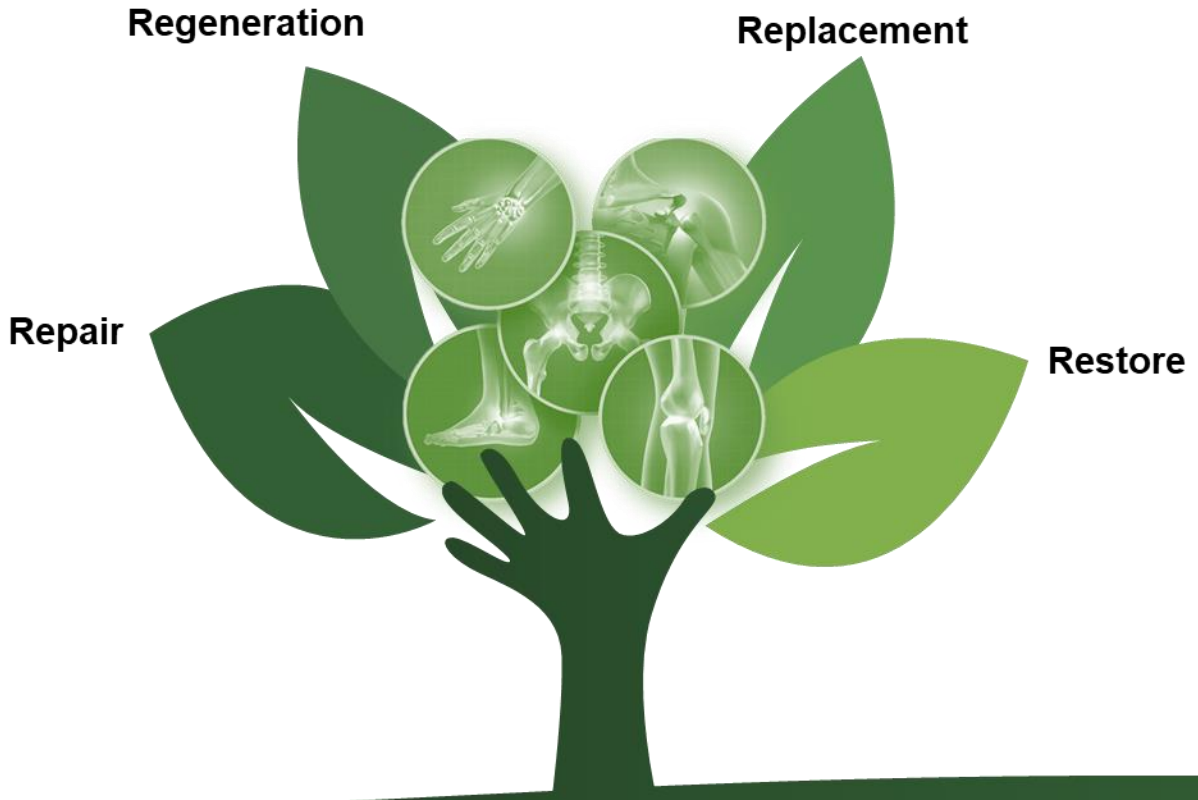
Cell Therapy in Bone & Joint Disorders, Royan Institute

Bahareh Sadri, PhD

January 2026

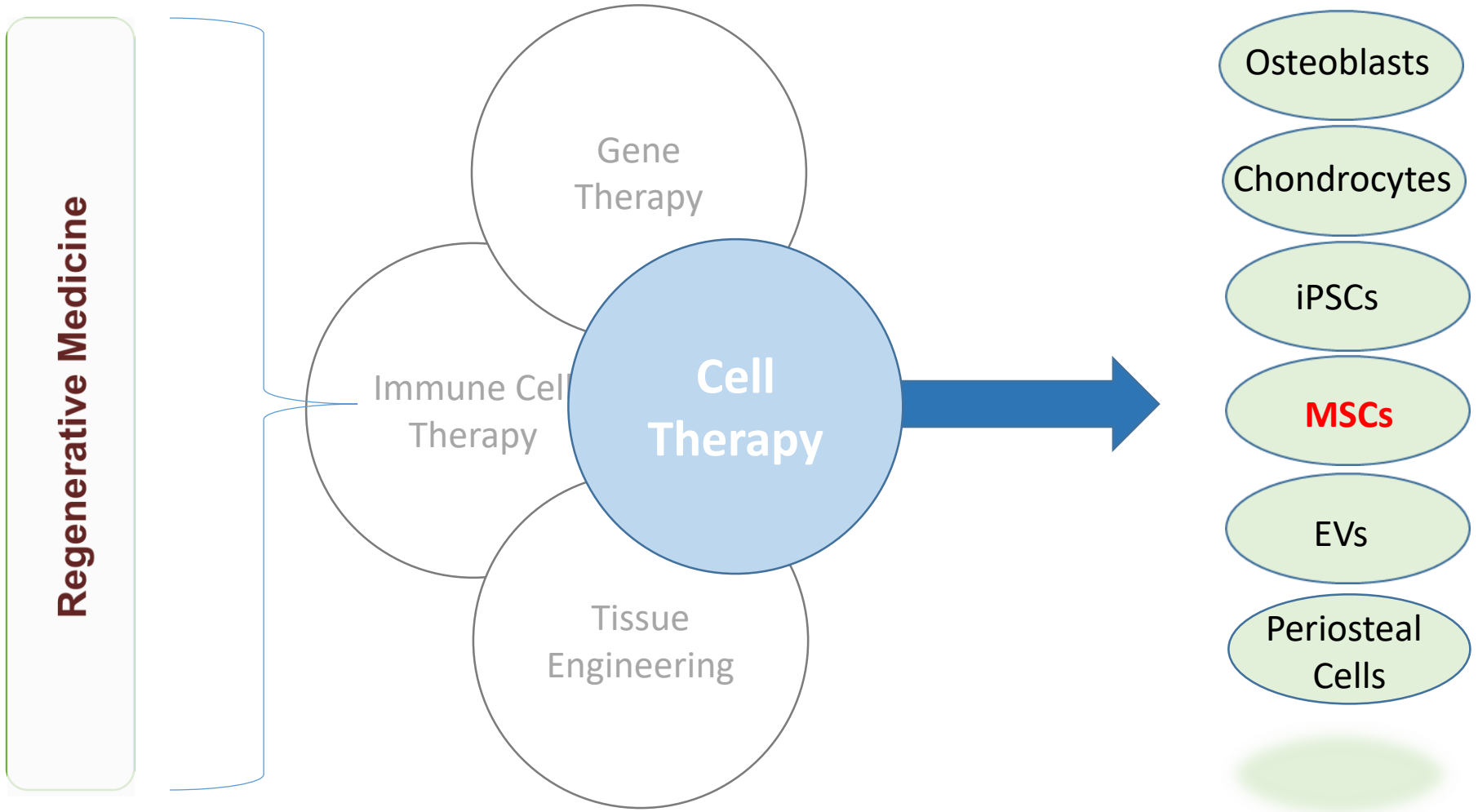
Regenerative Medicine, a Novel Therapeutic Strategy



Advanced Therapy Medicinal Products (ATMPs) in Regenerative Medicine

1. **Cell Therapy Medicinal Products (CTMPs)**
2. **Gene Therapy Medicinal Products (GTMPs)**
3. **Tissue-Engineered Products (TEPs)**
4. **Immune Cell Therapy Products (GMCTs) –** Officially recognized as a separate category from CTMPs since 2021.

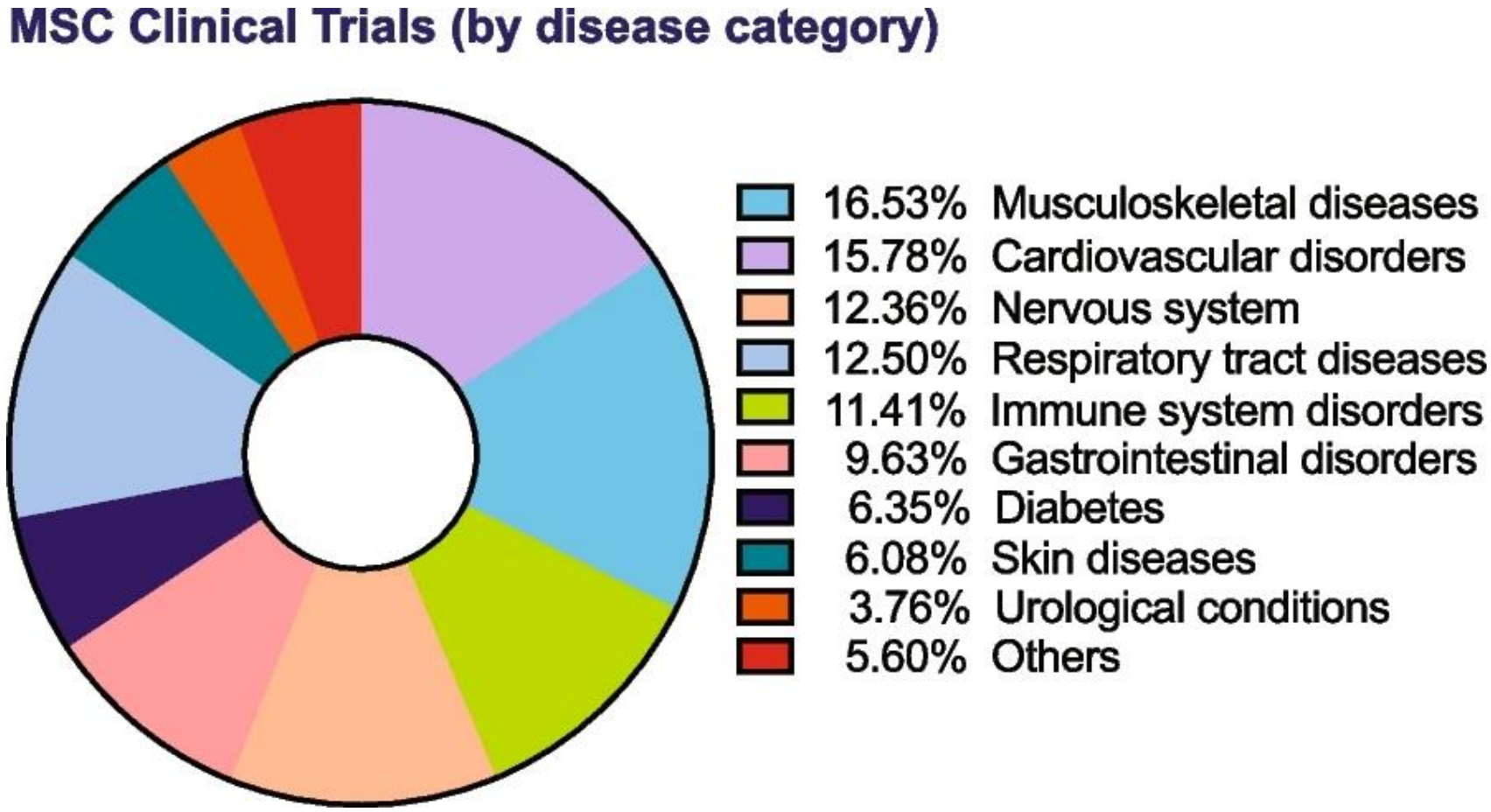
Regenerative Medicine



Regenerative Medicine, What's Real and What's Hype?

