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SUMMARY WITH CRITICAL APPRAISAL

Belimumab Treatment for Adults with Systemic Lupus Erythematosus: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

ACR	American College of Rheumatology
AE	adverse effect
AHRQ	Agency for Healthcare Research and Quality
ANA	anti-nuclear antibody
BILAG	British Isles Lupus Assessment Group
BLyS	B lymphocyte stimulator
CDR	Common Drug Review
CI	confidence interval
CNS	central nervous system
CRD	Centre for Reviews and Dissemination
DMARD	disease-modifying anti-rheumatic drug
dsDNA	double stranded deoxyribonucleic acid
ECG	electrocardiography
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
Ig	immunoglobulin
IV	intravenous
IVIG	intravenous immunoglobulin
LN	lupus nephritis
mITT	modified intent-to-treat
NSAID	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PGA	physician global assessment
PK	pharmacokinetics
QALY	quality-adjusted life-year

QOL	quality of life
RR	relative risk
SAE	serious adverse effect
SC	subcutaneous
SELENA-SLEDAI	Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index
SF-36	36- Item Short Form Survey
SLAM	Systemic Lupus Activity Measure
SLE	systemic lupus erythematosus
SLEDAI	SLE Disease Activity Index
SR	systematic review
SRI	SLE Responder Index
TNF	tumour necrosis factors
USA	United States of America

Context and Policy Issues

Systemic lupus erythematosus (SLE) is a chronic, remitting autoimmune disease related to autoantibody production and abnormal B lymphocyte function.[1,2] In 2005, it was estimated that there were 322,000 Americans with definite or probable SLE.[3] Individuals with SLE have varying degrees of symptoms, including fever, joint pain, fatigue, rash, and oral ulceration.[3,4] Certain parts of the population are more likely to be affected – particularly those aged 15 to 45 years, those who are female, and those who belong to certain ethnic groups,[3] In the long run, kidneys, joints, lungs, nervous system, skin, and serous membrane may be affected.[4] Among all complications, nephritis is a leading cause of morbidity and mortality, and renal involvement occurs in 40% to 70% of all patients with SLE.[5] People with SLE are at higher risk of death from infection, heart disease, or certain malignancies, particularly hematologic cancers and lung cancer.[6,7] In addition to increased morbidity and mortality, SLE has been associated with poorer quality of life for patients and with a large economic burden to the healthcare system.[8]

SLE Evaluation, Treatment and Monitoring

The American College of Rheumatology (ACR) has defined criteria to diagnose SLE, including rash, photosensitivity, oral ulcers, arthritis, serositis, and renal and neurological disorder.[9] Despite the diagnostic criteria, clinical assessment remains difficult and diagnosing flares, complications, and comorbidity remains challenging.[9]

A major advance in SLE treatment was the invention of corticosteroid pulse treatment in 1976,[10] and until 2011, no other major treatment advances were made.[4,10] In 2011, belimumab was approved by the FDA for the treatment of SLE in the USA.[3] Currently SLE is primarily treated with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antimalarial agents, and immunosuppressant drugs.[4] The treatment objective is to reduce

inflammation and supress the immune system.[4] Immunosuppressant and immune-modulating drugs are used as second-line treatment.[4] Even with treatment, about half of those with the condition have persistent or relapsing SLE.[4] Existing treatment approaches are known to have serious adverse effects, especially with long-term.[7]

B lymphocyte stimulator and Belimumab

B lymphocyte stimulator (BLyS) is overexpressed in patients with SLE and correlates with changes in disease activity.[11,12] In studies with 2 years of observation, BLyS levels correlated with changes in SLE severity and anti-dsDNA antibody titers.[12] The increases in serum BLyS concentrations are associated with worsening disease activity measured by the Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) and elevated anti-dsDNA antibody titers.[12] The levels of anti-dsDNA and complement (C3 and C4) are also considered predictors of disease activity, exacerbations, and response to treatment.[12]

Belimumab is a human immunoglobulin (Ig)-G1λ monoclonal antibody that binds to and inhibits soluble human BLyS.[12] Belimumab can be injected intravenously or subcutaneously and is indicated for SLE in adults with a positive auto-antibody test whose disease is still highly active (e.g., anti-dsDNA positive and low complement) even with standard treatment.[4] Contraindications include severe active lupus nephritis or severe active central nervous system (CNS) lupus.[4]

Common Drug Review and Recommendation in 2012

In Canada, the Common Drug Review (CDR) committee did not recommend listing belimumab in public drug formularies in 2012.[13] The recommendation was based on two major randomized controlled trials.[8,11,14-20] The conclusion was that significantly higher proportions of patients receiving belimumab 10 milligrams (mg) per kilogram (kg) responded compared to those receiving placebo at 52-week follow-up in BLISS-52 trial,[13] however, this was not observed at the 76-week follow-up (in the BLISS-76 trial).[13] This led to uncertain clinical benefit of using belimumab in treating patients with SLE.[13] The report further concluded that the incremental cost per quality-adjusted life-year (QALY) may be higher than the $112,883 estimated by the manufacturer.[13]

Recently, new trials examining belimumab have been published [1,2,21,22] and it is unclear whether the latest evidence would support or change the 2012 CDR recommendation. The objective of this report is to review the latest evidence in order to further determine the clinical and cost-effectiveness of belimumab for the treatment of SLE, as well as to review the evidence-based guidelines.

Research Question

1. What is the clinical effectiveness of belimumab for the treatment of adults with systemic lupus erythematosus?
2. What is the cost-effectiveness of belimumab for the treatment of adults with systemic lupus erythematosus?
3. What are the evidence-based guidelines associated with belimumab for the treatment of adults with systemic lupus erythematosus?

Key Findings

Belimumab administered intravenously or subcutaneously in addition to standard of care was effective in improving SLE severity measures among patients with moderate to severe SLE based on three fair- to good- quality RCTs and three low-quality SRs that followed patients for a maximum of 76 weeks. The affected measures included better SRI4 response, musculoskeletal and immunological manifestation, decreasing autoantibodies, and higher serum complement levels based on the SRs. To avoid the adverse effects of corticosteroid treatment, patients with SLE treated with belimumab intravenously or subcutaneously might be able to reduce the dosage of corticosteroid. Certain patient groups might benefit from adjuvant belimumab treatment more than others, such as those with more severe SLE, low serum complement levels, positive ds-DNA antibodies, or active steroid treatment. Belimumab administered intravenously or subcutaneously was well tolerated with the incidence of adverse effects or serious adverse effects similar to placebo.

