Received: 11 August 2021 | Revised: 26 August 2021 | Accepted: 28 August 2021

DOI: 10.1111/1756-185X.14214

International Journal of Rheumatic Diseases | WILEY

COCHRANE CORNER

What are the benefits and harms of belimumab for patients with systemic lupus erythematosus?: A Cochrane Review summary with commentary

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Keywords: belimumab, Cochrane Review summary, systemic lupus erythematosus

Cochrane Rehabilitation

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The aim of this commentary is to discuss the published Cochrane Review "Belimumab for systemic lupus erythematosus"[1] by Singh et al.,[a] under the direct supervision of Cochrane Musculoskeletal Group. This Cochrane Corner is produced in agreement with *International Journal of Rheumatic Diseases* by Cochrane Rehabilitation.

1 | BACKGROUND

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease associated with significant morbidity and mortality. Genetic, immunological, endocrine, and environmental factors contribute to the etiopathogenesis of SLE.[2] Clinical features of SLE vary from a mild phenotype to a very severe multiorgan involvement, characterizing a life-threatening disease with no cure.[3] Poor functioning and quality of life frequently affect people with SLE, requiring a multidisciplinary approach, that includes specific physical and lifestyle measures, particularly to avoid flare-ups of the disease.[4]

Furthermore, several drugs such as glucocorticoids (GCs), antimalarials or cytotoxic drugs are largely used to treat mild to severe manifestations in this disease, often causing significant adverse events.[4] To date, new therapeutic strategies to treat the acute phase of SLE are available, such as anifrolumab and belimumab. This latter was the first biologic disease-modifying anti-rheumatic drug (DMARD) approved for SLE. Belimumab is a human monoclonal antibody directed against cytokine B-lymphocyte stimulator (BLyS).[5]

2 | BELIMUMAB FOR SYSTEMIC LUPUS ERYTHEMATOSUS

(Jasvinder A Singh, Nipam P Shah, Amy S Mudano, 2021).

2.1 | What is the aim of this Cochrane Review?

The aim of this Cochrane Review was to assess the benefits and harms of belimumab (alone or in combination with other drugs) in SLE.

2.2 | What was studied in the Cochrane Review?

The population addressed in this review was people with SLE according to the American College of Rheumatology classification criteria.[6] The intervention studied was belimumab alone or in

[a]This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2021, Issue 2, Art. No.:CD010668, DOI: 10.1002/14651858.CD010668.pub2 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

The views expressed in the summary with commentary are those of the Cochrane Corner author and do not represent the Cochrane Library or Wiley.

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combination with other immunosuppressive drugs or another biologic, compared to placebo or other DMARDs, DMARD combinations, or biologics.

The major outcomes investigated were: intensity of disease assessed through the reduction of at least 4 points on Safety of Estrogen in Lupus National Assessment (SELENA) - Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, change in health-related quality of life (HR-QoL), glucocorticoid sparing (prednisone dose reduced by 50% or more), participants with at least 1 serious adverse event (AE) or serious infection, withdrawals due to AEs and deaths.

2.3 | What was the search methodology and search date of the Cochrane Review?

The Information Specialist searched for studies that had been published from inception to 25 September 2019. The search methods for identification of studies were: Cochrane Central Register of Controlled Trials (CENTRAL; August 2019) in the Cochrane Library; MEDLINE Ovid; Embase Classic +Embase; CINAHL (Cumulative Index to Nursing and Allied Health Literature); Web of Science; and the World Health Organization (WHO) International Clinical Trials Registry Platform.

2.4 | What are the main results of the Cochrane Review?

The review included 6 randomized controlled trials (RCTs) involving a total of 2917 people, aged from 22 to 80 years and the majority were women. The risk of bias was generally low except for attrition bias, which was high in two-thirds of the studies. All RCTs compared belimumab to placebo. Some studies contained multiple dose comparisons and various follow-up lengths (from 84 days to 76 weeks).

This Cochrane systematic review showed that people on belimumab 10 mg/kg (Food and Drug Administration [FDA]-approved dose) versus those receiving placebo experienced:

