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CELL THERAPY AIMED AT RESTORING JOINTS IN RHEUMATOID ARTHRITIS

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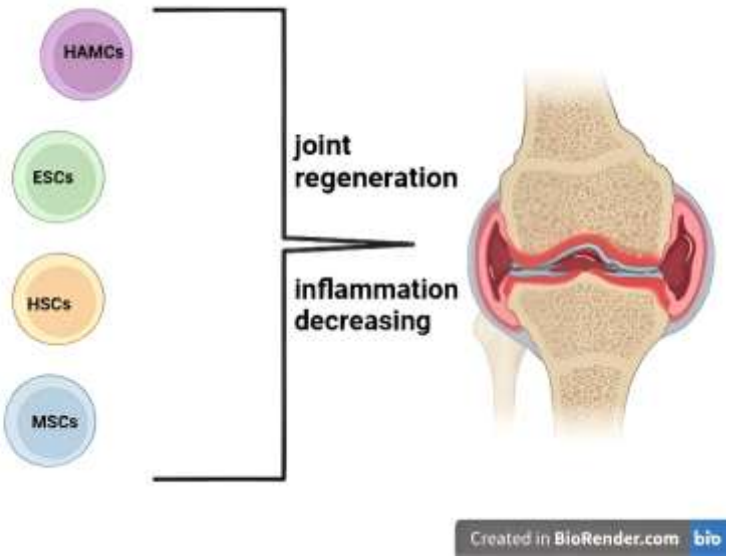
ABSTRACT
Autoimmune diseases, including rheumatoid arthritis, which is the most common rheumatic autoimmune disease, affect autologous connective tissues caused by the impairment of self-tolerance mechanisms of the immune system. Over the past two decades, cell therapy has been increasingly considered as a therapeutic option for various diseases. This is partly due to the unique properties of stem cells, which divide and differentiate from specialized cells in damaged tissue. Moreover, stem cells impart immunomodulatory properties that affect diseases caused by immunological abnormalities, such as rheumatic autoimmune diseases. This review will evaluate the efficacy of cell therapy with four major types of stem cells, including mesenchymal stem cells, hematopoietic stem cells, embryonic stem cells, and human amniotic membrane cells.



Different types of stem cells have high potential for the treatment of RA
HAMCs – human amniotic membrane cells
ESCs – embryonic stem cells
HSCs – hematopoietic stem cell
MSCs - mesenchymal stem cells

KEYWORDS: inflammation, joint, rheumatoid arthritis, stem cells, transplantation, chondrocytes

INTRODUCTION

Rheumatoid arthritis (RA) is a long-term, systemic illness that affects joints, muscles, tendons, connective tissues, and fibrous tissue. It also has a significant social impact. About five cases of RA are reported for every 1000 adult individuals globally. With a median age of 50, women are diagnosed with the condition 2-3 times more frequently than males [1]. Pre-RA phase, which precedes the onset of clinical symptoms by many months to years, is characterized by the presence of circulating autoantibodies, increased level of inflammatory cytokines and chemokines, and altered cellular metabolism [2]. Patients with the progressive type of the RA have severe, incapacitating chronic pain that lowers their quality of life. Insufficient care

exacerbates the illness and eventually causes the joints to erode, break down, and become malformed. In the past, over half of RA patients had increased mortality, disability, and incapacity to perform a full-time job. However, a deeper comprehension of the illness's pathogenesis and notable advancements in RA therapy have resulted in the creation of more potent therapeutic strategies that better manage pain, joint destruction, and disease activity [1].

In terms of RA treatment, glucocorticoids (GCs) and biological and synthetic disease-modifying antirheumatic medications (DMARDs) are now in use [3]. Non-steroidal anti-inflammatory medicines (NSAIDs) are the most often used medications for pain treatment in addition to them. Because of their strong anti-inflammatory properties, GCs are often taken in conjunction with NSAIDs or DMARDs [4]. DMARDs, one of the aforementioned conventional therapies, have demonstrated a strong ability to lessen RA patients' symptoms and stop the illness from progressing; yet, they are expensive and have significant adverse effects [5]. Furthermore, many patients endure clinically substantial signals of retained pain even after receiving therapy, and they continue to be intolerant of or resistant to these medications, despite the fact that several randomized controlled studies have demonstrated considerable pain reduction [6].