There were no relevant cost-effectiveness studies or evidence-based guidelines identified.

The limitations of this review include publication bias, limited lengths of follow-up in the trials, limited numbers of trials, and applicability of the existing evidence to patients with SELENA-SLEDAI scores less than eight.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between January 1, 2010 and April 23, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult (≥18 years of age) patients systemic lupus erythematosus (SLE)
Intervention	Belimumab (Benlysta)
Comparator	Q1-2: Biologics (e.g., but not limited to, anti-tumour necrosis factors [TNFs], Orencia); Disease-modifying anti-rheumatic drugs (DMARDs); Methotrexate; Corticosteroids; Placebo; Any other standard of care Q3: No comparator

Outcomes	Q1: Clinical effectiveness (especially long term efficacy/effectiveness and safety) Q2: Cost-effectiveness (e.g., cost per QALY increase, cost per hospitalization reductions, costs per increase in patient satisfaction) Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews/meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, guidelines

DMARD = disease-modifying anti-rheumatic drug, QALY = quality-adjusted life-year, SLE = systemic lupus erythematosus, TNF = tumour necrosis factors

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Studies included in a selected systematic review were also excluded. Publications based on the two trials that were reviewed in the 2012 CDR report,[13] BLISS-52 and 76 (ClinicalTrials.gov ID: NCT00424476 and NCT00410384 respectively), were not included. Additionally, systematic reviews were excluded if the list of included studies fully overlapped with an included systematic review or with the 2012 CDR report. Excluded publications that may be of interest are included in Appendix 5.

Critical Appraisal of Individual Studies

The included systematic reviews (SR) were critically appraised using the AMSTAR 2 tool.[23] The quality of randomized clinical trials (RCTs) was assessed using the Cochrane Risk of Bias Tool.[24] The quality of non-randomized studies was assessed using the Newcastle-Ottawa scale.[25] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations assessed in each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 415 citations were identified in the literature search. Following screening of titles and abstracts, 370 citations were excluded and 45 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 38 publications were excluded for various reasons, while 7 publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Additional details describing the characteristics of the included studies are reported in Appendix 2.

Study Design

Three systematic reviews (SR) were included in this report.[26-28] Oon et al. and Shamliyan et al. reviewed all adjuvant biologic response modifiers.[26,27] Oon et al. included 26 articles that were based on phase-3 trials and three RCTs of belimumab were identified: BLISS-52, -76, and -SC or NCT00424476, NCT00410384 and NCT01484496.[26] Shamliyan et al. included

seven meta-analyses, 33 publications of RCTs, and 5 observational studies.[27] Fourteen examined the effectiveness of belimumab.[27] Sciascia et al. focused on belimumab and included 11 studies: one RCT, two retrospective observational studies, two prospective observational studies, and six case reports.[28] The BLISS-52 and -76 trials were included in the three SRs.[26-28]

There were four publications based on three RCTs comparing belimumab at different dosages with placebo.[1,2,21,22] Two RCTs were multicenter trials.[1,22]

Year of Publication and Country of origin

Two of the SRs, Shamliyan et al. and Sciascia et al., were published in 2017[27,28] and Oon et al. published in 2018.[26] The corresponding authors of the SRs, Oon et al., Shamliyan et al. and Sciascia et al., were based in the Australia, the USA, and Italy respectively.[27,28]

Two articles published in 2017 and 2018 were based on one RCT, BLISS-SC or NCT01484496, that was conducted in 177 sites in 30 countries including the USA and Australia.[21,22] The corresponding authors of the two publications, Doria et al. and Stohl et al., were based in Italy and the USA respectively.[21,22] Another RCT, Zhang et al., was published in 2018.[1] Zhang et al. was conducted in China, Japan, and South Korea.[1] The corresponding author of Zhang et al. was based in China.[1] The other RCT, Yamada et al., were published in 2013.[2] Yamada et al. was conducted in Japan.[2,22]

Study population

The SR by Oon et al. included 26 citations, of which three RCTs examined belimumab and were relevant to this review.[26] There were 865, 819, and 836 SLE patients included in the three RCTs.[26] The patients were seropositive (anti-nuclear antibody [ANA] and/or anti-dsDNA antibody positive) patients with moderate to severe SLE, either according to SLEDAI or BILAG definitions.[26] The SR by Shamliyan et al. included 14 publications on belimumab which ranged from including 37 to 1,349 patients with SLE in primary studies.[27] All patients were adults diagnosed with SLE according to the ACR classification and more than 80% were female.[27] Moderate to severe SLE was defined as SELENA- SLEDAI score equal to or more than six and the BILAG A or B category.[27] The SR by Sciascia et al. included 2,004 SLE patients in total, 326 of whom were diagnosed with lupus nephritis (LN) at baseline.[28]

In the BLISS-SC trial, the patients had SELENA- SLEDAI sores higher than or equal to eight and had antinuclear antibodies (ANA) and/or anti-dsDNA antibodies according to the ACR classification.[21,22] Severe complications, severe lupus kidney disease, and CNS lupus, were exclusion criteria.[21,22] Stohl et al. was based on 836 SLE patients of the trial and Doria et al. focused on 358 patients who were hypocomplementemic and anti-dsDNA-positive at baseline.[21,22] In another RCT, Zhang et al. included people with SLE with SELENA-SLEDAI scores greater than or equal to eight, positive ANA test result, and a stable SLE treatment regimen for more than 30 days: 677 for modified intent-to-treat (mITT) analysis and 705 for safety outcomes. [1] Yamada et al. included 12 Japanese adults diagnosed with SLE based on the ACR criteria and with positive ANA or anti-dsDNA antibody.[2]

Interventions and Comparators

Belimumab was initially designed to be administered intravenously every four weeks in addition to standard of care.[26-28] When used intravenously, the volume of the drug was injected based on body weight.[26-28] Two dosages, 1 mg/kg and 10 mg/kg intravenously, were identified in the three SRs.[26-28] In the RCT by Zhang et al., only belimumab 10 mg/kg

was used.[1] In the dose-ascending RCT by Yamada et al., both dosages were compared with placebo.[2]