- ❌ Miracle cures
- ❌ Unproven & unregulated treatments
- ✓ These therapies could transform treatment for chronic and degenerative diseases, with realistic expectations.

Bone and Cartilage, Success Rates of Cell Therapy



Pie chart was plotted using MSC clinical trial numbers obtained from clinical trials.gov (as of March 2023).
Maldonado VV *et al*. Journal of biological engineering, 2023.

Bone and Cartilage, Interests of Regenerative Medicine

Bone and Cartilage

- **Mineralized structure allows for easier biomimetic approaches like using scaffolds**
- **Regeneration potential**
- **Mechanical rather than metabolic**
- **More accessible for biopsy and harvesting cells**
- **Research and development progress**
- **Relatively straightforward structure compared to internal organs**

Bone and Joint Disorders: Different common diseases

- By 2050, nearly **one billion people** globally are projected to be living with **osteoarthritis** (Lancet Rheumatology)
- **Bone defects**
- **AVN**

Approved ATMPs for Bone and Cartilage Disorders, Around the world

Product	Approved in:	Approved for:	Description
Cartistem	Korea	Knee Cartilage defects	Human UC-MSCs
JACC	Japan	Knee Cartilage defects	Autologous chondrocytes + Collagen gel
MACI	USA	Knee Cartilage defects	Autologous chondrocytes + porcine Collagen Membrane
Novocart 3D	EU	Articular Cartilage Defects	Autologous Chondrocytes + 3D Collagen Chondroitin Sulphate Scaffolds
Ortho-ACI	Australia	Symptomatic Defects of Articular Cartilage	Autologous Chondrocytes
Ossron	Korea and India	Bone Defects	Autologous Osteoblasts
Spherox	EU	Cartilage Defects	Spheroids of Human Autologous Matrix-associated Chondrocytes
Chondron	Korea and India	Knee Cartilage Defects	Autologous Chondrocytes

Bone and Joint Disorders: Not Purely Mechanical

Multifactorial Nature

Mechanical

Biological/Inflammatory

Immune signaling, synovitis, molecular remodeling

Biochemical/Molecular

Cartilage matrix turnover, cytokine activity

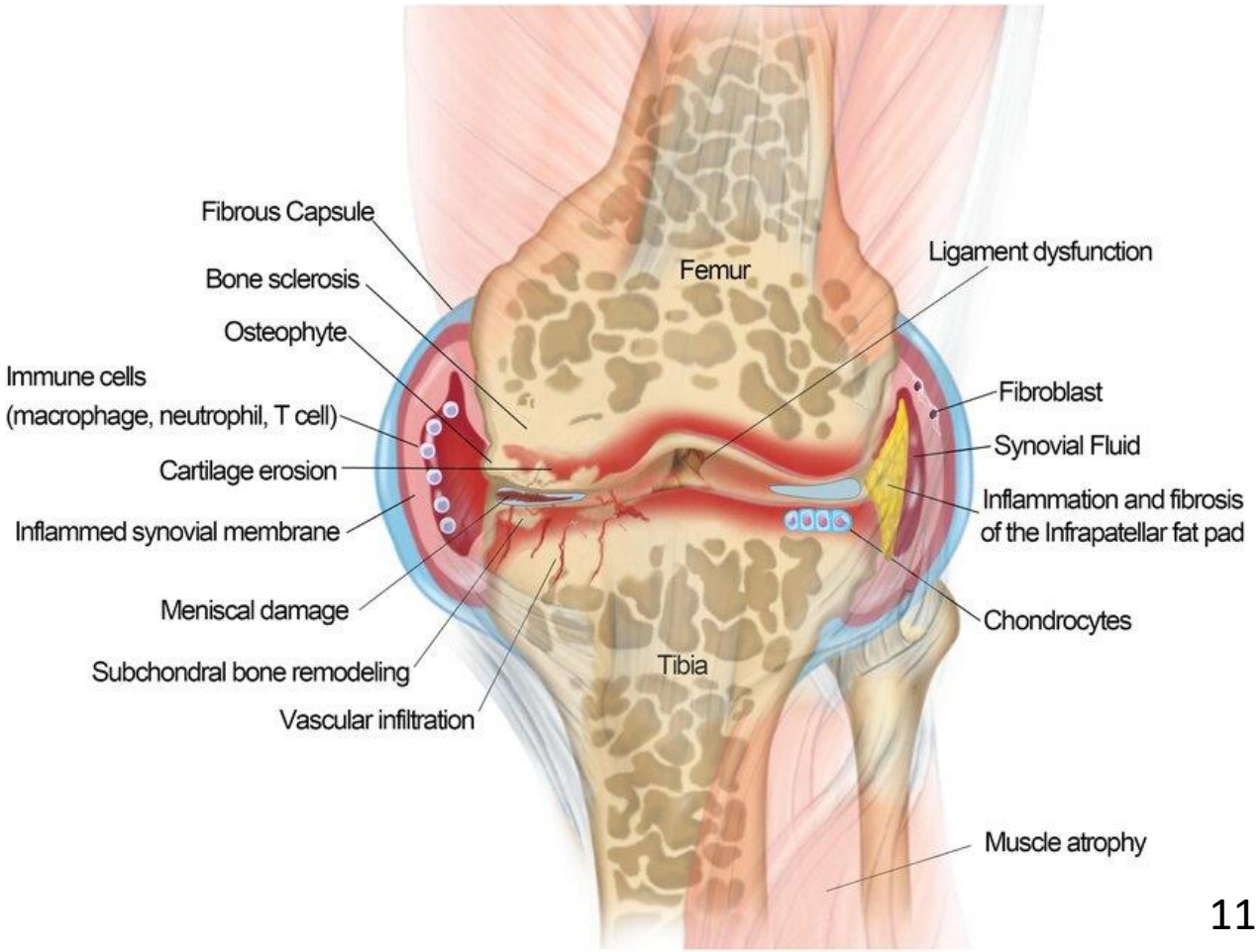
Bone and Joint Disorders: Not Purely Mechanical

Rheumatoid Arthritis

➞ Structural damage is driven by immune biology, not wear-and-tear.

Hemophilic Arthropathy

➞ Joint degeneration results from a pathological biological environment, not primary biomechanics.



10.2147/DDDT.S357386

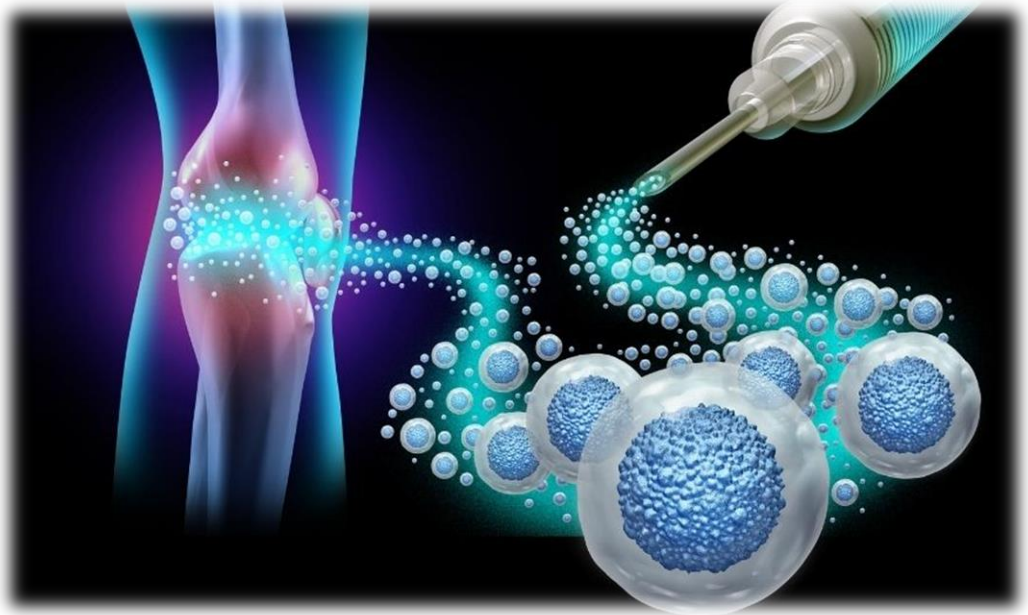
How Regenerative Medicine Play a Role?

Clinical Implication

- Mechanical correction **alone** is insufficient
- Effective treatment must target:
  - Inflammation
  - Tissue biology
  - Regenerative capacity

➞ **This is where regenerative medicine becomes relevant.**

Bone and joint disorders in these patients are often driven by biological dysfunction, mechanical stress is only part of the story.

