

BMJ Open Is mesenchymal stem cell effective for allergic rhinitis? A protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Allergic rhinitis (AR) is a kind of widespread but unrecognised inflammatory disorder of nasal mucosa, characterised by itching, sneezing, runny nose and nasal congestion. The efficacy of mesenchymal stem cells (MSCs) in the treatment of AR remains controversial. This protocol describes a systematic review and meta-analysis approach to assess the efficacy and safety of MSCs in the treatment of AR.

Methods and analysis Eight databases (PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP and Wanfang) will be searched from the database inception to 1 December 2023. All randomised controlled trials related to MSCs for AR will be included.

The primary outcomes will be therapeutic effect, serum IgE index and Visual Analogue Scale score for nasal symptoms. Risk of bias will be assessed using the Cochrane Collaboration's tool for assessing risk of bias. Article selection, data extraction and risk of bias assessment will be performed in duplicate by two independent reviewers.

Ethics and dissemination Ethics approval is not required because individual patient data are not included. This protocol was registered in the international Prospective Register of Systematic Reviews on 22 January 2022. The systematic review and meta-analysis will be submitted for publication in a peer-reviewed journal. The findings will also be disseminated through conference presentations.

PROSPERO registration number CRD42022303146.

INTRODUCTION

Allergic rhinitis (AR) is a prevalent yet unrecognised inflammatory disorder of nasal mucosa,¹ which is characterised by pruritus, sneezing, rhinorrhoea and nasal congestion.^{2,3} Although it mainly affects the nose, AR is now considered to affect the entire respiratory tract. Approximately 10%–20% of the global population, with around 500 million patients worldwide, has been bothered by this disease.⁴ AR can markedly influence the quality of life and performance, including learning and working.⁵ Moreover, patients with AR usually experience emotional burden.⁶ Allergic rhinitis related to the health of absence (absent) and attendance (to work but work efficiency to reduce the cost of

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This protocol will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
- ⇒ This protocol is registered with PROSPERO, an international prospective systematic review registry.
- ⇒ Full-text screening and extraction will be done by two authors (LY and HZheng).
- ⇒ There may be significant clinical or statistical heterogeneity among eligible studies that may not be amenable to meta-analysis.
- ⇒ Our results will be based on the restrictions on the number and quality of qualified research.

increasing one of the main reasons). In the USA, for example, the cost of AR and allergic conjunctivitis estimates to be more than 6 billion dollars a year.^{7,8} Treatment strategies for AR should consider the following factors: patient education, prevention of allergen or irritant exposure, drug therapy and immunotherapy.⁹ At present, the regular medication can alleviate the symptoms but cannot relieve allergic reactions. Treatment of patients with recurrent symptoms and side effects has brought obvious resistance, which is a serious impact on the patient's quality of life. On the other hand, this situation has also prompted relevant medical scientists to find more effective AR treatment strategies.^{10,11}

Mesenchymal stem cells (MSCs) are a kind of pluripotent progenitor cells, which can differentiate into fat cells, osteoblasts, chondrocytes and other cell types.¹² As a result, these can promote maintenance and regeneration of various connective tissues, including bone, muscle, fat and cartilage.^{13–15} In addition to the potential of tissue repair, more and more evidence of MSCs' interaction with T lymphocytes and B lymphocytes, natural killer (NK) cells and dendritic cells (DCs) also shows strong immunomodulatory potential.^{16,17} Therefore, a number of studies have confirmed that MSCs from bone marrow and adipose tissue have immunosuppressive

effects on allergic airway inflammation.^{18 19} MSCs are known to cause a shift in AR responses from Th2 to Th1 and to modulate the function of regulatory T cells (Tregs).²⁰ Possible mechanisms include MSCs regulating the adaptive and innate immune system by inhibiting the maturation of T cells and DCs, reducing the activation and proliferation of B cells, inhibiting the proliferation and cytotoxicity of NK cells, and promoting Treg production through soluble factors or cell–cell contact mechanisms.^{21 22} MSCs could interact with immune cells that can secrete a variety of soluble factors to interact with immune cells and play an immunosuppressive role,¹¹ and produce and release various soluble factors, including prostaglandin E2, which have immunosuppressive functions.²³ We put forward the first systematic review and meta-analysis scheme based on animal experiments, to investigate between the efficacy and safety of MSCs in the treatment of patients with AR.

MATERIAL AND METHODS

Patient and public involvement

There will be no patients or members of the public directly involved in this review. Only data already existing in the literature and the aforementioned sources will be used for this study.