In the BLISS-SC trial, it was administered by patients subcutaneously weekly after training in addition to standard of care.[21,22,26] This dosage was reviewed or reported in the SR by Oon et al. and two publications.[21,22,26]

Belimumab plus standard of care was compared to placebo with standard of care in all publications.[1,2,21,22,26-28]

Outcomes

The outcomes evaluated in the SR by Oon et al. were composite responder indices incorporating the SLEDAI, BILAG, PGA, and SRI.[26] The secondary outcomes included changes in biomarkers, such as anti-dsDNA antibodies, serum complement levels, and changes in quality of life.[26] The outcomes evaluated in the SR by Shamliyan et al. were mortality, SRI response, SF-36 response, FACIT-Fatigue score, severe lupus flare, SLE severity, prednisolone reduction, BILAG worsening, SELENA-SLEDAI worsening, and treatment discontinuation due to adverse effect after 40 to 76 weeks of follow-up.[27] The outcomes in the other SR that focused on renal outcomes by Sciascia et al. were renal flares, renal remission, renal improvement, arthritis, rash, proteinuria, SLAM, SLEDAI, and adverse events after 6 months to 52 weeks of follow-up.[28]

The primary outcome in the BLISS-SC RCT included SRI4 by visit, SRI4 components by visit, and the SRI5–8 by visit.[21,22] The secondary outcomes included time to first severe flare and reduction in corticosteroid dosage.[21,22] The primary outcome in Zhang et al. was SRI4 response rate at Week 52 and the secondary outcomes included the changes in SELENA-SLEDAI scores, SRI7 responses, time to first severe flare, and reduction in daily prednisone dose.[1] The RCT by Yamada et al. evaluated safety and tolerance, i.e. adverse events and serious adverse events, clinical laboratory values, vital signs, and 12-lead electrocardiography (ECG) from randomization through study day 84.[2]

Summary of Critical Appraisal

Additional details describing the critical appraisal of the included studies are reported in Appendix 3.

The three SRs described the population, intervention, comparator, and outcome (PICO) components and research objectives, study selection criteria and rationale were described, reasons for study exclusion were described or shown in figures, and a comprehensive literature search was conducted in multiple databases.[26-28] However, only Shamliyan et al. published a review protocol *a priori*, extracted data in duplicate, assessed risk of bias in the primary studies, and reported review authors' financial conflicts.[27] Shamliyan et al. and Sciascia et al. performed study selection in duplicate.[26] Oon et al. and Sciascia et al. described the included studies in detail.[26,28] Oon et al. and Shamliyan conducted meta-analyses.[26,27] The authors of the three SRs did not provide a list of excluded studies, report funding sources of the included studies, adjust for risk of bias of included studies while summarizing or discussing the results, describe the heterogeneity between included studies, or assess publication bias.[26-28]

With more than one weakness in the critical domains, including not providing a list of excluded studies and not adjusting for risk of bias in the meta-analysis, the risk for bias in the reviews is high.

The four RCTs mentioned randomization,[1,2,21,22] but only Zhang et al. and Stohl et al. described randomization methods that ensured that patient characteristics in different arms were balanced.[2,22] Allocation concealment that prevented the patients or physicians to predict whether active agents were used was described in Zhang et al. and Yamada et al.[1,2] Yamada et al. was a single-blinded study and did not mention who was blinded.[2] The other three RCTs were double blinded.[1,21,22] All RCTs reported patient attrition and did not selectively report outcomes.[1,2,21,22] The manufacturer of belimumab funded the RCTs.[1,2,21,22] Unbalanced groups, failure to conceal the treatment allocation, and unblinding study participants could lead to differential behavior in patients and thus bias results. Zhang et al. met all criteria in the appraisal tool and the quality was rated good. The other three RCTs did not clearly describe sequence generation or allocation concealment and the quality was rated fair.

Summary of Findings

1. *What is the clinical effectiveness of belimumab for the treatment of adults with systemic lupus erythematosus?*

Clinical effectiveness

Moderate evidence suggested that adjunctive IV belimumab at 1 and 10 mg/kg improved clinical response compared to immunosuppressive agents alone.[26,27] However, very low quality evidence from a subgroup analysis suggested that patients of Latin American, Asian, and Pacific Islander descent treated with the dose of 1 mg/kg might not have improvement compared to placebo.[27] The SR by Oon et al. suggested that belimumab administered subcutaneously also improved the SRI4 response among SLE patients.[26] Patients with more severe disease (baseline SELENA-SLEDAI score of 10 or higher and low complement levels) experienced a greater improvement in the lupus response index.[26,27] Belimumab 10 mg/kg prevented flare and reduced the dose of prednisone but did not prevent worsening of damage in specific organ systems.[27] Belimumab 10 mg/kg compared to 1 mg/kg improved only the rates of auto-antibody normalization.[27] Oon et al. noted that there was considerable publication bias due to the fact that only 58% of the registered studies on biologic response modifiers were published.[27]

In the SR by Sciascia et al., belimumab 1 or 10 mg/kg was associated with an improvement in renal parameters assessed either by SELENA-SLEDAI, SLEDAI-2K, BILAG, and/or SLAM indexes.[28] Belimumab was related to a higher percentage of renal remission (68.1% vs. 58.7%, $P = 0.025$) and a shorter time to renal remission.[28] Belimumab was not significantly associated with the rates of renal flare.[28] For patients with biopsy-proven LN, 100% therapeutic response was found in seven patients.[28]

The RCTs by Zhang et al. and Yamada et al. examined intravenous administration of belimumab.[1,2] The use of belimumab was associated in the improvement in SRI4, SELENA-SLEDAI score, SRI7, and severe flare, as well as less prednisolone use in Zhang et al.[1] The pharmacokinetics profile of belimumab showed dose proportional, long half-life, low clearance, small volume of distribution, and evidence of effectiveness on B cells.[2]

In the BLISS-SC trial (reported in two publications), belimumab 200 mg was administered subcutaneously weekly and could achieve steady-state exposure similar to 10 mg/kg IV every four weeks.[21,22] In Stohl et al., belimumab improved SRI4 response, decreased the risk of severe flare, reduced corticosteroid dosages during weeks 40 to 52, compared to placebo.[22] In Doria et al. that analyzed patients who were hypocomplementemic and anti-

dsDNA-positive, better SRI4 response, lower incidence of severe SLE Flare Index flare, reduced corticosteroid use were also observed in the belimumab group.[21]

Adverse effects

Belimumab administered intravenously or subcutaneously was well tolerated.[1,2,21,22,26] There are no differences in all-cause mortality and adverse effects between adjunctive belimumab 1 mg/kg and immunosuppressive agents alone.[27] The incidence of adverse effects was also similar in the treatment and placebo group if administered subcutaneously.[21] Yamada et al. found favorable clinical safety and tolerability profile of belimumab 1 or 10 mg/kg.[2] The incidence of adverse effects were also similar in the belimumab and placebo groups if administered subcutaneously in the BLISS-SC trial.[22]

Additional detail regarding the clinical effectiveness and adverse events is available in Appendix 4.

