RESEARCH PAPER

CELLULAR THERAPIES FOR AUTOIMMUNE RHEUMATIC DISEASES

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Abstract
Autoimmune rheumatic diseases (ARDs) such as systemic lupus erythematosus and rheumatoid arthritis (RA) arise from aberrant immune responses that lead to chronic inflammation and tissue damage. Conventional treatments, including biological disease-modifying antirheumatic drugs (bDMARDs), often provide limited effectiveness, failing to achieve lasting remission and sometimes causing significant adverse effects. This review aims to explore the transformative potential of innovative cellular therapies, particularly Chimeric Antigen Receptor (CAR) T cell therapy, which was initially developed for cancer treatment but may be repurposed to target and eliminate autoreactive immune cells in ARDs, thereby restoring immune balance. We synthesize current research on various cellular therapies such as stem cell therapy (SCT), tolerogenic dendritic cells (tolDCs), and regulatory T cell (Treg) therapy, focusing on their unique mechanisms of action and therapeutic effects in the context of RA. Emerging evidence from preclinical and clinical studies will be highlighted, along with the implications of epigenetic modifications that enhance the immunoregulatory potential of these therapies. While preliminary findings show promising efficacy in the management of RA, further research is crucial to establish safety profiles, clarify mechanisms of action, and evaluate long-term outcomes associated with these advanced treatments. Ultimately, this review emphasizes the critical role of cellular therapies in addressing the unmet needs of rheumatoid arthritis patients and outlines future research directions in this rapidly evolving field.

Keywords: CAR-T Cell Therapy, Mesenchymal Stem Cells (MSCs),Regulatory T Cells (Tregs),Dendritic Cells (DCs),cellular therapy,immune modulation
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Introduction

Connective tissue autoimmune syndrome like rheumatoid arthritis, disseminated lupus erythematosus, inflammatory myopathies, scleroderma, inflammation of blood vessels, and immune system attacks joints are a classification of diseases caused by an abnormal immune response [1-3]. In these diseases, the body's defenses incorrectly target and damages the body's own organs and flesh due to the presence of autoantibodies, which are triggered by factors such as genetics, infections, or environmental influences. The symptoms of autoimmune rheumatic diseases (ARDs) can differ significantly, but they often affect internal organs, leading to serious health issues and, in some cases, even death. While new treatments, particularly biological disease-modifying antirheumatic drugs (bDMARDs), have improved disease management, many patients still do not respond well to these medications. As a result, they continue to suffer from uncontrolled symptoms. Moreover, the immunosuppressants which are now in use can cause significant side effects and are not always effective in achieving long-term remission [4,5].

An artificial t cell receptor therapy is a rapidly evolving and innovative cure. It works by altering a patient's t lymphocytes with a virus to insert a specific Chimeric Antigen Receptor (CAR) protein. It functions by altering a patient's T cells with a virus to insert a specific CAR protein. These engineered T cells can then find and kill cells that have a certain antigen, which leads to strong immune responses against tumors [6-8]. This therapy has demonstrated impressive results in haematopoietic malignancies comparable with lymphoma, a cancer affecting the blood and bone marrow, and a cancer originating in plasma cells, as well as in some solid tumors. In some cases, it can even lead to a long-term remission or a cure [9-11].

Although an artificial t lymphocyte receptor therapy was initially developed to treat cancer, research has shown that it could also be a promising option for rheumatic autoimmune diseases. This is because CAR-T cells can target and remove immune cells that

are abnormally active or help restore balance in organs affected by immune system dysfunction [12-14]. Rheumatic autoimmune diseases often involve improper immune responses that cause chronic inflammation and tissue damage, so using CAR-T cells to specifically eliminate the cells driving these issues might minimize inflammation and improve results for patients [15-17]. However, this area of research is still new, and more investigation are needed to determine how safe and effective an artificial t lymphocyte receptor therapy is for inflammatory disorders. In this review, we will conclude the current research on an artificial t lymphocyte receptor therapy for autoimmune rheumatic diseases, discussing its potential advantages and limitations. In Table 1, we provided the summary of various cellular therapies for ARDs.

