

# Exploring the potential of Stem Cell Therapy for management of Rheumatoid Arthritis- Opportunities, Challenges and Future Prospective



Urvashi Panchal<sup>2</sup>, Sankalp Gharat<sup>2</sup> & Munira Momin\*<sup>1</sup>

1 SVKM's Dr. Bhanuben Nanavati College of Pharmacy, University of Mumbai, Maharashtra, India

2 SVKM's Shri C B Patel Research Centre for Chemistry and Biological Sciences, Mumbai, Maharashtra, India

munira.momin@bncp.ac.in

## Abstract:

Cell based therapies bid the potential of altering and treating the diseases which cannot be resolved or eased by the conventional methods, treatments and existing pharmaceuticals. Cell therapies are diversified depending on the types of cells such as Mesenchymal stem cells (MSC's), chimeric antigen receptor (CAR-T) cells and Regulatory T-cells (Treg). MSC's offer new prospects in the management of autoimmune disorders as they exhibit unique immunomodulatory properties, thus can serve as a promising approach in stem cell-based therapies for rheumatoid arthritis (RA). RA is an autoimmune disorder that causes degradation of the synovium membrane, causing pain, inflammation, and progressive destruction of bones and cartilage. The pathogenesis of RA is linked to dysregulation of adaptive and innate immunity. The rising incidence of rheumatoid arthritis is being attributed to changes in lifestyle and food habits. In clinical practise, conventional treatments such as antirheumatic drugs, steroid drugs, and biological agents are used. However, long-term use of these drugs causes side effects, and may develop drug resistance in some RA patients. Recent research on MSC-based therapy is seen as a viable strategy in the management of RA in this regard. Current advancements in MSC based pre-clinical and clinical studies and other strategies for enhancement of MSC's immunoregulatory properties are further discussed in the article.

**Keywords:** Cell therapies, Rheumatoid Arthritis, Mesenchymal stem cells, Inflammation

## Introduction:

Rheumatoid arthritis (RA) is an autoimmune disease that mainly affects the joints in the hands, wrists and knees. This chronic inflammation leads destruction of joints and if untreated leads to irreversible disabilities. The risk factors include genetics, environmental and socioeconomic factors. Apart from these, gender is also an important factor. Generally, RA is often two to three times as common in women than in men. The prevalence rate of RA is around 3 in 10,000 people, which rises with age and peaks between the ages of 35 and 50 (1). The annual incidence of RA is around 3 in 10,000 people, increasing with age and peaking between the ages of 35 and 50. RA affects roughly 14 million people worldwide (World Health Organization, 2021). In India, approximately 0.92% of adults have RA. Of these, 20 to 70 percent of patients become incapacitated 7 to 10 years after diagnosis (2).

In RA, the loss of cartilage over time, reduces the space between the joints and bones leading to a painful and unstable bone. This decreases joint mobility and an irreversible joint deformity (3). Conventional treatment strategies for RA include the use of Disease modifying anti rheumatoid drugs (DMARDs) and Non-steroidal anti-inflammatory drugs (NSAIDs). The first line of treatment includes a combination of Methotrexate (MTX) and glucocorticoids such as prednisolone. This combination has shown a benefit and improvement in RA. However, only 25% of patients experience remission. In addition, most of the patients develop side effects from these conventional therapies. These side effects include renal dysfunction, increased cardiovascular risk and nonspecific inhibition of immune responses, and obesity leading to further worsening of the condition. However, recent development in disease pathophysiology has led to new therapies including biological DMARDs, monoclonal antibodies, cytokine and chemokine inhibitors, several immune therapies, and stem cell therapies. Of these, stem cell therapies are gaining importance in the field of health care sector. It is the most recent and a growing area of research for the treatment of RA.

Stem cells are cells with self-renewal pluripotent ability. These cells can differentiate into several cell types depending either on the environmental factors or stimuli received. Stem cells can replace damaged and dead cells in the body. In RA, Stem cell therapy helps in reducing the inflammation of the joints and also increases the presence of healthy cells in the body. Mesenchymal stem cell (MSCs), a type of stem cell, has the ability to differentiate into bone and cartilage. Direct injection of MSCs into the tissues around the injured joints is the basis of synovial MSC therapy as shown in figure 1. MSCs can also suppress the immune system and lessen the body's inflammatory reaction. Because of this, MSC therapy represents a promising therapeutic alternative for autoimmune diseases like RA (4). Clinical proof-of concept studies have shown that management of RA with MSCs has a favourable safety profile. Stem cell based therapies may benefit patients who are not responsive to conventional therapies and are willing to lessen on their medication use, or want to try stem cell therapy first before starting a drug treatment. This article further focuses on recent developments, challenges and future perspectives of stem cell therapies for the management of RA.

### **Potential of MSC's for Rheumatoid Arthritis:**

Previous investigations have demonstrated a dramatic reduction in disease progression using several preclinical experimental models. Of them, collagen induced arthritis mice model is one of the most widely studied models. The encouraging findings from the experimented models have cleared the path for MSCs to become a promising therapy for RA. Adult bone marrow is the most common source of MSCs, followed by adipose tissue, umbilical cord and amniotic fluid. Apart from these, MSCs have recently been found in nasal tissues, amniotic fluid, gingiva, placenta, synovial fluid or membrane. The majority of RA preclinical research carried out uses MSCs derived from bone marrow cells.

