Mesenchymal Stem Cell Applications in Graft Versus Host Disease

Graft Versus Host Hastalığı'nda Mezenkimal Kök Hücre Uygulamaları

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation stands as a promising cure for a variety of diseases. However, the potential of acute or chronic graft-versus-host disease (GvHD), which leads to significant morbidity and mortality, remains a cause for concern. GvHD occurs due to the complex interactions of immune cells from the graft and the host cells. Despite the existence of prophylactic treatments, GvHD may still occur, and the resistance to conventional therapies necessitates novel approaches and treatments.

Mesenchymal stem cells, which are pluripotent stem cells capable of self-renewal and multilineage differentiation, have gained attention for their low immunogenicity and ability to be sourced from various origins. They have shown promise as therapeutic tools for the cell-based treatment of inflammatory, immune-mediated, and degenerative diseases owing to their remarkable abilities in immunomodulation, immunosuppression, and tissue regeneration. In GvHD, MSCs have demonstrated therapeutic potential through paracrine activity and organelle transfer via nanotubes, microvesicles, or exosomes.

The emergence of MSCs as a treatment for severe steroid-resistant GvHD gained attention in the early 2000s. While initial studies have demonstrated encouraging results in the use of MSCs for the prevention of GvHD, there is still a need for further investigation. Therefore, in this current review, we aim to delve deeper into MSC's features and their clinical applications in the case of GvHD treatment.

Key Words: Mesenchymal stem cell, Hematopoietic stem cell, Immunomodulation, Stem cell transplantation, Graft-versus-host disease

ÖZ

Allojenik hematopoetik kök hücre transplantasyonu, pek çok hastalık için umut verici bir tedavi yöntemidir. Ancak tedavinin bir komplikasyonu olabilen akut veya kronik greft-versus-host hastalığı (GvHH) mortalite ve morbidite riskini önemli ölçüde artırabilmektedir. GvHH, donörden gelen bağışıklık hücreleri ile konak hücreleri arasındaki uygunsuz immün yanıttan kaynaklanmaktadır. Profilaktik tedavilerin varlığına rağmen, GvHH hala görülebilmekte olup konvansiyonel tedavilere direnç, yeni tedavi çalışmalarının gerekliliğini ortaya koymaktadır. Mezenkimal kök hücreler (MKH), kendini yenileyebilme, farklı doku hücrelerine farklılaşma, düşük immunojenite özelliklerine sahip olup çeşitli dokulardan elde edilebilirler. İmmünomodülasyon, immünsüpresyon ve doku rejenerasyonu özelliklerinden dolayı, inflamatuar, immün aracılı, dejeneratif hastalıkların tedavisinde umut vaat etmektedirler. GvHH'de, MKH'ler, parakrin aktivite ve nanotüpler,

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mikroveziküller veya eksozomlar yoluyla terapötik potansiyel gösterebilmektedirler. Steroid tedavisine dirençli GvHH'nin tedavisi için MKH'ler 2000'lerin başında kullanılmaya başlanmış olup, yapılan çalışmalar MKH'lerin etkili bir teröpötik araç olduğunu göstermiştir, ancak daha fazla araştırmaya ihtiyaç duyulmaktadır. Bu derlemede MKH'lerin özelliklerini ve GvHH tedavisindeki klinik uygulamalarını incelemeyi amaçladık.

Anahtar Kelimeler: Mezenkimal Kök Hücre, Graft Versus Host Hastalığı, Kök Hücre Nakli, Hematopoetik Kök Hücre, Immunmodülasyon

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) provides a potential cure for various diseases, including hematological and non-hematological diseases. Despite significant advances in transplantation technologies, including high-resolution HLA typing and the advancement of immunosuppressive medications, poor treatment-related survival remains a problem, with disease relapse, graft rejection, and acute or chronic graft-versus-host disease (GvHD) (1, 2).

Systemic inflammation arises from donor lymphocytes within the transplanted tissue recognizing the recipient as foreign. This triggers an immune response where activated T cells strive to eliminate antigen-carrying cells in the host, leading to severe organ damage. This condition can be classified into acute or chronic forms, traditionally distinguished by the onset time; if it occurs within the first 100 days, it is classified as acute GvHD (1). Nevertheless, acute GvHD can extend beyond the first 100 days, leading to an overlap between the acute and chronic syndromes (3).

