META-ANALYSIS ON THE EFFICACY AND SAFETY OF BELIMUMAB FOR LUPUS NEPHRITIS BY USING THE PUBMED DATABASE

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disease associated with loss of immunological tolerance (LIT). Lupus nephritis (LN) is a serious manifestation of SLE, affecting the majority of patients and posing a significant threat to the well-being and survival of SLE patients. More research and evidence are needed to determine whether belimumab can be used to treat active LN, as data on the safety and efficacy of belimumab in the treatment of active LN are currently lacking. The search criteria utilised were “belimumab”, “lupus nephritis”, “systemic lupus erythematosus” and “lupus treatment”. The search was limited to articles published between January 2000 and May 2022. The analysis and evaluation were performed using Rev Man 5.3 and Stata, the risk of bias (RoB) of the included articles was assessed, and the heterogeneity was assessed using the Q-test and the I2 statistics. The results showed that in the 6 included references, the OR for efficacy of belimumab in the treatment of LN was 0.30, the OR for safety was 0.22, and no heterogeneity was observed between study groups (I2 = 0.00%; I2 = 0.00%). The OR for renal involvement of belimumab in the treatment of LN was 0.22, and the OR for complications was -0.37, indicating apparent heterogeneity (I2 = 54.46%; I2 = 30.79%). The heterogeneity gap was small, indicating credible results after further testing. Belimumab treatment was safer in LN, renal involvement was less severe in LN receiving belimumab treatment, and the likelihood of complications was lower in LN receiving belimumab treatment.

Keywords: lupus nephritis, belimumab, systemic lupus erythematosus, efficacy analysis, meta-analysis

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease characterised by a loss of immune tolerance leading to multisystem inflammation and organ damage. It mainly affects women of reproductive age [1]. SLE has a multifaceted aetiology. Immune responses, whether innate or adaptive, are involved in the pathogenesis of SLE. This interaction of genes and environmental factors leads to various immune changes and culminates in a persistent immune response to self-nucleic acid [2, 3]. Tissue damage, resulting in significantly increased morbidity and mortality, has been observed in various organs due to the deposition of autoantibodies or immune complexes. Over the past 50 years, the survival rate of patients has improved significantly due to the application of early diagnosis and early treatment [4, 5]. However, the all-cause mortality rate in SLE patients is still 4.6 times higher than in the general population. Lupus nephritis (LN) is a severe clinical manifestation of SLE that affects the largest number of patients. The main manifestations are haematuria, proteinuria,
tubuluria, oedema, renal insufficiency and hypertension [2, 6, 7]. The association between the development of circulating and in situ immune complexes and their subsequent deposition in the glomeruli and tubulo-interstitium is intricately connected to the pathogenesis of renal damage in SLE. Autoantigen-antibody complexes trigger chronic inflammatory infiltration and cause kidney injury through complement activation and the release of inflammatory mediators, cytokines, superoxide and proteases [8]. In addition, some patients have antiphospholipid antibodies that cause local endothelial damage and platelet dysfunction, leading to thrombosis, renal thrombotic microangiopathy and exacerbating renal injury [9].

Belimumab inhibits B-cell survival and differentiation and promotes B-cell apoptosis by specifically binding to tumour necrosis factor family B-cell activating factor (BAFF), thereby suppressing the generation of immature B-cells, activated B-cells and plasma cells in the circulation to achieve SLE treatment goals. Based on the bliss-52 and bli55-76 clinical trials, belimumab was approved by the US Food and Drug Administration (FDA) in 2011 as the first biologic treatment for SLE. It was also the first new drug approved for SLE worldwide in the last 60 years. In 2019, belimumab achieved breakthrough results in the treatment of children with SLE, expanding the population eligible for belimumab. FDA-approved for SLE in children aged 5 years and older than 5 years, belimumab is the first medicine approved in the United States for paediatric SLE [10-12]. In the United States and EU countries, the monoclonal antibody belimumab is used in children and adults with SLE older than 5 years who are receiving standard of care and are positive for active autoantibodies. However, this drug is not recommended for severe and active LN (24-hour urine protein > 6 g and/or serum creatinine > 2 mg/dL) and severe and active neuropsychiatric lupus [13]. In China, belimumab was approved in July 2019 for use in combination with standard-of-care SLE. It is suitable for adult SLE patients who are still highly active and positive for autoantibodies based on conventional treatment. Patients with severe central nervous system and kidney involvement should also be excluded [14].

