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JSM Gastroenterology and Hepatology

Review Article

Management of Crohn's Disease: Advances in Mesenchymal Stromal Cell Therapy

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Submitted: 14 November 2018
Accepted: 14 December 2018
Published: 17 December 2018

Abstract

Crohn's disease (CD) is a chronic intestinal inflammatory disorder that is hypothesized to develop mainly due to a dysregulated immune response and dysbiosis in genetically predisposed individuals. Current treatment of CD with available agents like immunomodulators and biological drugs is poor and associated with various adverse effects. Mesenchymal stromal cells (MSC) with their immunomodulatory and tissue regenerative properties have shown great promise in the management of treatment-refractory CD patients with good safety profile.

CROHN'S DISEASE (CD)

Introduction

Crohn's disease is an inflammatory bowel disease (IBD), which is an immune-mediated chronic intestinal condition. With its increased incidence in the developing countries, IBD has emerged as a global disease [1]. CD can affect any part of the digestive tract, but it predominantly involves the small and large intestine and perineum. CD is a transmural disease, involving all the layers of the gut wall [2]. CD is still not a curable disease with frequent relapses and frequent complications like fistula, sinus and abscess formation, but treatment strategies have been improved significantly [3]. Pharmacological therapy includes either anti-inflammatory drugs like corticosteroids and immunomodulators or specific biological drugs or a combination of both [4].

Introduction of anti-tumor necrosis factor alpha (anti TNF-α) agent therapy has revolutionized the treatment for CD. But two-thirds of CD patients under anti-TNF therapy were shown to develop adverse effects over time [5]. In addition, loss of response or intolerance has been recorded in about one-third of patients. Another drawback of anti-TNF therapy is that even with combined administration of immunomodulators, mucosal healing is seen in less than 50% of CD patients. Pharmacokinetic failures of anti-TNF agents can be managed by dose escalation or shortening of dose intervals whereas, [6] therapeutic failures (seen in primary non-responders) are largely managed by switching to another biological agent [7].

Ustekinumab, an antibody against the p40 subunit of interleukin (IL) 12 and 23 and Vedolizumab that acts on integrin α4β7 expressed by circulating leukocytes, are such alternative agents targeting alternate inflammatory pathways. Even with Ustekinumab therapy, no improved mucosal healing response has been recorded compared to placebo [8].

Failed response to these therapeutic agents directed against isolated target cells is mainly due to the compensatory mechanisms developed by human immune system, like increased expression of the novel cytokine oncostatin M and the transcriptional pathway for its activation seen in patients on anti TNF-α therapy leading to poorer response. This led to the development of novel therapeutic approaches that target not only isolated cells, but also promote mucosal healing through repair and remodeling [9,10]. This goal is achieved by cell therapies like mesenchymal stromal cells (MSCs) therapy.

Etiopathogenesis

IBD is a state of chronic dysregulated inflammation, which results from the disruption of normal intestinal homeostasis that exists between the intestinal commensal microbiota, intestinal epithelial cells (IECs) and intestinal tissue immune cells. This dysregulated immune response is hypothesised to occur because of a cumulative effect of both environmental and genetic factors [11].

Host genetics play a major role in increasing the susceptibility to CD. 2-14% of patients have a family history of CD as demonstrated by familial clustering and sibling relative risk ratio is between 15-42% [12]. The concordance rate of CD in monozygotic twins is about 30-50%. NOD2 gene on chromosome 16 is the first CD associated gene to be identified by linkage studies [13] following which Genome-wide association studies identified about 160 genetic loci enriched with immune genes associated with CD [14].

Most notable immune mechanisms associated with identified genes include bacterial sensing (NOD2), autophagy (ATG16L1 and IRGM) [15] involving innate immune pathways (TLR4, CARD9, IL23R, STAT3) and adaptive immune pathways (HLA, TNFSF15, IRF5, PTPN22) [16]. Certain genetic loci are found to have an association with phenotypic subtypes of CD such as location and clinical course of disease. One such strong association has been recorded with coding variants in NOD2, which are strongly predictive for ileal disease, stenosis, fistula and Crohn's related surgery [17].

