journal of clinical practice 2021 Том 12 №1

MSC THERAPY FOR INFLAMMATORY BOWEL DISEASE

M.A. Konoplyannikov[1, 2], O.V. Knyazev[3, 4], V.P. Baklaushev[1]

[1] Federal Research and Clinical Center of Specialized Medical Care and Medical Technologies FMBA of Russia, Moscow, Russian Federation

[2] Institute for Regenerative Medicine, Sechenov First Moscow State Medical University, Moscow, Russian Federation

[3] Moscow Clinical Scientific Center, Moscow, Russian Federation

[4] State Scientific Centre of Coloproctology, Moscow, Russian Federation

Inflammatory bowel disease (IBD) belongs to the group of diseases characterized by idiopathic inflammation of the digestive tract organs. Two basic IBD types are distinguished: ulcerative colitis and Crohn's disease. The IBD symptoms including vomiting and diarrhea, abdominal pain, rectal bleeding, anemia have a significant negative impact on the general patient's state of health. Besides, IBD patients are susceptible to the risk of a number of serious diseases such as colorectal cancer, thrombosis and primary sclerosing cholangitis. More than 4 million people in the USA and Europe suffer from IBD, with 70000 new cases diagnosed yearly in the USA only.

In some cases, a surgical removal of the damaged digestive tract fragments is required to treat severe IBD forms. However, drug therapy of IBD has mainly been used in the last decades. The rate of remission with application of traditional IBD therapy is estimated as 20-30%, and is still no higher than 50% with the combined therapy. Cell therapy has been proven to be a very promising approach in the IBD treatment. In our review, we discuss mesenchymal stromal cells (MSC) and the most important preclinical and clinical results of their application for the IBD therapy.

Keywords: *clinical trials; inflammatory bowel disease; ulcerative colitis; Crohn's disease; cell therapy; mesenchymal stromal cells; regenerative medicine.*

For citation: Konoplyannikov MA, Knyazev OV, Baklaushev VP. MSC Therapy for Inflammatory Bowel Disease. *Journal of Clinical Practice.* 2021;12(1):53–65. doi: 10.17816/clinpract64530

Submitted 15.02.2021 Revised 25.02.2021 Published 01.04.2021

BACKGROUND

Inflammatory bowel disease (IBD) is a group of chronic inflammatory conditions of the gastrointestinal tract characterized by an increased mucosal immune response. The most significant IBDs include Crohn's disease and ulcerative colitis, which are common symptoms of chronic inflammation and structural damage to the gastrointestinal tract. Crohn's disease can affect any part of the gastrointestinal tract, from the mouth to the anal sphincter; most often the distal parts of the small intestine (ileum) are affected in the area of the ileocecal junction. Sometimes there is a selective lesion of the parts of the gastrointestinal tract, in other cases, the pathological process extends to the entire thickness of the intestinal wall [1].

In ulcerative colitis, only the colon and rectum are damaged. Inflammation occurs in the innermost layer of the intestinal mucosa, usually in the rectum and lower colon, but can also spread progressively and affect the entire colon. Common symptoms for all IBD are chronic diarrhea, abdominal pain, rectal bleeding, weight loss, asthenia, and decreased quality of life. In some rare cases, the diagnosis of Crohn's disease and ulcerative colitis is difficult to differentiate, and then the diagnosis of unspecified colitis is made [2]. The etiology of IBD is not fully understood: it is assumed that they are the result of a pathology of the immune system. In IBD, the immune system is thought to inadequately respond to environmental triggers, which causes inflammation of the gastrointestinal tract. This abnormal immune response is thought to occur in people with a relevant family history who have inherited certain alleles of HLA and other genes that predispose to IBD [3].

More than 4 million people in the United States and Europe suffer from IBD, while the overall prevalence of the disease exceeds 0.5% among the population of the developed world. 70,000 new cases of IBD are diagnosed in the United States each year, adding to the country's overall annual financial burden by more than $ 31 billion [4, 5]. Most patients are diagnosed with

these chronic lifelong diseases before the age of 35, which significantly affects the quality of life and financial costs of patients. In addition, IBD patients are at risk of developing a number of serious diseases, such as colon cancer, venous thrombosis and primary sclerosing cholangitis [4, 5].

In some cases, the treatment of severe IBD requires surgical removal of damaged areas of the gastrointestinal tract, however, in recent decades, drug therapy has been mainly used with the help of five main groups of drugs [4] — aminosalicylates, corticosteroids, immunosuppressants, antibiotics, and tumor necrosis factor inhibitors.

Aminosalicylates such as sulfasalazine, balsalazide, mesalamine, and olsalazine, taken orally or rectally, reduce inflammation of the intestinal wall and are used primarily to treat ulcerative colitis, but are not as effective in Crohn's disease.

Corticosteroids, such as prednisolone and budesonide, reduce immune inflammation, but are effective only for short-term use during exacerbations. Chronic use of corticosteroids is fraught with side effects associated with immunosuppression, the development of steroid-type obesity, sleep disturbance and other complications.

Immunosuppressants such as azathioprine, 6-mercaptopurine (6-MP), and methotrexate affect the immune system, are toxic, and are commonly used to maintain remission in patients who are not responding to other drugs or who are only responding to steroids.

Antibiotics, in particular ciprofloxacin and metronidazole, are of moderate benefit in patients with Crohn's disease affecting the colon or the area around the anus. The drugs are used when pararectal abscesses and fistulas occur.

