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REVIEW

Issues and opportunities of stem cell therapy in autoimmune diseases

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Abstract

The purpose of regenerative medicine is to restore or enhance the normal function of human cells, tissues, and organs. From a clinical point of view, the use of stem cells is more advantageous than differentiated cells because they can be collected more easily and in larger quantities, their proliferation capacity is more pronounced, they are more resistant in cell culture, their aging is delayed, they are able to form a number of cell lines, and they are able to promote vascularization of tissue carriers. The therapeutic use of stem cells for disease modification, immunomodulation, or regenerative purposes are undoubtedly encouraging, but most studies are still in their early stages, and the clinical results reported are not clear with regard to therapeutic efficacy and potential side effects. Uniform regulation of the clinical application of stem cells is also indispensable for this highly customizable, minimally invasive, individualized therapeutic method to become a successful and safe treatment alternative in many different autoimmune and autoinflammatory disorders.

Key words: Stem cell therapy; Autoimmune; Autoinflammatory; Immunomodulation; Disease modification

Core tip: The therapeutic use of stem cells in autoimmune diseases for disease modification, immunomodulation, or regenerative purposes are undoubtedly encouraging. However, the clinical results reported are not clear about therapeutic efficacy and potential side effects. Uniform regulation of the clinical application of stem cells is indispensable.

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INTRODUCTION

Stem cells with extraordinary self-renewal capabilities have an extensive differentiation capacity to create a wide range of tissues and organs. There are small numbers of stem cells in the human body that after division with mitosis can differentiate into daughter cells or create newer stem cells. Maintenance and activation of their differentiation potential is fundamentally influenced by the microenvironment (cellular and humoral)[1].

Depending on the differentiation potential, self-renewal ability, and origin many types of stem cells can be distinguished. According to their plasticity totipotent, pluripotent, multipotent and unipotent stem cells exist. Totipotent cells (*e.g.*, zygote, spore, or morula) can create any human cell or even an entire organism. In the case of pluripotent cells, the possibility of forming a complete functional organization is lacking. Multipotent stem cells are able to create limited types of daughter cells. Under physiological conditions, they ensure the continuous regeneration of the tissue, replace the dead somatic cells, and after injury participate in the regeneration of the affected organ. Unipotent cells are precursor/progenitor cells with limited plasticity. Based on their origin, embryonic, adult (including fetal), tumorous, and induced pluripotent stem cells are known[1].

Human stem cell therapy, except for bone marrow transplantation, is still in the experimental phase, so it is difficult to predict how efficiently and with the expected risk it can become applicable in daily clinical practice. Since 2009, the use of all cell and gene therapy products in the European Union has been regulated solely by a centralized authorization (European Medicines Agency-The Committee for Advanced Therapies).

TYPES OF STEM CELLS

Embryonic stem cells

Embryonic stem cells originating from the inner cell mass of blastocyst are pluripotent cells. They have two characteristics: they can produce all the derivatives of the three primary germinal plates, and in some circumstances their division is unlimited. In the last few decades a significant number of embryonic stem-cell specific markers have been identified[2]. Although embryonic stem cells carry the ability to create differentiated cell types, complex regulation of cell proliferation through differentiation and development-specific signal pathways is indispensable. However, the safety of their clinical use is a cause for serious concern, as the risk of teratomas or teratocarcinomas is high as a serious adverse reaction. Due to these difficulties, the use of human embryonic stem cells was initially limited primarily to *in vitro* and animal experiments, but several clinical trials have been started in recent years (*e.g.*, macular degeneration, retinitis pigmentosa, ischemic heart disease, spinal cord injury, Parkinson's disease, diabetes mellitus)[3].

Embryonic stem cells from primordial germline cells have many properties of human embryonic stem cells but are also different from them. Primordial germline cells can be isolated from fetal tissues and the gonadal spine within a relatively narrow time interval. After *in vitro* cultivation, they are pluripotent but do not lead to teratoma formation in mice[2,4]. Their laboratory or clinical use is subject to strict legal regulations. When embryonic stem cells are used, Good Laboratory Practice and Good Manufacturing Practice quality assurance systems are required to test and manufacture conditions that dramatically make the method more expensive.

Adult stem cells

Adult stem cells and primitive cells in fetal organs (*i.e.*, fetal stem cells) are multipotent tissue (somatic) stem cells. In current medical practice, they are particularly suited to treating hematopoietic diseases, but the risk of tissue rejection, which is similar to that seen in heart or kidney transplants, may limit their clinical use[5].

According to their source, adult stem cells can originate from the endoderm, mesoderm, and ectoderm[6]. The adult bone marrow contains two types of multipotent

stem cells: hematopoietic and bone marrow stromal (mesenchymal) cells. While hematopoietic stem cells are present in the peripheral blood, umbilical cord, and bone marrow, bone marrow stromal cells can be recovered from several other tissues (*e.g.*, umbilical cord, fetal tissues)[7]. Hematopoietic stem cells can maintain the production of all blood cells. However, bone marrow stromal cells bone, cartilage, smooth muscle, fat, and hematopoietic supportive stromal cells may be differentiated[7,8]. Adult stem cells from mature tissues have limited potential compared to embryonic or fetal stem cells. Most adult stem cells are lineage-restricted and generally refer to their tissue origin. Cells originating from the endothelial, mesenchymal, and adipose tissue can be distinguished[7-9]. In addition to the bone marrow, mesenchymal stem cells can be isolated from a wide variety of tissues (adipose tissue, peripheral blood, placenta, dental pulp, synovial membrane, periodontal ligaments, endometrial, trabecular and compact bones). Under appropriate culture conditions they can mature to mesodermal, endodermal, and ectodermal cells. They can be used safely to aid tissue regeneration because they do not form teratomas[10-14].

Adult stem cells play a prominent role in local tissue repair and regeneration. Based on ethical considerations, the isolation and therapeutic use of adult stem cells, in contrast to embryonic stem cells, is significantly more favorable. On the other hand, adult stem cells are also available from autograft, thereby substantially eliminating the risk of tissue rejection[6]. Adult stem cells are essential creators of both single- and multilayered epithelium[6,14-17].

Cancer stem cells

Within the heterogeneous cancer cell population hierarchy, it is believed that only a specific set of cancer stem cells, specifically self-renewing, pluripotent tumor-initiating, and repopulating cells have a direct tumor and metastasis-promoting property. In malignant tumors, these cells contribute greatly to the development of resistance against cell death, uncontrolled proliferation, aggressive spread, and resistance to conventional therapies. Tumor stem cells stimulate cancer cell dormancy and initiate relapse. Initially it was hypothesized that tumor stem cells were derived from normal stem cells. However, recent studies have shown that progenitor cells on genetic (*e.g.*, tumor suppressor and oncogenes, chromosomal changes, microsatellite instability, *etc*) and/or epigenetic (*e.g.*, post-transcriptional microRNA regulation, promoter hypo-/hypermethylation, histone acetylation, *etc*) levels contribute to the development of a tumor stem cell pool. Tumor stem cells are not necessarily descendants of normal progenitors or stem cells. The emergence and accumulation of genetic/epigenetic changes in both tumor and normal cells can contribute to the expression of stem cell properties by dedifferentiation, and thus to the formation of tumor stem cells. Tumor stem cells may also be formed as a result of cell fusion between normal stem cells and somatic cells[6,18,19]. Due to their long lifetime, cancer cells accumulate many mutations essential for malignant transformation.

Although cancer cells are predominantly derived from oncogenic transformed aberrant adult stem cells, epithelial-mesenchymal transition also facilitates the transdifferentiation mechanism of cancer cells to acquire stem cell-like properties. In the early spread of preinvasive tumors, epithelial-mesenchymal transition is of paramount importance. Due to mesenchymal-epithelial transition changes the second phenotypic status of the cancer cells contributes to metastasis formation[20-24]. Like normal adult stem cells, metastatic cancer cells can enter a dormant state because of inhibitors from microenvironmental signals or in the absence of appropriate stimulating signals. At the same time, the nonproliferative, dormant phenotype of cancer cells from different primary tumors can be overwritten by the microenvironmental properties (*i.e.*, specific survival signals) of the target organs[22-25].