Dysbiosis (an alteration and disturbances in the normal gut microbiota) is another significant etiological factor associated with CD [18]. Environmental factors which influence the composition of gut microbiota include dietary habits [19] antimicrobial therapy [20] and smoking [21]. Most common changes observed in the composition of the gut microbiota include a reduction in Firmicutes and an increase in Proteobacteria.

Intestinal microbiota plays a major role in the dysregulation of the immune response with their effects on both innate and acquired immunity. In CD patients, major immune changes in the intestinal wall include increased accumulation of mucosal CD4+ helper T cells leading to production of effector cytokines such as TNF-α and interferon-γ (for Th1 cells) and IL17 and IL22 (for Th17 cells) [22,23]. In addition to this, tissue damage also occurs because of mononuclear phagocyte-mediated activation of T-cells which results in stimulation of CD14+ inflammatory monocytes (for Th1 cells) and neutrophils (for Th17 cells).

Other set of lymphocytes increased in number and involved in chronic intestinal inflammation are innate lymphoid cells (ILCs), which lack antigen-specific receptors (unlike other lymphocytes). They respond to the environmental stress signals and initiate early immune response against various stressors. Intestinal mucosal cells consist mostly of innate lymphoid cells type 3 that are associated with higher local IL17 expression. ILC act like messengers that react in response to cytokines produced by other innate cells, by secreting more cytokines to orchestrate the local immune response. IL23 responsive ILCs are found to be accumulated in the inflamed small bowel of patients with CD and implicated in the pathogenesis of colitis through the production of IL17, IFN-γ, and GM-CSF [24].

In patients with CD, there is an increased pro-inflammatory response mediated by lymphocytes. In addition to this, there are mechanisms that can decline immunomodulatory activity like decreased production of FOXP3+ regulatory T cells (Tregs) which reduces the production of anti-inflammatory cytokines (IL10 and TGF-β).Thus intestinal inflammation in CD is actually a combination of both pro-inflammatory and anti-inflammatory mechanisms.

MESENCHYMAL STROMAL CELLS

Introduction

Mesenchymal stromal cells (MSCs) are spindle-shaped, plastic adherent pluripotent cells derived from bone marrow and are also known as mesenchymal stem cells, multipotent stromal cells, or colony forming unit-fibroblastic cells. Besides bone marrow, these cells can also be isolated from various other tissues like adipose tissue, skeletal muscle, skin, liver, dental pulp, placenta and umbilical cord blood [25]. MSCs are cultured by growing bone marrow cells in a plastic tissue culture vessel for 1-5 days at 37°C [26].

One of the characteristic features of MSCs is their capacity to differentiate into osteoblasts, adipocytes, and chondroblasts which helps in the identification of MSCs in vitro, besides their property of plastic adherence. Based on these characteristics and the cell surface markers, a unique criterion was postulated by the International Society for Cellular Therapy (ISCT) [27] for the identification of MSCs which include:

1. Plastic adherence in standard culture conditions.
2. Positive for expression of CD105, CD73, and CD90, and negative for expression of CD45, CD34, CD14 or CD11b, CD79-alpha or CD19 and HLA-DR surface molecules.
3. Ability to differentiate into osteoblasts, adiposites and chondroblasts in vitro.

MSCs have significant therapeutic potential in various disorders, mainly because of their immunomodulatory properties and capacity to produce multiple soluble factors needed for tissue regeneration.

MSCs are widely being investigated for different routes. Local and systemic deliveries are the two routes of administration. Local delivery is through intraperitoneal, intramuscular and intracardiac injections. Systemic delivery is through intravenous and intra-arterial route. Among all the routes of administration, intravenous injection has the maximum advantage of being minimally invasive and wide distribution in the body.

