

# Stem cell therapeutics: potential in the treatment of inflammatory bowel disease

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**Abstract:** Stem cell therapies may be valuable in treatment of inflammatory bowel disease (IBD). Here we focus on two very different types of stem cells – hematopoietic stem cells and mesenchymal stem cells. Myeloablation and hematopoietic stem cell transplantation alter host immune response by reconstituting the recipient's blood cell lines with donor cells. Autologous hematopoietic reconstitution may “reboot” mucosal immunity to a normal baseline state, but does not alter any underlying genetic predisposition to IBD. In contrast, allogeneic hematopoietic transplantation reconstitutes all blood lineages from a tissue-matched donor who presumably does not have a genetic predisposition to IBD. Compared with autologous hematopoietic transplantation, allogeneic hematopoietic transplantation carries a much greater risk of complications, including graft-versus-host disease. Mesenchymal stem cells can give rise to cartilage, bone and fat in vitro, but do not reconstitute hematopoiesis after transplantation. Systemically infused mesenchymal stem cells appear to favorably downregulate host immune responses through poorly understood mechanisms. In addition, mesenchymal stem cells may be applied topically to help close fistulas associated with Crohn's disease. For all of these stem cell therapy applications for IBD, only cases and small series have been reported. Larger clinical trials are planned or ongoing.

**Keywords:** inflammatory bowel disease, Crohn's disease, stem cell therapy, bone marrow transplant, mesenchymal stem cell

## Introduction

Stem cells are defined by asymmetric cell division, self-renewal, and multilineage differentiation. Stem cell-based therapies hold great promise for many diseases. Embryonic stem cells (ES) are pluripotent cells derived from the preimplantation embryo, capable of forming tissues from all three germ layers in vitro and in vivo. The ability of ES cells to expand in culture and differentiate to specific phenotypes under various culture and growth factor conditions makes them an attractive source of cells for therapy. Induced pluripotent stem cells (iPS) can be derived from adult somatic cells forced to reprogram to an ES-like state in culture. Like ES cells, iPS cells can be redirected toward other phenotypes under specific culture conditions. iPS cells are not derived from embryos, avoiding ethical concerns regarding the use of human embryos. iPS cells can also be made from any patient, allowing the production of patient-specific and disease-specific cells for research and treatment. Undifferentiated ES and iPS cells can both give rise to teratomas after transplantation, so complete eradication of undifferentiated cells is a critical step toward the clinical use of cell therapy when ES or iPS cells are used to produce differentiated cells for therapy.

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In contrast, adult stem cells are derived from mature organs and are much more limited in differentiation potential compared with ES or iPS. As such, adult stem cells might be better considered as multipotent “progenitor” cells rather than stem cells. However, the language of “adult stem cells” is well established so we will follow this convention. The best understood adult stem cells are hematopoietic stem cells, which can be enriched from the bone marrow or collected from peripheral blood. After transplantation into properly conditioned recipients, hematopoietic stem cells reconstitute and maintain all the mature blood lineages. Bone marrow transplantation has become an accepted treatment for leukemias, lymphomas, and other blood diseases. For patients facing otherwise incurable and fatal blood diseases, the potential benefits of bone marrow transplantation outweigh the risks of infection, hemorrhage and graft-vs-host disease.

Mesenchymal stem cells (MSC) are an entirely different type of adult stem cell. MSC can be derived from bone marrow, fat, or other tissues. MSC are perhaps more restricted in their differentiation potential to mesodermal tissues such as fat, cartilage and bone. Transplanted MSC do not reconstitute hematopoietic lineages, but can alter the host immune response. In this review we will consider cell therapy based on hematopoietic stem cell transplantation or MSC infusion for the treatment of Crohn’s disease (CD) and ulcerative colitis (UC). To date, there are no reports of therapeutic interventions for inflammatory bowel disease (IBD) using ES or iPS-derived cells.