At present, the safety and efficacy of belimumab in treating active LN are not fully understood. Therefore, more research and evidence are needed to determine whether belimumab can be used to treat LN. In patients with SLE who were receiving mycophenolate mofetil or were seropositive at baseline, the renal benefit of belimumab was significantly greater than that of placebo, suggesting that belimumab in combination with standard SLE therapy may better improve renal involvement in SLE patients. Limitations of this analysis include the insufficient number of cases and the post-hoc nature of the combined analysis, which warrant further studies in patients with active and severe-staged LN.

Hence, this study incorporates recent studies on the utilisation of belimumab in the management of LN and assesses the therapeutic impact of belimumab treatment on LN using a meta-analysis framework to assess the effectiveness and safety of belimumab. The objective is to furnish a clinical foundation for the application of belimumab in LN treatment.

Materials and Methods

Literature research

The Cochrane Library, PubMed, MEDLINE, EBSCO, Science Direct and CNKI databases were searched to identify relevant literature on the treatment of LN with belimumab. The search criteria utilised were “belimumab”, “lupus nephritis”, “systemic lupus erythematosus” and “lupus treatment”. The search was limited to articles published between January 2000 and May 2022. All database searches were adjusted according to the specific database. The search strategy was determined after several preliminary searches. Journals were further searched manually to avoid omissions, and the research subjects mentioned in the retrieved article had to be humans. Subject terms and free words (e.g., “treatment”, “curative effect”, etc.) were combined to perform multiple searches to obtain potentially eligible references, and each article was traced for further details. Rev Man 5.3 of the Cochrane Collaboration was used to assess the quality of the included literature.

Literature inclusion and exclusion criteria

Articles were included in the study if they fulfilled all of the following criteria: (1) all subjects had a diagnosis of LN; (2) all articles were randomised controlled trials (RCTS); (3) all patients were treated with belimumab; (4) all patients signed relevant informed consent forms with complete clinical data; (5) results included complications or safety endpoints.

Articles had to be excluded if they had any of the following conditions: (1) The sample size was < 5 patients. Too small a sample size can lead to bias and insufficient power; (2) multi-arm study (> 2); for improvement, prospective studies were preferred, so retrospective studies were not included. RCTs were not included because of different outcome indicators; (3) conference abstracts, case reports, reviews, communication articles, clinical experience reports with incomplete information, animal or cell experiments and other studies; (4) complete information and data are ambiguous or not extractable.

Data extraction

Two experts independently performed the literature search and data extraction using a standardised Microsoft Excel tool (Microsoft, USA). The extracted information was cross-checked to ensure its inclusion in the final results. Any discrepancies were resolved
through consensus discussions. The extracted data included the following aspects: (1) general study details, including title, first author, year of publication, etc.; (2) basic characteristics of the study population, such as the number of patients, age, gender distribution, etc.; (3) treatment procedures, including drug dosages, the severity of disease, etc.; (4) critical components of bias assessment, including randomization technique, blinding, allocation concealment, etc.; (5) outcome measures and relevant data, such as odds ratios (OR), complete response (CR), partial response (PR) and adverse events (AE).

**Literature evaluation criteria**

The QUADAS criteria were used to assess the quality of the studies included in the analysis. Each rating criterion was used to assess the quality of each original paper. Each study was categorised as “consistent”, “inconsistent”, or “uncertain” on the basis of the rating indices.