Tissue regenerative properties

MSCs reach the injured tissue through a mechanism called homing, in response to various signaling molecules released from the damaged tissue. The process of MSC homing mechanism involves molecules like chemokines, adhesion molecules and even matrix metalloproteinases (MMPs). Among the chemokines, C-X-C chemokine receptor type 4 (CXCR4) and SDF-1 CXCL12,

assist MSCs in their migration process [28]. Initial involvement in adhesion process with the vascular endothelial cells mediated by the very late antigen-4/vascular cell adhesion molecule-1 (VLA-4/VCAM-1) is necessary prior to transendothelial migration of MSCs [29]. In addition to these, membrane type 1 MMP (MT1-MMP) and MMP-2 also assist in the migration process of MSCs [30].

Even at very low concentration, MSCs can exert their tissue healing properties by paracrine effects mediated through secretion of a variety of cytokines, chemokines, and growth factors. MSCs mediated tissue repair occurs mainly due to secreted growth factors, like vascular endothelial growth factor VEGF-alpha, keratinocyte growth factor, insulin-like growth factor and angiopoietin [31]. These factors assist in the migration of fibroblasts and macrophages to the damaged tissue site, leading to enhanced collagen production and angiogenesis promoting tissue repair.

In case of intestinal wall inflammation, injected MSCs act through a similar mechanism mediated by homing mechanism and secretion of growth factors promoting tissue healing. In addition to these effects, immunomodulatory properties of MSCs are also responsible for their tissue healing properties.

Immunomodulatory properties

Immunomodulatory effects of MSCs are exerted through both soluble factors and cell-cell contact mechanisms [32,33]. They act on both adaptive and innate immune responses. MSCs have long been considered hypo-immunogenic cells, because of the lack of expression of MHC class II molecules on their surface [34]. However certain pro-inflammatory cytokines like IFN-γ (majorly), TNF-α and IL1β released in response to inflammation, stimulate the MSCs to release soluble growth factors and enzymes promoting their immunomodulatory effects [35]. This has been the key reason for the enhanced immune response of injected MSCs which are pretreated with IFN-γ.

Major soluble factors secreted by MSCs that are implicated in mediating their immunosuppressive effects are cyclooxygenase 2 (COX-2), prostaglandin E2 (PGE2) indoleamine-pyrrole 2,3-dioxygenase (IDO), nitric oxide (NO) and interleukin-10 (IL-10). Soluble factors like PGE2 [36] and NO [37] secreted by MSCs, play a significant role in the inhibition of T-cell proliferation. T-cell proliferation is also inhibited by another factor, IDO through depletion oftryptophan (by catalyzing the conversion of tryptophan to kynurenin) [38]. Other soluble factors secreted by MSCs and involved in immunomodulation include transforming growth factor-β1 (TGF-β1), hepatocyte growth factor (HGF), IL-6, galectins, and leukemia inhibitory factor.

Other than T-cell regulation by soluble factors, MSCs can also regulate T-cells by cell-cell contact-dependent mechanisms. Interaction of a cell surface adhesion molecule secreted by MSCs known as programmed death ligand 1 or CD274 (PD-1), with its ligands PD-L1 and PD-L2 have been shown to be responsible for the inhibition of T-cell proliferation through a cell-cell direct contact-mediated mechanism [39].

MSCs also exert their immunosuppressive effects by interfering with the proliferation, differentiation, and chemotaxis of B-cells [40]. After receiving paracrine signals from B-cells, MSCs secrete various soluble factors like transforming growth factor β1 and hepatocyte growth factor, prostaglandin E2, and indoleamine 2,3-dioxygenase which inhibit the B-cell proliferation by causing a block in G_0/G_1 phases of the cell cycle.

MSCs also have a role in the inhibition of differential of B-cells into antibody-producing cells resulting in decreased secretion of IgM, IgG, and IgA. MSCs also causes inhibition of CXCR4- and CXCR5-mediated B-cell chemotaxis in response to their corresponding ligands CXCL12 and CXCL13.Other immune cells namely natural killer cells (NK), were thought to have a cytolytic effect on MSCs mediated by NK receptors NKp30, NKG2D, and DNAM-1. In contrast to this, it has also been found that MSCs through both soluble factors and cell-cell contact dependent mediated mechanisms play a role in the inhibition of NK cell proliferation and secretion of IFN-γ by IL-2–stimulated NK cells [41].