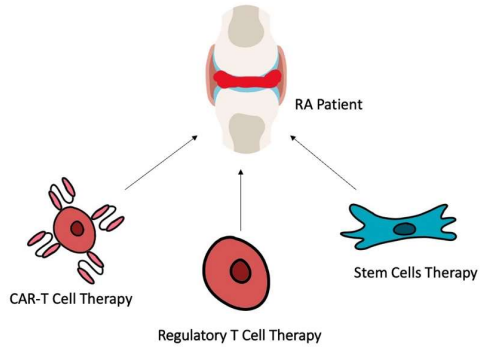

Figure 1. Main cellular approaches to ARDs treatment, example of RA.

Table 1. Summary of Cellular Therapies for Autoimmune Rheumatic Diseases (ARDs)

Therapy	Mechanism	Therapeutic Effects	Clinical Evidence
CAR-T Cell Therapy	Alters patient T lymphocytes to express a specific CAR protein, enabling them to target and eliminate autoreactive immune cells [6-8]	Aims to restore immune balance and has the potential to address autoimmune diseases by modifying T cells to target autoantigens, thereby reducing chronic inflammation [18,19]	Significant success has been observed in oncology, particularly in treating refractory and relapsed blood cancers. Emerging studies suggest promise in expanding this therapy's application to autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [15-17,20,21].
Stem Cell Therapy (SCT)	Regulates immune response through immunomodulation by targeting specific immune cells and promoting Treg differentiation [22-27]	Reduces disease activity and enhances differentiation of Tregs, as well as improves symptoms in patients with RA during and post-infusion with autologous and UC-MSCs [28-31]	Both autologous BM-MSCT and UC-MSC therapies improve RA symptoms, contributing to reduced disease activity and inflammatory markers post-infusion [32-35]
Tolerogenic DCs (tolDCs)	Modulates T cell responses by promoting anergy in effector T cells, achieved through pharmacological modification of dendritic cells to enhance immune tolerance [36,37]	Induces regulatory T cells (Tregs) and lowers inflammation, with tolDCs showing promise in inhibiting pro-inflammatory cytokine production and reducing arthritis severity in animal models of	Early clinical trials indicate that autologous tolDCs administered intra-articularly may be safe and could potentially induce immune tolerance, with initial studies showing reduced arthritis

Therapy	Mechanism	Therapeutic Effects	Clinical Evidence
		rheumatoid arthritis [38,39]	severity in murine models [39,40]
Regulatory T Cells (Tregs)	Expands Tregs to suppress effector immune responses, promoting immune regulation and counteracting proinflammatory environments [41-43]	Alleviates autoimmune pathology, promotes tissue repair, and reduces osteoclast-mediated bone destruction, thereby preventing joint damage [44-49]	Positive outcomes have been seen in early clinical trials for graft-versus-host disease and autoimmune diseases, including significant efficacy in CIA models, which are relevant for studying RA [47-49]

Immunotherapy

Mechanisms of Immunotherapy

Immune system attacks joints as a long-lasting inflammatory disorder that causes joint inflammation. In rheumatoid arthritis (RA), this inflammation leads to the growth of abnormal tissue, called pannus, which damages gristle and os. The disease influences about 1% of the global population and is greater common among women compared to men. An exact cause of RA isn't fully understood, but certain factors, like the presence of arthritic aspect and a disparity among different types of immune cells (Th1/Th2 and Th17/Treg), are linked to the disease, leading to persistent inflammation [50-52]. Some inflammatory substances, like cytokine involved in cell signaling: tumor necrosis factor-alpha (TNF-alpha), a cytokine involved in various inflammatory processes interleukin-1 (IL-1), and cytokine playing a role in mediating inflammation interleukin-17 (IL-17), contribute to the disease, while others, like interleukin-10 (IL-10) and tumor growth factor beta (TGF-β), help reduce inflammation. Apart from immune cells attacking the joints, changes in certain cells in the joint lining, called synovial membrane cells, largely influence on damaging cartilage and bone [53-55].

In the last ten years, traditional treatments like medications for rheumatoid arthritis, among which are amethopterin, and organic treatments like biologic drugs blocking the activity of TNF-alpha have been proven to treat RA patients. If these conventional and biological therapies are not recommended for patients, they might be prescribed stem cell therapy (SCT) [56-58].

CAR T Cell Therapy

Immunotherapy with genetically engineering a patient's own T cells represents a main progress in oncology medication, offering a personalized and targeted approach. Unlike standard oncology therapies such as irradiation methods and ray therapy, which can harm normal cells, Immunotherapy with genetically engineering a patient's own T cells aims definite inoculations present on malignant cells, reducing side effects [59,60].