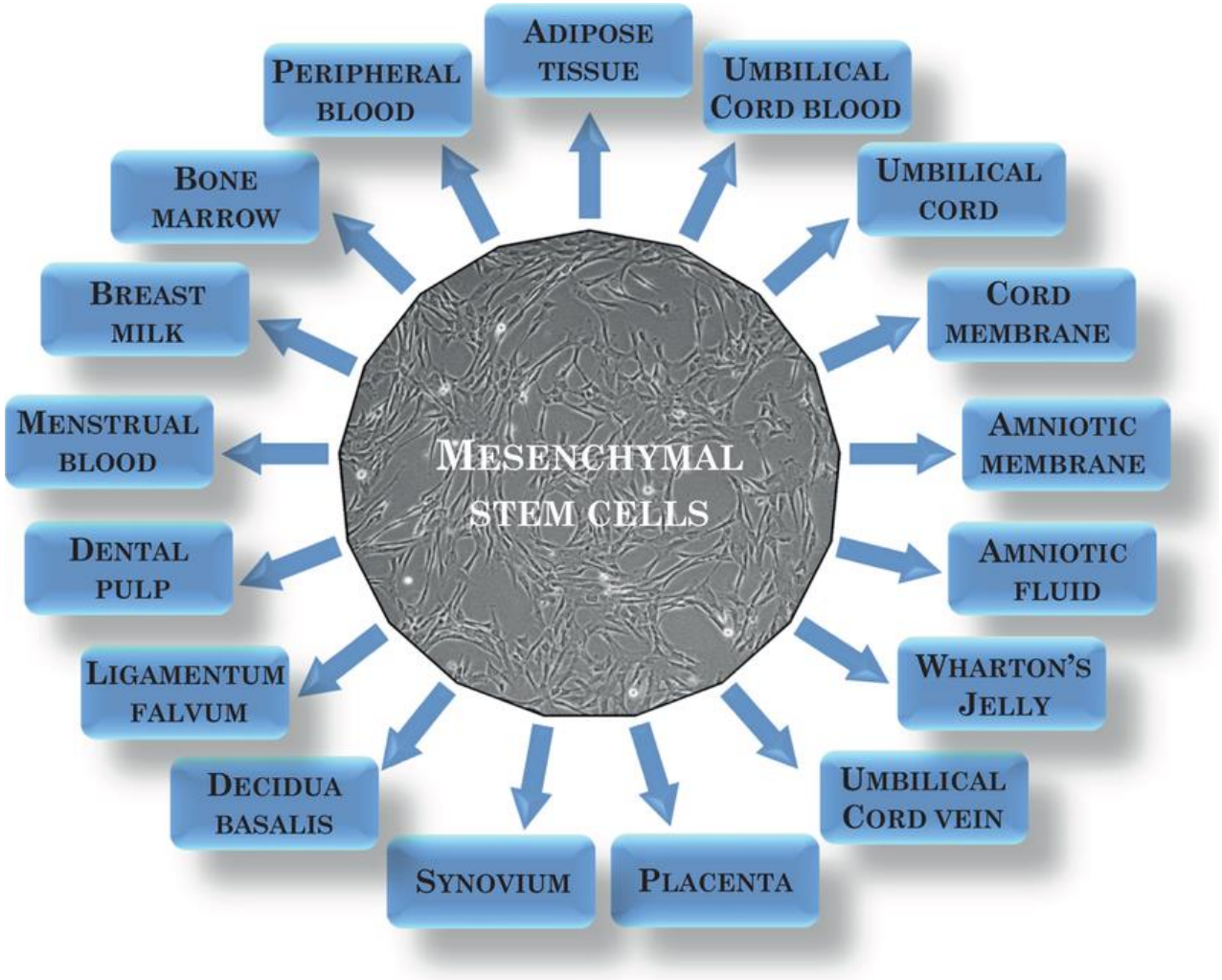


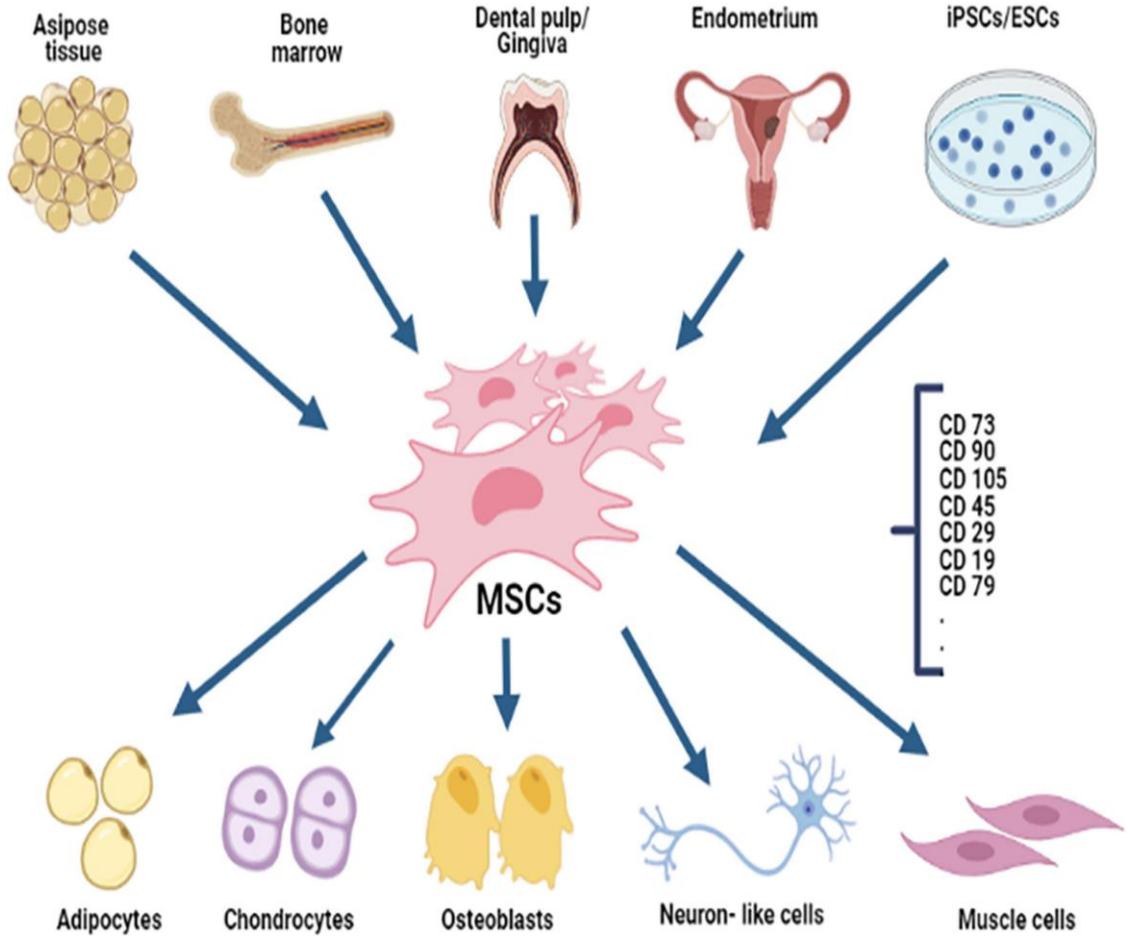
How Regenerative Medicine Could Play a Role?

Mesenchymal Stromal Cells (MSCs)

- Different Tissue Sources
- Multipotent Differentiation Capacity
- **Strong Immunomodulatory Properties**
- **Paracrine & Secretory Function**
- Low Immunogenicity

Mesenchymal Stromal Cells





10.1177/096368971983789710.3389/fcell.2021.661532

Mesenchymal Stromal Cells

Allogeneic MSCs

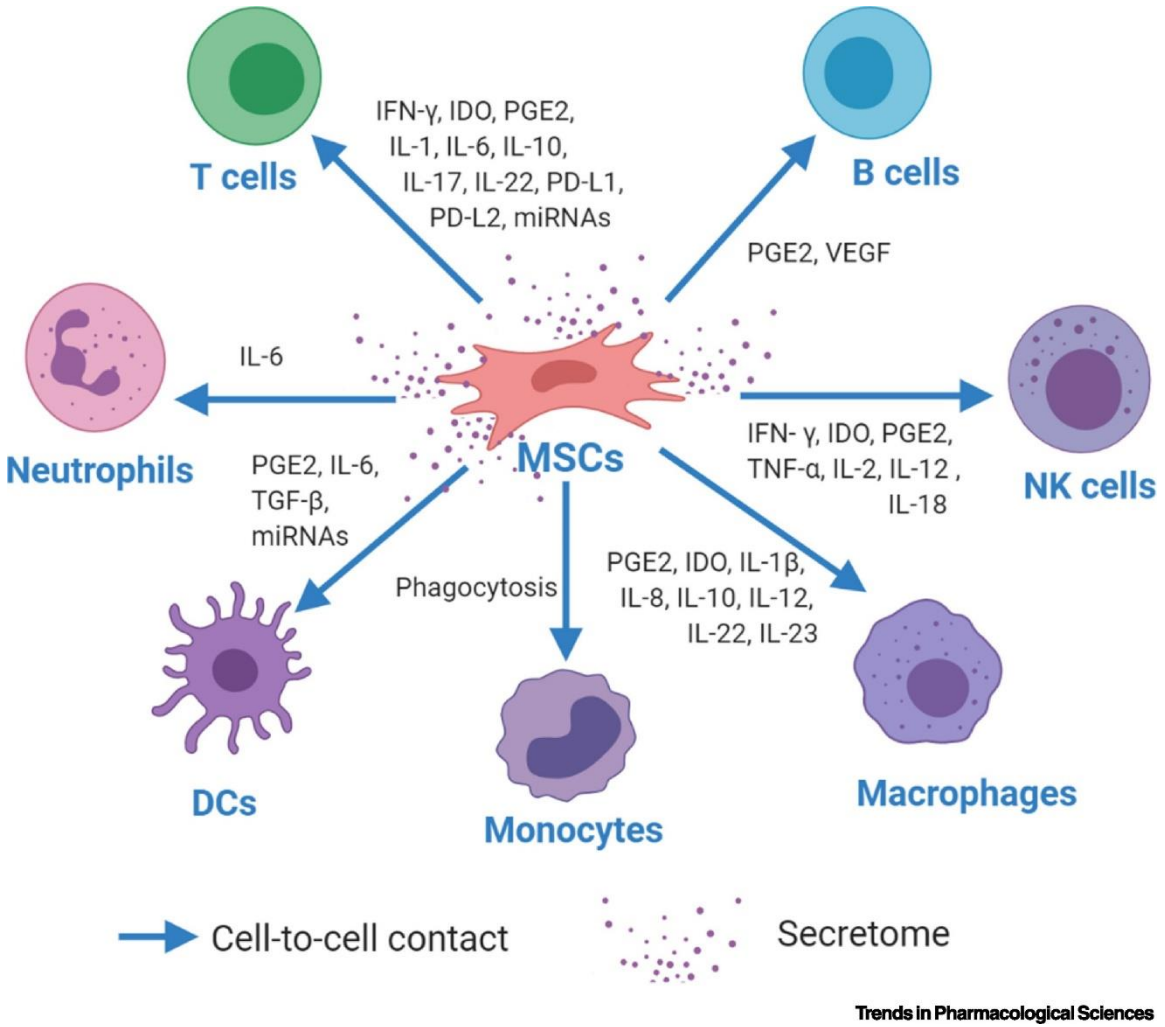
Minimal expression of **MHC class I** molecules

Lack of **co-stimulatory molecules** (e.g., CD80, CD86)

