

Additional Improvements in Clinical Response From Adjuvant Biologic Response Modifiers in Adults With Moderate to Severe Systemic Lupus Erythematosus Despite Immunosuppressive Agents: A Systematic Review and Meta-Analysis

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ABSTRACT

Purpose: The role of biologic disease-modifying drugs in patients with systemic lupus erythematosus (SLE) remains controversial.

Methods: Following systematic review and meta-analysis protocol, we searched PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov in January 2017 to identify all studies of people with SLE treated with biologic response modifiers. We performed direct frequentist random effects meta-analyses, calculated pooled relative risk and number needed to treat to achieve an outcome in 1 patient (NNT) as reciprocal to statistically significant absolute risk difference, and graded the quality of evidence by using the Grading of Recommendations Assessment, Development, and Evaluation criteria.

Findings: Seven meta-analyses, 33 publications of randomized controlled trials (RCTs), and 5 observational studies met inclusion criteria. All studies enrolled previously treated adults with moderate to severe SLE despite conventional immunosuppression. In patients with extrarenal SLE, adjunctive belimumab (10 mg/kg) increases the rates of clinical response (moderate quality evidence from 2 RCTs, 1125 patients, NNT = 8 [95% CI, 6–16]), whereas adjunctive rituximab or abatacept are ineffective. In adults with lupus nephritis, adjunctive rituximab (4000 mg, very-low-quality evidence from 1 RCT, 144 patients, NNT = 5 [95% CI, 3–18]), but not abatacept, improves renal function. Belimumab and rituximab do not increase the risk of serious intolerable adverse effects leading to treatment discontinuation. Rigerimod, blisibimod, sifalimumab, and anifrolumab show promising results in early RCTs,

whereas epratuzumab and tabalumab have an unfavorable benefit-to-harm balance.

Implications: In adults with moderate to severe SLE despite conventional immunosuppressive agents, adjunctive belimumab in extrarenal SLE and off-label rituximab in lupus nephritis may offer additional modest benefits. (*Clin Ther.* 2017;■:■■■–■■■) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: systemic lupus erythematosus, belimumab, rituximab, abatacept, rigerimod, blisibimod.

INTRODUCTION

The prevalence of systemic lupus erythematosus (SLE) has increased over the past decade, with a significant burden on individual quality of life, disability, and treatment utilization.^{1,2}

Despite available standard treatment options that include NSAIDs, corticosteroids, antimalarial agents, and additional immunosuppressive agents (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil), patients with SLE have a high risk of mortality, end-stage renal disease, and frequent disease flares.^{3–5} Novel treatments with biologic response modifiers target key cells in immune dysregulation and show great potential in helping patients who experience moderate to severe active SLE despite conventional care.⁶

Accepted for publication May 30, 2017.

<http://dx.doi.org/10.1016/j.clinthera.2017.05.359>
0149-2918/\$ - see front matter

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However, the effectiveness and safety of biologic response modifiers in individuals with SLE are relatively unknown. The evidence regarding all available biologic response modifiers has not been systematically appraised and included in recommendations of clinical guidelines. In fact, the National Guideline Clearinghouse does not include any recent guidelines that meet the Institute of Medicine criteria for trustworthy guidelines.⁷ A systematic literature review and critical appraisal of 9 clinical practice guidelines and 5 consensus statements concluded a lack of high-quality, evidence-based recommendations.⁸

We conducted a systematic literature review, meta-analyses, and critical appraisal of all available evidence regarding the benefits and harms of biologic response modifiers in adults with SLE.

MATERIALS AND METHODS

A protocol ([Supplemental Appendix I](http://dx.doi.org/10.1016/j.clinthera.2017.05.359) in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>) was developed for a systematic literature review following recommendations from the Cochrane Collaboration and the Agency for Healthcare Research and Quality.^{9,10}

The objective of the present study was to examine patient-centered benefits and harms after treatment with biologic response modifiers compared with placebo, usual care without biological response modifiers, and with each other in patients with SLE. We tested the null hypotheses of no differences in patient benefits and harms after active interventions versus control interventions.

We refined the clinical questions and defined the target population as patients with SLE according to classification criteria from the American College of Rheumatology regardless of age or previous treatment status.^{8,11,12} Interventions eligible for this review investigated the role of biologic response modifiers such as tumor necrosis factor- α inhibitors, interleukin inhibitors, and targeted monoclonal antibodies and novel biologic agents, compared with conventional immunosuppressive agents (eg, prednisone, hydroxychloroquine, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) ([Supplemental Appendix A](http://dx.doi.org/10.1016/j.clinthera.2017.05.359) in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>). We used definitions of previous treatment response and treatment failure

after conventional immunosuppressive agents as defined in the studies.

A comprehensive search in PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov was conducted in April 2015, May 2016, and January 2017 to find published and unpublished meta-analyses, randomized controlled trials (RCTs), and population-based, controlled observational studies that used sampling within national registries or databases and reported adjusted effect estimates (strings are available in [Supplemental Appendix B](http://dx.doi.org/10.1016/j.clinthera.2017.05.359) in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>).^{13,14} RCTs were excluded that enrolled <75% of patients with SLE, examined comparative effectiveness of conventional treatment options, or reported intermediate pharmacokinetic outcomes. We also excluded uncontrolled case series or uncontrolled clinical trials and meeting abstracts presenting the results of RCTs that have been published in peer-reviewed journals or have results in ClinicalTrials.gov.

Both of the authors and the medical librarians determined the studies' eligibility, and disagreements were resolved by consensus. All citations found during the searches are stored in a reference database.

An external contractor (DOC Data Software Platform v2.0 [Doctor Evidence LLC, Santa Monica, California]) performed dual abstraction and quality control of the data ([Supplemental Appendix C](http://dx.doi.org/10.1016/j.clinthera.2017.05.359) in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>). We performed direct frequentist meta-analyses by using random effects models of hypotheses with the similar definitions of the active and control intervention and patient outcomes, as well as similar follow-up time.¹⁵ Both authors decided if patient and treatment characteristics, time of follow-up, and outcomes definitions were deemed similar for meta-analyses.

The Agency for Healthcare Research and Quality-recommended methodologic approach was used in the integration of existing systematic reviews into our comprehensive synthesis of evidence.¹⁶ The study goal was the integration of previously published high-quality reviews and consistent ranking of the quality of evidence by using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods. When analyzing the evidence from RCTs, de novo meta-analyses were conducted by using random effects models for relative risk and absolute risk

differences.⁹ To avoid redundancy in the analyses, we did not combine in the models pooled estimates from published meta-analyses with the data from primary studies. When analyzing the evidence from observational studies, pooled estimates from published systematic reviews and adjusted estimates from individual studies were used.

The rates of the outcomes after active and control interventions were abstracted; for each hypothesis, relative risks and absolute risk differences were calculated based on data from the published RCTs, using STATA software (StataCorp LP, College Station, Texas).⁹ Statistical significance was evaluated at a 95% confidence level. When the absolute risk difference was statistically significant, we calculated number needed to achieve an outcome in 1 patient as 1/absolute risk difference; we calculated attributable events per 1000 treated as the absolute rate difference multiplied by 1000.

A random effects model was used to incorporate inevitable differences across trials in patient populations, baseline rates of outcomes, drug dosage, and other factors.¹⁵ Consistency in results was examined across studies with χ^2 tests and I^2 statistics, and we concluded statistically significant heterogeneity if I^2 was $>50\%$.⁹ Statistically significant heterogeneity did not preclude statistical pooling. However, we planned exploring heterogeneity with a priori-defined patient demographic characteristics, baseline risk for cardiovascular morbidity and mortality, exact drug doses, and study quality if this information was available in the studies.

Consensus method guidelines for systematic review and meta-analyses were used that do not recommend conducting post hoc analyses of statistical power.^{17–20} Instead, we downgraded our confidence in true treatment effects based on calculated optimal information size as the number of patients required for an adequately powered individual trial.²¹ Because power is more closely related to number of events than to sample size, imprecision in treatment effects was concluded if <250 patients experienced the event.²¹

The quality of systematic reviews was evaluated by using the Assessment of Multiple Systematic Reviews.²² For primary RCTs, the Cochrane risk-of-bias tool on a 3-point scale was used: high bias, low bias, and unclear.^{23,24} A low risk of bias was assumed when RCTs met all the risk-of-bias criteria, a medium

risk of bias if at least 1 of the risk-of-bias criteria is not met, and a high risk of bias if ≥ 2 risk-of-bias criteria are not met. An unknown risk of bias was assigned for the studies with poorly reported risk-of-bias criteria. A high risk of bias was assigned to all observational studies, and the New Castle scale was used for the evaluation.

A high quality of evidence was assigned to well-designed RCTs (low risk of bias in the Cochrane tool) with consistent findings ($I^2 < 50\%$). The quality of evidence was downgraded to moderate if at least 1 of 4 quality of evidence criteria was not met; for example, moderate quality of evidence was assigned if there was a high risk of bias in the body of evidence or if the results were not consistent or precise. The quality of evidence was downgraded to low if ≥ 2 criteria were not met. We concluded a high risk of bias in the body of evidence if at least 1 RCT had high risk of bias. The body of evidence was downgraded when we suspected high risk of publication bias due to unavailability of the results in ClinicalTrials.gov or journal articles.

A low quality of evidence was assigned to non-randomized studies, and the rating was upgraded if there was a strong or dose-response association.²⁵ Evidence was defined as insufficient when no studies provided treatment effects. This approach was applied regardless of whether the results were statistically significant.

The quality of evidence ratings were assigned as high, moderate, low, or very low, according to risk of bias in the body of evidence, directness of comparisons, precision and consistency in treatment effects, and the evidence of reporting bias, by using GRADE methods (Supplemental Appendix A in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>).²⁶

RESULTS

A total of 775 references were identified, and 43 references were included in this review (Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram in Supplemental Appendix A in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>). The small eligibility rate (6%) from our searches in PubMed, EMBASE, and the Cochrane Library is typical in methodologically rigorous systematic reviews.²⁷ We included individual patient data meta-analyses and meta-analyses of aggregate

data when outcome rates or mean values are reported in treatment groups, primary RCTs, and observational studies.^{28–68}

The list of excluded studies is available in **Supplemental Appendix A** in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>. Eligible studies examined rituximab, abatacept, atacicept, blisibimod, belimumab, epratuzumab, rontalizumab, ocrelizumab, tabalumab, rigerimod, sifalimumab, and anifrolumab. The evidence regarding other biologic response modifiers is insufficient.

All studies enrolled adults with SLE diagnosed according to the American College of Rheumatology classification criteria (**Supplemental Appendix A** in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>). Women constituted >80% of enrollees (**Supplemental Appendix C** in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>).

No studies enrolled pediatric patients with SLE. No studies enrolled treatment-naïve patients with SLE. Primary studies enrolled adults with moderate to severe SLE despite use of corticosteroids, antimalarial agents (hydroxychloroquine), and additional immunosuppressive agents such as mycophenolate mofetil, azathioprine, cyclophosphamide, and cyclosporine.^{44–46,48–54,56–58,61,65–67,69,70} Primary studies consistently defined moderate to severe active SLE as demonstrated by the Safety of Estrogens in Lupus Erythematosus National Assessment– Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score ≥ 6 and the British Isles Lupus Assessment Group A or B category. Lupus nephritis was diagnosed based on renal biopsy results and proteinuria.^{41–43,59,62}

Precise reporting of previous treatments was inconsistent across studies but practically all RCTs required stable doses of background treatments, including corticosteroids, antimalarial agents (hydroxychloroquine), and additional immunosuppressive agents. All enrolled subjects had to be naïve to the examined drugs and had to stop taking other biologic response modifiers at least 1 month before the enrollment. No single RCT reported previous treatments with biologic response modifiers or patient response to such drugs. Poor reporting of comorbidities and concomitant treatment did not allow inclusion of this information in the meta-analyses. However, reported diagnostic criteria for moderate to severe SLE despite previous conventional treatments were deemed similar for meta-analyses.

All RCTs were sponsored by industry. We concluded that there was a low risk of selection bias in 29% of RCTs and unclear risk of selection bias in 68% of RCTs because investigators did not provide complete information to judge the adequacy of allocation concealment (**Supplemental Appendix C** in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>). The majority of RCTs were double-blinded, although authors did not provide details about procedures to ensure and evaluate masked status of interventions. We concluded publication bias because only 58% of registered studies have been published.

Belimumab

Belimumab, an anti-B-lymphocyte stimulator monoclonal antibody, is indicated for the treatment of adult patients with active, autoantibody-positive, extrarenal SLE who are receiving standard therapy. We identified individual patient data meta-analyses^{28,29,31–34} and published and unpublished results from RCTs with extensions that examined the benefits and harms of off-label belimumab in adults with SLE who have already been treated with standard of care immunosuppressive agents.^{37–39,44,48–50,61} Trials enrolled adults with moderate to severe SLE who have had an inadequate response to standard of care immunosuppressive agents, excluding patients with active lupus nephritis.

Moderate evidence suggests that adjunctive belimumab (1 mg/kg) increases the rates of clinical response compared with immunosuppressive agents alone, regardless of baseline severity and seropositivity (**Table I**).^{29,31–34,61} However, patients of Latin American, Asian, and Pacific Islander descent do not experience an equally positive clinical response after adjunctive belimumab (very low quality of evidence from subgroup analyses of RCTs) (**Table I**; **Supplemental Appendix D Table I** in the online version at <http://dx.doi.org/10.16/j.clinthera.2017.05.359>). Adjunctive belimumab (1 mg/kg) prevents flares and reduces the dose of prednisone but does not prevent worsening of damage in specific organ systems. There are no differences in all-cause mortality and adverse effects between adjunctive belimumab (1 mg/kg) and immunosuppressive agents alone.

A higher dose of adjunctive belimumab (10 mg/kg) has a very similar effect, increasing the rates of clinical response compared with immunosuppressive agents

Table I. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary of findings: Immunosuppressive agents plus adjunctive belimumab versus immunosuppressive agents alone in adults with moderate to severe extrarenal* systemic lupus erythematosus (SLE) who have had an inadequate response to immunosuppressive agents. The study setting was outpatient; the intervention comprised prednisone alone or combined with antimalarial drugs, NSAIDs, and/or immunosuppressive therapies plus adjunctive belimumab (1 mg/kg IV on days 0, 14, and 28; then every 28 days for 48 weeks); and the comparator was prednisone alone or combined with antimalarial drugs, NSAIDs, and/or immunosuppressive therapies.

Outcomes	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
All-cause mortality, 52–76 weeks	7	4	RR, 1.7 (0.4–7.0)	1348 (3 RCTs) ^{33,48–50,61}	Low	No difference
All-cause mortality, 52–76 weeks Subgroup: low complement/anti-dsDNA-positive	7	3	RR, 2.0 (0.2–22.2)	571 (2 RCTs) ^{32,49,50,61}	Low	No difference
SRI response,* 52 weeks	460	390 Attributable events per 1000 treated, 70 (12; 128)	RR, 1.2 (1.03–1.4) NNT, 14 (8–81)	1121 (2 RCTs) ^{31,49,50,61}	Moderate	Favors belimumab
SRI response,* 52 weeks Subgroup: low complement/anti-dsDNA-positive	415	317 Attributable events per 1000 treated, 98 (20; 177)	RR, 1.3 (1.1–1.6) NNT, 10 (6–51)	571 (2 RCTs) ^{32,49,50,61}	Low	Favors belimumab
4-point or greater reduction in SELENA-SLEDAI score at week 52	481	407 Attributable events per 1000 treated, 74 (16; 132)	RR, 1.2 (1.04–1.3) NNT, 14 (8–64)	1121 (2 RCTs) ^{29,44,61}	Moderate	Favors belimumab
SF-36 response that health is “better” or “much better,” 48 weeks	560	470 Attributable events per 1000 treated, 90 (32; 148)	RR, 1.2 (1.1–1.3) NNT, 11 (7–31)	1121 (2 RCTs) ^{31,49,50,61}	Moderate	Favors belimumab

(continued)

Table I. (continued).

Outcomes	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
FACIT-Fatigue score improvement from baseline at week 52	NR	NR	MD, 2.94 (0.83–5.05) SMD, 0.23 (0.06–0.39)	571 (2 RCTs) ^{32,49,50,61}	Moderate	Favors belimumab
Subgroup: low complement/anti-dsDNA-positive						
SLE severity: no. of subjects with improvement/good result, 52 weeks	618	364 Attributable events per 1000 treated, 254 (22; 486)	RR, 1.7 (1.01–2.9) NNT, 4 (2–45)	67 (1 RCT) ⁶¹	Very low	Favors belimumab
Subgroup: Eastern Europe						
Normalization of anti-dsDNA, 52 weeks	150	68 Attributable events per 1000 treated, 82 (33; 131)	RR, 2.2 (1.3–3.7) NNT, 12 (8–31)	594 (2 RCTs) ^{34,44,61}	Low	Favors belimumab
Severe lupus flare over 52 weeks	204	296	RR, 0.7 (0.5–0.9)	571 (2 RCTs) ^{32,49,50,61}	Low	Favors belimumab
Subgroup: low complement/anti-dsDNA-positive		Attributable avoided events per 1000 treated, 92 (21; 163)	NNTp, 11 (6–47)			
Prednisone reduction by ≥ 25% from baseline to ≤ 7.5 mg/d during weeks 40–52	229	121	RR, 1.9 (1.3–2.7)	571 (2 RCTs) ^{32,49,50,61}	Low	Favors belimumab
Subgroup: low complement/anti-dsDNA-positive		Attributable events per 1000 treated, 107 (45; 169)	NNT, 9 (6–22)			

(continued)

Table I. (continued).

Outcomes	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
BILAG worsening: hematologic, 52 weeks Subgroup: baseline BILAG <9 (no A domain score)	56	91 Attributable avoided events per 1000 treated, 35 (5; 66)	RR, 0.6 (0.4–0.9) NNTp, 28 (15–209)	1118 (2 RCTs) ^{29,44,61}	Low	Favors belimumab
SELENA-SLEDAI worsening: renal, 53 weeks Subgroup: baseline BILAG <9 (no A domain score)	47	85 Attributable avoided events per 1000 treated, 38 (7; 70)	RR, 0.6 (0.3–0.9) NNTp, 26 (14–153)	939 (2 RCTs) ^{29,44,61}	Low	Favors belimumab
Treatment discontinuation due to adverse effects, 52–76 weeks	62	70	RR, 0.9 (0.6–1.3)	1348 (3 RCTs) ^{33,48–50,61}	Low	No difference
≥ 1 serious adverse effect, 52–76 weeks	195	166	RR, 1.2 (0.9–1.5)	1348 (3 RCTs) ^{33,48–50,61}	Low	No difference
≥ 1 severe adverse effect, 52–76 weeks	159	159	RR, 1.003 (0.78–1.28)	1348 (3 RCTs) ^{33,48–50,61}	Low	No difference

Population: Adults with moderate to severe extrarenal* SLE who have had an inadequate response to immunosuppressive agents

Setting: Outpatient

Intervention: Prednisone alone or combined with antimalarial drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or immunosuppressive therapies plus adjunctive belimumab (1 mg/kg intravenously on days 0, 14, and 28; then every 28 days for 48 weeks)

Comparator: Prednisone alone or combined with antimalarial drugs, NSAIDs, and/or immunosuppressive therapies.

BILAG = British Isles Lupus Assessment Group; dsDNA = double-stranded DNA; FACIT = Functional Assessment of Chronic Illness Therapy; MD = mean difference; NNT = number needed to treat; NNTp = number needed to treat to prevent 1 event; NR = not reported; RCT = randomized controlled trial; RR = relative risk; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index; SF-36 = 36-Item Short Form Survey; SMD = standardized mean difference; SRI = SLE Responder Index.

*Extrarenal manifestations: vasculitis, hematologic, mucocutaneous, neurologic, musculoskeletal, cardiovascular, and respiratory.

Table II. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary of findings: Immunosuppressive agents plus adjunctive belimumab versus immunosuppressive agents alone in adults with moderate to severe extrarenal* systemic lupus erythematosus (SLE) who have had an inadequate response to immunosuppressive agents. The study setting was outpatient; the intervention comprised prednisone alone or combined with antimalarial drugs, NSAIDs, and/or immunosuppressive therapies plus adjunctive belimumab (10 mg/kg IV on days 0, 14, and 28; then every 28 days for 48 weeks); and the comparator was prednisone alone or combined with antimalarial drugs, NSAIDs, and/or immunosuppressive therapies.

