https://doi.org/10.31925/farmacia.2023.5.2 **REVIEW**

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.

Rezumat

Lupusul eritematos sistemic (LES) este o boală autoimună cronică a țesutului conjunctiv asociată cu pierderea toleranței imunologice. Nefrita indusă de lupus (NL) este o complicație majoră a LES. Datele actuale privind siguranța și eficacitatea belimumabului în tratamentul LN activ sunt limitate, necesitând mai multe cercetări și dovezi pentru a susține utilizarea acestuia. Utilizând termenii „belimumab", „nefrita indusă de lupus", „lupus eritematos sistemic" și „tratament pentru lupus" au fost căutate articolele relevante publicate din ianuarie 2000 până în aprilie 2022. Analiza și evaluarea acestora au fost efectuate cu ajutorul Rev Man 5.3 și Stata. A fost evaluat indicele RoB al articolelor incluse, iar heterogenitatea a fost evaluată cu ajutorul testului Q și I2. Rezultatele au arătat că, în cele 6 referințe incluse, OR pentru eficacitatea belimumabului în tratamentul LN a fost de 0,30, OR pentru siguranță a fost de 0,22 și nu s-a observat nicio heterogenitate între grupurile de studiu (I2 = 0,00%; I2 = 0,00%). OR pentru implicarea renală a belimumabului în tratamentul LN a fost de -0,22, iar OR pentru complicații a fost de -0,37, indicând o heterogenitate aparentă (I2 = 54,46%; I2 = 30,79%). Nivelul de eterogenitate al datelor a fost scăzut, ceea ce sugerează că rezultatele sunt credibile și pot fi confirmate prin teste suplimentare. Tratamentul cu belimumab a fost asociat cu un profil de siguranță îmbunătățit în LN, cu o afectare renală mai mică și o probabilitate mai mică de complicații.

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, super-oxide 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, balimumab 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. A = 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.