- statistically significant reduction in SELENA - SLEDAI score (at least 4 points), with an absolute risk difference of 13% better in the treated group (95% confidence interval [CI] 8%-17%) (risk ratio [RR] 1.33, 95% CI 1.22-1.45 [high-certainty evidence]) (4 studies with 2666 participants)
- no clinically meaningful difference in terms of HR-QoL, with a mean difference of 1.6 points, 95% CI 0.30-2.90 (moderate-certainty evidence) (2 studies with 801 participants)
- statistically significant reduction of GC dose (at least 50%), with a RR of 1.59 (95% CI 1.17-2.15); 11% better absolute difference (95% CI 4%-18%) (high-certainty evidence) (2 studies with 537 participants)
- no significant difference in the number of participants who experienced serious AEs with an absolute risk difference of 2% less (RR 0.87, 95% CI: 0.68-1.11) (5 studies with 2890 participants) or deaths (0% of absolute risk difference; Peto odds ratio 1.15, 95% CI 0.41-3.25) (6 studies with 2917 participants) (low-certainty evidence), as well as for serious infections (0% of absolute risk difference; RR 1.01, 95% CI: 0.66-1.54) (4 studies with 2185 participants) and numbers of AEs that caused people to withdraw (1% of absolute risk difference; RR 0.82, 95% CI: 0.63-1.07) (5 studies with 2890 participants) (moderate-certainty evidence).

2.5 | What did the authors conclude?

Compared to placebo, belimumab (10 mg/kg) probably reduces SLE intensity and glucocorticoid doses, while data about QoL and safety (AE, infections, withdrawals due to AE and death) are inconclusive.

3 | WHAT ARE THE IMPLICATIONS OF THE COCHRANE EVIDENCE FOR PRACTICE IN RHEUMATOLOGY?

SLE is a disabling chronic autoimmune disease with high clinical variability and mortality.[7] The fluctuating disease course characterized by sudden flares interspersed with a period of remission represents a huge challenge to the clinician.[8] For patients affected by SLE, the pharmacological control of disease activity is the main goal, even if this target is not so commonly obtained in daily practice.[9] In this scenario, the biologic therapies, particularly belimumab, are showing promising results in the clinical management of SLE.[9] Based on Cochrane Systematic Review evidence, belimumab showed benefits in terms of modifying SLE disease activity. Moreover, this drug promotes GC sparing, which might further avoid bone and muscle impairments due to the chronic use of high-dose GC.[10] However, its safety profile is still unclear, also due to the short-term duration of the included trials, and therefore long-term studies should clarify this unmet outcome. Moreover, investigating the efficacy and/or effectiveness of belimumab versus an active comparator should be an interesting topic for both research and clinical practice.

ACKNOWLEDGEMENTS

The author thanks Cochrane Rehabilitation and Cochrane Musculoskeletal Group for reviewing the contents of the Cochrane Corner. Open Access Funding provided by Universita degli Studi della Campania Luigi Vanvitelli within the CRUI-CARE Agreement. [Correction added on 20 May 2022, after first online publication: CRUI funding statement has been added.]

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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REFERENCES

1. Singh JA, Shah NP, Mudano AS. Belimumab for systemic lupus erythematosus. *Cochrane Database Syst Rev*. 2021;2(2):CD010668. https://doi.org/10.1002/14651858.CD010668.pub2
2. Justiz Vaillant AA, Goyal A, Bansal P, et al. *Systemic Lupus Erythematosus. [Updated 2020 Dec 30]*. In: StatPearls [Internet]. StatPearls Publishing; 2021 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK535405/
3. Kiriakidou M, Ching CL. Systemic lupus erythematosus. *Ann Intern Med*. 2020;172(11):ITC81-ITC96. https://doi.org/10.7326/AITC202006020
4. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78(6):736-745. https://doi.org/10.1136/annrheumdis-2019-215089
5. Parodis I, Axelsson M, Gunnarsson I. Belimumab for systemic lupus erythematosus: a practice-based view. *Lupus*. 2013;22(4):372-380. https://doi.org/10.1177/0961203313476154
6. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for systemic lupus erythematosus. *Arthritis Rheumatol*. 2019;71(9):1400-1412. https://doi.org/10.1002/art.40930. Epub 2019 Aug 6. PMID: 31385462; PMCID: PMC6827566
7. Kaul A, Gordon C, Crow MK, et al. Systemic lupus erythematosus. *Nat Rev Dis Primers*. 2016;2:16039. doi:https://doi.org/10.1038/nrdp.2016.39
8. Shaikh MF, Jordan N, D'Cruz DP. Systemic lupus erythematosus. *Clin Med (London, England)*. 2017;17(1):78-83. https://doi.org/10.7861/clinmedicine.17-1-78
9. He J, Li Z. An era of biological treatment in systemic lupus erythematosus. *Clin Rheumatol*. 2018;37(1):1-3. https://doi.org/10.1007/s10067-017-3933-x
10. Porta S, Danza A, Arias Saavedra M, et al. Glucocorticoids in systemic lupus erythematosus. Ten questions and some issues. *J Clin Med*. 2020;9(9):2709. https://doi.org/10.3390/jcm9092709