The most modern group of drugs for the treatment of IBD are inhibitors of tumor necrosis factor alpha (TNF-α), including adalimumab, certolizumab pegol, golimumab and infliximab, etc. These drugs have a pronounced anti-inflammatory effect, are used to treat patients suffering from IBD in severe form, in the absence of a sufficient effect from standard treatment, but, unfortunately, their use is also not always effective. In particular, the experience of long-term use of infliximab showed that up to 1/3 of patients do not respond to anticytokine therapy due to primary resistance to it or due to the development of secondary resistance [6]. In addition, sometimes severe complications can occur, including bacterial, viral, and fungal infections, and an increased risk of lymphoma, colorectal cancer, and other cancers.

THERAPY OF INFLAMMATORY INTESTINAL DISEASES USING MESENCHIMAL STROMAL CELLS

Remission when using traditional methods of IBD therapy is, according to some estimates, 20-30%, maximum 50% with combination therapy [7]. A very promising direction in the treatment of IBD is the use of cell therapy using mesenchymal stromal cells (MSC).

Properties and mechanisms of action of MSCs

MSCs are multipotent stromal cells that can be isolated from bone marrow, adipose tissue, dental pulp, skeletal muscle, etc. [8–11]. MSCs express class I molecules of the major histocompatibility complex (MHC) at a low level and do not express MHC class II; therefore, they can be used for allogeneic transplantation [12]. MSCs express markers CD73, CD90, and CD105 but do not express hematopoietic markers CD34 and CD45, as well as the endothelial marker CD31 [13], and can differentiate into adipocytes, osteoblasts, chondrocytes, myoblasts, and neural progenitor cells [14, 15].

The first mechanism of action of MSCs described for autologous cell preparations is their ability to migrate to the pathological focus and differentiate with the formation of fibroblasts, pericytes, osteo- and myoblasts and thus replenishment of damaged cells and tissues of the body (skin, cartilage, bones, muscles, etc.) [14, 16]. The second mechanism of action of MSCs, characteristic of both autologous and allogeneic transplanted cells, is their paracrine activity. Migrating to sites of injury and inflammation, MSCs secrete a large amount of cytokines (mainly anti-inflammatory) and growth factors (VEGF, FGF, IGF, PDGF, etc.) and thus help to reduce inflammation, activate their own mechanisms of regeneration and restore damaged tissues (Fig. 1) [17]. MSCs have immunomodulatory and anti-inflammatory effects, suppressing the proliferation and differentiation of T cells (both CD4 + and CD8 + lymphocytes), decreasing NK activity and activating T regulatory cells. MSCs reduce the secretion of pro-inflammatory (IL-1β, IL-6, TNF-α, IFN-γ) and increase the secretion of anti-inflammatory cytokines IL-4 and IL-10 [18], which leads to a decrease in immune inflammation, activation of angiogenesis, inhibition of apoptosis and decrease in the degree of oxidative stress [19].

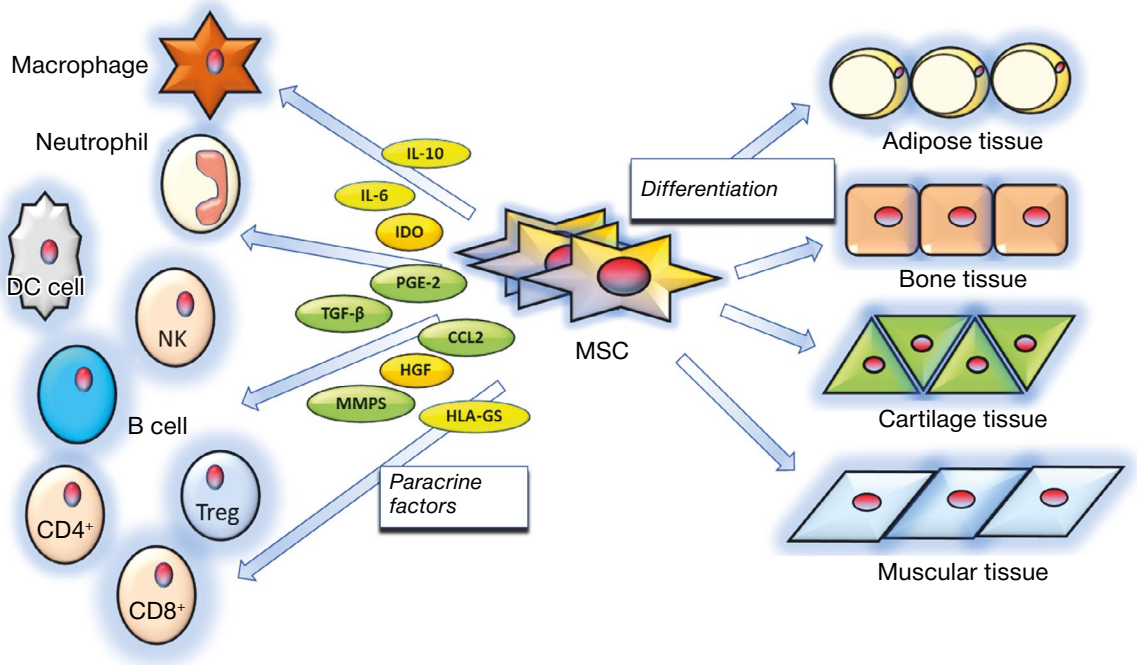
Nonclinical studies

T. Yabana et al. [20] demonstrated in rats with simulated colitis caused by dextran sodium sulfate (DSS) that MSCs administered intravenously to animals mi-