In the preclinical studies, MSCs are delivered via intravenous (IV) and intraperitoneal (IP) routes. Alternative routes such as intra-muscular, subcutaneous, intranodal, intra-articular (IA) and peri-articular deliveries have been suggested with positive outcomes.

In these experimental models, the animals are dosed either once or several times during the disease progression. A usual dose is an infusion of 2-3x10<sup>6</sup> MSCs per animal. Numerous studies have demonstrated that injecting MSCs at the early stages results in greater efficacy. These findings show a decrease in inflammatory cytokine levels along with a lowering in autoantibodies against collagen. Additionally, the MSC therapy causes an increase in the levels of chemokine receptor 3-alternative (CXCR3), IFN-induced protein 10, and anti-inflammatory cytokines such IL-10 in blood and synovium. These outcomes have been demonstrated by MSCs to be independent of tissue origin and administration method. More interestingly, MSC-based therapies have been shown to reduce inflammation by 70% in most experimental models. Autologous MSC therapy in RA patients has an acceptable safety profile and shows promising clinical efficacy in the latest clinical studies completed by various researchers worldwide (6).

Other cell therapies being researched include (Treg) regulatory T-cell therapy and (CAR-T) chimeric antigen receptor cell therapy, in addition to MSC-based therapies. These therapies have also proven their beneficial effects so far. CAR-T cell based therapy has also been explored for the management of Rheumatoid Arthritis. Rheumatoid-associated helper T-cells were able to recognise the new CAR T cells when tested by the researchers. However, it was observed that the helper T-cells could only be triggered when the CAR T-cell carried the matching antigen. The pathogenic helper T cells were efficiently eradicated by the synthetic T cells as well. This treatment delayed the onset and severity of rheumatoid arthritis on mice when given early on in disease development (7).

### **Safety and Regulatory requirements:**

According to the "New Medications and Clinical Trial Rules, 2019" published in March by the Union Health Ministry, stem cell-derived products are to be considered as "new drugs". This implies that every physician using stem cell therapy must obtain an approval. Only bone marrow-derived blood stem cells can be used to treat various blood diseases and blood malignancies both. Studies on the clinical use of stem cells for additional diseases or stem cell types are continuously being studied (8). For the past 20 years, stem cell therapies have been under preclinical development. A constantly shifting regulatory environment has prevented the majority of these innovations from making the transition from the bench to the bedside. Despite the fact that the clinical safety of these therapies on a large scale has not yet been completely demonstrated, the overall number of patients who have safely received stem cell therapies is significant and growing. Since the safety profile of stem cells and present regulation are interwoven, understanding one requires understanding the other (9).

### **Challenges and Future Prospective:**

There are many challenges that need to be tackled if stem cell treatment is to advance more quickly. The challenges involve the manufacturing issues, genetic instability, stem cell culture conditions, stem cell distribution after transplant, pharmacological issues and many more (10). The promising results of the completed and ongoing clinical trials on MSCs for RA, support the fact that the stem cell therapy would prove as a better alternative to the existing therapies.

The rising frequency and recurrence of the disease are the primary factors anticipated to accelerate the growth of the stem cell therapy market for RA over time. Although, precise etiology for rheumatoid arthritis is unknown, some risk factors have been linked to the disease. In Hyderabad, a 67-year-old patient with severe arthritis recently underwent stem cell therapy instead of knee replacement surgery, and the treatment was proved to be successful (11). On the other hand, a face mask was developed in the Springs Rejuvenation Centre, Los Angeles to heal skin and grow collagen and also for treatment of burns and chronic wounds, the results have been shown to be astounding in terms of all aspects, gives a hope for further research on cell based therapies for other ailments as well as cosmetics (12). The global market for management of RA using stem cell therapy is expanding as a result of the development and inclusion of novel medicines in combination with cell based therapies. In the global market for rheumatoid arthritis stem cell therapy, North America is anticipated to hold a disproportionate amount of market share due to the presence of numerous important companies. Some of the key players in the global market for rheumatoid arthritis stem cell therapy are Mesoblast Ltd., Roslin Cells, ReNeuron Group plc, International Stem Cell Corporation, TiGenix and Regeneus Ltd. (13). With the improvements in the field of stem cells and the expanding market share, it is anticipated that more businesses can enter the field of cell-based therapies.

### **Conclusion:**

In RA, early diagnosis is necessary for prevention of severe damage of joints and loss of essential bodily functions. In-depth knowledge of disease mechanism has been made possible by advancements in MSC-based stem cell therapies, which is important for developing more effective treatment strategies. Given the complexities of the pathogenic processes underlying the disease, MSCs are a viable alternative strategy that has the potential to have significant immunomodulatory effects for the management of RA. The microenvironment, which is produced by factors secreted by immune cells both innate and adaptive, has an impact on MSCs' ability to develop either a pro- or anti-inflammatory phenotype. For better comparisons of outcomes among RA with MSC-based therapy, improvements in the harmonization of MSC treatment protocols in terms of large scale production, sources of MSCs, delivery routes and comprehensive assessment of the findings would be needed.

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