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Intra-articular knee implantation of autologous bone marrow–derived mesenchymal stromal cells in rheumatoid arthritis patients with knee involvement: Results of a randomized, triple-blind, placebo-controlled phase 1/2 clinical trial

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Abstract

Background. In this study, we intend to assess the safety and tolerability of intra-articular knee implantation of autologous bone marrow–derived mesenchymal stromal cells (MSCs) in patients with rheumatoid arthritis (RA) and to determine the preliminary clinical efficacy data in this population. The trial registration numbers are as follows: Royan Institute Ethics Committee: AC/91/1133; NCT01873625. *Methods.* This single-center, randomized, triple-blind, placebo-controlled phase 1/2 clinical trial randomized RA patients with knee involvement to receive either an intra-articular knee implantation of 40 million autologous bone marrow–derived MSCs per joint or normal saline (placebo). Patients were followed up for 12 months to assess therapy outcomes. *Results.* A total of 30 patients, 15 in the MSC group and 15 in the placebo group, enrolled in this study. There were no adverse effects reported after MSC administration or during follow-up. Patients who received MSCs had superior findings according to the Western Ontario and McMaster Universities Arthritis Index (WOMAC), visual analogue scale (VAS), time to jelling and pain-free walking distance. However, this improvement could not be significantly sustained beyond 12 months. The MSC group exhibited improved standing time ($P = 0.01$). In addition, the MSCs appeared to contribute to reductions in methotrexate and prednisolone use. *Conclusion.* Intra-articular knee implantation of MSCs appeared to be safe and well tolerated. In addition, we observed a trend toward clinical efficacy. These results, in our opinion, have justified the need for further investigations over an extended assessment period with larger numbers of RA patients who have knee involvement.

Key Words: *bone marrow, mesenchymal stromal cells, osteoarthritis, rheumatoid arthritis*

Introduction

Rheumatoid arthritis (RA) is an inflammatory polyarthritis with a worldwide prevalence of approximately 0.5–1% in adults 40–50 years of age [1]. Knee involvement is one of the major consequences of this disease that causes chronic pain and disability. Adaptive immune responses mediated by B and T cells have an important role in pathogenesis of autoimmune diseases, such as RA, in which joint fibroblast activation contributes to joint destruction [1,2]. Knee involvement in RA occurs because of a chronic inflammatory

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process that results in tissue destruction due to leukocyte infiltration into the synovial compartment and secretion of inflammatory cytokines [1,2]. Recommendations for three primary treatments to be used in RA patients with knee joint pain include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease-modifying anti-arthritic drugs (DMARDs) such as methotrexate (MTX). Unfortunately, these medications exhibit numerous adverse effects that may cause additional problems (e.g., osteoporosis) for patients [3,4]. In addition, a significant number of patients do not respond to these drugs and need new therapies. Although total knee arthroplasty (TKA) is the last option for RA patients with knee involvement, there exists a higher risk for systemic complications, infections and further replacement after TKA in these patients [5,6]. Medication adverse effects and younger age justify the use of TKA. Researchers are motivated to find a less-invasive treatment method with decreased adverse effects for RA patients with knee involvement.

In the previous year, mesenchymal stromal cells (MSCs) have been proposed as a possible biological therapy for various diseases [7]. MSCs not only have the potential to differentiate into diverse cell lineages, they also mediate a wide spectrum of immunoregulatory activities that usually modulate innate and adaptive immune responses. These properties have led to interest in the prospect for developing novel cell therapies for autoimmune disease. The preclinical results have been promising in experimental models of autoimmune/inflammatory disorders such as RA [8–10], systemic lupus erythematosus (SLE) [11–13], Crohn's disease (CD) [14,15] and multiple sclerosis (MS) [16,17]. Clinical trials show encouraging results for autoimmune/inflammatory disorders such as knee osteoarthritis [18–22], SLE [23,24], CD [25], MS [26,27] and graft-versus-host disease (GVHD) [28,29].

There are a limited number of clinical trials that evaluated MSCs for RA patients. Until now, two articles have been published that discussed the treatment of RA patients with intravenous infusion of MSCs [30,31]. A nonrandomized comparative trial of 172 RA patients considered unresponsive to classical medications assigned 136 patients to receive umbilical cord MSCs and vehicle for 36 patients [30]. Treatment with MSCs induced significant disease remission for 3–6 months. Repeated infusions administered twice at 3-month intervals enhanced therapeutic efficacy. Alvaro-Gracia *et al.* [31] recently reported results from a multicenter, dose escalation, randomized, single-blind, placebo-controlled, phase 1/2 clinical trial that enrolled 53 patients with RA who received adipose-derived MSCs. The results showed the safety of MSCs. The treatment was well-tolerated and they observed a trend for clinical efficacy during 6 months of follow-up.

Therefore, there is a need to explore the effect of MSCs in a randomized trial to gain insight into efficacy for RA patients with knee involvement. In this triple-blind placebo-controlled clinical trial, we have sought to randomly assess the safety and tolerability of intra-articular knee injection of autologous bone marrow MSCs in RA patients with knee involvement. We also obtained preliminary clinical efficacy information in this controlled study.

Materials and methods

Study design

This was a triple-blind, single-center, placebo-controlled phase 1/2 clinical trial of intra-articular knee implantation of MSCs into the knee joints of RA patients with knee involvement. We used autologous bone marrow MSCs that fulfilled the International Society of Cellular Therapy (ISCT) criteria [32]. A single, trained physician evaluated eligible patients to collect baseline characteristics and select one knee joint for intervention. In this study, a statistician calculated a sample size of 60 patients. We randomly assigned patients to the study (MSC) or placebo (normal saline) groups based on the block (size 4) randomization method. For this purpose, the statistician used a random process to generate the sequences.

Patients could continue taking DMARDS during the study. However, we excluded the use of NSAIDs to avoid confounding effects with MSCs. Patients with postimplantation or injection pain for less than 1 month could take NSAIDs for pain relief under physician supervision.

Ethics

The Royan Ethics Committee approved this study, which we conducted according to good clinical practice standards and the amended Declaration of Helsinki (Seoul, October 2008). All patients signed a written informed consent form for study participation.

Patients and procedures

This study included patients 18–65 years of age. After we evaluated patients' medical histories, each patient underwent a physical examination to confirm the preliminary diagnosis of RA according to the American College of Rheumatology (ACR) 2010 criteria. Serum and urine biochemical tests were conducted to evaluate the presence of any acute and/or chronic underlying diseases. Exclusion criteria consisted of any history of uncontrolled chronic diseases other than RA, any injections into the studied knee in the last 3 months and any congenital or acquired diseases that re-