Advanced cell therapy can be viewed as an alternate approach to treat RA, due to the constraints of standard medications [7]. In this review, we examine the latest most promising studies in the field of cell therapy in rheumatoid arthritis, evaluate the mechanisms of action, and provide recommendations for future developments in this direction.

Model of pathological joint destruction in rheumatoid arthritis

Osteoclasts, osteoblasts, chondrocytes, synovial cells, and as well as different immune cell types such T and B cells make up joints. To preserve joint homeostasis, these cells collaborate and engage in interactions with one another [8].

Stage of RA targeting to joints

When RA affects joints, symmetrical small joints typically have a distinctive pattern of synovitis [9]. Following immunological activation, synovial inflammation manifests externally as joint swelling [10]. Leukocytes infiltrate the normal synovial compartment, and proinflammatory mediators are present in the synovial fluid. Fibroblast-like synoviocytes (FLS) interact with both innate immune system cells, including mast cells, monocytes, and macrophages, and adaptive immune system cells, including B lymphocytes (humoral immunity) and T lymphocytes (cellular immunity), resulting in an inflammatory cascade [11]. The development of RA, which leads to the failure of inflammatory clearance (chronic synovitis), is directly influenced by the interactions between innate and adaptive immunity. It has been discovered that monocytes and macrophages heavily penetrate synovial membranes and are crucial to the pathophysiology of inflammation [12]. In the setting of inflammatory RA, it is also important to take into account the distortions between proinflammatory M1 macrophages and anti-inflammatory M2 macrophages [13]. Dendritic cells (DCs) have also been observed to accumulate in the joint cavity [14]. T cell differentiation has been demonstrated to be induced by myeloid DCs [15]. Neutrophil NETosis and the stimulation of natural killer cells are examples of other potential innate immune mechanisms [16]. However, a lot of experts believe that the pathophysiology of RA illness is mostly driven by the adaptive immune system [17]. The antigen-mediated function of T cells and the production of cytokines by certain T cell subsets have garnered the majority of attention regarding their significance. The development of autoantibodies and the maintenance of chronic synovitis are primary causes of aberrant immunity in RA, and the absence of reactive oxygen species could drive proinflammatory T cells, highlighting the significance of energy metabolism in RA [18]. Effector CD4 T cells are also important in this regard. Research on B cells focuses on the presentation of antigens, the creation and release of antibodies, and the release of cytokines into the environment [19].

Hyperplastic synovial membrane

Distinctive cells called SLC and macrophages generated from bone marrow combine to form the synovial membrane [20]. Synovial cells maintain the integrity of joints by reprocessing waste products and depositing lubricant and hyaluronic acid to hydrate joints and maintain their normal condition [20]. Hyperplastic synovium is the outcome of SLC dysfunction in RA. Loss of contact inhibition, that produces inflammatory cytokines and proteases including matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), promote joint deterioration, is the cause of abnormal SLC proliferation in RA [21]. They provide a milieu that endorses neutrophil accumulation, T cell and B cell survival [22]. The idea that pathway-specific resistance to apoptosis is the source of hyperplastic synovium is probably another one [23]. These pathways include aberrant p53 tumor protein function, which in RA leads to synovial growth and joint degeneration; in RA synovial tissues, elevated heat shock protein 70 expression and enhanced heat shock factor 1 activation, which support FLC survival [24]. Its anti-apoptotic properties drive the synoviolin/Hrd1 murine model of synovial cell growth. In lethally irradiated animals after bone marrow transplantation, synovial hyperplasia appears to be associated with infiltration of bone marrow-derived cells and propagation of resident slowly deviding cells, such as mesenchymal stromal/stem cells [25].

Cartilage damage

Synovial joints depend on on cartilage, which is made up of chondrocytes and a thick, well-organized extracellular matrix (ECM) that these chondrocytes create and that contains type II collagen and glycosaminoglycans (GAGs) [26]. In RA, hyperplastic synovium targets adhesion and invasion, leading to significant cartilage destruction [27]. On the other hand, inflammatory signals—including those that come from the ECM—can increase the FLC's activity. MMP, a disintegrin-like metalloprotease with thrombospondin type 1, 4, and 5 motifs, and cathepsins are mediators of cartilage destruction [28]. FLC produces MMPs, which have the ability to encourage the type II collagen network's disintegration and result in biomechanical failure. It has been proposed that the main protease responsible for breaking down cartilage's collagen matrix is membrane type I MMP [29]. The articular cartilage itself, however, lacks adequate capacity for regeneration. Consequently,

chondrocytes eventually disappear from the cartilage due to apoptosis, which is influenced by synovial cytokines, specifically IL-1 and 17A, and reactive nitrogen species [30]. This leads to cartilage breakdown, which is readily seen as joint space shortening on radiographs [31]. These findings might contribute to the understanding of how RA is a type of systemic autoimmune disease, wherein articular joints experience unique cellular activation of FLC due to early cartilage degradation in the setting of changed immune initiation [32]. But a deeper comprehension of the processes behind cartilage deterioration is needed.