In patients with IBD, mucosal ulceration and inflammation may cause abdominal pain, chronic diarrhea, anemia and malnutrition. In UC, the inflammation is generally limited to the mucosa of the colon. In contrast, the inflammation in CD affects all layers of the bowel wall and is not limited to the colon. The transmural inflammation of CD may lead to bowel obstruction or fistula formation requiring surgical intervention. In both conditions, chronic inflammation is associated with an increased risk of intestinal malignancy. IBD may be considered an autoimmune disease, resulting from inappropriate immune reactivity against one’s own tissues in the digestive tract. The mainstay of clinical treatment is a combination of anti-inflammatory agents such as 5-aminosalicylates and immunosuppressive medications, including corticosteroids and immunomodulators such as azathioprine. Newer agents, including monoclonal antibodies directed against tumor necrosis factor or alpha-4-integrin, are available for patients who are unable to achieve remission with standard immunosuppression. Despite treatment, the morbidity and

cost of IBD remain high. Corticosteroids are not effective for maintaining remission of IBD and induce well-known adverse side effects, including weight gain, diabetes and osteoporosis. Immunosuppression carries significant risk for infection by opportunistic pathogens. New treatment approaches are needed.

Recent advances reveal a primary role of dysregulation of the immune system in the pathogenesis of IBD. Sophisticated genome-wide association studies implicate maladaptive signaling of a number of cytokines and their receptors.<sup>1</sup> Examples include variants in genes encoding NOD2/CARD15, IL23R, TNFSF15<sup>2,3</sup> and IL-10R.<sup>4</sup> Mouse models of IBD may be categorized as chemical, genetic, immunologic, and spontaneous.<sup>5</sup> Each approach offers different strengths and limitations, but it is now clear that the mucosal immune response to luminal antigens plays a central role in the pathogenesis of IBD. Genetically susceptible mice reared under germ-free conditions fail to develop disease, demonstrating the essential role of luminal flora. Classic experiments demonstrated that IBD-like illness can be transmitted by adoptive transfer of pathogenic T cells in mice.<sup>6</sup> In a susceptible host, inappropriate and prolonged immunologic response to mucosal flora results from failure of regulatory T cells to restrict the activity of self-reactive effector T cells.<sup>7-9</sup> While bone marrow transplant from IL-10 knockout mice into wild-type recipients does not transfer IBD, colitis can be markedly ameliorated in IL-10 knockout mice after bone marrow transplantation with normal bone marrow. The improvement of colitis after transplantation of normal bone marrow into IL-10 deficient mice appears to be due to engraftment of donor-derived subepithelial myofibroblasts.<sup>10</sup> A possible human case of adoptive transfer of IBD was reported in a patient undergoing allogeneic bone marrow transplant (BMT) for Hodgkin’s disease. Though the patient had no prior history of IBD, she developed acute fulminant Crohn’s colitis 6 months after allogeneic BMT. While the stem cell donor had no personal or family history of IBD, genomic analysis showed that the donor, but not the recipient, carried a CD-associated polymorphism in the NOD2/CARD15 gene. Donor and recipient also had numerous HLA class III haplotype mismatches at the IBD3 locus.<sup>11</sup>

While immunosuppression can reduce and control inflammation, it fails to fundamentally interrupt the underlying disease process. Advances in bone marrow transplantation now allow the ablation and replacement of the hematopoietic system with autologous or allogeneic hematopoietic stem cells. In some cases, this appears to effectively interrupt the cycle of inflammation by “resetting” the immune system with

naïve cells. Another novel treatment approach is the use of mesenchymal stem cells (MSC), typically derived from bone marrow or fat, as immunosuppressive agents to downregulate mucosal immune reactivity.

There are many case reports and small retrospective series of patients experiencing dramatic improvement in chronic non-IBD autoimmune conditions following autologous or allogeneic hematopoietic stem cell transplantation for unrelated malignancies. These unexpected successes led to trials of hematopoietic stem cell transplantation (mostly autologous) as a salvage therapy for autoimmune diseases refractory to standard immunosuppressive therapy.<sup>12</sup> Similarly, unexpected remission of IBD in patients undergoing BMT for other reasons inspired examination of BMT as a therapy for IBD.