Immunotherapy with genetically engineering a patient's own T cells has demonstrated significant success in treating refractory and relapsed blood cancers. Patients with conditions like hematologic malignancies have experienced a long-term remission due to the capacity of immunotherapy with genetically engineering a patient's own t cells to persist and proliferate in the body [19,20].

The process of immunotherapy with genetically engineering a patient's own t cells involves several key steps. The first is collection. A plasma specimen is taken out of an individual, and t lymphocytes are separated. The second step is engineering. genetic sequences are introduced into the T cells using various gene delivery systems, creating CAR-T cells. The next stage is enlargement. The developed CAR-T lymphocytes are expanded in the research center. After this comes injection. The enlarged genetically engineering a patient's own T cells are returned to the individual. The last step is targeting [61,62]. In the individual's flesh, genetically engineering a patient's own T cells identify and focus on oncology cells which express the specific immune trigger, leading to the destruction of those cells. Since the development of genetically engineering a patient's own T cells, various constructs have been explored to improve their effectiveness. The single-chain variable fragment (scFv) is commonly used for antigen recognition, but newer constructs such as designed ankyrin repeat alternative binding domains that can be used to design novel Chimeric Antigen Receptors are being developed to treat existing restrictions [6,63,64].

Immunotherapy with genetically engineering a patient's own T cells has evolved across different formations. The initial CARs formation includes an extracellular and intracellular parts of Chimeric Antigen Receptors enabling CAR-T cells to identify and kill cancer cells, The next CARs formation adds an intracellular signaling region to improve critical processes in the immune response. The evolution in Chimeric Antigen Receptor T cell therapy feature signaling components inside the CAR for even higher antigen recognition. The fourth/Next-generation CARs may include extra components like cells releasing cytokines to enhance productiveness, protection, and flexibility [65-67]. New approaches

are also being developed, such as an advanced form of immunotherapy with genetically engineering a patient's own T cells which focus on different proteins or molecules on the surface of cancer cells for broader productiveness, universal genetically engineering T cells, designed to be used across different patients without needing to match specific antigens, genetically engineering T cells with a safety mechanism that allow control over activation or deactivation of genetically engineering T cells, maintaining immune homeostasis cells, which modify Tregs to modulate natural defenses, genetically engineered T cells aim autoantigens, potentially useful in autoimmune diseases [21,22].

These innovations aim to overcome existing challenges, expand biomedical use, and refine the safety and effectiveness of Immunotherapy with genetically engineering a patient's own T cells for an increased number of illnesses, including ARDs.

Tolerogenic Dendritic Cells (tolDCs)

Hilkens and Isaacs created a procedure producing specialized subset of dendritic cells inducing and maintaining immune tolerance for treating autoimmune joint damage [68]. This was achieved by pharmacologically modifying antigen-presenting cells that bridge innate and adaptive immunity. with substances reducing the strength of the immune system, including a synthetic corticosteroid, the active form of vitamin D, and a component of the outer membrane of gram-negative bacteria agonist (Lipid A+ Core oligosaccharide+ O-antigen). The resulting tolerogenic dendritic cells (tolDCs) exhibited the following characteristics: the first one is greater presence of major histocompatibility complex on the surface of certain immune cells compared to adult DCs; the second is medium generation of molecules interacting between antigen-presenting cells (APCs) and T cells like a glycoprotein B7-1and a glycoprotein B7-2 with miserable levels of co-stimulatory protein on the surface of immune cells and glycoprotein expressed on the surface of dendritic cells, and the third is an increased production of anti-inflammatory cytokines, involving significant grades of an anti-inflammatory cytokine produced by macrophages and multifunctional cytokine produced by t lymphocytes, and miserable or unnoticeable grades of phlogistic interleukins such as pro-inflammatory cytokine primarily produced by activated macrophages, heterodimeric cytokine composed of two subunits, and a key mediator of inflammation.

