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REVIEW ARTICLE

Intravenous mesenchymal stromal cell therapy for inflammatory bowel disease: Lessons from the acute graft versus host disease experience

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Abstract

Bone marrow–derived mesenchymal stromal cells (BMSCs) are primitive, supportive cells of the bone marrow with trilineage potential to differentiate into bone, cartilage, fat and muscle. These cells possess both *in vitro* and *in vivo* immunomodulatory and wound-healing properties. Several studies have demonstrated efficacy of intravenously administered BMSCs in treating acute graft-versus-host disease (GvHD). Use of intravenous (IV) BMSCs in inflammatory bowel diseases (IBD) in humans has been limited to small studies in adults, but results have been promising. There remain many unanswered questions regarding safety, tolerability, effectiveness and optimal use of BMSCs to treat IBD, particularly in immunocompromised patients. This article reviews the evidence for using BMSCs to treat acute GvHD and how this experience may inform the potential use of BMSCs as a treatment for IBD.

Key Words: *graft-versus-host disease, inflammatory bowel disease, mesenchymal stromal cell*

Introduction

Acute graft-versus-host disease (GvHD) is a common and unfortunate cause of morbidity and mortality in patients undergoing hematopoietic stem cell transplant (HSCT), affecting the skin, liver and gastrointestinal (GI) tract. Symptoms of acute GvHD are reminiscent of those seen in patients with inflammatory bowel disease (IBD): typically diarrhea, but there may also be vomiting, abdominal pain and anorexia [1]. Diarrhea in GvHD is secretory and usually voluminous; bleeding and ulceration of the mucosa is also common and a poor prognostic factor [2]. The histology in GvHD is characterized by crypt apoptosis, glandular atrophy and flattening of the surface epithelium. Glandular architectural distortion, diagnostic of IBD, is not a typical characteristic of GvHD [3]. Both conditions involve a disruption and injury of the intestinal epithelium. Acute GvHD and IBD are often treated using similar drugs, including corticosteroids, methotrexate, calcineurin inhibitors and anti-tumor necrosis factor alpha (TNFα) agents. Administration of corticosteroids is standard first-line therapy for acute GVHD but leads to remission in less than half of patients. Second-line therapy is variable, depending on the experience of the clinician and availability of therapies [4–6]. Anti-thymocyte globulin, pentostatin, mycophenolate mofetil and other monoclonal antibodies (e.g., rituximab, etanercept) have been used to treat steroid-refractory GvHD [7–11]. Patients with acute GvHD are immunosuppressed and already at high risk of mortality from infection and organ damage from GvHD, but these therapies may compound risk of infection. Thus, there is a need for novel strategies to treat GvHD and other systemic inflammatory diseases, while minimizing global immune suppression.

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Intravenously administered bone marrow–derived mesenchymal stromal cells (BMSCs) are a newly established therapy for steroid-refractory GvHD. BMSCs are primitive, supportive cells of the bone marrow with tri-lineage potential to differentiate into bone, cartilage, fat and muscle [12]. A recent systemic review and meta-analysis identified 13 nonrandomized studies comprising 336 patients with acute, steroid-refractory GvHD and reported that survival at 6 months after MSC treatment was >50%, although with a paucity of randomized clinical trial data [13]. Secondary to their immunomodulatory and wound healing properties, both allogeneic and autologous intravenously infused BMSCs have been studied as a potential therapy for both acute GvHD and IBD. As more therapeutic options become available for these conditions, the goal is optimizing efficacy of drugs (alone and in combination) while minimizing side effects. This review focuses on of the experience with BMSCs in GI GvHD and how this experience might inform further study and therapeutic use in IBD.