This review will focus on two “stem cell therapy” approaches to treating IBD by fundamentally altering the mucosal immune response: bone marrow hematopoietic stem cell transplantation and mesenchymal stem cell transplantation.<sup>13</sup>

## Autologous bone marrow stem cell transplantation for IBD

The first report of remission of IBD after autologous hematopoietic stem cell transplantation was that of a 41-year-old woman with more than 20 years of fistulizing CD, who subsequently developed non-Hodgkins' lymphoma (NHL). Her NHL was treated with chemotherapy and autologous bone marrow stem cell rescue. Six months after BMT, the lymphoma was in remission and she was free of CD symptoms for the first time in many years. The authors speculated that the improvement in her CD resulted from the BMT, and concluded that CD need not be an absolute contraindication to autologous BMT.<sup>14</sup> Several more anecdotal reports

of clinical remission of IBD in patients who underwent chemotherapy and autologous hematopoietic stem cell rescue for coincidental malignancies followed (Table 1).

Based in part on the successful treatment of patients with CD and coincident malignancies using stem cell mobilization, myeloablation, and autologous stem cell rescue, this approach has been attempted as salvage therapy for IBD in patients who did not have malignancies (Table 2). The patients reported in those studies had active, refractory CD with multiple complications. Oyama et al<sup>15</sup> reported clinical remission in 11 of 12 patients, while Cassinotti et al<sup>16</sup> reported remission in 3 of 4 patients. This approach effectively takes immunosuppression to the extreme, completely ablating the immune system and reconstituting it with hematopoietic stem cells which give rise to naïve lymphoid and myeloid cells. The effectiveness of this approach is consistent with the model that dysregulation of T cell activity against mucosal self antigens plays a major role in the pathogenesis of IBD. The lack of recurrent disease after autologous BMT indicates that interruption of the pro-inflammatory T cell response is sufficient to break the maladaptive cycle of self-reactivity. However, the number of patients reported is very small and there were no controls. The success of this approach might be overestimated by reporting bias, since therapeutic failures and treatment-related adverse events may be less frequently reported. One patient with remission of CD following autologous BMT for NHL experienced relapsed of her CD 8 years later, indicating that long-term follow up is essential.<sup>17</sup>

Despite these limitations, the clinical improvements are very impressive in a group of patients refractory to even the best available standard treatment. While the risk of morbidity and mortality from sepsis and hemorrhage during the interval between myeloablation and autologous hematopoietic reconstitution is significant, a carefully designed, prospective clinical

**Table 1** Case reports of IBD outcomes after myeloablation and autologous stem cell transplantation for coincidental malignancy

Disease (n)	Indication	Conditioning	Graft	IBD outcome	Ref
CD (n = 1)	NHL	Chemo	BMSC 3 × 10e8/kg	Remission at 6 mos Off immunosuppression	14
UC (n = 1)	Breast cancer	Chemo	mPBSC ?dose	Remission > 2 yrs	67
CD (n = 1)	Breast cancer	Chemo	mPBSC ?dose	Remission > 2 yrs	67
CD (n = 1)	T cell NHL	Chemo	mPBSC 9.8 × 10e8/kg	Remission 7 yrs Off immunosuppression	68
CD (n = 1)	Hodgkin's	Chemo	mPBSC ?dose	Remission > 3 yrs Off immunosuppression	69
CD (n = 1)	AML	Chemo TBI	BMSC, mPBSC ?dose	Remission > 6 yrs Off immunosuppression	70

**Abbreviations:** See list in text.

**Table 2** Case reports and small series of inflammatory bowel disease outcomes after myeloablation and autologous stem cell transplantation for Crohn's disease