Furthermore, immunomodulatory effects of MSCs are also mediated through the modulation of dendritic cells to upregulate the production of anti-inflammatory cytokine interleukin (IL)10 and down-regulate the secretion of pro-inflammatory tumor necrosis factor alpha (TNF-α) and IL12 [42]. This results in a decrease in pro-inflammatory Th1 cells and an increase in anti-inflammatory Th2 cells. Apart from this, MSCs can also inhibit the differentiation and maturation of monocytes into dendritic cells.

MSCs also have their immunomodulatory effects on macrophages. It was found that exposure of cultured macrophages to zymozan resulted in an increased secretion of TNF-α, mediated via TLR2–nuclear factor kappa-B (NF-kB) axis. This TNF-α, in turn, stimulates extracellular protein TNF-α stimulated gene protein (TSG)6TSG6 expression by MSCs, which engages in a negative feedback loop mechanism by inhibiting NF-kB via activation of the CD44 receptor [43]. Additionally TNF-α also stimulates MSCs to secrete PGE2, which promotes the release of anti-inflammatory molecule IL10 by macrophages [44].

In addition to the inhibition of T-cell proliferation, MSCs also induce the production of regulatory T cells (Tregs) which act by suppressing self-reactive T-effector responses [45]. Tregs, thus produced in the presence of MSCs are found to have immense expansion potential and play a significant role in immune regulation [46,47].

ROLE OF MSC THERAPY IN CD

There has long been an unmet need for newer therapeutic advances in patients who have not benefitted even after a combination of both biological and immunomodulatory therapies. Development of MSC therapy has dramatically reduced the need for surgery in CD patients because of its immunomodulatory and tissue regenerative properties. Evidence regarding the efficacy of allogeneic MSC therapy in graft-versus-host disease has prompted the researchers to evaluate their use in CD. Hematopoietic stem cells (HSCs) constitute another cellular therapy which also was studied in patients with CD. However, in contrast to therapy with MSCs, transplantation of HSCs can induce graft-versus-host disease in the patient [48].

Even though, MSC therapy has promised a great deal in the

treatment of Crohn's disease there are a few adverse effects, associated with it. Injection related side effects such as transient fever and headache. Long term side effects such as increase in tumor potential, metastatic potential, and increased risk of infection can occur due to their immunomodulatory potential, yet such adverse events can be successfully prevented with further clinical trials.

Autologus and allogenic are both being investigated in MSCs. Allogenic MSC are more sought for their potential for immediate care during tissue injury or diagnosis and are immune privileged. Autologous MSCs have been used in the management of multiple sclerosis, osteoarthritis and are still under trials. Numerous clinical trials have been conducted on the application of both allogenic and autologous systemic MSC therapies in CD patients in the recent past. One of these initial human trials with systemic MSC therapy was conducted by Onken et al. [49], on patients with active CD who were refractory to combination treatment with steroids and other immunosuppressants (CDAI ≥220 and C-reactive protein ≥5 mg/L). Test subjects were given allogenic MSCs through intravenous route, first dose followed by a second dose after one week.

A reduction of ≥100-point in Crohn's Disease Activity Index (CDAI) was considered as the primary endpoint. Results showed clinical improvement in all ~~the~~ nine patients evaluated with a significant reduction in mean CDAI from baseline by day 28 (341 vs. 236, mean reduction- 105 points, P = 0.004, Wilcoxon signed rank). An increase in the mean IBD quotient score from baseline to day 28 was also observed (113 vs. 146, P = 0.008, Wilcoxon signed rank test). None of these patients developed any therapy-related adverse effects.

In 2010 Duijvestein et al. [50], studied the efficacy of autologous MSC therapy in patients with luminal CD refractory to steroids and other biologicals. MSCs from 9 selected patients out of 10 were expanded and administered as two intravenous doses of 1-2×106 cells/kg body weights, at one week apart. Patients were clinically monitored with CDAI scores and colonoscopy was done at weeks 0 and 6 to assess mucosal inflammation by the endoscopic index of severity. Although there was a failure to achieve remission, three patients showed positive response with a reduction in CDAI of ≥70 from baseline. Improved endoscopic response at six weeks was recorded in two patients. But conversely, three patients developed worsening disease and required surgery.