Outcomes	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
All-cause mortality, 52–80 weeks	0	1	RR, 0.3 (0.0–8.1)	1349 (3 RCTs) ^{48–50}	Low	No difference
All-cause mortality, 52–76 weeks	10	3	RR, 2.8 (0.3–27.0)	592 (2 RCTs) ^{32,49,50,61}	Low	No difference
Subgroup: low complement/anti-dsDNA-positive						
SELENA-SLEDAI score, reduction, ≥ 4 , 52 weeks	526	408 Attributable events per 1000 treated, 118 (60; 175)	RR, 1.3 (1.1–1.5) NNT, 8 (6–17)	1125 (2 RCTs) ^{49,61}	Moderate	Favors belimumab
SRI response,* 52 weeks	510	390 Attributable events per 1000 treated, 120 (62; 178)	RR, 1.3 (1.1–1.5) NNT, 8 (6–16)	1125 (2 RCTs) ^{31,49,50,61}	Moderate	Favors belimumab
SRI response,* 52 weeks	515	317 Attributable events per 1000 treated, 198 (120; 275)	RR, 1.6 (1.3–2.0) NNT, 5 (4–8)	592 (2 RCTs) ^{32,49,50,61}	Low	Favors belimumab
Subgroup: low complement/anti-dsDNA-positive						
SELENA-SLEDAI renal, 52 weeks	632	278	RR, 2.27 (1.001–5.164)	37 (2 RCTs) ^{34,44,61}	Low	Favors belimumab

(continued)

Table II. (continued).

Outcomes	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
Subgroup: mycophenolate mofetil at baseline		Attributable events per 1000 treated, 354 (54; 654)	NNT, 3 (2–19)			
SF-36 response that health is “better” or “much better,” 48 weeks	550	470 Attributable events per 1000 treated, 81 (23; 139)	RR, 1.17 (1.04–1.32) NNT, 12 (7–44)	1125 (2 RCTs) ^{31,49,50,61}	Moderate	Favors belimumab
Average prednisone dose has been reduced by ≥25% from baseline to ≤7.5 mg/d during weeks 40–52	210	142	RR, 1.5 (1.1–2.1)	728 (3 RCTs) ^{48,49}	Low	Favors belimumab
Prednisone reduction by ≥25% from baseline to ≤7.5 mg/d during weeks 40–52	185	121	RR, 1.51 (1.02–2.22)	592 (2 RCTs) ^{32,49,50,61}	Low	Favors belimumab
Subgroup: low complement/anti-dsDNA-positive		Attributable events per 1000 treated, 62 (4; 119)	NNT, 16 (8–248)			
Anti-dsDNA, positive to negative, 76 weeks	84	40 Attributable events per 1000 treated, 44 (4; 85)	RR, 2.1 (1.05–4.24) NNT, 23 (12–252)	548 (1 RCT) ⁴⁴	Very low	Favors belimumab

(continued)

Table II. (continued).

Outcomes	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
Normalization of anti-dsDNA, 52 weeks	160	68 Attributable events per 1000 treated, 92 (42; 142)	RR, 2.4 (1.4–3.9) NNT, 11 (7–24)	593 (2 RCTs) ^{34,44,61}	Low	Favors belimumab
Normalization of low C3 (<90 mg/dL), 76 weeks	513	186 Attributable events per 1000 treated, 327 (184; 471)	RR, 2.8 (1.6–4.7) NNT, 3 (2–5)	148 (1 RCT) ⁴⁴	Very low	Favors belimumab
Normalization of low C4 (<16 mg/dL), 76 weeks	510	183 Attributable events per 1000 treated, 327 (202; 452)	RR, 2.8 (1.7–4.5) NNT, 3 (2–5)	195 (1 RCT) ⁴⁴	Very low	Favors belimumab
SLE severity: no. of subjects with improvement/good result, 52 weeks Subgroup: Eastern Europe	742	364 Attributable events per 1000 treated, 378 (153; 603)	RR, 2.0 (1.2–3.4) NNT, 3 (2–7)	64 (1 RCT) ⁶¹	Very low	Favors belimumab
Severe flare over 52 weeks Subgroup: low complement/anti-dsDNA-positive	190	296 Attributable avoided events per 1000 treated, 106 (37; 175)	RR, 0.6 (0.5–0.9) NNTp, 9 (3–27)	592 (2 RCTs) ^{32,49,50,61}	Low	Favors belimumab

(continued)

Table II. (continued).

Outcomes	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
SELENA-SLEDAI worsening: immunologic, 52 weeks	74	187	RR, 0.4 (0.2–0.8)	231 (2 RCTs) ^{29,44,61}	Low	Favors belimumab
Subgroup: baseline BILAG <9 (no A domain score)		Attributable avoided events per 1000 treated, 113 (28; 198)	NNTp, 9 (5–36)			
SELENA-SLEDAI worsening: hematologic, 52 weeks	33	65	RR, 0.5 (0.3–0.9)	1043 (2 RCTs) ^{29,44,61}	Low	Favors belimumab
Subgroup: baseline BILAG <9 (no A domain score)		Attributable avoided events per 1000 treated, 33 (6; 59)	NNTp, 31 (14–156)			
≥ 1 serious adverse effect, 52–76 weeks	180	166	RR, 1.1 (0.9–1.4)	1349 (3 RCTs) ^{33,48–50,61}	Low	No difference
≥ 1 severe adverse effect, 52–76 weeks	154	159	RR, 1.0 (0.8–1.2)	1349 (3 RCTs) ^{33,48–50,61}	Low	No difference

Population: Adults with moderate to severe extrarenal* SLE who have had an inadequate response to immunosuppressive agents

Setting: Outpatient

Intervention: Prednisone alone or combined with antimalarial drugs, NSAIDs, and/or immunosuppressive therapies plus adjunctive belimumab (10 mg/kg intravenously on days 0, 14, and 28; then every 28 days for 48 weeks)

Comparator: Prednisone alone or combined with antimalarial drugs, NSAIDs, and/or immunosuppressive therapies.

BILAG = British Isles Lupus Assessment Group; dsDNA = double-stranded DNA; NNT = number needed to treat; NNTp = number needed to treat to prevent 1 event; RCT = randomized controlled trial; RR = relative risk; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index; SF-36 = 36-Item Short Form Survey; SRI = SLE Responder Index.

*Extrarenal manifestations: vasculitis, hematologic, mucocutaneous, neurologic, musculoskeletal, cardiovascular, and respiratory.

alone regardless of baseline severity and seropositivity (Table II).^{29,31–34,44,48–50,61} However, patients with more severe disease (baseline SELENA-SLEDAI score ≥ 10 and low complement levels) experience a greater improvement in the lupus response index after belimumab.³² In addition, post hoc analysis of RCTs suggests that patients with baseline renal involvement and higher serologic activity have greater renal organ disease improvement with belimumab.³⁴

Adjunctive belimumab (10 mg/kg) prevents flare and reduces the dose of prednisone but does not prevent worsening of the damage in specific organ systems (Table II; Supplemental Appendix D Table II in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>). The larger dose of belimumab (10 mg/kg) compared with the lower dose improved only 1 outcome, the rates of autoantibody normalization (data not shown).

Rituximab

Rituximab is a chimeric monoclonal antibody against protein CD20⁺ in B cells currently approved for treating adult lymphomas and rheumatoid arthritis.⁷¹ We identified published and unpublished results from 3 RCTs that examined benefits and harms from off-label rituximab in adults with moderate to severe SLE with and without lupus nephritis and an inadequate response to immunosuppressive agents.^{42,55,57,62}

In adults with moderate to severe extrarenal SLE and an inadequate response to immunosuppressive agents, very-low-quality evidence suggests that there is no difference in all-cause mortality, clinical response, or harms between immunosuppressive agents plus adjunctive rituximab versus immunosuppressive agents alone (Table III).^{55,57}

In adults with severe SLE and lupus nephritis who have had an inadequate response to immunosuppressive agents, low-quality evidence suggests that adjunctive rituximab increases the rates of partial but not complete renal response compared with immunosuppressive agents alone (Table IV, Figure 1).⁶² Very-low-quality evidence suggests that there are no differences in adverse effects between immunosuppressive agents plus adjunctive rituximab and immunosuppressive agents alone. Patient ethnicity does not modify the effects of rituximab (very-low-quality evidence from subgroup analysis of a single RCT).

Abatacept

Abatacept is a selective T-cell co-stimulation modulator indicated for treating adult rheumatoid arthritis that may benefit patients with SLE.^{72,73} We identified published and unpublished results from 3 RCTs that examined the benefits and harms of off-label adjunctive abatacept in adults with moderate to severe SLE and with or without lupus nephritis who have had an inadequate response to immunosuppressive medicines.^{41,43,56}

In adults with moderate to severe extrarenal SLE and an inadequate response to immunosuppressive agents, very-low-quality evidence suggests that there is no difference in all-cause mortality, clinical response, or adverse effects leading to treatment discontinuation between immunosuppressive agents plus adjunctive abatacept versus immunosuppressive agents alone (Table V).⁵⁶ Adjunctive abatacept improves physical health and slightly reduces fatigue, at the expense of an increased risk of serious adverse effects.

In adults with moderate to severe SLE and lupus nephritis despite immunosuppressive medicines, low-quality evidence suggests that there are no differences in any measured benefits or harms between immunosuppressive agents plus adjunctive abatacept and immunosuppressive agents alone (Table VI). Patient ethnicity does not modify abatacept effects (data not shown).^{41,43} Post hoc subgroup analysis suggests that patients with baseline nephrotic-range proteinuria experienced greater reductions in the mean urinary protein-to-creatinine ratio after treatment with abatacept versus placebo.⁴³

Novel Anti-B-Lymphocyte Stimulator Monoclonal Antibodies Atacicept and Blisibimod

The novel anti-B-lymphocyte stimulator monoclonal antibodies atacicept and blisibimod show some promise in the treatment of adult autoimmune diseases, including SLE.^{3,74} We identified published and unpublished results from 2 RCTs that examined the benefits and harms of off-label atacicept and blisibimod in adults with SLE already treated with immunosuppressive agents.^{46,47,51}

In adults without active disease taking stable doses of immunosuppressive agents, very-low-quality evidence suggests that prednisone and adjunctive atacicept (150 mg) prevent flares compared with prednisone alone (Supplemental Appendix D Table III in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>).

Table III. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary of findings: Comparative effectiveness of immunosuppressive agents plus off-label adjunctive rituximab in adults with moderate to severe extrarenal* systemic lupus erythematosus who have had an inadequate response to immunosuppressive agents. The study setting was outpatient; the intervention comprised immunosuppressive agents (prednisone and either azathioprine [100–250 mg/d], mycophenolate mofetil [1–4 g/d], or methotrexate [7.5–27.5 mg/week]) plus off-label adjunctive rituximab (1000 mg twice 14 days apart); and the comparator was immunosuppressive agents (prednisone and either azathioprine [100–250 mg/d], mycophenolate mofetil [1–4 g/d], or methotrexate [7.5–27.5 mg/week]).

Outcomes at 52 weeks	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
All-cause mortality	24	11	RR, 2.1 (0.2–18.4)	257 (1 RCT) ⁵⁷	Very low	No difference
Overall response rate (major or partial response)	296	284	RR, 1.0 (0.7–1.6)	257 (1 RCT) ⁵⁷	Very low	No difference
Overall response rate (major or partial response)	269	357	RR, 0.8 (0.5–1.2)	193 (1 RCT) ⁵⁷	Very low	No difference
Subgroup: non-African-American/Hispanic subjects						
Overall response rate (partial or complete response)	338	157	RR 2.0 (0.8–5.5)	65 (1 RCT) ⁵⁷	Very low	No difference
Subgroup: African-American/Hispanic subjects						
Major clinical response [†]	124	159	RR, 0.8 (0.4–1.5)	257 (1 RCT) ⁵⁷	Very low	No difference
Major clinical response [†]	138	94	RR, 1.8 (0.4–8.0)	65 (1 RCT) ⁵⁷	Very low	No difference
Subgroup: African-American/Hispanic subjects						
Major clinical response [†]	115	196	RR, 0.6 (0.3–1.1)	193 (1 RCT) ⁵⁷	Very low	No difference
Subgroup: Non-African-American/Hispanic subjects						
Partial clinical response [‡]	172	125	RR, 1.4 (0.7–2.6)	257 (1 RCT) ⁵⁷	Very low	No difference
Partial clinical response [‡]	154	161	RR, 1.0 (0.5–2.0)	193 (1 RCT) ⁵⁷	Very low	No difference
Subgroup: non-African-American/Hispanic subjects						
Partial clinical response [‡]	200	63	RR, 2.5 (0.6–10.8)	65 (1 RCT) ⁵⁷	Very low	No difference

(continued)

Table III. (continued).

Outcomes at 52 weeks	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
Subgroup: African-American/Hispanic subjects						
Low disease activity [§]	751	659	RR, 1.14 (0.96–1.36)	257 (1 RCT) ⁵⁵	Very low	No difference
Low disease activity without subsequent flare [§]	497	352	RR, 1.41 (1.02–1.95) NNT, 7 (4–51)	257 (1 RCT) ⁵⁵	Very low	Favors rituximab
		Attributable events per 1000 treated, 145 (20; 270)				
Total adverse events leading to treatment discontinuation	112	148	RR, 0.8 (0.4–1.5)	257 (1 RCT) ⁵⁷	Very low	No difference
Bacteremia or fungemia or sepsis or viremia	12	34	RR, 0.3 (0.1–2.0)	257 (1 RCT) ⁵⁷	Very low	No difference
Bacterial infection, serious	24	45	RR, 0.5 (0.1–2.0)	257 (1 RCT) ⁵⁷	Very low	No difference

Population: Adults with moderate to severe extrarenal* SLE who have had an inadequate response to immunosuppressive agents

Setting: Outpatient

Intervention: Immunosuppressive agents (prednisone and either azathioprine [100–250 mg/day], mycophenolate mofetil [1–4 g/day], or methotrexate [7.5–27.5 mg/week]) plus off-label adjunctive rituximab (1000 mg twice 14 days apart)

Comparator: Immunosuppressive agents (prednisone and either azathioprine [100–250 mg/day], mycophenolate mofetil [1–4 g/day], or methotrexate [7.5–27.5 mg/week]).

NNT = number needed to treat; RCT = randomized controlled trial; RR = relative risk.

*Extrarenal manifestations: vasculitis, hematologic, mucocutaneous, neurologic, musculoskeletal, cardiovascular, and respiratory.

†Major clinical response was defined as achieving British Isles Lupus Assessment Group (BILAG) C scores or better (score ≤ 1) in all organ systems at week 24 and maintaining this response without a flare to week 52.

‡Partial response was defined as follows: (1) achieving total BILAG C scores or better (score ≤ 1) at week 24 and maintaining this response for 16 consecutive weeks; (2) achieving no more than 1 organ with a BILAG B score (score = 3) at week 24 without worsening remaining organs to week 52; or (3) achieving a maximum of 2 BILAG B scores (score = 3) at week 24 without developing BILAG A or B scores in new domains until week 52.

§Low disease activity was defined as achievement of BILAG C or better (score ≤ 1), without subsequent occurrence of ≥ 1 domain with BILAG A score (score = 9).

Table IV. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary of findings: Comparative effectiveness of immunosuppressive agents plus off-label adjunctive rituximab in adults with severe systemic lupus erythematosus and lupus nephritis who have had an inadequate response to immunosuppressive agents. The study setting was outpatient; the intervention comprised immunosuppressive agents (mycophenolate mofetil 1–3 g/d), prednisone plus off-label adjunctive rituximab 1000 mg, 4 injections, days 1, 15, 168, and 182; and the comparator was immunosuppressive agents (mycophenolate mofetil 1–3 g/d) and prednisone.

Outcomes	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality GRADE)	Comments
All-cause mortality, 52–78 weeks	24	0	RR, 4.9 (0.2–99.6)	163 (2 RCTs) ^{42,62}	Low	No difference
Overall response, 52 weeks	569	458	RR, 1.2 (0.9–1.7)	144 (1 RCT) ⁶²	Very low	No difference
Overall response, 78 weeks	556	444	RR, 1.3 (0.9–1.7)	144 (1 RCT) ⁶²	Very low	No difference
Overall response, 52 weeks	700	450	RR, 1.6 (0.9–2.7)	40 (1 RCT) ⁶²	Very low	No difference
Subgroup: African-American subjects						
Overall response, 78 weeks	600	350	RR 1.7 (0.9–3.4)	40 (1 RCT) ⁶²	Very low	No difference
Subgroup: African-American subjects						
Overall response, 52 weeks	552	478	RR, 1.2 (0.7–2.0)	52 (1 RCT) ⁶²	Very low	No difference
Subgroup: Hispanic patients						
Overall response, 78 weeks	448	435	RR, 1.0 (0.6–1.9)	52 (1 RCT) ⁶²	Very low	No difference
Subgroup: Hispanic patients						
Complete renal response, [*] 52 weeks	264	306	RR, 0.9 (0.5–1.5)	144 (1 RCT) ⁶²	Very low	No difference
No renal response, 52 weeks	431	542	RR, 0.8 (0.6–1.1)	144 (1 RCT) ⁶²	Very low	No difference
Partial renal response, [†] 52 weeks	306	153	RR, 2.00 (1.05–3.82)	144 (1 RCT) ⁶²	Very low	Favors rituximab
		Attributable events per 1000 treated, 153 (18; 288)	NNT, 7 (3–56)			
BILAG renal domain improvement, [‡] 52 weeks	753	540	RR, 1.4 (1.1–1.8)	144 (1 RCT) ⁶²	Very low	Favors rituximab
		Attributable events per 1000 treated, 208 (56; 361)	NNT, 5 (3–18)			

(continued)

Table IV. (continued).

Outcomes	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality GRADE)	Comments
UPC ratio, reduction by $\geq 50\%$, 52 weeks	667	569	RR, 1.2 (0.9–1.5)	144 (1 RCT) ⁶²	Very low	No difference
UPC ratio, reduction by $\geq 50\%$, 78 weeks	708	542	RR, 1.31 (1.01–1.69)	144 (1 RCT) ⁶²	Very low	Favors rituximab
		Attributable events per 1000 treated, 167 (11; 322)	NNT, 6 (3–92)			
Total serious adverse events, 52–78 weeks	313	388	RR, 0.8 (0.5–1.2)	163 (2 RCTs) ^{42,62}	Low	No difference
Total adverse events leading to treatment discontinuation, 78 weeks	14	42	RR, 0.3 (0.0–3.0)	144 (1 RCT) ⁶²	Very low	No difference
Opportunistic infections, 52–78 weeks	36	13	RR, 2.9 (0.3–27.4)	163 (2 RCTs) ^{42,62}	Low	No difference
Any infection, 78 weeks	849	901	RR, 0.9 (0.8–1.1)	144 (1 RCT) ⁶²	Very low	No difference
Total adverse events, 78 weeks	986	958	RR, 1.03 (0.97–1.09)	144 (1 RCT) ⁶²	Very low	No difference

Population: Adults with severe SLE, lupus nephritis, and inadequate response to immunosuppressive agents

Setting: Outpatient

Intervention: Immunosuppressive agents (mycophenolate mofetil 1-3 g/day), prednisone plus off-label adjunctive rituximab 1000 mg, 4 injections, days 1, 15, 168, and 182

Comparator: Immunosuppressive agents (mycophenolate mofetil 1-3 g/day) and prednisone.

BILAG = British Isles Lupus Assessment Group; NNT = number needed to treat; RCT = randomized controlled trial; RR = relative risk; UPC = urine protein: creatinine.

*Complete renal response: normal serum creatinine level, inactive urinary sediment, and UPC ratio <0.5 .

†Partial renal response: serum creatinine level $\leq 115\%$ of baseline; inactive urinary sediment and at least a 50% decrease in the UPC ratio.

‡Improvement in BILAG renal domain consisted of systolic blood pressure (mm Hg); diastolic blood pressure (mm Hg); accelerated hypertension; urine dipstick protein (+ = 1, ++ = 2, +++ = 3); urine albumin:creatinine ratio (mg/mmol); UPC ratio (mg/mmol); 24-hour urine protein (g); nephrotic syndrome; creatinine (plasma/serum; $\mu\text{mol/l}$); glomerular filtration rate (calculated; mL/min/1.73 m^2); active urinary sediment; active nephritis.