MSCs express low or no MHC class II molecules

Mesenchymal Stromal Cells

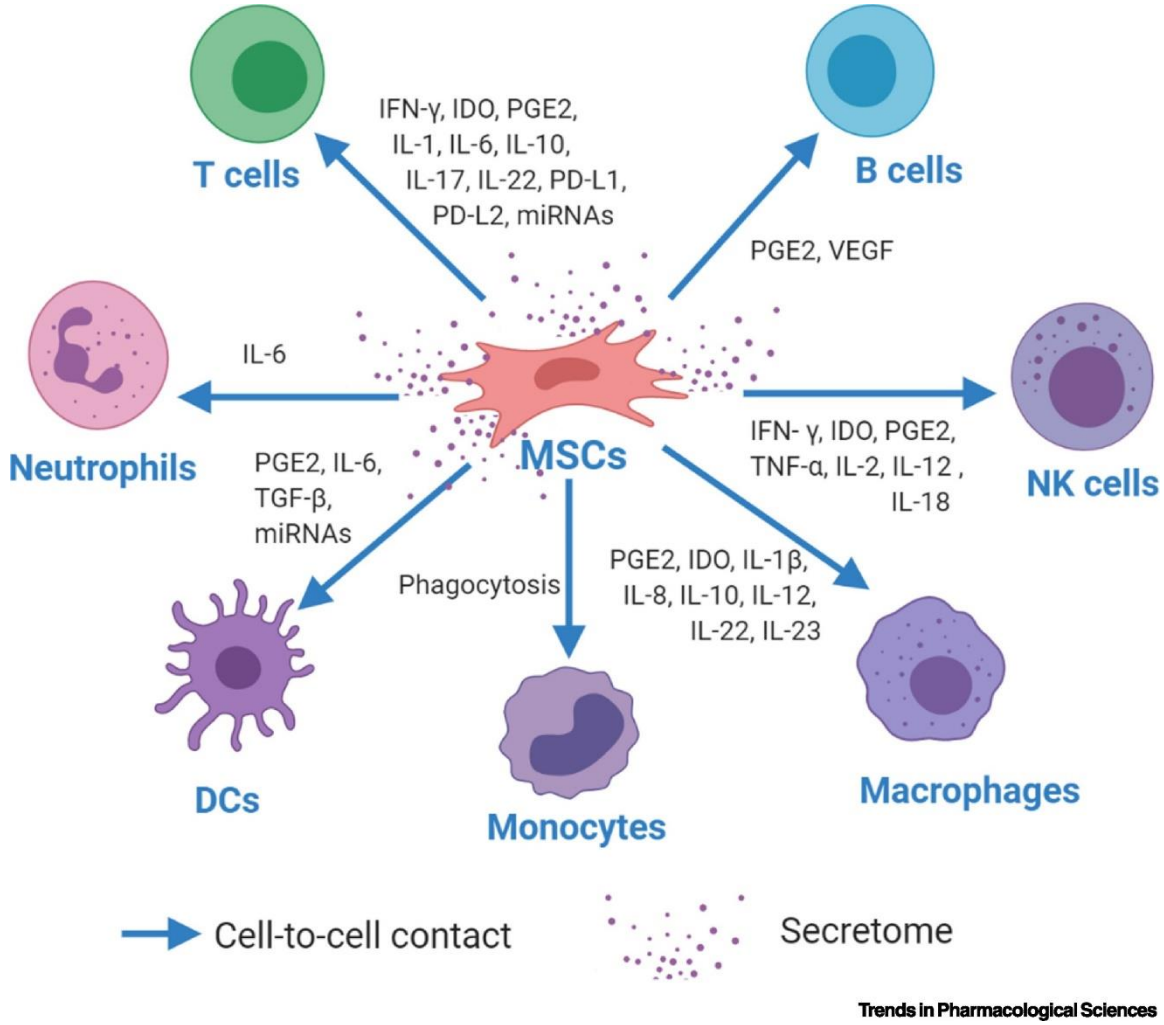
- Suppress **T-cell and B-cell activation**
- Modulate **macrophages (M1 → M2)**
- Inhibit **NK cell cytotoxicity**
- Reduce pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)
- **Paracrine & Secretory Function** (IL-10,TGF-β, PGE2)



10.1016/j.tips.2020.06.009

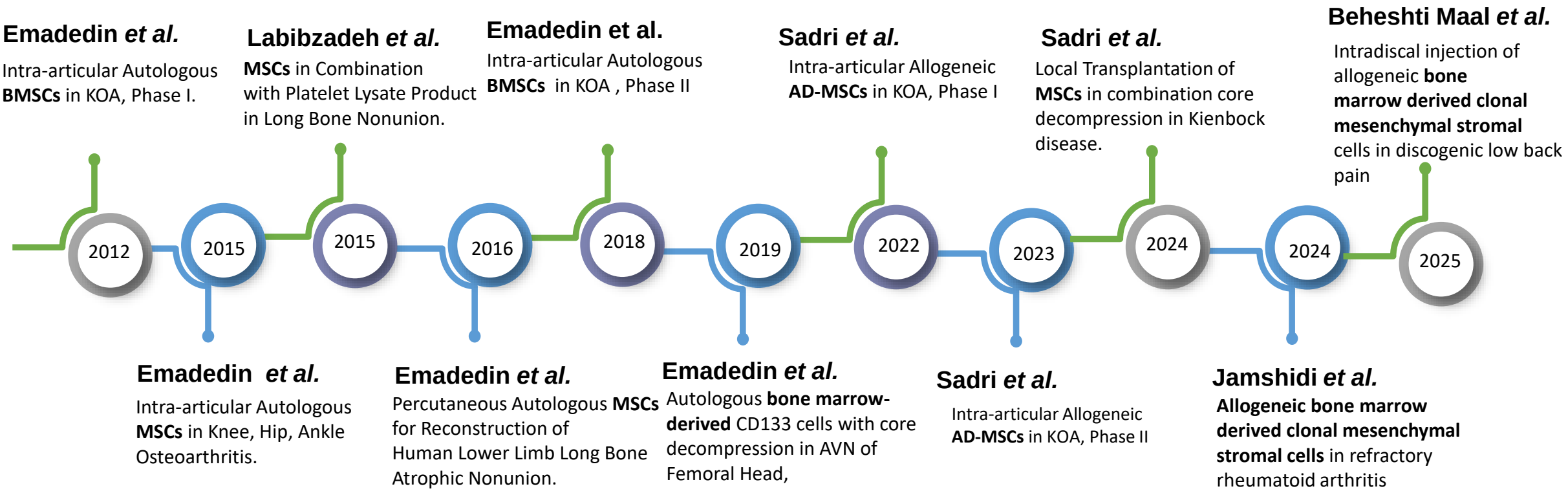
Mesenchymal Stromal Cells in Bone & Joint Disorders

- ✓ **Modulate immune responses**
- ✓ **Suppress chronic synovial inflammation**
- ✓ **Reprogram the joint microenvironment**
- ✓ **Support endogenous repair via paracrine signaling**



10.1016/j.tips.2020.06.009

MSCs in Bone and Joint Disorders, Clinical Trials at Royan Institute



Emadedin *et al.*
Intra-articular Autologous **BMSCs** in KOA, Phase I.

Labibzadeh *et al.*
MSCs in Combination with Platelet Lysate Product in Long Bone Nonunion.

Emadedin et al.
Intra-articular Autologous **BMSCs** in KOA , Phase II

Sadri *et al.*
Intra-articular Allogeneic **AD-MSCs** in KOA, Phase I

Sadri *et al.*
Local Transplantation of **MSCs** in combination core decompression in Kienbock disease.

Beheshti Maal *et al.*
Intradiscal injection of allogeneic **bone marrow derived clonal mesenchymal stromal** cells in discogenic low back pain

Emadedin *et al.*
Intra-articular Autologous **MSCs** in Knee, Hip, Ankle Osteoarthritis.

Emadedin *et al.*
Percutaneous Autologous **MSCs** for Reconstruction of Human Lower Limb Long Bone Atrophic Nonunion.

Emadedin *et al.*
Autologous **bone marrow-derived** CD133 cells with core decompression in AVN of Femoral Head,

Sadri *et al.*
Intra-articular Allogeneic **AD-MSCs** in KOA, Phase II

Jamshidi *et al.*
Allogeneic bone marrow derived clonal mesenchymal stromal cells in refractory rheumatoid arthritis

2012

6 Patients
6 Month F/U
No AEs & SAEs
Improvement up to 6 M

Original Article

Intra-articular Injection of Autologous Mesenchymal Stem Cells in Six Patients with Knee Osteoarthritis

Mohsen Emadedin MD[1], Naser Aghdami MD PhD[1,2], Leila Taghiyar MSc[2], Roghayeh Fazeli MD[1], Reza Moghadasali MSc[1], Shahrbanoo Jahangir MSc[2], Reza Farjad MD[3], , Mohamadreza Baghaban Eslaminejad PhD•[1,2]

Abstract

Background: Osteoarthritis (OA) is a progressive disorder of the joints caused by gradual loss of articular cartilage, which naturally possesses a limited regenerative capacity. In the present study, the potential of intra-articular injection of mesenchymal stem cells (MSCs) has been evaluated in six osteoarthritic patients.

Methods: Six female volunteers, average age of 54.56 years, with radiologic evidence of knee OA that required joint replacement surgery were selected for this study. About 50 ml bone marrow was aspirated from each patient and taken to the cell laboratory, where MSCs were isolated and characterized in terms of some surface markers. About 20-24×10^6 passaged-2 cells were prepared and tested for microbial contamination prior to intra-articular injection.

Results: During a one-year follow-up period, we found no local or systemic adverse events. All patients were partly satisfied with the results of the study. Pain, functional status of the knee, and walking distance tended to be improved up to six months post-injection, after which pain appeared to be slightly increased and patients' walking abilities slightly decreased. Comparison of magnetic resonance images (MRI) at baseline and six months post-stem cell injection displayed an increase in cartilage thickness, extension of the repair tissue over the subchondral bone and a considerable decrease in the size of edematous subchondral patches in three out of six patients.

Conclusion: The results indicated satisfactory effects of intra-articular injection of MSCs in patients with knee OA.