https://doi.org/10.17816/clinpract64530

journal of clinical practice 2021 Том 12 №1

Fig. 1. General MSC's effects grouped by the two fundamental mechanisms: 1) direct cell differentiation of recruited MSC (into cells of adipose, bone, cartilage and muscle tissues) to replace damaged cells and 2) induction of cytokines secreted by MSC into the inflammatory medium, affecting the recipient's immune system (IL-6: interleukin-6; PGE2: prostaglandin E2; TGF-β: β-transforming growth factor; IDO: indoleamine-2,3-dioxygenase; CCL-2: C-C-chemokine ligand 2; IL-10: interleukin -10; HGF: hepatocyte growth factor; MMP: matrix metalloproteinases; HLA-G: human leukocyte antigen-G). Adapted from [7].



grated into the lamina propria of the damaged colon, where they activated the expression of smooth muscle actin (a- SMA), which contributed to the restoration of the epithelium. It was also shown that MSCs were involved in maintaining the function of the epithelial barrier by activating the assembly of claudins, apical tight gap junction proteins.

In the pathogenesis of IBD, the most important role is apparently played by increased proliferation and defective apoptosis of immune cells, which is presumably associated with an imbalance of Bcl-2 and Bax, key proteins that affect apoptosis [21].

Among the pathogenetic mechanisms of the development of IBD, an imbalance in T-cell subpopulations is distinguished. As a result, the level of pro-inflammatory cytokines increases: in Crohn's disease due to differentiation of Th1 and Th17 cells, in ulcerative colitis due to differentiation of Th2 cells. On the contrary, the level of T-regulatory (Treg) cells is reduced in the peripheral blood of patients with IBD [23]. Among Treg cells, CD4 + CD25 + FoxP3 + cells play a key role in suppressing the immune system and maintaining tolerance [22]. K. Akiyama et al. [22] showed that systemic infusion of bone marrow-derived MSCs (BM-MSCs) induces apoptosis of T cells via the Fas ligand-dependent pathway (FasL) and can improve the course of the disease in experimental DSS-induced mice colitis. It has been shown that Fas-regulated secretion of the BM-MSC protein MCP-1 recruits T cells for FasL-mediated apoptosis. Apoptosis of T cells leads, in turn, to the induction of macrophages producing high levels of transforming growth factor beta (TGF-β), which is accompanied by an increase in the number of T-regulatory cells and, ultimately, contributes to a decrease in the degree of immune inflammation. Q. Chen et al. [24] demonstrated that intravenous administration of MSCs greatly alleviates the clinical severity of trinitrobenzenesulfonic acid (TNBS) -induced ulcerative colitis in mice (weight loss, diarrhea, and inflammation) and improves animal survival. It was also shown that MSCs reached the damaged colon and promoted the proliferation of intestinal epithelial cells and the differentiation of intestinal stem cells (determined by the detection of Lgr5 + cells), which was mediated by the suppression of autoimmune and inflammatory reactions (IL-2, TNF-α, IFN-γ, T-bet; IL-6, IL-17, RORγt) caused by Th1-Th17 cells, as well as increased activity of Th2 cells (IL-4, IL-10, GATA-3). In addition, it was shown that MSCs induced activated CD4 + CD25 + Foxp3 + T regulatory cells (TGF-β, IL-10, Foxp3).

Macrophages, dendritic cells, and other antigen-presenting cells are also involved in the pathogenesis of IBD due to their specialization in presenting antigen to T cells and, in turn, generating a generated T cell response. Tissue macrophages play a key role in maintaining normal intestinal homeostasis, but may also be involved in the pathogenesis of IBD. In a healthy intestine, resident macrophages exhibit the M2 phenotype, while pro-inflammatory M1 macrophages dominate in the inflamed intestinal mucosa. In this regard, changing the balance of macrophage populations to the M2 phenotype has become a new approach in the treatment of IBD. Numerous preclinical studies have shown that MSCs can induce immunomodulatory macrophages, and their therapeutic efficacy in experimental ulcerative colitis is mediated by macrophages with an M2-like phenotype [25].

H. Jo et al. [26] cultured immature dendritic cells (imDC) and lipopolysaccharide (LPS) treated mature dendritic cells (mDC) together with MSCs for 48 h, and then analyzed the profiles of surface markers and cytokines and the regulatory role of these DCs for primary splenocytes. In addition, the therapeutic effects of MSCs and DCs co-cultured with MSCs were compared in mice with chronic colitis. The authors demonstrated that after co-cultivation of MSCs with immature dendritic cells (MSC-DC) or LPS-treated mature dendritic cells (LPS + MSC-DC), the expression of CD11c, CD80, CD86, IL-6, TNF-α and IFN-γ was decreased, and the expression of CD11b, IL-10 and TGF-β — increased. In addition, MSC-DC and LPS + MSC-DC induced the expression of CD4, CD25 and Foxp3 in primary splenocytes isolated from mice. In mice with DSS-induced colitis, MSC and MSC-DC increased colon length, body weight, and survival; caused the restoration of normal morphology, recorded by histological examination of the intestinal walls. Moreover, in the MSC and MSC-DC groups, in the colon tissues, the expression of IL-6, TNF-α and IFN-γ also decreased, while the expression of IL-10, TGF-β and Foxp3 increased. These data suggest that MSCs stimulate the differentiation of dendritic cells into regulatory dendritic cells, which improves the effectiveness of chronic colitis therapy.

