Efficacy of sifalimumab for treatment of skin injury caused by systemic lupus erythematosus

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Abstract

Background: This study aims to provide the best possible evidence-based information on the efficacy and safety of sifalimumab for treatment of skin injury (SI) caused by systemic lupus erythematosus (SLE).

Methods: In this study, electronic databases of MEDLINE, EMBASE, Cochrane Library, PsycINFO, CINAHL Plus, Global Health, WHO Global Index Medicus, Virtual Health Library, Social Care Online, Cumulative Index to Nursing and Allied Health Literature, Allied and Complementary Medicine Database, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure will be searched comprehensively from inceptions to June 30, 2019 without language restrictions. We will include randomized controlled trials (RCTs) on evaluating the efficacy and safety of sifalimumab for SI caused by SLE. Two investigators will conduct study selection, data extraction, and risk of bias assessment independently. We will use RevMan 5.3 Software to perform statistical analysis.

Results: This study will lie in the exhaustive and systematic nature of the literature search and its methods for evaluating quality and analyzing RCTs data. Considering the controversial efficacy of the treatment for sifalimumab, this study is responsible for improving the existing evidence on the efficacy and safety of sifalimumab for SI caused by SLE.

Conclusion: The results of this study will provide latest evidence for judging whether sifalimumab is an effective intervention for patients with SI caused by SLE or not.

Study registration: CRD42019148225.

Abbreviations: RCT = randomized controlled trial, SI = skin injury, SLE = systemic lupus erythematosus.

Keywords: efficacy, safety, sifalimumab, skin injury, systemic lupus erythematosus.

1. Introduction

Systemic lupus erythematosus (SLE) is a serious chronic autoimmune disease,[11–31] which characterized by a wide spectrum of clinical and serological symptoms.[4–6] It mainly manifests as joint pain and swelling, chest pain, fever, general discomfort, hair loss, weight loss, mouth sores, sensitivity to sunlight and skin rash, swollen lymph nodes, and skin injury (SI) in some patients.[6–10] Previous studies have found that several factors may be responsible for this disorder, such as genetic, environmental, hormonal, and certain medicines.[11–16] It has been estimated that its prevalence and incidence are about 100–150/100,000 persons and more than 5/100,000 people annually, respectively.[17–19] Although a variety of managements are reported to treat SI caused by SLE, their efficacy is still limited.[20–24] Fortunately, sifalimumab is reported to treat patients with SI caused by SLE.[25–29] However, its results are still inconsistent. Therefore, this study will systematically assess the efficacy and safety for the treatment of patients with SI caused by SLE.

2. Methods and analysis

2.1. Ethics and dissemination

This study is secondary analysis of published studies; therefore, no ethical approval is needed. Planned disseminations include a peer-reviewed publication and conference proceedings.

2.2. Inclusion criteria for study selection

2.2.1. Types of studies. We will include all published and unpublished randomized controlled trials (RCTs), comparing sifalimumab with other treatments for patients with SI caused by SLE. All other studies except RCTs will be excluded.

2.2.2. Types of participants. Participants with a clinically confirmed diagnosis of SI caused by SLE will be considered for inclusion regardless their race, gender, age, education, or economic status.

2.2.3. Types of interventions. Any forms of sifalimumab in the experimental group will be included.
Any interventions, except sifalimumab in the control group will be considered for inclusion.

2.2.4. Type of outcome measurements. Primary outcomes include time to complete healing of injury skin, and number of SI healed.

Secondary outcomes consist of hospital readmission rate, SLE Response Index, SLE Flare Index rate, changes in inflammatory and hemostatic markers, and adverse events.

2.3. Literature search

We will comprehensively carry out searches in bibliographic databases of MEDLINE, EMBASE, Cochrane Library, PsycINFO, CINAHL Plus, Global Health, WHO Global Index Medicus, Virtual Health Library, Social Care Online, Cumulative Index to Nursing and Allied Health Literature, Allied and Complementary Medicine Database, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure. We will search all databases from inceptions to June 30, 2019 without language restrictions. Exemplary search strategy for MEDLINE is provided in Table 1. We will apply other similar search strategies to other electronic databases. Additionally, we will also search unpublished and conference proceedings to avoid any missing potential studies.

2.4. Data collection and management

2.4.1. Study selection. For studies obtained via all literature records, 2 investigators will independently scan titles and abstracts of all studies and retrieve potentially relevant studies.