Disease (n)	Conditioning	Graft	IBD outcome	Ref
CD (n = 1)	Cyc	T-cell depleted CD34+ mPBSC 6.4 × 10e6/kg	Remission for 9 mos Recurrent aphthous ulcers Maint. corticosteroids and MTX	71
CD (n = 1)	Cyc ATG	T cell-depleted CD34+ mPBSC 3.4 × 10e6/kg	Symptomatic remission for 5 mos Endoscopic and pathologic improvement, off immunosuppression	72
CD (n = 12)	Cyc ATG	T-cell depleted CD34+ mPBSC 2 × 10e6/kg	Remission in 11 of 12 7–37 mos follow-up Corticosteroids tapered over 2–6 mos	15
[*2 of these subjects were already reported by Burt et al in 2003]				
CD (n = 1)	Not stated	Not stated	Remission for 8 yrs followed by relapse	17
CD (n = 1)	Not stated	Not stated	Remission for 6 yrs	73
CD (n = 4)	Cyc ATG	mPBSC ?dose	Remission in 3 of 4 11–20 mos follow-up Off immunosuppression	16

**Abbreviations:** See list in text.

trial is warranted for patients who have failed conventional therapy and are willing to accept the risk of autologous BMT. A multicenter, prospective, randomized Phase III trial, “Autologous Stem Cell Transplantation in Crohn's Disease (ASTIC)” is underway in Europe. All patients enrolled in this trial will undergo stem cell mobilization and leukapheresis. Patients will then be randomized to undergo either immediate or delayed (one year) immunoablation and autologous stem cell transplantation. Patients in the delayed transplant group will continue to receive optimal conventional care for CD. This design allows all patients in the trial the opportunity to undergo autologous BMT, with the delayed transplant group serving as controls. The immediate transplant group will be compared with the delayed transplant group in terms of disease remission, defined as a CD activity index of  $\leq 150$  without steroids or immunosuppressive drugs and no mucosal erosion or ulceration at ileocolonoscopy, and no definite evidence of small bowel Crohn's Disease on barium studies. A total of 48 patients will be recruited. As of July, 2009, 14 patients had been enrolled, 7 of whom have undergone autologous BMT. Additional details are available at <http://www.nottingham.ac.uk/icr/astic/index.php>. It is not clear whether autologous BMT will benefit patients with germline polymorphisms in CD-susceptibility genes, which will not be altered by autologous BMT. This issue will need to be considered in the outcome analysis of the clinical trials.

## Allogeneic bone marrow stem cell transplantation

There have been numerous reports of fortuitous resolution of non-IBD autoimmune diseases such as rheumatoid arthritis

and psoriasis in patients who underwent allogeneic BMT for leukemias.<sup>18–21</sup> The first reported case of a patient with UC undergoing allogeneic BMT was a 39-year-old woman with a 12-year history of UC, who subsequently developed AML. Following induction and consolidation treatment with chemotherapy, she received an allogeneic BMT from her HLA-matched brother. Four years later, her AML remained in remission and her UC was clinically inactive.<sup>20</sup> The first reported case of a patient with CD undergoing allogeneic BMT was a 35-year-old man with stricturing CD who subsequently developed acute myelocytic leukemia (AML). The AML was treated with multiagent chemotherapy and the patient underwent allogeneic BMT from his HLA-matched brother. His post-transplant course was complicated by mild GVHD of the skin, which responded to corticosteroids. All immunosuppression was tapered off over the next 7 months and he remained in remission of both AML and CD for at least 8 years.<sup>22</sup>

Two retrospective series of patients with both IBD and leukemia who underwent allogeneic BMT reported a substantial number of remissions from IBD (Table 3). Lopez-Cubero<sup>23</sup> reported 6 CD patients who underwent allogeneic BMT for CML or AML. All were treated with multiagent chemotherapy for leukemia. Transplant conditioning regimens included cyclophosphamide and total body irradiation. Allogeneic donor cells were HLA-matched in all but one case and were not T cell-depleted. CD activity could not be assessed in the patient with AML, who died from sepsis 97 days after transplant. Of the five survivors, four achieved symptomatic remission from CD over 4 to 15 years of follow-up. Both acute and chronic GVHD of the

**Table 3** Case reports and small series of inflammatory bowel disease outcomes after myeloablation and allogeneic stem cell transplantation