From a therapeutic point of view, it is possible to induce differentiation of cancer cells before and during chemotherapy. While this strategy can be effective in treating hematological cancers (*e.g.*, childhood acute promyelocytic leukemia), in solid tumors differentiation promoting factors and proper delivery of chemotherapeutic agents to the tumor mass have been less successful[6].

Induced pluripotent stem cells

These cells are artificially created from nonpluripotent cells. They are typically generated from mature somatic cells by the induction of genes that determine the stem cell phenotype[25]. In many respects (such as expression of stem cell specific genes and proteins, chromatin methylation pattern, cell duplication time, creation of embryo-like body, formation of teratomas and viable chimeras) these cells are similar to natural pluripotent stem cells, such as embryonic stem cells[25-27]. The emergence of human induced pluripotent stem cells is an important step in stem cell research, as the method allows the development of pluripotent stem cells without sacrificing of embryos, graft-versus-host disease, and immunological rejection. Induced pluripotent

stem cells have already been used for drug development and modeling of many diseases and will be beneficial in transplant medicine[25-27]. However, induced pluripotent stem cells may also present a risk that may limit their clinical use. Genetically modified adult cells may increase expression of protumor genes and oncogenes. There are, however, methods that can eliminate oncogenes after induction of pluripotence and even induce pluripotent stem cells without genetic alteration of adult stem cells (so-called protein-induced pluripotent stem cells)[25-28].

THERAPEUTIC USE OF STEM CELLS

From a clinical and research point of view, stem cells can be used for drug research and toxicity studies, development and gene regulation studies, genetic modification of laboratory and farm animals (*i.e.*, production and propagation of transgenic animals), and tissue engineering and cell replacement for therapeutic purposes.

The purpose of regenerative medicine is to restore or enhance the normal function of human cells, tissues, and organs. In terms of their clinical applicability including in autoimmune disorders, cell replacement procedures and therapies that alter the natural course of diseases should be considered.

Cell replacement

The idea of using stem cells as a paradigm for replacing damaged tissues with impaired function was first introduced after World War II. Essentially, experiments that led to the fight against radiation injury were the basis for the practical applicability of stem cells. To date, stem cell therapy has become an alternative (experimental) tool, not only for the treatment of malignant hematological diseases and bone marrow failure, but also for almost all other systemic diseases[6,29]

Modifying the course of diseases

Certain stem cells possess the specific ability to alter the cellular response to injury or abnormal immune activity in the absence of being incorporated into the recipient's organism. These stem cells act on the outcome of the disease without directly replacing the damaged cells. Bone marrow mesenchymal stem cells were initially believed to promote tissue regeneration by direct cell replacement; however, these cells stimulate tissue repair mainly by paracrine control signals. The mesenchymal stem cell population by altering immune functions can modify the response to injuries and can alleviate the mainly inflammatory consequences of autoimmune processes[6,7,12].

From a clinical point of view, the use of stem cells is more advantageous than differentiated cells because they can be collected more easily and in larger quantities, their proliferation capacity is more pronounced, they are more resistant in cell culture, their aging is delayed, they are able to form a number of cell lines, and they are able to promote vascularization of tissue carriers[29]. Clinically, many arguments support the therapeutic use of adult stem cells. They are present in virtually all organs and body fluids and can be isolated and used in an autologous manner. In adult stem cells, similarly to stem cells derived from extrafetal tissues, there is a low risk of mutation-dependent side effects. On the other hand, the clinical applicability of adult stem cells, in contrast to the ethical and legal norms regulating the use of stem cells from human ova, embryos, and fetuses, is considerably more relaxed[1,6,29].

While storing stem cells derived from extrafetal tissues provides the opportunity for future regenerative therapy, the relatively high costs, the limited storage capacity, and the time-dependent loss of cell viability has not allowed the method to spread in developed countries. Such stem cells are mainly suitable for allogeneic use. Although the immunogenicity of stem cells, apart from induced pluripotent stem cells, is generally low, the potential immunological response to an allogeneic graft may require immunosuppressive treatment. For the time being the use of adult stem cells seems more advantageous for both cell therapy and tissue formation[29].

It is also important to emphasize that the regenerative capacity of tissue-specific progenitor cells is affected by both the natural process of aging and many diseases (*e.g.*, arthrosis, osteoporosis, cardiovascular, endocrine and metabolic diseases, inflammatory diseases, tumors). The stem cell properties of progenitor cells may be adversely influenced by genomic instability, telomere shortening, epigenetic differences, loss of protein balance, nutrient deficiency, mitochondrial dysfunction, and intercellular communication disorders[30].

STEM CELLS THERAPY IN AUTOIMMUNE DISEASES

In the following, we summarize the clinical results of stem cell therapy in select autoimmune diseases.

Hematopoietic stem cells

Between 1996 and 2017, around 4500 bone marrow transplantations were performed in autoimmune and autoinflammatory diseases worldwide. Preclinical studies in animal models of genetically determined (*e.g.*, diabetes, lupus) and induced immunological disorders (*e.g.*, acute arthritis) have been suggested for the possible use of hematopoietic stem cell therapy (HSCT) in autoimmune disorders. In autoimmune diseases in the introductory phase of HSCT, intensive immunosuppression for the elimination of autoreactive lymphocytes is clinically useful. In the second phase of treatment, autologous or allogeneic hematopoietic CD34+ progenitor cells recolonize the bone marrow and immune system, and in addition to preventing severe cytopenias and/or hematopoietic disorders, also develop a new immune system. HSCT is believed to permanently alter the immune system by losing T-cell mediated immunological memory[30,31] (Figure 1). Table 1 summarizes the indication of stem cell transplantation in autoimmune and autoinflammatory diseases (European Bone Marrow Transplantation Recom-mendation 2017).

Systemic sclerosis

In most systemic sclerosis (SSc) patients, conventional therapeutic agents are less effective. Regarding autologous HSCT, to date three controlled, prospective, randomized trials in SSc have been conducted in the world: The American Scleroderma Stem Cell versus Immune Suppression Trial, The Autologous Stem Cell Transplantation International Scleroderma Trial, and The Scleroderma: Cyclophosphamide Or Transplantation Trial. The selection criteria of patients with predominantly diffuse cutaneous SSc were the same, but the duration of conditioning treatments, stem cell mobilization and selection techniques, and follow-up were different in each study. All in all, the results are promising. In The Scleroderma: Cyclophosphamide Or Transplantation Trial study, skin condition and lung function improved after HSCT compared to patients with standard treatment in which the disease progressed. The rate of event-free survival was 79% (*vs* 50%) after 54 mo, while overall survival was 91% (*vs* 77%). On the other hand, long-term follow-up of patients undergoing HSCT is mandatory in order to identify potential serious complications (such as secondary autoimmune diseases, malignant tumors, cardiovascular consequences) in a timely manner[31,32]. Even with adequate selection criteria, mortality is about 5%-6%[33]. According to the latest European League Against Rheumatism recommendation for refractory SSc, autologous HSCT is an optional therapy in sufficiently prepared centers. The goal is to make HSCT available as early as possible in the course of the disease.

Systemic lupus erythematosus and antiphospholipid syndrome

Conventional treatment of systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) aims at inhibiting adaptive immune responses, primarily by reducing T and B cell activation and/or reducing autoantibody production.

Following autologous HSCT, disease activity, duration of remission, and overall survival improved in the majority of SLE cases. In the case of APS, one-tenth of the patients had lost their antiphospholipid autoantibodies, and in 75% of the cases the anticoagulants were also excluded. Although initial results are encouraging (because there was complete symptom relief in the case of a positive therapeutic response), the remission-inducing effect of HSCT in SLE requires further testing. The previous studies are far from sufficient. The number of patients enrolled in the studies was low, and the patients formed a heterogeneous group, both clinically and in terms of immunosuppressive treatment and HSCT methods. Furthermore, the effect of the so-called publication bias is not negligible (*i.e.*, the studies only reported positive results). Although the combination of autologous HSCT with fludarabine and anti-CD20 therapy appears to be beneficial, it is important to note that many infections and other adverse events occurred in patients receiving high-dose immunosuppression prior to stem cell transplantation[34,35].

