Review Article

Stem Cell INVESTIGATION

Stem cell transplant in inflammatory bowel disease: a promising modality of treatment for a complicated disease course

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Contributions: (I) Conception and design: GA Salem; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: GA Salem; (V) Data analysis and interpretation: GA Salem; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Inflammatory bowel disease (IBD) is a complex, relapsing and remitting, disease characterized by an exaggerated immune response in a susceptible host. The symptoms and complications of the disease can be debilitating. Advances in medical treatment in the last decade changed the course of the disease in many patients. Despite the use of novel agents for controlling disease, a proportion of patients' disease courses continue to be either refractory, or become resistant, to available therapeutic options. Stem-cell therapy, with hematopoietic stem cells (HSCs) or mesenchymal stem cells (MSCs), is a promising modality of treatment for severe refractory cases, mainly Crohn's disease (CD) patients. HSCs have the ability to migrate to damaged tissue, which provides them with further properties to differentiate to epithelial or immune-modulatory cells to restore normal mucosal tissue and integrity. MSCs therapy is a promising model for patients with perianal CD due to their immunosuppressive properties, ability to migrate to areas of injury, and demonstration of colonic healing, including fistulizing tracts. The results from ongoing clinical trials will provide a valuable understanding of the future of stem-cell therapy as a treatment option in refractory cases of IBD, a disease whose pathogenesis remains unknown, and is notoriously difficult to treat.

Keywords: Stem cell transplant; inflammatory bowel disease (IBD); hematopoietic stem cell (HSC); mesenchymal stem cell (MSC); perianal disease

Received: 01 October 2017; Accepted: 01 November 2017; Published: 29 November 2017.
doi: 10.21037/sci.2017.11.04
View this article at: http://dx.doi.org/10.21037/sci.2017.11.04

Introduction

Inflammatory bowel disease (IBD) is a complex disease characterized by an exaggerated mucosal immune response, manifesting as a chronic inflammatory process of the gastrointestinal tract in a genetically susceptible host (1). The two main subtypes are Crohn's disease (CD) and ulcerative colitis (UC). At the time that gastrointestinal manifestation of UC tends to be more confined to the colon, with superficial continuous ulcerative process, CD can affect any part of the gastrointestinal tract, from mouth to anus, in a transmural, stricturing, and/or fistulizing patterns. Both results in significant alterations in quality of life due to remitting and relapsing symptoms of pain, increased stool frequency, hematochezia, anemia, intestinal obstruction, and potentially, surgery. However, these diseases are systemic disorders, and can affect many other organ systems. Extraintestinal manifestations are well described in the literature. While in many cases, these symptoms are believed to be a result of the underlying intestinal inflammatory process, the activity of other manifestations is found to be independent of the luminal disease activity.

The peak incidence is between ages 15–30, with a second,

relatively smaller, peak is in late adulthood in the 6th and 7th decade of age (2). Approximately 10–25% of IBD patients have one first degree relative with IBD (3). Interestingly, patients with family history of CD show similar disease phenotypes within affected family members (4). Having a positive family history of IBD remains the strongest risk factor for developing IBD (5).

Before 1998, when the Food and Drug Administration (FDA) first approved infliximab for the treatment of IBD, the cornerstones of medical therapy for IBD were corticosteroids and 5-aminosalicylate. Since then, biologic therapy has taken a prominent role in the treatment of IBD, and drugs in the anti-tumor necrosis factor (TNF) alpha (infliximab, adalimumab, certolizumab pegol, golimumab), anti-integrins (natalizumab, vedolizumab), and anti-interleukins (ustekinumab) classes have since been FDA-approved for the treatment of IBD. However, their cost, side effects, potential to develop loss of response, and, most importantly, their limited effect in some IBD patients, made scientists explore further treatment options. Patients who become refractory to medical management eventually require surgery; as up to 60% of patients with CD will require a surgical intervention at some point during their disease course (6), and 15% of UC patients will need colectomy (7). The ultimate goal in treating IBD is to achieve deep remission (symptom control and endoscopic healing of mucosal lesions), maintain maximal intestinal function, reduce long-term disability, and maintain a normal quality of life.

It has been reported that 33% of patients with CD do not respond to anti-TNF alpha therapy (8-10), and one third of responders will lose response at some point of their disease course to their current medical regimen (11). Based on all the foregoing and on advances in understanding of the pathophysiological mechanisms involved in IBD development, new biological drugs and stem-cell therapies continue to be investigated.