Currently, 30–50% of patients undergoing allogeneic stem cell transplantation develop acute GvHD, while 30–70% develop chronic GvHD. Despite the prophylactic use of calcineurin inhibitors and methotrexate, GvHD still occurs, and corticosteroids are the mainstay of treatment (4). The increasing resistance to steroids necessitates the development of new therapeutics (5).

Mesenchymal stem cells (MSCs) are pluripotent stem cells which can be derived from various sources like bone marrow, adipose or placental tissue (5,6). These cells have been shown to have an immunosuppressive effect on GvHD by inhibiting T cell and natural killer cell proliferation, inhibiting Th17 and B cell differentiation, increasing the number of regulatory T cells, interfering with the maturation of antigen-presenting cells, and increasing the secretion of immunomodulatory molecules , including prostaglandin E2, transforming growth factor-β (TGF-β), Interleukin-10, and heme oxygenase (6-8). They can reduce the incidence of acute GvHD and decrease the severity of both acute and chronic GvHD after HSCT (9, 10).

Within the past twent years, there has been significant interest in exploring the potential therapeutic applications of MSCs in various clinical scenarios, including their role in supporting hematopoietic stem cell transplantation (HSCT) and their use in treating GvHD (11-13). This review focuses on using MSCs in GvHD.

What is GvHD?

The development of GvHD is influenced by the intricate interactions of immune cells from the graft and pro-inflammatory cytokines, which are affected by differences in tissue histocompatibility between donor and recipient. B and T lymphocytes have vital functions in identifying and eliminating host cells. Inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and platelet-derived growth factor (PDGF) are released due to tissue injury by the pre-transplantation conditioning regimen. These cytokines activate donor alloreactive T cells along with antigen-presenting cells, causing host tissue damage through the expansion of donor helper T cells (including Th17), cytotoxic T lymphocytes, and natural killer cells. Inflammatory immune responses against these cells lead to significant tissue harm, affecting various organs and body areas such as the skin, oral cavity, eyes, digestive system, liver, lungs, joints, and reproductive tract and promoting GvHD (14-17).

Patients receive high doses of immunosuppressive drugs during allogeneic HSCT to enable the transplantation and prevent GvHD. Dysregulation of lymphocyte reconstitution can compromise self-tolerance, leading to an increase in self-reactive B and T cells. This situation may result in the overproduction of autoantibodies by self-reactive B cells, causing immune complexes to accumulate in healthy tissues and blood. Activation of inflammatory cells can also lead to collagen production and fibrosis while promoting chronic GvHD (15).

Treatment options for GvHD include the use of broad-spectrum immunosuppressives, but these treatments may be ineffective and could potentially increase the risk of cancer recurrence (14, 15, 17). The standard treatment depends on the affected organ or site and can be either local or systemic, with more adverse effects associated with systemic treatments. Steroids such as prednisone (2 mg/kg per day) are recommended by NIH guidelines for their lymphopenic and anti-inflammatory properties when used alone or combined with calcineurin inhibitors (18).

What are MSCs and their abilities?

Mesenchymal stem cells, alternatively known as multipotent stromal cells or mesenchymal stromal cells (MSCs), have been the focus of extensive scientific research since their initial identification in the late 1960s (19). Mesenchymal stem cells are postnatal stem cells that can self-renew and maintain a versatile capacity to differentiate into multiple lineages, such as