In two recent independent Chinese studies during 10-year follow-up, the progression-free survival values in SLE were 86% and 68%, while the HSCT-related mortality was reduced to 2%. Currently, a controlled multicenter clinical trial involving SLE patients is being conducted in Germany (NCT00750971). The aim is to compare the therapeutic efficacy of HSCT with the best available standard treatment options including rituximab therapy[36]. Although autologous HSCT is a theoretically accepted therapeutic alternative in SLE and APS patients, it is currently only referred to as salvage therapy in severe, refractory cases[33,36].

Table 1 Indication of autologous hematopoietic stem cell transplantation in autoimmune diseases

Indication	Level of recommendation	Level of evidence
Systemic sclerosis	Clinical opportunity: a careful evaluation of the benefit / risk ratio is required	I
Multiple sclerosis		II
Chronic inflammatory demyelinating polyneuropathy		II
Myasthenia gravis		II
Crohn's disease		II
Systemic lupus erythematosus		II
Rheumatoid arthritis		II
Juvenile idiopathic arthritis		II
Autoimmune cytopenias		II
Polymyositis/dermatomyositis		III
Vasculitides		III
Neuromyelitis optica		III
Paraneoplastic neurological symptoms		III
Type 1 diabetes mellitus	Under construction	III
Refractory celiac disease		III

Evans syndrome

Evans syndrome (ES) is a chronic, autoimmune disease associated with multiple immunocytopenia (hemolytic anemia + thrombocytopenia). The secondary cases of ES mainly occur in SLE. Based on a limited number of studies, allogeneic HSCT may be the only curative therapeutic option through reprogramming the immune system[37]. Comparing the clinical efficacy of autologous and allogeneic HSCTs in ES and immunothrombocytopenia, overall survival was similar in both methods (84%), while relapse-free survival was more favorable in allogeneic HSCT (78% *vs* 45%)[37]. In the case of chronically relapsing ES, and if an HLA-identical blood relative is available, allogeneic HSCT may be preferred. In the absence of a suitable donor or severe co-morbidity, autologous HSCT is recommended[38].

Rheumatoid arthritis

Autologous HSCT has been investigated in many studies in rheumatoid arthritis patients who do not respond to conventional treatments. According to retrospective analyses, 2/3 of them had remission, mostly 6 mo after transplantation, but the relapse rate was also significant, probably due to inadequate T cell repertoire ablation. The 5-year survival rate was 94%, clearly indicating the safety of HSCT. Yet, the latest, effective biological treatments in rheumatoid arthritis have reduced the use of autologous HSCT[31-33,35].

Juvenile idiopathic arthritis

Autologous HSCT has been used primarily in children with systemic juvenile idiopathic arthritis. Although the drug-free relapse period was favorable during long-term follow-up, the method did not spread due to high mortality associated with transplantation (9%-11%)[32].

Vasculitides

There is only limited data available on HSCT treatment in the heterogeneous group of vasculitides. To date, autologous HSCT has been used in nearly 50 patients in Europe. In a recent retrospective analysis of 14 autologous and 1 allogeneic HSCT patients (cryoglobulinemic vasculitis: 4; Behcet's disease: 3; granulomatosis with polyangitis 3; eosinophil granulomatosis with polyangitis: 1; nondifferentiated vasculitides: 2; Takayasu arteritis: 1; polyarteritis nodosa: 1) the response rate was 93%, and complete remission was found in 46%. Because of relapse, 3 patients received another transplant. Unfortunately, 3 patients died[33].

Crohn's disease

According to prospective studies and case reports, the autologous HSCT in Crohn's disease is a suitable method for achieving remission. The rate of 5-year drug-free remission was 60%[34,37]. However, for 45 patients enrolled in the Autologous Stem Cell Transplantation for Crohn Disease study, the results were not convincing. Only 2/23 patients had permanent remission, and one patient died of transplantation-related

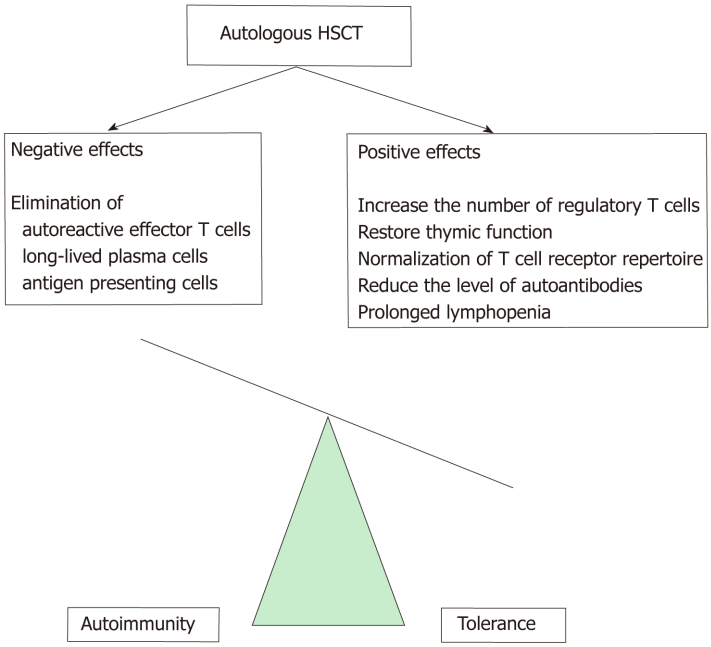

Figure 1 Immunobiological effects of autologous hematopoietic stem cell therapy in autoimmune diseases.
HSCT: Hematopoietic stem cell therapy.

complications[33,36,38,39]. According to the official European Crohn's and Colitis Organization recommendation, HSCT should only be considered for Crohn's disease patients with severe illness accompanied by active luminal inflammation and refractory to any available medication, and surgery alone is not enough (Figure 2).

Multiple sclerosis

In multiple sclerosis, autoreactive CD4+ T cells are crucial for the development of inflammatory plaques, demyelination, and consequent axon loss. During autologous HSCT, significant regeneration of circulating T cell clones results in immunological resetting. Multiple sclerosis is categorized into four types: rapidly aggravating, relapsing-remitting, secondary progressive, and primarily progressive. Various autoimmune diseases have occurred in most autologous HSCT patients with multiple sclerosis. In the early stages of the disease, autologous HSCT performed in relapsing-remitting types is more effective than in severe progressive cases[33,36].

Chronic inflammatory demyelinating polyneuropathy

In the chronic inflammatory demyelinating polyneuropathy patients who require long-term high-dose immunosuppressive therapy, initial experience with autologous HSCT is hopeful. In Europe, nearly 30 patients underwent intervention, with a clear positive trend in their neurological status. Currently a phase II study (Haemopoetic Stem Cell Transplantation in Chronic Inflammatory Demyelinating Polyneuropathy) is ongoing[33].

Mesenchymal stem cells

After 4 years of follow-up of patients with severe SLE who underwent allogeneic bone marrow transplantation, it was found that nearly 50% of patients experienced clinical remission and the overall survival rate was 94%. Despite encouraging clinical efficacy and apparent safety, the biological mechanisms explaining the therapeutic effect of mesenchymal stem cells in SLE have not yet been elucidated[35,40]. For SSc, there are only a small number of case reports suggesting that the use of mesenchymal stem cells is safe and effective, but comprehensive clinical trials have not yet been conducted. In severe refractory rheumatoid arthritis, two studies have been investigated for the therapeutic use of intravenously administered bone marrow-derived mesenchymal stem cells. Based on the results, the method was safe, no serious adverse effects occurred, and clinically significant remission was observed. Three to six months after the intervention, the level of inflammatory cytokines in the peripheral blood decreased and the number of Treg cells increased. Mesenchymal stem cells derived from adipose tissue have been shown to have similarly good results, but in order to maintain the therapeutic effect, the introduction of stem cells was repeated every 3 mo[35,41]. Fifty percent of patients with Crohn's disease were in

