Abstract

The application of cell therapy in the treatment of inflammatory bowel disease currently is of increasing scientific interest. Cell therapy in the treatment of Crohn’s disease and ulcerative colitis includes 2 approaches: immunosuppressant followed by hematopoietic stem cells transplantation and systemic or local application of mesenchymal stem cells. The latter were reported to exhibit immunosuppressive and regenerative effect. Actually more than 1,500 patients with inflammatory bowel disease have been treated with mesenchymal stem cells worldwide. The introduction of cell therapy into gastroenterology will significantly expand the arsenal of therapeutic arrangements for the treatment of inflammatory bowel disease, in particular resistant forms of the disease and will allow to increase the effectiveness of treatment.

Keywords
Crohn’s disease; Ulcerative colitis; Stem cells

Abbreviations
IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn’s Diseases; TNF-α: Tumor Necrosis Factor α; IL-12/23: Interleukin 12/23; IL-6R: Interleukin 6R; iRNA: information Ribonucleic acid; SC: Stem Cells; CT: Cell Therapy; MSC: Mesenchymal Stem Cells; HSC: Hematopoietic Stem Cells; 2,4,6-TNB: 2,4,6-Trinitrobenzene Sulfonic Acid; SDF-1: Stromal Derived Factor-1; VEGF: Vascularendothelial Growth Factor; EGF: Epidermal Growth Factor; DSS: Dextran Sulphate Sodium; HSCT: Hematopoietic Stem Cells Transplantation; EPC: Endothelial Progenitor Cells

Introduction

Achievements of modern science changed the ideas about etiology and pathogenesis of IBD, mainly UC and CD, what resulted in the emergence of novel approaches to the treatment of these disorders [1-6]. Environmental, genetic factors and microbiota flora were elicited to play an important role in the development of inflammatory process in the intestinal wall, activating immune response [1,7,8]. The disruption of balance between proinflammatory and anti-inflammatory factors in intestinal mucosa becomes the trigger of the development of pathologic process in which numerous cellular and molecular mechanisms are involved [1,7]. Genetic nature of IBD is confirmed by wide studies of human genome and studies on twins [3]. The efficiency of conventional methods of UC and CD treatment leaves much to be desired [1,9-11]. Modern therapy of IBD includes biological therapy (antibodies to TNF-α, adhesion molecules, IL-12/23, IL-6R, endoscopic application of artificially grown pieces of tissues etc) and gene therapy (iRNA-technologies aimed at inhibition of the necessary genes) [2,3,7,12,13]. The application of nanoparticles for the transportation of drugs despite its high cost is also promising [2].

In recent years an increasing number of experimental and clinical studies are devoted to the evaluation of therapeutic potential and effectiveness of SC in the treatment of UC and CD [7,9-11,14,15]. According to experts’ prognoses, CT will become the next generation of therapeutic arrangements in the treatment of IBD, in particular for patients with the secondary resistance to anticytokine therapy [4,12].

Discussion

Actually several tens of adult SC is distinguished, that in health contribute to natural processes of tissues regeneration, play crucial role in wounds healing [1,6-18]. SC derived from bone marrow, peripheral and cord bloods, tissue of umbilical cord, amniotic fluid, adipose tissue have got wide use [4,16,17,19]. Remedial effect of SC is explained both by paracrine effect-stimulation of regenerative processes through the synthesis of growth factors and other biologically active compounds and ability to transformation into damaged tissues cells [14,17,18,20,21]. Effectiveness of MSC in the treatment of autoimmune diseases is mediated by their potent immunosuppressive effect [22-24].

Immunosuppressant followed by transplantation of allogeneic Hematopoietic Stem Cells (HSC) is a promising method of radical treatment of many autoimmune diseases, including CD and UC [5,11,23-25]. Another direction of CT of IBD is the use of MSC due to their immunosuppressant effect, what was mentioned above [9,10,23,24]. In vivo and in vitro studies showed the interaction of MSC with regulatory T-lymphocytes [22]. In vitro studies also showed that MSC inhibit proliferation and cytotoxicity of T-lymphocytes, in particular natural killer cells, dendritic cells, production of cytokines, antibodies and antigen presentation what provides basis for the use of MSC in the treatment of autoimmune pathology [23,24].