It was also shown that the introduction of MSCs can suppress the activation and proliferation of B cells secreting IgG, and, conversely, stimulate the formation of CD5+ regulatory B cells (Bregs) producing IL-10. In addition, it was shown that MSCs can suppress the proliferation of NK -cells secreting proinflammatory cytokines [27].

Exosomes from MSCs for experimental treatment of IBD

Exosomes — extracellular vesicles secreted by MSCs, contain a large number of biologically active factors. Exosomes play an important role in intercellular communications, transferring microRNAs, regulatory and functional proteins and peptides, lipids, glycoproteins, mRNAs, intracellular messengers, etc. from cell to cell [28]. Thus, exosomes from MSCs, similarly to the MSCs themselves, have powerful physiological properties that affect the restoration of damaged tissues [29]. At the same time, exosomes are more stable than MSCs and safer, because in principle, they cannot cause an immune response of the host organism and provoke any other reactions of the organism, which are potentially possible in response to the introduction of a cell preparation.

Earlier, a number of researchers have demonstrated that exosomes secreted by MSCs have a pronounced restorative effect in the treatment of many diseases that cause tissue damage, including IBD [30–32]. Thus, F. Mao et al. showed that exosomes released from human umbilical cord-derived MSCs (hucMSC) have a positive effect on the treatment of DSS-induced colitis, and studied their main mechanism of action [32].

Indocyanine green (ICG) -labeled exosomes enter the colon tissues of IBD mice 12 hours after injection. The expression of the IL-10 gene increased, while the expression of the TNF-α, IL-1β, IL-6, iNOS, and IL-7 genes decreased in the tissues of the colon and spleen of mice treated with MSC exosomes. In addition, the infiltration of macrophages into the colon tissue was reduced. It was also shown that in vitro co-cultivation with exosomes inhibited the expression of iNOS and IL-7 in mouse enterocelium macrophages. At the same time, the researchers found that the expression of IL-7 is higher in the tissues of the colon of patients with colitis than in healthy people from the control group. Overall, these results demonstrated that exosomes from hucMSCs have a strong effect on recovery in DSS-induced IBD, this effect may be mediated through modulation of IL-7 expression in macrophages.

In a study by R. Yang et al. [33] exosomes isolated from MSCs preconditioned with IFN-γ were transplanted into mice with DSS-induced colitis, which significantly improved the disease activity index and histological assessment of colitis, and also decreased the Th17 ratio and increased the ratio of Treg cells. The introduction of exosomes significantly reduced the expression of Stat3 and p-Stat3, suppressing the differentiation of Th17 cells, while exosomes from MSCs

https://doi.org/10.17816/clinpract64530

journal of clinical practice 2021 Том 12 №1

preconditioned with IFN-γ showed the highest inhibition efficiency. IFN-γ pretreatment increased the levels of miR-125a and miR-125b in MSC exosomes, which directly targeted Stat3, which inhibits Th17 cell differentiation. Moreover, co-infusion of miR-125a and miR-125b also demonstrated a therapeutic effect in colitis, accompanied by a decrease in the ratio of Th17 cells. Overall, this study demonstrates that IFN-γ treatment stimulated the effectiveness of exosomes from MSCs in reducing colitis by increasing levels of miR-125a and miR-125b, which bind to Stat3 3'-UTR to suppress Th17 cell differentiation.

Clinical studies

Completed clinical studies

Due to their therapeutic properties, MSCs obtained from bone marrow, placenta, or adipose tissue are actively used in clinical trials for the treatment of patients with IBD both in the form of local endoscopic cell injections and by systemic (intravenous) infusion.

Local administration of MSC

Local administration of MSCs is used mainly for the treatment of fistulous (extraluminal) forms of Crohn's disease [34]. Thus, J. Panés et al. [35] conducted a double-blind, randomized, placebo-controlled study to determine the long-term efficacy and safety of a single local administration of allogeneic MSCs derived from adipose tissue (Cx601) in the treatment of patients with Crohn's disease and difficult to treat draining complex perianal fistulas. The study was conducted in 49 clinical centers in Europe and Israel, and included 212 patients (ClinicalTrials.gov: NCT01541579). Patients were randomly assigned (1: 1) into groups, which in addition to standard care received a single local injection, or 120×10^6 Cx601 cells, or placebo (control). Efficacy endpoints assessed in a modified treatment intent population (randomly assigned, treated, and with one or more post-baseline efficacy evaluations) at Week 52 included combined remission (closure of all treated external holes draining at baseline in the absence of congestion > 2 cm, confirmed by magnetic resonance imaging) and clinical remission (absence of draining fistulas). Previously, the same investigators reported the primary study endpoint at 24 weeks (combined remission in 51.5% of patients receiving Cx601 versus 35.6% in the control group: difference of 15.8 percentage points; 97.5% confidence interval [CI] 0.5–31.2; $p = 0.021$). On the Week 52 a significantly larger proportion of patients treated with Cx601 achieved combined remission (56.3%) compared with the control group (38.6%) (a difference of 17.7 percentage points; 95% CI 4.2–31.2; $p = 0.010$), and clinical remission (59.2% versus 41.6% of the control group with a difference of 17.6 percentage points; 95% CI 4.1–31.1; $p = 0.013$). Security was maintained for 52 weeks; side effects were observed in 76.7% of patients in the Cx601 group and in 72.5% of patients in the control group. Based on the results of a phase III study of patients with Crohn's disease and treatment-resistant perianal fistulas, the authors concluded that Cx601 is safe and effective for closing external fistulas compared with placebo after 1 year of the study.