Keywords: Cell therapy, mesenchymal stem cells, osteoarthritis

2015

18 Patients
30 Month F/U
No SAEs,
Local rash and erythema
Improvement
(VAS, WOMAC, WD)

Original Article

Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis

Mohsen Emadedin MD[1#], Maede Ghorbani Liastani MD[2#], Roghayeh Fazeli MD[1], Fatemeh Mohseni MD[1], Reza Moghadasali PhD[1], Soura Mardpour MSc[1], Seyyedeh Esmat Hosseini BS[1], Maryam Niknejadi MD[1], Fatemeh Moeinina MD[1], Aslan Aghahossein Fanni MSc[1], Reza Baghban Eslaminejhad PhD[1], Ahmad Vosough Dizaji MD[1,2], Narges Labibzadeh MD[1], Ali Mirazimi Bafghi MD[1], Hossein Baharvand PhD[1], Nasser Aghdami MD PhD•[1]

Abstract

Background: Osteoarthritis (OA) is a debilitating disease that typically affects a large number of the middle-aged and elderly population. Current treatment strategies have had limited success in these patients. This study aims to investigate the safety of treatment with autologous bone marrow (BM)-derived mesenchymal stem cells (MSCs) transplanted in patients with OA of the knee, ankle, or hip.

Methods: We enrolled 18 patients with different joint involvements (knee, ankle, or hip OA) and one was lost to follow-up. BM samples were taken from the patients, after which BM-derived MSCs were isolated and cultured. Each patient received one MSC injection. Patients were followed with clinical examinations, MRI and laboratory tests at 2, 6, 12, and 30 months post-transplantation.

Results: We observed no severe adverse events such as pulmonary embolism, death, or systemic complications. A limited number of patients had very minor localized adverse effects such as rash and erythema. There were no changes in liver function, hematology, or biochemistry analyses before and after cell therapy. There was no evidence of tumor or neoplastic changes in the patients during the 30-month follow-up period. All patients exhibited therapeutic benefits such as increased walking distance, decreased visual analog scale (VAS), and total Western Ontario and McMaster Universities OA Index (WOMAC) scores which were confirmed by MRI.

Conclusions: Our study has shown that injection of MSCs in different OA affected joints is safe and therapeutically beneficial. However, further studies are needed with larger sample sizes and longer follow-up periods to confirm these findings.

Keywords: Ankle osteoarthritis, autologous mesenchymal stem cell transplantation, hip osteoarthritis, knee osteoarthritis, safety

2016

7 Patients
12 Month F/U
No AEs & SAEs
Improvement in 4 Patients
(X-ray)

Original Article

Mesenchymal Stromal Cells Implantation in Combination with Platelet Lysate Product Is Safe for Reconstruction of Human Long Bone Nonunion

Narges Labibzadeh, M.D.[#], Mohsen Emadedin, M.D.[#], Roghayeh Fazeli, M.D., Fatemeh Mohseni, M.D., Seyedeh Esmat Hosseini, M.Sc., Reza Moghadasali, Ph.D., Soura Mardpour, M.Sc., Vajiheh Azimian, M.Sc., Maede Ghorbani Liastani, M.D., Ali Mirazimi Bafghi, M.D., Mohamadreza Baghaban Eslaminejad, Ph.D., Nasser Aghdami, M.D., Ph.D.*

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[#]; The first two authors equally contributed to this manuscript.

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Received: 12/Oct/2015, Accepted: 3/Jan/2016

Abstract

Objective: Nonunion is defined as a minimum of 9 months since injury without any visible progressive signs of healing for 3 months. Recent literature has shown that the application of mesenchymal stromal cells is safe, *in vitro* and *in vivo*, for treating long bone nonunion. The present study was performed to investigate the safety of mesenchymal stromal cell (MSC) implantation in combination with platelet lysate (PL) product for treating human long bone nonunion.

Materials and Methods: In this case series clinical trial, orthopedic surgeons visited eighteen patients with long bone nonunion, of whom 7 complied with the eligibility criteria. These patients received mesenchymal stromal cells (20 million cells implanted once into the nonunion site using a fluoroscopic guide) in combination with PL product. For evaluation of the effects of this intervention all the patients were followed up by taking anterior-posterior and lateral X-rays of the affected limb before and 1, 3, 6, and 12 months after the implantation. All side effects (local or systemic, serious or non-serious, related or unrelated) were observed during this time period.

Results: From a safety perspective the MSC implantation in combination with PL was very well tolerated during the 12 months of the trial. Four patients were healed; based on the control X- ray evidence, bony union had occurred.

Conclusion: Results from the present study suggest that the implantation of bone marrow-derived MSCs in combination with PL is safe for the treatment of nonunion. A double blind, controlled clinical trial is required to assess the efficacy of this treatment (Registration Number: NCT01206179).

Keywords: Fractures Ununited, Mesenchymal Stromal Cells, Platelet Lysate

Cell Journal(Yakhteh), Vol 18, No 3, Oct-Dec (Autumn) 2016, Pages: 302-309

2017

5 Patients
12 Month F/U
No AEs & SAEs
Improvement in 3 patients
(X-ray)

Original Article

Percutaneous Autologous Bone Marrow-Derived Mesenchymal Stromal Cell Implantation Is Safe for Reconstruction of Human Lower Limb Long Bone Atrophic Nonunion

Mohsen Emadedin, M.D.#, Narges Labibzadeh, M.D.#, Roghayeh Fazeli, M.D., Fatemeh Mohseni, M.D., Seyedeh Esmat Hosseini, M.Sc., Reza Moghadasali, Ph.D., Soura Mardpour, M.Sc., Vajiheh Azimian, M.Sc., Alireza Goodarzi, M.Sc., Maede Ghorbani Liastani, M.D., Ali Mirazimi Bafghi, M.D., Mohamadreza Baghaban Eslaminejad, Ph.D., Nasser Aghdami, M.D., Ph.D.*

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Received: 2/Feb/2016, Accepted: 7/May/2016

Abstract

Objective: Nonunion is defined as a minimum of a 9-month period of time since an injury with no visibly progressive signs of healing for 3 months. Recent studies show that application of mesenchymal stromal cells (MSCs) in the laboratory setting is effective for bone regeneration. Animal studies have shown that MSCs can be used to treat nonunions. For the first time in an Iranian population, the present study investigated the safety of MSC implantation to treat human lower limb long bone nonunion.

Materials and Methods: It is a prospective clinical trial for evaluating the safety of using autologus bone marrow derived mesenchymal stromal cells for treating nonunion. Orthopedic surgeons evaluated 12 patients with lower limb long bone nonunion for participation in this study. From these, 5 complied with the eligibility criteria and received MSCs. Under fluoroscopic guidance, patients received a one-time implantation of 20-50×10^6 MSCs into the nonunion site. All patients were followed by anterior-posterior and lateral X-rays from the affected limb, in addition to hematological, biochemical, and serological laboratory tests obtained before and 1, 3, 6, and 12 months after the implantation. Possible adverse effects that included local or systemic, serious or non-serious, and related or unrelated effects were recorded during this time period.

Results: From a safety perspective, all patients tolerated the MSCs implantation during the 12 months of the trial. Three patients had evidence of bony union based on the after implantation X- rays.

Conclusion: The results have suggested that implantation of bone marrow-derived MSCs is a safe treatment for nonunion. A double-blind, controlled clinical trial is required to assess the efficacy of this treatment (Registration Number: NCT01206179).

Keywords: Nonunion, Mesenchymal Stromal Cells, Autologous, Bone Marrow

Cell Journal(Yakhteh), Vol 19, No 1, Apr-Jun (Spring) 2017, Pages: 159-165

2018

43 Patients
6 Month F/U
No AEs & SAEs
Improvement VAS, WOMAC

Cytotherapy, 2018; 0001–9

International Society for Cellular Therapy ISCT

ROYAN

Intra-articular implantation of autologous bone marrow–derived mesenchymal stromal cells to treat knee osteoarthritis: a randomized, triple-blind, placebo-controlled phase 1/2 clinical trial

MOHSEN EMADEDIN[1,*], NARGES LABIBZADEH[1,*], MAEDE GHORBANI LIASTANI[1,*], ALIASGHAR KARIMI[2], NEDA JAROUGHI[1], TINA BOLURIEH[1], SEYYEDEH-ESMAT HOSSEINI[1], HOSSEIN BAHARVAND[3,4] & NASSER AGHDAMI[1]

[1]*Department of Regenerative Medicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, The Academic Center for Education, Culture and Research (ACECR), Tehran, Iran,* [2] *Noncommunicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran,* [3] *Department of Stem Cells and Developmental Biology, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, The Academic Center for Education, Culture and Research (ACECR), Tehran, Iran, and* [4] *Department of Developmental Biology, University of Science and Culture, Tehran, Iran*

Abstract

Background. The intra-articular implantation of mesenchymal stromal cells (MSCs) as a treatment for knee osteoarthritis (OA) is an emerging new therapy. In this study, patients with knee OA received intra-articular implantations of autologous bone marrow–derived MSCs. We sought to assess the safety and efficacy of this implantation. *Materials and Methods.* This was a phase 1/2 single-center, triple-blind, randomized controlled trial (RCT) with a placebo control. The subjects consisted of patients with knee OA randomly assigned to either an intra-articular implantation of MSCs (40×10^6 cells) or 5 mL normal saline (placebo). Patients were followed up for 6 months after the implantations. The pain level and function improvements for patient-reported outcomes were assessed based on a visual analog scale (VAS), Western Ontario and McMaster Universities Arthritis Index (WOMAC) and its subscales, walking distance, painless walking distance, standing time and knee flexion compared with the placebo group at 3 and 6 months following the implantations. *Results.* Overall, 43 patients (Kellgren-Lawrence grades 2, 3 and 4) were assigned to either the MSCs (n = 19) or placebo (n = 24) group. Patients who received MSCs experienced significantly greater improvements in WOMAC total score, WOMAC pain and physical function subscales and painless walking distance compared with patients who received placebo. There were no major adverse events attributed to the MSC therapy. *Conclusion.* This randomized, triple-blind, placebo-controlled RCT demonstrated the safety and efficacy of a single intra-articular implantation of 40×10^6 autologous MSCs in patients with knee OA. Intra-articular implantation of MSCs provided significant and clinically relevant pain relief over 6 months versus placebo and could be considered a promising novel treatment for knee OA. We propose that further investigations should be conducted over an extended assessment period and with a larger cohort.