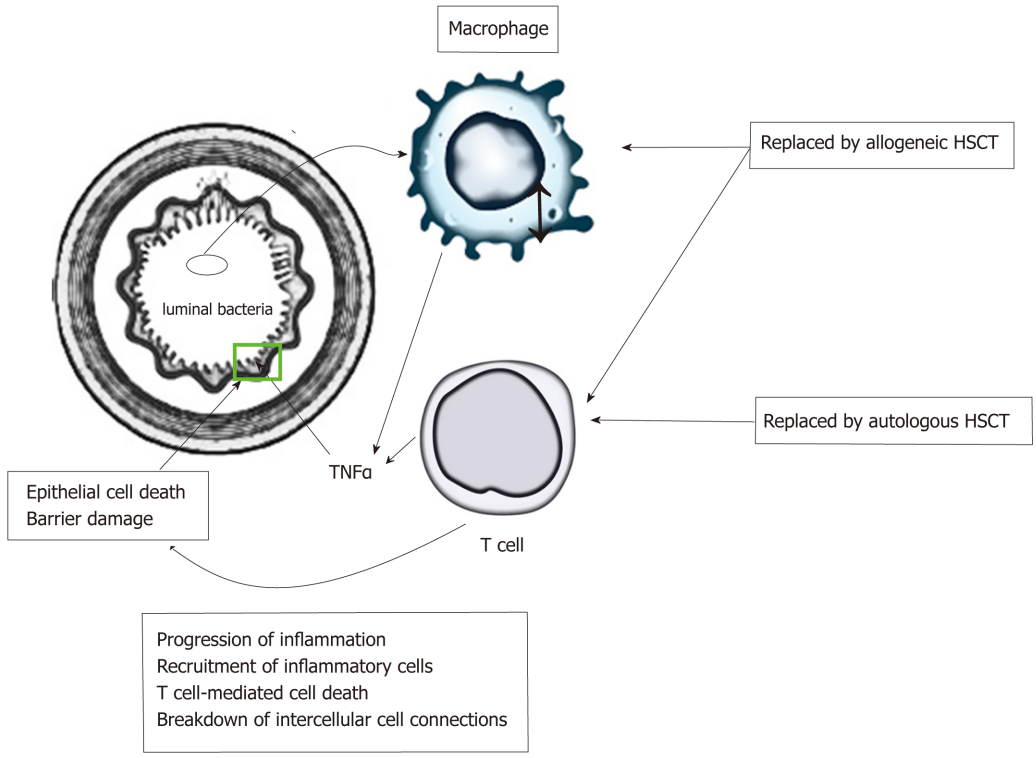

Figure 2 Schematic pathogenesis of Crohn's disease and the role hematopoietic stem cell therapy in its treatment. HSCT: Hematopoietic stem cell therapy; TNFα: Tumor necrosis factor alpha.

remission after half a year with parenteral administration of mesenchymal stem cells isolated from placenta. At the same time, by increasing the number of stem cells administered, only one-third of the patients had an appreciable therapeutic effect, and after 6 mo none of them were in remission[42,43].

CONCLUSION

In summary, the progress in clinical trials using stem cells for disease modification, immunomodulation, or regenerative purposes are undoubtedly encouraging, but most are still in the early stages, and the clinical results reported are not clear about therapeutic efficacy and potential side effects. Uniform regulation of the clinical application of stem cells is also indispensable for this highly customizable, minimally invasive, and individualized therapeutic method to become a successful and safe treatment alternative in many different disorders.

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REVIEW

Application of mesenchymal stem cell therapy for the treatment of osteoarthritis of the knee: A concise review

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Abstract

Osteoarthritis (OA) refers to a chronic joint disease characterized by degenerative changes of articular cartilage and secondary bone hyperplasia. Since articular cartilage has a special structure, namely the absence of blood vessels as well as the low conversion rate of chondrocytes in the cartilage matrix, the treatment faces numerous clinical challenges. Traditional OA treatment (*e.g.*, arthroscopic debridement, microfracture, autologous or allogeneic cartilage transplantation, chondrocyte transplantation) is primarily symptomatic treatment and pain management, which cannot contribute to regenerating degenerated cartilage or reducing joint inflammation. Also, the generated mixed fibrous cartilage tissue is not the same as natural hyaline cartilage. Mesenchymal stem cells (MSCs) have turned into the most extensively explored new therapeutic drugs in cell-based OA treatment as a result of their ability to differentiate into chondrocytes and their immunomodulatory properties. In this study, the preliminary results of preclinical (OA animal model)/clinical trials regarding the effects of MSCs on cartilage repair of knee joints are briefly summarized, which lay a solid application basis for more and deeper clinical studies on cell-based OA treatment.

Key words: Osteoarthritis; Mesenchymal stem cells; Stem cell therapy; Clinical trials

Core tip: The key points include: (1) Animal studies have reported that the expanded culture of mesenchymal stem cells (MSCs) is conducive to repairing cartilage and subchondral bone, and regulating the progression of secondary osteoarthritis (OA); (2) Recent studies on the treatment of OA by MSCs have progressed to clinical trials, and most clinical trials have achieved significant positive results with minimal side effects; and (3) Intra-articular injection of MSCs can offer OA patients a safe and effective treatment, yet some problems still remain to be solved for the clinical application of

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INTRODUCTION

Osteoarthritis (OA) refers to a common chronic degenerative joint disease, namely the degenerative injury of articular cartilage caused by still multiple factors (*e.g.*, aging, obesity, fatigue injury, trauma, joint congenital abnormalities, joint deformity, *etc*). Pathological changes largely include articular cartilage destruction, subchondral osteosclerosis and synovial hyperplasia[1]. OA occurs primarily after middle age, and it is more widespread in women than in men. Clinical manifestations include joint pain, joint stiffness and loss of function, which impairs patient mobility, and OA will turn out to be the fourth most disabling disease by 2020[2,3]. The cartilage has poor self-repair and regeneration abilities since the hyaline cartilage tissue on the joint surface has no nerves nor blood vessels, and it is hard to recover by itself once damaged. At present, the main clinical treatment methods for OA include non-drug therapy, drug therapy and surgical treatment, which is only capable of relieving pain, and can to a certain extent improve symptoms, delay illness and correct malformation. Nevertheless, the progressive degeneration of articular cartilage cannot be thoroughly delayed for patients with OA disease[4-8]. Autologous chondrocyte transplantation has been successfully employed to repair damaged cartilage, yet *in vitro* cultured chondrocytes show dedifferentiation and decreased chondrocyte-specific gene expression, thereby affecting its therapeutic effect. In recent years, new stem cell-based therapies for OA have aroused increasing attention. Mesenchymal stem cells (MSCs) have the potential of self-renewal and directional differentiation, which can repair cartilage tissue and suppress chondrocyte secretion of inflammatory factors and homing characteristics, which make MSCs the ideal seed cells for gradual OA treatment. This study reviews the potential applications of MSCs in preclinical models, as well as the clinical applications of OA.

CHARACTERISTICS OF MSCS

MSCs are adult stem cells that are not hematopoietic stem cells, and exist in various tissues (*e.g.*, bone marrow, umbilical cord, placenta, tendon, periodontal, adipose, and many other tissues)[9]. In the 1970s, Friedenstein isolated MSCs from whole bone marrow cultures, and the cells were subsequently extensively studied. In 1995, Lazarus *et al*[10] reported in the journal of bone marrow transplant the first clinical study of bone marrow derived from MSCs for the treatment of marrow transplant patients. The international society for cell therapy (ISCT) defines MSCs with three criteria: (1) Plastic-adherent; (2) Expression of CD105, CD73 and CD90, and lack of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR surface molecules; and (3) MSC must differentiate into osteoblasts, adipocytes and chondroblasts *in vitro*[11]. Besides their differentiation potential, MSCs also express enzymes and secrete numerous nutritional factors involved in paracrine activities, including growth factors, cytokines and chemokines[12], which nourish cartilage by activating cellular and angiogenesis pathways. Moreover, it is noteworthy that MSCs participate in the local immune regulation mechanism, which can suppress T cell proliferation, dendritic cell maturation, as well as the activation, proliferation and antibody secretion of B cells, thereby affecting the polarization of macrophages and the differentiation of antibody-secreting cells, thus essentially eliminating the risk of rejection and disease transmission[13]. However, the immunomodulatory function of MSCs may vary among individuals, species, tissue sources, culture conditions and activation states. ISCT proposed the standardization of MSC immunomodulatory characteristics[14]. Finally, MSCs also play a homing role, actively migrating to cartilage ischemia or damaged sites under the action of the microenvironment *in vivo*. Besides, repair and reconstruction can be performed by secreting growth factors,

cytokines and extracellular matrix[15]. In brief, further understanding of MSC function will have therapeutic significance for slowing cartilage degeneration in OA patients.