Lazebnik et al., also published the results of their study testing the response to a single intravenous dose of allogenic MSC therapy in 39 patients with ulcerative colitis and 11 patients with CD. Patients were followed up, and at the end of 4-8 months, statistically significant drop in the indices of the inflammatory process was observed in all 11 patients with CD and thus enabled the researchers to reduce the required dose of corticosteroids in these patients [51].

Following the positive results of these studies, a multicenter phase II study was undertaken by Forbes et al. [52], in which included are 16 active luminal CD patients (CDAI > 250) who were refractory to biologic therapy. These patients were infused with intravenous injections of allogenic MSCs, weekly for four weeks. Primary endpoint was set as clinical improvement with decrement in CDAI >100 points at 42 days.

Various secondary set points included were clinical improvement with CDAI <150, evidence of endoscopic response with CD endoscopic index of severity [CDEIS] value <3 , improved quality of life and better safety profile patients evaluated who completed the study in the subject group mean CDAI score declined from 370 to 203 at day 42 (P < .0001). 12 patients (80%) showed positive clinical response with reduction in CDAI score, 8 showed clinical remission (53%) and 7 showed endoscopic evidence of improvement (47%) with decrease in mean CDEIS scores from 21.5 to 11. One patient with pre-existing history of low-grade dysphasia developed malignant dysplastic lesion, although unrelated to MSC therapy, consideration of this adverse event is necessary.

Currently there is one ongoing phase 3 randomized multicentered trial studying the safety profile and efficacy of MSCs in refractory CD, which is expected to be completed in 2018. In this study, randomized test subjects are given four doses of intravenous MSCs and followed up with a primary endpoint of clinical remission set at 28 days [53].

Another major challenge in the management of Crohn's disease is the therapy for fistulizing CD. Fistulas constitute one of the major complications of CD, frequently requiring surgical intervention in view of their poor response to existing medical therapies and frequent recurrences. Perianal fistulas are commonly seen in patients with colonic CD involving rectum rather than with isolated ileal disease. About one-third of patients with CD develop fistulae during their disease course.

Transition of intestinal epithelial cells to mesenchymal cells, a process labeled as epithelial-to-mesenchymal transition (EMT) is considered as one of the major underlying factors in the pathogenesis of CD fistula formation. Fistulas in CD are infiltrated by various immune cells, the majority of which are CD45R0+ T-cells centrally and CD20+ B-cells in the outer wall [54]. Perianal fistulas in particular, show preponderance of infiltration with IL17A and IFN-γ secreting CD4+ CD161+ T-cells [55]. The presence of fistulizing CD is well correlated with increased levels of these pro-inflammatory cytokines in the serum.

Fistulas are also associated with extra-cellular matrix degradation which occurs due to an imbalance caused by increased expression of matrix remodeling enzymes, matrix metalloproteinase (MMP)-3 and MMP-9 and decreased expression of tissue inhibitors of MMP, (TIMP)-1, TIMP-2 and TIMP-3. Thus immunological component plays a major role in the pathogenesis of fistulizing CD and so the local injections of MSCs around fistulas has been started to be considered as a good treatment approach.

In 2005 Garcia-Olmo et al. [56], have published the results of the very first phase 1 clinical trial testing the efficacy and safety of autologous MSC therapy in fistulizing CD. After excluding one patient (out of 5) due to bacterial contamination of culture cells, nine fistulas were inoculated with autologous adipose tissue-derived mesenchymal stem cells in the remaining four patients. After following up eight inoculated fistulas for a period of eight weeks, complete healing was recorded in six fistulas (75%) and

incomplete healing in two (25%), without the evidence of any other adverse effects. Also Molendijk I et al., Eur J Gastroenterol Hepatol 2018 and Cao Y, Ding Z, Han C, Shi H, Cui L, Lin R, in their research on fistula treatment on CD have successfully established that local administration of MSC for perianal fistulizing CD is an effective method of treatment.