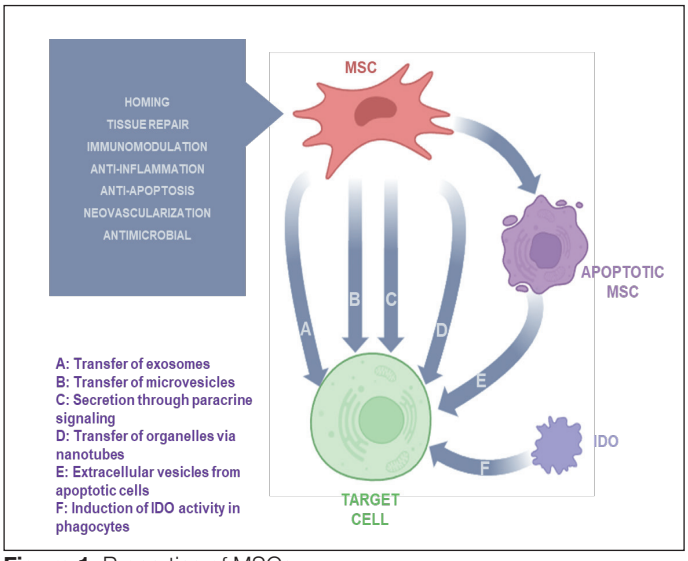

Figure 1: Properties of MSCs

osteoblasts, adipocytes, and chondroblasts (20). Mesenchymal stem cells typically display low immunogenicity. They exhibit only moderate levels of major histocompatibility complex I (MHC) expression and show little to no expression of MHC II antigens and co-stimulatory molecules (21).

In addition, they have several unique characteristics, which will be explained in this review and given in Figure 1.

Homing Capacity:

Homing is the process of MSCs selectively migrating towards the sites of injury, facilitated by specific receptors or ligands expressed by damaged tissues, enabling MSC's to adhere and infiltrate. This process involves three major steps: First chemoattraction to sites of inflammation, achieved by chemotaxis, through the accumulation of chemokines and cytokines such as epidermal growth factor (EGF), insulin-like growth factor (IGF), PDGF, vascular endothelial growth factor (VEGF), TNF-α, interleukin (IL)-1, IL-6 and IL-8; than adhesion to injured cells with molecules such as selectins and integrins; finally infiltration into sites of inflammation aided by enzymes such as matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) (22).

Tissue Regeneration:

Several functional properties of MSCs make them suitable for tissue regeneration and repair. These properties include differentiating into various cell types, migrating to injured tissues, promoting angiogenesis, exhibiting anti-apoptotic activity, and releasing bioactive soluble factors. The secretion of paracrine factors by MSCs alters the tissue microenvironment, significantly influencing proliferation, antioxidant activity, and differentiation. Paracrine signaling recruits macrophages and endothelial cells and likely stimulates resident stem cells to assist in the tissue repair process. Another vital function of MSCs is activating local stem cells through the secretion of growth factors. The trophic factors secreted by MSCs have been linked to the stimulation and expansion of internal stem cell populations, emphasizing the intricate paracrine and cell-to-cell communication essential for tissue recovery and restoration (22,23).

Regulation of the immune system:

Mesenchymal stem cells create an immunosuppressive and immunoregulatory environment through the secretion of cytokines, chemokines, growth factors, and extracellular vesicles (24, 25)

Several factors, such as IL10, transforming growth factor beta (TGF-β), prostaglandin E2, indoleamine 2,3-dioxygenase (IDO), nitric oxide, and FAS/ FAS ligand, play a role in the immunomodulatory features of MSCs by inhibiting the proliferation and function of various immune cells. Mesenchymal stem cells can impact B and T lymphocytes, dendritic cells, natural killer (NK) cells, monocytes, neutrophils, and macrophages. They may suppress B-cell proliferation while enhancing IgG secretion; inhibit chemotaxis; upregulate antibody secretion; decrease pro-inflammatory cytokine secretion by Th1 cells; increase IL-4 secretion by Th2 cells; inhibit T cell proliferation; decrease cytotoxic effects of cytotoxic T cells; suppress dendritic cell differentiation, antigen presentation to T cells and NK cell activation. Additionally, they may decrease local infiltration and activation of neutrophils while upregulating genes responsible for phagocytosis in macrophages to improve bacterial clearance (23, 26).

Anti-Inflammatory effect:

Utilizing their immunomodulatory abilities, MSCs have been shown to have a systemic anti-inflammatory effect, by reducing the levels of pro-inflammatory cytokines and procalcitonin (27).