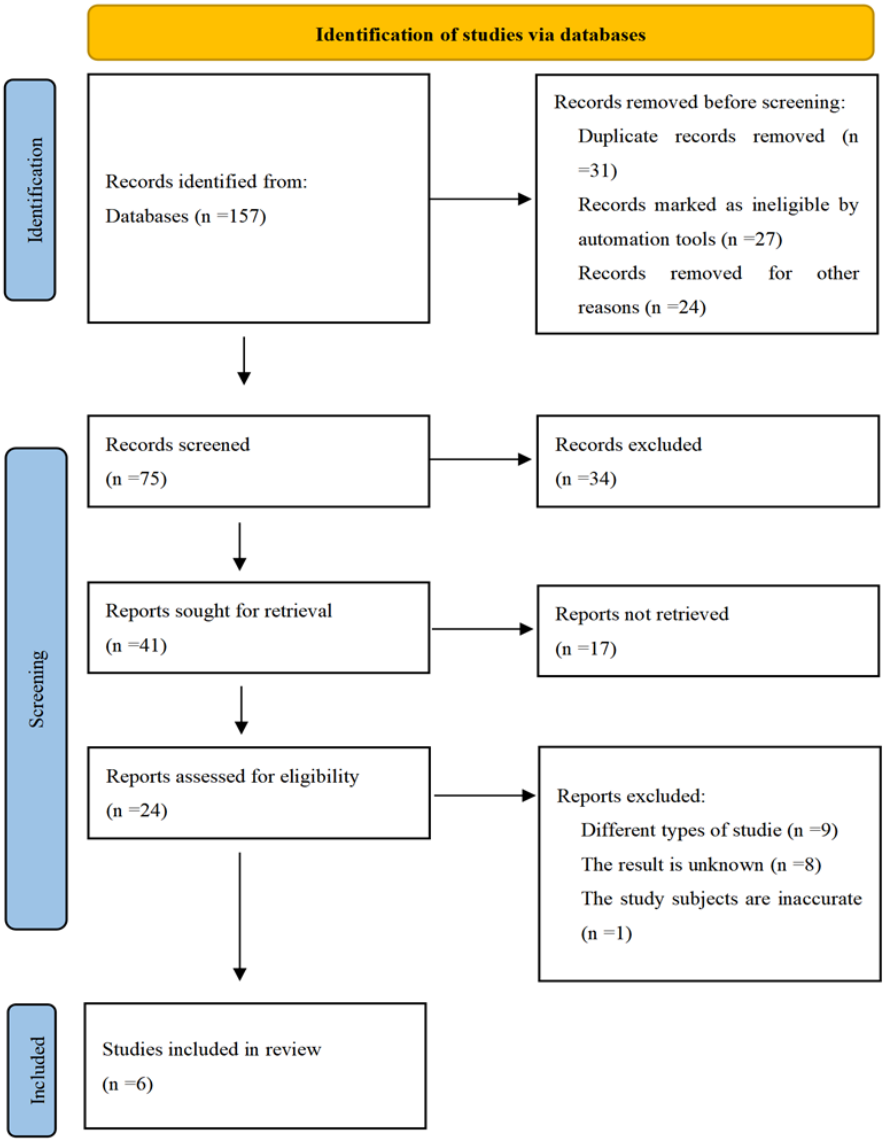

Figure 1.
Flowchart of searching literature

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

Related data of the enrolled literature

Author	Year	Treatment method	Age	Case		
				Total	Treatment	Control
Atisha-Fregoso [15]	2021	Belimumab	≥ 18	43	22	21
Brunner [9]	2020	Belimumab	5 - 17	93	53	40
Dooley [16]	2013	Belimumab	9 - 12	1684	562	559/563
Furie [17]	2020	Belimumab	≥ 18	446	223	223
Furie [18]	2022	Belimumab	18 - 75	125	63	62
Rovin [4]	2022	Belimumab	≥ 18	446	223	223

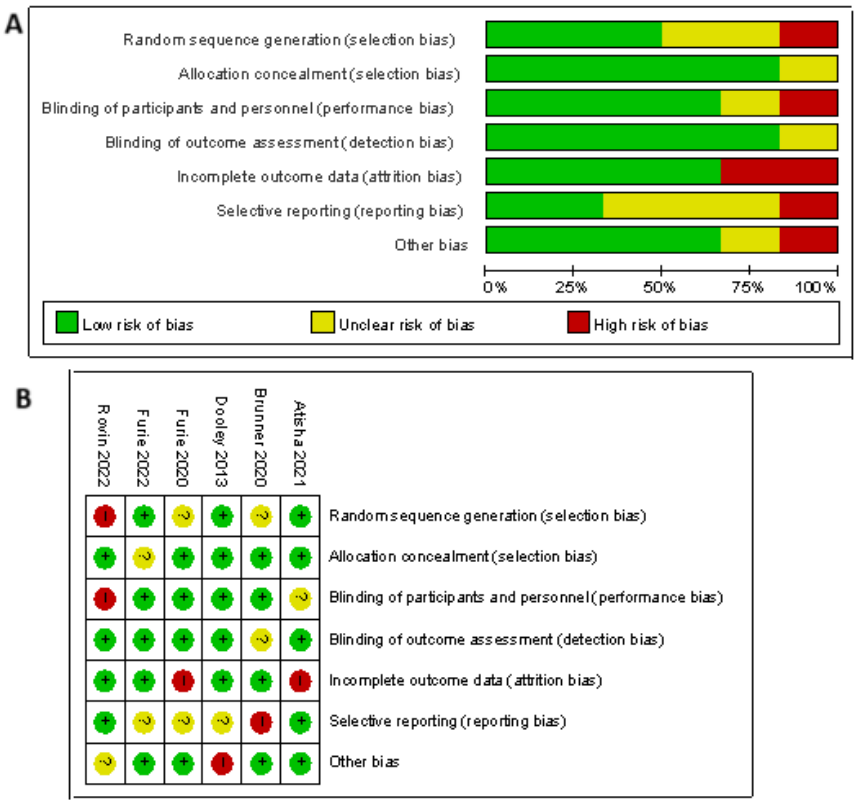

Figure 2.

(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 I2 = 0.00%). The heterogeneity of LN involvement in belimumab treatment showed an I2 = 54.46% and that the complication profile was low (I2 = 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), I2 = 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).

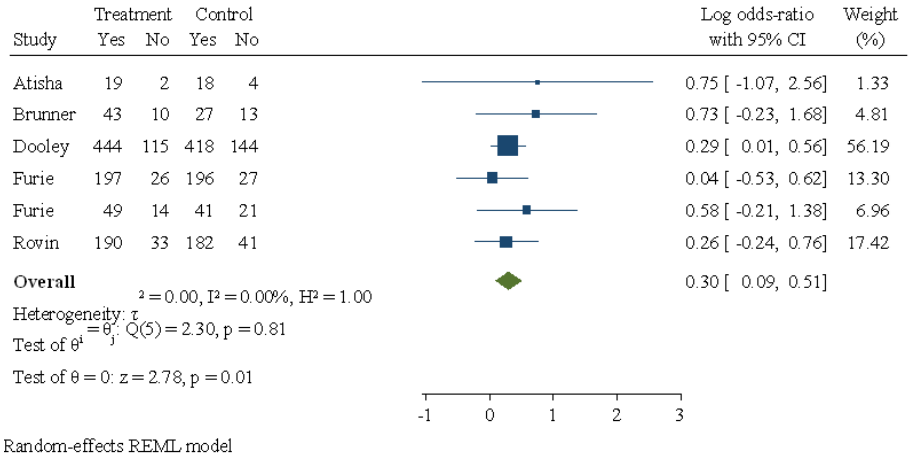

Figure 3.

