Stem mesenchymal bone marrow cells in the treatment of ulcerative colitis based on morphological and immunological research (literature review)

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Key words: ulcerative colitis, mesenchymal stem cells, transplantation, regenerative medicine, clinical studies

Ulcerative colitis (UC) is one of the most complex and unresolved problems of modern gastroenterology. The last decade noted constant growth of morbidity of this disease in the world [8].

According to the National Center for Health Development of the Republic of P K azakhstan, by sources of the automated information system "Polyclinic", in Kazakhstanfor the period of only 7 months 2017. 858 patients with dispensary UC.

The urgency of the pathology is confirmed by the increase in morbidity among persons of working age, the development of life threatening complications, the need for long, often repressed, costly therapy [7, 10].

In the conditions of chronic inflammatory process, deep morphofunctional changes occur in all organs of the immune system (bone marrow, thymus, spleen), characterized by the development of a secondary immunodeficiency state with a weakening of cellular and humoral immunity, cytokine imbalance, redistribution of immune cells in the body and violation of their information and migration activity. Imbalance in the immune regulation system leads to a disturbance of the morpho-regulatory functions of the lymphoid tissue, which is the result of a disorder in the regeneration processes [2].

Lthough the achievements of modern methods of UC therapy, the search for new treatments for patients with UC is still relevant. A promising therapeutic strategy for the treatment of IBD has recently been the use of stem cells (SC) in complex therapy of IBD. Currently, the treatment of SC is not part of standard medical care and, as a rule, is performed only in the context of clinical trials.

For IBD therapy used mesenchymal stem cells (MSC) which have immunomodulating, anti-inflammatory properties and a large regenerative potential, which makes them attractive for clinical application [9]. SK therapy can be carried out either autologous cells, ie. the introduction of cellular material into the same organism from which they were isolated, or allogeneic cells, i. e. when the donor is another person.

According to the International Register of Clinical Studies of the National Institutes of Health, ClinicalTrials.gov in 2016. registered 26 studies using MSCs in inflammatory bowel disease, of which 23 -x studies used autologous and allogeneic MSC in Crohn's disease, and in 3 studies with UC spolzovat and

allogeneic cells. In all three studies, about when UC with a total of 118 patients The Mayo median score decreased and the morphological data improved [6].

Study by LB Lazebnik and co-author, which includes application of allogenic MSC in complex therapy of one patient with YaK, total lesion, hormone-dependent form with moderate activity in 2008 It was found otutstvie effect from the wire to the m th The standard therapy with use of m metipred a 40 mg/day, prednisolone a 60 mg/day locally in microclysters, azathioprine and 150 mg/day, in connection with what was decided on the transplantation of MSCs. 2 months after systemic transplantation of allogenic MSCpatient marked by a positive clinical effect: improvement of general condition, slowing stool frequency up to 1 — 2 times a day, improving its consistency, a significant reduction, and in the subsequent relief of pain, the disappearance of weakness and malaise, the normalization of body temperature, increase in body weight 5 kg. The index of clinical activity of the YaK decreased to 0. During this period, glucocorticosteroids were completely abolished. As a result, The index endosk opicheskoy activity was 1, histologicalstudies f showed a significant positive dynamics y. Findings of the study was the conclusion that the donor MSCs provides both reparative potential of the colon mucosa, andanti-inflammatory effect, allowing you to reverse azatiop Rin glyukortikosteroidy and 5-ASA to the rum of the article is marked on the safety of this therapy [5].

In another study, LB Lazebnik et al was carried out for 2 years from February 2008 to March 2010, observed three groups of pain UC: 40 patients treated with standard therapy with 5-amino salicylic acid (5-ASA), glucocorticosteroids (GCS) (group 2), 44 patients (1- group I) who additionally underwent systemic transplantation of allogeneic MSCs grown in culture and 12 patients who underwent induction and maintenance therapy with infliximab (3rd group). C o to morphological studies, m ikroskopicheski inflamed changes at Yelnia YaK localized in the mucous membrane and under the mucous layer, were infiltrated by plasma cells and lymphocytes, the presence of crypt abscesses, microerosion and ulceration, expansion of blood vessels, swelling of the endothelium, strands of granulation tissue. In UC exacerbation mucosal also noted axis ra Expansion capillaries and hemorrhage, ulceration of the epithelial necrosis RESULT ate, m and creep destruction of crypt abscess formation, reducing the number bokalovidnyh cell infiltration laminapropria lymphocytes, plasma cells, her trophils and eosinophils.