Key Words: *bone marrow, clinical trial, intra-articular, knee osteoarthritis, mesenchymal stromal cells*

2019

9 Patients
12 Month F/U
No AEs & SAEs
Improvement
(VAS, WOMAC, WD)

Cytotherapy, 2019; 21: 107–112

International Society
ISCT
Cell & Gene Therapy

ORTHOPEDICS

Autologous bone marrow–derived CD133 cells with core decompression as a novel treatment method for femoral head osteonecrosis: a pilot study

MOHSEN EMADEDIN[1,*], SHAHEDEH KARIMI[1,*], ALIASGHAR KARIMI[2], NARGES LABIBZADEH[1], MARYAM NIKNEJADI[1], HOSSEIN BAHARVAND[3,4] & NASSER AGHDAMI[1]

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Abstract

Background. Avascular necrosis (AVN) of femoral head is a progressive bone disease due to ischemia of femoral head; patients experience pain and they can not do normal activity. There is not an effective way to treat the cause of this disease. In recent studies, treatment of this disease using pluripotent stem cell–derived mesenchyme is safe and effective, but this method needs more investigation. In this study, the safety and efficacy of CD133+ cells were evaluated as a novel method of stem cell therapy to treat AVN. *Methods.* In this prospective quasi-experimental study, the participants were selected among patients with AVN who were referred to the Royan Cell Therapy Center. Autologous bone marrow–derived CD133+ cells were injected into the necrotic site of the femoral head during core decompression (CD). The Visual Analogue Scale (VAS), Harris Hip Score (HHS), Western Ontario and McMaster Universities Arthritis Index (WOMAC) and walking distance (WD) were measured before and 2, 6 and 12 months after CD. *Results.* Overall, nine patients (six men and three women) were investigated in this study. Their mean age was 26 years old. All of them significantly improved in VAS, HHS, WOMAC and WD scores and they could do more activity without pain. Also, imaging findings demonstrated significant reductions in joint injuries. Significant complications were not seen in patients. *Discussion.* This prospective quasi-experimental study demonstrated that, in patients with AVN, a single bone marrow–derived CD133+ cell injection into the necrotic site of the femoral head during CD is safe and effective in providing significant, clinically relevant pain relief and patients could do more activity over 2, 6 and 12 months. This pilot study suggested further clinical trials over an extended assessment period to approve bone marrow–derived CD133+ cell injection to treat AVN.

Key Words: *avascular necrosis, CD133 cells, cell therapy, core decompression, femoral head osteonecrosis, Harris Hip Score, Visual Analogue Scale*

2024

3 Patients
6 Month F/U
No AEs & SAEs
Improvement
(VAS, DASH, ROM, X-ray)

Cell J
Cell Journal (Yakhteh)
Homepage: https://www.celljournal.org/
Original Article
Vol 26, No 7, July 2024, Pages: 446-453

ROYAN

Local Transplantation of Mesenchymal Stromal Cells Is Safe and Could Alleviate Kienböck Disease's Complications: A Clinical Trial Study

Bahareh Sadri, M.Sc.[1], Narges Labibzadeh, M.D.[1], Lida Mirmorsali, M.Sc.[1], Marzieh Ebrahimi, Ph.D.[1], Abolfazl Bagherifard, M.D.[2], Leila Arab, M.D.[1], Nasser Aghdami, Ph.D.[1], Hoda Madani, M.D.[1], Alireza Beheshti Maal, M.D.[1], Shahedeh Karimi, M.D.[1], Saeed Reza Mehrpour, M.D.[3], Mohsen Emadedin, M.D.[1], Massoud Vosough, Ph.D.[1*]

1. Department of Regenerative Medicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran
2. Bone and Joint Reconstruction Research Center, Department of Orthopedics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
3. Department of Orthopedics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Objective: Kienböck disease is a rare condition characterized by severe pain and restricted wrist movement. Various palliative methods have been proposed as therapeutic strategies for alleviating symptoms. Mesenchymal stromal cell transplantation has been suggested as an innovative and promising approach due to its potential for inducing regeneration and immunomodulation in the necrotic tissue. This study aims to evaluate the safety of autologous bone marrow derived mesenchymal stromal cells (BM-MSCs) transplantation after core decompression in Kienböck disease.

Materials and Methods: In this phase I of an open-label clinical trial, three patients (one female and two males) with stage 2 Kienböck disease underwent autologous BM-MSCs transplantation following lunate core decompression. The patients were followed up for six months to assess safety as well as secondary clinical outcomes, including pain level, range of motion (ROM), and functional disability.

Results: Safety of BM-MSCs injection following the core decompression was evaluated by recording post-treatment complications during the six-month follow-up. No adverse events (AEs) or severe AEs (SAEs) were reported, indicating that BM-MSCs injection after core decompression is a safe intervention. All patients showed a remarkable reduction in visual analog scale (VAS) scores and "Disabilities of the Arm, Shoulder, and Hand" (DASH) questionnaire scores, suggesting the therapeutic potential of this intervention. Moreover, an increase in the ROM indicated that BM-MSCs transplantation can improve wrist functionality. Additionally, radiographic assessments before and after cell infusion demonstrated a reduction in lunate sclerosis after six months of follow-up.

Conclusion: The transplantation of autologous BM-MSCs following lunate core decompression seems to be a safe clinical intervention and may lead to pain relief in patients with Kienböck disease. Furthermore, this procedure may help prevent disease progression during the follow-up period (registration number: NCT02646007).

Keywords: Avascular Necrosis, Kienböck Disease, Mesenchymal Stromal Cell, Regenerative Medicine

Citation: Sadri B, Labibzadeh N, Mirmorsali L, Ebrahimi M, Bagherifard A, Arab L, Aghdami N, Madani H, Beheshti Maal A, Karimi S, Mehrpour SR, Emadedin M, Vosough M. Local transplantation of mesenchymal stromal cells is safe could alleviate kienböck disease's complications: a clinical trial study. Cell J. 2024; 26(7): 446-453. doi: 10.22074/cellj.2024.2028891.1572

Maal et al. Stem Cell Research & Therapy (2025) 16:525
https://doi.org/10.1186/s13287-025-04606-w

ROYAN

2025

5 Patients
6 Month F/U
No SAEs
Transient injection site pain
Improvement of VAS, ODI, SF-36 in 3 patients and MRI in 2 patients

RESEARCH Open Access

Intradiscal injection of allogeneic bone marrow derived clonal mesenchymal stromal cells in discogenic low back pain: a phase I study on safety and feasibility (RELIEF: phase I)

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Abstract

Aims This is a phase I trial, assessing the feasibility, safety, and potential efficacy of intradiscal injection of allogeneic bone marrow-derived clonal mesenchymal stromal cells (BM-cMSCs) in patients suffering from discogenic low back pain (DLBP).

Methods Five patients underwent single intradiscal injection of 9×10^6 allogeneic BM-cMSCs and were followed at predefined intervals for 24 weeks. Safety outcomes included monitoring adverse events (AEs), serious adverse events (SAEs), and laboratory assessments. Efficacy endpoints were evaluated over 24 weeks and included Visual Analog Scale (VAS), Oswestry Disability Index (ODI), and SF-36 quality-of-life scores. MRI was performed to assess disc height, apparent diffusion coefficient (ADC), and modified Pfirrmann grading.

Results No SAE was observed. Transient injection site pain was the most common AE which resolved within 4–8 days after injection. VAS decreased significantly in three patients, with pain relief sustained through 24 weeks. ODI indicated functional improvement in three patients, with two achieving minimal disability. SF-36 quality of life questionnaire outcomes demonstrated improvements in physical functioning and pain domains in three patients. MRI findings showed modest increases in disc height and apparent diffusion coefficient (ADC) improvements in 2 patients.

2022

3 Patients
6 Month F/U
No AEs & SAEs
Slight improvement in 2 patients (MRI)
Decrease in inflammatory biomarkers (COMP, HA, IL-6)

Clinical and laboratory findings following transplantation of allogeneic adipose-derived mesenchymal stromal cells in knee osteoarthritis, a brief report

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ABSTRACT

Background: Mesenchymal stromal cells (MSCs) injection has been proposed as an innovative treatment for knee osteoarthritis (KOA). Since, allogeneic MSCs can be available as off-the-shelf products, they are preferable in regenerative medicine. Among different sources for MSCs, adipose-derived MSCs (AD-MSCs) appear to be more available.

Methods: Three patients with KOA were enrolled in this study. A total number of 100×10^6 AD-MSCs was injected intra-articularly, per affected knee. They were followed up for 6 months by the assessment of clinical outcomes, magnetic resonance imaging (MRI), and serum inflammatory biomarkers.

Results: The primary outcome of this study was safety and feasibility of allogeneic AD-MSCs injection during the 6 months follow-up. Fortunately, no serious adverse events (SAEs) were reported. Assessment of secondary outcomes of visual analogue scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and knee osteoarthritis outcome score (KOOS) indicated improvement in all patients. Comparison between baseline and endpoint findings of MRI demonstrated a slight improvement in two patients. In addition, decrease in serum cartilage oligomeric matrix protein (COMP) and hyaluronic acid (HA) indicated the possibility of reduced cartilage degeneration. Moreover, quantification of serum interleukin-10 (IL-10) and interleukin-6 (IL-6) levels indicated that the host immune system immunomodulated after infusion of AD-MSCs.

Conclusion: Intra-articular injection of AD-MSCs is safe and could be effective in cartilage regeneration in KOA. Preliminary assessment after six-month follow-up suggests the potential efficacy of this intervention which would need to be confirmed in randomized controlled trials on a larger population.

Trial registration: This study was registered in the Iranian registry of clinical trials (https://en.irct.ir/trial/46) in 24 April 2018 with identifier IRCT20080728001031N23.

