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Stem cells in animal asthma models: a systematic review

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Abstract

Background aims. Asthma control frequently falls short of the goals set in international guidelines. Treatment options for patients with poorly controlled asthma despite inhaled corticosteroids and long-acting β-agonists are limited, and new therapeutic options are needed. Stem cell therapy is promising for a variety of disorders but there has been no human clinical trial of stem cell therapy for asthma. We aimed to systematically review the literature regarding the potential benefits of stem cell therapy in animal models of asthma to determine whether a human trial is warranted. *Methods.* The MEDLINE and Embase databases were searched for original studies of stem cell therapy in animal asthma models. *Results.* Nineteen studies were selected. They were found to be heterogeneous in their design. Mesenchymal stromal cells were used before sensitization with an allergen, before challenge with the allergen and after challenge, most frequently with ovalbumin, and mainly in BALB/c mice. Stem cell therapy resulted in a reduction of bronchoalveolar lavage fluid inflammation and eosinophilia as well as Th2 cytokines such as interleukin-4 and interleukin-5. Improvement in histopathology such as peribronchial and perivascular inflammation, epithelial thickness, goblet cell hyperplasia and smooth muscle layer thickening was universal. Several studies showed a reduction in airway hyper-responsiveness. *Conclusions.* Stem cell therapy decreases eosinophilic and Th2 inflammation and is effective in several phases of the allergic response in animal asthma models. Further study is warranted, up to human clinical trials.

Key Words: *animal studies, asthma, stem cells, systematic review, therapy*

Introduction

Asthma is a worldwide problem [1]. In the developed world, 20–30% of people are affected by allergic disorders such as anaphylaxis, hay fever, eczema, and asthma [2]. Furthermore, asthma control frequently falls short of the goals set in international guidelines [1]. Although definitions and estimates vary, approximately 15% of asthmatics may be classified as having severe asthma [3]. Unfortunately, there are few treatment options for patients with poorly controlled asthma already receiving inhaled corticosteroids and long-acting β-agonists. These options include leukotriene receptor antagonists, tiotropium, omalizumab or theophylline, which are either expensive, cumbersome, of modest benefit or marred by potentially serious side effects. New therapeutic options are needed.

There has been much enthusiasm about the therapeutic potential of mesenchymal stromal cells (MSCs) in several clinical disorders such as multiple sclerosis, stroke, myocardial infarction, diabetes, sepsis, hepatic and renal failure, as well as asthma [4,5]. However, to our knowledge, there has been no human clinical trial of MSC therapy for asthma. We therefore aimed to review the literature about the potential benefits of MSC therapy in animal models of asthma.

Methods

Study selection

We sought to include studies of *in vivo* animal models of asthma, in which the effects of stem cell administration on clinical or biological outcomes relevant to

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asthma were compared with the effects of control therapy. We identified studies from two databases: Embase (1996 to 2014 week 24) and MEDLINE (Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE, 1996 to June 13, 2014). The search query "(exp Stem cells/ or exp Stromal Cells/ or exp Bone Marrow Cells/ or exp Stem Cell Transplantation/ or exp Bone Marrow Transplantation/) and (exp asthma/ or exp Airway Remodeling/ or exp Bronchial Hyperreactivity/ or exp Bronchoconstriction/ or airway inflammation.ti,ab.)" was run on both databases. We then used Ovid's deduplication feature to identify unique studies, with higher preference given to the Embase database. Limits were used to identify reviews, editorials and conference abstracts. The remaining abstracts and the full text of selected abstracts were then reviewed for inclusion criteria: (i) an animal model of asthma was used; (ii) there was administration of stem cells or progenitor cells that were not used as a vector for other agents; (iii) the study reported on original data.

Data extraction

Data were extracted from the selected studies. In a first step, the following information was recorded: animal model; sensitizing agent, route, dose and time used to sensitize the animal and induce asthma; type of stem cells, dose, route and time of administration; outcomes reported; time of outcome measurement. Outcomes were identified from the Methods section, the Results section, tables and figures and were classified into quantitative, semi-quantitative and qualitative.

Data analysis

We had planned for a meta-analysis of the 2 most commonly reported quantitative outcomes, which were bronchoalveolar lavage (BAL) total cell and eosinophil counts. This was not possible, mostly because of heterogeneity in study design. Furthermore, the data were presented graphically, and only a few authors responded to our request for numerical data. The remaining BAL total cell and eosinophil count data were therefore extracted from the published vector or raster graphics. Although a meta-analysis was not performed, the data for these 2 outcomes are presented by use of the ratio of means method [6]. We assessed the risk of bias for these 2 outcomes through the use of funnel plots. For the latter purpose, only 1 experimental group was included for each control group; preference was given to groups that received bone marrow–derived cells and syngeneic cells. Graphs were prepared with the use of Review Manager (Version 5.2; Cochrane Collaboration, Oxford, United Kingdom). Publication bias refers to the tendency for "negative" studies (in which the null hypothesis is not refuted) to be less likely to be published than "positive" studies (or to be published faster, in English, etc). For the current systematic review, this is relevant because it might be more interesting for a journal to publish a study in which MSC treatment improved asthma outcomes than a study in which outcomes were not improved. Thus published literature can then overestimate the effect of an intervention or show an effect when in fact there is none.

A funnel plot is one technique than can be helpful to detect publication bias. It plots a measure of effect size on the x-axis with a measure of its dispersion on the y-axis. In the absence of publication bias, less precise studies should be scattered symmetrically around more precise studies. This classically leads to a funnel appearance. An asymmetry can indicate publication bias, but there are other possible explanations.

Results

The search query returned 1873 entries (Figure 1), 874 of which were not identified as duplicates, reviews, editorials or conference abstracts by use of the Ovid system and were reviewed. Of these, 30 studies were selected for full text review, 19 of which met the inclusion criteria. Two studies were excluded because bone marrow–derived mononuclear cells were used rather than stem cells [7,8] and another

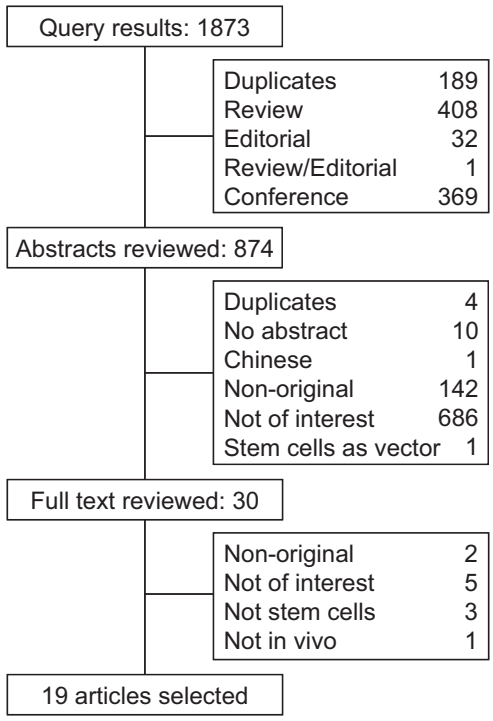

Figure 1. Study selection.