2. *What is the cost-effectiveness of belimumab for the treatment of adults with systemic lupus erythematosus?*

No relevant cost-effectiveness studies regarding the use of belimumab for the treatment of adults with SLE were identified.

3. *What are the evidence-based guidelines associated with belimumab for the treatment of adults with systemic lupus erythematosus?*

No evidence-based guidelines regarding the use of belimumab for the treatment of adults with SLE were identified.

Limitations

There are several limitations to this report. One of the primary limitations is the potential lack of generalizability of the body of evidence to patients with SELENA-SLEDAI scores less than eight. All three of the included RCTs[1,2,21,22] included patients with SELENA-SLEDAI scores of eight or higher and within the included SRs, most primary studies included patients with moderate to severe SLE.[26-28] Thus, it is unclear if the results generalize for people with mild to moderate SLE. Further, the evidence regarding patients with LN was limited; the BLISS trials excluded patients with severe LN[26] and the number of patients diagnosed with LN were limited in a SR.[28] It is therefore unclear if the results presented in this review are relevant to patients with SLE and LN.

The lengths of follow-up in RCTs were also limited, a maximum of 76 weeks.[26-28] Some of trials continued following up the patients receiving belimumab.[7,12] However, there was no control group to understand the long-term effectiveness. In addition, there were a limited number (three) of RCTs published after the 2012 CDR report,[1,2,21,22] one of which used subcutaneous administration of belimumab.[21,22] This may lead to a difficulty in generalizing the effectiveness of belimumab between trials.

Publication bias was a further concern; many of the trials on biologic response modifiers were not published according to the SR in 2017.[27] It is unclear how this might impact our assessment.

Additionally, the authors of the two SRs, Oon et al. and Shamliyan et al., did not properly assess the risk of bias of the included studies.[26-28] Only Shamliyan et al. explicitly declared

the use of critical appraisal tool and graded accordingly.[27] Further ,the heterogeneity of the results were not discussed with risk of bias in the primary studies.[26-28]

Conclusions and Implications for Decision or Policy Making

Three SRs and four fair- to good-quality RCTs on the clinical effectiveness of belimumab were identified.[1,2,21,22,26-28]The overall confidence on the results of the three SRs was low.[26-28] There were no relevant cost-effectiveness studies or evidence-based guidelines identified.

In the included RCTs that were rated fair- to good-quality, belimumab administered intravenously or subcutaneously in addition to standard of care was effective in improving SLE severity measures among patients with moderate to severe SLE at week 52.[1,21] The affected measures included better SRI4 response, musculoskeletal and immunological manifestation, decreasing autoantibodies, and higher complement levels based on the trials (that had a maximum of 76 weeks of follow-up).[26-28] When administered subcutaneously, belimumab improved the time to and the risk of severe flare at week 52.[21,22] Belimumab administered intravenously or subcutaneously was well tolerated with the incidence of adverse effects or serious adverse effects similar to placebo.[2,26-28]

Belimumab treatment may result in the need for reduced corticosteroid doses and thus fewer adverse effects for patients with SLE. [21,22,26] In the post hoc analyses, the use of belimumab intravenously was associated with improvement in quality of life.[26] Certain patient groups might benefit from adjuvant belimumab treatment more than others, such as those with more severe SLE, low complement levels, positive ds-DNA antibodies, or active steroid treatment.[26,27]

For renal outcomes, patients with severe LN were not included in the BLISS trials.[26] However, the improvement in renal outcomes could be observed in the patients with LN included in the RCTs.[26,28] The evidence on biopsy-proven LN patients was limited.[28]

Due to findings of lack of clinical effectiveness at 76 weeks and uncertain cost-effectiveness, the 2012 CDR report recommended not listing belimumab for the treatment of patients with SLE.[3] The findings in this report are somewhat different with respect to clinical effectiveness, however, the majority of the positive findings were with respect to 52 week outcomes. As previously stated the results of this review must be interpreted in light of the limitations of the body of evidence and may not generalize for people with mild to moderate SLE flares. Additionally, there is some evidence that many trials examining biological response modifiers remain unpublished.[27]

Based on current evidence, the potential impact of belimumab may be positive but is unclear with respect to both clinical and cost-effectiveness; particularly for patients with mild to moderate SLE flares and with respect to outcomes longer than 52 weeks. The evidence is particularly lacking with respect to subcutaneous administration. Future research examining those factors may help to reduce the uncertainty in long-term effectiveness and cost-effectiveness. The use of belimumab in combination of other biological response modifiers remains to be studied.

