor necrosis factor that aids in B-cell proliferation and differentiation [13,14]. In SLE, B-cells and autoantibodies are overproduced, and this contributes to the autoimmune response by attacking the body's own tissues; belimumab binds to BLyS and inhibits its function by blocking its ability to bind to receptors on B-cells (TACI, BCMA, and BR3 receptors) [13,14]. Additionally, through its mechanism of action, belimumab helps in decreasing B-cell differentiation into immunoglobulin-producing plasma cells [13]. By inhibiting the function of BLyS, belimumab leads to a decrease in the survival and production of B-cells, thereby alleviating the autoimmune response and, ultimately, reducing symptoms and complications that are associated with SLE and LN [14].

3.1 Clinical Insights: Belimumab and its Role in Lupus Nephritis

Routinely, the first-line standard therapy for lupus nephritis typically involves a combination of glucocorticoids (prednisone) and immunosuppressive medications, such as mycophenolate mofetil and cyclophosphamide. Mycophenolate mofetil can be used as an induction therapy in patients who do not have severe renal dysfunction. It works by inhibiting enzyme inosine monophosphate dehydrogenase (IMPDH) and suppression T and B lymphocytes. It is often combined with prednisone, a glucocorticoid, to help reduce inflammation in the kidneys [15,16].

Similarly, cyclophosphamide has also been used as a standard therapy in the treatment of lupus nephritis, typically in more severe cases. It is an alkylating agent that works by destroying DNA structures in T and B lymphocytes, thereby preventing the proliferation and function of these immune cells. Cyclophosphamide is the most used standard therapy in the treatment of severe lupus nephritis and is typically combined with methylprednisolone to induce renal remission and to prevent renal flares [17].

A study by Appel GB et al., stated the advantages of using mycophenolate mofetil (MMF) were superior to the use of intravenous cyclophosphamide (IVC) in the treatment of active lupus nephritis, by comparing both treatment regimens amongst the patient population. The outcome of the study resulted in five deaths in the IVC group and nine deaths in the MMF group. Therefore, as a conclusion, the study did not meet the primary objective [18].

Notably, for patients with class V LN- with nephrotic range proteinuria- alternative treatment such as a combination of MMF with tacrolimus (TAC) is recommended. Furthermore, the latest European Alliance of Associations for Rheumatology (EULAR) recommendations show belimumab as the only biologic. On the other hand, rituximab (RTX) should also be taken into consideration in refractory disease. RTX has been also discussed in the EULAR recommendations as an (off-label) treatment option and recently RTX increased interest while it was combined with belimumab based on one large trial [19].

Belimumab (trade name Benlysta) is an anti-BAFF monoclonal antibody, specifically targeting the B-lymphocyte stimulator (BLyS) protein to reduce B-cell activity. In the management of lupus nephritis, other immunomodulators and immunosuppressive medications, such as cyclophosphamide, mycophenolate mofetil, azathioprine, tacrolimus, cyclosporine, and anti CD20 rituximab, are utilized to suppress the immune system's abnormal response and mitigate inflammation. Overall, the use of belimumab as an adjunctive therapy alongside other immunosuppressive medications proved to enhance treatment effectiveness.

The aim of the highly regarded BLISS-76 trials was to evaluate the efficacy and safety of IV belimumab in treatment of lupus nephritis. Patients were randomized 1:1 based on race and type of standard induction therapy either IV cyclophosphamide (500 mg every 2 weeks) or mycophenolate mofetil (3g per day), followed by maintenance therapy, with dosage adjustments permitted after six months. The treatment schedule of 10 mg IV belimumab or placebo was administered at specific intervals up to week 100. Prior studies of lupus trials established protocols for treatment regimens, thus recommending the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and hydroxychloroquine as part of the treatment protocol. Predominantly, the risk of death was decreased for the patients who received belimumab compared to the patients who just received the placebo (hazard ratio, 0.51; 95% CI, 0.34 to 0.77; P = 0.001) [20].

The CALIBRATE trial by Yemil Atisha Fregoso et al. explored the addition of belimumab therapy in

individuals with active lupus nephritis who had previously undergone treatment with cyclophosphamide (CYC) or mycophenolate mofetil (MMF). In view of the limited number of samples, it used a design based on randomised control and open-labeling without stratification factors. Participants initially received induction therapy of IV methylprednisolone, rituximab, and CYC, followed by a prednisone taper. In week 4, participants were randomized into two groups: rituximab/CYC (RC) or rituximab/CYC/belimumab (RCB). Additional belimumab infusions of 10 mg per kilogram were administered to the RCB group, whereas there was no such infusion in the RC group. The use of hydroxychloroquine during the study was permitted, however, other immunosuppressive treatments were considered in specific circumstances only [21].