The involvement of members of the Toll-like receptor family, in the crucial process promoting immune tolerance and modulating immune responses serves such purposes as: (1) the stimulation of a crucial component of the innate immune system is important for tolDCs to treat and introduce outward antigens on heterodimeric proteins composed of alpha and beta chains, a function also observed in immunogenic dendritic cells (DCs). Without a proinflammatory signal like endotoxin in the process of immune trigger consumption, heterodimeric proteins composed of alpha and beta chains may not form successfully. (2) TLR-4 activation also enables tolDCs to relocate in a biological process relying on the chemokine receptor towards peripheral immune organs, in which cooperation with t lymphocytes is possible [69]. While this mobile ability plays a vital role in inducing immune tolerance in general, its necessity in RA remains uncertain, as evidence from transplantation models suggests that CCR7 expression in tolDCs can prolong allograft survival.

In RA, where synovial membrane is passed through by T lymphocytes and macrophages, including DCs, it is likely that autoantigen presentation occurs within the junction itself. For this reason, it is assumed that tolDCs in autoimmune joint damage should perfectly function both in diseased joints to induce anergy in T lymphocytes activated in response to specific antigens and in the lymph receiving lymphatic fluid from a particular area of the body to stimulate regulatory T cells (Tregs) from lymphocytes that have not yet encountered their specific antigen [70,71]. Nevertheless, T cells from RA patients might resist some tolerogenic signals, like IL-10 and IDO. TolDCs, which operate at least partly through TGF-β, have been shown to inhibit the growth and a key pro-inflammatory cytokine production of lymphocytes originated from hematopoietic stem cells artificially, but it is still unclear whether they can prevent lymphocytes recognizing self-antigens in arthritic joints [71].

Although tolDCs have a similar ability to process and present exogenous antigens as mature DCs, they have a lower capacity to stimulate T cells due to their miserable exhibition of proteins providing necessary second signals for T cell activation and reduced generation of immune response amplifiers. Besides, tolDCs can provoke immune response, or a state when cells are unable to effectively respond to their specific antigens, in lymphoid tissues cells and promote a specific set of cytokines produced by immune cells that help downregulate inflammatory responses in naive T lymphocytes [72,73].

Isaacs et al. demonstrated that cells isolated from the bone marrow of mice tolDCs produced with a synthetic glucocorticoid, the active form of vitamin D, and a component of the outer membrane of Gram-negative bacteria had curative effects in an animal example of adjuvant arthritis model [74]. Mice treated with tolDCs showed seriously decreased arthritis intensity and development, while therapy by means mature insusceptible DCs worsened the condition. TolDCs only demonstrated healing productiveness when filled with biomarker assessing cartilage degradation, and this was connected with a reduction in a distinct subset of CD4+ T helper cells characterized by their production of pro-inflammatory cytokines, an increase in a subset of T cells producing an anti-inflammatory cytokine, and decreased growth of T cells recognizing collagen.

A medical study has been conducted recently to investigate the use of autologous tolDCs in RA individuals. This Phase I study is recombined, sightful, and objective, with snooze enhancement. The main difference between this and previous studies is the

route of administration The current and last studies distinguish seriously in the way of managing; in this trial, tolDCs are delivered intra-articularly under arthroscopic guidance [75]. The primary goal is to evaluate the safety of promoting immune tolerance cells injections in RA individuals, with insignificant goals assessing patient tolerability and the feasibility of innovative therapeutic approach aimed at inducing immune tolerance. Exploratory aims include assessing the result of therapeutic approach inducing immune tolerance on autoimmune joint damage vitality and identifying possible reply immunosensors through a hypothesis-free approach involving flow cytometry, transcriptional profiling, and immunohistochemistry.

In an animal example, researchers addressed such key questions: the first one - whether a growth motivation is required for features primarily promoting immune tolerance both artificially and in natural conditions, particularly in animal models of arthritis, and the second - whether cells promoting immune tolerance can regulate cell replies of versatile and pivotal players in the immune system [71,76]. The study compared adult and young tolDCs produced with synthetic glucocorticoid with strong anti-inflammatory properties/the active form of vitamin D artificially, and found that cells promoting immune tolerance can modulate both naive and effector of cell replies of versatile and pivotal players in the immune system, as demonstrated either by reduced proliferation or activation of these T lymphocytes in a living system. Additionally, Treg expansion was observed in the presence of tolDCs, and administered tolDCs were able to restrain rheumatics in an experimental example of autoimmune joint damage. However, therapeutic approach inducing immune tolerance require a growth motivation to apply this permissive function in the phlogistic conditions, which is important for improving therapeutic approach inducing immune tolerance for inflammatory disorders like autoimmune joint damage.