HOW MSCS CAN TREAT OA DISEASE IN PRECLINICAL TRIALS?

In vivo experiments on various animal models have been performed in the literature. These studies include the following models: Sodium iodoacetate (MIA) model in guinea pigs/rabbits, oophorectomy in rats, and anterior cruciate ligament amputation in rats/rabbits (ACLT). In addition, some chemical agents (*e.g*., papain, quinolone and collagenase) can induce the OA model in animals[16,17]. ACLT on the anterior feet of rabbits is one of the classic ways to build an OA model in rabbits. This type of rabbit model has been successfully modeled in 3 to 8 wk, which also exhibits similar biochemical and pathological variations to those of humans[17]. It was reported in animal experiments that local intra-articular injection of MSCs, MSC-derived exosomes, implants with MSC-laden scaffolds, and MSC suspensions with carrier media can effectively alleviate OA disease.

Use of MSCs seeded on scaffolds in articular cartilage repair

MSCs can serve as cartilage progenitor cells or regenerative cells, which can be seeded onto three-dimensional scaffolds in order to repair damaged cartilage through the stimulation of endogenous cells[18]. MSCs can be differentiated into chondrocytes *in vitro*, which is similar to the structural characteristics of hyaline cartilage. However, there are differences in the chondrocyte differentiation capacity of MSCs derived from different sources, cells can tend to hypertrophy during differentiation, and the phenotypic stability of mature chondrocytes remains difficult to ensure[19]. Many previous experiments have verified that connective tissue growth is vital for cartilage repair, *i.e*., it can promote cartilage and extracellular matrix repair. Accordingly, studies show that tissue growth factors can be loaded onto scaffolds to assist cartilage repair and increase the degree of integration of new cartilage units with surrounding tissues[20,21]. However, this method is usually employed to repair the small area cartilage defect model, yet it does not address the large area of cartilage defects related to OA. At present, several scaffolds [polylactic-co-glycolic acid, polyethylene glycol, polylactic acid, polyglycolic acid, collagen, gelatin, hyaluronic acid (HA), and fibrin] are applied for the implantation of articular cartilage defects in experimental animal models[22]. They are still not used as routine treatments in clinical practice, although several studies have shown the safety and efficacy of MSC-based tissue engineering methods. This is largely because: (1) Since both allogeneic MSCs and scaffold materials may cause unnecessary graft-versus-host reactions, the acquisition and culture of autologous MSCs and the selection of scaffold materials are major limitations to clinical application; and (2) At present, the selection of cytokines is more diversified, and the function of promoting chondrogenic and osteogenic differentiation is also favored by researchers. However, studies have demonstrated that different levels of growth factors have bidirectional effects on promoting chondrogenic and osteogenic differentiation. How to minimize osteogenic differentiation in the new cartilage area while maximizing chondrogenic differentiation ability remains one of the problems to be solved. Thus, more studies are required to prove their effectiveness in larger groups of OA patients before they can be implemented at a large scale.

Therapeutic MSC exosomes

In recent years, a growing number of researchers think that exosomes secreted by MSCs also play a role in the treatment of OA[23]. Exosomes are generally hypothesized to be intercellular communication vehicles and function to transfer lipids, nucleic acids (mRNAs and microRNAs) and proteins between cells to elicit biological responses in recipient cells that are reflective of the cargo contents[24]. MSC exosomes are abundant in a considerable amount of microRNA, which can specifically bind to transcribed mRNA from their target genes, thereby silencing the expressed target genes or forming an interaction network of multiple signals[24-26]. Accordingly, microRNA may be vital to mediate the efficacies of MSC exosomes in the treatment of OA[27-30]. For example, Tao *et al*[30] reported that exosomes derived from human synovial MSCs overexpressed with microRNA-140-5p can promote cartilage regeneration and suppress OA in rat models, suggesting that miroRNA-140 may be a protective factor in the pathogenesis of OA. It can also prevent and alleviate OA by upregulating the expression of SOX9 and aggrecan (ACAN) to maintain cartilage homeostasis[27-30]. Toh *et al*[23] reported that microRNA-23b, 92a, 125b, 320, 145, 22 and

221 were involved in the regulation of chondrogenesis and homeostasis. Besides, MSC exosomes are rich in ECM proteins and enzymes, thereby regulating and restoring ECM balance. The increase in enzyme activity is proportional to the loss of normal equilibrium, *i.e.*, exosome-based enzymes promote tissue repair and regeneration by restoring homeostasis during injury and disease. In contrast, homeostasis was restored, and exosome enzyme activity was terminated after subsided injury[31]. According to the study on both the pathogenesis of OA and the drug treatment of OA, MSC exosomes exhibit infinite potential, with a good tolerance and minimal risk of immunogenicity and toxicity. However, how to obtain large-scale purified exosomes, as well as how to improve the utilization efficiency, biosafety and therapeutic efficacy of exosomes, should be further explored and studied. The study on the effect and mechanism of MSC exosomes on OA will remain one of the important hotspots for future research. In brief, MSC exosomes will soon become the main treatment modality for clinical OA with the continuous innovation of technology and in-depth research.

Local intra-articular injection of MSCs and mixed injections

In recent years, local intra-articular injection of MSCs has been reported to promote the regeneration and repair of cartilage tissue and alleviate the degeneration caused by OA. MSCs are capable of significantly improving local microenvironmental, immune-regulation and anti-inflammatory biological activities through the secretion of exosomes, growth factors, cytokines, anti-inflammatory factors and other bioactive molecules, thereby gradually becoming the simplest and easiest method to treat OA. For example, Zhou *et al*[32] found that local intra-articular injection of adipose-derived MSCs (AD-MSCs) can effectively alleviate the condition in rat OA models through autophagy induction to reduce the secretion of pro-inflammatory cytokines. Toghraie *et al*[33] reported the establishment of an OA model by resection of anterior cruciate ligaments in rabbits. Radiology revealed OA symptoms after 12 wk, and then a single dose of 1×10^6/mL AD-MSCs was injected into the joint cavity of the OA model. It was found that cartilage tissue was significantly repaired and improved as the result of imaging, morphology and histology at 20 wk. In the meantime, platelet-rich plasma (PRP) with the active substance can promote cell proliferation, collagen synthesis and inflammatory chemotaxis. Thus, it is conducive to tissue repair and can assist tissue reconstruction. Pre-clinical studies have verified that PRP/MSCs can also improve knee joint function, and the repaired tissue exhibits good compatibility with the original articular facial cartilage tissue by MRI analysis. Additionally, HA combined with MSCs can effectively repair damaged cartilage, and its mechanism may be to promote the repair of damaged cartilage by suppressing the inflammatory response and apoptosis of chondrocyte. It has been reported that PRP/MSCs or HA/MSCs has a significantly better effect on the repair of damaged cartilage than the individual treatment group in the OA animal model (HA, PRP or MSCs were used alone, respectively). Table 1 shows the summary of pre-clinical trials of MSCs in the treatment of the OA animal model from 2015 to 2018.

Mechanism of MSCs in the treatment of OA

Immunomodulatory effects of MSCs is one of the vital mechanisms of its treatment of OA. MSCs can be activated by inflammatory factors, then the secretion of PGE_2, IDO, NO and other factors by MSCs can directly or indirectly suppress immune cells[40]. For instance, PGE_2 secreted by MSCs can promote the production of immunosuppressive IL-10 by binding EP2 and EP4 receptors on macrophages, and participate in the regulation of CD4+ effector T cells[41]. Moreover, MSCs have been shown to suppress T cell proliferation and induce T cell apoptosis, resulting in fragments that stimulate phagocytes to produce tumor growth factor beta and increase the number of regulatory T cells[42]. MSCs also regulate innate immunity by inhibiting dendritic cell maturation and reducing natural killer (NK) cytotoxicity[43]. MSCs can also reverse the polarization of macrophages from pro-inflammatory (M1) to anti-inflammatory (M2) phenotypes[44]. Jo *et al*[45] found that MSCs can interact with macrophages to suppress the activation of macrophages and the secretion of IL-1β, TGF-α and another inflammatory factors.