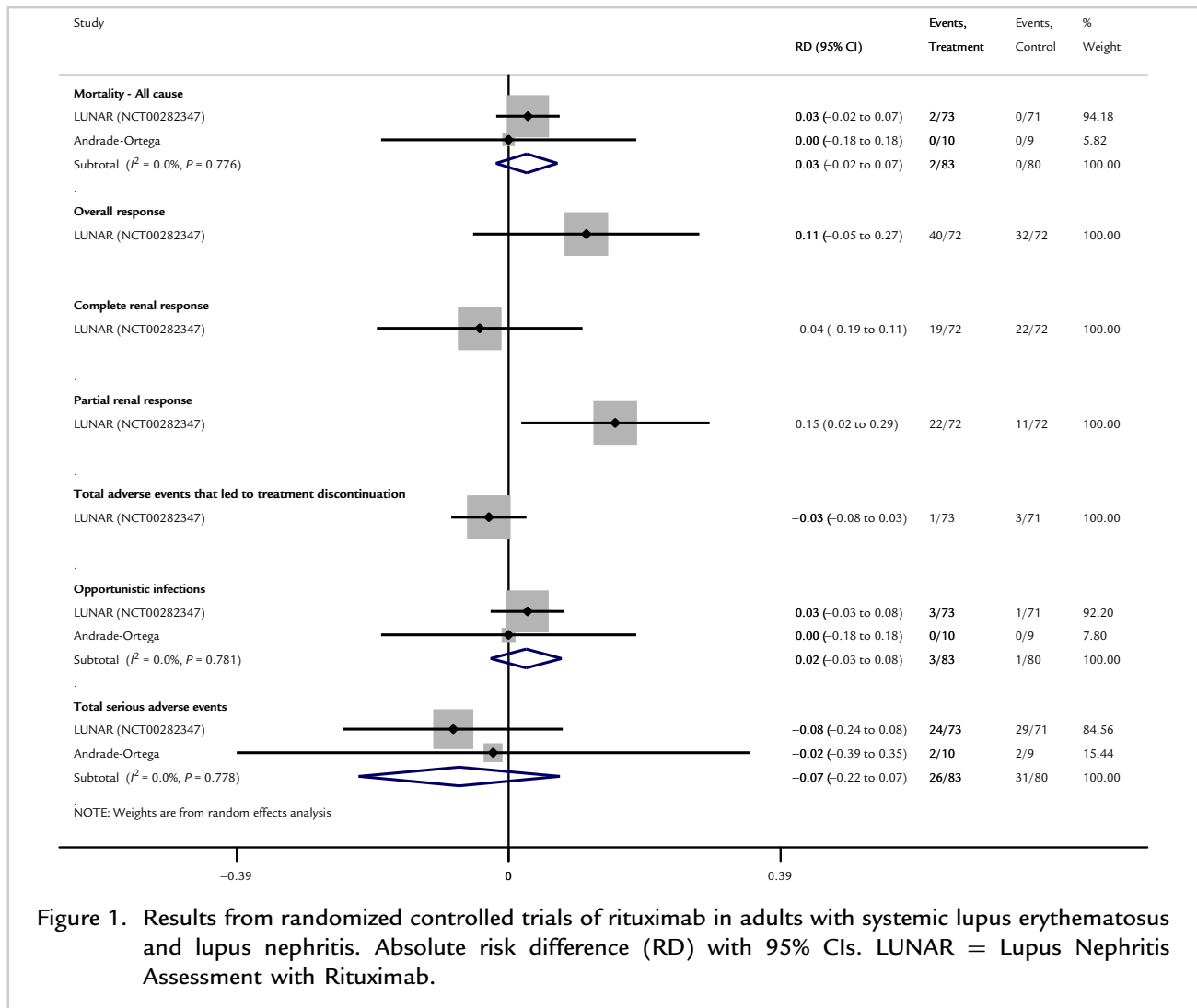


Figure 1. Results from randomized controlled trials of rituximab in adults with systemic lupus erythematosus and lupus nephritis. Absolute risk difference (RD) with 95% CIs. LUNAR = Lupus Nephritis Assessment with Rituximab.

clinthera.2017.05.359).⁵¹ However, evidence suggests that adjunctive atacept does not change the rates of all-cause mortality and adverse effects (very low quality of evidence). A lower dose of atacept (75 mg) does not prevent flares and has no effect on other outcomes (data not shown).⁵¹ This study was terminated early due to concerns regarding serious infections and hypogammaglobulinemia.

In adults with active moderate to severe SLE with inadequate response to immunosuppressive agents, very-low-quality evidence from a single RCT suggests that adjunctive blisibimod (200 mg/week) increases the rates of clinical response compared with immunosuppressive agents alone (Supplemental Appendix D Table IV in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>).⁴⁶ The lower doses of blisibimod (100

mg/week or 200 mg/month) provide no additional benefit compared with immunosuppressive agents alone (data not shown). Very-low-quality evidence from an ongoing RCT suggests that there are no differences in all-cause mortality of adverse effects between standard care with or without any dose of adjunctive blisibimod.⁷⁵ Subgroup analysis suggests that patients with severe disease (baseline SELENA-SLEDAI score ≥ 10) receiving corticosteroids experience greater response rates with blisibimod compared with placebo.⁴⁶

Novel Investigational Biologic Response Modifiers

Published and unpublished RCTs were identified that examined the benefits and harms of the novel

biologic response modifiers epratuzumab (3 RCTs), rontalizumab (1 RCT), ocrelizumab (1 RCT), tabalumab (2 RCTs), and rigerimod (1 RCT).^{40,52,53,58,59,63–65,67} Trials enrolled adults with moderate to severe SLE despite treatments with immunosuppressive agents.

Low-quality evidence suggests that immunosuppressive agents plus adjunctive epratuzumab (any dose) increase the rates of clinical response at the expense of increased risk of opportunistic infections at the longer time of follow-up compared with immunosuppressive agents alone (**Supplemental Appendix D Table V** in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>). Higher doses (600–1800 mg) do not demonstrate a linear increase in rates of clinical response compared with the lower doses (100–360 mg), but they do increase the risk of total adverse effects, specifically infections (data not shown).^{63,65,76,77} More trials failed to show benefits from adjunctive epratuzumab in adults with SLE.^{78–80}

Very-low-quality evidence suggests that immunosuppressive agents plus adjunctive rigerimod (200 µg every 2 weeks) increases the rate of clinical response without increasing the risk of adverse effects compared with immunosuppressive agents alone (**Table VII**). The lower dose of adjunctive rigerimod (200 µg every 4 weeks) offers no benefits over immunosuppressive agents alone (data not shown).⁶⁷

Very-low-quality evidence suggests that background therapy with prednisone alone or combined hydroxychloroquine plus adjunctive anti-interferon-α monoclonal antibody rontalizumab (750 mg IV or 300 mg SC) offers no additional benefits compared with background therapy alone (**Supplemental Appendix D Table VI** in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>).⁵⁹ Post hoc subgroup analysis showed that only patients with a low level of interferon-regulating gene expression had a better response to adjunctive rontalizumab. There are no differences in outcomes between subcutaneous versus intravenous adjunctive rontalizumab (data not shown).⁵³

In patients with severe lupus nephritis despite previous use of immunosuppressive agents, adjunctive ocrelizumab (400 or 1000 mg IV) does not improve clinical response but results in increased rates of infections (**Supplemental Appendix D Table VII** in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>).⁵⁹ The study was terminated

due to increased risk of serious infections in ocrelizumab-treated patients.

The evidence is conflicting regarding the benefits from tabalumab in patients with moderate to severe SLE despite previous use of immunosuppressive agents (**Supplemental Appendix D Table VIII** in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>).^{30,52,58} Large Phase III RCTs failed to show consistent improvement in SLE Responder Index 5.^{52,58}

A new class of biologic response modifiers that target against interferon-α includes sifalimumab (**Supplemental Appendix D Table IX** in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>), anti-interferon-α monoclonal antibody, and anifrolumab (**Supplemental Appendix D Table X** in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>), anti-interferon-α receptor antibody.^{45,54} Both drugs showed improvement in SLE severity at the expense of a higher risk of herpes zoster compared with placebo in adults with moderate to severe SLE enrolled in Phase II RCTs.^{45,54} Both drugs failed to demonstrate dosage-dependent increases in the clinical response rate but resulted in a dose-dependent increase in adverse effects, including herpes zoster.^{45,54}

Table VIII and **Figure 2** present the overall summary of evidence and the risk of clinical response after treatment with biologic response modifiers compared with usual care in patients with SLE.

DISCUSSION

The present review concluded that the quality of evidence is low or very low for the majority of examined interventions. We concluded that adults with moderate to severe extrarenal SLE despite use of immunosuppressive agents might benefit from adjuvant belimumab and off-label rigerimod without increased risk of serious adverse effects. In this population, off-label abatacept and epratuzumab increase the rates of clinical response at the expense of a higher risk of serious adverse effects. Clinicians have to treat 5 to 8 patients with adjuvant biologic response modifiers to achieve a clinical response in 1 additional patient. The evidence also suggests that in the subset of adults with moderate to severe SLE and lupus nephritis who had an inadequate response to immunosuppressive agents, off-label rituximab improves

Table V. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary of findings: Comparative effectiveness of prednisone plus off-label adjunctive abatacept versus prednisone alone in adults with moderate to severe systemic lupus erythematosus despite prior immunosuppressive agents. The population comprised adults with moderate to severe systemic lupus erythematosus who have had 1 of the following primary manifestations: active polyarthritis (musculoskeletal organ system), active discoid lesions (mucocutaneous organ system), or active pleuritis and/or pericarditis (cardiovascular/respiratory organ system) despite prior treatment with immunosuppressive agents. The study setting was outpatient. The intervention comprised prednisone (20 mg/d tapered to 5 mg/d) plus off-label adjunctive abatacept (10 mg/kg IV on days 1, 15, 29, and every 4 weeks thereafter until day 337). (Background immunosuppressive agents [azathioprine, cyclophosphamide, methotrexate, or mycophenolate mofetil] were permitted.) The comparator was prednisone (20 mg/d reduced to 5 mg/d). (Background immunosuppressive medicines [azathioprine, cyclophosphamide, methotrexate, or mycophenolate mofetil] were permitted.).

Outcomes at 52 Weeks	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
All-cause mortality	8	0	RR, 1.5 (0.1 to 35.7)	180 (1 RCT) ⁵⁶	Very low	No difference
Quality of life, physical health domain of SF-36, change from baseline to 52 weeks	NR	NR	MD, 3.92 (1.22 to 6.6) SMD, 2.05 (1.66 to 2.4)	175 (1 RCT) ⁵⁶	Very low	Favors abatacept
Quality of life, mental health domain of SF-36, change from baseline to 52 weeks	NR	NR	MD, 2.24 (-1.19 to 5.7) SMD, 1.00 (0.66 to 1.3)	175 (1 RCT) ⁵⁶	Very low	No difference
Fatigue score (0–100 mm visual analog scale), change from baseline to 52 weeks	NR	NR	MD, -9.45 (-17.65 to -1.3) SMD, -4.50 (-5.07 to -3.9)	175 (1 RCT) ⁵⁶	Very low	Favors abatacept
MOS-Sleep domain, change from baseline to 52 weeks	NR	NR	MD, -7.59 (-12.27 to -2.9) SMD, -3.98 (-4.50 to -3.5)	175 (1 RCT) ⁵⁶	Very low	Favors abatacept
Total adverse events leading to treatment discontinuation	83	51	RR, 1.6 (0.5 to 5.7)	180 (1 RCT) ⁵⁶	Very low	No difference

(continued)

Table V. (continued).

Outcomes at 52 Weeks	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
Total serious adverse events	198	68 Attributable events per 1000 treated, 131 (35; 226)	RR, 2.9 (1.1 to 8.0) NNT, 8 (4 to 29)	180 (1 RCT) ⁵⁶	Very low	Favors prednisone alone
Total adverse events	909	915	RR, 1.0 (0.9 to 1.1)	180 (1 RCT) ⁵⁶	Very low	No difference
Bronchopneumonia	0	17	RR, 0.2 (0.0 to 4.0)	180 (1 RCT) ⁵⁶	Very low	No difference

Population: Adults with moderate to severe SLE who have had 1 of the following primary manifestations: active polyarthritis (musculoskeletal organ system), active discoid lesions (mucocutaneous organ system), or active pleuritis and/or pericarditis (cardiovascular/respiratory organ system) despite prior treatment with immunosuppressive agents

Setting: Outpatient

Intervention: Prednisone (20 mg/day tapered to 5 mg/day) plus off-label adjunctive abatacept (10 mg/kg intravenously on days 1, 15, 29, and every 4 weeks thereafter until day 337). (Background immunosuppressive agents, e.g., azathioprine, cyclophosphamide, methotrexate, or mycophenolate mofetil were permitted.)

Comparator: Prednisone (20 mg/day reduced to 5 mg/day). (Background immunosuppressive medicines, e.g., azathioprine, cyclophosphamide, methotrexate, or mycophenolate mofetil were permitted.)

MD = mean difference; MOS-Sleep = Medical Outcomes Study Sleep Problems Index; NNT = number needed to treat; NR = not reported; RCT = randomized controlled trial; RR = relative risk; SF-36 = 36-Item Short Form Survey; SMD = standardized mean difference.

renal function over immunosuppressive medicines alone, whereas adjuvant abatacept offers no additional benefit.

We downgraded the quality of evidence due to a higher risk of bias in the body of evidence and imprecision in treatment effects. We found no observational studies of adults with SLE that reported long-term safety of biologic response modifiers. However, biologic response modifiers are associated with a higher risk of serious infections in patients with other autoimmune diseases.^{1-8,13,14} This indirect evidence may suggest similar association in patients with SLE. Patients with SLE treated with standard care experience a higher risk of mortality and opportunistic infections compared with the general population, and this risk is higher among men and African-American adults.^{36,81} Our review found no evidence suggesting improvement in survival and rates of long-term SLE remission after treatment with biologic response modifiers in adults with SLE and specifically high-risk groups (eg, men, African-American adults).

The present study has several limitations. We did not contact sponsors or principal investigators regarding unregistered and unpublished studies and unreported patient outcomes in conducted studies. We did not estimate a degree of the reporting bias because formal statistical tests for publication bias have questionable validity ([Supplemental Appendix A](http://dx.doi.org/10.1016/j.clinthera.2017.05.359) in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>). We found no long-term studies that have statistical power to address rare but potentially serious events. Postmarketing surveillance ([Supplemental Appendix C](http://dx.doi.org/10.1016/j.clinthera.2017.05.359) in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>) suggests various serious adverse effects in patients taking biologic response modifiers, mostly in combination with other drugs. However, passive postmarketing surveillance does not have a population denominator to compare the rates of specific harms attributable to biologic response modifiers and does not address the frequency of all adverse effects associated with each drug. Despite these limitations, we provide clinicians with all

Table VI. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary of findings: Comparative effectiveness of immunosuppressive medicines plus off-label adjunctive abatacept versus immunosuppressive medicines in adults with moderate to severe systemic lupus erythematosus (SLE) and lupus nephritis who have had an inadequate response to immunosuppressive agents. The study setting was outpatient; the intervention comprised immunosuppressive agents (cyclophosphamide plus azathioprine or mycophenolate mofetil), prednisone plus off-label adjunctive abatacept (10–30 mg/kg/month); and the comparator was immunosuppressive medicines (cyclophosphamide plus azathioprine or mycophenolate mofetil) and prednisone.

Outcomes	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
All-cause mortality, 52 weeks	27	42	RR, 0.46 (0.17–1.26)	432 (2 RCTs) ^{41,43}	Low	No difference
Mortality: SLE disease-specific, 52 weeks	20	30	RR, 0.7 (0.1–3.9)	199 (1 RCT) ⁴³	Very low	No difference
Total response (complete or partial), 52 weeks	675	641	RR, 1.1 (0.8–1.4)	79 (1 RCT) ⁴¹	Very low	No difference
Complete renal response, [*] 24 weeks	333	309	RR, 1.1 (0.7–1.8)	134 (1 RCT) ⁴¹	Very low	No difference
Partial renal response, [†] 52 weeks	135	151	RR, 0.99 (0.58–1.69)	334 (2 RCTs) ^{41,43}	Low	No difference
Complete patient response, [‡] 52 weeks	242	200	RR, 1.2 (0.7–2.0)	199 (1 RCT) ⁴³	Very low	No difference
Total adverse events that led to treatment discontinuation, 52 weeks	141	90	RR, 1.6 (0.7–3.5)	199 (1 RCT) ⁴³	Very low	No difference
Total serious adverse events, 52 weeks	250	214	RR, 0.99 (0.70–1.39)	432 (2 RCTs) ^{41,43}	Low	No difference
Infections (total), 52 weeks	232	170	RR, 1.4 (0.8–2.4)	199 (1 RCT) ⁴³	Very low	No difference
Total adverse events, 24–52 weeks	902	893	RR, 0.99 (0.93–1.05)	432 (2 RCTs) ^{41,43}	Low	No difference

Population: Adults with moderate to severe SLE and lupus nephritis who have had an inadequate response to immunosuppressive agents

Setting: Outpatient

Intervention: Immunosuppressive agents (cyclophosphamide plus azathioprine or mycophenolate mofetil), prednisone plus off-label adjunctive abatacept (10–30 mg/kg/month)

Comparator: Immunosuppressive medicines (cyclophosphamide plus azathioprine or mycophenolate mofetil) and prednisone.

RCT = randomized controlled trial; RR = relative risk.

^{*}Complete renal response: urinary protein: creatinine ratio <0.5 based on a 24-hour urine collection, serum creatinine level ≤1.2 mg/dL or ≤125% of baseline, and adherence to the prednisone taper to 10 mg/d by week 12.

[†]Partial renal response: urinary protein: creatinine improvement of 50% from baseline in a 24-hour urine collection, serum creatinine level of ≤1.2 mg/dL or ≤125% of baseline, and adherence to the prednisone taper to 10 mg/day by week 12.

[‡]Normal serum creatinine level, urinary protein: creatinine ratio <0.5, and inactive urinary sediment.

Table VII. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary of findings: Immunosuppressive agents plus adjunctive rigerimod versus immunosuppressive agents alone in adults with moderate to severe systemic lupus erythematosus (SLE) who have had an inadequate response to immunosuppressive agents. The study setting was outpatient; the intervention comprised prednisone alone or combined with immunosuppressive therapies plus adjunctive rigerimod (200 µg every 2 weeks); and the comparator was prednisone alone or combined with immunosuppressive therapies.

Outcomes	Risk With Intervention Per 1000	Risk With Comparator Per 1000	Relative Measure of Association (95% CI)	No. of Participants (Studies)	Quality (GRADE)	Comments
Mortality, all-cause, 24 weeks	20	0	RR, 3.0 (0.1–71.9)	98 (1 RCT) ⁶⁷	Very low	No difference
SLE severity: number of subjects with improvement/good result, 24 weeks	592	531	RR, 1.1 (0.8–1.6)	98 (1 RCT) ⁶⁷	Very low	No difference
SLE severity: number of subjects with improvement/good result, 24 weeks	690	565	RR, 1.2 (0.9–1.7)	88 (1 RCT) ⁶⁷	Very low	No difference
Subgroup: SLEDAI ≥ 6 at baseline						
SLE responder index, [*] 24 weeks	842	458	RR, 1.8 (1.1–3.0)	43 (1 RCT) ⁶⁷	Very low	Favors rigerimod
		Attributable events per 1000 treated, 384 (126; 642)	NNT, 3 (2–8)			
Total adverse events that led to treatment discontinuation, 24 weeks	20	82	RR, 0.3 (0.0–2.2)	98 (1 RCT) ⁶⁷	Very low	No difference
Total serious adverse events, 24 weeks	61	61	RR, 1.0 (0.2–4.7)	98 (1 RCT) ⁶⁷	Very low	No difference
Serious soft-tissue infection, 24 weeks	20	41	RR, 0.5 (0.0–5.3)	98 (1 RCT) ⁶⁷	Very low	No difference
Serious pneumonia, 24 weeks	20	0	RR, 3.0 (0.1–71.9)	98 (1 RCT) ⁶⁷	Very low	No difference

Population: Adults with moderate to severe SLE who have had an inadequate response to immunosuppressive agents

Setting: Outpatient

Intervention: Prednisone alone or combined with immunosuppressive therapies plus adjunctive rigerimod (200 µg every 2 weeks)

Comparator: Prednisone alone or combined with immunosuppressive therapies.