M. Herreros et al. [36] published data from a clinical study evaluating 45 patients with 52 surgically resistant anal fistulas of various etiologies (including 18 patients with perianal fistulas caused by Crohn's disease) and their response to therapy with MSCs of various types, including allogeneic MSCs from fat (adipose- derived mesenchymal stem cell, ASC), autologous ASC, and stromal-vascular fraction (SVF), which is believed to contain ASC with minimal adipocyte and erythrocyte counts. Considering 42 cases of perianal fistula, 40 (95.2%) of them showed healing or improvement/partial response after an average of 6.6 weeks (range 2–36 weeks). Cure occurred in 22/42 (52.4%) cases, with the majority of patients cured in 5.8 months on average (range 0.5–24 months). The cure of these 42 patients was assessed depending on the type of cell preparations used. The cure rate with SVF was 13/23 (56.5%) cases, with autologous ASC — 3/9 (33.3%), with allogeneic ASC — 6/10 (60%). The injected cell dose was also analyzed in perianal fistulas with a mean of 43.9 million (range 3–210 million) in cases of cure.

Considering only the perianal fistula due to Crohn's disease [36, 37], 18/18 patients (100%) showed healing or improved / partial response starting at an average of 5.3 weeks (range 2-12 weeks). Cure occurred in 10/18 (55.5%) cases, with most patients cured in 6.5 months (range 0.5-24 months). The cure of these 18 patients was also assessed depending on the type of cell preparations. The cure rate with SVF was observed in 40% of cases, with autologous ASC — in 66.6%, with allogeneic ASC — in 55.5%. The injected dose of cells averaged 43.9 million (range 3–210 million) in cases of cured patients. In all cases of perianal fistula therapy in Crohn's disease, a surgical technique was used — curettage, closure of the internal opening of the fistula, and cell injection [36, 37].

In the case of a perianal cryptoglandular fistula [38], 18 patients underwent curettage, closure, and ASC injections, showing healing in 9/18 (50%) cases; 6 under-

went curettage, endoanal flap advancement, and ASC injection, with fistula closure observed in 3/6 (50%) cases.

A phase II clinical trial using autologous adipose-derived MSCs (ASCs) for the treatment of Crohn's disease fistulas, characterized by a devastating condition with a high recurrence rate, demonstrated safety and therapeutic potential with a sustained response over 2 years [39]. This phase II study initially enrolled 41 patients. After 24 months, complete healing was observed in 27 (75.0%) of 36 patients (data for 5 of 41 patients were absent after 24 months). No side effects associated with ASC administration were observed. Moreover, complete closure of the fistula after initial treatment was sustained. The results provide strong evidence of the effectiveness of autologous ASCs in the treatment of Crohn's fistulas.

L. Scott et al. [40] published the results of the use of the drug darvadstrocel (Alofisel), which is a suspension of multiplied human allogeneic MSCs (eASC) obtained from adipose tissue. It is the first MSC-based drug approved by the European Union for the treatment of complex perianal fistulas in adult patients with inactive/moderately active luminal Crohn's disease when the fistula has shown an inadequate response to one or more standard therapies. In a pivotal Phase III study of ADMIRE-CD, this difficult-to-treat population of patients following fistula therapy, following standard treatment, received adjunctive therapy with localized administration of a single dose of darvadstrocel (120 million eASC) into the tissue surrounding the perianal complex: fistula healing was significant more effective than in the placebo group (patients were injected with saline), while patients in the darvadstrocel group had a higher combined remission rate (closure of fistulas by clinical assessment + absence of abscesses by magnetic resonance imaging) after 24 weeks after the appointment of treatment. Clinical remission persisted in more than 50% of patients after 52 weeks of observation. Given the very limited treatment options for this intractable rare condition, Darvadstro Whole therapy is an innovative and promising minimally invasive approach.

Y. Cao et al. in 2021, a meta-analysis and a systematic review were published to assess the effectiveness of stem cells (MSCs from bone marrow and adipose tissue) for the treatment of any form of fistula in Crohn's disease [41]. A total of 29 clinical studies were analyzed in this review, including 1252 patients. As a result, it was shown that in the group of patients with fistulas in Crohn's disease who received stem cells transplanted there was a higher rate of fistula healing compared with the group of patients receiving placebo (61.75% versus 40.46%, odds ratio, 2, 21; 95% CI 1.19–4.11; p <0.05). The group of patients receiving stem cells 3×10^7 cells/ml had an advantage in the rate of fistula healing by 71.0% compared to the group of stem cells with other doses (relative risk, RR, 1.3; 95% CI 0.76 -2.22), and the rates of recovery in patients with perianal and transsphincteric fistulas were higher than with rectovaginal ones (77.95 versus 76.41%). Interestingly, the Crohn disease activity index (CDAI) and perianal disease activity index (PDAI) clearly temporarily increased with stem cell use after 1 month, while returning to baseline after administration stem cells after 3 months. Moreover, the incidence of treatment-related adverse events was significantly lower in the stem cell group than in the placebo group (RR 0.58; 95% CI 0.30-1.14). This study has shown that the use of stem cells, especially ASC from adipose tissue, is a promising treatment for fistula in Crohn's disease due to its higher efficacy and lower incidence of adverse events.