The supernatant from MSCs stimulated by INF-γ and IL-1β can increase the expression of arginine, IDO and nitric oxide synthase (iNOS) in macrophages, which lead to the transformation of macrophages from M1 to M2 types. MSCs also secrete an abundant of chemokines (SDF-1α, MCP-1 and MCP-2), which can attract monocytes, macrophages, lymphocytes and dendritic cells, *etc*, and then these cells are recruited to sites of injury and inflammation by chemotaxis, which participate in the repair of tissue injury[46]. A study reported that mature chondrocytes and the secretion of cytokines can promote the differentiation of MSCs into chondrocytes. In the meantime, cytokines secreted by MSCs can also promote the proliferation of

Table 1 Summary of mesenchymal stem cell preclinical trials in osteoarthritis animal models from 2015 to 2018

Animal models (osteoarthritis)	MSC type	Interventions	Results	Ref.
Sheep	AD-MSCs	AD-MSCs/HA *vs* HA	μCT, MRI and immunohistochemistry: AD-MSCs/HA > HA	Lv *et al*[34], 2018
Sheep	Allogeneic AD-MSCs	AD-MSCs/HA *vs* HA	MRI and macroscopy examinations: AD-MSCs/HA > HA	Feng *et al*[35], 2017
Rabbits	BMSCs	BMSCs/HA *vs* PRP *vs* PRP/HA	Histological scores and immunohistochemistry: BMSCs/HA > PRP/HA > PRP	Desando *et al*[36], 2017
Rabbits	Allogeneic BMSCs	BMSCs/HA *vs* HA	Histological scores and cartilage content: BMSCs/HA > HA	Chiang *et al*[37], 2016
Dogs	AD-MSCs	AD-MSCs/PRP *vs* PRP	Focal compressive strength: AD-MSCs/PRP > PRP function and pain: AD-MSCs/PRP > PRP	Yun *et al*[38], 2016
Rabbits	AD-MSCs	AD-MSCs/PRP *vs* PRP	Macroscopic and histological examinations: AD-MSCs/PRP > PRP	Hermeto *et al*[39], 2016

OA: Osteoarthritis; AD-MSCs: Adipose-derived mesenchymal stem cells; HA: Hyaluronic acid; MRI: Magnetic resonance imaging; PRP: Platelet-rich plasma; BMSCs: Bone marrow-derived mesenchymal stem cells.

chondrocytes and the synthesis of an ECM matrix, which can repair damaged bone and cartilage[47,48]. It has been reported that cytokines secreted by MSCs can target synovial membranes and chondrocytes, which can regulate anabolic and catabolic factors, as well as induce the expression of anti-inflammatory and chondrogenic molecules[49]. However, in recent years, most studies have suggested that MSCs primarily regulate local inflammation, apoptosis and proliferation of cells through paracrine mechanisms, rather than directly differentiating into chondrocytes to participate in tissue repair (Figure 1). Barry and Murphy thought that endogenous MSCs contribute to the maintenance of healthy tissues by acting as reservoirs for cell repair or as immunomodulatory sentinels to reduce inflammation, but also, paracrine signaling by MSCs might be more important than differentiation in stimulating repair responses[50]. In other words, MSCs are not specifically designed to replace damaged and lost cartilage, but rather coordinate and enhance this repair response.

CLINICAL TRIALS OF MSC-BASED THERAPY IN OA DISEASE

Local intra-articular injection of MSCs and mixed injections

Mixed injections means that MSCs are combined with growth factors, cytokines and scaffolds in order to improve efficacy. The commonly used support scaffolds are polymer scaffolds such as HA, fibrin gel, and nutrient-rich liquid such as serum platelet rich plasma (PRP). Among them, there are many studies on the treatment of OA by injecting MSCs/PRP suspensions into the articular cavity. Details of the case report of MSCs combined with PRP in the treatment of OA are shown in Table 2. It is generally known that PRP is an autologous tissue, rich in chondrogenic growth factors (*e.g.*, TGF-β and platelet-derived growth factor). It can serve as a source of tissue for the treatment of damaged cartilage[51]. PRP composite scaffolds have high osteogenic induction activity, and are capable of promoting bone healing. The combination of PRP with MSCs (adipose MSCs: AD-MSCs/vascular stroma of adipose tissue: SVF) is used for treating knee OA, which can create a suitable microenvironment for MSC growth (promote the supplying of blood, reduce the responding of local inflammatory), promote the synthesis of cartilage matrix, and also improve the therapeutic effect of MSCs in knee arthritis[52-54]. The problem of PRP still lies in its preparation and the variability of the synthesis number of bioactive factors it expresses. Some growth factors secreted in PRP (*e.g.*, vascular endothelial growth factor) may have adverse effects on both joints and MSCs[51,52].

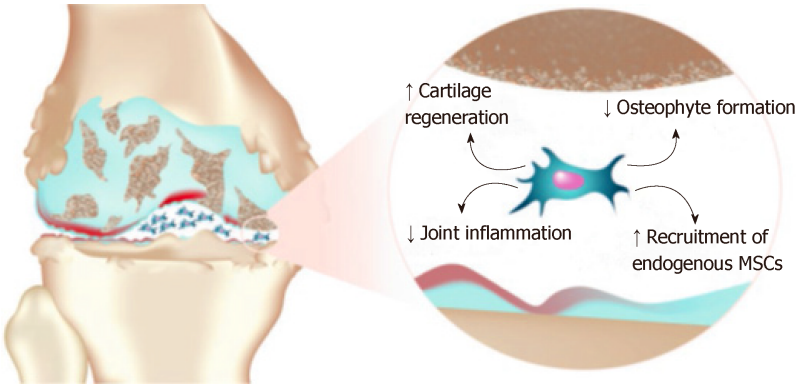

Figure 1 Paracrine activity of mesenchymal stem cells in an osteoarthritis articular environment (Professional illustration by Matilde Bongio, GoArts – Istituto Ortopedico Galeazzi). MSCs: Mesenchymal stem cells.

Clinical trials using MSCs for OA disease

MSCs were first proposed to reside in bone marrow and have since been demonstrated to exist in other tissues (*e.g.*, fat, placenta, umbilical cord, dental pulp, peripheral blood, and synovium)[60,61]. With the increase in evidence for the application of stem cell technology in animal and *in vitro* experiments, the application of MSC-based transplantation technology in the treatment of OA to achieve cartilage regeneration has shown promise. Thus far, clinical studies on mesenchymal stem cell therapy for OA have been conducted globally, and 74 of them have been registered on clinicaltrial.gov, some of which have completed clinical trials as well as preliminary evaluations of safety and efficacy. In China, research on the treatment of OA with MSCs is also in full swing. Currently, there are six studies registered on clinicaltrial.gov, taking up 8.1%, four of which (one UC-MSCs and three AD-MSCs) focus on the treatment of OA have been completed, and one study (UC-MSCs) is in the recruitment state. According to the results of the completed studies, mesenchymal stem cell (bone marrow, adipose and umbilical cord) therapy shows highly efficacy in the research of OA diseases, and has great potential to replace traditional therapies in the future. PubMed, Wiley, Elsevier ScienceDirect, Springer, Taylor and Francis were searched for the relevant studies published from 2015 to 2018. The search strategy included the keywords "mesenchymal stem cells", "bone marrow-derived mesenchymal stem cells (BM-MSCs)", "umbilical cord-derived mesenchymal stem cells (UC-MSCs)", "adipose-derived mesenchymal stem cells (AD-MSCs)", "stem cell therapy", "osteoarthritis" and "clinical trial". Inclusion criteria: (1) Clinical research journal articles or reviews were included; (2) The content of this study closely links to the application of MSC therapy in OA treatment; and (3) Select articles that have been recently published or published in an authoritative journal in the same field. Exclusion criteria: (1) Non-English literature in foreign languages; (2) Literature with repetitive content; and (3) Cannot get the full text of the document. In the end, 14 studies were included here, including eight on the clinical study of BM-MSCs in OA treatment (Table 3), three on the clinical study of UC-MSCs in OA treatment (Table 4), and three on the clinical study of AD-MSCs in OA treatment (Table 5).