The immunomodulatory characteristics of MSCs efficiently regulate adaptive and innate immune responses. Focusing specifically on T cells, MSCs can suppress the proliferation of activated CD4+ and CD8+ T cells and hinder the differentiation of CD8+ cytotoxic T cells by preventing T cell proliferation and arresting them in the G0/G1 phases of the cell cycle and potentially inducing T cell apoptosis (28,29). Substantial evidence supports that MSCs prompt the polarization of T cells towards a regulatory phenotype, potentially contributing to the suppression of inflammation (30).

Mesenchymal stem cells have been associated with the inhibition of B lymphocytes. In vitro studies consistently demonstrate that human MSCs suppress B-cell proliferation in the presence of anti-immunoglobulin antibodies, soluble CD40 Ligand, and various cytokines like IFN-γ (31-33).

In addition, MSCs exhibit constitutive secretion of IDO, and when activated by inflammatory cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), IDO secretion is upregulated (33,34). IDO, in turn, plays a crucial role in suppressing the proliferation of allogeneic T cells (35).

The apoptosis of MSCs in vivo also contributes to their immunomodulatory effects. The production and release of apoptotic extracellular vesicles potentially mediate this. During apoptosis, MSCs also induce the production of IDO in recipient phagocytes, adding another layer to their multifaceted immunoregulatory capabilities (19, 36, 37).

Suppression of Apoptosis:

The anti-apoptotic activity of MSCs has been well-documented, with evidence suggesting that they can protect injured cells and maintain organ function by inhibiting programmed cell death. This mechanism involves the up-regulation of DNA repair, down-regulation of mitochondrial death pathways, and alteration of anti- and pro-apoptotic protein expression. Additionally, the secretion of specific mediators by MSCs, such as stromal cell-derived factor 1 (SDF-1), insulin-like growth factor 1 (IGF-1), nuclear factor erythroid 2-related factor 2 (Nrf2), hypoxia-inducible factor (HIF), heme oxygenase contributes to the downregulation of pro-apoptotic proteins (22,23,38).

Neo-angiogenesis:

Furthermore, MSCs have also demonstrated the ability to stimulate the neovascularization in tissue through the expression of angiogenic cytokines including, vascular endothelial growth factors, fibroblast growth factors, and angiopoietin-1. By secreting these soluble factors, MSCs can improve tissue vascularity by stimulating endothelial cell growth and inducing neo-angiogenesis (22, 23).

Antimicrobial Effect:

Mesenchymal stem cells have been found to have antimicrobial effects due to their ability to secrete antimicrobial peptides such as human antimicrobial peptide LL-37 and Lipocalin-2 in response to pathogenic stimulation. These antimicrobial factors contribute to the disruption of bacterial membranes and aid in bacterial clearance, further displaying the diverse therapeutic potential of MSCs (22, 23).

MSC treatment in GvHD

Clinical trials of MSCs for various diseases and phases have been documented on the National Institutes of Health website, including cardiovascular diseases, neurodegenerative diseases, bone and cartilage diseases, cancers, autoimmune diseases such as GvHD (22).

MSCs' self-renewal and differentiation capacity, along with their ability to prevent T cell proliferation in response to antigenic stimuli and their anti-proliferation effects on B cells, natural killer, and dendritic cells, render them well suited for immunosuppression. Mesenchymal stem cells are characterized by the absence of human leukocyte antigen (HLA) class II expression, enabling their allogeneic administration without the need for donor-recipient matching.

The therapeutic effects of MSCs are multifaceted and include paracrine activity through the secretion of proteins, peptides, and hormones. Additionally, MSCs demonstrate capabilities such as the transfer of mitochondria through tunneling nanotubes or microvesicles, as well as the transfer of exosomes or microvesicles containing RNA and various bioactive molecules. These diverse mechanisms contribute to the potential therapeutic impact of MSCs in various clinical applications, including the treatment of conditions such as GvHD (19, 39).

The effectiveness of mesenchymal stem cell treatment relies on various factors, including the origin of the cells, their expansion methods, and their capacity to migrate to the tissues affected by GvHD. While MSCs from a particular donor may work for one recipient, they may not be effective for another. Therefore, recipient factors are crucial in determining how mesenchymal stem cells function (40-42).