Forest plot of the efficacy of belimumab in LN treatment (CI: Confidence interval)

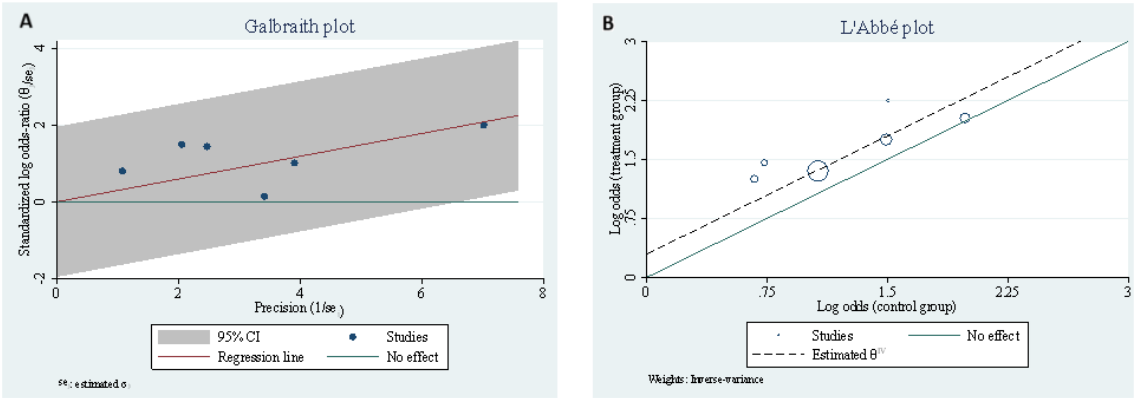

Figure 4.

(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

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.

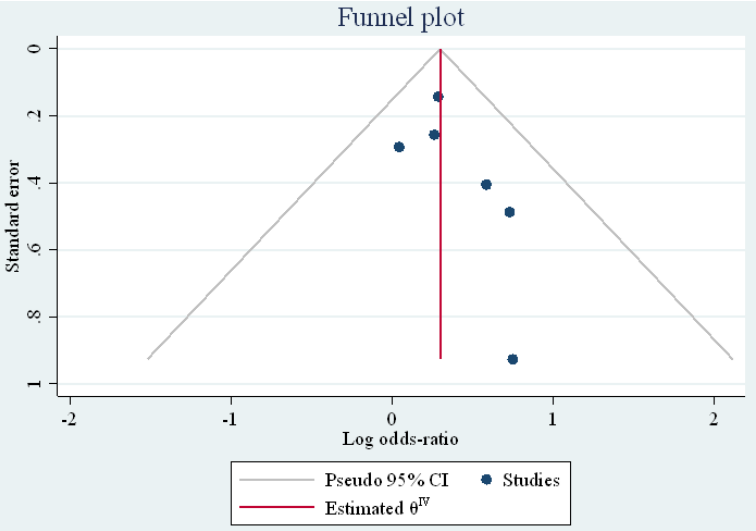

Figure 5.
Funnel plot of the efficacy of belimumab in treating LN

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.