Intravenous administration of MSC

Systemic (intravenous) administration of MSCs is used mainly for the treatment of luminal (inflammatory) forms of IBD [34].

In a randomized placebo-controlled clinical trial, J. Hu et al. (registration number NCT01221428) [42] studied the safety and efficacy of MSCs derived from human umbilical cord in moderate to severe ulcerative colitis, while 34 patients with ulcerative colitis were included in group I and received infusion of MSCs in addition to the main treatment and 36 patients entered group II and received saline in addition to the main treatment. One month after therapy, in 30 patients in group I, the formation of diffuse and deep ulcers and the course of severe inflammatory processes on the mucous membrane significantly decreased. During follow-up, the mean Mayo score and histology score in Group I decreased, while the IBDQ scores were significantly improved over pretreatment and in comparison with group II (p <0.05). Among other positive effects, the authors note the absence of obvious adverse reactions after infusion of MSCs, as well as chronic adverse or protracted reactions during the entire observation period. Thus, it has been reliably demonstrated that MSC infusion is a safe and effective method for the treatment of ulcerative colitis.

J. Zhang et al. [43] studied the efficacy and safety of the use of umbilical cord MSCs (UC-MSCs) for the treatment of Crohn's disease. The study included

https://doi.org/10.17816/clinpract64530

journal of clinical practice 2021 Том 12 №1

82 patients diagnosed with Crohn's disease who received maintenance therapy with steroids for more than 6 months, of whom 41 patients were randomly selected to receive four peripheral intravenous infusions of 106 UC-MSCs / kg, 1 infusion / week. Patients were followed up to 12 months with an assessment of CDAI, Harvey-Bradshaw index (HBI), and corticosteroid dosage. 12 months after treatment, CDAI, HBI, and corticosteroid dosage decreased by 62.5 ± 23.2; 3.4 ± 1.2; 4.2 ± 0.84 and 23.6 ± 12.4; 1.2 ± 0.58; 1.2 ± 0.35 mg/day, respectively, in the UC-MSC and control groups (p <0.01, p <0.05 and p <0.05 for UC-MSC compared to the control, respectively). In 4 patients, after cell infusion, the temperature rose. No serious adverse events were observed. The researchers conclude that UC-MSCs are effective in treating Crohn's disease, although they sometimes cause minor side effects.

In a study by our group (O. Knyazev et al.) [44], 22 patients with exacerbation of moderate and severe forms of ulcerative colitis were treated with the use of allogeneic MSCs from the bone marrow. Patients with acute ulcerative colitis (less than 6 months from the onset of the disease) were divided into 2 groups. Patients with nonspecific ulcerative colitis of group 1 (n = 12), in addition to standard anti-inflammatory therapy, received MSCs according to the following scheme: 0, 1, and 26 weeks, then every 6 months in subsequent years of follow-up. Group 2 patients (n = 10) received standard anti-inflammatory therapy with 5-aminosalicylic acid (5-ASA) and glucocorticoids. Patients with severe exacerbation of ulcerative colitis in group 1 were 58.3%, in group 2 — 60%, with moderate exacerbation — 41.7 and 40%, respectively. In group 1, total colitis was diagnosed in 33.3% of patients, in group 2 — in 40%, left-sided colitis — in 66.7 and 60%, respectively. Patients of group 1 were reduced the dose of glucocorticoids to 0.5 mg per 1 kg of body weight and systemic administration of MSCs was carried out at a dose of 1.5–2 million cells per 1 kg of body weight according to the scheme of 0, 1 and 26 week 3–5 days after administration, the dose of previously prescribed glucocorticoids (no more than 30 mg / day) was reduced for 6–8 weeks. until complete cancellation. Later, in the absence of a relapse of the disease, the patients received maintenance therapy with 5-ASA and / or probiotics. Group 2 patients received standard therapy in accordance with international recommendations. The date of introduction of the cell culture was the point of inclusion in the clinical study. The criterion for the effectiveness of therapy was a relapse-free course of the disease for 12 months. The clinical activity of ulcerative colitis was assessed by the Rakhmilevich scale, endoscopic — by the Mayo scale. Monitoring the dynamics of clinical, laboratory and endoscopic parameters was carried out after 2; 6 and 12 months, then annually for 3 years. The results of the study demonstrated that the inclusion of MSCs in the complex therapy of acute attack of ulcerative colitis did not affect the frequency of relapses, the duration of remission and the average level of indices of clinical and endoscopic activity during 1 year of follow-up: in group 1, recurrence of ulcerative colitis occurred in 2 (16, 7%) patients, in the group 2 — in 3 (30%): RR 0.3; 95% CI 0.08–1.36; p = 0.2; χ^2 = 1.47). The Rakhmilevich index in the Group 1 of patients was 3.33 ± 0.54 points, in the 2nd — 4.4 ± 1.13 (p = 0.81), the Mayo index — 3.1 ± 0.85 and 3.9 ± 1.06 points, respectively (p = 0.66). Over 2 years of follow-up, the risk of recurrence of ulcerative colitis in group 1 is 3 times lower than in group 2 (p = 0.03). The average duration of remission in the Group 1 was 22 months, in the group 2 — 17 months (p = 0.049). After 3 years of follow-up, the duration of remission in groups 1 and 2 was 22 and 20 months, respectively (p = 0.66). The Rakhmilevich index in the Group 1 of patients was 4.75 ± 1.13 points, in the 2nd — 8.1 ± 1.1 (p = 0.001). As a result, it was reliably shown that the administration of MSCs increases the effectiveness of anti-inflammatory therapy in patients with acute ulcerative colitis.