Bone marrow is the most common and earliest effective source of MSCs for the treatment of OA diseases. BM-MSCs have achieved a promising effect in the clinical repair of knee articular cartilage using stem cell transplantation technology. In 2008, Centeno *et al*[62] reported a case of severe OA of the knee joint. Bone marrow MSCs in suspension culture with phosphate buffered saline were injected for treatment, and 10% platelet lysate (PL) and 10 ng dexamethasone injection were supplemented for cartilage stimulation. Six months after injection, MRIs showed the significant growth of articular cartilage and meniscus, ROM score increased and the pain score of modified VAS decreased. A single injection of BM-MSCs into the articular cavity without using adjuvant analgesics, anti-inflammatory drugs or immunosuppressants has also achieved positive results[62,63]. Studies have shown that BM-MSC transplantation is more effective than either autologous chondrocyte transplantation or no transplantation, with relatively fewer complications. Finally, though BM-MSCs have been extensively studied and its effectiveness and safety have been confirmed, further clinical application of BM-MSCs is limited by the fact that it is difficult to obtain sufficient numbers of primary generations due to factors such as trauma and differentiation ability affected by donor age. Intra-articular injection of AD-MSCs was also used in the treatment of OA. It is usually obtained by liposuction or is subpatellar

Table 2 Summary of mesenchymal stem cells/platelet-rich plasma clinical trials in osteoarthritis patients from 2012 to 2018

Defect type	MSC type	Delivery system	Type of study	Results	Ref.
OA	AD-MSC	MSCs/PRP	Case series (n = 21); Final follow-up: 6 mo	Significant positive changes at MRI	Bui *et al*[55], 2014
OA	AD-MSC	MSCs/PRP	Case series (n = 18); Final follow-up: 24.3 mo	Clinical improvement; Function and pain improvement at 24.3 mo	Koh *et al*[52], 2013
OA	AD-MSC	MSCs/PRP	Case series (n = 30); Final follow-up: 24 mo	Reducing pain and improving function in patients with knee OA	Koh *et al*[56], 2012
OA	AD-MSC	MSCs/PRP	Case series (n = 21); Final follow-up: 24 mo	Function and pain improvement as compared with PRP only	Koh *et al*[57], 2014
OA	Autologous SVF	SVF/PRP	Case series (n = 21); Final follow-up: 24 mo	All patients' scores of pain improved to > 96; and quality of life scores to > 93	Gibbs *et al*[58], 2015
OA	Autologous SVF	SVF/PRP	Case series (n = 10); Final follow-up: 24 mo	Cartilage thickness improvement	Bansal *et al*[59], 2017

OA: Osteoarthritis; AD-MSCs: Adipose-derived mesenchymal stem cells; MRI: Magnetic resonance imaging; PRP: Platelet-rich plasma; SVF: Vascular stroma of adipose tissue.

fat pad-derived, and then the liposome is centrifuged and digested by collagenase I to prepare concentrated AD-MSCs[52,57,64]. It has been reported that intra-articular injection of 1.0×10^8 AD-MSCs can significantly improve knee joint pain ($P < 0.001$) and function ($P < 0.001$) without adverse events. Patients in the medium dose group (5.0×10^7) showed some improvement in clinical results, while those in the low dose group (1.0×10^7) showed no improvement in most outcome indicators[45]. These results suggest that intra-articular injection of MSCs has a significant dose-response effect, and that further large-scale trials are needed to confirm the long-term safety and clinical advantages of high-dose injection. However, comparative studies have shown that AD-MSCs have lower chondrogenic potential, lower cartilage specificity of matrix protein production, and low expression rate of the collagen type I gene as compared with BM-MSCs. Thus, scholars should work to further optimize the chondrogenic potential of AD-MSCs[65]. Umbilical cord-derived MSCs (UC-MSCs) are a type of pluripotent stem cell existing in neonatal umbilical cord tissues, which can be obtained from discarded umbilical cord or umbilical cord blood banks. At present, clinical trials have shown that injecting human umbilical cord-derived MSCs into the joint cavity for the treatment of degenerative knee OA can significantly improve the joint function and quality of life of patients[66]. In January 2012, the Korean Food and Drug Administration approved the manufacture and sale of Cartisem in South Korea as a safe and effective stem cell drug (containing UC-MSCs and sodium hyaluronate) for treating degenerative OA and cartilage injury. Since it was listed in South Korea in 2012, more than 5,000 patients have been treated at an effective rate of 97.67%, and the treatment effect is not limited by the age of the patients. More importantly, Cartistem uses allogeneic stem cells rather than autologous stem cells, and has become the world's first user of allogeneic stem cells to produce therapeutic drugs. Cartistem utilizes umbilical cords to isolate and cultivate UC-MSCs that meet the needs of clinical treatment, and they are implanted into damaged cartilage. In the microenvironment of the implanted location, UC-MSCs coordinate and enhance the repair response of damaged cartilage tissue by a paracrine mechanism, thereby creating a new avenue for the treatment of OA. UC-MSCs are a little backwards compared with other MSCs because of their unique properties, whereas they are expected to be widely used in clinical practice and will make an important contribution to the repair of damaged cartilage, which will be the focus of future research.

Although the initial efficacy of intra-articular MSC injections in patients with severe knee OA deserves to be confirmed, prospective and placebo-controlled studies are still needed to verify the effectiveness of this method. New clinical trials should focus on the efficacy of MSC injections in patients with moderate OA and early radiology. Koh *et al*[67] showed that the effects of MSC implantation in level 3 OA patients were better than those in level 4 OA patients. Accordingly, MSC-based therapies should be more effective in preventing or limiting the progression of early stages of OA disease.

Table 3 Summary of intra-articular injection of expanded bone marrow-derived mesenchymal stem cells in knee osteoarthritis treatment (2015-2018)

Cell type	Type of study	Experimental design	Cell dosage	Measurement	Results	Ref.
Autologous	Case series (n = 61); Final follow up: 6 mo	Phase I/II study	Not mentioned	VAS, WOMAC and X-ray	Significantly reductions in knee pain and increased quality of life at 6 mo follow-up	Garay-Mendoza *et al*[68], 2018
Autologous	Case series (n = 13); Final follow up: 24 mo	Phase I/II study	Intra-articular injection of 30.5×10^6 MSCs	MRI and KOOS	After intra-articular injection with BM-MSCs had significantly improved the KOOS and knee cartilage thickness	Al-Najar *et al*[69], 2017
Allogeneic	Case series (n = 60); Final follow up: 24 mo	Double-blind, multicentric, placebo-controlled, phase II study	Four dose levels were studied in this trial: 25×10^6, 50×10^6, 75×10^6, and 150×10^6	VAS, ICOAP and WOMAC	A 25×10^6 cell dose may be the most effective among the doses; WOMAC, ICOAP, and VAS scores decreased by the time of the final follow-up period	Gupta *et al*[70], 2016
Autologous	Case series (n = 30); Final follow up: 12 mo	Double-blind, multicentric, phase I/II study	Two dose levels were studied in this trial: 10×10^6 and 100×10^6	VAS, WOMAC, X-ray and MRI	A clinical and functional improvement of knee OA by the injection of 100×10^6 cell dose; Improvement of pain and knee function of OA patients at 12 mo follow-up	Lamo-Espinosa *et al*[71], 2016
Autologous	Case series (n = 4); Final follow up: 60 mo	Phase I study	Intra-articular injection of $8\text{-}9\times10^6$ MSCs	Walking time, X-ray and VAS	Earlier transplantation may give better results in long-term follow-up	Soler *et al*[72], 2016
Allogeneic	Case series (n = 30); Final follow up: 12 mo	Multicentric, phase I/II study	Intra-articular injection of 40×10^6 MSCs	VAS, WOMAC, and LEQUESNE; MRI	Significantly improves cartilage quality and provides pain relief	Vega *et al*[73], 2015
Autologous	Case series (n = 30); Final follow up: 30 mo	Not mentioned	Intra-articular injection of 0.5×10^6 MSCs	Walking distance, VAS, WOMAC and MRI	Significantly improves cartilage quality and knee function, and reduces pain level	Emadedin *et al*[74], 2015
Autologous	Case series (n = 4); Final follow up: 60 mo	Phase I study,open label	Intra-articular injection of 8×10^6 MSCs	VAS, Knee motion, Range, X-ray	Earlier transplantation may give better results in long-term follow-up	Davatch *et al*[75], 2016

VAS: Visual Analogue Scale/Score; WOMAC: The Western Ontario and McMaster Universities; MRI: Magnetic resonance imaging; MSCs: Mesenchymal stem cells; KOOS: Knee Injury and Osteoarthritis Outcome; BM-MSCs: Bone marrow-derived mesenchymal stem cells; ICOAP: The Intermittent and Constant Osteoarthritis Pain Score; OA: Osteoarthritis.