Disease (n)	Indication	Conditioning	Graft	IBD outcome	Ref
UC (n = 1)	AML	Not stated	Not stated	Remission 4 yrs	20
CD (n = 1)	AML	Chemo	AlloBMT CSA for 7 mos Steroids for 2 mos	Remission 7 years off immunosuppression	22
CD (n = 5)	CML	Chemo TBI	AlloBMT, varied	Remission in 4 of 5 patients followed for 4–15 yrs	23
(A sixth CD patient with AML died 97 days after alloBMT; recurrent CD could not be evaluated)					
CD (n = 7) UC (n = 4)	AML, CML, MF	Varied	AlloBMT, varied	Remission in 9 of 10 survivors	24
CD (n = 1)	IBD, IL-10RB mutation	Chemo	Sibling AlloBMT	Remission 1 yr	4

**Abbreviations:** See list in text.

skin and/or liver were noted in the same four patients who achieved remission from CD.

Ditschkowski and colleagues<sup>24</sup> reported a retrospective review of 7 CD patients and 4 UC patients who underwent allogeneic BMT for AML, CML or myelofibrosis. Five of the CD patients had a history of fistula or luminal stenosis. Prior to BMT, five patients had inactive IBD, while six were described as having mild or low activity based on symptoms, endoscopic findings, or histology. The chemotherapy, myeloablative conditioning regimen and transplantation protocols varied. One patient died within the first year after transplant from pulmonary fungal infection. Of the 10 survivors, only 1 had mild CD after transplant, while the other 9 achieved remission from IBD during a median followup period of 34 months (range 3 to 117 months). Eight patients developed Grade I or II GVHD, which was managed successfully with steroids. None developed severe or chronic GVHD. A very recent report identified loss-of-function mutations in IL10-RA and IL-10RB in patients with early onset, severe enterocolitis.<sup>4</sup> One patient with a mutation in the IL1-10RB gene suffered from severe anocutaneous fistula, refractory to standard therapy. He underwent allogeneic BMT from an HLA-matched sibling who did not carry the IL-10RB mutation. He achieved full donor hematopoietic chimerism, and his post-transplant course was marked by mild GVHD, treated successfully with corticosteroids. More than 1 year after transplantation, his IBD was fully in remission.<sup>4</sup> In the case where the genetic mutation underlying IBD could be clearly identified, autologous transplantation would not have been helpful. An HLA-matched sibling donor without that mutation was available, so allogeneic transplantation was both ethical and practical. To our knowledge, there are

no planned prospective clinical trials of allogeneic BMT in IBD, presumably due to concerns for the greater incidence of transplant-related complications in allogeneic BMT recipients compared with autologous BMT.

## Immunomodulatory stem cell therapy with MSC

MSC are a fibroblast-like cell population, first recognized as a population of non-hematopoietic bone marrow cells which adhere to plastic tissue culture dishes.<sup>25</sup> MSC are a multipotent stem cell population, capable of differentiating into osteocytes, chondrocytes and adipocytes under appropriate culture conditions.<sup>26</sup> In an attempt to standardize the definition of MSC, minimal criteria were proposed (Table 4).<sup>27</sup> MSC have now been isolated from a wide variety of adult tissues,<sup>28</sup> though most attention has focused on MSC derived from bone marrow or fat. A great deal of interest has focused on potential therapeutic uses for MSC due to their reported ability to suppress inflammation and promote tissue healing.<sup>29</sup>

Several potential mechanisms have been proposed for the potential immunomodulatory effects of MSC, including release of soluble factors (cytokines, chemokines, growth factors), induction of cell cycle arrest in pro-inflammatory

**Table 4** Minimal criteria for defining multipotent mesenchymal stem cells<sup>27</sup>

1. Adherent to plastic under standard culture conditions
2. Express CD105, CD73 and CD90
3. Lack expression of CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-DR
4. Differentiate to osteoblasts, adipocytes and chondroblasts in vitro

**Abbreviations:** See list in text.



lymphocytes, and induction of T cell apoptosis.<sup>30</sup> A likely role for nitric oxide in MSC-mediated immunosuppression has been recently identified.<sup>31</sup> In addition to modulating immune activity, MSC may also regulate wound healing through direct or indirect interactions with resident tissue-committed stem cells.<sup>32</sup> The immunomodulatory and wound healing effects of MSC provide the rationale for investigation of their therapeutic value in autoimmune and inflammatory disease conditions.