NNT = number needed to treat; RCT = randomized controlled trial; RR = relative risk; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index.

^{*}A reduction from baseline in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) score ≥ 4 points, no increase in the Physician Global Assessment score of > 0.3 point on a visual analog scale of 0 to 3, and no new A score and ≤ 1 new B score on the British Isles Lupus Assessment Group–2004.

Table VIII. Summary of evidence.

Confidence in Evidence	Conclusion
Evidence suggests that in adults with active moderate to severe extrarenal SLE who have had an inadequate response to immunosuppressive agents:	
Moderate	Adjunctive belimumab (10 mg/kg) increases the rates of clinical response compared with immunosuppressive agents alone regardless of baseline severity and seropositivity but has no effect on rates of mortality or adverse effects
Very low	There is no difference in clinical response and harms after immunosuppressive medicines plus adjunctive off-label rituximab (total dose 2000 mg) over immunosuppressive medicines alone
Very low	There are no differences in all-cause mortality, clinical response, or adverse effects leading to treatment discontinuation between immunosuppressive agents plus adjunctive abatacept versus immunosuppressive agents alone Adjunctive abatacept slightly improves physical health and reduces fatigue at the expense of increased risk of serious adverse effects
Low	Adjunctive epratuzumab (any dose) increases the rates of clinical response at the expense of increased risk of opportunistic infections compared with immunosuppressive agents alone
Very low	Adjunctive rigerimod (200 µg every 2 weeks) increases the rates of clinical response without increasing the risk of adverse effects compared with immunosuppressive agents. The lower dose of adjunctive rigerimod (200 µg every 4 weeks) offers no benefits over immunosuppressive agents alone
Very low	Tabalumab fails to show consistent improvement in SLE Responder Index 5 in patients with moderate to severe lupus nephritis and inadequate response to immunosuppressive agents.
Very low	Sifalimumab and anifrolumab reduces SLE severity at the expense of higher risk of herpes zoster compared with placebo. Both drugs fail to demonstrate dosage-dependent increase in clinical response rate but result in dose-dependent increase in adverse effects, including herpes zoster
Evidence suggests that in adults with severe SLE who have had an inadequate response to immunosuppressive agents:	
Very low	Adjunctive blisibimod (200 mg/week) increases the rates of clinical response over standard care with immunosuppressive agents alone
Evidence suggests that in adults with moderate to severe SLE and lupus nephritis who have had an inadequate response to immunosuppressive agents:	
Low	There are no differences in any measured benefits or harms between immunosuppressive agents plus adjunctive abatacept and immunosuppressive agents alone
Low	Adjunctive off-label rituximab (total dose 4000 mg) improves renal function over immunosuppressive medicines alone
Evidence suggests that in adults with SLE but without active disease taking stable doses of immunosuppressive agents:	
Very low	Adjunctive atacept (150 mg) prevents flares compared with prednisone alone A lower dose of adjunctive atacept (75 mg) provides no additional benefits compared with prednisone and immunosuppressive agents

SLE = systemic lupus erythematosus.

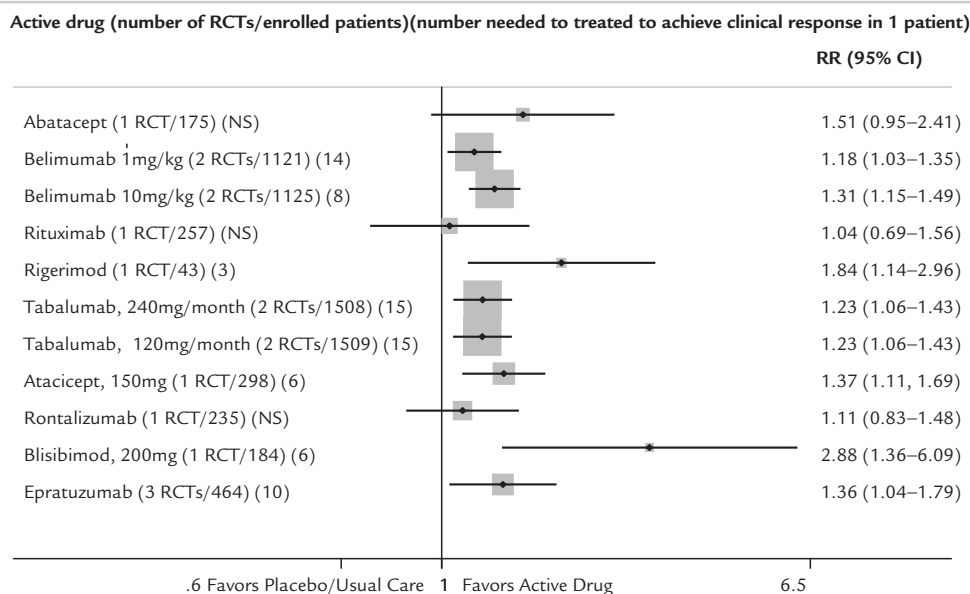


Figure 2. Relative risk of clinical response (as defined in primary studies) after biologic response modifiers compared with usual care in patients with systemic lupus erythematosus. Relative risk (RR) with 95% CIs. NS = not significant difference in absolute risk; RCT = randomized controlled trial.

available evidence critically appraised by using GRADE methods.

Clinical guidelines provide weak recommendations for adding belimumab or rituximab in adults with moderate to severe extrarenal SLE and an inadequate response to immunosuppressive agents.^{6,8} For adults with refractory lupus nephritis, guidelines recommend off-label rituximab in some patients.^{6,12} Current guidelines do not recommend belimumab for adults with lupus nephritis.¹² Guidelines do not consider other novel biologic response modifiers. The evidence regarding comparative effectiveness of biologic agents or benefits and harms from biologic agents in patients with SLE who failed biologic response modifiers is insufficient. Published high-quality systematic reviews and meta-analyses of available treatments for lupus nephritis focused on immunosuppressive drugs and corticosteroids and did not provide treatment effects from rituximab or other biologic response modifiers.^{82–85} The 2012 Cochrane review included 2 RCTs of rituximab; 1 RCT examined the effects of cyclophosphamide in patients treated with rituximab and the second RCT examined the effects of rituximab in patients treated with mycophenolate mofetil.⁸⁴ Review authors concluded no differences between treatment arms in any of the examined outcomes, including mortality, kidney function, or infections.

Future research should shed light on the comparative effectiveness of biologic response modifiers in patient subpopulations according to demographic characteristics, SLE severity and seropositivity, baseline risk of infections, and comorbidities.

CONCLUSIONS

In adults with moderate to severe SLE despite conventional immunosuppressive agents, adjunctive belimumab in extrarenal SLE and off-label rituximab in lupus nephritis may offer additional modest benefit.

ACKNOWLEDGMENTS

This work was supported by Elsevier Clinical Solutions, Evidence-Based Medicine Center.

The authors thank David Goldmann, MD, for his contribution to the protocol development and drafting early versions of evidence analyses. They also thank Maura Sostack, MLIS, for the development of literature search strings.

Both authors had access to the data, contributed to the writing of the manuscript, and approved this submission.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

SUPPLEMENTARY MATERIAL

Supplemental appendices accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.clinthera.2017.05.359>.

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SUPPLEMENTARY MATERIAL**Appendix A****Evidence Report Protocol**

Start date: April 2015

Title: Biologic response modifiers for systemic lupus erythematosus

Authors: Paula Dospinescu, Tatyana A. Shamliyan

PICO question this report is addressing:

What is the comparative effectiveness and safety of biologic response modifiers for patients with systemic lupus erythematosus (treatment naïve or previously treated)?

Population	Children and adults diagnosed with systemic lupus erythematosus regardless of prior treatment status Disease manifestations , organ involvement and severity Patient demographics; (age, gender, ethnicity, geography), disease duration, response to prior therapy; family history of SLE or rheumatologic disease, genetic predisposition (specific mutations), infections, present pregnancy or menopausal status; oral contraceptive use, exposure to UV light, smoking, immunosuppression (diseases or drugs); concomitant and concurrent medications; comorbidities
Intervention	L04AB Tumor necrosis factor alpha (TNF- α) inhibitors: Etanercept Infliximab Adalimumab Certolizumab pegol Golimumab L04AC Interleukin inhibitors: Daclizumab Basiliximab Anakinra Rilonacept Ustekinumab Mepolizumab Tocilizumab Canakinumab Briakinumab Secukinumab Siltuximab L04AA Selective immunosuppressants: Belimumab, Rituximab, Ocrelizumab, Atacept, Abatacept, Sifalimumab, Rontalizumab, Blisibimod, Tabalumab Sifalimumab, anti interferon alfa monoclonal antibody and Anifrolumab, anti interferon alfa receptor antibody Immunosuppressive agents: corticosteroid and conventional immunosuppressive agents (e. g., Hydroxychloroquine, Azathioprine, Cyclophosphamide, Methotrexate, or Mycophenolate mofetil, Drug dose route, frequency, duration, combinations
Comparator	Non-steroidal anti-inflammatory drugs, corticosteroids, anti-malarials and additional immunosuppressives, e.g. azathioprine, cyclophosphamide, methotrexate, or, mycophenolate mofetil)

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**Primary
outcome(s)**

All-cause mortality, quality of life measured with validated scales, disability measured with validated scales, hospitalization and length of stay

Secondary: Renal function, need for dialysis/kidney transplantation, change in composite measures of disease activity and damage*; change in pain measures (VAS); functional status (HAQ)

Complications (opportunistic infections, osteoporosis, neurologic and cardiovascular disease)

Fatigue (Fatigue Severity Scale or other validated scale)

Intermediate outcomes: change in autoantibody levels (see above) measures of inflammation (ESR, CRP), renal biopsy

All harms **

* composite measures of disease activity (increase in score indicates worse severity):

British Isles Lupus Assessment Group (BILAG) severity categories: A (severe lupus) = 9 score, B (moderate to severe lupus) = 3 score, C (moderate severity lupus) = 1 score, D (no present disease activity) = 0, E (no present or prior disease activity) = 0

European Consensus Lupus Activity Measurements (ECLAM) – scale of 33 items with a range is 0-17.5

Systemic Lupus Activity Measure, revised (SLAM-R) - 9 organs/systems scored from 0 to 3 points and 7 laboratory categories can score of maximum of 21 points; maximum total score 81; score of 7 is considered clinically important and affects decision to treat

Systemic Lupus Activity Questionnaire for Population Studies

(SLAQ) - patient self-completed questionnaire with 24 items in 9 organs/systems; scores can range from 0-44

Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) - 24 items covering 9 organs systems; the score range is 0-105 points; a score of 6 is considered clinically important and affects decision to treat.

Systemic Lupus International Collaborating Clinics/American College of

Rheumatology Damage Index (SDI) - 41 items covering 12 organ systems; total score range 0-46 points

** Glossary of adverse effects¹³

Term	Definition
Adverse drug reaction	An adverse effect specific to a drug
Adverse effect	An unfavourable outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it
Adverse event	An unfavourable outcome that occurs during or after the use of a drug or other intervention and the causal relation between the intervention and the event is at least a reasonable possibility
Complication	An adverse event or effect following surgical and other invasive intervention
Harm	The totality of possible adverse consequences (if single or multiple) of an intervention or therapy; harms are the direct opposite of benefits
Safety	Substantive evidence of an absence of harm. The term is often misused when there is simply absence of evidence of harm
Side effect	Any unintended effect, adverse or beneficial, of a drug that occurs at doses normally used for treatment
Toxicity	Drug related harm. The term may be most appropriate for laboratory determined measurements, although it is also used in relation to clinical events. The disadvantage of the term “toxicity” is that it implies causality. If authors cannot prove causality, the terms “abnormal laboratory measurements” or “laboratory abnormalities” are more appropriate

Study Eligibility**Inclusion criteria**

Participants	Patients with systemic lupus erythematosus
Language restrictions	English
Publication dates (from and to) for searching	2010- January 2017 (published high quality reviews should address early publications of randomized trials)
Inclusion of guidelines	ECRI appraised, published since 2010
Inclusion of clinical performance measures	Yes
Inclusion for systematic reviews (review quality, reviews with quantitative analyses)	Yes (we do not use ranking of evidence from the published reviews)
Inclusion of randomized trials	Yes, published since 2010
Inclusion of observational studies for harms (study characteristics, design, applicability, sample size, statistical methods to reduce bias)	Nationally representative prospective cohort studies of adverse effects with multivariate adjustment of adverse effects

Clinical Features of Systemic Lupus Erythematosus^{14,15}

Affected organ system	Prevalence %	Signs and symptoms
Constitutional	50 to 100	Fatigue, fever (in the absence of infection), weight loss
Skin	73	Butterfly rash, photosensitivity rash, mucous membrane lesion, alopecia, Raynaud's phenomenon, purpura, urticaria, vasculitis
Musculoskeletal	62 to 67	Arthritis, arthralgia, myositis
Renal	16 to 38	Hematuria, proteinuria, cellular casts, nephrotic syndrome
Hematologic	36	Anemia, thrombocytopenia, leukopenia
Reticuloendothelial	7 to 23	Lymphadenopathy, splenomegaly, hepatomegaly
Neuropsychiatric	12 to 21	Psychosis, seizures, organic brain syndrome, transverse myelitis, cranial neuropathies, peripheral neuropathies
Gastrointestinal	18	Nausea, vomiting, abdominal pain
Cardiac	15	Pericarditis, endocarditis, myocarditis
Pulmonary	2 to 12	Pleurisy, pulmonary hypertension, pulmonary parenchymal disease

American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus^{14,16,17}

The diagnosis of systemic lupus erythematosus requires the presence of four or more of the following 11 criteria, serially or simultaneously, during any period of observation:

1. Malar rash: fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash: erythematous, raised patches with adherent keratotic scaling and follicular plugging; possibly atrophic scarring in older lesions
3. Photosensitivity: skin rash as a result of unusual reaction to sunlight, as determined by patient history or physician observation
4. Oral ulcers: oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis: nonerosive arthritis involving two or more peripheral joints, characterized by swelling, tenderness, or effusion
6. Serositis: pleuritis, by convincing history of pleuritic pain, rub heard by physician, or evidence of pleural effusion; or pericarditis documented by electrocardiography, rub heard by physician, or evidence of pericardial effusion
7. Renal disorder: persistent proteinuria, > 500 mg per 24 hours (0.5 g per day) or $> 3+$ if quantitation is not performed; or cellular casts (may be red blood cell, hemoglobin, granular, tubular, or mixed cellular casts)
8. Neurologic disorder: seizures or psychosis occurring in the absence of offending drugs or known metabolic derangement (e.g., uremia, ketoacidosis, electrolyte imbalance)
9. Hematologic disorder: hemolytic anemia with reticulocytosis; or leukopenia, $< 4,000$ per mm³ (4.0×10^9 per L) on two or more occasions; or lymphopenia, $< 1,500$ per mm³ (1.5×10^9 per L) on two or more occasions; or thrombocytopenia, $< 100 \times 10^3$ per mm³ (100×10^9 per L) in the absence of offending drugs
10. Immunologic disorder: antibody to double-stranded DNA antigen (anti-dsDNA) in abnormal titer; or presence of antibody to Sm nuclear antigen (anti-Sm); or positive finding of antiphospholipid antibody based on an abnormal serum level of IgG or IgM anticardiolipin antibodies, a positive test result for lupus anticoagulant using a standard method, or a false-positive serologic test for syphilis that is known to be positive for at least 6 months and is confirmed by negative *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibodies: an abnormal antinuclear antibody titer by immunofluorescence or equivalent assay at any time and in the absence of drugs known to be associated with drug-induced lupus

International Society of Nephrology/Renal Pathology Society 2003 classification of lupus nephritis¹⁷

- Class I Minimal mesangial LN
- Class II Mesangial proliferative LN
- Class III Focal LN (<50% of glomeruli)
 - III (A): active lesions
 - III (A/C): active and chronic lesions
 - III (C): chronic lesions

- Class IV Diffuse LN (>50% glomeruli) Diffuse segmental (IV-S) or global (IV-G) LN
 - IV (A): active lesions
 - IV (A/C): active and chronic lesions
 - IV (C): chronic lesions

- Class V Membranous LN
- Class VI Advanced sclerosing LN (>90% globally sclerosed glomeruli without residual activity)

Exclusion criteria for studies that would otherwise be eligible

Criteria	
Population	<75% patients with SLE
Interventions	Comparative effectiveness of immunosuppressive drugs
Outcomes	Intermediate pharmacokinetic outcomes
Study design	Uncontrolled case series or uncontrolled clinical trials Meeting abstracts presenting the results of RCT which have been published in peer reviewed journals or have results in clinicaltrials.gov

Search strategy

The medical librarian develops specific search strategies based on the PICO's formulated by our clinical and epidemiology staff. We search for all relevant articles published in English from 2010 up to April 2015, May 2016, and January 2017, in PubMed, Embase, and the Cochrane Library. To

identify unpublished trial data, we conduct a search of the trial registry clinicaltrials.gov.

We conduct the following searches:

PubMed searches for:

1. RCTs
2. Observational studies of harms (multivariate adjusted estimates from population-based cohorts or national administrative databases)
3. Clinical practice guidelines

Embase searches for full publications of:

1. RCTs
2. Observational studies of harms (multivariate adjusted estimates from nationally representative cohorts or administrative databases)

The bibliographies of identified articles are scanned, and study investigators are contacted for additional publications.

Study Selection

The study epidemiologist, an author- subject matter expert, and medical librarian who contribute equally to resolving differences decide the determination of eligibility collaboratively.

The study epidemiologist and medical librarian to determine eligibility for full text review first screen title and abstracts. All citations found during the searches are stored in a reference database.

Data extraction and strategy for data synthesis

Data extraction

An external contractor, DOC™ Data Software Platform v2.0, Doctor Evidence LLC, Santa Monica, California, United States, 2014; services available through <http://www.doctorevidence.com>, performs dual abstraction and quality control of the data.

Doctor Evidence Extraction & Quality Assurance Process Overview:

Doctor Evidence's (DRE) Methodology Lead (ML) works with Elsevier's EBM Center Analyst to determine and finalize the data configuration protocol (DCP). The ML then drafts the project instructions

and reviews the DCP and project instructions with the team of DRE trained, evidence-based clinical analysts.

The clinical analyst extracts data directly from published clinical studies into a DRE created and customized electronic extraction form in accordance with the DCP and project instructions. DRE extraction technology highlights mismatches in the data (i.e. data reported in percentiles conflicting with unit data and vice versa; values outside a normal range) for the analyst to review during extraction and before final submission.

Then, a second evidence-based clinical analyst (Quality Control Analyst) quality-checks the data in accordance with the DCP. The QC Analysts identifies all data that he/she would categorize as an error and reviews those data points with the clinical analyst who completed the original data extraction. If both agree that a data point identified as an error is such, the error is corrected. If there is a disagreement between the analysts, the ML is notified and he/she may adjudicate or if needed address the issue with the Chief Medical Officer (CMO) for final adjudication. Once all quality issues have been addressed appropriately, the study is finalized in the DOC Data environment.

For Elsevier, DRE produces a data export in Microsoft Excel. The DRE ML works with the DRE tech team to produce the export file then reviews the file prior to sending the file to Elsevier. The ML reviews all data points specific to the DCP and chooses several data points at random to review. If the ML identifies errors in the file export, he/she investigates the source of the error. If the error is a technology related error and the original data point in the database is correct, the ML corrects the error in the export but does not count that as an error. If the error, however, is a data collection/qc error, then the ML counts that as an error. The error rate that DRE reports to Elsevier is based on the total number of data points collected for the data set and the total number of data collection/QC errors identified when the ML reviews the data export file.

We define epidemiologic terms according to the recommendations from Cochrane collaboration (<http://community-archive.cochrane.org/glossary>).

We abstract the information about study population, interventions, comparators, and outcomes. We abstract minimum datasets (e.g., number of the subjects in treatment groups and events) to estimate

absolute risk difference, relative risk, and number needed to treat for each hypothesis of categorical variables. When absolute risk difference was statistically significant, we calculated number needed to achieve an outcome in one patient as $1/\text{absolute risk difference}$, we calculated attributable events per 1000 treated as absolute rate difference multiplied by 1000.

Means and standard deviations of continuous variables, e.g. total scores from the quality of life scales are abstracted. Statistical significance is evaluated at a 95% confidence level (including the use of p values). All authors have access to the data.