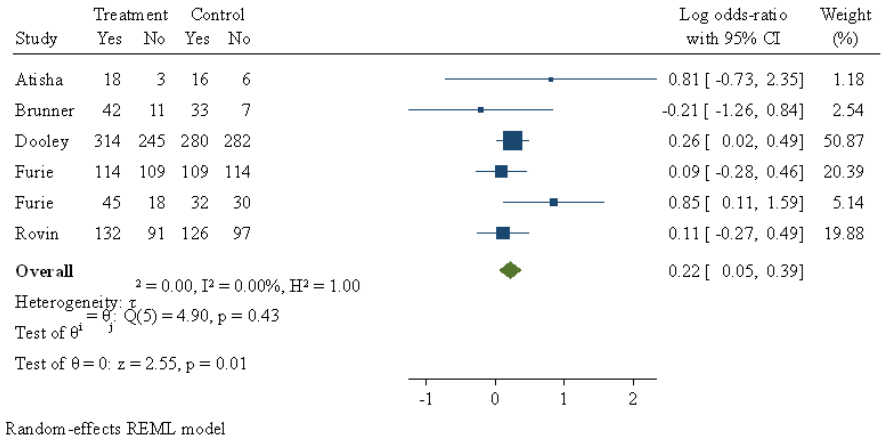

Figure 6.
Forest plot of the safety of belimumab treatment for LN

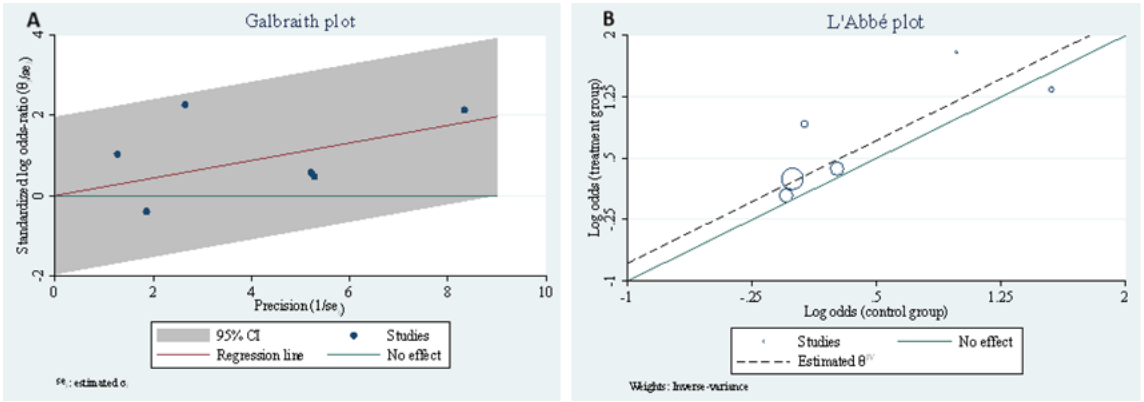

Figure 7.
(A) Heterogeneity results for safety of belimumab treatment for LN
(B) L'Abbe heterogeneity for the safety of belimumab in LN treatment

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.

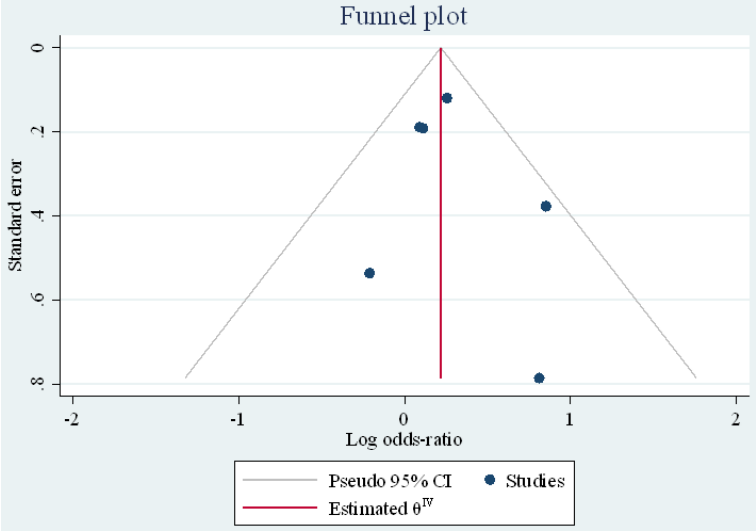

Figure 8.
Funnel plot of the safety of belimumab in the treatment of LN

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.

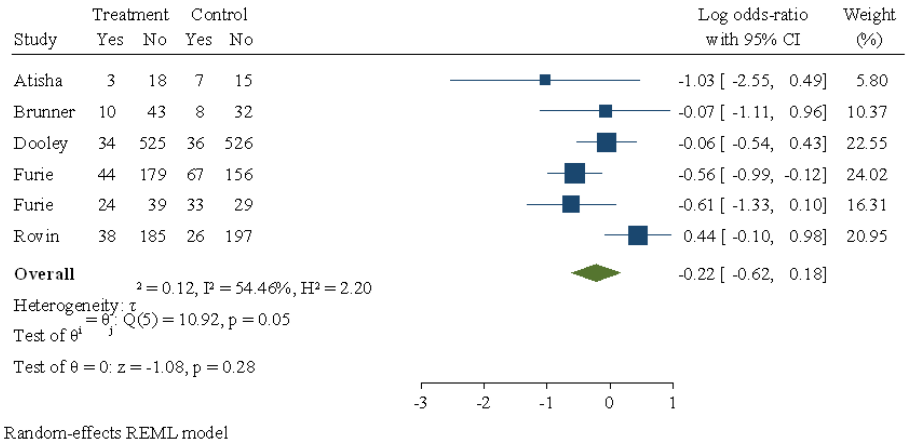

Figure 9.
Forest plot of the effects of belimumab on renal involvement in LN. CI: Confidence interval

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.