Bone erosion

Bone loss is a pathological characteristic of RA and presents as regional, intraarticular, and systemic bone loss. Osteoblast inhibition and osteoclast induction lead to bone loss. "Periarticular" bone loss most likely relates to cellular alterations in the subchondral bone marrow, such as osteoclast differentiation and inflammatory infiltrates [33]. Whether inflammatory response or autoimmune disorders is the primary cause of bone loss is still up for debate. Tumor necrosis factor alpha (TNF-α), IL-6, IL-1β, IL-17, and other inflammatory cytokines associated in RA are evidence supporting the classic inflammatory hypothesis [34]. In the right context, these cytokines can repress bone formation and exhibit pro-osteoclastogenic effects through signals like macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-B ligand (RANKL). In the setting of inflammation, they encourage the inflow and maturation of monocytes into osteoclasts, and in RA, anti-inflammatory medication halts the advancement of bone loss and vice versa [35].

There are two autoimmune processes associated with RA that might produce structural bone destruction, which is the second potential route of bone loss. The first pathway is mediated by Fc receptor-driven osteoclast differentiation and immune complex formation. Second, osteoclasts become appropriate antigenic targets for anti-citrullinated protein antibodies (ACPA) as a result of the production of anti-citrullinated vimentin antibodies directed to the most citrullinated protein. The binding of ACPA to osteoclast precursors has been shown to stimulate osteoclastogenesis, bone resorption, and bone degradation [36]. Actually, a gap is created is by bone resorption and is usually located where the synovial membrane enters the periosteum [37]. Based on certain anatomical characteristics, this region is referred to as the bald area. Subchondral bone serves a key role in preserving weight-bearing joint physiology, and subchondral bone degradation may ultimately contribute to articular cartilage deterioration [38]. Human bone marrow edema is frequently observed in the subchondral bone area during the early stages of RA, and in animal models, the initiation of joint deterioration in RA has been linked to transforming growth factor-β (TGF-β) in subchondral bone [39].

Analysis of cell therapy studies in rheumatoid arthritis to restore joints

Mesenchymal Stem Cell Therapy for RA

Adult multipotent stem cells with fibroblast-like shape are called mesenchymal stem cells (MSCs). MSCs are taken into consideration for the therapy of autoimmune illnesses because of their immunomodulatory qualities [40]. Research conducted in vitro demonstrates that MSCs have the capacity to alter the innate immune system's cell activities. In addition to causing inflammation, these cells also stimulate T and B cells in the adaptive immune system [41]. Rheumatoid factor (RF) is produced by B cells that develop in RA, and they also function as antigen-presenting cells (APCs) to stimulate T lymphocytes [42]. The number of CD4+CD25+FoxP3 T regulatory cells, however, increased two-fold when MSCs were co-cultivated with T cells, B cells, and T regulators. In addition, MSCs blocked CD3+ T cell-mediated TNF-α release and boosted IL-10 synthesis [43].