**Statistical methods**

Rev Man 5.3 (Cochrane, UK) and Stata (IBM, USA) were used. OR was used as the effect index for dichotomous variables. Point estimates and 95% CIs were assessed for each effect index. Heterogeneity within included studies was assessed using the $\chi^2$ test ($\alpha = 0.1$), and I² was used to quantify heterogeneity. In cases where no apparent heterogeneity was observed in the results, a fixed-effects model (FEM) was used for further meta-analysis, or otherwise, a random-effects model (REM) was used, accompanied by subgroup analysis to explore potential sources of variation. $\alpha = 0.05$ was set. Forest plots (FPs), risk assessment curves and funnel plots were generated using asymmetric linear regression. FPs corresponding to different treatment indicators were used to explore potential publication bias, and sensitivity analysis was performed.

![Flowchart of searching literature](image)
Results and Discussion

Comparative Analysis of the Scientific Literature

One hundred fifty-seven articles were identified by searching the database. Firstly, 31 duplicate articles, 27 unqualified articles and 24 articles for other reasons were eliminated and 75 articles were initially included for further analysis. After reading the abstract and title, 34 articles were further excluded from this work. There were 17 research reports and reviews. In addition, eight articles with inappropriate types of research were excluded. After confirming the completeness and availability of the data, nine were excluded, and the research object of one article was not human, so six were finally analysed here. Figure 1 shows the flowchart of the literature search.

Baseline characteristics of the enrolled articles were extracted. Of the six included publications, 1,142 patients with LN were treated with belimumab (represented as the treatment group in the forest plot) and 1,132 patients with LN were treated with other drugs or usual care (represented as the control group in the forest plot). Furthermore, within the set of six included publications, the sample sizes ranged from 43 to 1,684 participants. These six articles comprehensively elucidated the use of belimumab in the treatment of LN and meticulously recorded changes in various patient parameters before and after treatment. In addition, the articles explored the nuances of complications and renal effects of belimumab intervention in LN (as outlined in Table I).

Four, one and one article were rated A, B and C, respectively, with proportions of 66.67%, 16.67% and 16.67%, respectively. Figure 2A and Figure 2B present the reference risk of bias (RoB) assessment graph and corresponding summary graph, respectively.

### Table I

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Treatment method</th>
<th>Age</th>
<th>Case</th>
<th>Total</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
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<td>Brunner [9]</td>
<td>2020</td>
<td>Belimumab</td>
<td>5-17</td>
<td>93</td>
<td>53</td>
<td>40</td>
<td></td>
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<tr>
<td>Dooley [16]</td>
<td>2013</td>
<td>Belimumab</td>
<td>9-12</td>
<td>1684</td>
<td>562</td>
<td>559/563</td>
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<tr>
<td>Furie [17]</td>
<td>2020</td>
<td>Belimumab</td>
<td>≥18</td>
<td>446</td>
<td>223</td>
<td>223</td>
<td></td>
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<tr>
<td>Furie [18]</td>
<td>2022</td>
<td>Belimumab</td>
<td>18-75</td>
<td>125</td>
<td>63</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2.
(A) Bibliographic RoB assessment chart; (B) Summary graph of reference RoB
“+” meant low risk, “-” meant high risk and “?” meant unclear risk
Heterogeneity

The heterogeneity of treatment efficacy analysed in the included articles was assessed [4, 9, 15-18]. Heterogeneity in the efficacy of belimumab in the treatment of LN was not observed, and that in the safety of belimumab in the treatment of LN was not found (both $I^2 = 0.00\%$). The heterogeneity of LN involvement in belimumab treatment showed an $I^2 = 54.46\%$ and that the complication profile was low ($I^2 = 30.79\%$).

To comprehensively assess the heterogeneity of the data between the two assessment methods and to contrast the variances in the indicators associated with different treatment approaches, a REM was applied. At the same time, an FP was constructed to evaluate the distribution.

Efficacy of belimumab treatment

As shown in Figure 3, the OR of the six studies on the efficacy of belimumab in the treatment of LN was $0.30$, the $95\%$ CI was $(0.09, 0.51)$, $I^2 = 0.00\%$ and $P = 0.81$. The OR values showed improved efficacy in LN patients treated with belimumab, with no heterogeneity. The lowest and highest OR values were $0.04$ and $0.75$, respectively, with $95\%$ CI of $(-0.53, 0.62)$ and $(-1.07, 2.56)$.