Regulatory T Cell Therapy

Multiple studies have explored the regenerative functions of Treg cells, aiming to stimulate immune regulation prior to significant flesh degradation. Investigators have developed different methods to enhance Treg cell function. These include reducing the proinflammatory environment in vivo, using Treg cell-specific stimulators to promote their expansion, and expanding Treg cells in vitro with immune complexes before injecting them into patients [41-43]. Adoptive transfer of Treg cells has been shown to improve survival in Scurfy mice, which are prone to autoimmune diseases, and prevents the onset of these diseases. Conversely, removing Treg cells before they can exert their protective effects can increase disease incidence and severity. Evidence suggests that transferring regulatory T cells can inactive illness evolution and offer potential for treating autoimmune conditions [44-46]. cell-based immunotherapy involves isolating regulatory t plasma cells according to their identificators of regulatory T cells, expanding them with commonly used in immunology research and therapeutic applications, and afterwards reintroducing them inside the flesh. Amplified regulatory T cells have been tested in autoimmune disease models in mice and have shown promise. Early clinical studies in patients with insulin dependent diabetes and the illness recognizing the recipient's tissues as foreign due to differences in human leukocyte antigens reported firm productivity with minimal significant adverse reactions. In collagen-induced arthritis (CIA) models, which are used to study rheumatoid arthritis (RA), Treg cell therapy significantly inhibited disease development. Importantly, Treg cells not only suppressed T and B cell activity but also directly reduced osteoclast-mediated bone destruction, thus preventing joint damage [47-49].

Stem Cell Therapy

Mesenchymal Stem Cell Therapy (MSCT)

In curious research, the characteristics of hematopoietic stem cells derived from RA patients were paralleled to those from healthy individuals. The results showed that the molecular, protein, and physical characteristics, as well as the immune profile and regularity of hematopoietic stem cells in the bone marrow sufferers of immune system attacks joints were similar to those in healthy people [77-79]. This suggests that using a patient’s own mesenchymal stem cells (MSCs (autologous MSCT) could be as effective as using MSCs from a donor (allogenic MSCT) in treating RA. However, the MSCs from RA patients had a lower ability to multiply, which was linked to shorter telomeres and alterations in the gene activity related to cell attachment and phase of cell division.

Researchers looked at how the treatment using stem cells from umbilical cords (UC-MSCs) affects certain immune cells in individuals with immune system attacks joints [22-24]. They found that UC-MSCs could slow down the growth and movement of specific cells in the joints (FLSs) by producing anti-inflammatory substances like IL-10 and TGF-β, while reducing harmful enzymes. They also discovered that UC-MSCs could stop T cells from growing by producing other substances (PGE2, IDO-1, and NO) and increasing the number of t lymphocytes which assist to control the body's defenses [25-27].

Autologous bone marrow derived-mesenchymal stem cells therapy (BM-MSCT) helped to improve the condition in unresponsive individuals. A separate injection of hematopoietic stem cells lowered a quantifiable score in rheumatoid arthritis which determines disease activity in RA. Additionally, after 12 months, there was a reduction in erythrocyte sedimentation rate and a reduction in a continuous rating scale measurement, which assessed an individual’s perception of hurt. Cell sorting conclusions demonstrated the reduction in a subset of T helper cells and enhancement of Tregs after hematopoietic stem cells cure [28-30]. The cure showed a considerable drop in serum RF grades after the hematopoietic stem cells cure, though no significant changes were observed in biomarker of

inflammation and biomarkers of rheumatoid arthritis levels. Different research was conducted to explore the disease-modifying anti-rheumatic properties of subset of T cells recognizing collagen from immune system attacks joints sufferers. Multipotent stem cells derived from adipose tissue reduced the inflammatory interleukins creation and decreased the growth of T cells activated in response to collagen [77-79]. Additionally, multipotent stem cells didn't produce only a key anti-inflammatory cytokine besides they encouraged either white blood cells or monocytes to produce IL-10 and promote the division of Tregs. multipotent stem cells and cells producing cartilage-specific matrix components inhibit T lymphocytes in immune system attacks joints sufferers. This inhibitory influence may occur through various mechanisms, including inhibiting multiplication of t cells, reducing protein presence on the immune cells, suppressing critical cytokines emitted primarily by T helper 1cells and cytotoxic T lymphocytes, and increasing maintaining immune homeostasis cytokines secretion [80-82].