In our other study (O. Knyazev et al.) [45], we evaluated the effectiveness of therapy for MSCs from the bone marrow in patients with the inflammatory (luminal) form of Crohn's disease (n = 34) receiving azathioprine. In group 1 (n = 15), patients received anti-inflammatory therapy using MSC culture in combination with azathioprine, in group 2 (n = 19) — received MSC without azathioprine. The severity of the attack was scored according to the CDAI index. In the blood serum, immunoglobulins (IgA, IgG, IgM) were examined; interleukins (IL) 1β, 4, 10; TNF-α, IFN-γ, TGF-β, C-reactive protein (CRP), platelets and erythrocyte sedimentation rate (ESR) after 2; 6 and 12 months from the start of MSC therapy. As a result, the initial mean CDAI in group 1 was 337.6 ± 17.1 points, in group 2 — 332.7 ± 11.0 (p = 0.3). In both groups of patients, a significant decrease in CDAI was noted 2 months after the start of MSC therapy: in group 1 — to 118.9 ± 12.4 points, in group 2 — to 120.3 ± 14.1 (p = 0, 7), after 6 months — 110.3 ± 11.1 and 114.3 ± 11.8 (p = 0.8), after 12 months — 99.9 ± 10.8 and 100.6 ± 12.1 (p = 0.8), after 24 months — 133.2 ± 28.3 and 120.8 ± 15.5 (p = 0.2), after 36 months — 139.9 ± 23.4 and 141.7 ± 20.8 points

(p = 0.9), respectively. The levels of IgA, IgG, IgM were significantly lower in the group of patients with a longer history of the disease and taking azathioprine for a long time. After the administration of MSCs in both groups of patients, there was a tendency for an increase in pro- and anti-inflammatory cytokines with a significantly lower level of pro-inflammatory cytokines (IFN-γ, TNF-α, IL-1β) in group 1, indicating a potentiation of the immunosuppressive action of MSCs and azathioprine , which provides a more pronounced anti-inflammatory effect. As a result, it was demonstrated that MSC transplantation promotes an increase in the blood serum of patients with Crohn's disease of the initially reduced concentration of immunoglobulins and cytokines and restoration of their balance as clinical remission occurs, and in combination with azathioprine it has a more pronounced anti-inflammatory effect.

Interesting results were obtained when comparing the effect of combined (local and systemic) administration of MSCs from the bone marrow, anticytokine therapy (infliximab), and antibiotic and immunosuppressive therapy on the healing of simple perianal fistulas in Crohn's disease [46]. The first group of patients aged 19 to 58 (Me 29) years (n = 12) received MSCs systemically according to the scheme and locally; the second group from 20 to 68 (Me 36) years (n = 10) received infliximab according to the scheme; the third group from 20 to 62 (Me 28) years old (n = 14) received antibiotics and immunosuppressants. According to the results of the study, after 12 weeks. among patients of the Group 1, healing of simple fistulas was noted in 8 (66.6%), in the Group 2 — in 6 (60%), in the Group 3 — in 1 (7.14%); after 6 months — in 8 (66.6%), 6 (60%) and 1 (7.14%); after 12 months — in 7 (58.3%), 6 (60%) and 2 (14.3%); after 24 months — in 5 (41.6%), 4 (40%) and 0 (0%) patients, respectively. As a result, it was demonstrated that combined cellular and anticytokine therapy for Crohn's disease with perianal lesions significantly promotes more frequent and prolonged closure of simple fistulas in comparison with antibiotic and immunosuppressive therapy, as well as a decrease in the frequency of disease relapses.

J. Ko et al. [34] published in January 2021 a detailed analysis of the safety and efficacy of MSC therapy for IBD based on 24 studies (17 used local administration of MSCs, 7 — systemic). Overall, the authors conclude that local injections of MSCs in fistulous (extraluminal) Crohn's disease demonstrate long-term efficacy and a favorable safety profile. The evidence for the effectiveness of systemic infusion of MSCs for the treatment of inflammatory IBD remains, according to the authors, ambiguous, due to the pronounced methodological heterogeneity of studies (primarily due to the different source of MSCs), aggravated by the lack of evidence showing that MSCs reach the intestine after intravenous injection. , and not always a clearly demonstrated safety profile. At the same time, in the already mentioned studies of our group, rather unequivocal evidence was obtained of the effectiveness of systemic infusion of allogeneic MSCs for the treatment of IBD [44–46].

Proceeding clinical studies

To date, the website Clinicaltrials.gov has registered 14 active clinical trials (as of March 2021) using MSC therapy for the treatment of IBD — in 2 cases with autologous MSCs and in 12 with allogeneic MSCs (Table 1). Seven trials used MSCs from bone marrow, five used MSCs from adipose tissue, one used MSCs from umbilical cord blood, and one used MSCs from Wharton's jelly. In 10 cases, trials are conducted for the treatment of Crohn's disease, in 4 cases for the treatment of ulcerative colitis. Local administration of MSCs is used in 12 trials, systemic administration in 2.