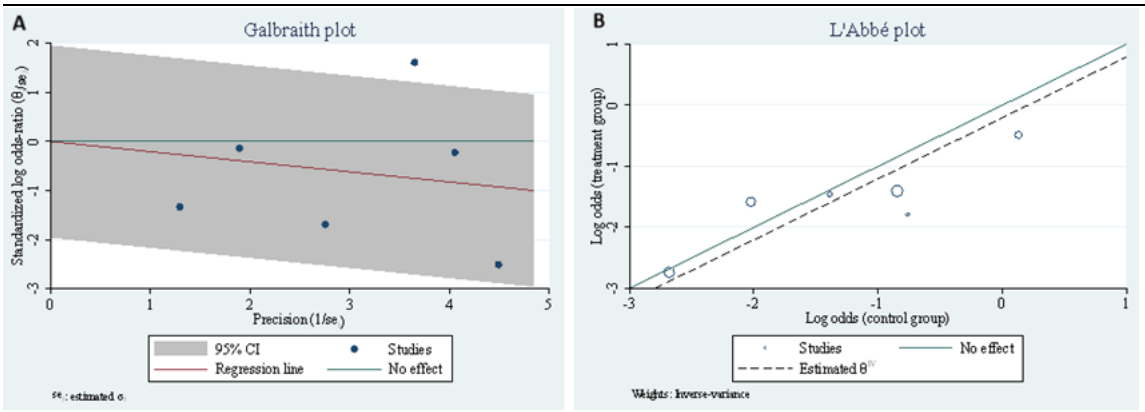

Figure 10.

(A) Heterogeneity in effect of belimumab on renal involvement in LN

(B) Heterogeneity test for the effect of belimumab on renal involvement in LN

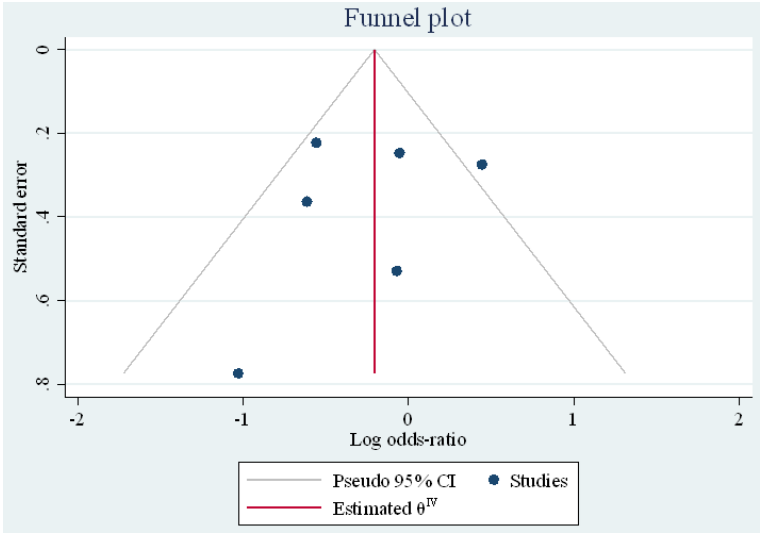

Figure 11.

Funnel plot of the effect of belimumab on renal involvement in LN

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), $I^2 = 30.79\%$, 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.

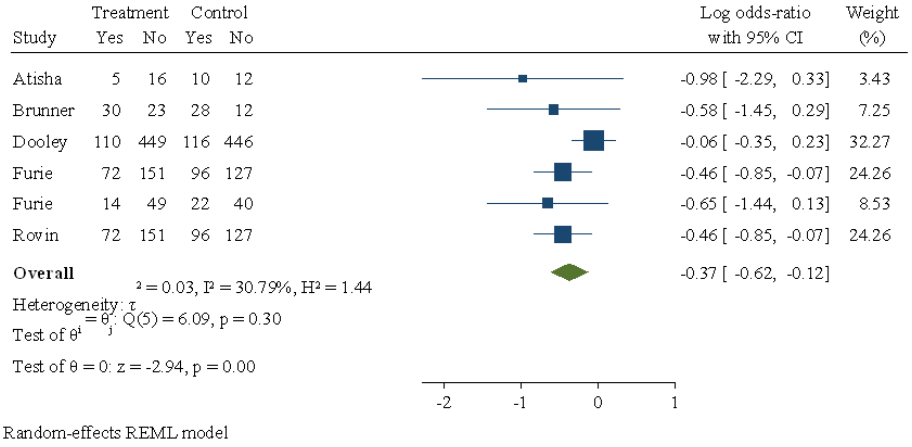

Figure 12.