According to preclinical research, allogeneic MSCs were administered more advantageously than autologous MSCs [44]. Through their connections with lymphocytes as well as through paracrine pathways, MSCs have the ability to decrease inflammation. Macrophages are among the innate immune cells that are crucial to the pathophysiology of RA. It has been demonstrated that RA patients' synovium contains phagocytically active, proinflammatory macrophages [45]. According to these findings, RA patients' synovial macrophages can affect T cell activation, which in turn affects B cell activation and migration, which in turn triggers an inflammation [46]. MSCs have an impact on macrophage polarization in this way, which keeps pro- and anti-inflammatory phenotypes in check. MSCs constitutively generate IL-6, which polarizes pro-inflammatory M1 macrophages toward anti-inflammatory M2 macrophages that produce IL-10, either by themselves or in conjunction with pro-inflammatory cytokines like IFN-γ. High concentrations of TGF-β1 and IL-10 are secreted by M2 macrophages, which encourage tissue regeneration and reduce inflammation [47]. Cell-cell contact processes and the synthesis of soluble molecules including IDO, PGE2, IL-10, and COX-2 are probably what start polarization. For instance, research found that MSCs increased the generation of M2 macrophages while inhibiting the growth of M1 macrophages [48]. Moreover, in mice with collagen-induced arthritis (CIA), MSCs inhibited the nucleotide-binding domain, leucine-rich repeat pyrin 3 (NLRP3), inflammasome-mediated IL-1β secretion, and caspase-1 production in macrophages through the IL-1β feedback loop [49]. Furthermore, osteoblast and osteoclast action are controlled in healthy settings, promoting appropriate levels of bone production and resorption. In contrast, increasing osteoclast in RA further exacerbates bone deterioration [50]. Additionally, synovial fibroblasts are activated by TNF-α and IL-1β released by proinflammatory macrophages, leading to the release of receptor activator of NF-κB ligand (RANKL) and macrophage colony-stimulating factor 1 (M-CSF) [51]. These elements are necessary for the production of osteoclasts. Accordingly, MSCs prevented systemic bone loss in CIA mice by inhibiting RANKL-induced osteoclastogenesis and reducing osteoclast precursors in the bone marrow [52].

Eighteen clinical studies have examined various MSC-based treatments for the treatment of RA [53]. The remaining clinical studies have been finished and published, however nine of these trials are currently in progress. The primary goal of clinical studies examining the therapeutic potential of MSCs derived from diverse tissue sources has been to evaluate the effectiveness and safety of MSC transplantation in RA. According to preliminary clinical research, individuals with refractory RA can be safely and effectively treated with both autologous and allogeneic MSC transplantation [54]. In these clinical studies, none

of the RA patients experienced any major side effects [54]. MSC-treated patients saw a notable improvement in their symptoms, a modest drop in serum inflammatory markers, and a complete remission of their illness [54]. Furthermore, studies involving MSC-treated RA patients have shown that the therapeutic benefits have a consistent clinical result for up to three years, demonstrating the long-term safety and effectiveness of MSC-based therapy [55 - 61].

Hematopoietic stem cell transplantation in RA

According to one study, bone marrow transplantation (BMT) clearly had a therapeutic impact on rats with advanced stage RA [62]. Total body irradiation was used in conjunction with BMT as a conditioning regimen in this trial, which led to a long-term remission of the illness. Hematopoietic stem cell transplantation (HSCT) was presented in this study as a possible treatment for RA. A small number of patients participated in the first human research in this field, and the findings were reported as case reports. The first HSCT was carried out in RA patients by Jacobs et al. in 1986 and Yoske et al. in 1997, who included a male RA patient and a female RA patient with aplastic anemia. Both trials' findings showed that RA symptoms have improved. Further research on the therapeutic benefits of HSCT in RA was made possible by these trials [63].

Cyclophosphamide is frequently used in HSCT as a pre-transplant conditioning regimen. Clinical indices such as DAS-28, ACR, and HAQ-DI are evaluated, together with molecular markers, to determine the effectiveness and responsiveness of patients with RA to HSCT therapies [64]. Fifty percent of RA patients exhibited a substantial decrease in disease activity, according to the DAS 28 evaluation. Additionally, it was shown that 67% of RA patients had an ACR of 50% six months following HSCT [65]. HAQ-DI is an additional criteria used to evaluate the functional state of RA patients. The HAQ-DI index significantly decreased in RA patients treated with HSCT during the course of long-term follow-up. Furthermore, following HSCT, patients' 5-year overall survival and relapse-free survival rates were 94% and 18%, respectively [63]. All these findings imply that HSCT could help certain RA patients to slow down the disease exacerbation.

The immunological impact of high-dose chemotherapy (HDC) and HSCT on RA patients' synovial tissue was examined in another study [66]. At three and six months following transplantation, RF IgM and anti-cyclic citrullinated peptide (ACP) antibody levels dropped, but they rose once more at one year. This is most likely caused by the body's inability to fully eliminate autoreactive B cells, which result in autoantibodies and prevent RA patients from recovering fully following transplantation. However, in individuals receiving treatment, human Ig, CRP, and other inflammatory biomarkers decreased. The impact of HDC and HSCT on joint injury was examined in another research [67]. In the first year following transplantation, there was a notable reduction in both joint degeneration and CRP, which may indicate a reduction in T cell invasion into the synovium. Joint injury and osteoclast activity are inhibited as a result [63].