Another important question is the optimal dose of the experimental cells. Cell dosages range from 2×10^6 to 3×10^8, with significant differences between clinical trials. However, the dose described by different researchers for the improvement of pain function and histological scores is also different, so there is still no clinical criteria for guiding treatment.

SAFETY AND QUESTIONS

As early as 2005, Rubio *et al*[81] transplanted AD-MSCs into immunodeficient mice, and the results suggested that spontaneous stem cell transformations and malignant tumors occurred in mice. Later, several studies revealed that this malignant

Table 4 Summary of intra-articular injection of expanded umbilical cord-derived mesenchymal stem cells in knee osteoarthritis treatment (2015-2018)

Cell type	Type of study	Experimental design	Cell dosage	Measurement	Results	Ref.
Allogeneic	Case series (n = 7); Final follow-up: 60 mo	Open-label, single-arm, single-center, phase I/II study	A dose of 500 μL/cm^2 of the defect area with a cell concentration of 0.5 ×10^7 MSCs per milliliter	ICRS, VAS, IKDC and MRI	Improvements in pain and knee function at 6 mo follow-up; Without significant deterioration over 7 yr of follow-up; Efficacy and safety	Park *et al*[66], 2017
Allogeneic	Case series (n = 36); Final follow up: 12 mo	Not mentioned	Intra-articular injection of (2-3) × 10^7 MSCs	Lysholm, WOMAC and SF-36 scale score	Improvement of the joint function and quality of life	Wang *et al*[76], 2016
Allogeneic	Case series (n = 40); Final follow up: 12 mo	randomized, triple-blind trial, phase I/II trial	Intra-articular injection of 20 ×10^6 (single-dose and repeated doses) MSCs	OARSI, WOMAC, VAS and SF-36 score	Efficacy and safety; Repeated injections of UC-MSCs had lower scores than others at 12 mo; Improvement of pain and knee function of OA patients at 12 mo follow-up	Matas *et al*[77], 2018

ICRS: International Cartilage Repair Society; VAS: Visual Analogue Scale/Score; IKDC: The International Knee Documentation Committee; MSCs: Mesenchymal stem cells; WOMAC: The Western Ontario and McMaster Universities; OARSI: Osteoarthritis Research Society International; SF-36: The MOS item short from health survey; UC-MSCs: Umbilical cord-derived mesenchymal stem cells; OA: Osteoarthritis.

transformation is due to cell line contamination, and is therefore not correlated with MSCs themselves. Thus, this study was withdrawn[81,82]. In recent years, numerous animal studies have reported that intra-articular injection of MSCs can promote cartilage regeneration and reduce joint inflammation to improve the OA function of joints, and no malignant transformation of MSCs has been found. A total of 14 studies reported intra-articular injection of MSCs for the treatment of OA in clinical trials from 2015 to 2018. In general, whether intra-articular injection of autogenous and allogeneic MSCs (bone marrow, adipose and umbilical cord) were used, the clinical manifestations, radiological and histological scores of OA patients were improved, no graft-related death, tumorigenesis and infection occurred, and no serious adverse reactions were observed. However, there are still some problems with the intra-articular injection of MSCs for the treatment of OA in clinical trials: (1) It has been reported that MSCs could promote cartilage repair *via* the secretion/stimulation of biomolecules, and if these results are true, the duration of stimulation and whether the biomolecules secreted by MSCs can be characterized as drugs and used accumulatively should be considered; (2) How to improve the effectiveness of MSCs in the OA microenvironment. Also, the transfer of cells from *in vitro* atmospheric culture conditions to the *in vivo* niche may affect the survival rate of MSCs after transplantation; (3) How to accurately assess the progress of OA repair. There are many different clinical scoring systems that have been widely used until now, but the popularity of scoring systems and the debate over their relative merits suggest that they do not accurately assess the progression of OA disease; (4) How to eliminate the blindness of clinical research. While MSCs are usually packaged into syringes, there is a tendency for cells to aggregate and become fuzzy at the bottom of the syringe, which may affect the results of blind clinical trials compared with transparent placebos; and (5) Transport problem: how can cells be effectively transported from the laboratory to OA patients without losing their efficacy and quantity.

CONCLUSION

Since analgesics and anti-inflammatory drugs often cause gastrointestinal, liver, kidney and heart problems, many common side effects arise from current arthritis treatments, which may cause significant injury to the patient. Also, ACI surgery may cause morbidity in the donor site, and requires two operations under general anesthesia. With the advancement of research on the characteristics, pre-clinical and clinical applications of MSCs, regenerative medicine based on stem cell therapy has

Table 5 Summary of intra-articular injection of expanded adipose-derived mesenchymal stem cells in knee osteoarthritis treatment (2015-2018)

Cell type	Type of study	Experimental design	Cell dosage	Measurement	Results	Ref.
Autologous	Case series (n = 18); Final follow-up: 24 mo	Randomized and Double-blinded, A phase I/II study	Three dose groups: The low-dose (1 × 10^7), mid-dose (2 × 10^7) and high-dose group (5 × 10^7) cells	WOMAC, SF-36 and NRS-11	The dosage of 5 × 10^7 MSCs exhibited the highest improvement in pain, function and cartilage volume of the knee joint	Song *et al*[78], 2018
Autologous	Case series (n = 18); Final follow-up: 24 mo	A phase I/II study	Phase I: 10 × 10^6 (low-dose), 50 × 10^6 (mid-dose), 100 × 10^6 (high-dose); Phase II:100 × 10^6 (high-dose)	VAS, WOMAC and MRI	A 100 × 10^6 cell dose may be the most effective among the doses	Jo *et al*[79], 2017
Autologous	Case series (n = 18); Final follow-up: 20 mo	A phase I, bicentric, single-arm, open-label	Three dose levels were studied in this trial: 2 × 10^6 (low-dose), 10 × 10^6 (mid-dose) and 50 × 10^6 (high-dose) cells	WOMAC, VAS, SF-36, KOOS and OARSI	The group of patients injected with 2 × 10^6 cells exhibited the best response to MSC treatment, which can improve pain and induce structural benefit	Pers *et al*[80], 2016

WOMAC: The Western Ontario and McMaster Universities; SF-36: The MOS item short from health survey; NRS-11: The 11-point Numerical Rating Scale; MSCs: Mesenchymal stem cells; VAS: Visual Analogue Scale/Score; MRI: Magnetic resonance imaging; OARSI: Osteoarthritis Research Society International; KOOS: Knee Injury and Osteoarthritis Outcome.

gradually presented its advantages in the treatment of OA disease. Previous studies have injected bone marrow-, umbilical cord- and adipose-derived MSCs into the joint cavity using the ultrasound detection technique. This study summarizes the contents of preclinical and clinical trials in the recent three years as follows: intra-articular injection of MSCs can lead to the reduction of index-pain, improve the function and significantly increase the volume of cartilage.

Despite many researchers' initial worries about mesenchymal stem cell therapy, a systematic review of clinical trials has suggested that MSCs are relatively safe for both intravascular and intra-articular injection. It is noteworthy that umbilical cord MSCs can serve as allogeneic stem cell drugs, which can replace damaged tissue in the microenvironment of the implanted site, which creates a new approach for OA treatment. Finally, although these initial studies show promising therapeutic effects, their long-term therapeutic effects need further investigation. Furthermore, more reliable studies with larger sample sizes and randomized controls are also required for higher levels of evidence, and to comprehensively standardize and optimize MSC therapy in the treatment of OA diseases.

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