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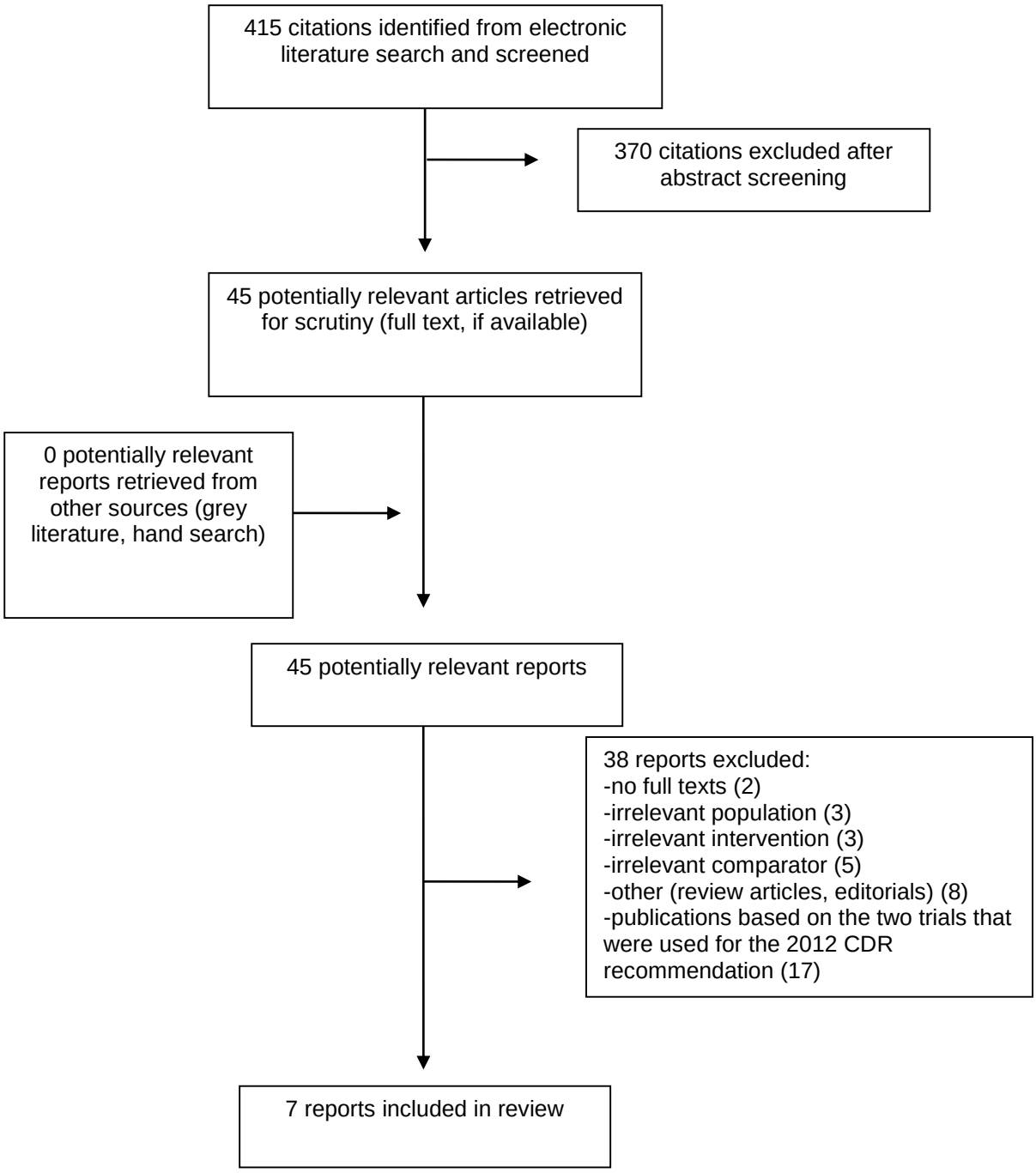
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Oon et al. 2018,[26] Australia	26 articles based on phase-3 trials testing the following biologic agents: belimumab, tabalumab, rituximab, epratuzumab, and atacicept Belimumab trials: n = 3 (BLISS-SC, BLISS-52, and BLISS-76 or NCT00424476, NCT00410384 and NCT01484496.)	"seropositive (ANA and/or anti-dsDNA antibody positive) patients with moderate to severe SLE, either according to SLEDAI or BILAG definitions" (n= 865, 819, and 836 respectively) Exclusion: "Patients with severe organ-threatening SLE, such as CNS lupus or severe active LN, were generally excluded." (p 2)	Belimumab, tabalumab, rituximab, epratuzumab, and atacicept in addition to standard of care (see the SR for details) 3 Belimumab dosages identified: 1 mg/kg IV every four weeks; 10 mg/kg IV every four weeks; 200 mg SC weekly	Placebo in addition to standard of care	Primary: BILAG criteria (rituximab, epratuzumab and atacicept trials), or composite responder indices incorporating the SLEDAI, BILAG, and PGA, or SRI. Secondary: alterations in biomarkers (anti-dsDNA antibodies, complement, B- and T-cell subsets), steroid-sparing effects, and changes in QOL measures such as the Lupus QOL and SF-36
Shamliyan et al. 2017,[27] USA	7 meta-analyses,33 publications of RCTs, and 5 observational studies Belimumab studies: n = 14	"All studies enrolled adults with SLE diagnosed according to the American College of Rheumatology classification criteria... Women constituted >80% of enrollees. No studies enrolled pediatric patients with SLE. No studies enrolled treatment-naïve patients with SLE. Primary studies enrolled adults with moderate to severe	"biologic response modifiers such as tumor necrosis factor–α inhibitors, interleukin inhibitors, and targeted monoclonal antibodies and novel biologic agents" (p 1480) Two Belimumab dosages identified: 1	"conventional immune-suppressive agents (eg, prednisone, hydroxy-chloroquine, azathioprine, cyclophosphamide, methotrexate, mycophenolatemofetil)" (p 1480)	40 to 76 weeks of follow-up for the following outcomes: mortality, SRI response, SF-36 response, FACIT-Fatigue score, severe lupus flare, SLE severity, prednisolone reduction, BILAG worsening, SELENA-SLEDAI worsening, and

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		SLE despite use of corticosteroids, antimalarial agents (hydroxychloroquine), and additional immune-suppressive agents such as mycophenolate mofetil, azathioprine, cyclophosphamide, and cyclosporine. Primary studies consistently defined moderate to severe active SLE as demonstrated by SELENA- SLEDAI score ≥6 and the BILAG A or B category. LN was diagnosed based on renal biopsy results and proteinuria." (p 1482) Belimumab studies: n = 14, 37 to 1349 participants	mg/kg IV on days 0, 14, and 28; then every 28 days for 48weeks; 10 mg/kg IV on days 0, 14, and 28; then every 28 days for 48 weeks		treatment discontinuation due to adverse effect
Sciascia et al. 2017,[28] Italy	n = 11 (1 RCT, 2 retrospective observational studies, 2 prospective observational studies, 6 case reports)	2004 patients with SLE in total. "326 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" (p 289)	Belimumab 1 or 10 mg/kg	Placebo or none	6 months to 52 weeks for outcomes including renal flares, renal remission, renal improvement, arthritis, rash, proteinuria, SLAM, SLEDAI, and adverse event

