Ulcerative Colitis

Subjects: Pharmacology & Pharmacy | Oncology
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The worldwide epidemiology of inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), still shows an increasing trend in Asia and Iran. Despite an improvement in the treatment landscape focused on symptomatic control, long-term colectomies have not decreased over the last 10-year period. Thus, novel therapies are urgently needed in clinics to supplement the existing treatments. Mesenchymal stem cells (MSCs) are multipotent adult stem cells with immunosuppressive effects, targeting IBD as a new treatment strategy. They have recently received global attention for their use in cell transplantation due to their easy expansion and wide range of activities to be engrafted, and because they are home to the mucosa of the intestine. Moreover, MSCs are able to differentiate into epithelial and other cells that can directly promote repair in the mucosal damages in UC. It seems that there is a need to deepen our understanding to target MSCs as a promising treatment option for UC patients who are refractory to conventional therapies. Here, we overviewed the therapeutic effects of MSCs in UC and discussed the achievements and challenges in the cell transplantation of UC.

Keywords: inflammatory bowel disease ; ulcerative colitis ; therapy ; mesenchymal stem cells

1. Introduction

Dynamic interactions between the gastrointestinal epithelium and the mucosal immune system result in intestinal homeostasis and optimal immunosurveillance, but a destabilization in these interactions among predisposed people can lead to development of chronic inflammatory diseases called inflammatory bowel disease (IBD), which mainly covers Crohn's disease (CD) and ulcerative colitis (UC) [1]. UC affects the rectum and may involve any part of the colon in a continuous pattern, whereas CD can affect any part of the gastrointestinal tract [2]. UC has a remitting and relapsing course that can vary from asymptomatic mild inflammation to extensive inflammation of the colon leading to colonic motility dysfunction, frequent bloody stools, potentially permanent fibrosis, and tissue damages [2]. It is usually characterized by abdominal pain, fever, weight loss, diarrhea, rectal bleeding and atrophy, and intestinal obstruction. It has an easy relapse that may result in surgical options to remove the affected bowel [3].

UC has also several extra-intestinal manifestations in eyes, skin, joints, and the oral cavity and is associated with hepatobiliary diseases, osteoporosis, and amyloidosis [3]. Histologically, the lesions in UC are mostly inflammatory and ulceration limited to the mucosa and submucosa layers in the colon and rectum [4]. UC is associated with secretion of a variety of chemokines and cytokines, including interleukin (IL) 1β, IL-6, IL17A, and IL-21, Gro-α, macrophage inflammatory protein (MIP)-1α, MIP-2, eotaxin, tumor necrosis factor α (TNF-α), and reactive oxygen species (ROS) [5].

2. Epidemiology of UC

An episode of acute severe UC was shown to be a life-threatening condition among one-fourth of patients [6]. Approximately 31% of patients with limited UC at diagnosis would have disease extension by 10 years [7], while 74% of them may experience at least one relapse during a 5-year period [8]. In 10–15% of patients, the disease can ultimately lead to colectomy [6]. Both male and female individuals are affected equally, and the adult population aged 30–40 years old are affected more [6], although younger patients between 15 and 25 years old may experience a flare up too [6].

It is known that these patients are prone to increased risks of developing colorectal cancer (CRC), which has global incidence and mortality rates of 10.2% and 9.2%, respectively [9], with an increasing trend in newly industrialized countries in Asia and Latin America [10]. The overall incidence rate for UC is coalescing around 5–15 per 100,000 person-years, which varies depending on geography [10]. The highest annual incidence was reported 6.3 per 100,000 person-years in Asia, while in the Middle East and in North America and Europe approximately 10–200 cases per 100,000 individuals were reported [11].

3. The Etiology and Pathogenesis of UC

Though the etiology of UC has not been defined clearly, the disease is believed to be multi-etiological. It is driven by immune dysregulation of mucosa toward luminal bacterial floral, an immune imbalance between regulatory and effector T cells, and the inflammatory cascade induced by leukocyte recruitment, infection, genetic alterations, and environmental factors such as diet, lifestyle, and socioeconomic development that lead to destruction of the epithelial barrier. Recent studies indicated both innate and adaptive immunity to play a part in disease pathogenesis [12]. Various factors, such as inflammatory reaction, tight junction epithelial barrier dysfunction, and apoptosis are also associated with the disease [13].

4. The Medical Therapy of UC

The goals in the medical therapy of UC are to ameliorate major symptoms of the disease, to treat extraintestinal manifestations and to prevent complications. Clinically, treatment is mainly focused on anti-inflammatory properties, mucosal repair, management of risking future relapse, and protection to lower the risk of requiring colectomy [6], because a colectomy can be associated with complications in one-third of patients [14]. The therapies administered during the early course of the disease were shown to modify the disease progression [15]; still, despite an improvement in the treatment landscape, long-term colectomy rates have not seriously decreased over a 10-year period [6].

Current treatment of UC primarily consists of 5-aminosalicylates, glucocorticoid (GC), and antimicrobials, as well as immunomodulators such as azathioprine, 6-mercaptopurine (6-MP), cyclosporine, methotrexate, and thiopurines, and biologics such as monoclonal antibodies and anti-tumor necrosis factor (TNF)-α, but these treatment methods may cause side effects and can lead to treatment resistance and remission [16]. The use of corticosteroids was demonstrated to be associated with weight gain, hyperglycemia, cutaneous side effects, osteoporosis, adrenal insufficiency, and an increase in the risk of opportunistic infections, especially when administered in combination with other immunosuppressive drugs that may not be well tolerated—these side-effects cause nearly one-fourth of patients to discontinue their treatments [16].

Treatment resistance may need surgical intervention, and can lead to a total colectomy that can severely compromise the quality of life in UC patients [6]. A meta-analysis based on seven population-based studies published between 2008 and 2013 regarding 5140 UC patients showed that post-operative mortality of emergency colectomy for UC was 5.3% [17], and the risk of carcinogenesis should also not be ignored [9]. Thus, promising new strategies and safe treatments for UC are urgently needed to improve the control of the disease, such as emerging therapies with mesenchymal stem cells (MSCs) [18]. In our review, a comprehensive literature review was undertaken in August 2020 across Medline, Embase, Google Scholar, and ClinicalTrials.gov databases on the achievements and challenges in the treatment of UC using MSCs. Keywords used were “Inflammatory bowel diseases,” “Mesenchymal stem cells,” and “Ulcerative colitis.” The findings were categorized based on clinical trials and in vivo studies and further based on the type of MSCs used. The animal model and the method of colitis induction were described too.

5. The Characteristics of MSCs as Emerging Therapy of UC

MSCs were primarily recorded as a group of non-hematopoietic, self-renewing, plastic-adherent and fibroblast-like stromal cells [19] that have the ability to transdifferentiate into ectodermal and endodermal cells (e.g., chondrogenic, adipogenic, and osteogenic) [20]. They express cell surface markers such as CD44, CD73, CD90, and CD105, and lack the expression of hematopoietic markers such as CD34 and CD45 [21]. They have been isolated from various sources such as bone marrow (BM) [22], adipose tissue [23], and umbilical cord Wharton’s jelly [24]. MSCs have therapeutic effects in various inflammatory diseases due to its hypoimmunogenic and immunoregulatory properties and can be the home to the site of injury, limit inflammation through cytokine release, stimulate healing through growth factor expression, alter host immune responses through secretion of immune-modulatory proteins, and secrete anti-apoptotic factors [25].

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