Evidence has illustrated that SLE patients with extrarenal disease who are suffering from inadequate control and frequent flares of ongoing disease should be treated with belimumab as first-line in patients with high disease activity as well as patients with persistent disease [22].
Furthermore, the effect of combination therapy for patients with LN should be considered as well. According to a recent study by Bao H. et al., essentially reported a higher incidence of complete remission in patients receiving combination therapy, as well as significant membranous features in the kidney biopsy compared with intravenous CYC and steroids. As a result, the group of patients treated with the combination therapy experienced fewer adverse events compared to the intravenous CYC group [23].

3.2 Efficacy of Belimumab in the Treatment of Lupus Nephritis

Even with comprehensive therapeutic measures, achieving a favorable outcome and complete remission for lupus nephritis remains a crucial goal. Therefore, contemporary pharmaceutical approaches emphasizing the preservation of kidney function are imperative in lupus nephritis; there is a marked elevation in the generation of serum B cell activating factor. This suggests the rationale for interventions aimed at regulating B-cell function and counteracting B-cell activating factor [20].

In the 2023 meta-analysis conducted by Zhang et al., a total of 2960 patients were included. The results indicated that the combination of belimumab and standard therapy demonstrated significantly higher rates of Total Renal Response with a (p=0.001) and Complete Renal Response (CRR) with a (p=0.02). Additionally, reductions were seen in serum proteinuria and creatinine levels, suggesting its potential efficacy [24]. Research findings show a notable correlation between specific racial backgrounds and the outcomes of lupus nephritis among individuals with systemic lupus erythematosus (SLE). In comparison to Caucasians and Hispanics, individuals of African American ethnicity exhibit heightened renal complications and a more unfavorable prognosis [20].

Another randomized study among the Asian population, carried out by Xeuqing Yu et al., in 2022 revealed noteworthy reductions in Primary Efficacy Renal Response (PERR) and CRR coupled with a 10% decrease in the occurrence of renal events compared to the control group's 25% [25]. Six clinical randomized trials were included with follow-up periods ranging from 52 to 104 weeks, and variations in definitions for renal response [24]. In the recent BLISS-LN study, 448 patients were randomized, and 279 completed the double-blind study: 123 placebo-to-belimumab and 132 belimumab-to-belimumab, receiving intravenous belimumab 10 mg/kg. The study was completed by 97% of 254 patients, in which the belimumab-to-belimumab group demonstrated trends indicative of more effective disease management than the placebo group, at the start of the open-label phase. These trends were suggested by lower initial Urine Protein Creatine Ratio values (UPCR), a higher percentage of patients with an SLE Activity Index Score (SLEDAI) below eight, reduced average prednisone-equivalent doses, and fewer patients testing positive for autoantibodies or having low C3/C4 levels. The course of the investigation saw enhanced disease management within the belimumab-to-belimumab subgroup over their placebo-to-belimumab subgroup [26].

Meng Tan et al., 2023 conducted an observational study on the Chinese population. A belimumab treatment period of over six months, in patients, demonstrated significant improvement in renal response and overall disease activity, coinciding with a decrease in the need for the dosage of steroids. A reduction in proteinuria, hematuria, leukocyturia, and cylindruria was observed, maintaining stable renal function. Additionally, almost 79% of patients achieved either Complete Renal Response or Partial Renal Response. Notably,

belimumab exhibited potential in averting lupus nephritis recurrence while minimizing steroid reliance, thereby suggesting a protective role in preventing organ damage [27]. A Phase 3 clinical trial has been conducted, where a combination therapy of rituximab and belimumab was administered to target autoantibody-mediated diseases like systemic lupus erythematosus (SLE) and lupus nephritis (LN). The trial duration of two years primarily focused on auto-reactive B-cells and B-cell depletion [11].

3.3 Safety Profile of Belimumab in the Treatment of Lupus Nephritis

The consensus of the trials conducted so far has reported a similar safety profile for the addition of belimumab to standard therapy versus treatment with standard therapy alone. The safety of belimumab treatment in the BLISS-76 trials by Furie et al., disclosed a negligible disparity as compared to that of standard therapy alone (54.9 vs. 53.1%, respectively), with similar incidences of serious adverse events, infection, and death in both groups (10.3 vs. 11.2%; 6.7 vs. 8%; 2.7 vs. 2.2%) [20].

Multiple post hoc articles of the BLISS-76 trials (Weeding et al., Rovin et al., Petri et al.) acknowledged the surge in primary efficacy response rate (PERR) and complete renal response (CRR) in patients receiving belimumab therapy as well as a decrease of ≥ 4 points in the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index (SELENA–SLEDAI) [28,29,30].

Analogous with the BLISS-76 trials' safety profile, another double-blind placebo-controlled study conducted in China, Japan, and South Korea by Zhang F et al., reported a congruent incidence of adverse events between both belimumab group and placebo group (74.9 vs 75.7%) of mild and moderate severity., the group. Notably, patients receiving the placebo treatment disclosed a greater incidence of serious adverse events (18.3%) and serious infections of interest (8.5%) as compared to the belimumab group (12.3%; 7.7%, respectively) [31].