ANA = anti-nuclear antibody, BILAG = British Isles Lupus Assessment Group, CNS = central nervous system, dsDNA = double stranded deoxyribonucleic acid, FACIT = Functional Assessment of Chronic Illness Therapy, LN = lupus nephritis, PGA = physician global assessment, QOL = quality of life, SC = subcutaneous, RCT = randomized controlled trial, SF-36 = 36- Item Short Form Survey, SELENA-SLEDAI = Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index, SLAM = Systemic Lupus Activity Measure, SLE = systemic lupus erythematosus, SLEDAI = SLE Disease Activity Index, SR = systematic review, SRI = SLE Responder Index, USA = United States of America

Table 3: Characteristics of included primary studies

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Doria et al. 2018,[21] Italy	RCT, double-blind, placebo-controlled (BLISS-SC; BEL112341; NCT01484496)	The same trial as Stohl 2017[22], but only included patients that were hypocomplementemic and anti-dsDNA-positive at baseline (n = 358) Inclusion and exclusion criteria: SELENA-SLEDAI score of ≥8 at screening, antinuclear antibody and/or anti-dsDNA positivity (inclusion criteria); severe lupus kidney disease (proteinuria >6 g/24 hour or equivalent using spot urine protein to creatinine ratio, or serum creatinine >2.5 mg/dL) or severe central nervous system (CNS) lupus (exclusion criteria)"	Weekly SC belimumab 200 mg plus standard SLE therapy, similar to that obtained with 10 mg/kg intraveneously every 4 weeks	Placebo plus standard SLE therapy	Primary: SRI4 at Week 52. Secondary: time to severe flare and reduction in corticosteroid dose (Weeks 40–52). Safety assessed throughout
Zhang et al. 2018,[1] China, Japan and South Korea	RCT, phase III, multi-centre, double-blinded (BEL113750; NCT01345253)	n = 677 mITT; n = 705 safety population Inclusion criteria: ≥18 years of age with a clinical diagnosis of SLE according to ACR classification criteria and clinically active disease, defined as a SELENA-SLEDAI score ≥8 at screening; positive antinuclear antibody test result; receiving a stable SLE treatment regimen for ≥30 days prior to baseline Exclusion criteria: severe lupus kidney disease or active nephritis requiring acute therapy within 90 days prior to baseline or CNS lupus requiring therapeutic intervention within 60 days prior to	belimumab 10 mg/kg intravenously in addition to standard of care, on Days 0, 14 and 28 and then every 28 days up to Week 48	Placebo	Primary outcome: SRI4 response rate at Week 52 Secondary outcome: percentage of patients with a ≥4 point reduction from baseline in SELENA-SLEDAI score at Week 52, the percentage of patients with an SRI7 response (see article for definitions) at Week 52, time to first severe flare over 52 weeks and number of days of daily prednisone dose (or equivalent) ≤7.5 mg/day and/or reduced by 50% from

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		baseline and those requiring new SLE medications other than corticosteroids within 60 days prior to baseline were excluded, as were those who had received B cell-targeted therapy at any time.			baseline over 52 weeks in patients with baseline dose >7.5 mg/day. Other outcomes: duration of SRI4 response at 52 weeks and BILAG improvement by organ domain in patients with an A or B domain score at baseline.
Yamada et al. 2013,[2] Japan	RCT, single-blinded (patients likely blinded, but not mentioned), dose-ascending	N = 12 Female (92%); Asian-Japanese heritage (100%); median age of 46.5 years, 42.0 years and 37.0 years in the placebo, belimumab 1 mg/kg and 10 mg/kg groups, respectively. Inclusion criteria: aged 20 years or older with SLE, as defined by the ACR criteria; born in Japan with four ethnic Japanese grandparents; Japanese citizenship; stable SLE disease activity judged by investigators; positive for ANA or anti- dsDNA antibody. Exclusion criteria: severe active lupus nephritis requiring hemodialysis, cyclophosphamide, or high-dose (460 mg) prednisone, or who had received intravenous immunoglobulin, or plasmapheresis within 6 months of screening (see article for other criteria)	belimumab 1 mg/kg or 10 mg/kg, intravenously	Placebo	safety and tolerability of belimumab: adverse events and serious adverse events, clinical laboratory values, vital signs, and 12-lead ECG from randomization through study day 84
Stohl et al. 2017,[22] USA	RCT, double-blind, placebo-controlled,	n = 836, mostly female (93.7% receiving	belimumab 200 mg	Placebo	Primary: SRI4 by visit, SRI4

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
	multi-center, multi-country (BLISS-SC; BEL112341; NCT01484496) at 177 sites in 30 countries in North, Central, and South America, Eastern and Western Europe, Australia, and Asia	belimumab, 95.7% receiving placebo), with a mean age of 38.6 years and a mean/median baseline SELENA–SLEDAI score of 10.4/10.0 Inclusion criteria : Patients >18 years of age, a diagnosis of SLE according to the ACR criteria, with antinuclear antibodies and/or anti-dsDNA antibodies and a score of ≥8 on the SELENA version of the SLEDAI at screening. Exclusion criteria : severe lupus kidney disease (proteinuria > 6 gm/24 hours or equivalent according to a spot urinary protein-to-creatinine ratio or a serum creatinine level > 2.5 mg/dl) or severe CNS lupus	subcutaneuous weekly, comparable to 10mg/kg IV every 4 weeks		components by visit, and the SRI5–8 by visit Secondary: time to first severe flare (see the article for details) and reduction in corticosteroid dosage

ACR = American College of Rheumatology, ANA = anti-nuclear antibody, BILAG = British Isles Lupus Assessment Group, CNS = central nervous system, dsDNA = double stranded deoxyribonucleic acid, ECG = electrocardiography, LN = lupus nephritis, mITT = modified intent-to-treat, SC = subcutaneous, RCT = randomized controlled trial, SELENA-SLEDAI = Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index, SLE = systemic lupus erythematosus, SRI = SLE Responder Index

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[23]