Pathogenesis of acute GvHD

Allogeneic HSCT is an established curative treatment for many malignant diseases and immunodeficiencies. High doses of chemotherapy with or without irradiation ablate the recipient's hematopoietic system before the infusion of hematopoietic cells from a closely matched donor. The graft reconstitutes the recipient's hematopoietic and immune systems, but can also damage host tissues when alloreactive, activated donor T cells respond to disparities in major or minor histocompatibility antigens. Removing alloreactive T cells from the graft to prevent acute GvHD increases risk of rejection, infection and relapse [14,15]. Chronic GvHD may also follow complete resolution of acute GvHD or may present de novo [16]. The development of chronic GvHD ranges from 30% in recipients of fully histocompatible sibling donor transplants to 60–70% in recipients from mismatched or unrelated donors [17]. Although a leading cause of late, non-relapse death after HSCT [18], the pathophysiology of chronic GvHD remains poorly understood and is not discussed in this review.

In acute GI GvHD, the mucosa is disrupted due to conditioning with radiation and, in some cases, infection or underlying disease. As lipopolysaccharides and other components of bacteria leak through the intestinal mucosa, macrophages and monocytes are stimulated to produce pro-inflammatory cytokines such as TNF-α [19–22]. Interaction of donor T cells with host antigen presenting cells (APCs) leads to donor T-cell activation, proliferation and differentiation [23] (see Figure 1). To activate donor T cells, host

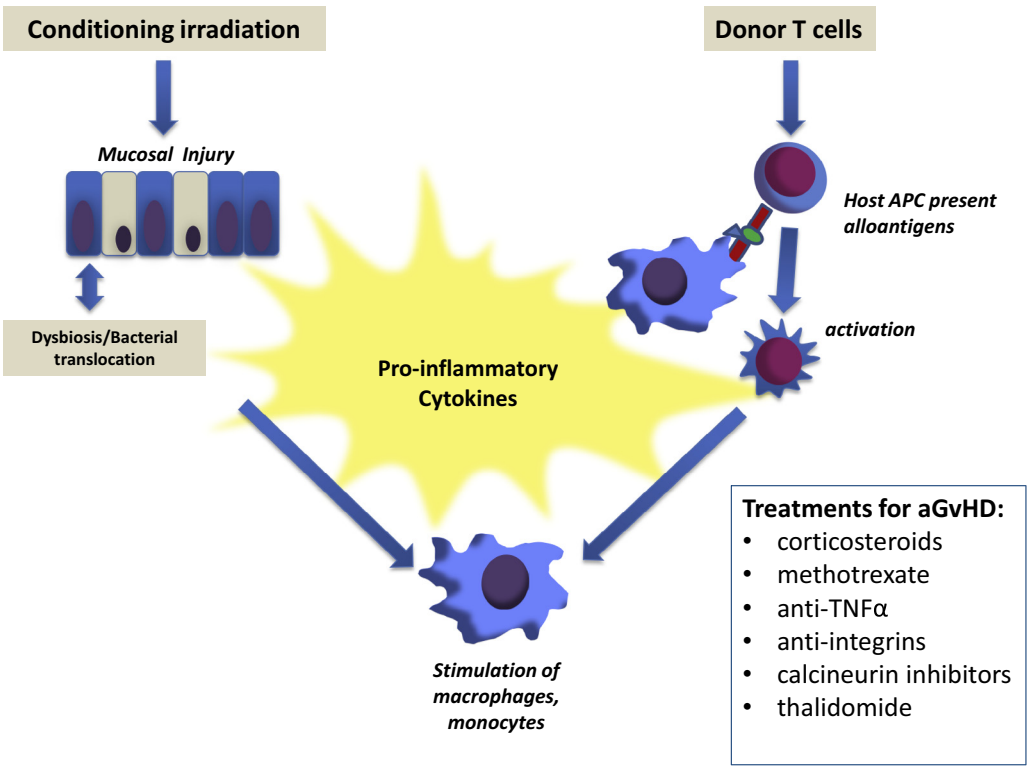

Figure 1. In acute GvHD, there is massive release of pro-inflammatory cytokines. This occurs secondary to mucosal injury and bacterial translocation, leading to stimulation of macrophages and monocytes, as well as the activation of donor T cells. Similar therapies are used for treating both acuate GvHD and IBD.