After 2 months, transplantation of MSC significantly reduces the Hebs index to 0.7±0.1 as compared to the group of patients receiving 5-ASA/GCS therapy, 1.0±0.1 ($p < 0.05$), and is comparable in effectiveness with infliximab therapy, with the latter index of Gebs being 0.66±0.16. After 12 months, the Hebs index in the 1 st group is at the same level — 1.0±0.1, while in the second group the Hebs index increases by more than 1.5 times — up to 1.2±0, 02, in the third group of patients receiving the influx of thesimab, the degree of inflammation of the mucosa on the Gebs scale is 0.6±0.18. Microscopically observed hyperplasia of glasses of id cells, cleavage of crypts, the appearance of a large number of goblet cells among the cells of the superficial epithelium. The obtained data of the histological picture

of the mucous membrane of the colon indicate that MSCs have high proliferative activity and a large reparative potential. In the study, the patients also determined the effect of cells on the immune system: with the systemic single transplantation of MSC, they caused a significant increase in the initially lowered level of cytokines on average from 11.4 to 23.6 pg/ml, while the transplantation of MSCs in patients in the acute period caused a significant decrease in the level of proinflammatory cytokines. At 6 and 12 months after the administration of MSC, a significant increase in anti-inflammatory cytokines TGF-1p, IL-4, IL-10 and a decrease in pro -inflammatory cytokines INF-γ, α-TNF, IL-1β, which testifies to the regulatory properties of MSCs and their readiness for the induction of reducing (reparative) processes. The content of immunoglobulins in the blood serum of patients with YaK before the injection of MSC and after 2, 6 and 12 months, respectively, was: IgG — 11.2 — 14.8 -12.8-11.8 g/l; IgM — 0,9 — 2,2 -1,6 — 1,1 g/l; IgA — 1,82 — 3,8 -2,6 — 1,5 g/l (the norm — IgM — 1,3, IgG — 13,0, IgA -2.3 g/l) ($p < 0.05$). The most significant increase was in concentration IgA ($p < 0.05$), mediating the local humoral immune response. We analyzed the level of immunoglobulins G, A, M in 2 groups of patients, depending on the effect of the transplantation of MSC of the bone marrow — in patients with a pronounced positive clinical effect and in patients who had no effect from MS injection or was short-lived. The content of immunoglobulins in the blood serum prior to the administration of MSCs in the group of patients where the transplantation had a positive effect ($n = 32$), was : IgM — 1,5±0,04 g/l, IgG — 12,5±0,71 g/l, IgA — 2,2±0,8 g/l. In the group of patients ($n = 12$), where the effect was short, the initial level of immunoglobulins was: IgG — 8,8±0,9 g/l, IgM — 1,3±0,01 g/l, IgA — 0,9±0.01 g/l ($p < 0.05$). The dynamics of the indices of humoral immunity and cytokine status at 2 months after transplantation was also significantly different in these two groups. In the group of patients ($n = 12$), where the effect was short, the level of immunoglobulins was: IgG — 7.3±0.2 g/l, IgM — 1.4±0.01 g/l, IgA — 1.0±0.01 g/l ($p < 0.05$), in the group with a positive effect ($n = 30$), IgG-18.5±0.9 g/l, IgM — 2.5±0.1 g/l, IgA — 2,1±0,8 g/l. Level of pro- and anti-inflammatory cytokines in the group of patients, where transplantation is effective, also proved to be significantly higher after 2 months compared to the group where the effect of this therapy was not the indices — α- TNF in the group with effective transplantation was 12.9±1, 3pg/ml, IL-1β — 8.7±0.4 pg/ml, IL-4 40.1±2.5 pg/ml; α — TNF — 22.3±1.1 pg/ml, IL-1β — 14.2±0.2 pg/ml, IL-4 — 14.6±2.4 pg/ml in the group without effect,respectively. In the authors' opinion, these changes support the concept that MSC transplantation is most effective in the early stages of the disease, and not at a later time, when the body's own immune reserves are depleted and the progression of the autoimmune process, and a prolonged intake of immunosuppressors. According to research data,prevalent in UC increased circulation (18–92 U/ml in the control — 10 U/ml) IgG autoantibodies to immunoglobulin neutrophil cytoplasmic antigens — Proteus naze, lactoferrin,myeloperoxidase, BP1, at least — neutrophil elastase. Systemic administration of MSC caused a decrease in the initially increased concentration of autoantibodies to neutrophils (IgG- BPI) on average from 42.6 to 12.4 units/ml,

which confirmed a decrease in the activity of the inflammatory process in the intestine, while standard therapy did not affect the level of autoantibodies to neutrophils during 12 months of follow their concentration was maintained at 38.4 — 42.2 U/ml.