![Figure 3. Forest plot of the efficacy of belimumab in LN treatment (CI: Confidence interval)](image)

![Figure 4. (A) Heterogeneity for the efficacy of belimumab in treating LN (B) L’Abbe heterogeneity test of the efficacy of belimumab in the treatment of LN](image)

Figure 4A and Figure 4B present the heterogeneity test graphs for the efficacy of belimumab in treating LN. The heterogeneity and potential abnormal values among these studies revealed a small heterogeneity gap and high accuracy.

Figure 5 shows the funnel plot of the efficacy of belimumab in treating LN, which suggested a small RoB. As a result, the efficacy of belimumab treatment was superior in LN. Conversely, the data pertaining to the individual study outcomes of LN treatment with belimumab demonstrated superior results in comparison to conventional treatment methods, thereby establishing belimumab as a more efficacious treatment option.
Safety of belimumab treatment

As demonstrated in Figure 6, the safety of belimumab in treating LN exhibited an OR value of 0.22 and a 95% CI of (0.05, 0.39), $I^2 = 0.00\%$ and $P = 0.43$. The OR values showed improved safety in LN patients treated with belimumab, presenting no heterogeneity. Among them, the lowest and highest OR values were -0.21 and 0.85, respectively, showing 95% CI values of (-1.26, 0.84) and (0.11, 1.59), respectively.

Figure 5.
Funnel plot of the efficacy of belimumab in treating LN

Figure 6.
Forest plot of the safety of belimumab treatment for LN

(A) Heterogeneity results for safety of belimumab treatment for LN  
(B) L’Abbe heterogeneity for the safety of belimumab in LN treatment

Figure 7.
Figure 7A and Figure 7B present the heterogeneity test charts for the safety of belimumab in treating LN. The heterogeneity and potential abnormal values among studies were assessed, suggesting a small heterogeneity gap and high accuracy.

Figure 8 shows the funnel plot for the safety of belimumab in LN. It illustrated that the RoB was small. Consequently, the safety profile of belimumab treatment was better in LN. On the other hand, the results of the single study on the LN application of belimumab treatment were better than those of conventional treatment, so the effect of belimumab treatment was better in terms of safety.

Figure 8.
Funnel plot of the safety of belimumab in the treatment of LN

Effects of belimumab therapy on renal involvement
As demonstrated in Figure 9, six studies regarding belimumab treatment for LN renal involvement showed an OR of -0.22 and a 95% CI of (-0.62, 0.18), $I^2 = 54.46\%$ and $P = 0.05$. The OR values were reduced in renal involvement in patients with LN treated with belimumab, with heterogeneity across study groups. The range of the OR value was (-1.03, 0.44), and the resulting 95% CI was (-2.55, 0.49) and (-0.10, 0.98), respectively.

Figure 9.
Forest plot of the effects of belimumab on renal involvement in LN. CI: Confidence interval

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Log odds ratio</th>
<th>Weight</th>
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<td>Yes</td>
<td>Yes</td>
<td>-1.03 [-2.55, 0.49]</td>
<td>5.80</td>
</tr>
<tr>
<td>Brunner</td>
<td>Yes</td>
<td>No</td>
<td>-0.07 [-1.11, 0.96]</td>
<td>10.37</td>
</tr>
<tr>
<td>Dooley</td>
<td>Yes</td>
<td>No</td>
<td>-0.06 [-0.54, 0.43]</td>
<td>22.55</td>
</tr>
<tr>
<td>Fure</td>
<td>Yes</td>
<td>No</td>
<td>-0.56 [-0.99, -0.12]</td>
<td>24.02</td>
</tr>
<tr>
<td>Fure</td>
<td>Yes</td>
<td>No</td>
<td>-0.61 [-1.33, 0.10]</td>
<td>16.31</td>
</tr>
<tr>
<td>Rivin</td>
<td>Yes</td>
<td>No</td>
<td>0.44 [-0.10, 0.98]</td>
<td>20.95</td>
</tr>
</tbody>
</table>

Overall
$x^2 = 0.12, P = 0.4646, I^2 = 2.20$

Figure 10A and Figure 10B show the heterogeneity test for the effect of belimumab treatment on renal involvement in patients with LN. The findings suggested one study deviated, and the remaining studies had a small heterogeneity gap and high accuracy.

