Seminars in Arthritis and Rheumatism ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at SciVerse ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Cell therapy for the treatment of tendinopathy – A systematic review on the pre-clinical and clinical evidence ☆, ☆☆

Pauline Po Yee Lui [a,b,c,*], Sze Wing Ng [a]

[a] Department of Orthopaedics and Traumatology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China
[b] The Hong Kong Jockey Club Sports Medicine and Health Sciences Center, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China
[c] Program of Stem Cell and Regeneration, School of Biomedical Science, The Chinese University of Hong Kong, Hong Kong SAR, China

ARTICLE INFO

Keywords:
Cell therapy
Tendinopathy
Tendinosis
Collagenase-induced tendon injury
Systematic review

ABSTRACT

Objectives: This review aimed to summarize the current evidence on the safety/efficacy of cell therapy for the treatment of tendinopathy.
Methods: A systematic literature search was conducted using various databases with relevant keywords. Both original animal and human controlled studies, covering any cell type for the treatment of naturally occurring, overuse or collagenase-induced tendinopathy, and with full text available, were included. The quality of all included studies was assessed. Relevant data on study design, safety and efficacy outcomes were extracted.
Results: Eleven original studies were selected, of which nine were pre-clinical studies using the collagenase-induced tendon injury model and two were clinical studies. Types of cells, scaffolds, dosages and treatment regimens used varied. All the studies performed cell injection once. A critical appraisal of the included studies showed sub-optimal blinding. Cell therapy was generally reported to be safe, except minor complications, in the short term. Cell therapy was reported to improve tendon architecture in histology but equivocal finding was observed in sonographic/MRI examination, functional and biomechanical performance.
Conclusions: The current evidence was inadequate to make a conclusion whether cell therapy was safe and effective. Further study with adequate sample size and follow-up time, appropriate controls and optimal blinding is required. Confirmation of finding, using different tendinopathy animal models, by systematic investigation of the effects of cell sources, dosages and regimens on the outcomes, and by the inclusion of tendon pain assessment in both animals and human, is recommended. Research on the mechanisms of how cell worked in tendon repair is essential.

Introduction

Tendinopathy is a tendon disorder characterized by activity-related chronic tendon pain and local tenderness. Tendon "overuse" injuries has been claimed to account for 30–50% of all sports-related injuries [1], and almost half of all occupational illnesses in the United States [2]. Because the affected tendon is weakened, it is predisposed to rupture. Despite the high morbidity of tendinopathy, evidence-based management for this tendon disorder is lacking due to its unclear pathological mechanism.

Among different strategies tested for the management of tendinopathy, cell therapies with different study qualities have been reported to promote healing with varying success [3,4]. Some studies were clinical case series of naturally occurring tendinopathy in horses [5–7] or human [8–10]. Other studies, while having a control group, have small sample size or have not implemented blinding in outcome assessment [11,12].

The optimal time for cell injection has not been determined. Some authors suggested that early implantation has better prognosis and recommended injecting cells at the granulation phase which would support the survival of the implanted cells [7]. One study reported a significant difference in the re-injury rate and injury to implantation interval (44 versus 83 days) [7]. However, a subsequent larger study failed to show the differences between interval and re-injury rate [13]. Is cell therapy safe and effective in the treatment of tendinopathy?

☆The work was conducted in the Department of Orthopaedics and Traumatology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China.

☆☆Supported in part by the Hong Kong Jockey Club Charities Trust. The sponsor has no involvement in the study design, collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

* Corresponding author. 74025, 5/F, Clinical Sciences Building, Prince of Wales Hospital, Shatin, Hong Kong SAR, China. Tel.: 852 2632 3072; fax: 852 2646 3020.
E-mail address: pauline@ort.cuhk.edu.hk (P.P.Y. Lui).

0049-0172/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.semarthrit.2012.10.004

Obaid and Connell [14] has systematically reviewed the current evidence to assess the applicability and effectiveness of cell therapy for the treatment of tendinosis. However, the quality of the included studies was not assessed in the review. Studies on acute tendon or tendon-bone tunnel injury were included in the review, the injury which was different from the degenerative characteristic as observed in tendinopathy. The safety of cell therapy was not addressed and there was no discussion on the relationship between treatment regimen and the outcome. There were new published studies on the use of tenocyte, adipose-derived mesenchymal stem cell (AdMSC), human umbilical cord perivascular cells (HUCPVCs) and fetal-derived embryonic stem cell (fdESC) for tendon repair which were not included in the review.