There is a growing evidence that stem-cell therapy can be an alternative method to treat ongoing tissue damage by resetting the underlying disease process, through alteration of the mucosal immune response (12,13). However, results from current clinical trials using both, hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), continue to be inconsistent.

HSCs are multipotent cells that can be isolated from bone marrow, umbilical cord, or peripheral blood (14). They have self-renewal capabilities, and the potential to differentiate into blood and immune cells. Their ability to migrate to damaged tissue provides them with further properties to differentiate to epithelial or immune-modulatory cells to restore normal mucosal tissue and integrity (15). MSCs are multipotent cells with potentials to differentiate to multiple mesoderm lineage cell types, such as adipocytes, myocardiocytes, chondrocytes, and osteoblasts (13,16,17). Their major sources of isolation for therapeutic purposes are bone marrow, umbilical cord, and adipose tissues. In addition to differentiation, MSCs have immunomodulatory capabilities to downregulate mucosal immune reactivity by promoting regulatory T-cell (Treg) formation (18), most potent immunosuppressive T cells, including inhibition of proliferation and function of Th1 and Th17 cells, and promote tissue healing (19).

Hematopoietic stem cell transplant (HSCT) in IBD

Current studies continue to focus on autologous HSCT, which is intended to reset the immune system by *de novo* regeneration of T-cell repertoire, and repopulation of epithelial cells by bone-marrow derived cells to help patients achieve clinical and, potentially, endoscopic remission. Allogeneic HSCT carries high morbidity and mortality rate for treatment of IBD, and has been used for monogenic diseases, like IL-10 deficiency, as it would correct the disease by building a new immune system in the host (18,19).

There has been an increasing interest in autologous HSCT in patients with severe CD who are refractory to treatment. A single-center cohort from Spain studied the effect of autologous HSCT in 29 patients with CD, unresponsive to current available therapies (20). Seventy percent of patients achieved drug-free clinical remission at 6 months of follow up. The proportion of patients who remained in drug-free remission state at 5 years of follow up was 15%. Interestingly, 80% of patients who relapsed were successfully managed with medical therapy. The largest multi-center randomized trial published to date, the ASTIC Trial, reported no benefit of HSCT over mobilization alone at 1 year, for primary endpoint of steroid-free clinical remission for 3 months with mucosal healing and absence of radiological evidence of active inflammation (21). Yet, critics of this trial have deemed autologous HSCT as a promising treatment for severe refractory CD, as the predefined primary endpoint for the ASTIC trial was the most stringent ever used for a clinical trial in CD compared to drug trials. Data was further analyzed using traditional

endpoints for clinical trials of conventional therapy in CD, and autologous HSCT showed a statistically significant clinical and endoscopic benefits, although it was associated with a high burden of adverse events, with infections being the most common (22).