After receiving positive outcome from this phase 1 study, the same investigators have started a phase 2 randomized, [57] multicentered trial to further establish the efficacy and safety of these adipose-derived stem cells in the treatment of complex perianal fistulas. On comparison of patients who were treated intralesionally with fibrin glue alone and those treated with a combination of fibrin glue with stem cells, better rate of healing with no adverse effects was observed in the combined stem cell therapy group ($P < 0.001$).

Another pilot study was undertaken by Ciccocioppo et al. [58], in 2007 to study the effectiveness and safety of serial intrafistular injection therapy with autologous marrow-derived MSC in refractory fistulizing CD. Ten patients were given serial injections of MSCs scheduled every four weeks and were followed up with both radiologic and endoscopic monitoring. Additional evaluation of percentage of FoxP3 expressing regulatory T cells and influence of MSCs on T cell apoptosis was also performed. 7 out of 10 patients showed complete closure of fistulous track and remaining 3 showed incomplete closure. Rectal mucosal healing was also recorded in subjects along with a reduction in both Crohn's disease activity index and perianal disease activity index without any adverse effects. Long-term outcome assessment of the same patients was carried out by further monitoring until 2014, the results of which established the efficacy and safety of locally injected MSCs in rescuing refractory fistulizing CD patients [59].

In the year 2013, three different studies were published by De la Portilla et al. [60], Cho et al. [61], and Lee et al. [62], which further established the positive efficacy and safety of adipose tissue-derived mesenchymal stem cells in the treatment of fistulous CD. Recently a double-blinded placebo-controlled study was done in Netherlands by Molendijk I et al. [63], in which 21 patients with refractory fistulizing CD were treated with intrafistular injections of marrow-derived MSCs. Patients were randomly divided into three different groups, with each group receiving different dosages of treatment. Fistula healing at 12 weeks as established by the absence of discharge clinically and fluid collection < 2 cm size on MRI, was set as primary endpoint.

Positive clinical outcome with stable results through 24 weeks and without any adverse effects was observed in all the three groups.

Recently data from a large phase 3, double-blinded, placebo-controlled, randomized trial studying the efficacy and safety of MSCs in perianal fistulizing CD was published [64]. This study was performed over a period of three years from 2012 to 2015, and included a total of 212 treatment-refractory CD patients (divided at a ratio of 1:1 into treatment and placebo groups) with complex perianal fistulas from 49 hospitals in Europe and Israel. Treatment group were given a single intralesional dose of 120 million, allogenic adipose tissue-derived MSCs.

A combined remission at week 24 with both the clinical evidence of closure of all external draining fistula openings and absence of collections > 2cm as observed on MRI was set as a primary endpoint. Out of the 107 patients randomly assigned to MSC treatment group, primary endpoint was achieved in 50 % and it was 30% in the placebo group (difference 15·2%, 97·5% CI 0·2-30·3; p=0·024). No therapy-related adverse effects were observed except for local events including anal abscess and proctalgia suggestive of poor disease control.

CONCLUSION

With their varied immunomodulatory properties and tissue regenerative effects, the future of MSC therapy in the management of treatment-refractory CD patients will change significantly. Data from recent clinical trials, particularly of the phase III trial in patients with perianal fistulizing CD has managed to offer better treatment outcomes with MSC therapy and its safety profile. However, substantive work is in due progress such as determination of best source of MSCs, optimum dose, best route, frequency and site of administration. There is currently also no data available regarding the combined administration of MSC therapy with immunosuppressants and concomitant adjunctive surgical therapy in patients with perianal fistulae. There is also a need for further studies to establish the long-term safety of MSC therapy.

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Cite this article

Ali A, Kumar S, Sayyed Z, Shakuntulla NFN, Khetpal R, et al. (2018) Management of Crohn's Disease: Advances in Mesenchymal Stromal Cell Therapy. JSM Gastroenterol Hepatol 6(1): 1093.