

Cell Therapies in the Treatment of Temporomandibular Osteoarthritis: A Systematic Review of the Literature

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Abstract

Therapeutic strategies for the management of temporomandibular osteoarthritis ideally involve the improvement in pain and functional disability, as well as delay the progression and promote the repair of joint cartilage defects. Cell therapies have emerged as a new, minimally invasive therapeutic modality that allows for the use of autologous cell transplantation, and may involve adult undifferentiated mesenchymal stem/stromal cells (MSC) or differentiated cell lineage, like chondrocytes. The aim of this study was to review the existing controlled clinical trials that evaluate the efficacy and safety of these different types of cell therapy in adult patients with temporomandibular joint (TMJ) osteoarthritis. The parameters used to search the literature and retrieve these studies, as well as the assessments of eligibility criteria, have followed the recommendations of the PRISMA Statement. A highly sensitive search strategy was held in the Medline (1966-2013) and Central Register of Controlled Trials (1960-2013) databases. The latest search was carried out on Dec 27, 2013. Different combinations of keywords were used, temporomandibular joint, temporomandibular disorders, craniomandibular dysfunction, stem cells, mesenchymal cells and autologous chondrocytes, yielded 101 clinical trials. Most of these trials, however, were related to osteoarthritis of the knees. No clinical trials were conducted in patients with TMJ osteoarthritis. There is no evidence from randomized controlled trials to demonstrate the safety and effectiveness of different types of cellular therapies for the treatment of osteoarthritis of the TMJ. There is an urgent need to perform clinical trials in this area in order to benefit patients with advanced processes who are refractory to conservative or conventional minimally invasive therapeutic modalities.

Introduction

The term temporomandibular disorder (TMD) encompasses a set of painful and/or dysfunctional conditions affecting the masticatory muscles and/or temporomandibular joints (TMJ) [1]. The most prevalent chronic articular TMD can be classified into two diagnostic subgroups which are not mutually exclusive: disc displacements and degenerative changes in the TMJ [2].

In general, the degenerative process affecting the TMJ is characterized by the presence of clinical signs, namely, ongoing joint noises in the form of crepitus, which may occur with or without arthralgia, a spontaneous or pre-auricular pain caused by palpation and/or function. Ideally, diagnosis should be confirmed by acquiring CT scans or magnetic resonance imaging capable of providing relevant information about the shape and integrity of the articular cartilage and underlying cortical bone [3].

Articular cartilage is a metabolically active tissue which under normal conditions is maintained at a relatively slow state of cell renewal, with a sparse cell population of chondrocytes distributed throughout this tissue [4]. Chondrocytes strike a balance between synthesis and degradation of extracellular matrix, which composes cartilage. In the case of injury, there is an excess of extracellular matrix degradation and, despite the activity of the chondrocytes, the self-repair of cartilage tissue is limited. Even minor injuries can lead to progressive damage [5]. Chondral or osteochondral lesions are hardly capable of spontaneous healing, which manifests itself only under

certain circumstances, critically dependent on the extent of tissue destruction.

Lesions confined to isolated articular cartilage have little or no capacity for tissue regeneration, since they do not penetrate the subchondral bone, and therefore do not have access to bone marrow space and chondro-progenitor cells. Moreover, defects extending to the subchondral bone cause micro-bleeds in the area of the lesion and can form a hematoma that fills this site [6]. During this process, the mesenchymal stem/stromal cells (MSCs) migrate to the lesion. These cells are considered as a population of adult stem cells since they are clonogenic, form colonies in culture conditions and could differentiate in vitro into bone, cartilage, tendon, muscle, fibrous and adipose tissue [7,8]. In response to the presence of undifferentiated MSCs at the lesion site, they form a repair tissue that normally has an intermediate composition and structure somewhere between fibrocartilage and hyaline cartilage, which impairs biomechanical competence through reduced stiffness and increased permeability [9].

Thus, the ability of chondrocytes to produce changes in the composition of the extracellular matrix and synthesize new molecules is the basis for the processes of tissue regeneration. However, the lack of blood supply to cartilage and the consequent absence of undifferentiated cells at the lesion site undermine the ability of residing chondrocytes in their role of promoting tissue repair. Thus, the partial loss of these cells implies the possible progressive degeneration of the TMJ.

