MINI-REVIEW

Mesenchymal stem cell based therapy for osteo-diseases

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Abstract

Stem cell therapy in recent years has gained much attention as the modern therapeutic approach to treat diseases. Mesenchymal stem cells (MSCs) are seen as the most reliable cells applied in therapy over other stem cells because of their versatility. Bone and cartilage diseases (osteo-diseases) are the major target of therapy using MSCs. In this perspective, we have statistically analyzed the data available on clinical trials registry databases regarding the mesenchymal stem cell based therapy for a number of mentioned diseases and paid attention towards the osteodiseases. We report that MSC therapy for osteo-diseases needs optimization in its standards to achieve acceptable results so that we can apply it in daily routine clinical practice.

Keywords: bone and cartilage diseases; cell based therapy; clinical trials; mesenchymal stem cells

Introduction

Stem cells are the specific cells having unlimited proliferation and differentiation capacities. Since their first discovery in 19th century (Reiser et al., 2005), these cells have been applied in cell-based therapeutic approaches in clinics (Brodie and Humes, 2005). From clinically applied stem cells, mesenchymal stem cells (MSCs) have been described as well-characterized stem cells that can be isolated from adult tissues (Jiang et al., 2002). Positive indications of their applications in various diseases have made them clinically promising (Bang et al., 2005, Garcia-Olmo et al., 2005, Kuo et al., 2008, Le Blanc et al., 2008, Nakamizo et al., 2005, Pisati et al., 2007). Many advantages in their application over the embryonic stem cells have made them potential candidates in regenerative medicine (Thomson et al., 1998).

MSCs have been isolated from almost all parts of the body, for example, skin (Toma et al., 2005), blood (Campagnoli et al., 2001), umbilical cord blood (Rosada et al., 2003), dentine (Perry et al., 2008), pancreas (Seeberger et al., 2011), adipose (Zuk et al., 2002), liver (Wenceslau et al., 2011), brain, heart, lungs, and kidneys (Salem and Thiemermann, 2010).

Adipose tissue is the largest source of these stem cells as they can be isolated from the lipoasparate in daily routine liposuction (Yoo et al., 2009) and have limited oncogenicity (Vilalta et al., 2008). MSCs derived from different organs should have the following characteristics: self-renewal and differentiation ability to osteocyte, adipocyte and chondrocyte (Zuk et al., 2002); should express CD105, CD90, and CD73 antigens; and should not express CD11b, CD14, CD34, CD45, and HLA-DR1 (Ghannam et al., 2010). Clinical methodology (clinical trial) is the follow-up study of a disease treatment on humans under the supervision of expert scientists. Every clinical study has a strong experimental basis performed on animals. In this perspective, we will discuss clinical trials of osteo-
diseases using MSCs and their follow-up complications and results.

**Cell-based therapy using MSCs**

Data were collected from the website of clinical trials of the US government (www.clinicaltrials.gov), using the keywords “mesenchymal stem cell therapy.” A total of 288 registered studies were found from 2001 to October 2013 (Figures 1 and 2). Sixty-seven clinical studies have been completed so far, whereas 183 are ongoing or recruiting; and results for 38 studies are still unknown (Figure 3). A total of 108 studies have been sponsored by academic bodies and 180 by industry (e.g., hospitals, clinical institutes, and private sectors). Most of these studies have been done in Asia (146) and Europe (71) (Figure 4). Five countries around the world, China, USA, Spain, South Korea, and Iran, have done ~70% of all clinical research (Figure 4). All clinical trials are in different phases of study (Phase 0, I, II, III; see Figure 5). Phase 0 deals with basic study. Upon approval of its findings by the associated boards or committees, it would enter into Phase I. In Phase I, safety measurements are the main area of focus, whereas in Phase II effectiveness of the treatment and its reliability are tested. In Phase III, final authentication of effectiveness and safety measurement are included. Most of the above studies are still in Phase I/II, indicating their status of authenticity.

**Clinical trials of osteo-diseases using MSCs**

MSC therapy has proved a promising approach to treat osteo-diseases, which globally are a major health issue.

According to the data submitted to the National Library of Medicine, deposited in ClinicalTrials.gov website until October 2013, 57 clinical trials have been registered for these series, while only 12 studies have been completed (National Library of Medicine, 2013). Culture expanded MSCs with culturing times of 2 weeks to 4 months have been used in these studies. There is an exception for one case, in which fresh stem cells were used (6S). Statistical analysis of these data showed that 52% of these MSCs were derived from BM, 13% from adipose, 11% from umbilical cord and 24% from other or unidentified sources.

While studying the above-mentioned data, we found no link between the source of stem cells and the type of diseases. Some interesting matters caught our attention, as all the stem cells used in Iran were from bone marrow origin,
whereas in South Korea they were derived mainly from adipose and umbilical cord. In most of these studies, cells for injection purposes ranging between 2 and 100 million were used as an exact figure followed by 1–40 million cells, on an estimated basis. Optimization of specific number of cells for clinical purposes also remained a target (18S, 20S, 43S). Researchers also focused on the volume of cellular injection as a significant factor in clinical therapy. They have applied cells in different volumes and components, for example, cells with 10 mL bone marrow plasma (13S), cells with 2–4 mL plasmalyte and 2 mL hyaluronan (17S); cells with 8–10 mL PRP (27S); and cells in 10 mL normal saline (14S, 18S, 57S). Hyaluronic acid has been used for injecting, whereas in some cases it was used as a control (5S). It also has been combined with cells as an experimental group (10S).