Adipose-derived mesenchymal stem cells (AD-MSCs) developed on the articular membranes of individuals suffering from rheumatoid arthritis have the ability to differentiate into adipocytes, chondrocytes, and osteoblasts. Additionally, these cells are capable of inhibiting the proliferation of CD4+ T cells [79,85,86] T follicular helper cells (TFH) are found in higher amounts in the blood of people with RA, and their levels are linked to the amount of anti-cyclic citrullinated peptide (anti-CCP) antibodies. Genetically different stem cells from the umbilical cord restrained the separation and expansion of t cytotoxic cells in immune system attacks joints sufferers by generation indoleamine 2,3-dioxygenase 1 (IDO-1). This action helped to restore the equilibrium of t lymphocytes and a subset of T helper cells and promoted the generation of multifunctional regulatory cytokines [87-89]. Since TFH and TH17 cells have a crucial function in the evolution of RA, inhibiting these cells may help to alleviate the symptoms of the disease. MSCs may also influence memory T cells, which could alter the equilibrium of phlogistic and resolvent replies in sufferers of immune system attacks joints instead. After 12 months of BM-MSCT treatment, patients with refractory rheumatoid arthritis exhibited higher mRNA levels of master regulator of t lymphocytes, a key cellular regulator that controls Treg protein production, in lymphocytes and monocytes [90-92]. This indicates an increase in Treg differentiation, which subsequently led to elevated levels of multifunctional regulatory cytokines and maintaining immune homeostasis cytokines. Above mentioned changes could improve the disease's progression and activity. Furthermore, when AD-MSCs were co-cultured with peripheral blood mononuclear cells (PBMCs) from RA patients, they triggered the emission of molecules diffusing through the extra cellular space such as a key mediator of the immune response, lipid mediator, and a factor crucial for angiogenesis. This interaction also helped establish an equilibrium of t lymphocytes and a subset of T helper cells, favoring Treg differentiation [93-95]. Additionally, there was an increase in multifunctional regulatory cytokines production as well as a decreasing in immune response amplifiers like critical cytokines emitted primarily by T helper 1cells, cytokine regulating immune responses, and pro-inflammatory mediating immune responses cytokine. The impacts could help to slow down the disorder's development. Similarly, when UC-MSCs were co-cultured with PBMCs from RA patients, there was a decrease either in DNA translating process and amino acid grades of transcriptional nuclear receptor, a key controller of protein production of pro-inflammatory mediating immune responses cytokine, particularly in patients with serious rheumatic fever. This suggests that UC-MSCs may have a suppressive effect on Th17 cell differentiation [96-98]. Respectively, co-culturing multipotent stem cells derived from adipose tissue with lymphocytes and monocytes from rheumatic persons reduced IL-17 emission and also prevented the expression of cytokines regulating immune responses in PBMCs, due to the managing role of multipotent stem cells derived from adipose tissue. Overall, above mentioned findings indicate that hematopoietic stem cells could be a promising option for a stem cell treatment in rheumatic persons [99-101].

Sporadic alterations in human hematopoietic stem cells can influence on their immunoregulatory abilities and the expression of molecules like maintaining immune homeostasis cytokines and enzymes involved in the catabolism of the amino acid tryptophan, which boost antigenic competition. The sporadic modifications in hematopoietic stem cells have been shown to inhibit Th17 cell differentiation, lymphocytes division, and signaling proteins synthesis. When small-size cells from the articular serum of rheumatic persons were taken care of these modified hematopoietic stem cells, they generated smaller grades of pro-inflammatory mediating immune responses cytokines and critical cytokines involved in the immune response. Indicated findings show that sporadic alterations in hematopoietic stem cells may impact their curative effectiveness in rheumatic persons [102-104].