The aims of this review were thus to (1) summarize the current pre-clinical and clinical evidence on the safety and efficacy of cell therapy for the treatment of tendinopathy; (2) identify the relationship between cell types, dosages and administration regimens on the efficacy of cell therapy for the treatment of tendinopathy and (3) identify limitations of current studies and hence provide suggestions for the planning of future studies. The current evidence was systematically searched and critically appraised. Information related to the study design, treatment regimen, safety and efficacy of cell therapy for the treatment of tendinopathy was extracted. The efficacy of cell therapy was systematically evaluated based on histology, ultrasound/magnetic resonance imaging (US/MRI), functional and biomechanical performance, which was not done in the previous systematic review [14].

Methodology

We followed the PRISMA guidelines for reporting the results in this systematic review as appropriate.

Search strategy

Electronic databases including Pubmed, ScienceDirect, EMBASE, SPORTDiscus and Cochrane were searched for relevant articles and the last access date was on 11 July 2012. The search was performed by using the following combinations of keywords:

1. (Cell therapy OR stem cell OR tenocytes OR adipose-derived cell OR fibroblasts) AND (tendinopathy OR tendinosis OR tendinitis).
2. (Cell therapy OR stem cell) AND (tendon) AND (collagenase).
3. (Cell therapy OR stem cell) AND (tendon) AND (exercise-induced OR overuse OR repetitive strain injury).
4. (Cell therapy OR stem cell) AND (tendon degeneration OR rotator cuff injuries OR epicondylitis).

Relevant articles were firstly screened by title and then abstract or full text if the available information was unclear or insufficient to decide whether the article ought to be included. Studies were selected independently by the two authors using the criteria cited and the results were then compared. Discussion was carried out to reach a consensus. Reference lists of identified studies and cell therapy-related reviews were also reviewed to identify additional relevant studies that met the inclusion criteria.

Search criteria

Original pre-clinical and clinical studies, written in any language, that investigated the safety and efficacy of cell therapy compared to a control group, were selected. Only those studies with full-text, clearly established methodology and outcome measures and clear data were included in this review. Studies that covered any cell types in the treatment of tendinopathy were selected. Studies on naturally occurring, overuse-induced or collagenase-induced tendinopathy were included and those studies on surgically induced tendon or tendon-bone defects were excluded. Conference papers, book chapters and review papers were not included although the reference lists of review papers were hand-searched to include any applicable studies that were not captured by our search.

Quality assessment of included studies

The quality of all included studies, both pre-clinical and clinical, was evaluated based on if random group assignment and blinding were implemented. For clinical trials, their quality was further assessed using the PEDro scale (range 0–11) (http://www.pedro.org.au/english/downloads/pedro-scale/) by both authors and discussion was carried out to reach a consensus [15]. One score was given for each criterion that the study was satisfied.

Data extraction

Information on the tendinopathy model used, study design, number of subjects/animals, cell type, dosage, scaffold, cell administrative method, injury to treatment interval, longest follow-up time, outcomes on safety and efficacy were extracted. For outcomes on efficacy, data on histology, US/MRI examination, functional and biomechanical performance was extracted.

Data analysis

As outcome measures used in the included studies were heterogeneous, no data was suitable for statistical pooling or meta-analysis. The result was therefore only described qualitatively.

Results

Search results

A total of 5050 studies were identified from the electronic databases. After screening the titles or abstracts, there were 22 relevant articles. Further screening of these articles was done. Nine studies did not have control group and hence were excluded. Another three articles were excluded as no data and figures were shown (Appendix 1). Reference lists of relevant articles and review papers were screened; and one study was additionally identified. A total of 11 eligible studies were hence selected for analysis in this review. The selection process was summarized in Figure 1. The list of eligible studies is shown in Appendix 2.

Characteristics of included studies

Of the 11 eligible articles, nine of them were pre-clinical studies (one rabbit study; six equine studies, one sheep study and one rat study) and two were human studies (Table 1). For the pre-clinical studies, the tendinopathy-like changes were all induced by collagenase injection; and the tendon injury sites included Achilles tendon (three studies) and superficial digital flexor tendon (SDFT) (six studies) (Table 1). However, the concentrations and types of collagenase used to induce tendon injury varied. For the two clinical studies, one study was on refractory Achilles tendinopathy and the other study was on refractory patellar tendinopathy (Table 1).

A summary of cell source and treatment regimen used in different studies was shown in Table 2. The included studies were