The decrease of clinical and histopathological signs of 2,4,6-TNBA-induced colitis, treated with MSC was accompanied by redistribution of regulatory T-lymphocytes from tissues to circulation [22]. SDF-1, produced by MSC was reported to play
important role in chemo taxis regulation and SC engraftment in tissues, interacting with specific chemokine receptors [20].

Another mechanism of therapeutic effect of MSC is their prominent regenerative effect as these cells are the precursors of the connective tissue [14,15,19]. MSC were revealed to release numerous trophic factors (VEGF, EGF etc) and affect all stages of the complex process of wound healing - inflammatory, proliferative and tissue remodeling [21]. The advantage of MSC use is the lack of immunogenicity what allows wider allogeneic application [14]. MSC above all are recommended to patients with fistulizing CD [14]. Systemic MSC therapy was shown to be effective in resistant radiation colitis, decreasing pain, diarrhea, inflammation, bleeding, increasing the number of T-regulatory lymphocytes and decreasing of activated effector cells [14].

Preclinical studies on the models of necrotizing colitis as well as experimental colitis induced by DSS and 2,4,6-TNBS showed positive effect of systemic and local use of MSC derived from the bone marrow, amniotic fluid, cord blood, adipose tissue on the course of colitis and stimulation of reparation [15,16,19,26]. CT was shown to increase survival and stimulate reparation of the damaged mucous membranes of the large intestine of newborn rats with necrotizing colitis. Animals were divided into 2 groups: control group was intraperitoneally injected bone marrow MSC and investigation group was treated with amniotic fluid SC. Positive effect of CT was accompanied by modulation of cyclooxygenase-2 expression in stromal cells of lamina propria of colonic mucosa. In amniotic fluid SC differentiated expression of genes of Wnt/beta-kinine pathway was detected as well as the migration of these cells and production of growth factors contributing to regeneration of colonic mucosa [15].

In mice with DSS-induced colitis intraperitoneal injection of bone marrow or cord blood MSC was shown to decrease inflammation in colonic mucosa. Simultaneously the regulatory impact of MSC on the course of immune processes in spleen and mesenterial lymphatic nodes was noted [27]. The application of adipose tissue MSC mixed with thrombin and fibrin significantly facilitated reparative processes in walls of the colon due to angiogenesis stimulation, what was proved in ischemia-induced colitis in mice [19]. Immunosuppressive effects of MSC in the treatment of experimental colitis in mice were reported to be potentiated by interferon-γ [26].

Currently more than 200 clinical trials on MSC are registered worldwide, from which 22 trials are devoted to the treatment of autoimmune diseases and 27-IBD [14]. Due to literary data 1500 patients with IBD were carried out systemic and local treatment with MSC worldwide. The 1st and 2nd phases of clinical studies confirmed the safety of CT in the treatment of IBD and its advantages above the fibrin glue in fistulizing colitis [4,14].

As mentioned above, CT is of special importance for the treatment of Patients with the resistance to anti-cytokine drugs. The level of anticytokine drugs antibodies was shown to correlate with the severity of clinical and endoscopic picture [12]. CT was also reported to decrease the need for glucocorticosteroid therapy and other drugs, what results in the decrease of treatment cost [28].

MSC therapy was carried out in a group of 39 patients with UC and 11-CD. Control groups included 20 patients with UC and 11 with CD. Treatment with immunodepressing drugs was stopped 2-3 days before MSC introduction. Glucocorticosteroids dose was decreased up to 15-20mg/day and aminosalicylates up to 2g/day. After MSC transplantation significant decrease of inflammation signs was noted in 39 patients with UC and 11 patients with CD compared to control groups. In 40 patients clinical and morphological remission was stated. MSC therapy was ineffective in 8 patients with UC and 2 patients with CD. In 34 from 50 patients with hormone-dependent or hormone-resistant forms of UC and CD MSC use allowed to decrease prednisolone dose up to 5mg/day. Thus, the authors consider MSC therapy as a novel strategic direction in the treatment of IBD due to its potent immunomodulating effect, decrease of autoimmune inflammation and stimulation of reparation processes in mucous membranes [9].