Several investigations have evaluated the therapeutic effectiveness of combining MSCs with other treatments. In patients with refractory RA, an association of multipotent stromal cells and medications slowing down the progression of autoimmune and inflammatory diseases was found to be a safe and an effective durable treatment. Zero harmful impacts were noticed, and there were significant improvements in various measures of RA symptoms, including the American College of Rheumatology (ACR) scores, DAS28, and HAQ-DI, which assess disease activity and functional ability [32-34]. After 12 months of treatment, patients experienced relief from osteoarthritis, bulging, and rigidity. Additionally, levels of CRP, autoantibodies, and chemokines like a key mediator of the immune response and critical cytokines decreased, while the number of regulatory T cells and cells defending against extracellular pathogens generating central to

the Th2 response cytokine enlarged in the patients' peripheral blood. This suggests that DMARDs alone were not as effective in improving the disease as the combination therapy [31]. In another study, Ahmed and other researchers investigated the effects of hematopoietic stem cells, curcumin, and the amalgamation of the effects on bloodstream cytokines and nucleic acids chemistry in complete Freund's adjuvant-induced arthritis in laboratory rats [105]. The combination treatment returned blood concentration of pro-inflammatory cytokines, bioactive lipid mediators, and regulating allergic responses cytokines to usual state, while DNA-dependent RNA synthesis of pro-inflammatory cytokines promoting immune activation and enzyme generating prostaglandins increased and key cytokines involved in regulating immune responses decreased, leading to a reduction in inflammation. The combined treatment was more effective in reducing inflammation and had additional benefits for the articulatio talocruralis, glandular tissue, and milt compared to using either treatment alone. Similarly, one of the researchers showed that a therapeutic strategy including multipotent stem cells derived from the Wharton's jelly and cytokines produced by activated T cells significantly improved clinical results in RA patients [106]. Additionally, Pan and others studied the impacts of combined treatment with multipotent stem cells isolated from the bone marrow and small interfering RNAs (siRNA) aiming key pro-inflammatory cytokines that play significant roles in the pathogenesis of a commonly used animal example for studying rheumatoid arthritis [107]. The researchers found that this combination therapy had synergistic effects, reducing soreness and promoting joint recovery in rheumatic fever animals more effectively than either treatment alone.

Hematopoietic Stem Cell Transplantation (HSCT)

In a medical procedure treating hematological diseases cyclophosphamide is commonly used as a part of the conditioning regimen before the procedure. The effectiveness of haematopoietic stem cell transplantation (HSCT) in treating RA patients is assessed through molecular markers and clinical indices like tools and measures for the assessment and management of rheumatoid arthritis and other inflammatory arthritis conditions [108,109]. According to Verburg et al., 50% of RA patients experienced a significant reduction in illness function based on measure focusing on 28 specific joints [35]. Similarly, Snowden and other researchers found that 67% of rheumatic fever individuals achieved an ACR 50% response six months after HSCT [110]. Their findings also indicated that patients who were rheumatic factor (RF)-negative responded better to HSCT, suggesting that RF levels could be a predictor of treatment outcomes. Another study found that 39.4% of rheumatic fever individuals achieved a criteria for diagnosing rheumatic diseases of 70% response following the infusion of hematopoietic stem cells to replace damaged bone marrow. Additionally, a durable following demonstrated a serious decrease according to the measurement of the functional ability and quality of life, indicating improved functional status. The five-year total endurance and healthy endurance grades were 94% and 18%, correspondingly, post-HSCT. These results suggest that HSCT can lead to a partial improvement in RA for some patients [111].

Some researchers also investigated the clinical effects of infusion of hematopoietic stem cells for replacing damaged bone marrow combined with excessive in amount medical treatment on joint membranes and peripheral blood in rheumatic fever individuals [35]. They found that titers of serological markers used in the diagnosis and management of rheumatoid arthritis decreased at a quarter and a half a year post-transplantation but enlarged once more in a year, likely because of the partial elimination of acting against the organism B lymphocytes, which continue to produce autoantibodies and hinder long-term recovery. However, in patients who responded to the treatment, there was a reduction in human Ig, C-reactive protein (CRP), and inflammation [112-114]. Different investigation examining the impact of medical procedure involving the infusion of hematopoietic stem cells and administration of significantly higher doses of chemotherapy drugs on junction destruction observed a significant reduction in joint damage and CRP levels during the initial post-transplant, implying a decrease in T cell penetration into the joint lining. This reduction likely prevents osteoclast activation and a subsequent joint damage [115-117].

To enhance treatment efficacy, researchers compared two groups of RA patients undergoing HSCT: one group received CD34+ stem cells that were depleted of T cells, while the other group received unmanipulated HSCs. The findings revealed no significant differences in ACR scores or the duration of remission for the both clusters. This suggests that t lymphocyte reduction from hematopoietic stem cells is not significant for the effectiveness of HSCT treatment [118-120].