Forest plot of the effect of belimumab on complications of LN; (CI: Confidence interval)

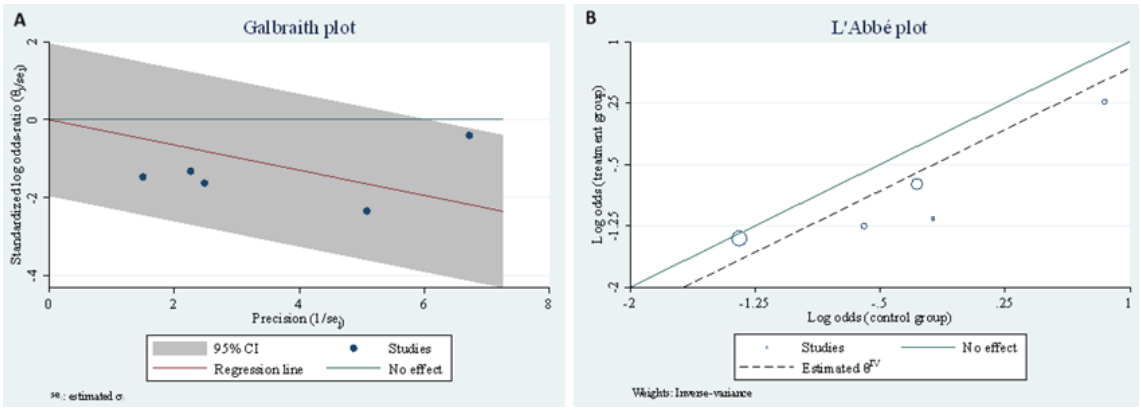

Figure 13.

(A) Heterogeneity test plot for the effect of belimumab on complications of LN

(B) Labbe'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.

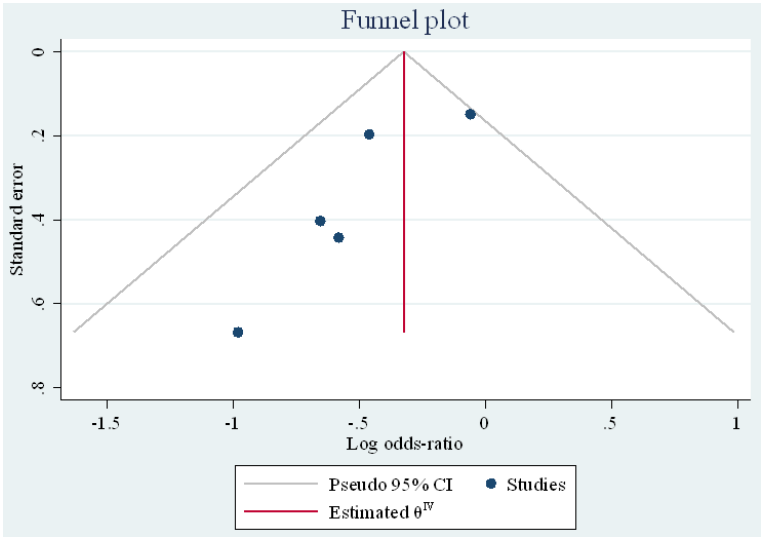

Figure 14.

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 renal injury [22]. The core pathogenesis of LN is closely linked to the formation of circulating and *in situ* immune complexes and their deposition in the glomerulus. DNA, RNA and proteins released from dying cells activate dendritic cells, monocytes and macrophages *via* toll-like receptors (TLRs), leading to the release of pro-inflammatory mediators. Abnormal T-cell activation and prolonged B-cell survival and maturation result in increased numbers of self-reactive B-cells, memory B-cells and plasma cells [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

criteria for assessing adverse events. The number of RCTs was limited, and their outcome measures varied. This meant that they could not be included in this meta-analysis, which affected the overall level of evidence. The aim of future research is the collection of a wider range of indicators and a more detailed analysis of the differences in drug concentrations. This approach should provide more precise evidence to guide clinical treatment decisions.

Conflict of interest

The authors declare no conflict of interest.