Two patient groups underwent differentiated HSC transplants: one group got CD34+ stem cells depleted from T cells, while the other group got untampered HSCs. This was done because it was thought that the decrease of autoreactive T cells in infused HSCs could increase the effectiveness of treatment. The findings indicated that there was no significant difference in the ACR score or the length of remission between the two groups, indicating that the therapeutic effectiveness of HSCT is not significantly impacted by T cell reduction from HSCs [68].

Embryonic stem cells in RA

Embryonic stem cells are located in the inner cell mass of the human blastocyst, an initial stage of the growing embryo that occurs between days four and seven following conception. In normal development, they start forming the three layers of embryonic tissue and vanish by day seven [69]. The first effective experimental production of human embryonic stem cells occurred in 1998. The capacity of embryonic stem cells to continuously self-renew, or produce additional multipotent cells like themselves, has been shown to be remarkable under the right culture circumstances [70].

According to research on transplantation, embryonic stem cells (ESCs) can inhibit the local immune response by interacting with other cells. Genomic instability and an rise in MSC antigenicity are caused by the constraints of mature MSCs and the long-term procedure for their proliferation. The impact of MSCs produced from human embryonic stem cells on the restoration of animals with CIA was examined in the study [71]. According to the findings, this type of therapy stimulates Treg, Th1, and IDO-1 cells, which lessens the disease's severity and progression [70].

The stage-specific embryonic antigen-3 positive cell, which functions as a blood stem cell, is another cell whose therapeutic impact has been investigated in RA. According to this research, such cells can be detected in synovial tissue even in diseases like RA. These cells were isolated from RA patients' synovium, cultivated, and then injected intravascularly into mice. They were found to obtain an arresting action on joint degeneration and arthritis [72].

Human amniotic membrane cells in RA

In vitro, human amniotic membrane cells (HAMCs) have immunosuppressive properties, including decreased activation and proliferation of lymphocytes, maturation of dendritic cells (DCs), generation of inflammatory cytokines, and induction of M2 macrophages and Tregs [73]. By administering HAMCs to cells derived from RA patients in CIA mice, the immunosuppressive capabilities of such cells were examined [74]. The findings demonstrated Th1/Th17 pathway suppression and an inflammatory synovial response. Peripheral Treg formation was stimulated and inflammatory chemokine and cytokine production was decreased in treated CIA mice. Therefore, HAMCs could be a desirable option for RA cell treatment [75].

Benefits and Limitations of Cell Therapy for Joint Restoration

There are several restrictions when it comes to using MSCs to treat RA, even given the encouraging outcomes of clinical trials. Initially, the majority of research was carried out on RA patients who were enrolled from a single facility, occasionally without a placebo control group. Furthermore, there was a dearth of patient enrollment in several clinical trials intended to

assess efficacy and safety. Consequently, to validate the present clinical evidence on the effectiveness of MSC treatment, a multicenter controlled trial including a large number of RA patients is required.

Second, there isn't yet a perfect technique for using MSCs to treat RA. This is caused by a variety of factors, including the inconsistent MSC sources as well as the various doses, treatment plans, and delivery methods employed in clinical studies. When taken as a whole, these discrepancies in trial designs have made it challenging to compare therapy results [76]. Nonetheless, the majority of clinical research has demonstrated that, irrespective of the mode of delivery, the therapeutic effectiveness of MSCs is attained at a dose of a minimum of 1×10^6 cells/kg body mass following one or more injections. Despite the dose-response relationship demonstrating a therapeutic impact, there is currently no well-defined and efficacious therapy strategy for RA using MSCs. Thus, in subsequent clinical studies, treatment plans and dose modifications should be thoroughly investigated.

Third, it is well recognized that MSC therapy is a costly course of treatment. Long-term medication therapy, however, causes 15–40% of RA patients to become resistant to the medications and increases the likelihood of side effects, both of which are detrimental to the patient's health. Finalized clinical trials have demonstrated that MSC infusion is a safe, efficient method of treating RA patients without causing major adverse effects. Additionally, while employing cell preconditioning techniques to increase the immunomodulatory and anti-inflammatory qualities of MSCs may not increase therapeutic effectiveness, it may lower the cost of MSC manufacturing for the purpose of effectively treating RA patients [77].