Protocol and registration

The protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. The study is expected to begin on 1 March 2022 and end on 1 March 2024. The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (online supplemental material 1).²⁴ This protocol was registered in PROSPERO and the registration number is CRD42022303146 (online supplemental material 2).

Eligibility criteria

Inclusion criteria

For adults diagnosed with AR, the experimental group was treated with MSCs, and the control group was treated with placebo or blank intervention. Using the Allergic Rhinitis and its Impact on Asthma 2008 guidelines,²⁵ the primary outcomes were treatment effect, serum IgE index, and Visual Analogue Scale (VAS) score of nasal symptoms, and the secondary outcomes were Quality of Life Questionnaire, 12-item Short-Form Health Survey, 36-item Short-Form Health Survey and adverse events: incidence and severity of adverse events. This study will only consider randomised controlled trials (RCTs).

Exclusion criteria

The following studies will be excluded: duplicate articles, meta-analyses, reviews, protocols, animal experiments, letters and those with no available full text.

Search methods for identification of studies

The following electronic databases—PubMed, Web of Science, Cochrane Library, Embase, CNKI, Chinese

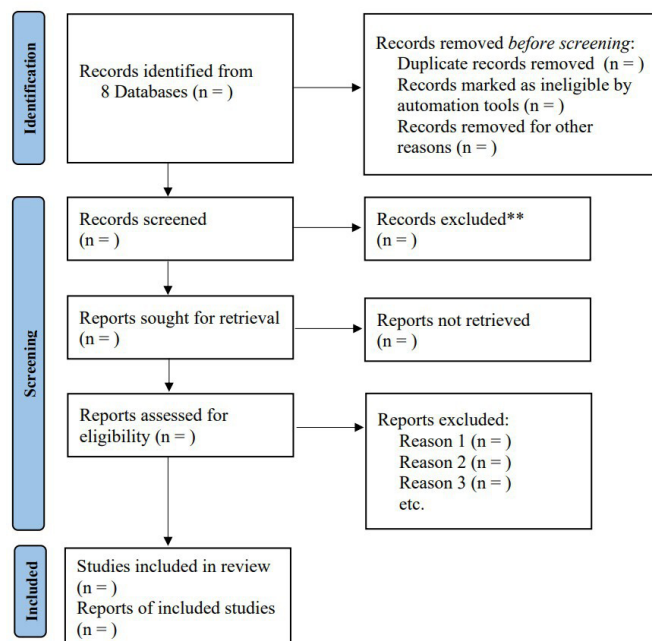


Figure 1 Flow diagram of the study design.

Biomedical Literature, Wanfang Database and VIP Database—will be searched from inception to December 2023. In addition, we will review the list of references, relevant conference literature and trial registry databases (WHO International Clinical Trials Registry Platform and ClinicalTrials.gov) to identify additional studies.

The search strategy is shown in online supplemental material 3. The following search terms will be used singly or in combination (Medical Subject Headings terms and free words): mesenchymal stem cell and allergic rhinitis.

Data collection and analysis

Selection of studies

Two reviewers will be required to screen the retrieved studies independently. Briefly, they will exclude duplicate studies and those not matching the inclusion criteria by reading titles and abstracts. They will read the full text of each study to select those meeting the inclusion criteria. Any disagreements will be resolved through discussion with a third reviewer.²⁶ The entire study selection process is shown in the flow diagram (figure 1).

Data extraction

Data extraction from the included studies will be done independently by two reviewers following a data acquisition list. The list will include the basic information (author, title, journal, year of publication and country of publication), study design (study size, randomisation, allocation concealment, blinding methods, type of interventions and treatment duration), outcome measures and conflicts of interest. If necessary, a third reviewer will double-check the data to ensure consistency.²⁷

If data are missing or incomplete in any study, we will contact the authors to obtain these data. In the absence of available data, we will delete the study.

Assessment of risk of bias

The risk of bias in the included studies will be determined by two reviewers independently using the Cochrane risk of bias tool,²⁸ which has five domains (randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result) judged as 'low risk', 'some concern' or 'high risk' of bias. The response options for an overall risk-of-bias judgement are the same as for individual domains. If any disagreements occur, the risk assignment will be settled through arbitration of a third reviewer.²⁷

Measures of treatment effect

The RevMan V.5.4 software was used for statistical analysis, and the Stata V.15.0 software was used for the evaluation of sensitivity and publication bias. For continuous outcome data, the standard mean difference or weighted mean difference with 95% CI will be used. For dichotomous data, the risk ratio or risk difference with 95% CI will be used for analysis.