References

1. Teng YKO, Rabelink TJ, Will New Treatment Options for Lupus Nephritis Be Affordable?. *Clin J Am Soc Nephrol.*, 2022; 17(3): 340-341.
2. Rovin BH, Teng YKO, Ginzler EM, Arriens C, Caster DJ, Romero-Diaz J, Gibson K, Kaplan J, Lisk L, Navarra S, Parikh SV, Randhawa S, Solomons N, Huizinga RB, Efficacy and safety of voclosporin *versus* placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*, 2021; 397(10289): 2070-2080.
3. Mititelu M, Stanciu TI, Udeanu DI, Popa DE, Draganescu D, Cobelschi C, Grigore ND, Pop AL, Ghica M, The impact of COVID-19 lockdown on the lifestyle and dietary patterns among Romanian population. *Farmacia*, 2021; 69(1): 1-11.
4. Rovin BH, Furie R, Teng YKO, Contreras G, Malvar A, Yu X, Ji B, Green Y, Gonzalez-Rivera T, Bass D, Gilbride J, Tang CH, Roth DA, A secondary analysis of the Belimumab International Study in Lupus Nephritis trial examined effects of belimumab on kidney outcomes and preservation of kidney function in patients with lupus nephritis. *Kidney Int.*, 2022; 101(2): 403-413.
5. Mandrik O, Fotheringham J, Ren S, Tice JA, Chapman RH, Stevenson MD, Pearson SD, Herron-Smith S, Agboola F, Thokala P, The Cost-Effectiveness of Belimumab and Voclosporin for Patients with Lupus Nephritis in the United States. *Clin J Am Soc Nephrol.*, 2022; 17(3): 385-394.
6. Parodis I, Houssiau FA, From sequential to combination and personalised therapy in lupus nephritis: moving towards a paradigm shift?. *Ann Rheum Dis.*, 2022; 81(1): 15-19.
7. Karasawa K, Ogura S, Takabe T, Miyabe Y, Iwabuchi Y, Akiyama K, Sato M, Moriyama T, Uchida K, Nitta K, Successful Treatment with Belimumab in a Patient with Refractory Systemic Lupus Erythematosus after Initiation of Hemodialysis: Considering the Synergistic Effect of Belimumab and Immunological Burn-Out Phenomenon in End-Stage Renal Disease Patients on Hemodialysis. *Blood Purif.*, 2022; 51(2): 182-188.
8. Chang A, Clark MR, Ko K, Cellular aspects of the pathogenesis of lupus nephritis. *Curr Opin Rheumatol.*, 2021; 33(2): 197-204.
9. Brunner HI, Abud-Mendoza C, Viola DO, Calvo Penades I, Levy D, Anton J, Calderon JE, Chasnyk VG, Ferrandiz MA, Keltsev V, Paz Gastanaga ME, Shishov M, Boteanu AL, Henrickson M, Bass D, Clark K, Hammer A, Ji BN, Nino A, Roth DA, Struemper H, Wang ML, Martini A, Lovell D, Ruperto N, Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG), Safety and efficacy of intravenous belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial. *Ann Rheum Dis.*, 2020; 79(10): 1340-1348.
10. Dimelow R, Ji B, Struemper H, Pharmacokinetics of Belimumab in Children With Systemic Lupus Erythematosus. *Clin Pharmacol Drug Dev.*, 2021; 10(6): 622-633.
11. D'Alessandro R, Garcia Gonzalez E, Frediani B, Efficacy of belimumab monotherapy in high infectious risk patient affected by lupus nephritis. *Rheumatol Adv Pract.*, 2021; 5(1): rkab023.
12. Restrepo-Escobar M, Granda-Carvajal PA, Jaimes F, Development and Internal Validation of a Prediction Model to Estimate the Probability of Needing Aggressive Immunosuppressive Therapy With Cytostatics in de Novo Lupus Nephritis Patients. *Reumatol Clin (Engl Ed.)*, 2019; 15(1): 27-33.
13. Staveri C, Karokis D, Liossis SC, New onset of lupus nephritis in two patients with SLE shortly after initiation of treatment with belimumab. *Semin Arthritis Rheum.*, 2017; 46(6): 788-790.
14. Liu T, Neuner R, Thompson A, Pottackal G, Petullo D, Liu J, Nikolov N, Sahajwalla C, Doddapaneni S, Chen J, Clinical pharmacology considerations for the approval of belimumab for the treatment of adult patients with active lupus nephritis: A regulatory perspective. *Lupus*, 2022; 31(4): 424-432.
15. Atisha-Fregoso Y, Malkiel S, Harris KM, Byron M, Ding L, Kanaparthi S, Barry WT, Gao W, Ryker K, Tosta P, Askanase AD, Boackle SA, Chatham WW, Kamen DL, Karp DR, Kirou KA, Sam Lim S, Marder B, McMahon M, Parikh SV, Pendergraft WF3rd, Podoll AS, Saxena A, Wofsy D, Diamond B, Smilek DE, Aranow C, Dall'Era M, Phase II Randomized Trial of Rituximab Plus Cyclophosphamide Followed by Belimumab for the Treatment of Lupus Nephritis. *Arthritis Rheumatol.*, 2021; 73(1): 121-131.
16. Dooley MA, Houssiau F, Aranow C, D'Cruz DP, Askanase A, Roth DA, Zhong ZJ, Cooper S, Freimuth WW, Ginzler EM, Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in patients with SLE. *Lupus*, 2013; 22(1): 63-72.
17. Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, Amoura Z, Yu X, Mok CC, Santiago MB, Saxena A, Green Y, Ji B, Kleoudis C, Burriss SW, Barnett C, Roth DA, Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. *N Engl J Med.*, 2020; 383(12): 1117-1128.
18. Furie RA, Aroca G, Cascino MD, Garg JP, Rovin BH, Alvarez A, Fragoso-Loyo H, Zuta-Santillan E, Schindler T, Brunetta P, Looney CM, Hassan I, Malvar A, B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis.*, 2022; 81(1): 100-107.

