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

Tatyana A. Shamliyan, MD, MS[1]; and Paula Dospinescu, MD, MRCP[2]

[1]*Elsevier, Philadelphia, Pennsylvania; and* [2]*Department of Rheumatology, NHS Grampian, Aberdeen, United Kingdom*

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;39:1479–1506)

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]

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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** 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** 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** 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** 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