Efforts to improve the engraftment of transplanted human hematopoietic stem cells by coinfusion of MSC met with variable success but little persistent stromal chimerism, so the mechanism of benefit is unclear.<sup>33–36</sup> Many reports claim that donor MSC need not be immunologically compatible with the recipient because they are non-immunogenic,<sup>37</sup> though there is some evidence to the contrary.<sup>38</sup> Much of the evidence for immunosuppressive effects of MSC is based on *in vitro* work, which may not translate to *in vivo* efficacy.

Nonetheless, there are numerous reports of beneficial effects of MSC in animal models of autoimmune disease.<sup>39,40</sup> The mouse myelin oligodendrocyte glycoprotein 35–55 experimental autoimmune encephalomyelitis (EAE) model shares features with human multiple sclerosis. Using the EAE model, syngeneic MSC administration was shown to ameliorate neurologic and histologic abnormalities by inducing T cell anergy, but only when the MSC were administered early in the course of disease.<sup>41</sup> In a similar model of EAE, MSC administration reduced inflammation and demyelination through induction of T cell anergy. The infused MSC were not found in the central nervous system, indicating that the beneficial effect may have been achieved through immunomodulation rather than engraftment.<sup>42</sup> MSC therapy has also been reported to exert a protective effect in mouse models of rheumatoid arthritis<sup>43,45</sup> and diabetes.<sup>46,47</sup>

## What is the fate of transplanted MSC *in vivo*?

Systemically infused MSC appear to migrate toward sites of injury and inflammation. The mechanism by which MSC find their way is not fully understood and likely varies among tissues, but involves interactions between chemokines and their receptors (reviewed in).<sup>29,48</sup> The goal of developing MSC for therapy requires understanding of the fate of transplanted cells, which depends on the dose and route of administration. Few studies have addressed this concern directly. Systemic administration may be sufficient if MSC can home to damaged tissues, but local administration may

be necessary if high level tissue engraftment is required for therapeutic effect.

To investigate this issue, <sup>111</sup>In-labeled syngeneic rat bone marrow MSC were expanded in culture, delivered to normal rats by intraarterial, intravenous or intraperitoneal injection, and followed by whole-body gamma imaging. Immediately after administration, tracer localized mostly in lungs and liver. After 48 hours, most of the tracer appeared in the liver.<sup>49</sup> Major limitations of this approach are that individual organs were not examined in detail, and live donor cells were not distinguished from dead cell debris being cleared by the reticuloendothelial system.

Using a very sensitive PCR DNA ELISA assay, Devine et al<sup>50</sup> showed that gene-marked autologous or allogeneic bone marrow MSC could be detected in baboon bone marrow for as long as one year after systemic infusion. In subsequent investigations, gene-marked bone marrow MSC could also be detected by PCR in the digestive tract, liver, pancreas, lung kidney and skin of recipient baboons from 9 to 21 months after intravenous infusion. The engraftment of gene-marked cells was estimated from 0.1% to 2.7%, but histologic localization of MSC-derived cells was not reported.<sup>51</sup>

Another approach to monitoring MSC trafficking after transplantation is to label cells in culture with iron particles and follow their distribution *in vivo* using magnetic resonance imaging (MRI). Iron particles are phagocytosed by MSC or hepatocytes and stably retained without overt toxicity. Iron-labeled cells can be directed to desired sites of engraftment, such as the liver, using an externally-applied magnetic field.<sup>52</sup> Using this approach, single MSC can be detected by MRI in the liver after intrasplenic injection.<sup>53</sup> Tracking of infused MSC using MRI has not been reported in models of IBD.