Different methods have been used to inject the cells. Intra-articular injections followed by intra distal (47S) and open surgery or arthroscopy (2S) leads the cellular injection methodologies. Scaffold-based studies also have been conducted using different materials, for example, hydroxyapatite (6S), collagen I (9S), and calcium phosphate ceramic (46S). In some experiments, scaffolds have been used in combination with cells or combination of cells and chemical compounds, for example, BMP2 (32S).

We also encountered some interesting experimental designs with regard to the control groups. For example, there were reports of chondrocytes cultured on scaffold (22S), and defined volumes of plasmalyte (42S) and mepivacaine (47S). Follow-up times were also variable in all studies, ranging from 24 weeks to 5 years, irrespective to the nature of the disease. For example, in one case of rheumatoid arthritis (RA) disease, a 6-month follow-up period was considered (38S), whereas in another study with the same disease the followed-up time was extended for 5 years (36S, 37S) (Table 1). All of these studies, deposited in the above-mentioned database, are in different phases of their clinical trials. Overall different phases of 0, I, II, III, I/II, and II/III account for 7%, 23%, 19%, 3.5%, 41%, and 3.5%, respectively.

**Conclusion and perspectives**

Statistical-based analysis of MSC therapy for osteo-diseases inferred that most studies are still under investigation. There are different follow-up times that indicate we are still far from reaching the final conclusion. The major problems in the optimization of MSC therapy are the standardization and mutual coordination globally among the scientists. There is no any news or report planning to standardize the stem cell therapy. We need different standards to optimize therapeutic approaches in osteo-diseases. These standards include number, type, and source of cells; follow-up times; use of scaffolds; and patients indications.
<table>
<thead>
<tr>
<th>Country</th>
<th>Disease (no.)</th>
<th>Phase (no.)</th>
<th>Enrollment</th>
<th>Status (no.)</th>
<th>Type of cell (no.)</th>
<th>Follow up</th>
<th>N</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iran</td>
<td>Osteoartirid (5), rheumatoid arthritis (1), cartilage disease (1), non-union (3), bone cyst (1)</td>
<td>I (7), II (3), III (1)</td>
<td>5–60</td>
<td>Ongoing (1), recruiting (2), complete (8)</td>
<td>BM (11)</td>
<td>6 to 12 M</td>
<td>11</td>
<td>(15, 73, 95, 115, 125, 145, 195, 290, 305, 325, 555, 575)</td>
</tr>
<tr>
<td>Spain</td>
<td>Osteoartirid (4), knee defect (1), bone cyst (1), rheumatoid arthritis (1), lumbar disease (2), spinal fusion (1)</td>
<td>I (10)</td>
<td>10–62</td>
<td>Ongoing (1), recruiting (6), complete (2), unknown (1)</td>
<td>BM (7), adipose (2), unknown (1)</td>
<td>6 to 24 M</td>
<td>10</td>
<td>(25, 45, 55, 255, 335, 385, 465, 475, 515, 565)</td>
</tr>
<tr>
<td>USA</td>
<td>Osteoartirid (1), rheumatoid arthritis (2), lumbar disease (2), cartilage disease (1), back pain (1)</td>
<td>I (2), II (2), III (3)</td>
<td>6–100</td>
<td>Ongoing (2), recruiting (3), complete (2)</td>
<td>BM (1), UC (1), other (5)</td>
<td>12 M to 5 Y</td>
<td>7</td>
<td>(135, 335, 375, 395, 485, 495, 505)</td>
</tr>
<tr>
<td>China</td>
<td>Osteoartirid (2), rheumatoid arthritis (2), ankylosing spondylitis (2)</td>
<td>O (2), I (1), VII (3)</td>
<td>10–200</td>
<td>Ongoing (2), recruiting (3), unknown (1)</td>
<td>BM (1), UC (3), adipose (1), other (1)</td>
<td>6 to 12 M</td>
<td>6</td>
<td>(155, 165, 345, 355, 405, 435)</td>
</tr>
<tr>
<td>Korea</td>
<td>Rheumatoid arthritis (1), cartilage disease (2), disk degenerative (1), femoral head (1)</td>
<td>III (3), IV (2)</td>
<td>8–104</td>
<td>Ongoing (1), recruiting (2), complete (2)</td>
<td>Adipose (3), UC (2)</td>
<td>6 to 60 M</td>
<td>5</td>
<td>(185, 195, 265, 455, 525)</td>
</tr>
<tr>
<td>France</td>
<td>Osteoartirid (2), cartilage disease (1), non-union (1),</td>
<td>O (1), I (1), II (1), VII (1)</td>
<td>18–50</td>
<td>Recruiting (4)</td>
<td>BM (3), Adipose (1)</td>
<td>3 M to 1 Y</td>
<td>4</td>
<td>(65, 205, 415, 445)</td>
</tr>
</tbody>
</table>

N, the number of respective category; BM, bone marrow; UC, umbilical cord; M, month; Y, year.

Data retrieved from US National Library of Medicine (http://www.clinicaltrials.gov) (detailed references for each study are given in Supporting Information, Appendix S1).
Conflict of interest
The authors declare no conflict of interest.

References


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Supporting Information
Additional Supporting Information should be found in the online version of this article at the publisher’s web-site.

Appendix S1. Supporting references.