Since 2008, there has been a substantial increase in attention towards MSCs for the management of GvHD following promising findings (41). However, the actual clinical effectiveness of these cells is questionable (43).

Clinical Studies

In treating severe steroid-resistant acute (aGvHD) and chronic graft-versus-host disease (cGvHD), mesenchymal stem cells have gained substantial attention in research and clinical practice. Here, we share a selection of contemporary studies and their corresponding outcomes, wherein the pediatric age cohort is included.

In 2008, Le Blanc et al. (41) published their phase II clinical trial with 55 patients, including children with severe aGvHD. It was shown that most of the patients had a complete response or improvement, and the effectiveness of the MSC treatment was not linked to donor HLA-match. No adverse effect was reported during or right after the infusions. Patients with a full response showed lower transplantation-related mortality and improved overall survival compared to those with partial or no response (41).

Another study that defined steroid-resistant grade IV acute GvHD in 42 cases, including pediatric cases, observed better overall survival in patients with GvHD grade less than 4, in those who initially had MSC treatment, and in pediatric patients. No immediate or delayed toxicity or side effects were documented (44).

Ball et al. (45) conducted a study with 24 patients with aGvHD, and a complete response to MSC infusion was observed in 65% of them. Transplantation-related mortality had a cumulative incidence of 17% in patients who achieved a complete response and 69% in those who did not. Overall survival after a median follow-up of 2.9 years was 37%, with early initiation of multiple MSC infusions showing better outcomes (45).

In a research in 2014, Kurtzberg et al. (46) demonstrated that an external administration of MSCs significantly increased survival rates at day +100 following in pediatric patients with

treatment-resistant acute GvHD. This outcome was associated with patient response by day +28, and treatment was generally well received without any indication of the development of ectopic tissue (46).

Introna et al. (47) conducted a phase I multicenter study involving 40 patients with steroid-resistant grade II to IV GvHD, supplied a median cell dose of 1.5×10/kg per infusion, with an overall response rate of 67.5% at 28 days after the last MSC injection. Overall survival at 1 and 2 years was reported as 50.0% and 38.6%, respectively (47).

In 2015, Zhao et al. (48) published a study of 47 patients suffering from resistant acute GvHD and found that the group treated with MSCs had an overall response rate of 75%, while the non-MSC group had a response rate of 42.1%. The incidence and severity of chronic GvHD were reduced in the MSC group. Additionally, MSC treatment enhanced thymus function, stimulated regulatory T cells, and did not increase the risk of infections or tumor recurrence (48).

In 2016, Kuçi and colleagues reported that MSC end-products showed an overall response of 77% in GvHD patients and an overall survival rate of 71±11% at two-year follow-up in severe acute GvHD patients (49). In the same year, in another study with 25 participants (grade III, 22 patients; grade IV, 3 patients), four weeks after the initial MSC infusions, a complete response was observed in 24% of the patients, while partial response was seen in 36%. By week 24, 48% of the participants achieved a durable, complete response. At the end of week 52, patients who had shown an overall response (complete and partial response) exhibited significantly better survival rates. No adverse effects associated with MSC infusions were reported (50).

In 2017, Dotoli et al. (51) published their clinical trial, in which 46 children and adults with steroid-refractory aGvHD III/IV received MSC infusions as a salvage therapy, showing clinical improvement in half of the cases. The estimated survival rate at two years was 17.4%, and only 4.3% of patients experienced temporary side effects during the MSC infusion, suggesting this treatment's safety and potential applicability (51).

Mazic et al. (52) in 2018 reported that three patients who underwent allogeneic hematopoietic cell transplantation and later developed steroid-refractory GvHD were treated with MSC infusions, resulting in complete remission of a GvHD in two patients and partial remission in one, confirming the feasibility of using MSCs to treat severe steroid-refractory acute GvHD in clinical practice in 2018 (52).

In a retrospective study published in 2021, 25 patients who received MSCs for acute GvHD were monitored for a median of 9.3 years. Partial response to GvHD was observed in 76.0% of the cases, while complete remission was 24.0%. Patients in complete remission had no transplant-related mortality. The use of MSCs led to an average improvement of one stage in GvHD. Long-term adverse effects like secondary malignancy were not detected (53).