We conduct an overview of the reviews following the framework of the Cochrane Collaboration. We perform direct frequentist random effects meta-analyses or update published meta-analyses. Pooling criteria include similar definitions of the active and control intervention, patient outcomes, and similar follow-up time.

We define harms as the totality of all possible adverse consequences of an intervention. Investigators sometimes defined harmful effects as unrelated to examined treatments. Harms are analyzed regardless of how investigators related them to treatments.

We calculate absolute risk difference, number needed to treat, and the number of attributable events based on data from the published randomized trials, using Meta- Analyst and STATA software. Correction coefficients for zero events are used as a default option in both software programs, and intention to treat is used for evidence synthesis. Superiority of interventions under comparison is hypothesized.

We assess reporting bias as a proportion of published among all registered studies, unreported outcomes compared with published protocols, or unreported minimum data sets for reproducibility of the results. We did not conduct formal statistical tests for publication bias due to questionable validity of such tests.¹⁸

To examine the role of patient characteristics, a search is undertaken for subgroup analyses by patient demographics, baseline disease severity and duration, prior treatment response, and comorbidities in systematic reviews and randomized trials, including significant interaction effects.

Study design, study phases, number of participants, and inclusion/exclusion criteria, will be collected. We also collect the following study-level characteristics:

- ☒ Study Objective/Aim/Purpose
- ☒ Primary/Secondary/Tertiary Efficacy Outcome description
- ☒ Primary/Secondary/Tertiary Safety Outcome description
- ☒ Statistical Power Statement (study-wide or outcome specific; the effect size, and the expected attrition rate)
- ☒ Study Phases (*e.g. run-in, treatment period*)
 - ☒ Did Phase Occur Pre-Randomization, Post-Randomization or NR
 - ☒ % Total Excluded from Study during Phase
- ☒ Early Termination (Y/N)
- ☒ Clinical Trial Number (source: Clinicaltrials.gov OR World Health Organization portal) to ensure that the data from original studies are not duplicated in reviews
- ☒ Clinical Trial Phase
- ☒ Randomization Method (Individual or Clustered)
 - ☒ If Clustered, # in Cluster and how 'clusters' are defined
 - ☒ If stratified randomization, define the stratifying variables
- ☒ Blinding
- ☒ Allocation Concealment (Y/N) & Method (Type)
- ☒ If randomization was stratified, variables for stratification (a priori subgroups)
- ☒ Study Years & description (date range given in study)
- ☒ Funding & Funding Institution/Conflict of Interests; if authors were employees or consultants of pharma

- ☒ Setting:
 - ☒ Country/Location – Name, Average Number per country/location, Total # countries/locations
 - ☒ Settings(*e.g. inpatient/outpatient*), Average Number per patients per setting, Total # settings
 - ☒ Name of Database/Registry Used, if applicable
 - ☒ Recruitment Location, Method & Notes

Please select from the following outcome-level data-points for inclusion, if applicable, in study summaries: All variance measures and *p*-values are collected by default.

- ☒ Responses Collected by whom (*e.g. Researcher, Observer, Self*)
- ☒ Outcome Collected at Final Timepoint Only (*i.e. no interim data collected*)
- ☒ Association Measures (*e.g. Odds Ratio, Hazard Ratio*), with Confidence Interval Range & P-value
- ☒ Statistical Test Used to Report Outcome
- ☒ Type & Description of Statistical Adjustments Made to Outcomes
- ☒ Qualitative Comments in Results Section (text with no data attached)

Other:

- ☒ Author Contact Information (name, address, email, and phone number, if given)

Treatment name (all drugs included), drug class, dose, frequency, route, duration, and schedule will be collected.

Treatment Datapoint	Type	Note
Medication Name	Text	using WHO International Nonproprietary name (http://www.who.int/medicines/services/inn/en/); separate variables for each drug in active and control groups
Drug Class	Text	separate variables for each drug in active and control groups
Dose	Continuous, Variance, Range	separate variables for each drug in active and control groups
Frequency	Continuous	separate variables for each drug in active and control groups
Route	Text	separate variables for each drug in active and control groups
Duration	Continuous, Variance, Range	separate variables for each drug in active and control groups
Schedule	Text	

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Treatment Datapoint	Type	Note
Concurrent medication	Binary (#/%)	<i>Concurrent treatments are treatments for the condition under investigation other than the study intervention taken during the course of the study by research subjects.</i>
Concomitant medication	Binary (#/%)	<i>Concomitant treatments are treatments taken by research subjects during the course of the study that are unrelated to the condition under investigation.</i>
Adherence	Binary (#/%)	% with adherence as measured in the studies
Prior treatments for SLE	Binary (#/%)	
Setting	Text	
Intervention administration	Text	Any additional drug management interventions

By default, mean age, age range, and gender will be collected. This table will be finalized based on frequency report.

Patient Baseline Characteristic	Type	Note
Ethnicity	Binary (#/%)	Native Americans/Alaskan Native, Asians, Black or African-American, Hispanics, Native Hawaiian/Pacific Islanders, White not of Hispanic origin, Multi-Racial
Education	Binary (#/%)	No diploma, high school diploma, college graduate, graduate degree
Residence	Binary (#/%)	Geographic areas, country, urban or rural; community dwelling
Smoking	Binary (#/%)	Never smoked, current smoker, former smoker
SLE definition	text	
Clinical manifestations	text	Organ involvement
Baseline severity of organ involvement	Continuous, Variance, Range	Baseline score for severity measures as reported
SLE duration	Binary (#/%)	% with mild, moderate or severe disease
Baseline assessment method for SLE severity	Text	As reported in studies including instruments used
Baseline disability levels	Binary (#/%)	% with ADL and IDL levels
Baseline pain measures		As reported in the studies
Baseline pain levels		As reported in the studies
Baseline quality of life measures		As reported in the studies
Baseline autoantibody levels		As reported in the studies
Baseline inflammatory markers levels (e.g. CRP)		As reported in the studies
Baseline renal function		As reported in the studies

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Patient Baseline Characteristic	Type	Note
Response to prior treatments		As reported in the studies
Family history of SLE or rheumatologic disease		As reported in the studies
Genetic predisposition (specific mutations)		As reported in the studies
Menopausal status		
Oral contraceptive use		
Exposure (UV light, others)		
Immuno-suppression- diseases		
Immuno-suppression- drugs		
Parity		
Chronic infections		
Comorbidities	Binary (#/%)	
Comorbidities: malignancies		

To be finalized based on frequency report:

Outcome	Type	Note
Mortality, all cause	Binary (#/%)	At reported time points
Mortality, disease-specific	Binary (#/%)	At reported time points
Improvement in Quality of life	Binary (#/%)	% with clinically important improvement in specific QOL scale
Quality of life	continuous	As reported
Disability	Binary (#/%)	As reported
Disability	continuous	ADL, IDL
Hospitalization	Binary (#/%)	As reported
Hospitalization	continuous	Number/patient
Length of stay	continuous	As reported
Improvement in SLE severity	continuous	Change in composite measures of disease activity and damage (BILAG, ECLAM, SLAM, SLEDAI, LAI, SLAQ, SLICC/ACE-DI, LDIQ, BILD, others) – separate variables for means and STDev for each measure
Improvement in SLE severity	Binary (%)	% with clinically important improvement in measures above
Pain	continuous	Change in pain measures
Pain	Binary (%)	% with clinically important improvement in pain
Autoantibody levels	continuous	As reported
Renal function	Binary (#/%)	As reported
Need for dialysis	Binary (#/%)	As reported
Need for kidney transplantation	Binary (#/%)	As reported
Fatigue		% with clinically important improvement in fatigue
Reduction in glucocorticoid dose		As reported

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Outcome	Type	Note
Time to reduction in glucocorticoid dose		As reported
Complications	Binary (#/%)	e.g., opportunistic infections, osteoporosis (separate outcomes for each)
Total harms (total adverse events)	Binary (#/%)	As reported
Total serious adverse events	Binary (#/%)	FDA definition
Total severe Adverse Events	Binary (#/%)	FDA definition
Total adverse events requiring concurrent drug dose adjustments	Binary (#/%)	As reported

Methodological assessment of the included studies

For systematic reviews (QIRs), we use the Assessment of Multiple Systematic Reviews (AMSTAR) scale to determine the methodological strength of the systematic reviews.

For randomized and observational studies we apply the Cochrane Risk of Bias tool. Risk of bias is assessed on a three-point scale: high bias, low bias and unclear. A low risk of bias is assumed when RCTs met all the risk of bias criteria, a medium risk of bias if at least 1 of the risk-of-bias criteria is not met, and a high risk of bias if 2 or more risk-of-bias criteria are not met. An unknown risk of bias is assigned for the studies with poorly reported risk-of-bias criteria. We assign high risk of bias to all observational studies.

For Clinical Practice Guidelines, we use the AGREE II (2009) tool that covers 23 items in six domains and two overall global ratings.

Quality assessment of the included studies and the body of evidence by outcome according to the GRADE framework

The authors assign the quality of evidence ratings as high, moderate, low, or very low, according to risk of bias in the body of evidence, directness of comparisons, precision and consistency in treatment effects, and the evidence of reporting bias, using GRADE methodology. We upgrade the risk of bias from low to high if at least one RCT had high risk of bias. We define indirectness in outcomes from intermediate

outcomes. We review published network meta-analyses but do not conduct indirect comparisons.

Treatment effect estimates is defined as precise when pooled estimates had reasonably narrow 95% confidence intervals and the number of events are greater than 250. Justification of the sample size is not included in grading of the evidence. We do not conduct post hoc statistical power analyses.

In assessing the quality of evidence in all studies, the authors look for a dose response association, the strength of association, and evidence of any reporting bias. The strength of the association is evaluated, defining a priori a large effect when the relative risk is greater than 2 and a very large effect when the relative risk is greater than 5. A small treatment effect is construed when the relative risk was significant but less than 2. For standardized continuous measures of secondary and intermediate outcomes, the magnitude of the effect is defined according to Cohen et al as small, moderate, and large, corresponding to mean differences in standard deviation units of 0 to 0.5, 0.5 to 0.8, and greater than 0.8, respectively.

A high quality of evidence is assigned to well-designed RCTs with consistent findings. The quality of evidence is downgraded to moderate if at least 1 of 4 quality of evidence criteria is not met; for example, moderate quality of evidence is assigned if there was a high risk of bias in the body of evidence or if the results are not consistent or precise. The quality of evidence is downgraded to low if 2 or more criteria are not met.

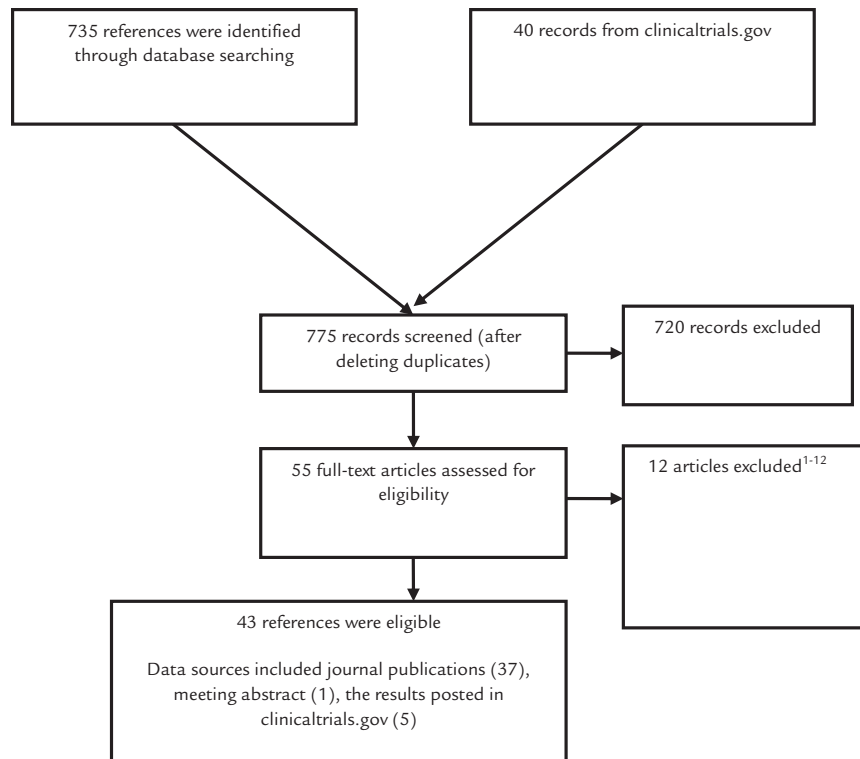


Figure A1. PRISMA diagram.

A low quality of evidence is assigned to non-randomized studies, and upgraded for the rating if there was a strong or dose-response association. Evidence is defined as insufficient when no studies provided valid information about treatment effects. This approach is applied regardless of whether the results were statistically significant.

The authors assign strength of the recommendations based on overall quality of evidence, balances between benefits and harms, healthcare consumers and clinician's values and preferences, and cost-effectiveness studies using the GRADE methodology (Figure A1).

PubMed Search of record (Harms, RCTs)

((((((((((((((("Lupus Erythematosus, Systemic/drug therapy"[Mesh] OR "Lupus Erythematosus, Systemic/therapy"[Mesh]))) OR "Systemic Lupus Erythematosus"[Title/Abstract] OR "SLE"[Title/Abstract] OR "Lupus Erythematosus Disseminatus"[Title/Abstract] OR "Libman-Sacks Disease"[Title/Abstract] OR "Libman Sacks Disease"[Title/Abstract])) AND (((((((((((((((("infliximab" [Supplementary Concept] OR "afelimomab" [Supplementary Concept] OR "adalimumab" [Supplementary Concept] OR

"certolizumab pegol" [Supplementary Concept]) OR "golimumab" [Supplementary Concept]) OR infliximab[Title/Abstract] OR afelimomab[Title/Abstract] OR adalimumab[Title/Abstract] OR "certolizumab pegol"[Title/Abstract] OR golimumab[Title/Abstract] OR "TNF inhibitor"[Title] OR "TNF inhibitors"[Title/Abstract] OR "TNFI"[Title/Abstract] OR "Tumor Necrosis Factor-alpha"[Mesh] OR "anti-TNF"[Title/Abstract] OR "antiTNF"[Title/Abstract]) OR (((((((((((((((("daclizumab" [Supplementary Concept] OR daclizumab[Title/Abstract] OR basiliximab[Title/Abstract] OR "basiliximab" [Supplementary Concept] OR anakinra[Title/Abstract] OR "Interleukin 1 Receptor Antagonist Protein"[Mesh] OR rilonacept[Title/Abstract] OR "rilonacept" [Supplementary Concept] OR ustekinumab[Title/Abstract] OR "ustekinumab" [Supplementary Concept] OR mepolizumab[Title/Abstract] OR "mepolizumab" [Supplementary Concept] OR tocilizumab[Title/Abstract] OR "tocilizumab" [Supplementary Concept] OR canakinumab[Title/Abstract] OR "canakinumab" [Supplementary Concept] OR briakinumab[Title/Abstract] OR "briakinumab" [Supplementary Concept] OR secukinumab[Title/

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Abstract]) OR "secukinumab" [Supplementary Concept]) OR siltuximab[Title/Abstract]) OR "siltuximab" [Supplementary Concept]) OR "belimumab" [Supplementary Concept]) OR belimumab[Title/Abstract]) NOT (((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type]) OR "Newspaper Article"[Publication Type])))) NOT

((("Animals"[Mesh]) NOT ((("Animals"[Mesh]) AND "Humans"[Mesh]))) AND (((((((random*[Title/Abstract]) AND trial*[Title/Abstract])) OR "Randomized Controlled Trials as Topic"[Mesh:noexp]) OR "Randomized Controlled Trial"[Publication Type:noexp])) OR (((multivar*[Title/Abstract]) OR "Multivariate Analysis"[Mesh]) OR adjust*[Title/Abstract]))) AND ("2010/01/01"[PDAT] : "3000/12/31"[PDAT])

Search Query	Items found
#107 Search (((((((((((((((("Lupus Erythematosus, Systemic/drug therapy"[Mesh] OR "Lupus Erythematosus, Systemic/therapy"[Mesh]))) OR "Systemic Lupus Erythematosus"[Title/Abstract]) OR "SLE"[Title/Abstract]) OR "Lupus Erythematosus Disseminatus"[Title/Abstract]) OR "Libman-Sacks Disease"[Title/Abstract]) OR "Libman Sacks Disease"[Title/Abstract])))) AND (((((((((((((((("infliximab" [Supplementary Concept]) OR "afelimomab" [Supplementary Concept]) OR "adalimumab" [Supplementary Concept]) OR "certolizumab pegol" [Supplementary Concept]) OR "golimumab" [Supplementary Concept]) OR infliximab[Title/Abstract]) OR afelimomab[Title/Abstract]) OR adalimumab[Title/Abstract]) OR "certolizumab pegol"[Title/Abstract]) OR golimumab[Title/Abstract]) OR "TNF inhibitor"[Title]) OR "TNF inhibitors"[Title/Abstract]) OR "TNFi"[Title/Abstract]) OR "Tumor Necrosis Factor-alpha"[Mesh]) OR "anti-TNF"[Title/Abstract]) OR "antiTNF"[Title/Abstract])) OR (((((((((((((((((((("daclizumab" [Supplementary Concept]) OR daclizumab[Title/Abstract]) OR basiliximab[Title/Abstract]) OR "basiliximab" [Supplementary Concept]) OR anakinra[Title/Abstract]) OR "Interleukin 1 Receptor Antagonist Protein"[Mesh]) OR rilonacept[Title/Abstract]) OR "rilonacept" [Supplementary Concept]) OR ustekinumab [Title/Abstract]) OR "ustekinumab" [Supplementary Concept]) OR mepolizumab[Title/Abstract]) OR "mepolizumab" [Supplementary Concept]) OR tocilizumab[Title/Abstract]) OR "tocilizumab" [Supplementary Concept]) OR canakinumab[Title/Abstract]) OR "canakinumab" [Supplementary Concept]) OR briakinumab[Title/Abstract]) OR "briakinumab" [Supplementary Concept]) OR secukinumab[Title/Abstract]) OR "secukinumab" [Supplementary Concept]) OR siltuximab[Title/Abstract]) OR "siltuximab" [Supplementary Concept]) OR "belimumab" [Supplementary Concept]) OR belimumab[Title/Abstract])))) NOT (((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type]) OR "Newspaper Article"[Publication Type])))) NOT ((("Animals"[Mesh]) NOT ((("Animals"[Mesh]) AND "Humans"[Mesh]))) AND (((((((random*[Title/Abstract]) AND trial*[Title/Abstract])) OR "Randomized Controlled Trials as Topic"[Mesh:noexp]) OR "Randomized Controlled Trial"[Publication Type:noexp])) OR (((multivar*[Title/Abstract]) OR "Multivariate Analysis"[Mesh]) OR adjust*[Title/Abstract]))) AND ("2010/01/01"[PDAT] : "3000/12/31"[PDAT])	71
#106 Search ("2010/01/01"[PDAT] : "3000/12/31"[PDAT])	5194823
#105 Search (((((((((((((((("Lupus Erythematosus, Systemic/drug therapy"[Mesh] OR "Lupus Erythematosus, Systemic/therapy"[Mesh]))) OR "Systemic Lupus	92

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(continued).