Therapeutic strategies are still under investigation in an attempt to develop protocols that can not only produce effects on pain and disability, but also in delaying the progression of articular cartilage defects. The conservative therapeutic approach to degenerative changes in the TMJ uses non-surgical or minimally invasive therapies based on suppression of parafunctional joint load through the use of oral splints and systemic administration of supplements such as glucosamine and chondroitin, or direct infiltration of drugs or biological materials such as hyaluronic acid.

However, patients with severe degenerative TMJ injuries and cases that prove refractory to conservative alternatives typically evolve into more invasive surgical intervention whose indication can be divided into relative and absolute, based on the extent of the injury [10]. The spectrum of surgical procedures for treating TMJ disorders is wide and ranges from simple arthrocentesis to open TMJ surgeries where autologous or alloplastic bone graft materials such as prostheses can be used for joint reconstruction. But all these extremely invasive alternatives entail long-term complications.

Within this complex scenario, cell therapies emerge as a new, minimally invasive therapeutic modality that provides the autologous cell transplantation and may involve mesenchymal stromal/stem cells, as its undifferentiated cell state or differentiated into chondrocytes. The primary goal of these therapies is to maintain, replace or repair preexisting joint functions [11,12]. The main potential advantages of cell therapy for the treatment of osteoarthritis are: the use of autologous cells with low risk of rejection or immunological complications; the anti-inflammatory and analgesic effect of the transplanted cells, especially MSCs; the ability of transplanted cells to rebuild cartilage tissue and brake the degenerative process; and the low-cost and minimally invasive nature of the therapeutic procedure.

Thus, in order to identify the different modalities of cell therapies capable of controlling the pain and disability associated with degenerative changes in the TMJ, and to some degree, inducing tissue regeneration, controlled trials that evaluated the efficacy and safety of these procedures were reviewed in adult patients with temporomandibular osteoarthritis.

Material and Methods

The method used to retrieve the studies, review criteria eligibility, data extraction and outcome measures as well as quality assessment followed the recommendations laid down by the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [13].

Retrieval of Published Studies

To retrieve articles that investigated the efficacy and safety of cell therapies to control pain and functional disability and tissue regeneration in adult patients with osteoarthritis of the TMJ, a highly sensitive search strategy was performed in the Medline (1966-2013) and Cochrane Central Registers of Controlled Trials (1960-2013) databases. The last survey was performed on December 27, 2013. Once the databases were organized into trees of specific terms (Medical Subject Headings [MeSH] or Emtree terms), the search strategy was performed by inserting relevant terms, shown in Table 1. In addition, reference lists and reports of relevant articles were verified for the absence of important items to complete the survey. Subsequently, the titles, abstracts and keywords of all articles identified were examined to determine if they were indeed relevant to the topic being studied.

Relevant articles were included to assess whether or not a full text article met the inclusion criteria.

N°	Search Strategy Medline and Central	Search Strategy Embase
1	Temporomandibular joint	Temporomandibular joint
2	Temporomandibular disorders	Temporomandibular disorders
3	Craniomandibular dysfunction	Craniomandibular dysfunction
5	1 or 2 or 3	1 or 2 or 3
6	Stem/Stromal cells	Stem/Stromal cells
7	Mesenchymal stem/ stromal cells	Mesenchymal stem/ stromal cells
8	Autologous chondrocyte	Autologous chondrocyte
9	6 or 7 or 8 or 9	6 or 7 or 8 or 9
10	5 and 9	5 and 9

Table 1: Search parameters used in the databases.

Eligibility Criteria

To be included in the review articles should match controlled clinical trials that investigated the efficacy and safety of different modalities of cell therapy in the treatment of TMJ osteoarthritis. Two independent reviewers assessed the articles in terms of their eligibility. No language restriction was applied during the selection process.