19. Gatto M, Saccon F, Andreoli L, Bartoloni E, Benvenuti F, Bortoluzzi A, Bozzolo E, Brunetta E, Canti V, Cardinaletti P, Ceccarelli F, Ciccia F, Conti F, De Marchi G, de Paulis A, De Vita S, Emmi G, Faggioli P, Fasano S, Fredi M, Gabrielli A, Gasparotto M, Gerli R, Gerosa M, Govoni M, Gremese E, Laria A, Larosa M, Mosca M, Orsolini G, Pazzola G, Petricca L, Ramirez GA, Regola F, Rossi FW, Rossini M, Salvarani C, Scarpato S, Tani C, Tincani A, Ubiali T, Urban ML, Zen M, Doria A, Iaccarino L, Durable renal response and safety with add-on belimumab in patients with lupus nephritis in real-life setting (BeRLiSS-LN). Results from a large, nationwide, multicentric cohort. *J Autoimmun.*, 2021; 124: 102729.
20. Trindade VC, Carneiro-Sampaio M, Bonfa E, Silva CA, An Update on the Management of Childhood-Onset Systemic Lupus Erythematosus. *Paediatr Drugs*, 2021; 23(4): 331-347.
21. Silva CA, Aikawa NE, Pereira RM, Campos LM, Management considerations for childhood-onset systemic lupus erythematosus patients and implications on therapy. *Expert Rev Clin Immunol.*, 2016; 12(3): 301-313.
22. Levy RA, Gonzalez-Rivera T, Khamashta M, Fox NL, Jones-Leone A, Rubin B, Burriss SW, Gairy K, Maurik AV, Roth DA, 10 Years of belimumab experience: What have we learnt?. *Lupus*, 2021; 30(11): 1705-1721.
23. Shrestha S, Budhathoki P, Adhikari Y, Marasini A, Bhandari S, Mir WAY, Shrestha DB, Belimumab in Lupus Nephritis: A Systematic Review and Meta-Analysis. *Cureus*, 2021; 13(12): e20440.
24. Smith RM, Clatworthy MR, Jayne DR, Biological therapy for lupus nephritis-tribulations and trials. *Nat Rev Rheumatol.*, 2010; 6(9): 547-552.
25. Ruiz-Irastorza G, Bertsias G, Treating systemic lupus erythematosus in the 21st century: new drugs and new perspectives on old drugs. *Rheumatology (Oxford)*, 2020; 59(Suppl5): v69-v81.
26. Ortiz-Aljaro P, Montes-Cano MA, García-Lozano JR, Aquino V, Carmona R, Perez-Florido J, García-Hernández FJ, Dopazo J, González-Escribano MF, Protein and functional isoform levels and genetic variants of the BAFF and APRIL pathway components in systemic lupus erythematosus. *Sci Rep.*, 2022; 12(1): 11219.
27. Ward M, Tektonidou MG, Belimumab as Add-on Therapy in Lupus Nephritis. *N Engl J Med.*, 2020; 383(12): 1184-1185.
28. Mucke J, Schneider M, Innovations in the pharmaceutical treatment of systemic lupus erythematosus. *Internist (Berl.)*, 2022; 63: 566-572, (available in German).
29. Parvu A, Orasan OH, Pop SV, Zsoldos IA, Catana C, Deac IS, Bojan AS, Efficacy and safety of thrombopoietin receptor agonists in modern treatment of immune thrombocytopenia. *Farmacia*, 2021; 69(2): 219-230.
30. Clottu A, Horisberger A, Comte D, Biologics and systemic lupus erythematosous: new insights and perspectives. *Rev Med Suisse*, 2021; 17(733): 684-689, (available in French).
31. Gimeno-Torres L, Carrión-Barberà I, Durán X, Villegas E, Monfort J, Salman-Monte TC, Prevalence and risk factors for serositis in patients with systemic lupus erythematosus: A case-control study. *Lupus*, 2021; 30(13): 2095-2101.
32. Ito Y, Tamada T, Okunishi Y, Mizutani S, Yamamoto Y, Nakajima A, Organizing pneumonia as a possible pulmonary manifestation of systemic lupus erythematosus: Three cases and a review of literature. *Lupus*, 2022; 31(6): 737-743.
33. Zeng X, Zheng L, Rui H, Kang R, Chen J, Chen H, Liu J, Risk factors for the flare of systemic lupus erythematosus and its influence on prognosis: a single-center retrospective analysis. *Adv Rheumatol.*, 2021; 61(1): 43.
34. Jacobs HM, Arkatkar T, Du SW, Scharping NE, Woods J, Li QZ, Hudkins KL, Alpers CE, Rawlings DJ, Jackson SW, TACI haploinsufficiency protects against BAFF-driven humoral autoimmunity in mice. *Eur J Immunol.*, 2021; 51(9): 2225-2236.