Search Query	Items found
<p>Erythematosus"[Title/Abstract]) OR "SLE"[Title/Abstract]) OR "Lupus Erythematosus Disseminatus"[Title/Abstract]) OR "Libman-Sacks Disease"[Title/Abstract]) OR "Libman Sacks Disease"[Title/Abstract])) AND (((((((((((((((("infliximab" [Supplementary Concept]) OR "afelimomab" [Supplementary Concept]) OR "adalimumab" [Supplementary Concept]) OR "certolizumab pegol" [Supplementary Concept]) OR "golimumab" [Supplementary Concept]) OR infliximab[Title/Abstract]) OR afelimomab[Title/Abstract]) OR adalimumab[Title/Abstract]) OR "certolizumab pegol"[Title/Abstract]) OR golimumab[Title/Abstract]) OR "TNF inhibitor"[Title]) OR "TNF inhibitors"[Title/Abstract]) OR "TNFI"[Title/Abstract]) OR "Tumor Necrosis Factor-alpha"[Mesh]) OR "anti-TNF"[Title/Abstract]) OR "antiTNF"[Title/Abstract])) OR (((((((((((((((((((("daclizumab" [Supplementary Concept]) OR daclizumab [Title/Abstract]) OR basiliximab[Title/Abstract]) OR "basiliximab" [Supplementary Concept]) OR anakinra[Title/Abstract]) OR "Interleukin 1 Receptor Antagonist Protein"[Mesh]) OR rilonacept[Title/Abstract]) OR "rilonacept" [Supplementary Concept]) OR ustekinumab[Title/Abstract]) OR "ustekinumab" [Supplementary Concept]) OR mepolizumab[Title/Abstract]) OR "mepolizumab" [Supplementary Concept]) OR tocilizumab[Title/Abstract]) OR "tocilizumab" [Supplementary Concept]) OR canakinumab[Title/Abstract]) OR "canakinumab" [Supplementary Concept]) OR briakinumab[Title/Abstract]) OR "briakinumab" [Supplementary Concept]) OR secukinumab[Title/Abstract]) OR "secukinumab" [Supplementary Concept]) OR siltuximab[Title/Abstract]) OR "siltuximab" [Supplementary Concept]) OR "belimumab" [Supplementary Concept]) OR belimumab[Title/Abstract])))) NOT (((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type])))) NOT ((("Animals"[Mesh]) NOT ((("Animals"[Mesh]) AND "Humans"[Mesh])))) AND (((((((random*[Title/Abstract]) AND trial*[Title/Abstract])) OR "Randomized Controlled Trials as Topic"[Mesh:noexp]) OR "Randomized Controlled Trial"[Publication Type:noexp])) OR (((multivar*[Title/Abstract]) OR "Multivariate Analysis"[Mesh]) OR adjust*[Title/Abstract]))</p>	1145818
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#103 Search ((multivar*[Title/Abstract]) OR "Multivariate Analysis"[Mesh]) OR adjust*[Title/Abstract]	582073
#102 Search (((random*[Title/Abstract]) AND trial*[Title/Abstract])) OR "Randomized Controlled Trials as Topic"[Mesh:noexp]) OR "Randomized Controlled Trial"[Publication Type:noexp]	845
#98 Search (((((((((((("Lupus Erythematosus, Systemic/drug therapy"[Mesh] OR "Lupus Erythematosus, Systemic/therapy"[Mesh]))) OR "Systemic Lupus Erythematosus"[Title/Abstract]) OR "SLE"[Title/Abstract]) OR "Lupus Erythematosus Disseminatus"[Title/Abstract]) OR "Libman-Sacks Disease"[Title/Abstract]) OR	(continued)

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Search Query	Items found
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Search	Query	Items found
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#95	Search (((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type]) OR "Newspaper Article"[Publication Type]	1575909
#93	Search (((((((("Lupus Erythematosus, Systemic/drug therapy"[Mesh] OR "Lupus Erythematosus, Systemic/therapy"[Mesh]))) OR "Systemic Lupus Erythematosus"[Title/Abstract]) OR "SLE"[Title/Abstract]) OR "Lupus Erythematosus Disseminatus"[Title/Abstract]) OR "Libman-Sacks Disease"[Title/Abstract]) OR "Libman Sacks Disease"[Title/Abstract]) AND (((((((((((((((("infliximab" [Supplementary Concept]) OR "afelimomab" [Supplementary Concept]) OR "adalimumab" [Supplementary Concept]) OR "certolizumab pegol" [Supplementary Concept]) OR "golimumab" [Supplementary Concept]) OR infliximab[Title/Abstract]) OR afelimomab[Title/Abstract]) OR adalimumab[Title/Abstract]) OR "certolizumab pegol"[Title/Abstract]) OR golimumab[Title/Abstract]) OR "TNF inhibitor"[Title]) OR "TNF inhibitors"[Title/Abstract]) OR "TNFI"[Title/Abstract]) OR "Tumor Necrosis Factor-alpha"[Mesh]) OR "anti-TNF"[Title/Abstract]) OR "antiTNF"[Title/Abstract]) OR (((((((((((((((((((("daclizumab" [Supplementary Concept]) OR daclizumab [Title/Abstract]) OR basiliximab[Title/Abstract]) OR "basiliximab" [Supplementary Concept]) OR anakinra[Title/Abstract]) OR "Interleukin 1 Receptor Antagonist Protein"[Mesh]) OR rilonacept[Title/Abstract]) OR "rilonacept" [Supplementary Concept]) OR ustekinumab[Title/Abstract]) OR "ustekinumab" [Supplementary Concept]) OR mepolizumab[Title/Abstract]) OR "mepolizumab" [Supplementary Concept]) OR tocilizumab[Title/Abstract]) OR "tocilizumab" [Supplementary Concept]) OR canakinumab[Title/Abstract]) OR "canakinumab" [Supplementary Concept]) OR briakinumab[Title/Abstract]) OR "briakinumab" [Supplementary Concept]) OR secukinumab[Title/Abstract]) OR "secukinumab" [Supplementary Concept]) OR siltuximab[Title/Abstract]) OR "siltuximab" [Supplementary Concept]) OR "belimumab" [Supplementary Concept]) OR belimumab[Title/Abstract])	977
#92	Search (((((((("Lupus Erythematosus, Systemic/drug therapy"[Mesh] OR "Lupus Erythematosus, Systemic/therapy"[Mesh]))) OR "Systemic Lupus Erythematosus"[Title/Abstract]) OR "SLE"[Title/Abstract]) OR "Lupus Erythematosus Disseminatus"[Title/Abstract]) OR "Libman-Sacks Disease"[Title/Abstract]) OR "Libman Sacks Disease"[Title/Abstract]	47431
#91	Search "Libman Sacks Disease"[Title/Abstract]	15
#90	Search "Libman-Sacks Disease"[Title/Abstract]	15

(continued)

Clinical Therapeutics

(continued).

	Search Query	Items found
#89	Search "Lupus Erythematosus Disseminatus"[Title/Abstract]	205
#88	Search "SLE"[Title/Abstract]	25431
#87	Search "Systemic Lupus Erythematosus"[Title/Abstract]	38767
#86	Search ("Lupus Erythematosus, Systemic/drug therapy"[Mesh] OR "Lupus Erythematosus, Systemic/therapy"[Mesh])	11013
#83	Search (((((((((((((((("infliximab" [Supplementary Concept]) OR "afelimomab" [Supplementary Concept]) OR "adalimumab" [Supplementary Concept]) OR "certolizumab pegol" [Supplementary Concept]) OR "golimumab" [Supplementary Concept]) OR infliximab[Title/Abstract]) OR afelimomab[Title/Abstract]) OR adalimumab[Title/Abstract]) OR "certolizumab pegol"[Title/Abstract]) OR golimumab[Title/Abstract]) OR "TNF inhibitor"[Title]) OR "TNF inhibitors"[Title/Abstract]) OR "TNFI"[Title/Abstract]) OR "Tumor Necrosis Factor-alpha"[Mesh]) OR "anti-TNF"[Title/Abstract]) OR "antiTNF"[Title/Abstract])) OR (((((((((((((((((((("daclizumab" [Supplementary Concept]) OR daclizumab[Title/Abstract]) OR basiliximab[Title/Abstract]) OR "basiliximab" [Supplementary Concept]) OR anakinra[Title/Abstract]) OR "Interleukin 1 Receptor Antagonist Protein"[Mesh]) OR rilonacept[Title/Abstract]) OR "rilonacept" [Supplementary Concept]) OR ustekinumab[Title/Abstract]) OR "ustekinumab" [Supplementary Concept]) OR mepolizumab[Title/Abstract]) OR "mepolizumab" [Supplementary Concept]) OR tocilizumab[Title/Abstract]) OR "tocilizumab" [Supplementary Concept]) OR canakinumab[Title/Abstract]) OR "canakinumab" [Supplementary Concept]) OR briakinumab[Title/Abstract]) OR "briakinumab" [Supplementary Concept]) OR secukinumab[Title/Abstract]) OR "secukinumab" [Supplementary Concept]) OR siltuximab[Title/Abstract]) OR "siltuximab" [Supplementary Concept]) OR "belimumab" [Supplementary Concept]) OR belimumab[Title/Abstract])	114667
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#80	Search belimumab[Title/Abstract]	244
#79	Search "belimumab" [Supplementary Concept]	172
#77	Search "siltuximab" [Supplementary Concept]	40
#75	Search siltuximab[Title/Abstract]	56
#74	Search "secukinumab" [Supplementary Concept]	29
#72	Search secukinumab[Title/Abstract]	86

(continued)

(continued).

Search Query	Items found
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#69 Search briakinumab[Title/Abstract]	31
#68 Search "canakinumab" [Supplementary Concept]	120
#66 Search canakinumab[Title/Abstract]	188
#65 Search "tocilizumab" [Supplementary Concept]	737
#63 Search tocilizumab[Title/Abstract]	1113
#62 Search "mepolizumab" [Supplementary Concept]	107
#60 Search mepolizumab[Title/Abstract]	144
#59 Search "ustekinumab" [Supplementary Concept]	321
#57 Search ustekinumab[Title/Abstract]	544
#56 Search "rilonacept" [Supplementary Concept]	58
#53 Search rilonacept[Title/Abstract]	86
#52 Search "Interleukin 1 Receptor Antagonist Protein" [Mesh]	4060
#50 Search anakinra[Title/Abstract]	962
#49 Search "basiliximab" [Supplementary Concept]	651
#46 Search basiliximab[Title/Abstract]	949
#45 Search daclizumab[Title/Abstract]	786
#44 Search "daclizumab" [Supplementary Concept]	611
#39 Search (((((((((((("infliximab" [Supplementary Concept]) OR "afelimomab" [Supplementary Concept]) OR "adalimumab" [Supplementary Concept]) OR "certolizumab pegol" [Supplementary Concept]) OR "golimumab" [Supplementary Concept]) OR infliximab[Title/Abstract]) OR afelimomab[Title/Abstract]) OR adalimumab[Title/Abstract]) OR "certolizumab pegol"[Title/Abstract]) OR golimumab[Title/Abstract]) OR "TNF inhibitor"[Title]) OR "TNF inhibitors"[Title/Abstract]) OR "TNFI"[Title/Abstract]) OR "Tumor Necrosis Factor-alpha"[Mesh]) OR "anti-TNF"[Title/Abstract]) OR "antiTNF"[Title/Abstract]	107661
#38 Search "antiTNF"[Title/Abstract]	26
#37 Search "anti-TNF"[Title/Abstract]	7209
#36 Search "Tumor Necrosis Factor-alpha" [Mesh]	98552
#32 Search "TNFI"[Title/Abstract]	152
#29 Search "TNF inhibitors"[Title/Abstract]	686
#28 Search "TNF inhibitor"[Title]	58
#27 Search golimumab[Title/Abstract]	409
#26 Search "certolizumab pegol"[Title/Abstract]	338
#25 Search adalimumab[Title/Abstract]	3523
#24 Search afelimomab[Title/Abstract]	9
#23 Search infliximab[Title/Abstract]	8179
#22 Search "golimumab" [Supplementary Concept]	239
#20 Search "certolizumab pegol" [Supplementary Concept]	299
#18 Search "adalimumab" [Supplementary Concept]	2864
#16 Search "afelimomab" [Supplementary Concept]	10
#14 Search "infliximab" [Supplementary Concept]	7211

Clinical Therapeutics

Embase
Session Results

No. Query Results

Results Date

#66. 'systemic lupus

486 26 May 2015

erythematosus'/exp/dm_dt,dm_th,dm_dr,dm_dm OR
'systemic lupus':ab,ti OR 'sle':ab,ti AND ('tumor
necrosis factor alpha converting enzyme
inhibitor'/de OR 'tace inhibitor':ab,ti OR 'tace
inhibitors':ab,ti OR 'tnf alpha converting enzyme
inhibitor':ab,ti OR 'tumour necrosis factor alpha
converting enzyme inhibitor':ab,ti OR 'tnf
inhibitor':ab,ti OR 'tnf inhibitors':ab,ti OR
'tnfi':ab,ti OR 'anti-tnf':ab,ti OR
'antirheumatic agent'/exp OR 'monoclonal
antibody'/exp OR infliximab:ab,ti OR
afelimomab:ab,ti OR adalimumab:ab,ti OR
'certolizumab pegol':ab,ti OR golimumab:ab,ti OR
daclizumab:ab,ti OR basiliximab:ab,ti OR
anakinra:ab,ti OR rilonacept:ab,ti OR
ustekinumab:ab,ti OR mepolizumab:ab,ti OR
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brikinumab:ab,ti OR secukinumab:ab,ti OR
siltuximab:ab,ti OR belimumab:ab,ti) NOT
(('letter'/de OR 'editorial'/de OR 'note'/de OR
'conference paper'/de OR 'short survey'/exp OR
'conference abstract'/it) NOT ('animal'/exp NOT
(('animal'/exp AND 'human'/exp)) AND ('randomized
controlled trial'/exp OR 'randomized controlled
trial (topic)'/exp OR (random*:ab,ti AND
trial*:ab,ti) OR multivar*:ab,ti OR adjust*:ab,ti
OR 'multivariate analysis'/exp) AND [1-1-2010])/sd

PubMed search of record for RCTs per Peer
Reviewer:

((((((((((((((((((("rituximab" [Supplementary Concept]) OR rituximab[Title/Abstract]) OR "TACI receptor-IgG Fc fragment fusion protein" [Supplementary Concept]) OR atacicept[Title/Abstract]) OR abatacept[Title/Abstract]) OR "abatacept" [Supplementary Concept]) OR "sifalimumab" [Supplementary Concept]) OR sifalimumab[Title/Abstract]) OR "rontalizumab" [Supplementary Concept]) OR rontalizumab[Title/Abstract]) OR blisibimod[Title/Abstract]) OR "AMG623 peptibody" [Supplementary Concept])) AND (((("Lupus Erythematosus, Systemic/drug therapy"[Mesh]) OR

lupus[Title/Abstract]) OR "SLE"[Title/Abstract])))) NOT (((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type])) NOT ((("Animals"[Mesh]) NOT ((("Animals"[Mesh]) AND "Humans"[Mesh])))) AND (((((((random*[Title/Abstract]) AND control*[Title/Abstract]) AND trial*[Title/Abstract])) OR "Randomized Controlled Trial"[Publication Type:noexp]) OR "Randomized Controlled Trials as Topic"[Mesh:noexp])) AND ("2010/01/01"[PDAT] : "3000/12/31"[PDAT]))

Search Query	Items found
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#40 Search ("2010/01/01"[PDAT] : "3000/12/31"[PDAT])	5298255
#39 Search (((((((((((((((((((("rituximab" [Supplementary Concept]) OR rituximab[Title/Abstract]) OR "TACI receptor-IgG Fc fragment fusion protein" [Supplementary Concept]) OR atacicept[Title/Abstract]) OR abatacept[Title/Abstract]) OR "abatacept" [Supplementary Concept]) OR "sifalimumab" [Supplementary Concept]) OR sifalimumab[Title/Abstract]) OR "rontalizumab" [Supplementary Concept]) OR rontalizumab[Title/Abstract]) OR blisibimod[Title/Abstract]) OR "AMG623 peptibody" [Supplementary Concept])) AND (((("Lupus Erythematosus, Systemic/drug therapy"[Mesh]) OR lupus[Title/Abstract]) OR "SLE"[Title/Abstract])) NOT (((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type]) OR "Newspaper Article"[Publication Type])) NOT ((("Animals"[Mesh]) NOT ((("Animals"[Mesh]) AND "Humans"[Mesh])))) AND (((((((random*[Title/Abstract]) AND control*[Title/Abstract]) AND trial*[Title/Abstract]) OR "Randomized Controlled Trial"[Publication Type:noexp]) OR "Randomized Controlled Trials as Topic"[Mesh:noexp]))	97
#38 Search (((((((random*[Title/Abstract]) AND control*[Title/Abstract]) AND trial*[Title/Abstract]) OR "Randomized Controlled Trial"[Publication Type:noexp]) OR "Randomized Controlled Trials as Topic"[Mesh:noexp])	545098
#37 Search (((((((((((((((((((("rituximab" [Supplementary Concept]) OR rituximab[Title/Abstract]) OR "TACI receptor-IgG Fc fragment fusion protein" [Supplementary Concept]) OR atacicept[Title/Abstract]) OR abatacept[Title/Abstract]) OR "abatacept" [Supplementary Concept]) OR "sifalimumab" [Supplementary Concept]) OR sifalimumab[Title/Abstract]) OR "rontalizumab" [Supplementary Concept]) OR rontalizumab[Title/Abstract]) OR blisibimod[Title/Abstract]) OR "AMG623 peptibody" [Supplementary Concept])) AND (((("Lupus Erythematosus, Systemic/drug therapy"[Mesh]) OR lupus[Title/Abstract]) OR "SLE"[Title/Abstract])) NOT (((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR	771

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Clinical Therapeutics

(continued).

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#35	Search (((((((((((("rituximab" [Supplementary Concept]) OR rituximab[Title/Abstract]) OR "TACI receptor-IgG Fc fragment fusion protein" [Supplementary Concept]) OR atacicept[Title/Abstract]) OR abatacept[Title/Abstract]) OR "abatacept" [Supplementary Concept]) OR "sifalimumab" [Supplementary Concept]) OR sifalimumab[Title/Abstract]) OR "rontalizumab" [Supplementary Concept]) OR rontalizumab[Title/Abstract]) OR blisibimod[Title/Abstract]) OR "AMG623 peptibody" [Supplementary Concept])) AND (((("Lupus Erythematosus, Systemic/drug therapy"[Mesh]) OR lupus[Title/Abstract]) OR "SLE"[Title/Abstract])))) NOT (((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type])	792
#34	Search (((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]	1584192
#32	Search (((((((((((("rituximab" [Supplementary Concept]) OR rituximab[Title/Abstract]) OR "TACI receptor-IgG Fc fragment fusion protein" [Supplementary Concept]) OR atacicept[Title/Abstract]) OR abatacept[Title/Abstract]) OR "abatacept" [Supplementary Concept]) OR "sifalimumab" [Supplementary Concept]) OR sifalimumab[Title/Abstract]) OR "rontalizumab" [Supplementary Concept]) OR rontalizumab[Title/Abstract]) OR blisibimod[Title/Abstract]) OR "AMG623 peptibody" [Supplementary Concept])) AND (((("Lupus Erythematosus, Systemic/drug therapy"[Mesh]) OR lupus[Title/Abstract]) OR "SLE"[Title/Abstract])	873
#31	Search ((("Lupus Erythematosus, Systemic/drug therapy"[Mesh]) OR lupus[Title/Abstract]) OR "SLE"[Title/Abstract]	65397
#30	Search "SLE"[Title/Abstract]	25589
#29	Search lupus[Title/Abstract]	61000
#28	Search "Lupus Erythematosus, Systemic/drug therapy"[Mesh]	7386
#25	Search (((((((((((("rituximab" [Supplementary Concept]) OR rituximab[Title/Abstract]) OR "TACI receptor-IgG Fc fragment fusion protein" [Supplementary Concept]) OR atacicept[Title/Abstract]) OR abatacept[Title/Abstract]) OR "abatacept" [Supplementary Concept]) OR "sifalimumab" [Supplementary Concept]) OR sifalimumab[Title/Abstract]) OR "rontalizumab" [Supplementary Concept]) OR rontalizumab[Title/Abstract]) OR blisibimod[Title/Abstract]) OR "AMG623 peptibody" [Supplementary Concept]	16559
#23	Search "AMG623 peptibody" [Supplementary Concept]	5
#21	Search blisibimod[Title/Abstract]	6
#20	Search rontalizumab[Title/Abstract]	5
#19	Search "rontalizumab" [Supplementary Concept]	2
#17	Search sifalimumab[Title/Abstract]	12

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(continued).

Search Query	Items found
#16 Search "sifalimumab" [Supplementary Concept]	9
#12 Search "abatacept" [Supplementary Concept]	2246
#10 Search abatacept[Title/Abstract]	762
#9 Search atacicept[Title/Abstract]	67
#8 Search "TACI receptor-IgG Fc fragment fusion protein" [Supplementary Concept]	52
#4 Search rituximab[Title/Abstract]	12397
#3 Search "rituximab" [Supplementary Concept]	9050

Embase Session Results

No. Query	Results
#31	212
#30 AND [1-1-2010]/sd	
#30	265
#25 AND #29	
#29	553,144
#26 OR #27 OR #28	
#28	301,631
random*:ab,ti AND control* AND trial*:ab,ti	
#27	66,246
'randomized controlled trial (topic)'/exp	
#26	359,537
'randomized controlled trial'/exp	
#25	2,182
#20 NOT #24	
#24	4,737,852
#21 NOT #23	
#23	15,578,685
#21 AND #22	
	15,578,685
	(continued)

Clinical Therapeutics

(continued).