Data Extraction and Result Measures

Data from included studies were extracted independently by two reviewers (RST and KM). The main data regarding the results of each study consisted of sample size and measures of pain and functional disability at the start and at the different follow-up periods. Tissue regeneration measures were also identified and evaluated based on images. Other relevant factors for the extraction of data included diagnosis and treatment modalities, study design, follow-up period, reports of patients who dropped out of treatment, and statistical analysis.

Quality Assessment: Bias risk

The same reviewers (RST and KM) independently assessed the quality of each study. The strengths and weaknesses of the design, implementation and review of data from each study were analyzed. Disagreements over quality factors were resolved by consensus.

These factors were: (1) concealed allocation, (2) size and composition of groups, (3) blinding of participants and investigators, (4) applying the criteria for inclusion and exclusion of participants, (5) description of follow-up failure, and (6) ensuring the appropriateness of the statistical analysis.

Results

The isolated use of the terms "temporomandibular joint" enabled the identification of 696 publications through the filter for clinical

trials in the Medline database. Moreover, the isolated use of the keywords "temporomandibular disorders" retrieved 213 publications through the same filter, only 13 of which had not been identified previously. Finally, a similar search using the keywords "craniomandibular disorders" allowed the identification of 25 new items among the 38 publications listed.

Using the same filters in the same database described above, use of the keywords "stem/stromal cells" allowed the identification of 6355 publications, while the use of the keywords "mesenchymal cells" found 25 publications, of which 22 articles had not been previously identified. A search using the keywords "autologous chondrocyte" detected 76 new articles.

A combination of both aforementioned searches resulted in the identification of 101 articles, but almost all were related to osteoarthritis of the knees, with no clinical trials conducted in patients with osteoarthritis of the temporomandibular joint.

Of a total of 80 articles identified in the Cochrane Center for Controlled Clinical Trials, 15 systematic reviews involved the keywords "temporomandibular joint" or "temporomandibular disorders" or "craniomandibular disorders", 2 the keywords "autologous chondrocytes," and 63 the keywords "stem/stromal cells" or "mesenchymal cells." Nevertheless, a combination of the terms "temporomandibular" or "craniomandibular" and "autologous

chondrocytes" or "stem/stromal cells" or "mesenchymal cells" yielded no results. None of these 80 articles could be added to those already identified.

The references of all articles selected for assessment of eligibility were checked, which resulted in no additional articles.

Of the two articles included for full text reading, both referred to auricular cartilage graft in temporomandibular joint arthroplasty, but no articles met the inclusion criteria because the study design did not match that of a controlled clinical trial [14,15].

The first article to be published aimed to evaluate the use of autologous auricular cartilage graft as an interposition material after arthroplasty in the treatment of TMJ ankylosis in 7 children with clinical follow-up of 4 and 6 years [14]. Over six years of clinical follow-up none of the patients relapsed, and no deformity of the ear cartilage was observed. The most recent article evaluates the results of arthroplasty in 23 TMJ with auricular cartilage grafts in 18 patients with osteoarthritis who were refractory to previous surgical and nonsurgical treatment [15]. The grafts had to be removed from 7 TMJ. In the 16 joints which still had the grafts in the correct position, a significant pain reduction and improvement of mandibular function were noted. The therapy appeared to be less favorable in patients who had previous TMJ surgery. The design features of both studies are shown in Table 2.

Study	Study Design	Diagnosis	Sample size	Treatment modality	Follow-up	Results
Svensson et al. [15]	Case reports	Osteoarthritis patients refractory to surgical and nonsurgical treatments	23 TMJ	Arthroplasty with auricular cartilage graft	7 ½ years	In 7 TMJ (30%) the graft was removed after 26 months because of persistent pain in function; 16 TMJ had significant improvement in pain and function
Lei et al. [14]	Case reports	TMJ ankylosis in children	7 patients	Autologous auricular cartilage graft	4 to 6 years	All 7 patients immediately preserved alignment of mandibular movement with adequate recovery, and had no ear deformity during follow-up

Table 2: Characteristics of studies included for full text reading.

Discussion

Noteworthy among the cell therapies currently used in dentistry are autologous or allogeneic transplants, which are performed by harvesting perichondrial or periosteal tissue for the treatment of defects in articular cartilage [10].