The safety of HSCT has been demonstrated by studies that found minimal rates of toxicity and death in individuals with severe RA who received high-dose chemotherapy before HSCT. Early disease recurrence is frequent even with HSCT and HDC's safety and partial effectiveness. Following HSCT, RF-positive individuals have been demonstrated to have a greater risk of illness recurrence. Notwithstanding the possibility of increased infections and mortality, a robust immunosuppressive program is employed during disease relapse in order to eradicate autoimmune memory cells and so manage the illness [78]. Three months following HSCT, patients who have high amounts of expressed receptors such as CD3, CD4, CD27, and CD45 on the surface of their T cells in synovial tissues react better to therapy, according to the results of synovial immunohistochemistry. A drop in T cells and a partial improvement in the illness are observed following HSCT. However, HSCT therapy does not work for individuals with high levels of IL-1 production and no T cells in their synovial regions [79]. These findings imply that the immunological makeup of synovial tissues harvested by biopsy might be a predictor of how well HSCT therapy would work.

Future research directions

With the accumulation of evidence and the development of technology, cell therapy has shown preliminary therapeutic potential for RA. However, careful preclinical and clinical studies are needed to apply cell therapy in clinical practice, as such a new practical therapeutic strategy still faces many challenges. The majority of research on stem cell-based treatment methods focuses on assessing safety and effectiveness; the formulation, dosage, such pharmacological parameters frequency, and mode of administration are yet unknown.

Additionally, a lot of research is presently being done to create fresh approaches to maximize stem cells' potential for therapeutic application in the treatment of RA. Various approaches have been suggested thus far to improve MSCs' immunomodulatory and anti-inflammatory capabilities in RA [80]. These include co-culturing techniques, cytokines and growth factors, receptor agonists, hypoxia, autophagy, and culture method alterations including 3D culture. The genetic alteration of MSCs is an entirely distinct strategy [81]. Genetically designed constructs, such as viral vectors or plasmids, influence genes that increase cell survival, immunomodulation, and regeneration [82].

Hypoxia and autophagy are two more effective ways to boost the immunomodulatory effects of MSCs in the therapy of RA. The prospective use of autophagy and hypoxic conditions in future MSC-based RA treatments is supported by recent discoveries. According to some research, autophagy is crucial for defending MSCs from reactive oxygen species (ROS) that are produced after oxidative stress or radiation. By upregulating produced immunoregulatory molecules such PGE2 and IDO, hypoxic preconditioning improves the immunomodulatory actions of MSCs [83]. Similarly, it has been demonstrated that priming human MSCs with hypoxia or IFN-γ inhibits the growth of CD4+ and CD8+ T cells. On the other hand, hypoxia and IFN-γ administration together effectively inhibited T cell growth and markedly raised IDO expression. The fact that treatment with one of the aforementioned priming variables alone had a lower impact indicates that proinflammatory cytokines and hypoxia may work better together to boost the immunomodulatory function of MSCs [84].

Priming with proinflammatory cytokines is another interesting approach to MSC preconditioning. This strategy is predicated on the observation that MSC function as sensors of inflammation, which can greatly augment their immunomodulatory and immunosuppressive characteristics [85]. When proinflammatory cytokines are abundant, MSC become activated and exhibit a marked immunosuppressive phenotype as a result of producing significant quantities of anti-inflammatory mediators, including PGE2, IDO, TGF-β, HGF, NO, and heme oxygenase. In light of these occurrences, MSC's immunosuppressive capabilities are boosted by preconditioning cells with elevated levels of proinflammatory cytokines. For instance, some research has shown that MSCs pretreatment with IFN-γ and/or IL-1β were more successful than untreated MSCs in reducing T cell proliferation, degranulation of CD8+ T cells, activation of NK cells and macrophages, and production of proinflammatory cytokines (TNF-α, IFN-γ, and IL-2) by activated T cells [86].

CONCLUSIONS

All of these findings point to the potential of cell treatment to reduce the severity and activity of RA in both people and animal models. Cell treatment changed immunological characteristics in help to manifistation of disease conditions betterment and improved clinical symptoms of illnesses. Additionally, cell treatment is safe, however there have been some documented side effects. Despite the apparent efficacy of cell therapy in the treatment of RA demonstrated in many studies,

some issues including the choice of tissue from which stem cells should be extracted, autologous or allogeneic or xenogeneic cell origin, the type of stem cells such as MSCs or HSCs, disease prognostic factors remain largely unknown and should be addressed in future studies to improve the therapeutic efficacy of cell therapy including stem and non-stem cells and minimize transplant complications.

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