#22 'human'/exp	20,265,320
#21 'animal'/exp	2,198
#20 #18 NOT #19	5,084,493
#19 'letter'/de OR 'editorial'/de OR 'note'/de OR 'conference paper'/de OR 'short survey'/exp OR 'conference abstract'/it	3,218
#18 #13 AND #17	92,609
#17 #14 OR #15 OR #16	37, 521
#16 'sle':ab,ti	83,674
#15 lupus:ab,ti	12,691
#14 'systemic lupus erythematosus'/exp/dm_dt	49,844
#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	17
#12 'blisibimod':ab,ti	96
#11 'blisibimod'/de	19
#10 'sifalimumab':ab,ti	132
#9 'sifalimumab'/de	1,981
#8 'abatacept':ab,ti	4,902

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(continued).

#7	
'abatacept'/de	99
#6	
'atacept':ab,ti	419
#5	
'atacept'/de	131
#4	
'ocrelizumab':ab,ti	588
#3	
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#2	
'rituximab':ab,ti	45,949
#1	
'rituximab'/de	



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Reference list

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APPENDIX B

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PubMed search of record for: CPGs

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PubMed search of record for RCTs per Peer Reviewer:

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Clinical Therapeutics

Trials as Topic"[Mesh:noexp])) AND ("2010/01/01"[PDAT] : "3000/12/31"[PDAT])

Embase

Session Results

No. Query Results

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No. Query

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APPENDIX D

GRADE Summary of Findings Appendix D Table I. Immunosuppressive agents plus adjunctive belimumab versus immunosuppressive agents alone in adults with moderate to severe extrarenal* SLE who have had an inadequate response to immunosuppressive agents

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
Mean utility (US) change from baseline, 52-76 weeks	NR	NR	MD 0.00 (-0.03;0.03) SMD 0.00 (-0.12;0.12)	1121 (2 RCTs) ^{31,49,50,61}	Moderate	No difference
Quality of life (mean EQ-5D VAS score), change from baseline, 52-76 weeks	NR	NR	MD 1.89 (-0.52;4.30) SMD 0.09 (-0.03;0.21)	1121 (2 RCTs) ^{31,49,50,61}	Moderate	No difference
SF-36, physical health score change from baseline at week 52	NR	NR	MD 1.38 (-0.28;3.04) SMD 0.14 (-0.03;0.30)	571 (2 RCTs) ^{32,49,50,61}	Moderate	No difference
Subgroup: low complement/anti-dsDNA-positive						
SLE severity: number of subjects with improvement/good result, 52 weeks	378	385	RR 1.0 (0.7;1.4)	220 (1 RCT) ⁶¹	Very low	No difference
Subgroup: Asia-Pacific						
SLE severity: number of subjects with improvement/good result, 52 weeks	594	490	RR 1.21 (0.98;1.50)	288 (1 RCT) ⁶¹	Very low	No difference
Subgroup: Latin America						
SELENA-SLEDAI renal, 52 weeks	526	278	RR 1.9 (0.8;4.5)	37 (2 RCTs) ^{34,44,61}	Low	No difference
Subgroup: mycophenolate mofetil at baseline						
BILAG renal, 52 weeks	324	200	RR 1.6 (0.7;3.7)	69 (2 RCTs) ^{34,44,61}	Low	No difference
Subgroup: mycophenolate mofetil at baseline						
Proteinuria grades 3/4 (> 2.0 g/24 h), 52 weeks	34	48	RR 0.7 (0.4;1.4)	862 (2 RCTs) ^{34,44,61}	Low	No difference
Creatinine serum grades 3/4 (> 3 ULN), 52 weeks	4	7	RR 0.5 (0.1;2.8)	1116 (2 RCTs) ^{34,44,61}	Low	No difference

(continued)

Appendix D Table I. (continued).

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
Renal flare, 52 weeks	25	30	RR 0.8 (0.4;1.7)	1121 (2 RCTs) ^{34,44,61}	Low	No difference
BILAG worsening: musculoskeletal, 52 weeks	39	50	RR 0.8 (0.4;1.4)	1030 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
BILAG worsening: mucocutaneous, 52 weeks	43	45	RR 1.0 (0.6;1.7)	1069 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
BILAG worsening: general, 52 weeks	29	32	RR 0.9 (0.5;1.7)	1115 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
BILAG worsening: renal, 52 weeks	49	75	RR 0.65 (0.41;1.04)	1114 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
BILAG worsening: vasculitis, 52 weeks	4	16	RR 0.22 (0.05;1.03)	1091 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
BILAG worsening: cardiovascular/respiratory, 52 weeks	9	9	RR 1.0 (0.3;3.5)	1112 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
BILAG worsening: neurologic, 52 weeks	5	7	RR 0.8 (0.2;3.4)	1118 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: musculoskeletal, 52 weeks	61	68	RR 0.9 (0.4;1.9)	387 (2 RCTs) ^{29,44,61}	Low	No difference

(continued)

Appendix D Table I. (continued).

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: mucocutaneous, 52 weeks	136	129	RR 1.1 (0.5;2.2)	196 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: immunologic, 52 weeks	149	187	RR 0.8 (0.4;1.4)	237 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: hematologic, 52 weeks	47	65	RR 0.7 (0.4;1.2)	1034 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: constitutional, 52 weeks	7	7	RR 1.0 (0.3;4.0)	1101 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: vasculitis, 52 weeks	4	4	RR 1.0 (0.1;7.1)	1048 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: serositis, 52 weeks	8	19	RR 0.4 (0.1;1.3)	1053 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: CNS	6	4	RR 1.5 (0.3;9.1)	1095 (2 RCTs) ^{29,44,61}	Low	No difference

(continued)

Appendix D Table I. (continued).

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
Subgroup: baseline BILAG <9 (no A domain score), 52 weeks						
Treatment discontinuation due to adverse effects, 52-76 weeks	62	70	RR 0.9 (0.6;1.3)	1348 (3 RCTs) ^{33,48-50,61}	Low	No difference
≥ 1 serious adverse effects, 52-76 weeks	195	166	RR 1.2 (0.9;1.5)	1348 (3 RCTs) ^{33,48-50,61}	Low	No difference
≥ 1 severe adverse effects, 52-76 weeks	159	159	RR 1.0 (0.8;1.3)	1348 (3 RCTs) ^{33,48-50,61}	Low	No difference
<p>Population: Adults with moderate to severe extrarenal* SLE who have had an inadequate response to immunosuppressive agents</p> <p>Setting: Outpatient</p> <p>Intervention: Prednisone alone or combined with antimalarial drugs, NSAIDs, and/or immunosuppressive therapies plus adjunctive belimumab (1 mg/kg intravenously on days 0, 14, and 28; then every 28 days for 48 weeks)</p> <p>Comparator: Prednisone alone or combined with antimalarial drugs, NSAIDs, and/or immunosuppressive therapies.</p> <p>Abbreviations: BILAG, British Isles Lupus Assessment Group; dsDNA, double-stranded DNA; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; NR, not reported; RCT, randomized controlled trial; RR, relative risk; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SF-36, 36-Item Short Form Survey; SMD, standardized mean difference; ULN, upper limit of normal; VAS, visual analog scale.</p> <p>*Extrarenal manifestations: vasculitis, hematologic, mucocutaneous, neurologic, musculoskeletal, cardiovascular, and respiratory.</p>						

GRADE Summary of Findings Appendix D Table II. Immunosuppressive agents plus adjunctive belimumab versus immunosuppressive agents alone in adults with moderate to severe extrarenal* SLE who have had an inadequate response to immunosuppressive agents

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
BILAG renal, 52 weeks	306	200	RR 1.5 (0.7;3.5)	71 (2 RCTs) ^{34,44,61}	Low	No difference
Subgroup: mycophenolate mofetil at baseline						
Mean utility (US) change from baseline, 52-76 weeks	NR	NR	MD 0.01 (-0.02;0.04) SMD 0.04 (-0.07;0.16)	1125 (2 RCTs) ^{31,49,50,61}	Moderate	No difference
Mean EQ-5D VAS score change from baseline, 52-76 weeks	NR	NR	MD 0.11 (-2.44;2.66) SMD 0.01 (-0.11;0.12)	1125 (2 RCTs) ^{31,49,50,61}	Moderate	No difference
SF-36 PCS score change from baseline, week 52	NR	NR	MD 1.57 (-0.09;3.23) SMD 0.15 (-0.01;0.31)	592 (2 RCTs) ^{32,49,50,61}	Moderate	No difference
Subgroup: low complement/anti-dsDNA-positive						
FACIT-Fatigue score improvement from baseline, week 52	NR	NR	MD 2.27 (0.16;4.38) SMD 0.17 (0.01;0.34)	592 (2 RCTs) ^{32,49,50,61}	Moderate	No difference
Subgroup: low complement/anti-dsDNA-positive						
BILAG, no worsening, 76 weeks	634	589	RR 1.1 (0.9;1.2)	548 (1 RCT) ⁴⁴	Very low	No difference
PGA, no worsening, 76 weeks	630	582	RR 1.1 (0.9;1.2)	548 (1 RCT) ⁴⁴	Very low	No difference
SLE severity: number of subjects with improvement/good result, 52 weeks	496	385	RR 1.29 (0.95;1.73)	228 (1 RCT) ⁶¹	Very low	No difference
Subgroup: Asia-Pacific						
Proteinuria grades 3/4 (> 2.0 g/24 h), 52 weeks	34	48	RR 0.7 (0.4;1.4)	862 (2 RCTs) ^{34,44,61}	Low	No difference
Creatinine grades 3/4 (> 3 ULN), 52 weeks	4	7	RR 0.5 (0.1;2.7)	1123 (2 RCTs) ^{34,44,61}	Low	No difference
Renal flare, 52 weeks	14	30	RR 0.5 (0.2;1.1)	1125 (2 RCTs) ^{34,44,61}	Low	No difference
BILAG worsening: musculoskeletal, 52 weeks	38	50	RR 0.8 (0.4;1.3)	1043 (2 RCTs) ^{29,44,61}	Low	No difference

(continued)

Appendix D Table II. (continued).

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
Subgroup: baseline BILAG <9 (no A domain score)						
BILAG worsening: mucocutaneous, 52 weeks	54	45	RR 1.2 (0.7;2.0)	1079 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
BILAG worsening: hematologic, 52 weeks	66	91	RR 0.7 (0.5;1.1)	1120 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
BILAG worsening: general, 52 weeks	34	32	RR 1.0 (0.6;2.0)	1117 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
BILAG worsening: renal, 52 weeks	61	75	RR 0.8 (0.5;1.3)	1121 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
BILAG worsening: vasculitis, 52 weeks	6	16	RR 0.3 (0.1;1.2)	1092 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
BILAG worsening: cardiovascular/respiratory, 52 weeks	11	9	RR 1.2 (0.4;3.9)	1119 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score), 52 weeks						
BILAG worsening: neurologic, 52 weeks	11	7	RR 1.5 (0.4;5.3)	1124 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: musculoskeletal, 52 weeks	41	68	RR 0.6 (0.3;1.4)	385 (2 RCTs) ^{29,44,61}	Low	No difference

(continued)

Appendix D Table II. (continued).

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: mucocutaneous, 52 weeks	128	129	RR 1.0 (0.5;2.0)	202 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: constitutional, 52 weeks	11	7	RR 1.5 (0.4;5.3)	1103 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: renal, 52 weeks	65	85	RR 0.8 (0.5;1.2)	948 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: vasculitis, 52 weeks	6	4	RR 1.5 (0.3;8.9)	1050 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: serositis, 52 weeks	8	19	RR 0.4 (0.1;1.3)	1056 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: CNS, 52 weeks	4	4	RR 1.0 (0.1;7.2)	1095 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: renal, 52 weeks	65	85	RR 0.8 (0.5;1.2)	948 (2 RCTs) ^{29,44,61}	Low	No difference

(continued)

Appendix D Table II. (continued).

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: vasculitis, 52 weeks	6	4	RR 1.5 (0.3;8.9)	1050 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: serositis, 52 weeks	8	19	RR 0.4 (0.1;1.3)	1056 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
SELENA-SLEDAI worsening: CNS, 52 weeks	4	4	RR 1.0 (0.1;7.2)	1095 (2 RCTs) ^{29,44,61}	Low	No difference
Subgroup: baseline BILAG <9 (no A domain score)						
Treatment discontinuation due to adverse effects, 52-76 weeks	68	70	RR 1.0 (0.7;1.5)	1349 (3 RCTs) ^{33,48-50,61}	Low	No difference
≥ 1 serious adverse effects, 52-76 weeks	180	166	RR 1.1 (0.9;1.4)	1349 (3 RCTs) ^{33,48-50,61}	Low	No difference
≥ 1 severe adverse effects, 52-76 weeks	154	159	RR 1.0 (0.8;1.2)	1349 (3 RCTs) ^{33,48-50,61}	Low	No difference

Population: Adults with moderate to severe extrarenal* SLE who have had an inadequate response to immunosuppressive agents

Setting: Outpatient

Intervention: Prednisone alone or combined with antimalarial drugs, NSAIDs, and/or immunosuppressive therapies plus adjunctive belimumab (10 mg/kg intravenously on days 0, 14, and 28; then every 28 days for 48 weeks)

Comparator: Prednisone alone or combined with antimalarial drugs, NSAIDs, and/or immunosuppressive therapies.

Abbreviations: BILAG, British Isles Lupus Assessment Group; CNS, central nervous system; dsDNA, double-stranded DNA; FACIT, Functional Assessment of Chronic Illness Therapy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; NR, not reported; PCS, physical component summary; PGA, Physician Global Assessment; RCT, randomized controlled trial; RR, relative risk; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SF-36, 36-Item Short Form Survey; SMD, standardized mean difference; ULN, upper limit of normal; VAS, visual analog scale.

* Extrarenal manifestations: vasculitis, hematologic, mucocutaneous, neurologic, musculoskeletal, cardiovascular, and respiratory.

GRADE Summary of Findings Appendix D Table III. Comparative effectiveness of prednisone plus off-label adjunctive atacept versus prednisone alone for flare prevention in adults with inactive SLE treated with stable doses of immunosuppressive agents

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
All-cause mortality, 52 weeks	14	0	RR 5.4 (0.3;111.8)	302 (1 RCT) ⁵¹	Very low	No difference
Flare,* 76 weeks	370	539 Attributable avoided events per 1000 treated 171 (60;282)	RR 0.7 (0.5;0.9) NNTp 6 (4;17)	298 (1 RCT) ⁵¹	Very low	Favors atacept
Total adverse events that led to treatment discontinuation, 52 weeks	111	110	RR 1.0 (0.5;1.9)	298 (1 RCT) ⁵¹	Very low	No difference
Total serious adverse events, 76 weeks	160	175	RR 0.9 (0.5;1.5)	298 (1 RCT) ⁵¹	Very low	No difference
Infections, 76 weeks	590	539	RR 1.1 (0.9;1.3)	298 (1 RCT) ⁵¹	Very low	No difference

Population: Adults with inactive SLE on stable doses of azathioprine (≤ 3 mg/kg/day), hydroxychloroquine (≤ 400 mg/day), chloroquine (≤ 250 mg/day), and/ or methotrexate (≤ 25 mg/week)

Setting: Outpatient

Intervention: Prednisone plus off-label adjunctive atacept (150 mg subcutaneous twice weekly for 4 weeks, then weekly for 48 weeks). Background immunosuppressive agents were continued

Comparator: Prednisone alone. Background immunosuppressive agents were continued.

Abbreviations: BILAG, British Isles Lupus Assessment Group; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNTp, number needed to treat to prevent 1 event; RCT, randomized controlled trial; RR, relative risk.

* Increase in BILAG A or B score due to new worsening in any of the 8 organ systems during treatment, or imputed for subjects who had premature treatment discontinuation.

GRADE Summary of Findings Appendix D Table IV. Adjunctive blisibimod in adults with moderate to severe SLE who have had an inadequate response to immunosuppressive agents

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
SRI-5 responder rate,* 24 weeks Subgroup: severe SLE	542	404	RR 1.3 (0.9;2.1)	95 (1 RCT) ⁴⁶	Very low	No difference
SRI-5 responder rate,* 24 weeks	435	348	RR 1.3 (0.9;1.8)	184 (1 RCT) ⁴⁶	Very low	No difference
SRI-6 responder rate,* 24 weeks	413	337	RR 1.2 (0.8;1.8)	184 (1 RCT) ⁴⁶	Very low	No difference
SRI-6 responder rate,* 24 weeks Subgroup: severe SLE	542	383	RR 1.4 (0.9;2.2)	95 (1 RCT) ⁴⁶	Very low	No difference
SRI-7 responder rate,* 24 weeks	250	87	RR 2.9 (1.4;6.1)	184 (1 RCT) ⁴⁶	Very low	Favors blisibimod
		Attributable events per 1000 treated 163 (57;269)	NNT 6 (4;17)			
SRI-7 responder rate,* 24 weeks Subgroup: severe SLE	417	128	RR 3.3 (1.4;7.4)	95 (1 RCT) ⁴⁶	Very low	Favors blisibimod
		Attributable events per 1000 treated 289 (120;458)	NNT 3 (2;8)			
SRI-8 responder rate,* 24 weeks	250	76	RR 3.3 (1.5;7.3)	184 (1 RCT) ⁴⁶	Very low	Favors blisibimod
		Attributable events per 1000 treated 174 (70;278)	NNT 6 (4;14)			
Serious adverse events leading to treatment discontinuation, 24 weeks	65	79	RR 0.8 (0.3;2.0)	358 (1 RCT) ⁴⁶	Very low	No difference
Total serious adverse events, 24 weeks	76	158	RR 0.48 (0.22;1.03)	358 (1 RCT) ⁴⁶	Very low	Favors blisibimod in absolute scale
		Attributable avoided events per 1000 treated 82 (12;151)	NNTp 12 (7;82)			
Total adverse events, 24 weeks	837	850	RR 1.0 (0.9;1.1)	358 (1 RCT) ⁴⁶	Very low	No difference

Population: Adults with moderate to severe SLE who have had an inadequate response to immunosuppressive agents

Setting: Outpatient

Intervention: Prednisone alone or combined with immunosuppressive therapies plus adjunctive epratuzumab (any dose intravenously, weekly)

Comparator: Prednisone alone or combined with immunosuppressive therapies

Abbreviations: BILAG, British Isles Lupus Assessment Group; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat; NNTp, number needed to treat to prevent 1 event; RCT, randomized controlled trial; RR, relative risk; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SRI, SLE Responder Index.

* Achieving ≥ 5 -8 point decrease in SELENA-SLEDAI score from baseline without new BILAG 1A or 2B organ domain flares and no worsening in Physician Global Assessment (<0.3 increase) or need for an increase in background steroid or immunosuppressive medication.

GRADE Summary of Findings Appendix D Table V. Immunosuppressive agents plus adjunctive epratuzumab versus immunosuppressive agents alone in adults with moderate to severe SLE who have had an inadequate response to immunosuppressive agents

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
Mortality, all-cause, 12 weeks	4	0	RR 5.49 (0.23;131.69)	342 (3 RCTs) ^{63,65}	Low	No difference
BILAG response, * 12-24 weeks	416	246	RR 1.95 (1.21;3.14) NNT 4 (3;12)	160 (3 RCTs) ^{63,65}	Low	Favors epratuzumab
		Attributable events per 1000 treated 225 (82;368)				
BILAG-based Combined Lupus Assessment response**, 12 weeks	432	211	RR 2.05 (1.05;4.01) NNT 5 (3;20)	112 (1 RCT) ⁶⁵	Very low	Favors epratuzumab
		Attributable events per 1000 treated 222 (50;394)				
Enhanced BILAG response, 12 weeks	311	211	RR 1.48 (0.73;2.98)	112 (1 RCT) ⁶⁵	Very low	No difference
Total adverse events that led to treatment discontinuation, 12 weeks	40	67	RR 0.83 (0.14;4.80)	302 (3 RCTs) ^{63,65}	Low	No difference
Total serious adverse events, 12 weeks	119	187	RR 1.10 (0.62;1.96)	302 (3 RCTs) ^{63,65}	Low	No difference
Adverse events, infection-related, 12 weeks	406	395	RR 1.03 (0.67;1.58)	226 (1 RCT) ⁶⁵	Very low	No difference
Opportunistic infections, 24 weeks (> 1 infection)	897	703	RR 1.3 (1.0003;1.6273) NNT 5 (3;105)	66 (2 RCTs) ^{63,76,77}	Low	Favors immuno-suppressive agents***
		Attributable events per 1000 treated 194 (10;378)				
Total adverse events, 12 weeks	749	813	RR 1.07 (0.97;1.18)	302 (3 RCTs) ^{63,65}	Low	No difference

Population: Adults with moderate to severe SLE who have had an inadequate response to immunosuppressive agents

Setting: Outpatient

Intervention: Prednisone alone or combined with immunosuppressive therapies plus adjunctive epratuzumab (any dose intravenously, weekly)

Comparator: Prednisone alone or combined with immunosuppressive therapies

Abbreviations: BILAG, British Isles Lupus Assessment Group; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat; RCT, randomized controlled trial; RR, relative risk.