Within today's scenario of major advances in cell therapy, autologous chondrocyte transplantation (ACT) has emerged as a promising therapeutic approach. In the last decade, ACT attracted scientific and commercial interest, making it the most widespread application in cartilage regenerative medicine [16]. Chondrocytes are self-renewable and have a great chondrogenic potential throughout their lifespan. It is believed that transplanted chondrocytes not only produce new chondroblasts that form the cartilaginous tissue through a process called cellular de-differentiation, but also provide the supplies needed to induce tissue healing [17].

The implantation of autologous chondrocytes to treat cartilage defects was first reported in 1994. In this procedure, autologous chondrocytes were expanded into a monolayer culture system and transplanted into an osteochondral lesion. The major findings disclosed in this trial were not confined to the repair potential of these cells, but their high expansion capacity *in vitro* (chondrocytes were expanded into 20 to 50 times the initial number) and de-differentiation when grown in monolayers with serum supplementation within the culture medium. De-differentiated chondrocytes exhibit features of primitive MSCs, and can therefore mimic pre-chondrogenic cell condensation and cartilage formation.

Preclinical studies with autologous chondrocyte implantation demonstrated that treatment improves joint function and relieves the pain [18]. A research demonstrated that MSCs could rebuild mandibular condyles. Rat bone marrow MSCs were isolated and induced to differentiate into chondrogenic and osteogenic cells in

vitro, and encapsulated in a biocompatible polymer, molded into the shape of a cadaver human mandibular condyle. Eight weeks following *in vivo* implantation of the bilayered osteochondral constructs, the mandibular condyles formed again [19]. Autologous chondrocytes associated with hyaluronic acid in early osteoarthritis lesions in rabbits succeeded in promoting the regeneration of cartilage tissue in the joint [20]. The same benefit is also achieved by using a molecule that induces differentiation of local MSCs into chondroblasts [21].

A recent study conducted in rabbits compared the effects of MSCs vs. MSCs differentiated *in vitro* into chondrocytes in a model of osteoarthritis of the TMJ. Four weeks after induction of osteoarthritis animals received a solution containing hyaluronic acid or MSCs or pre-differentiated chondrocytes. Changes in cartilage and subchondral cancellous bone were evaluated by histology and computed tomography. The animals that received MSCs differentiated into chondrocytes showed better histology than animals that received non-differentiated MSCs 4 and 12 months after implantation, but no difference was observed 24 months after the procedure. The experimental group of MSCs differentiated into chondrocytes showed lower bone volume fraction, trabecular thickness and density of the bone surface, in addition to more space in trabecular subchondral cancellous bone compared to the group that received non-differentiated MSCs. The study demonstrated that MSC delays the process of disease progression while their differentiation into chondrocytes enhances the therapeutic effect of this cell lineage [22].

Evidence of the benefits conferred by ACT led to approval in 1997 by the Food and Drug Administration (FDA - U.S.) of the use of autologous chondrocytes for repair of cartilage lesions in the knee. This was the first type of cell therapy regulated by industry for use of expanded autologous cells during transplantation in humans.

In the U.S. and Europe, the use of autologous chondrocytes is mainly applied in knee joints damaged by trauma, but the tendency of pre-clinical and clinical studies is to treat other joints. Because of its potential benefits for healing articular lesions, ACT is now considered a new therapy option for TMJ surgery.

Recently, a systematic review of the literature was published which evaluated the safety of cell therapies expanded in culture for intra-articular use in humans [23]. It was concluded that the application of cultured cells in human joints seems to be a safe procedure. One is advised however to remain on the alert for potential side effects. Thus, the continued development of new cell therapies to treat joint damage is hereby encouraged.

Conclusions

This systematic review of the literature revealed insufficient evidence in controlled clinical trials to demonstrate the safety and efficacy of different types of cell therapy for the treatment of TMJ osteoarthritis. Therefore, there is an urgent need to conduct clinical trials in this area with the purpose of identifying the most effective and safe methods to control pain and functional disability. Future studies should also target tissue regeneration and TMJ affected by advanced osteoarthritis processes but refractory to conservative or minimally invasive treatment modalities.

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