## Human MSC therapy for GVHD

Graft versus host disease (GVHD) in recipients of allogeneic BMT results from response of the donor-derived immune cells to host antigens. GVHD typically affects the skin, GI tract and liver, and often requires immunosuppression. Evidence from animal models suggests that MSC derived from adipose tissue can reduce GVHD.<sup>54</sup> Coinfusion of human MSC with HLA-identical hematopoietic stem cells at the time of transplantation may reduce acute and chronic GVHD.<sup>55</sup> The immunomodulatory effects of MSC may therefore provide beneficial effects on acute GVHD and also, thereby, points to the possibility that similar mechanisms might improve immune-mediated injury in IBD or modulate

GVHD if administered to IBD patients receiving allogeneic transplants for that disease.

The first reported case of MSC therapy for severe acute GVHD was that of a 9 year-old boy with ALL, who underwent BMT from an unrelated HLA-matched donor. His course was complicated by Grade IV GVHD, refractory to immunosuppression. He was treated with unmatched bone marrow MSC from his mother, administered in two separate systemic infusions. The patient experienced a gradual but dramatic clinical improvement over the next several months and remained asymptomatic of gastrointestinal GVHD 1 year after transplantation.<sup>56</sup>

In September, 2009 Osiris Therapeutics reported in a press release preliminary results of a Phase III double-blind, placebo-controlled trial of human MSC for steroid-refractory GVHD or as a first-line therapy for GVHD after allogeneic BMT. Among the patients with steroid-refractory GVHD of the gastrointestinal tract or liver, there was a significant improvement in GVHD. However, the primary end point (durable complete response) was not met.

## Potential benefit of MSC in animal models of colitis

The ability of MSC to induce tolerance has been investigated in animal models of immune-mediated inflammatory bowel diseases. Foxp3 mutant mice develop autoimmune disease affecting the small bowel due to failure to regulatory T cells to eliminate self-reactive T cell clones. Administration of syngeneic MSC ameliorated inflammatory disease in the ileum. Donor cells were detected in lymphoid tissue in the gut rather than in the epithelium, consistent with a model of immunoregulation by infused MSC, rather than epithelial engraftment.<sup>57</sup>

In the trinitrobenzene sulfonic acid (TNBS) model of colitis, intraperitoneal delivery of human or murine adipose-derived MSC improved diarrhea, body weight, histology and survival, in part by downregulating inflammatory cytokines and upregulating IL-10.<sup>58</sup> Similarly, human or murine adipose-derived MSC abrogated diarrhea, weight loss, while improving histology and survival in the dextran sulfate mouse model of colitis, also through downregulation of pro-inflammatory cytokines and upregulation of IL-10.<sup>59</sup>

## Human MSC therapy for IBD

Modest improvements in CD activity index and endoscopic appearance of CD were reported in abstract form in a small series of patients undergoing autologous systemic MSC treatments. Adverse effects were minimal, so the authors

concluded that MSC therapy is at least safe and feasible.<sup>60</sup> The trial is ongoing.

Osiris Therapeutics is testing an allogeneic human MSC product (OTI-010, Prochymal) for use in stem cell therapy treatments for GVHD and CD. A Phase II, randomized, multicenter, open-label pilot trial of OTI-010 for CD refractory to standard therapy began in 2005. Patients continued their standard treatment regimen for CD during the trial. In 2006, Osiris reported in a press release that CD patients treated with intravenous MSC (n = 9) had a significant decrease in CD activity index, from 341 to 236, 4 weeks after treatment. Three of the 9 patients had clinical response within 14 days. The trial was very small and lacked controls, but the MSC treatment was safe and well tolerated. A Phase III trial is planned.