Pluripotent Stem Cells and Other Sources

In the endoderm of the people's germinal vesicle, which is present during the stage of four days, there are pluripotent cells. These cells disappear after a week as the embryo begins to form the three primary germ layers. A team of scientists effectively cultivated pluripotent stem cells in the researching center in 1998. Under appropriate conditions, ESCs can continuously self-renew, generating more cells with the same multipotent abilities [121,122].

Studies have shown that ESCs have immunosuppressive properties and have the ability to restrain body's defenses activation in the intracellular collaboration. Adult MSCs face limitations due to their finite availability, the complexities of long-term culture, and issues such as genomic instability and increased antigenicity. Research into MSCs derived from human ESCs (hESC-MSCs) demonstrated that they can induce t cytotoxic cells, immune mediated cells, and metabolic important enzymes, which help to reduce the disorders' intensity and development like collagen-induced arthritis (CIA) in mice [123,124].

Additionally, research has explored the therapeutic potential of embryonic stem cells and certain cancer stem cells, making it an important marker, with the comparable action of the cells in the plasma [125,126]. Some researchers discovered that such cells are present in the joint lining of RA patients also in the stage of illnesses [127]. Following the separation, the cells from RA patients' joint lining and transferring them into mice with arthritis, they observed that these cells had a restrictive influence on rheumatism and synovial degradation.

Cells separated from human amniotic mesenchymal cells (HAMCs) exhibit immunosuppressive effects in vitro, including the inhibition of white blood cell multiplication, stimulation, monocyte growth, and chemokine generation, as well as the induction of Treg cells and M2 macrophages. Studies on these cells involved treating RA patient-derived cells with HAMCs and using them in CIA mice models [128,129]. The results indicated that HAMCs treatment suppressed the phlogistic joint lining reply and the mediated immune response cells pathways in the separated PBMCs from autoimmune joint damaged individuals. In experimental model for studying rheumatoid arthritis mice treated with HAMCs, there was a reduction in the generation of phlogistic interleukins and growth factors, along with an increase in peripheral Treg cell generation. These findings suggest that HAMCs could be a promising option for embryonic stem-cell research in autoimmune joint damage [130]. In Table 2, we compared the general points of traditional therapies to innovative cellular therapies.

Table 2. Comparison of Traditional and Innovative Therapies for ARDs

Feature	Traditional Therapies	Innovative Cellular Therapies
Mechanism of Action	Target inflammation and suppress immune activity	Modulate immune responses; enhance tolerance
Examples	DMARDs, bDMARDs, corticosteroids	CAR-T cells, MSCs, tolDCs, Tregs
Response Rate	Limited for many patients [4,5]	Early indications of higher efficacy and durability [20,21]
Side Effects	Significant, ranging from mild to severe [4,5]	Ongoing evaluation for safety and long-term effects [36,38]
Long-term Management	Requires continuous use and monitoring [4,5]	Potential for lasting remission with fewer treatments [18,19]

Conclusion

In summary, the landscape of treatment for autoimmune rheumatic diseases (ARDs) is evolving with the introduction of innovative cellular therapies. Traditional approaches, including conventional and natural reducing inflammation medications enhance management of these complex conditions. However, many patients still experience inadequate responses or adverse effects, highlighting the need for alternative strategies.

The artificial t lymphocyte receptor therapy depicts a transformative progress, demonstrating potential not just in oncology but also in modulating autoimmune responses by targeting autoreactive immune cells. Similarly, stem cell therapies—including autologous and allogeneic approaches—and the application of a subset of promoting immune tolerance dendritic cells and t lymphocytes offer promising avenues to restore immune balance and alleviate disease activity.

The preliminary results from ongoing research underscore the therapeutic potential of these advanced interventions, yet caution is warranted due to the complexities of immune regulation and individual variability in response. Future studies must prioritize elucidating the mechanisms of action, optimizing treatment protocols, and evaluating the long-term protection and productivity of these treatments in various groups of ARD patients.

Ultimately, continued collaboration between basic science and clinical research will be essential to translate these advancements into standard care practices. By leveraging the immunomodulatory capabilities of these cellular therapies, we may be able to achieve more effective, personalized treatment regimens that enhance quality of life and improve long-term outcomes for individuals affected by ARDs.

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