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KEYWORDS
Allogeneic mesenchymal stromal cells; cartilage regeneration; inflammatory biomarkers; knee osteoarthritis; regenerative medicine

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3 Patients
6 Month F/U
No AEs & SAEs
Slight improvement in 2 patients (MRI)
Decrease in inflammatory biomarkers (COMP, HA, IL-6)

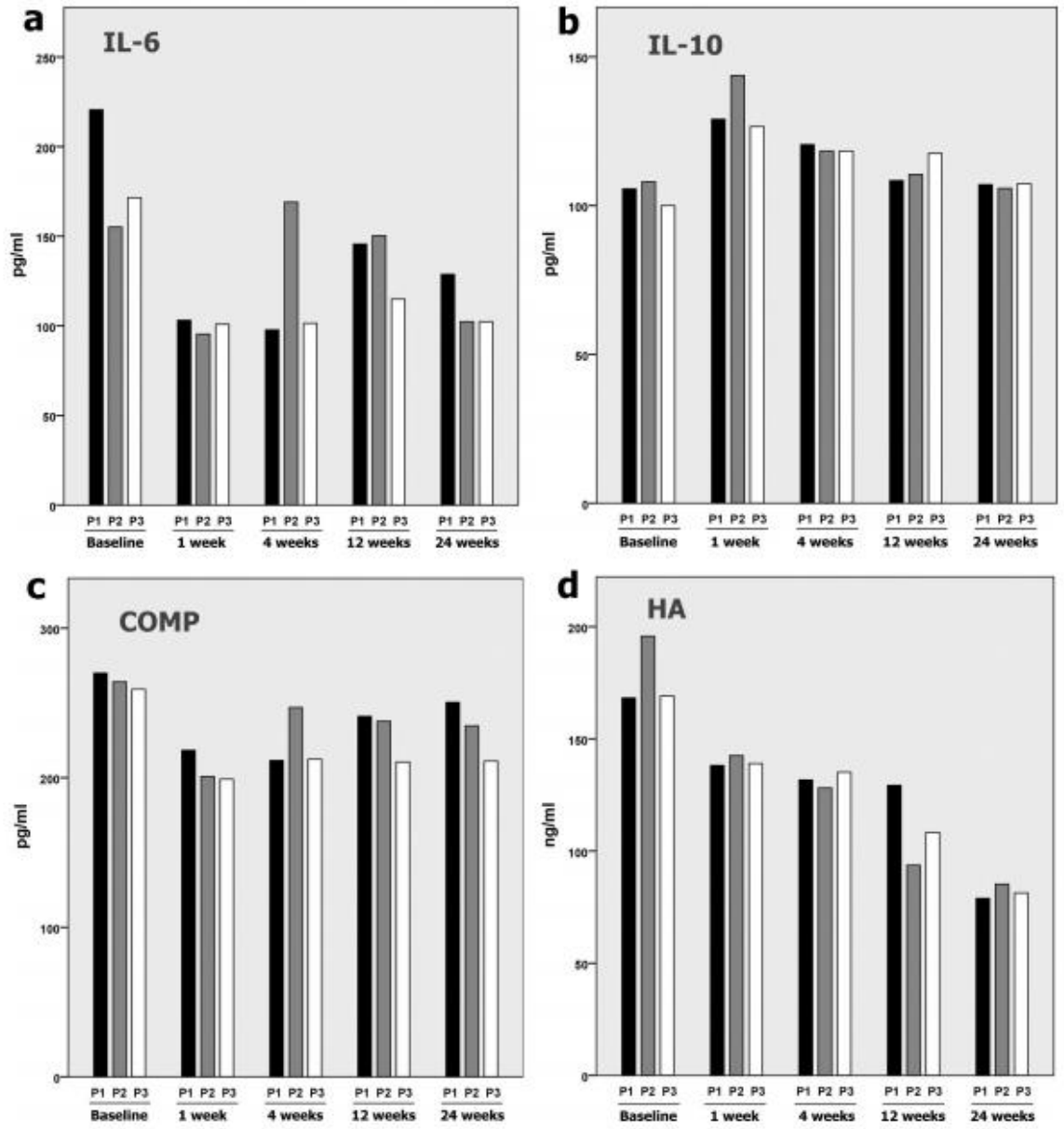

Figure 5. Changes in the expression of biomarkers in the serum of the patients. (a): IL-6, (b): IL-10, (c): COMP, (d): HA.IL-6, interleukin-6; IL-10, interleukin-10; COMP, cartilage oligomeric matrix protein; HA, hyaluronic acid; AD-MSCs, adipose derived mesenchymal stromal cells.

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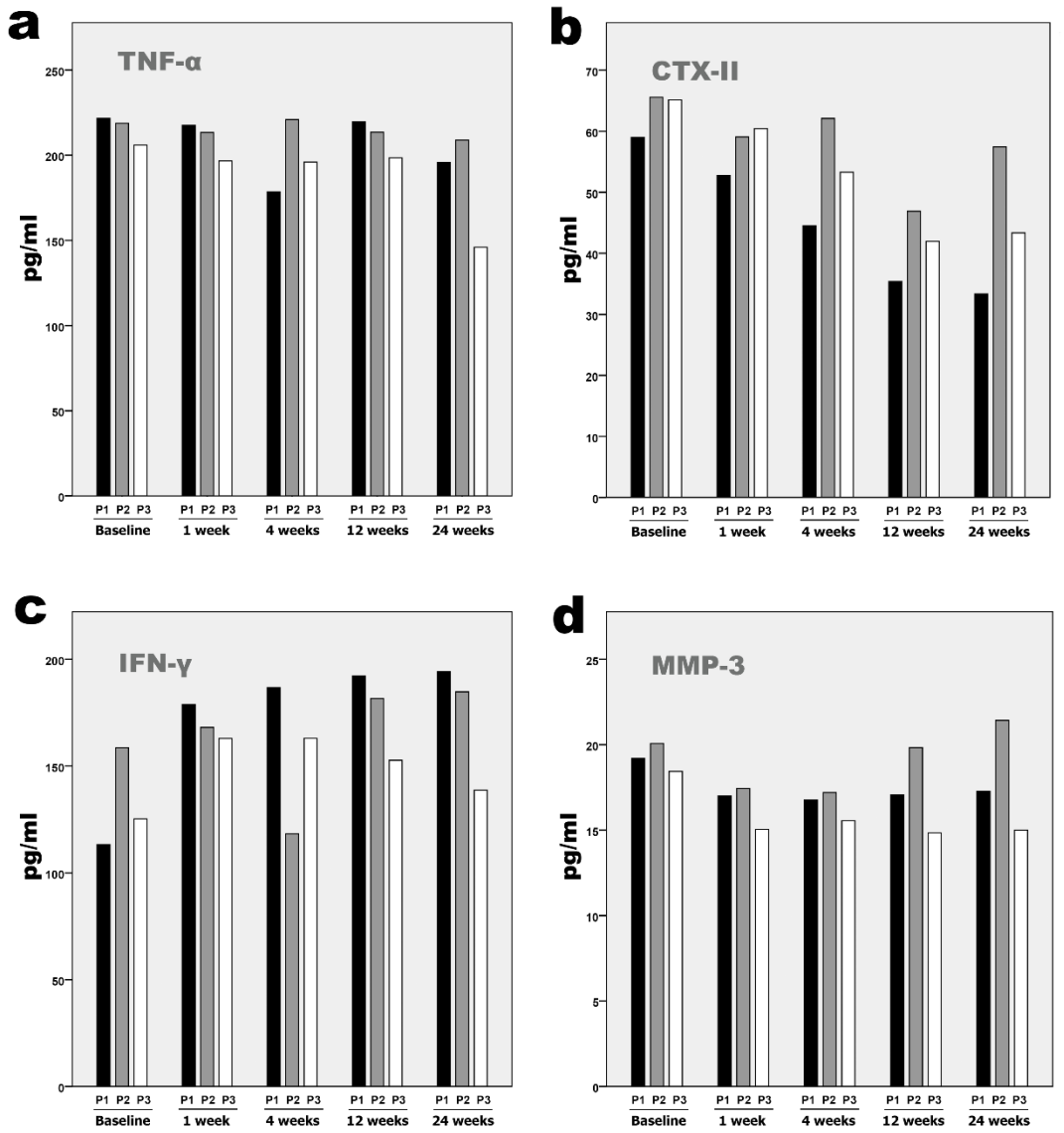

S.5 Changes in the Expression level of serum biomarkers.(a): TNF-α, (b): CTX-II, (c): IFN- γ, (d): MMP-3 TNF-α, Tumor necrosis factor-α; CTX-II, C-telopeptide fragments of type II collagen; IFN- γ, Interferon- γ; MMP-3, Matrix metalloproteinase-3; AD-MSCs, Adipose derived mesenchymal stromal cells.

2023

40 Patients
12 Month F/U
No SAEs
Swelling in 2 patients
Improvement
(VAS, WOMAC, KOOS, SF-36, MRI,
Serum Biomarkers)

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ROYAN

RESEARCH Open Access

Cartilage regeneration and inflammation modulation in knee osteoarthritis following injection of allogeneic adipose-derived mesenchymal stromal cells: a phase II, triple-blinded, placebo controlled, randomized trial

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Abstract

Background Intra-articular injection of mesenchymal stromal cells (MSCs) with immunomodulatory features and their paracrine secretion of regenerative factors proposed a noninvasive therapeutic modality for cartilage regeneration in knee osteoarthritis (KOA).

Methods Total number of 40 patients with KOA enrolled in two groups. Twenty patients received intra-articular injection of 100×10^6 allogeneic adipose-derived mesenchymal stromal cells (AD-MSCs), and 20 patients as control group received placebo (normal saline). Questionnaire-based measurements, certain serum biomarkers, and some cell surface markers were evaluated for 1 year. Magnetic resonance imaging (MRI) before and 1 year after injection was performed to measure possible changes in the articular cartilage.

Results Forty patients allocated including 4 men (10%) and 36 women (90%) with average age of 56.1 ± 7.2 years in control group and 52.8 ± 7.5 years in AD-MSCs group. Four patients (two patients from AD-MSCs group and two patients from the control group) excluded during the study. Clinical outcome measures showed improvement in AD-MSCs group. Hyaluronic acid and cartilage oligomeric matrix protein levels in blood serum decreased significantly in patients who received AD-MSCs ($P < 0.05$). Although IL-10 level significantly increased after 1 week ($P < 0.05$), the serum level of inflammatory markers dramatically decreased after 3 months ($P < 0.001$). Expressions of CD3, CD4, and CD8 have a decreasing trend during 6-month follow-up ($P < 0.05$), ($P < 0.001$), and ($P < 0.001$), respectively. However,

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40 Patients
12 Month F/U
No SAEs
Swelling in 2 patients
Improvement
(VAS, WOMAC, KOOS, SF-36, MRI,
Serum Biomarkers)

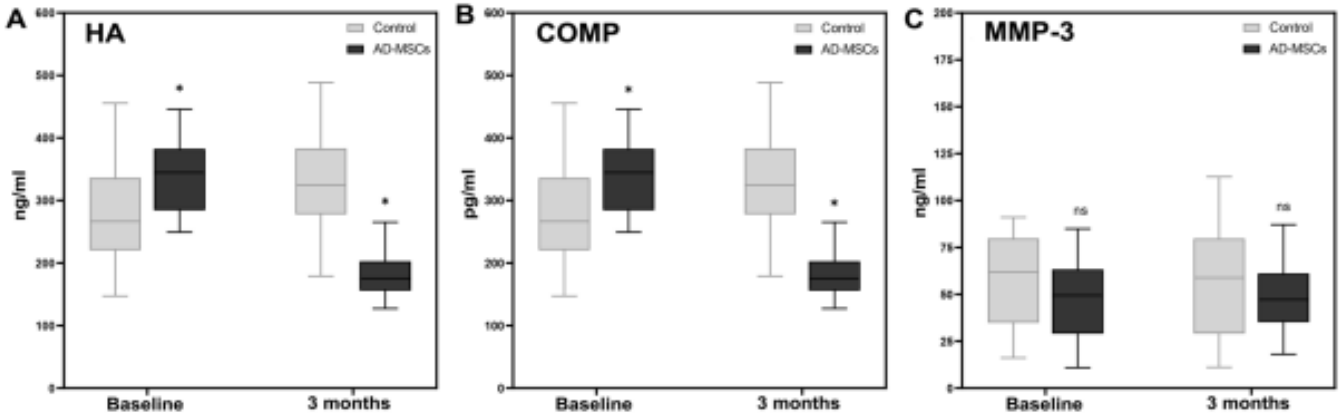

Fig. 8 Serum level of biomarkers. **A** HA levels decreased significantly in AD-MSCs group after 3 months ($P < 0.05$). **B** Levels of COMP declined remarkably in AD-MSCs group after 3 months ($P < 0.05$). **C** Level of MMP-3 does not change remarkably in AD-MSCs in comparison with the control group. Data markers represent means; error bars, 95% confidence interval; *$P < 0.05$, ns: not significant, between and within groups; and one-way repeated measures analysis of variance (ANOVA)