## Local MSC delivery to enhance healing of enterocutaneous fistula

Perianal fistulae resulting from CD can be very difficult to treat effectively, leading to pain, distressing leakage, abscess formation and reduced quality of life. Medical treatment with 6-mercaptopurine, metronidazole or Infliximab is often unsuccessful. Surgical treatment may be complicated by recurrence or anal incontinence. The ability of MSC to differentiate to a stromal phenotype led to investigation of adipose-derived autologous MSC to enhance healing of perianal fistula. In a Phase I study, 8 fistulae in 4 CD patients were treated with local injection of adipose-derived autologous MSC and fibrin glue. After 8 weeks, 6 of the 8 fistulae had epithelialized, while two continued to drain.<sup>61</sup>

In a Phase II study, 49 patients with perianal fistula were randomized to undergo attempted fistula closure using fibrin glue, with or without adipose-derived MSC. Fistula healing occurred in 71% of the patients receiving MSC with fibrin glue, compared with just 16% of patients treated with fibrin glue alone.<sup>62</sup> Whether the MSC directly engraft the fistula tract or simply promote closure could not be assessed because the cells were autologous. Adverse events were generally unrelated to the treatment, except in the case of one non-IBD patient who developed a perianal abscess after application of fibrin glue without MSC. Phase III trials are under way in Europe.<sup>63</sup>

## Potential risks of stem cell therapies

The risks of autologous or allogeneic hematopoietic stem cell transplantation are well known, and include hemorrhage, sepsis and graft-vs-host disease. Allogeneic bone marrow

donors are thoroughly screened to prevent transmission of infectious diseases, though acute infections may be missed and laboratory errors are always possible. The production of clinical-grade human MSC for therapy also requires rigorous exclusion of infectious bacterial and viral diseases. Unlike hematopoietic cells, MSC must be expanded in culture under Good Manufacturing Process conditions, with rigorous quality controls. In published reports, human MSC were prepared from autologous donors or from "normal" allogeneic donors without further description. It would appear that the risk of infectious disease or malignancy with autologous MSC therapy should be low. As with allogeneic hematopoietic or whole-organ transplantation, there is a small risk of transmission of malignancy from donor to recipient. MSC themselves may give rise to tumors, though evidence for this is limited. In one report, mouse bone marrow MSC transduced with nonviral transposons endoding firefly luciferase or DsRed2 for the purpose of cell tracking were infused along with whole bone marrow into irradiated recipients. Unexpectedly, several of the mice developed sarcomas of MSC origin in the lung or extremity.<sup>64</sup> Human MSC transduced with telomerase acquired a malignant phenotype during long-term culture, through loss of Ink4a locus and acquisition of activating mutations in K-ras.<sup>65</sup> Mouse MSC spontaneously transform in culture and contribute to fibrosarcomas in vivo, in part through acquisition of point mutations in p53.<sup>66</sup> These reports suggest that MSC-derived tumor formation may be a concern, and long-term MSC culture is best avoided. Suppression of GVHD by allogeneic MSC may also be coincident with reduction in the beneficial graft-vs-tumor effect, therefore it is essential to follow the long-term incidence of hematologic disease recurrence in patients treated with MSC.

## Conclusions

Autologous or allogeneic bone marrow transplant therapy for refractory IBD remains experimental. This approach should be limited to patients with severe disease who have exhausted standard treatment options, and is best performed in the context of an appropriately designed clinical trial. Systemic immunomodulatory MSC therapy does not appear to establish long-term engraftment in the recipient, and does not require additional immunosuppression. Whether systemic MSC therapy provides long-term remission of IBD remains to be determined in a clinical trial. Phase I and II studies have not raised concerns for safety, particularly with regard to tumor formation. Local or topical application of MSC to enhance healing appears to be a promising approach to the

very difficult clinical management of CD fistula which should be investigated further in clinical trials.

## Abbreviations

ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; ATG, antithymocyte globulin; BMSC, bone marrow stem cells; BMT, bone marrow transplant; CD, Crohn's disease; CML, chronic myelogenous leukemia; Cyc, cyclophosphamide; EAE, experimental autoimmune encephalomyelitis; ELISA, enzyme-linked immunosorbent assay; ES, embryonic stem cell; GVHD, graft versus host disease; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; iPS, induced pluripotent stem cell; mPBSC, mobilized peripheral blood stem cells; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; MTX, methotrexate; NHL, non-Hodgkin's lymphoma; PCR, polymerase chain reaction; TBI, total body irradiation; TNBS, trinitrobenzene sulfonic acid; UC, ulcerative colitis.

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## Disclosures

The authors report no conflicts of interest.

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