Strengths	Limitations
Oon et al. 2018[26]	
• PICO components included in the research questions or study inclusion criteria • Study selection rationale described and explained • Reasons for study exclusion listed in the flowchart in Figure 1 • Comprehensive search with MEDLINE (through Pubmed), EMBASE, CINAHL and SCOPUS databases, the Cochrane library, and clinicaltrials.gov, • Included studies described • Meta-analysis conducted with a random-effects model • Funding sources mentioned • Conflict of interest declared	• Protocol not established *a priori* • Search limited to publications in English • Critical appraisal with the relevant tools not mentioned in the Methods, though risk of bias mentioned in the Appendix 1 • Study selection and data extraction not in duplicate • Funding sources of the included studies mentioned in the protocol; no data shown • Risk of bias in individual studies not discussed regarding the results of meta-analysis • The list of excluded studies not found
Shamliyan et al. 2017[27]	
• PICO components included in the research questions or study inclusion criteria • Protocol established *a priori* • Study selection rationale described and explained • Reasons for study exclusion listed in the flowchart in Figure A1 • Comprehensive search with PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov • Study selection and data extraction in duplicate by an external contractor • Critical appraisal with the relevant tools • Funding sources of the included studies extracted • Meta-analysis conducted with a random-effects model • Conflict of interest declared	• Search limited to publications in English • Included studies not described • The list of excluded studies not found in Appendix A • Included studies not described in detail • Risk of bias in individual studies not discussed regarding the results of meta-analysis
Sciascia et al. 2017[28]	
• PICO components included in the research questions or study inclusion criteria • Study selection rationale described and explained • Reasons for study exclusion listed in the Results • Comprehensive search with Ovid MEDLINE and other sources • Potential studies in all languages screened • Study selection and data extraction in duplicate • Included studies described	• Protocol not established *a priori* • Critical appraisal of the included studies not mentioned • A list of excluded studies not provided • Funding sources of the included studies not mentioned • Meta-analysis not conducted • Risk of bias in individual studies not discussed regarding the results • Conflict of interest not declared

PICO = population, intervention, comparator, and outcome

Table 1: Strengths and Limitations of RCTs using the Cochrane Risk of Bias checklist[24]

Strengths	Limitations
Doria et al. 2018[21]	
• Double blinded study • Attrition reported in Figure 1 • Selective outcome reporting not likely	• Randomization method unclear • Allocation concealment not mentioned • Manufacturer-funded study
Zhang et al. 2018[1]	
• Randomization method reported • Allocation concealment described • Double blinded study • Attrition reported in Figure 1 • Selective outcome reporting not likely	• Manufacturer-funded study
Yamada et al. 2013[2]	
• Allocation concealment described • Single blinded study, but the target of blinding not described • Attrition reported in Table 1, no attrition • Selective outcome reporting not likely	• Randomization method unclear • Manufacturer-funded study
Stohl et al. 2017[22]	
• Randomization method reported • Double blinded study • Attrition reported in Figure 1 • Selective outcome reporting not likely	• Allocation concealment not described • Manufacturer-funded study

RCT = randomized controlled trial

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions
Oon et al. 2018[26]	

BLISS-52 and BLISS-76 trials, intravenous administration
• SRI-4 response rates :
  • Higher and modest with a dose effect in patients who received 10 mg/kg
• Week 76 response rates in BLISS-76:
  • Higher in belimumab-treated patients
  • 38.5% vs 32.4% for the 10 mg/kg, and 39.1% vs 32.4% for the 1 mg/kg dose
• Greater increase in complement, and decrease in anti dsDNA antibody levels, compared to placebo in BLISS-52 and -76 trials
• Steroid-sparing effect in the treatment arm (p 14)
 	
BLISS-SC trial, subcutaneous administration
• SRI-4 response rates:
• Favored belimumab at week 52 (61.4% vs 48.4% for placebo, p = 0.0006)
• Corticosteroid-sparing effect in patients receiving belimumab (p 14)
Tolerability and adverse events
• "Generally well tolerated, with mostly mild to moderate adverse events, and with serious adverse events occurring at similar rates between treatment and placebo groups."
• Depression:
  • "More frequently with belimumab treatment (6 to 7% vs 4% placebo) in the BLISS-76 trial, however no suicides or attempts occurred." (p 15)
Post-hoc analyses in SLE
• 14 post-hoc analyses:
  • 8 on intravenous belimumab (BLISS trials)
• Conclusion on belimumab:
  • Steroid-sparing effect
  • Efficacy for musculoskeletal, muco-cutaneous, immunological and haematological manifestations
  • Decreasing autoantibody
  • Raising complement levels
  • Improving QOL."
• LN outcomes
  • Original trials excluded severe active LN
  • "lower rates of renal flare, higher rates of renal remission and proteinuria reduction favoured belimumab"
• Subgroups better responding to belimumab
  • "Those with higher disease activity (SELENA-SLEDAI ≥ 10), low complement levels, positive anti-dsDNA Abs, or taking steroids at baseline"
• Steroid sparing effet:
  • Dosage decreased in 25 to 33% of patients (p 16)
	• "3 belimumab trials in SLE meeting their primary endpoints"
	• "a significant corticosteroid-sparing effect was also seen, and confirmed in our meta-analysis for belimumab IV and SC, tabalumab and epratuzumab, in the treatment of SLE" (p 17)

Table 6: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions
Ongoing and unpublished studies • "Further studies of belimumab; one in North-East Asia (NCT01345253), and a second specifically in LN (BLISS-LN, NCT01639339)" (p 16) • Note: NCT01345253 was published in Zhang et al.[1] Meta-anatysis of steroid-sparing effect, n = 3851 • "Belimumab, tabalumab and epratuzumab had a steroid-sparing effect, compared to placebo (pooled RR 1.36 (1.19 to 1.56), $I^2 = 0$, $P = 0.67$)" (p 17)	
Shamliyan et al. 2017[27]	
• Drugs identified: belimumab, rituximab, abatacept, other novel anti–B lymphocyte stimulator monoclonal antibodies, such as atacicept and blisibimod Rates of clinical response • Moderate evidence comparing adjunctive belimumab (1mg/kg) with immunosuppressive agents alone • Favoring belimumab regardless of baseline severity and seropositivity • Except for patients of Latin American, Asian, and Pacific Islander descent based on very low quality evidence. (p 1482) All-cause mortality and adverse effects • No differences between adjunctive belimumab (1 mg/kg) and immunosuppressive agents alone (p 1482) Dose-response effect of belimumab • Belimumab (10mg/kg) with similar effectiveness, compared with immunosuppressive agents alone (p 1482) • "Belimumab (10mg/kg) prevents flare and reduces the dose of prednisone but does not prevent worsening of the damage in specific organ systems" (p 1483) • Belimumab (10mg/kg) improved only the rates of auto-antibody normalization compared to belimumab (1 mg/kg) (p 1483) Patient susceptibility • Patients with more severe disease (baseline SELENA-SLEDAI score ≥10 and low complement levels) with a greater improvement in the lupus response index (p 1483) • "The larger dose of belimumab (10 mg/kg) compared with the lower dose improved only the rates of auto-antibody normalization" (p 1483)	• "adjunctive belimumab (10 mg/kg) increases the rates of clinical response" (moderate quality evidence) (p 1479) • "Belimumab and rituximab do not increase the risk of serious intolerable adverse effects leading to treatment discontinuation." (p 1479)' • "We concluded publication bias because only 58% of registered studies have been published." (p 1482)
Sciascia et al. 2017[28]	
Belimumab on renal parameters in SLE patients • "129 (55.1%) of the 234 patients with LN at baseline treated with belimumab between 2013 and 2016" • Improvement in renal parameters assessed either by SELENA-SLEDAI, SLEDAI-2K, BILAG, and/or SLAM indexes after belimumab treatment	• "Despite the limitations of the studies included in this analysis, available data are promising and provide preliminary support for targeting B lymphocyte stimulator to induce or maintain a renal response" (p 287)