Mesenchymal stem cell transplant (MSCT) in IBD

Due to their immunosuppressive properties and their role in tissue repair, MSCs seem to be a promising tool in immune-regulatory and regenerative cell therapy in a variety of medical conditions. Major advantages of MSCs over HSCT are their low immunogenicity properties, non-myeloablative technique; without total body irradiation, and eliminating the need for chemotherapy. The idea of low immunogenicity of MSCs originates from the fact that they express low levels of major histocompatibility complex (MHC) class I, not MHC class II, without costimulatory molecules that would activate T cells during the infusion process. MSCT has been evaluated for the treatment of IBD in two different modalities; intra-lesional injection to treat fistulas in CD, and intravenous administration to treat luminal CD and UC. Local injection of autologous and allogeneic MSCs have shown positive results in multiple case series and randomized controlled trials compared to placebo in patients with complicated fistulizing disease, not responding to traditional therapies with immunomodulators, anti-TNF alpha agents, and local management, including surgery (23,24). A 12-patient, 6-month, phase 1 trial has shown an 83% rate of complete clinical healing and radiological evidence of response of complicated fistulas in CD patients treated with intra-fistulous autologous MSCT (25). A different phase I study of four patients suffering from one or more refractory, complex CD fistulas were treated with a single intra-fistula injection of autologous MSCs. Healing was seen in 6 out of 8 fistulas at 8 weeks, and partial closure with decreased drainage was observed in the 2 remaining fistulas. There were no adverse effects at 12- to 22-month follow-up (26). The same investigator further looked at response to intra-fistula MSCs in a phase II trial. Forty nine patients with complex perianal fistulas were randomly assigned to treatment with intra-lesional injection of fibrin glue or fibrin glue plus adipose tissue-derived MSCs, followed by a second double dose of adipose tissue-derived MSCs if fistula healing was not achieved at 8 weeks. Seventeen out 24 patients receiving adipose tissue-derived MSCs had complete resolution of fistulas, 11 patients healed after the first injection and 6 patients needed a second injection, compared to 4 out of 25 in the control group. There was a significant improvement in quality of life in the treated group compared to controls (27). Allogeneic MSCT is an effective and safe treatment modality for complex perianal fistulas in patients with CD who did not respond to conventional or biological treatments, or both. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multi-center clinical trial of 212 patients with refractory, complex, active perianal fistulas were treated with surgical closure of the internal opening of the fistulas followed by a single injection of either MSCs or placebo into the tissue adjacent to all fistula tracts and internal openings, in addition to their current treatment. At 24 weeks of follow up, fistula closure rates—assessed by both clinical and MRI evaluation—were statistically significant higher in the MSC group compared to placebo, with a significantly shorter time to obtain closure of all treated external openings (28). Intravenous autologous MSCs therapy for luminal CD was evaluated in two studies with modest benefits, as it failed to sustain clinical remission with reported worsening of CD symptoms in some cases (29,30). Studies of allogeneic MSCs infused intravenously have shown superiority when compared to autologous studies in treatment of luminal CD. A phase I clinical trial of seven patients with IBD (four patients with CD and three with UC) were treated with intravenous allogeneic MSCs, while continuing their treatment regimens with steroids and/or immunosuppressors. After 3 months, a significant reduction in CD activity index (CDAI) and UC clinical activity index (CAI) scores were observed in all patients, as remission was achieved in 5 out of the 7 patients (2 patients with CD and 3 patients with UC). Endoscopic improvement was observed by a decrease in endoscopic index of severity score from 19.1 to 4.2 points at 4 months and from 14.5 to 3 points at 3 months in two CD patients, as well as a decrease in endoscopic activity index from 7 to 5 at 5 months in a UC patient (31). In a phase II trial, 15 patients with refractory active luminal CD were treated with allogeneic MSCs for 4 weeks. After 6 weeks, there was a reduction of the mean CDAI scores and improvement of mean quality of life scores in patients with luminal CD refractory to biologic therapy (32). The probably most important work in this field is a large (330 patients enrolled), multicenter, randomized, double-blind, phase III trial generated by Osiris Therapeutics. Patients will be treated with Prochymal™, an intravenous formulation

of MSCs derived from the bone marrow of healthy adult donors, at different IV doses for moderate-to-severe CD, with final results are expected in 2018. According to data reported to date, the safety profile appears to be favorable, and formation of aberrant tissue has not been detected (33).

Conclusions

IBD is a complex, relapsing and remitting, disease characterized by an exaggerated immune response in susceptible host. The symptoms and complications of the disease can be debilitating. Treat-to-target strategy in IBD focuses on achieving clinical and mucosal remission, prevent further disease progression, and maintain maximal function of the intestinal tract. The diversity of effective treatment modalities, with the emergence of new agents, changed the disease course in many patients with IBD, and provided more options in complicated, refractory cases. Hematopoietic and MSC therapy has been shown to be a potential alternative therapy for disease control in refractory IBD, mainly CD patients. MSCs offer a promising emerging therapy for patients with IBD due to their immunosuppressive properties, ability to migrate to areas of injury, and demonstration of colonic healing. Both intra-lesional autologous and allogeneic MSCs have demonstrated efficacy in fistulizing Crohn's disease, while intravenous allogeneic MSCs have shown more promising results than autologous MSCs in luminal Crohn's disease. The results from ongoing clinical trials will provide a valuable understanding of the future of stem-cell therapy as a treatment option in refractory cases of IBD, a disease whose pathogenesis remains unknown, and is notoriously difficult to treat.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/sci.2017.11.04
Cite this article as: Salem GA, Selby GB. Stem cell transplant in inflammatory bowel disease: a promising modality of treatment for a complicated disease course. Stem Cell Investig 2017;4:95.