Figure 11 illustrates the effect of belimumab treatment on renal involvement in LN. One study was biassed, and the remaining studies had a small RoB. Based on the aforementioned results, belimumab-treated renal involvement was less affected in LN. In contrast, data from individual studies of LN treated with belimumab were better than those of conventional treatment, and therefore, the effect of belimumab was better in terms of the effect of treated renal involvement.
Complications after Belimumab treatment

As displayed in Figure 12, the 6 belimumab treatments for LN complications showed an OR value of -0.37, and the resulting 95% CI was (-0.62, -0.12), \( F = 3.079\% \), and \( P = 0.30 \). The OR values showed a reduced effect of complications in LN patients treated with belimumab, with low heterogeneity across study groups. The lowest and highest OR values were -0.98 and -0.06, respectively, with corresponding 95% CIs of (-2.29, 0.33) and (-0.35, 0.23), respectively.

**Figure 12.**
Forest plot of the effect of belimumab on complications of LN; (CI: Confidence interval)
Figure 13.
(A) Heterogeneity test plot for the effect of belimumab on complications of LN
(B) Labbé’s heterogeneity test for the effect of belimumab on complications of LN

Figure 13A and Figure 13B present the heterogeneity test results for the effect of belimumab treatment on LN complications. The heterogeneity gap among these studies was observed to be small, indicating high accuracy.

Figure 14 demonstrated the effect of belimumab treatment on LN complications, and the RoB was small. Thus, the complication effects of belimumab treatment were less in LN. On the other hand, the data for the single study results of LN treatment with belimumab were better than those of conventional treatment, so the effect of belimumab treatment was better in terms of the effect of treatment complications.

Figure 14.
Funnel plot of the effect of belimumab on complications of LN

Sensitivity analysis
Sensitivity analysis was conducted by altering the analytical model. The outcomes of the meta-analysis demonstrated minimal alteration in the overall findings across different analytical models, implying robust stability in the included literature results. Moreover, model evaluations such as funnel plots with asymmetric linear regression indicated a harmonious alignment between specificity and sensitivity.

SLE is characterised by a loss of immune tolerance that can lead to multi-system inflammation and organ damage. The kidney is the main organ involved. Between 50% and 70% of patients with SLE have varying degrees of kidney damage, and the degree of kidney damage can have a direct impact on the prognosis of patients with SLE. Proliferative LNs often manifest microscopically as haematuria, non-nephrotic proteinuria, renal insufficiency and hypertension, while membranous LNs may manifest as nephrotic syndrome [19, 20]. Approximately 20% of individuals diagnosed with lupus nephritis (LN) will progress to end-stage renal disease (ESRD) within 5 years. The aetiology of SLE is not fully understood, and it is thought to be caused by multiple factors,
including heredity, environmental factors and viral infections [21]. The pathogenesis of LN includes an imbalance in inflammatory signalling pathways, an increase in cytokines and immune-mediated pathways, and an increase in cytokines and immune-mediated pathways. In addition, long-term use of GC, inhibits the bone marrow's ability to generate new cells and ultimately increasing platelet erosion, absorption and destruction by the reticuloendothelial system [23, 24]. A variety of autoantibodies are produced in the body, such as antinuclear antibodies, anti-dsDNA antibodies, cold response I anti-lymphocyte antibodies, anti-phospholipid antibodies and apoptotic cell autoantibodies. Self-antigens and antibodies continuously form immune complexes, which are deposited in different parts of the glomerulus according to their own physical and chemical properties. Renal injury is induced by the persistent infiltration of inflammatory cells, which is facilitated by the activation of complement and the subsequent production of inflammatory mediators such as cytokines, superoxide and proteases [25-27].