Results of clinical studies give evidence that allogeneic MSC transplantation significantly increases remission duration, decreases the risk of relapse and efficiency is comparable with TNFα antibodies. In majority of patients MSC treatment allowed to discontinue 5-acytsalicylic acid administration. Positive effect of CT was noted in hormone-resistant and hormone-dependent IBD [10]. Another study reports about 3 patients with the active form of CD, resistant to conventional therapy with the presence of antibodies to anti-TNFα drugs. These patients either refused from surgery or such treatment was not an acceptable alternative. 2 patients were successfully transplanted hematopoietic stem cells (HSC) with CD34+ selection. At the moment of examination 5 and 6 years after transplantation the patients were in remission. 1 patient got into remission after conditioning so HSCT was not performed [11].

Effectiveness of SC was also noted in genetically mediated diseases of the intestine. HSCT was shown to restore gluten tolerability in patients with celiac disease. 2 clinical cases of successful HSCT after myeloblation in celiac disease were reported. After this treatment introduction of gluten-containing diet did not cause any clinical, serological or histological markers of the disease during 5 year follow-up period [5].

Inherited deficiency of IL-10 and its receptors cause immune dysregulation in patients with the development of severe colitis, resistant to standard methods of treatment. HSCT was reported to be effective in patients with colitis on the background of deficiency of IL-10 [2,5]. Recent research data also gives evidence about the decrease of EPC number in patients with UC. Although, actually there is no data on the impact of infusion of EPC on the processes of mucosa regeneration [6].

**Conclusion**

Introduction of CT into gastroenterology significantly expands the arsenal of therapeutic arrangements for IBD treatment, in particular forms of the disease resistant to conventional therapy.

---

**Citation:** Nasadyuk CM (2014) Stem Cell Therapy in the Treatment of Inflammatory Bowel Disease. Gastroenterol Hepatol Open Access 1(1): 00006. DOI: 10.15406/ghoa.2014.01.00006

**DOI:** 10.15406/ghoa.2014.01.00006
Results of long-term observations and improvement of protocols of SC application in patients with CD and UC will allow increasing the effectiveness of IBD treatment.