Another phase 3 multicenter study was conducted in 2022, involving 203 participants aged 14 to 65 with steroid-refractory acute GvHD. The inclusion of MSCs in second-line treatment improved effectiveness, decreased drug toxicity, and reduced the occurrence of chronic GvHD without increasing relapse rates (54).

In the same year, research utilizing clinical-grade MSCs administered intravenously found an overall response rate of 58.7% for acute GvHD and 65.50% for chronic GvHD. The treatment was considered effective and safe, with four adverse events reported, all resolved without complication (55).

A meta-analysis conducted by Chen et al., including 13 studies with a total of 301 patients, revealed that the application of MSCs in treating steroid-resistant aGvHD led to an overall response rate of 68.1%. Among the patients, 136 showed complete remission, while 69 had partial remission or mixed response, making 205 patients with an overall response. Patients suffering from skin aGvHD exhibited more favorable clinical responses compared to those dealing with gastrointestinal or liver aGvHD conditions. Furthermore, recipients with Grade II steroid-refractory aGvHD showed better response to MSC therapy in comparison to Grade III/IV GvHD. Moreover, a trend showed that children had superior clinical responses than adults. Another meta-analysis involving 13 non-randomized studies at moderate risk of bias and comprising a total of 336 patients reported a survival rate of 63% (outcome of 119 patients from 6 studies) at six months following MSC treatment (56-58).

The first clinical use of MSCs for the treatment of refractory aGvHD in Türkiye was reported in 2016, with 33 pediatric patients, resulting in a complete response in 18 patients, a partial response in 7, and no response in 8. The estimated probability of overall survival at the two-year was significantly different between patients with a complete response and those with a partial or no response. Additionally, the incidence of transplant-related mortality at day 100 after the first MSC infusion was higher in patients with partial/none response compared to those with complete response (59).

Finally, in a multicenter study from Türkiye in 2023, seventy-six patients with grade III-IV acute GvHD were received weekly adipose or umbilical cord-derived MSC infusions in addition to standard treatment. The study concluded that MSC treatment was safe, with no adverse effects observed during over 190 infusions in 76 patients. Notably, the late aGvHD group showed significantly higher response rates (complete response: 23.3%, partial response: 36.7%) compared to the aGvHD group. Additionally, at the 2-year follow-up, patients with late aGvHD had a lower cumulative non-relapse mortality (40%) and a higher probability of survival (59%) compared to those with acute GvHD (71% and 28%, respectively) (60).

However, some studies suggest that MSC treatment may break the graft versus host reaction cycle rather than induce immune tolerance in aGvHD due to poor long-term survival (61, 62).

Furthermore, one of the main challenges in the clinical application of MSCs is their potential risks, including immunosuppressive effects, tumorigenic potential, immune responses, pathogen transmission, adipogenic differentiation, prothrombotic events, and various acute, intermediate, and long-term problems (22). Despite the widespread use of MSCs for immunomodulation and regenerative cell therapy, current evidence from clinical trials is inconclusive, adding complexity to their practical implementation (63).

These issues encompass immune-mediated reactions, embolic phenomena, graft-versus-host disease, secondary infections, and the risk of malignancy. As a result, the cautious use of MSCs is emphasized, taking into account factors such as the type or class of stem cells used, the level of manipulation, the culture history, the handling/storage conditions, and the components of the growth medium in clinical applications (22, 64, 65).

More high-quality, large-sample clinical trials are needed to verify the association between the clinical use of MSCs and tumor recurrence and infection. The current limitations of the literature and patient samples, which are small, underscore the importance of further research to establish a more pronounced understanding of the relationship between MSC therapy and clinical outcomes.

CONCLUSION

In conclusion, mesenchymal stem cells can be highly beneficial in hematopoietic stem cell transplantation for the prevention of graft-versus-host disease. Additionally, MSCs show promise in the treatment of acute and chronic GvHD. The clinical impact of MSC infusion for the treatment of GvHD needs to be further determined with high-quality clinical trials involving large numbers of patients.

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