* Reduction by ≥ 1 score in BILAG.

** Requirements for BICLA response were: BILAG-2004 improvement (all A scores at baseline improved to B/C/D, and all B scores improved to C or D); no worsening in disease activity (no new BILAG-2004 A scores and ≤ 1 new B score); no worsening of total SLEDAI-2K score from baseline; no significant deterioration ($< 10\%$ worsening) in 100 mm visual analogue PGA and no treatment failure (defined as non-protocol treatment, i.e., new or increased immunosuppressives or antimalarials; or increased or parenteral corticosteroids; or premature discontinuation from study treatment). *** NNT was calculated at the longest time of follow-up in SL0006 study

GRADE Summary of Findings Appendix D Table VI. Prednisone alone or combined hydroxychloroquine plus adjunctive rontalizumab in adults with moderate to severe SLE who have had an inadequate response to immunosuppressive agents

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
BILAG response,* 24 weeks	455	418	RR 1.1 (0.8;1.5)	235 (1 RCT) ⁵³	Very low	No difference
BILAG response, 24 weeks subgroup: ISM-High	431	473	RR 0.9 (0.6;1.3)	178 (1 RCT) ⁵³	Very low	No difference
BILAG response, 24 weeks subgroup: ISM-Low	545	417	RR 1.3 (0.7;2.3)	57 (1 RCT) ⁵³	Very low	No difference
SRI-4 response, [†] 24 weeks	506	456	RR 1.1 (0.8;1.5)	235 (1 RCT) ⁵³	Very low	No difference
SRI-4, 24 weeks subgroup: ISM-High	447	382	RR 1.2 (0.8;1.7)	178 (1 RCT) ⁵³	Very low	No difference
SRI-4, 24 weeks subgroup: ISM-Low	727	500	RR 1.5 (0.9;2.3) ARD 31.1% (8.9-51.0%) [‡]	57 (1 RCT) ⁵³	Very low	Favors rontalizumab
Total adverse events leading to treatment discontinuation, 24 weeks	38	51	RR 0.8 (0.2;2.6)	235 (1 RCT) ⁵³	Very low	No difference
Total serious adverse events, 24 weeks	103	114	RR 0.9 (0.4;1.9)	235 (1 RCT) ⁵³	Very low	No difference
Infection, serious adverse event, 24 weeks	6	38	RR 0.2 (0.0;1.6)	235 (1 RCT) ⁵³	Very low	No difference
Total adverse events, 24 weeks	821	861	RR 1.0 (0.8;1.1)	235 (1 RCT) ⁵³	Very low	No difference

Population: Adults with moderate to severe SLE who have had an inadequate response to immunosuppressive agents

Setting: Outpatient

Intervention: Prednisone alone or combined hydroxychloroquine plus adjunctive rontalizumab (750 mg intravenously every 4 weeks or 300 mg subcutaneously every 2 weeks)

Comparator: Prednisone alone or combined with immunosuppressive therapies

Abbreviations: ARD, absolute risk difference; BILAG, British Isles Lupus Assessment Group; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ISM, interferon signature metric gene expression; RCT, randomized controlled trial; RR, relative risk; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SRI, SLE Responder Index.

* BILAG Index response: reduction of all BILAG A domains present at randomization to BILAG B or better and all BILAG B domains to BILAG C or better, with no new BILAG A or more than one new BILAG B and without being classified as treatment failure due to additional therapies. A = most active disease; B = intermediate activity; C = mild, stable disease; D = previous involvement, currently inactive; E = no previous activity.

† A reduction from baseline in the SLE Disease Activity Index (SLEDAI-2K) score of ≥ 4 points, no increase in the *Physician Global Assessment* score of >0.3 point on a visual analogue scale of 0-3, no new A score on the BILAG-2004, and ≤ 1 new B score.

‡ Absolute risk difference adjusted for race/ethnicity and previous use of immunosuppressant agents.

GRADE Summary of Findings Appendix D Table VII. Adjunctive ocrelizumab in adults with severe SLE who have had an inadequate response to immunosuppressive agents

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
Mortality - All cause, 48 weeks	39	48	RR 0.8 (0.3;2.6)	252 (1 RCT) ⁵⁹	Very low	No difference
Overall Response Rate, 48 weeks	671	547	RR 1.2 (0.9;1.6)	148 (1 RCT) ⁵⁹	Very low	No difference
Complete renal response, 48 weeks	315	347	RR 0.9 (0.6;1.4)	148 (1 RCT) ⁵⁹	Very low	No difference
Partial renal response, 48 weeks	356	200	RR 1.78 (1.03;3.08) NNT 6 (3;72)	148 (1 RCT) ⁵⁹	Very low	Favors adjunctive ocrelizumab
		Attributable events per 1000 treated 156 (14;299)				
Total adverse events, 48 weeks	803	880	RR 0.91 (0.82;1.02)	252 (1 RCT) ⁵⁹	Very low	No difference
Total serious adverse events, 48 weeks	220	272	RR 0.81 (0.52;1.25)	252 (1 RCT) ⁵⁹	Very low	No difference
Opportunistic infections, 48 weeks	591	560	RR 1.05 (0.85;1.30)	252 (1 RCT) ⁵⁹	Very low	No difference

Population: Adults with severe SLE who have had an inadequate response to immunosuppressive agents

Setting: Outpatient

Intervention: Adjunctive ocrelizumab (1000 mg intravenously in days 1 and 15, followed by a single infusion at week 16 and then every 16 weeks until 48 weeks) plus standard care

Comparator: Standard care

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation;

Overall response as complete or partial response; complete renal response (normal serum creatinine [$\leq 25\%$ increase from baseline] and improvement in urinary protein: urinary creatinine ratio to < 0.5); partial renal response (serum creatinine $\geq 25\%$ above baseline, and 50% improvement in urinary protein: urinary creatinine ratio, and if baseline ratio > 3.0 , then urinary protein: urinary creatinine ratio < 3.0)

GRADE Summary of Findings Appendix D Table VIII. Adjunctive tabalumab in adults with moderate-to-severe SLE who have had an inadequate response to immunosuppressive agents

Outcomes at 52 weeks	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
SRI-5 after tabalumab every 2 weeks	318	293	RR 1.08 (0.87;1.34)	760 (1 RCT) ⁵²	Very low	No difference
SRI-5 after tabalumab every 2 weeks	384	277 Attributable events per 1000 treated 108 (41;175)	RR 1.39 (1.13;1.71) NNT 9 (6;24)	748 (1 RCT) ⁵⁸	Very low	Favors tabalumab
SRI-5	350	285 Attributable events per 1000 treated 65 (32;99)	RR 1.23 (1.11;1.37) NNT 15 (10;31)	3017 (2 RCTs) ^{52,58}	Moderate	Favors tabalumab
≥ 5 point improvement in SELENA-SLEDAI score	357	293 Attributable events per 1000 treated 65 (10;119)	RR 1.22 (1.03;1.44) NNT 15 (8;100)	2250 (2 RCTs) ^{52,58}	Moderate	Favors tabalumab
No worsening in BILAG	647	600 Attributable events per 1000 treated 47 (4;89)	RR 1.08 (1.01;1.15) NNT 21 (11;250)	2262 (2 RCTs) ^{52,58}	Moderate	Favors tabalumab
No worsening in PGA	638	576 Attributable events per 1000 treated 62 (19;104)	RR 1.11 (1.03;1.19) NNT 16 (10;53)	2262 (2 RCTs) ^{52,58}	Moderate	Favors tabalumab
Corticosteroid dose reduction	102	81	RR 1.25 (0.92;1.71)	2262 (2 RCTs) ^{52,58}	Low	No difference
Change in QIDS-SR16 Total score	NR	NR	MD -0.16 (-0.53;0.21) SMD -0.04 (-0.12;0.05)	2262 (2 RCTs) ^{52,58}	Low	No difference
Adjudicated MACE	10	14	RR 0.68 (0.31;1.48)	2286 (2 RCTs) ^{52,58}	Low	No difference
Adverse effects leading to treatment discontinuation	56	66	RR 0.85 (0.61;1.19)	2262 (2 RCTs) ^{52,58}	Low	No difference

(continued)

Appendix D Table VIII. (continued).

Outcomes at 52 weeks	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
AEs possibly related to study drug	420	389	RR 1.08 (0.97;1.20)	2286 (2 RCTs) ^{52,58}	Low	No difference
Anaphylaxis	0	0	RR inestimable	2286 (2 RCTs) ^{52,58}	Low	No difference
Deaths	5	7	RR 0.78 (0.25;2.45)	2286 (2 RCTs) ^{52,58}	Low	No difference
Depression after tabalumab every 2 weeks	31	34	RR 0.93 (0.43;2.00)	773 (1RCTs) ⁵²	Very low	No difference
Depression after tabalumab every 2 weeks	40	8 Attributable events per 1000 treated 32 (10;54)	RR 5.05 (1.48;17.31) NNT 31 (18;96)	748 (1RCTs) ⁵⁸	Very low	Favors placebo
Depression	38	21	RR 2.15 (0.42;11.08)	2286 (2 RCTs) ^{52,58}	Very low	No difference
Infections	574	564	RR 1.02 (0.91;1.13)	1124 (2 RCTs) ^{52,58}	Low	No difference
Injection-site reactions	53	33	RR 1.63 (1.05;2.52)	2286 (2 RCTs) ^{52,58}	Low	No difference
Malignancies	4	5	RR 0.75 (0.21;2.68)	2286 (2 RCTs) ^{52,58}	Low	No difference
Non-anaphylaxis hypersensitivity	17	8	RR 2.14 (0.88;5.20)	2286 (2 RCTs) ^{52,58}	Low	No difference
Serious adverse events	135	159	RR 0.85 (0.65;1.11)	2286 (2 RCTs) ^{52,58}	Low	No difference
Serious infections	51	55	RR 0.92 (0.62;1.36)	2286 (2 RCTs) ^{52,58}	Very low	No difference
Severe infections	35	45	RR 0.80 (0.52;1.21)	2286 (2 RCTs) ^{52,58}	Low	No difference
Suicide attempts	3	1	RR 1.24 (0.16;9.39)	2286 (2 RCTs) ^{52,58}	Low	No difference
Treatment-emergent adverse effects	821	809	RR 1.02 (0.97;1.06)	2286 (2 RCTs) ^{52,58}	Moderate	No difference
<p>Population: Adults with moderate-to-severe SLE who have had an inadequate response to immunosuppressive agents</p> <p>Setting: Outpatient</p> <p>Intervention: Tabalumab (subcutaneous injections of a loading dose 240 mg at week 0 and followed by 120 mg every two or four weeks)</p> <p>Comparator: Placebo</p>						

GRADE Summary of Findings Appendix D Table IX. Adjunctive sifalimumab in adults with moderate-to-severe SLE who have had an inadequate response to immunosuppressive agents

Outcomes at 52 weeks	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
SLE Responder Index	6	4	RR 3.03 (0.12;73.51)	215 (1 RCT) ⁵⁴	Very low	No difference
Cutaneous Lupus Erythematosus Disease Area and Severity Index	731	486	RR 1.51 (1.21;1.90)	215 (1 RCT) ⁵⁴	Very low	Favors sifalimumab
		Attributable events per 1000 treated 247 (121;374)	NNT 4 (3;8)			
Fatigue	356	305	RR 1.16 (0.79;1.70)	215 (1 RCT) ⁵⁴	Very low	No difference
Physician's Global Assessment (PGA) of disease activity ≤0.5	430	296	RR 1.45 (1.01;2.09)	215 (1 RCT) ⁵⁴	Very low	Favors sifalimumab
		Attributable events per 1000 treated 134 (6;261)	NNT 7 (4;159)			
Modified systemic lupus erythematosus responder index mSRI (5 points reduction)	542	393	RR 1.39 (1.04;1.87)	215 (1 RCT) ⁵⁴	Very low	Favors sifalimumab
		Attributable events per 1000 treated 153 (21;285)	NNT 7 (4;47)			
Modified systemic lupus erythematosus responder index mSRI (6 points reduction)	533	374	RR 1.44 (1.06;1.95)	215 (1 RCT) ⁵⁴	Very low	Favors sifalimumab
		Attributable events per 1000 treated 162 (31;294)	NNT 6 (3;32)			
Modified systemic lupus erythematosus responder index mSRI (7 points reduction)	444	245	RR 1.86 (1.25;2.77)	215 (1 RCT) ⁵⁴	Very low	Favors sifalimumab
		Attributable events per 1000 treated 208 (84;332)	NNT 5 (3;12)			
Modified systemic lupus erythematosus responder index mSRI (8 points reduction)	418	245	RR 1.75 (1.17;2.61)	215 (1 RCT) ⁵⁴	Very low	Favors sifalimumab
		Attributable events per 1000 treated 180 (56;303)	NNT 6 (3;18)			
mSRI (8) in Interferon-α-gene signature high	413	203	RR 2.02 (1.30;3.12)	215 (1 RCT) ⁵⁴	Very low	Favors sifalimumab
		Attributable events per 1000 treated 208 (87;328)	NNT 5 (3;11)			
mSRI (8) in interferon-α-gene signature low	444	421	RR 1.08 (0.79;1.46)	215 (1 RCT) ⁵⁴	Very low	No difference

(continued)

Appendix D Table IX. (continued).

Outcomes at 52 weeks	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
BILAG-2004-based Combined Lupus Assessment	481	361	RR 1.32 (0.96;1.82)	215 (1 RCT) ⁵⁴	Very low	No difference
BILAG-2004-based Combined Lupus Assessment in interferon- α -gene signature high	488	318	RR 1.54 (1.10;2.17)	215 (1 RCT) ⁵⁴	Very low	Favors sifalimumab
interferon- α -gene signature low	450	550	RR 0.82 (0.63;1.08)	215 (1 RCT) ⁵⁴	Very low	No difference
Systemic Lupus Erythematosus Disease Activity Index 2000	617	454	RR 1.36 (1.05;1.75)	215 (1 RCT) ⁵⁴	Very low	Favors sifalimumab
Any adverse events	889	870	RR 1.02 (0.94;1.11)	431 (1 RCT) ⁵⁴	Low	No difference
Serious adverse events	183	176	RR 1.04 (0.65;1.66)	431 (1 RCT) ⁵⁴	Very low	No difference
All-cause mortality	12	19	RR 0.67 (0.12;3.60)	431 (1 RCT) ⁵⁴	Very low	No difference
Adverse events leading to discontinuation	111	120	RR 0.93 (0.51;1.68)	431 (1 RCT) ⁵⁴	Very low	No difference
Grade 3 adverse events	139	157	RR 0.89 (0.53;1.48)	431 (1 RCT) ⁵⁴	Very low	No difference
Grade 4 adverse events	31	37	RR 0.84 (0.27;2.61)	431 (1 RCT) ⁵⁴	Very low	No difference
Treatment failure (worsening of SLE))	300	343	RR 0.88 (0.64;1.19)	431 (1 RCT) ⁵⁴	Very low	No difference
Urinary tract infection	176	139	RR 1.27 (0.75;2.15)	431 (1 RCT) ⁵⁴	Very low	No difference
Headache	133	139	RR 0.96 (0.56;1.65)	431 (1 RCT) ⁵⁴	Very low	No difference
Upper respiratory tract infection	130	93	RR 1.40 (0.73;2.70)	431 (1 RCT) ⁵⁴	Very low	No difference
Nasopharyngitis	105	93	RR 1.14 (0.58;2.22)	431 (1 RCT) ⁵⁴	Very low	No difference
Bronchitis	96	83	RR 1.15 (0.57;2.34)	431 (1 RCT) ⁵⁴	Very low	No difference
Diarrhea	65	74	RR 0.88 (0.40;1.92)	431 (1 RCT) ⁵⁴	Very low	No difference
Pharyngitis	65	37	RR 1.76 (0.62;5.00)	431 (1 RCT) ⁵⁴	Very low	No difference
Infusion-related reaction	62	56	RR 1.11 (0.46;2.70)	431 (1 RCT) ⁵⁴	Very low	No difference

(continued)

Appendix D Table IX. (continued).

Outcomes at 52 weeks	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
Cough	56	65	RR 0.86 (0.37;2.00)	431 (1 RCT) ⁵⁴	Very low	No difference
Herpes zoster	59	9	RR 6.35 (0.86;46.90)	431 (1 RCT) ⁵⁴	Very low	Favors placebo
		Attributable events per 1000 treated 50 (18;81)	NNT 20 (12;55)			
Back pain	53	28	RR 1.89 (0.57;6.34)	431 (1 RCT) ⁵⁴	Very low	No difference
<p>Population: Adults with moderate-to-severe SLE who have had an inadequate response to immunosuppressive agents</p> <p>Setting: Outpatient</p> <p>Intervention: Sifalimumab (200-1200 mg intravenously on days 1,15 and 29, and every 28 days there after until week 52)</p> <p>Comparator: Placebo.</p>						

GRADE Summary of Findings Appendix D Table X. Anifrolumab in adults with moderate-to-severe SLE who have had an inadequate response to immunosuppressive agents

Outcomes	Risk with intervention per 1000	Risk with comparator per 1000	Relative measure of association (95% confidence interval)	Number of participants (studies)	Quality (GRADE)	Comments
Systemic Lupus Erythematosus (SLE) Responder Index [SRI (4)] Response, 24 weeks	288	176	RR 1.63 (0.98;2.74)	206 (1 RCT) ⁴⁵	Very low	No difference
Systemic Lupus Erythematosus (SLE) Responder Index [SRI (4)] Response, 52 weeks	385	255 Attributable events per 1000 treated 130 (4;256)	RR 1.509 (1.000;2.277) NNT 8 (4;275)	206 (1 RCT) ⁴⁵	Very low	Favors anifrolumab
Hypertension	19	69	RR 0.28 (0.06;1.32)	206 (1 RCT) ⁴⁵	Very low	No difference
Pyrexia, 24 weeks	29	49	RR 0.59 (0.14;2.40)	206 (1 RCT) ⁴⁵	Very low	No difference
Total, serious adverse events, 24 weeks	171	188	RR 0.91 (0.51;1.63)	206 (1 RCT) ⁴⁵	Very low	No difference
Total, other adverse events, 24 weeks	438	356	RR 1.23 (0.87;1.73)	206 (1 RCT) ⁴⁵	Very low	No difference
Diarrhea, 24 weeks	76	40	RR 1.92 (0.60;6.19)	206 (1 RCT) ⁴⁵	Very low	No difference
Bronchitis, 24 weeks	86	40	RR 2.16 (0.69;6.81)	206 (1 RCT) ⁴⁵	Very low	No difference
Nasopharyngitis, 24 weeks	114	40 Attributable events per 1000 treated 75 (3;146)	RR 2.89 (0.96;8.65) NNT 13 (7;343)	206 (1 RCT) ⁴⁵	Very low	Favors placebo in absolute scale
Upper respiratory tract infection, 24 weeks	105	99	RR 1.06 (0.47;2.38)	206 (1 RCT) ⁴⁵	Very low	No difference
Urinary tract infection, 24 weeks	67	109	RR 0.61 (0.25;1.52)	206 (1 RCT) ⁴⁵	Very low	No difference
Headache, 24 weeks	114	129	RR 0.89 (0.43;1.85)	206 (1 RCT) ⁴⁵	Very low	No difference

Population: Adults with moderate-to-severe SLE who have had an inadequate response to immunosuppressive agents

Setting: Outpatient

Intervention: Anifrolumab (1000 mg as an intravenous infusion every 4 weeks for 48 weeks)

Comparator: Placebo.