References

1. Ricet E, Jauregui-Amezaga A, Ordei I, Pino S, Ramirez AM, et al. (2013) Cell therapies for IBD: what works? Curr Drug Targets 14(12): 1453-1459.
2. Dhma K, Chakraborty S, Mahima, Wani MY, Verma AK, et al. (2013) Novel and emerging therapies safeguarding health of humans and their companion animals: a review. Pak J Biol Sci 16(3): 101-111.
3. Parfenov AI (2013) Crohn’s disease: on the occasion of the 80th anniversary of description. Ter Arkh 85(8): 35-42.
4. Van Deen WK, Oktomonopoulou A, Hommes DW (2013) Stem cell therapy in inflammatory bowel disease: which, when and how? Curr Opin Gastroenterol 29(4): 384-390.
5. Ciccioppolo R, Bernardo ME, Russo ML, Vanoli A, Franco C, et al. (2013) Allogeneic hematopoietic stem cell transplantation may restore gluten tolerance in patients with celiac disease. J Pediatr Gastroenterol Nutr 56(4): 422-427.
6. Deng X, Szabo S, Chen L, Paunovic B, Khomenko T, et al. (2011) New cell therapy using bone marrow-derived stem cells/endothelial progenitor cells to accelerate neovascularization in healing of experimental ulcerative colitis. Curr Pharm Des 17(16): 1643-1651.
7. Fiorino G, Cesarini M, Danese S (2011) Biological therapy for ulcerative colitis: what is after anti-TNF? Curr Drug Targets 12(10): 1433-1439.
8. Molky M, Mildenpor S, Wiergincki CL, Witte M, Teunissen H, et al. (2014) Many inflammatory bowel disease risk loci include regions that regulate gene expression in immune cells and the intestinal epithelium. Gastroenterology 146(4): 1040-1047.
9. Lazeznik LB, Kniazov OV, Parfenov AI, Ruchkina IN, Rogozina VA, et al. (2010) Transplantation of allogeneic mesenchymal stem cells from the bone marrow increases duration of remission and reduces the risk of ulcerative colitis relapse. Eks Klin Gastroenterol (3): 5-10.
10. Parfenov AI (2012) Inflammatory bowel diseases in the XXI century. Eks Klin Gastroenterol (3): 3-6.
11. Hommes DW, Duijvestein M, Zelinkova Z, Stokkers PC, Ley MH, et al. (2011) Long-term follow-up of autologous hematopoietic stem cell transplantation for severe refractory Crohn’s disease. J Crohns Colitis 5(6): 543-549.
12. Kniazov OV, Parfenov AI, Ruchkina IN, Konoplannikova AG, Dronov VN, et al. (2013) New possibilities for overcoming the secondary inefficiency of anti-cytokine therapy in patients with inflammatory bowel diseases. Ter Arkh 85(2): 57-60.
13. Leggett CL, Gorospe EC, Lutzke L, Anderson M, Wang KK (2013) A new era: endoscopic tissue transplantation. Curr Opin Gastroenterol 29(5): 495-500.
14. Voswinkel J, Francois S, Gorin NC, Chapel A (2013) Gastro-intestinal autoimmunity: preclinical experiences and successful therapy of fistulating bowel diseases and gut graft versus host disease by mesenchymal stromal cells. Immunol Res 56(2-3): 241-248.
15. Zani A, Cananzi M, Fasceati Leon F, Lauriti G, Smith VV, et al. (2014) Amniotic fluid stem cells improve survival and enhance repair of damaged intestine in necrotizing enterocolitis via a COX-2-dependent mechanism. Gut 63(2): 300-309.
16. Nasadyuk CM (2010) The umbilical cord blood: medical and biological characteristics, storage, clinical use. Woman’s Doctor 5: 53-56.
17. Nasadyuk CM (2011) Current status and perspectives of cord blood cryo storage and clinical application in Ukraine. CTTE 6 (1): 98-104.
18. Nasadyuk CM (2013) Cell technologies in reproductology, obstetrics and gynaecology. Cell and organ transplant 1: 61-65.
19. Joo HH, Jo HJ, Jung TD, Ahn MS, Bae KB, et al. (2012) Adipose-derived stem cells on the healing of ischemic colitis: a therapeutic effect by angiogenesis. Int J Colorectal Dis 27(11): 1437-1443.
20. Liu X, Zuo D, Fan H, Tang Q, Shou Z, et al. (2014) Over-expression of CXCR4 on mesenchymal stem cells protect against experimental colitis via immunomodulatory functions in impaired tissue. J Mol Histol 45(2): 181-193.
21. Watanabe S, Arimura Y, Nagaishi K, Ishihiki H, Onodera K, et al. (2014) Conditioned mesenchymal stem cells produce pleiotropic gut trophic factors. J Gastroenterol 49(2): 270-282.
22. Zuo D, Liu X, Shou Z, Fan H, Tang Q, et al. (2013) Study on the interactions between transplanted bone marrow-derived mesenchymal stem cells and regulatory T cells for the treatment of experimental colitis. Int J Mol Med 32(6): 1337-1344.
23. De Miguel MP, Fuentes-Silva S, Blazquez-Martinez A, Pascual OY, Aller MA, et al. (2012) Immunosuppressive properties of mesenchymal stem cells: advances and applications. Curr Mol Med 12(5): 574-591.
24. Hayashi Y, Tsuji T, Tsuji M, Nishida T, Ishii S, et al. (2008) Topical implantation of mesenchymal stem cells has beneficial effects on healing of experimental colitis in rats. J Pharmacol Exp Ther 326(2): 523-531.
25. Engelhardt KR, Shah N, Faisalza-Goop I, Kocakci Uygun DF, Frede N, et al. (2013) Clinical outcome in IL-10- and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. J Allergy Clin Immunol 130(3): 825-830.
26. Duijvestein M, Wildenberg ME, Welling MM, Hennisk S, Molendijk I, et al. (2011) Pretreatment with interferon-g enhances the therapeutic activity of mesenchymal stromal cells in animal models of colitis. Stem Cells 29(10): 1549-1558.
27. Li L, Liu S, Xu Y, Zhang A, Jiang J, et al. (2013) Human umbilical cord-derived mesenchymal stem cells down regulate inflammatory responses by shifting the Treg/Th17 profile in experimental colitis. Pharmacology 92(5-6): 257-264.
28. Lazeznik LB, Gazesh-Zade MG, Kniazov OV, Efremov LL, Ruchkina IN (2010) Pharmacoeconomic benefits of patients with ulcerative colitis treatment with help of mesenchymalstem cells. Eks Klin Gastroenterol (3): 51-59.

Citation: Nasadyuk CM (2014) Stem Cell Therapy in the Treatment of Inflammatory Bowel Disease. Gastroenterol Hepatol Open Access 1(1): 00006. DOI: 10.15406/jghoa.2014.01.00006