A subgroup analysis of the BLISS-76 trials, reported by Yu et al., documented the tolerance of belimumab therapy in East Asian patients were in concordance to that of the trials [25]. Tan et al., recounted no discrepancies between belimumab and standard therapy versus nonstandard therapy, with a lower incidence of adverse events as compared to other studies (total of 41% in n=61 patients) [27]. A cohort study conducted in Japan by Tanaka et al. revealed a greater prevalence of therapy-related adverse events in the belimumab group (48.7%) as compared to the placebo group (23.8%), conversely, most adverse events reported were mild or moderate [32].

A higher incidence of serious adverse events was noted in the placebo group (28.6%) versus the belimumab group (23.1%). Additionally, a cohort study conducted in Italy (Binda et al.) did not document any severe adverse events resulting in hospitalization or suspension of therapy [33]. Table 1 provides summaries of the overall adverse event effects in the belimumab group as compared to the control group.

Neither of the cohort studies documented any incidences of death. Dooley et al. documented the largest sample which may result in a higher bias when compared to other studies in a meta-analysis. However, the incidences of adverse events matched the results of other studies (belimumab group 92.2% versus placebo group 91.9%), with normalized serologies, namely C3 and C4 and a reduction of anti-dsDNA which were predictors of SLE flares [34]. Another study by Atisha-Fregoso et al. reported that the addition of belimumab to cyclophosphamide and rituximab did not result in an increase in adverse events. Serious adverse effects were significantly greater in the standard therapy group (50%) as compared to the combination therapy group (19%) [21].

The most reported adverse events included infections such as upper respiratory tract infections, nasopharyngitis and urinary tract infections, asthenias as well as hematological disorders, namely hypokalemia. Incidences of depression, anxiety and malignancies were negligible in most instances. Remarkably, most of the infectious adverse events reported could be associated with concomitant steroid and immunosuppressant therapy instead of belimumab therapy. Overall, belimumab as a therapy for lupus nephritis was well tolerated in most patient populations.

Table 1. Comparison of adverse events associated with belimumab and control groups

Author	Year	Total Pool	Belimumab group						Control group					
			AE*	SAE**	Infection	Serious Infection.	Death	Total pool	C AE*	C SAE**	C Infection	C Serious Infection	C Death	Total pool
Furie R. et al [20].	2020	448	123 (54.9%)	23 (10.3%)	15 (6.7%)	9 (4.0%)	6 (2.7%)	224	119 (53.1%)	25 (11.2%)	18 (8.0%)	7 (3.1%)	5 (2.2%)	224
Atisha-Fregoso Y. et al [21].	2021	43	21 (100%)	4 (19.0%)	2 (9.5%)	0 (0.0%)	0 (0.0%)	21	22 (100%)	11 (50.0%)	5 (22.7%)	0 (0.0%)	0 (0.0%)	22
Tan M. et al [27].	2023	61	14 (36.8%)	0 (0.0%)	8 (21.1%)	0 (0.0%)	0 (0.0%)	38	13 (56.5%)	1 (4.3%)	5 (21.7%)	1 (4.3%)	0 (0.0%)	23
Zhang F. et al [31].	2018	705	352 (74.9%)	58 (12.3%)	250 (5.3%)	36 (7.7)	0 (0.0%)	470	178 (75.7%)	43 (18.3%)	129 (5.5%)	20 (8.5%)	1 (0.4%)	235
Tanaka Y. et al [32].	2019	60	19 (48.7%)	9 (23.1%)	3 (7.7%)	1 (2.6)	0 (0.0%)	39	5 (23.8%)	6 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21
Dooley MA. et al [34].	2013	1125	519 (92.2%)	102 (18.1%)	396 (70.3)	33 (5.9)	5 (0.9%)	563	516 (91.9%)	90 (16.0%)	373 (66.4%)	33 (5.9%)	3 (0.5%)	562

***AE = Adverse effects*

***SAE= Serious adverse effects*

4. LIMITATION

The combined studies have revealed limitations that underscore the necessity for a more extended follow-up period to comprehensively grasp the efficacy and safety profiles. An added notable challenge arises from the varying definitions of renal response among different authors. It is strongly recommended for future research to focus on the implementation of prolonged randomized controlled trials (RCTs).

5. CONCLUSION

Belimumab is a suitable drug candidate for the treatment of lupus nephritis due to its higher renal response rates, reduced proteinuria, and lower risk of disease flare. Belimumab has also been shown to potentially prevent LN recurrence and reduce steroid reliance. Belimumab shows promising potential as a treatment option for LN. While considering the individual circumstances of patients and their respective medical histories; the collective evidence supports the inclusion of belimumab in the therapeutic regimen for LN. Therefore, with the adoption of belimumab treatment in clinical practice, patients will be provided with a more comprehensive and effective approach to managing their condition, thereby enhancing their overall quality of life and prognosis.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/105855