Assessment of heterogeneity

We will evaluate heterogeneity using the Cochrane's Q test and I² statistics ($p > 0.05$ for Q statistics and $I^2 < 50\%$ indicating statistical homogeneity). Because studies may include different types of stem cells, as well as different numbers of stem cells, meta-analyses will be performed using random-effects models. A subgroup analysis will be performed to explore the possible causes. If the heterogeneity is greater than 75%, a meta-analysis will not be performed. We will provide a narrative, qualitative summary.

Assessment of the quality of evidence

The internationally accepted Grading of Recommendations Assessment Development and Evaluation²⁹ was used to grade the quality of evidence for outcomes. All RCTs were included in this study. RCTs were set as the highest level of evidence, and there were five factors that could reduce the quality of evidence which were as follows: study limitations, inconsistent findings, indirectness of findings, imprecision of findings and publication bias.

Assessment of publication biases

Publication bias was tested for inclusion of more than 10 studies using funnel plots and Egger's test. If the two sides of the funnel plot are asymmetrical, it means that there is a high possibility of publication bias, and Egger's test can be used. If the p value is < 0.05 , it means that there is a publication bias, and if $p > 0.05$, it is the opposite of the funnel plot result; at this time, we can further use the cut and complement method for further determination.

Subgroup analysis

If data are available, a subgroup analysis will be performed to assess the heterogeneity according to the types of interventions, treatment time, age, gender, type of AR,

and types of MSCs, number of stem cells and different outcomes.

Sensitivity analysis

If possible, sensitivity analysis will be used to evaluate how uncertain assumptions of data and usage affect the robustness of the combined results. We will judge the specific impact of an article on the results of the statistical analysis by eliminating literature one by one.

Ethics and dissemination

This review will not require ethical approval as it does not infringe on anyone's interests. The results will be published in a peer-reviewed journal or disseminated through conferences.

DISCUSSION

This systematic review will be performed based on previous studies of MSCs for AR. The conclusions obtained in this systematic review will be beneficial to patients with AR and clinicians.

The immune imbalance between Th1 and Th2 cells is the immunological basis of the incidence of AR, that is, the incidence of AR is mainly the advantage of Th2 cell immune response,³⁰ which leads to a series of nasal allergy symptoms by mediating the release of a variety of inflammatory mediators and cytokines.³¹ Th2 cells initiate and maintain inflammation in allergic immune response by releasing large amounts of Th2 cytokines (interleukin (IL)-4, IL-5, IL-13, etc). IL-4 is the characteristic factor, mainly causing type I allergy. Under normal circumstances, Th1 and Th2 cytokines antagonise each other, and the two are in a relative equilibrium state.³² When the body is stimulated by abnormal antigens, this balance is upset and an abnormal immune response will be the result. Therefore, regulating Th1/Th2 immune balance may play an important role in the treatment of allergic inflammation, which is also an important entry point in treatment.³⁰ Genç *et al*³³ co-cultured pulp-derived MSC (DFSC) with Peripheral blood mononuclear cell (PBMC) of patients with asthma, measured the proliferation of CD4+ T lymphocytes by carboxyfluorescein diacetate succinimidyl ester (CFSE) staining combined with flow cytometry, and found that DFSC could inhibit the proliferation of CD4+ T lymphocytes. The relative expression levels of IL-4 and GATA-3 mRNA were decreased, the relative expression levels of interferon- γ , T-bet and IL-10 were increased, and the percentage of Tregs was increased. Li *et al*³⁴ drew a similar conclusion with umbilical cord MSCs as the research object, suggesting that MSC of various sources can alleviate AR inflammation by correcting Th1/Th2 immune imbalance.

The proposed review has several advantages. We plan to search multiple Chinese and English databases to ensure a comprehensive search of the literature. A meta-analysis will be conducted according to the Cochrane Handbook for Systematic Reviews of Interventions. Another

advantage is that strict eligibility criteria will be applied to ensure the quality of the RCTs included. In addition, the VAS score for nasal symptoms was selected as the target outcome because it is an important indicator of effectiveness in the treatment of AR.

Contributors LY and HZheng originally conceptualised the study. All the authors contributed to the development of the protocol. LY and HZheng drafted the original manuscript. LD brought expertise in prediction model building. LY brought expertise in clinical management of osteoarthritis. LY and HZheng did the preliminary search, piloted the study selection process and developed the data analysis strategy, with assistance from LY, HZheng and HZhang. QZ polished the English language of the manuscript. QZ and LY supervised the protocol development process. QZ acquired the funding and is the guarantor of this manuscript. All authors critically reviewed and approved the final version of the manuscript.

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Competing interests None declared.

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