Thus, the authors showed that the administration of MSC stimulates the inhibited synthesis of cytokines, subsequently reducing the level of proinflammatory cytokines and increasing the growth of anti-inflammatory cytokines, reduces the intensity of immunopathological processes in YaK, which is simultaneously combined with the positivedynamics of the clinical and endoscopic picture of the disease. Systemic transplantation of allogeneic MSCs has a multidirectional regulating effect on the inflammatory process: it stimulates the functional activity of the depressed immune system, increasing the level of initially reduced immunoglobulins, as well as pro- and anti- inflammatory cytokines α-TNF and INF-γ, IL-1. In the dynamics of MSC increases the level of anti-inflammatory cytokines IL-4 and IL-10; reduces the intensity of autoimmune reactions and the activity of immunopathological processes, reducing for 12 months the increased content of autoantibodies to neutrophil cytoplasm antigens (IgG-BPI). transplantation of allogeneic MSC bone marrow contributes improve the efficiency of complex therapy, etc. otivovospalitelnoy YAK [1].

In the study conducted by O. Knyazev et al. study compared the results of treatment in two groups of patients with acute attack of th UC floor aspirants standard therapy and therapy with the use of culture and llogennyh MSCs. The first group of patients with YaK (n = 12) received standard MSC culture according to the 0-1-26 weeks schedule, then in the subsequent years of observation, every 6 months, in addition to standard anti-inflammatory therapy. The second group of patients (n = 10) received standard antiinflammatory therapy with preparations of 5- amino acid nosalicylic acid (5-ASA) and glucocorticoste rhoid (SCS). The severity of the YaK was assessed according to the criteria of SC True love and LJ Witts (1 955), supplemented by EA Belousova (2002) [3].

Based on the results of work carried out it is shown that MSCs improving clinical manifestations and microscopic colitis ensha mind dissolved systemic and local production of proinflammatory w GOVERNMENTAL cytokines, are capable of directional movement into the inflammatory region and suppress the inflammatory process, while simultaneously stimulating tissue regeneration, contribute to an increase in the duration of remission of the disease, reduce the risk of repeated attack of the YaK by 3 times.Transplantation of MSCs as a result can provide restoration of sensitivity to previously ineffective therapy and can races to be considered as a promising method for complex therapy of the acute form of the YaK. However, according to the conclusions of the authors, a one-two-fold administration of MSC does not allow for a long-term maintenance of YA remission and requires regular administration, the frequency of which remains to be determined [4].

Thus, the preliminary results of clinical and experimental studies carried out in the world justify the relevance, perspectivity and sufficient safety of the method of transplantation of allogenic MSCs kostnog of the brain for the treatment of

patients with UC, but the results of the research do not fully define the mechanisms of action of MSCsth bone marrow, do not answer the question of optimal timing, put s administration, and frequency of application SC. According to the data available to us a literature review,describes about use only allogeneic cells from a variety of sources (bone marrow, adipose tissue, I, innaya umbilical blood), d TED literature on the use of autologous MSC atYaK is absent, which indicates the need for further clinical studies to determine the potential of cells. Performan future clinical studies should enhance the efficiency of treatment, since amestitelnaya of cell therapy could transform medicine will be present.

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The use of stem cells in complex therapy of inflammatory bowel diseases has became perspective therapeutic strategy. Mesenchymal stem cells, which have immunomodulatory, anti-inflammatory properties and high regenerative potential, are used for therapy of inflammatory bowel disease, what is making them attractive to clinical application. According to the results of the conducted studies, mesenchymal stem cells improve clinical and microscopic manifestations of colitis, reduce system and local production of pro-inflammatory cytokines, suppress inflammatory process, stimulating tissue regeneration at the same time, promote the increase in the duration of remission of a disease, reduce the risk of the relapse of ulcerative colitis. Preliminary results of clinical and experimental studies carried out in the world justify the relevance, prospects and sufficient safety of the transplantation method of allogenic mesenchymal stromal cells of bone marrow for treatment of patients with the ulcerative colitis.