Table 6: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions

• Higher percentage of renal remission (68.1% vs. 58.7%, Chi square value = 4.9814, p = 0.025) compared to placebo
• Shorter time to renal remission (median time 139,5 vs. 167 days) compared to placebo
• Insignificant changes in the rate of renal flare (1.95% vs. 3%, chi-square value = 1.8742, p = 0.17), compared to placebo
 	
Patient susceptibility
• Patients with baseline proteinuria > 0.2 g/24 h, (n=687)
  • A median reduction in proteinuria during the follow-up of 38% (range 0–100).
• Patients with proteinuria ≥ 1 g/24 h (n: 228)
  • 70.7% (n:157) achieved a renal remission after treatment (p 290)
 	
Belimumab in patients with biopsy proven active LN
• "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)" (p 290)	

BILAG = British Isles Lupus Assessment Group, LN = lupus nephritis, QOL = quality of life, RR = relative risk, SELENA-SLEDAI = Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index, SLE = systemic lupus erythematosus, SLEDAI = SLE Disease Activity Index

Table 7: Summary of Findings of RCTs

Main Study Findings	Author's Conclusions
Doria et al. 2018[21]	
SRI4 Responders: • 47.2% placebo; 64.4% belimumab • *P* = 0.0014 Severe SLE Flare Index Flare • 14.1% placebo; 31.5% belimumab Reduced corticosteroid use by 25% to ≤7.5 mg/day during Weeks 40 to 52: • 11.4% placebo; 20.7% belimumab • *P* = 0.0844 AEs: Similar between groups	• "In patients with hypocomplementemic/anti-dsDNA-positive SLE, weekly belimumab 200 mg SC significantly improved SRI4 response, decreased severe flare incidence, and reduced corticosteroid use, versus placebo • "greater benefit compared with the overall intent-to-treat population" • "AEs were consistent with the known safety profile of belimumab."
Zhang et al. 2018[1]	
Sample sizes • Intent-to-treat population: belimumab n=451, placebo n=226 SRI4 response rate • Higher with belimumab versus placebo at week 52: 53.8% vs 40.1%; OR: 1.99 (95% CI: 1.40, 2.82; *P*=0.0001) ≥4 point reduction in SELENA-SLEDAI and an SRI7 response • Significantly greater percentages for belimumab versus placebo Severe flare • A 50% lower risk than those receiving placebo (*P*=0.0004) Steroid sparing effect • Significant reduction in steroid use in patients with baseline prednisone dose >7.5 mg/day compared to placebo (*P*=0.0228)." Adverse effects • Similar incidences between groups (p 355)	• "In patients with SLE from North East Asia, belimumab significantly improved disease activity, while reducing prednisone use, with no new safety issues." (p 355)
Yamada et al. 2013[2]	
Clinical safety and tolerability • Belimumab (1 mg/kg and 10 mg/kg, n = 4 for both) favorable in Japanese patients with SLE, compared to placebo (n =4) Adverse effects • Incidence similar among the two belimumab groups and placebo group." Dose response • Single-dose belimumab approximately dose proportional • Long terminal elimination half-life (12.4–15.7 days), low clearance (3.55– 4.65 mL/day/kg), and small volume of distribution (76.2–80.1 mL/kg) consistent with a fully humanized antibody Inhibitor of B lymphocyte stimulator • Some evidence on the expected effects of belimumab on B cells (p 40)	• "The preliminary safety, pharmacokinetic profile, and observed biological activity of belimumab support further evaluation of its safety and efficacy in Japanese patient with SLE" (p 40)
Stohl et al. 2017[22]	
SRI4 responders • Belimumab better than placebo (61.4% versus 48.4%; OR	• "In patients with moderate-to-severe SLE, weekly SC doses of belimumab 200 mg plus standard SLE therapy

Table 7: Summary of Findings of RCTs

Main Study Findings	Author's Conclusions
1.68 95% CI 1.25–2.25; *P* = 0.0006) Time to and risk of severe flare • Belimumab better than placebo (median 171.0 days versus 118.0 days; hazard ratio 0.51 [95% CI 0.35–0.74]; *P* = 0.0004) Steroid sparing effect • More reduction of corticosteroid dosage compared to placebo • **Belimumab vs placebo:** ≥25% (to ≤7.5 mg/day) during weeks 40 to 52 (18.2% versus 11.9%; OR 1.65 [95% CI 0.95–2.84]; *P* = 0.0732) Adverse effects • Comparable incidence Serious adverse effects • Belimumab vs placebo: 10.8% VS 15.7% Worsening of IgG hypoglobulinemia by ≥2 grades • Belimumab vs placebo: 0.9% vs 1.4% (p 1016)	significantly improved their SRI4 response, decreased severe disease flares as compared with placebo, and had a safety profile similar to placebo plus standard SLE therapy." (p 1017)

AE = adverse effect, CI = confidence interval, OR = odds ratio, SC = subcutaneous, SELENA-SLEDAI = Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index, SRI = SLE Response Index; vs = versus

Appendix 5: Additional References of Potential Interest

Systematic reviews, meta-analyses, post hoc analyses or modeling studies with full overlap of included systematic reviews or with the 2012 CDR report

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