SLE is an immune-inflammatory disease with multiple systemic lesions. As the disease progresses, the blood system may be affected. Approximately 60% of patients with active SLE have anaemia, 40% have leukopenia and 7% to 40% have thrombocytopenia. According to statistics, the overall mortality rate caused by blood disorders is as high as 17.7%. Among them, thrombocytopenia is one of the difficulties in clinical management, and there is currently a lack of effective therapeutic drugs [28, 29]. T cells and B cells are dysfunctional in SLE patients, leading to confusion about immune mechanisms. There are a variety of autoantibodies in the body (such as anti-leukocyte antibodies, anti-erythrocyte antibodies, anti-thrombopoietin antibodies and anti-neutrophil cytoplasmic antibodies). The destruction of erythrocytes can be mediated by self-antigen targets such as erythroid progenitor cells and erythropoietin. It can also directly destroy platelets or form immune complexes that adhere to and accumulate on the surface of platelets, affecting platelet adhesion and aggregation and ultimately increasing platelet erosion, absorption and destruction by the reticuloendothelial system [23, 30]. During the pathogenesis of SLE, inflammatory mediators produce and induce the synthesis of inflammatory factors and chemokines, as well as macrophage inflammatory proteins, which amplify the inflammatory response and increase the risk of infection. In addition, long-term use of GC, immunosuppressive drugs and other disease-controlling drugs inhibits the bone marrow's ability to generate new cells [31-33]. Together, these factors suppress the immune response and cause the blood system to intervene. So far, only a few foreign clinical trials have shown that belimumab has a good effect on SLE with thrombocytopenia. It is speculated that belimumab monoclonal antibodies may improve the blood system by correcting immune disorders, promoting B-cell depletion, reducing the number of plasma cells that differentiate to produce autoantibodies and attenuating inflammatory responses [34]. The treatment effect was assessed by collecting, sorting, screening and meta-analysing published clinical data, analysing heterogeneous treatment outcomes and examining OR indicators. The results showed that the OR of efficacy and safety of belimumab in the treatment of LN were 0.30 and 0.22, respectively, and no heterogeneity was observed (both I² = 0.00%). The OR of renal involvement in the treatment of LN with belimumab was -0.22 and the OR of complication was -0.37, with heterogeneity between studies (I² = 54.46%; I² = 30.79%). On further testing, the heterogeneity gap was small, so the results were credible. In general, the effectiveness of belimumab treatment in LN was shown to be superior when considering efficacy assessment. However, the available trial data comparing belimumab treatment to conventional therapy demonstrated a greater efficacy of belimumab treatment in terms of treatment effectiveness.

Regarding the influence of renal involvement, it was shown that belimumab treatment in LN resulted in a comparatively less significant effect of renal involvement. This suggests that belimumab treatment exhibited enhanced effectiveness in terms of mitigating the effects of renal involvement. Regarding problems, the incidence of complications in patients with lupus nephritis (LN) treated with belimumab was found to be relatively low. In summary, evaluating the efficacy of belimumab in the treatment of LN can provide evidence-based recommendations for clinical practice guidelines. In clinical trials, patients with different conditions will be re-examined to determine the therapeutic value of the drug, and subsequent studies will collect more indicators and compare the differences in treatment with different concentrations of belimumab in detail, providing a more accurate reference for clinical management.

Conclusions

In order to investigate the efficacy of belimumab treatment in LN, the literature on belimumab in the treatment of LN was reviewed. Overall, the efficacy and safety of belimumab treatment were better in LN; the renal involvement of belimumab treatment was less in LN; and the likelihood of complications from belimumab treatment was lower. Undoubtedly, this work exhibited inherent shortcomings. The drug concentrations in the included clinical trials were not consistent. There was also a lack of standardised
The authors declare no conflict of interest.

Conflict of interest
The authors declare no conflict of interest.

References