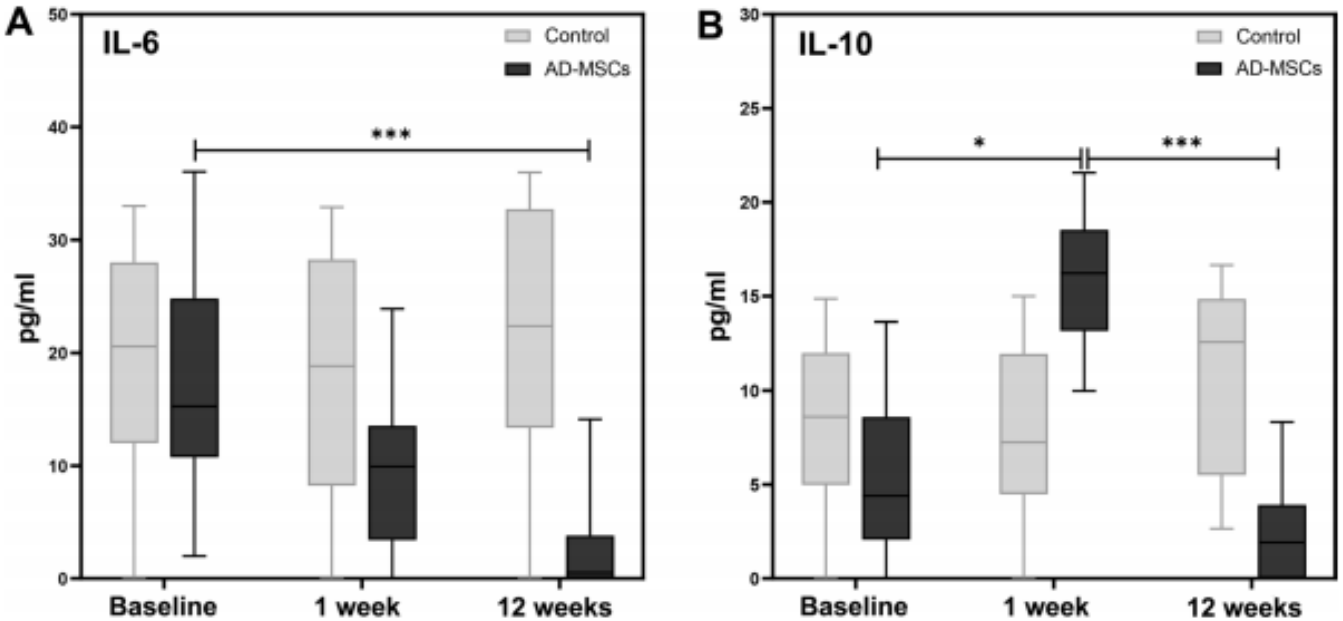

Fig. 9 Determination of inflammatory biomarkers in blood serum. **A** The level of IL-6 reduced significantly after 12 weeks of the injection in AD-MSCs group ($P < 0.001$). **B** IL-10 increased during the first week of injection ($P < 0.05$) and then decreased significantly 12 weeks after injection ($P < 0.001$). Data markers represent mean values; error bars, 95% confidence interval; *$P < 0.05$, ***$P < 0.001$, between and within groups; and one-way repeated measures analysis of variance (ANOVA)

2024

6 Patients
6 Month F/U
No SAEs
Improvement (VAS, Disease activity reduction), IL-10 reduction, TNF-α and IL-17 reduction.

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RESEARCH ARTICLE

Allogeneic bone marrow derived clonal mesenchymal stromal cells in refractory rheumatoid arthritis: a pilot study

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ABSTRACT

Aims: This phase I trial assessed the safety and potential efficacy of monthly 3 dose intravenous infusion of allogeneic bone marrow-derived clonal mesenchymal stromal cells (BM-cMSCs) in refractory rheumatoid arthritis (RA) patients over 24 weeks.

Patients & Methods: Six patients with refractory RA received BM-cMSC infusions at one-month intervals over a 24-week period. Safety outcomes included adverse events (AEs) and serious adverse events (SAEs). Clinical efficacy was assessed using the Visual Analog Scale (VAS), Simple and Clinical Disease Activity Indices (SDAI/CDAI), Health Assessment Questionnaire (HAQ), and American College of Rheumatology (ACR) response criteria. Serological makers including: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), IL-10, IL-17, TNF-α, and Treg/Th17 ratios were measured.

Results: BM-cMSC infusions were well-tolerated, with no SAEs reported. VAS scores improved in three patients, with two achieving sustained pain relief and quality-of-life enhancement. Four patients met ACR20 at week 16, while SDAI and CDAI scores indicated disease activity reduction in three patients. Anti-CCP and RF levels showed variable responses, with some increases not consistently correlating with clinical outcomes. Serological biomarkers showed mixed results; IL-10 increased in five patients, while pro-inflammatory markers TNF-α and IL-17 decreased in the same individuals.

Conclusions: BM-cMSC therapy demonstrated a favorable safety profile and potential efficacy in managing refractory RA. While preliminary results are promising, further studies with larger cohorts and long-term follow-up are needed to validate these findings and optimize therapeutic strategies.

Clinical Trial registration: IRCT20080728001031N29.

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KEYWORDS
Rheumatoid arthritis; clinical trial; regenerative medicine; mesenchymal stromal cells; Cell therpay

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6 Patients
6 Month F/U
No SAEs
Improvement (VAS, Disease activity reduction),
Increase in IL-10, TNF-α and IL-17 reduction.

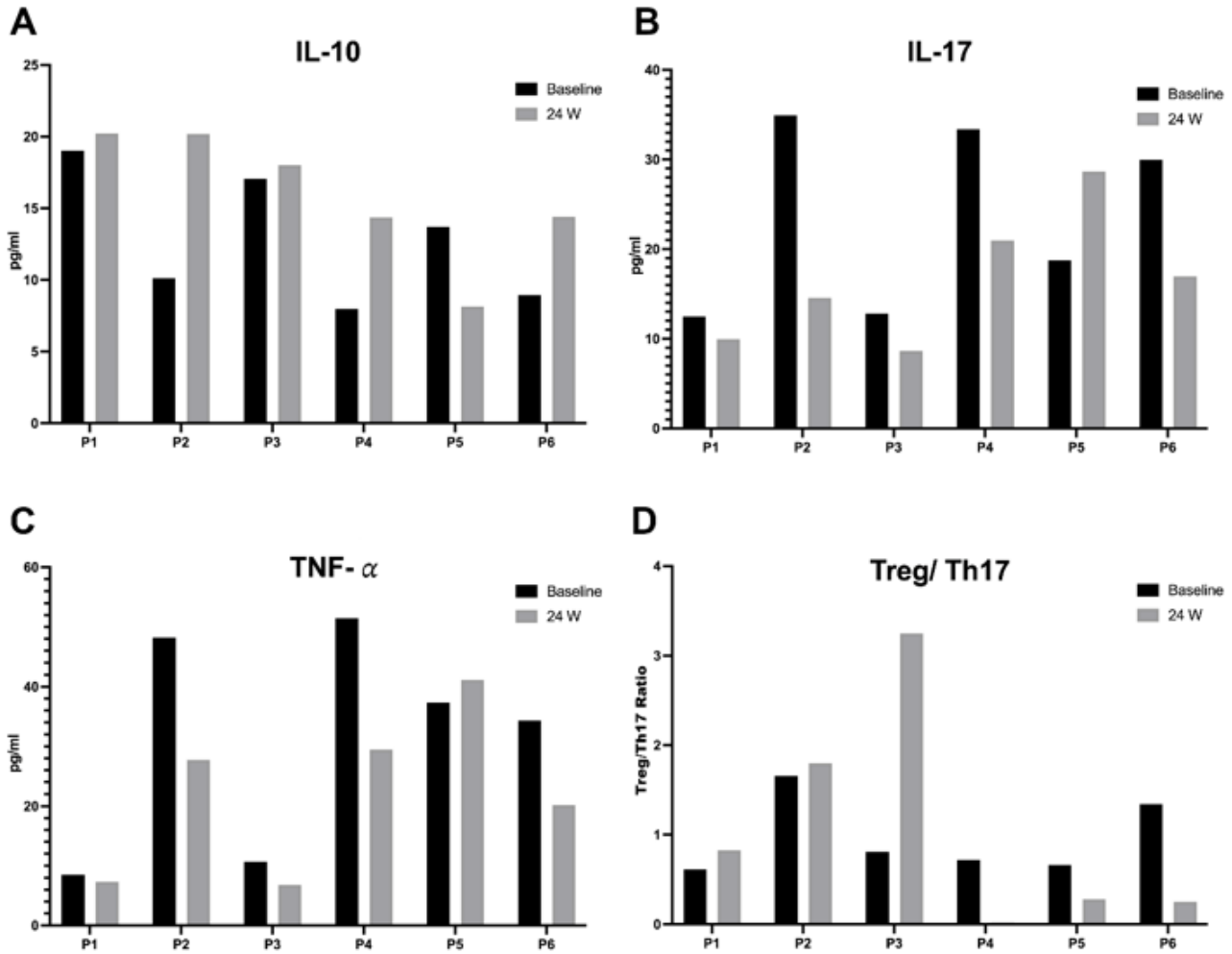

Figure S 1- Changes of inflammatory microenvironment of study patients. IL: Interleukin; TNF: Tumor necrosis factor; Th17: T helper 17; Treg: Regulatory T cells.

Thanks for your Attention!

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