After that, they will also review full-texts against all inclusion criteria. Any disagreements between 2 authors will be solved by consensus with a 3rd independent investigator. The process of study selection will be presented in the flowchart.

2.4.2. Data extraction and management. A data collection sheet will be designed before data extraction. Two investigators will independently extract relevant details about the study design, study methods, and outcome results. Any divergences will be solved by consensus or by independent assessment by a 3rd investigator. The extracted information will consist of title, study year and author, study region and setting, study design, sample size, eligibility criteria, baseline characteristics, intervention details, comparisons, treatment details, study methods, outcome measurements, safety, and funding resources.

2.4.3. Dealing with missing data. When information regarding any of the above is unclear or insufficient, we will contact primary author of the original studies in order to ask for further details. We will pool the available data if further details cannot be getable.

2.5. Assessment of risk of bias in included studies

Two independent investigators will use Cochrane Collaboration’s “Risk of bias” tool for included RCTs and eligibility criteria in the Cochrane Handbook for Systematic Reviews of Interventions to assess those in the associated domains of the reported methods and outcome results. Any disagreements between 2 independent investigators will be solved by a 3rd investigator through discussion.

2.6. Measures of treatment effect

2.6.1. Dichotomous data. For dichotomous data, we will exert the results as risk ratio with 95% confidence intervals.

2.6.2. Continuous data. For continuous data, we will utilize the results as mean difference or standardized mean difference with 95% confidence intervals.

2.7. Assessment of heterogeneity

We will evaluate statistical heterogeneity using I² statistic by 2 independent investigators. We will consider heterogeneity as acceptable if I² is 50% or less, and a fixed-effects model will be used. We will consider heterogeneity as substantial if I² is more than 50%, and a random-effects model will be applied.

2.8. Assessment of reporting biases

We will apply funnel plots and Eggers Regression test to assess publication bias when at least 10 RCTs are available for meta-analysis.

2.9. Data analysis

We will apply RevMan 5.3 software for data analysis. If heterogeneity is acceptable among included studies (I² ≤ 50%), we will carry out meta-analysis when it is possible. If heterogeneity is substantial among included studies (I² > 50%), we will perform subgroup analysis. If there is still significant heterogeneity after subgroup analysis, we will not pool the data, and report outcome results as a narrative review.

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**Table 1**

| Number | Search terms |
|--------|--------------|
| 1      | Systemic lupus erythematosus |
| 2      | Lupus erythematosus disseminatus |
| 3      | Libman–Sacks’ disease |
| 4      | Disseminated lupus |
| 5      | Disseminated lupus erythematodes |
| 6      | SLE |
| 7      | Or 1–6 |
| 8      | Skin injury |
| 9      | Skin wound |
| 10     | Or 8–9 |
| 11     | Sifalimumab |
| 12     | Immunoglobulin G1 monoclonal antibody |
| 13     | IFN-α subtype |
| 14     | IFN-α-induced genes |
| 15     | Or 11–14 |
| 16     | Randomized controlled trials |
| 17     | RCTs |
| 18     | Random |
| 19     | Randomly |
| 20     | Controlled |
| 21     | Control |
| 22     | Comparator |
| 23     | Blind |
| 24     | Allocation |
| 25     | Placebo |
| 26     | Study |
| 27     | Trial |
| 28     | Or 16–27 |
| 29     | Or 7 and 10 and 15 and 28 |
2.10. **Subgroup analysis**

Subgroup analysis will be exerted according to the different treatments, comparators, and outcome measurements to explore any possible reasons that may cause such significant heterogeneity.

2.11. **Sensitivity analysis**

We will conduct a sensitivity analysis to check robustness of outcome results by excluding studies with high risk of bias.

3. **Discussion**

SLE is a chronic, autoimmune, inflammatory disorder that often involves several systems and organs in patients with such condition. Some of such patients also have SI. Previous studies have highlighted the role of sifalimumab for the treatment of patients with SI caused by SLE. However, the conclusion is still inconsistent. This study aims to systematically investigate the efficacy and safety of sifalimumab for SI secondary to SLE. This study will comprehensively and systematically search more potential literatures to find more eligible high quality studies. It may present solid data and robust evidence, as well as provide helpful recommendation for both patients and clinical practice.

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