CONCLUSION

Numerous open and randomized clinical trials of MSCs in the treatment of IBD have unequivocally shown the safety of this approach and its potential effectiveness, including in cases resistant to traditional therapies. The therapeutic effect of MSCs is due to a powerful immunomodulatory effect, as a result of which the activity of autoimmune inflammation decreases and the repair process in the intestinal mucosa is stimulated, which in turn increases the duration of remission, reduces the risk of disease recurrence and the frequency of hospitalizations.

Based on clinical trials in the European Union, the first drug based on allogeneic MSCs from adipose tissue darvadstrocel (Alofisel, Takeda, Japan) was approved for the treatment of complex perianal fistulas in patients with luminal Crohn's disease. At the same time, there is currently no single established optimal protocol for MSC transplantation for the treatment of IBD, which makes additional randomized clinical trials of MSCs, their source, dosage, method, and optimal frequency of cell administration urgent. In addition to MSCs from bone marrow and adipose tissue, the use of MSCs from the placenta is promising, which, in combination with methods for increasing the efficiency of MSC production, such as 3D cultivation and the use of large-volume bioreactors, can significantly

https://doi.org/10.17816/clinpract64530

Table 1

Proceeding clinical trials on the MSC therapy of IBD (according to clinicaltrials.gov by March, 2021)

No.	Name, Clinical Trials.gov ID	Disease	Type of cell	Route of administration	Setting
1	Use of Mesenchymal Stem Cells in Inflammatory Bowel Disease; NCT03299413	UC	Allogeneic MSCs from gelatin of Wharton	Intravenous administration	Cell Therapy Center Amman, Jordan
2	Angiographic Delivery of AD-MSC for Ulcerative Colitis; NCT04312113	UC	Autologous MSCs from adipose tissue	Intra-arterial administration	Mayo Clinic in Rochester Rochester, Minnesota, USA
3	Adipose Mesenchymal Stem Cells (AMSC) for Treatment of Ulcerative Colitis (AMSC_UC); NCT03609905	UC	Allogeneic MSCs from adipose tissue	Local administration	Liaocheng city people's hospital Liaocheng, Shandong, China
4	Study of Mesenchymal Stem Cells for the Treatment of Medically Refractory Ulcerative Colitis (UC); NCT04543994	UC	Remestemcel-L (allogeneic MSCs from bone marrow)	Local administration	Cleveland Clinic Cleveland, Ohio, USA
5	Mesenchymal Stem Cells for the Treatment of Perianal Fistulizing Crohn's Disease; NCT04519671	CD	Allogeneic MSCs from bone marrow	Local administration	Cleveland Clinic Cleveland, Ohio, USA
6	Study of Mesenchymal Stem Cells for the Treatment of Ileal Pouch Fistula's in Participants With Crohn's Disease (IPAAF); NCT04519684	CD	Allogeneic MSCs from bone marrow	Local administration	Cleveland Clinic Cleveland, Ohio, USA
7	Mesenchymal Stem Cells for the Treatment of Rectovaginal Fistulas in Participants With Crohn's Disease; NCT04519697	CD	Allogeneic MSCs from bone marrow	Local administration	Cleveland Clinic Cleveland, Ohio, USA
8	Mesenchymal Stem Cells for the Treatment of Pouch Fistulas in Crohn's; NCT04073472	CD	Allogeneic MSCs from bone marrow	Local administration	Cleveland Clinic Cleveland, Ohio, USA
9	Study of Mesenchymal Stem Cells for the Treatment of Medically Refractory Crohn's Colitis; NCT04548583	CD	Allogeneic MSCs from bone marrow	Local administration	Cleveland Clinic Cleveland, Ohio, USA
10	A Follow-up Study to Evaluate the Safety of ALLO-ASC-CD in ALLO-AS-C-CD-101 Clinical Trial; NCT03183661	CD	Allogeneic MSCs from adipose tissue	Local administration	Anterogen Co., Ltd., Seoul, Korea
11	MSC Intratissular Injection in Crohn Disease Patients; NCT03901235	CD	Allogeneic MSCs from bone marrow	Local administration	CHU de Liège, Liege, Belgium
12	A Study to Evaluate the Safety of ALLO-ASC-CD for Treatment of Crohn's Disease; NCT02580617	CD	Allogeneic MSCs from adipose tissue	Local administration	Yonsei University College of Medicine Seoul, Seoul, Korea
13	Long-term Safety and Efficacy of FURESTEM-CD Inj. in Patients With Moderately Active Crohn's Disease(CD); NCT02926300	CD	Allogeneic MSCs from umbilicus	Local administration	Inje University Haeundae Paik Hospital Busan, Korea, Republic of Yeungnam University Medical Center Daegu, Korea, Republic of Seoul National Universty Bundang Hospital Seongnam-si, Korea (and 4 more...)
14	Pediatric MSC-AFP Sub-study for Crohn's Fistula; NCT03449069	CD	MSC-AFP (insert coated with autologous MSCs from adipose tissue)	Local administration	Mayo Clinic in Rochester Rochester, Minnesota, USA

Note. UC — ulcerative colitis; CD, Crohn's disease; MSC — mesenchymal stromal cells.

reduce the cost of MSC production and make this unique method of therapy available to a wide range of patients.

ADDITIONAL INFORMATION

Author contribution. M.A. Konoplyannikov — literature analysis, manuscript writing; O.V. Knyazev, V.P. Baklaushev — literature analysis, manuscript editing. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

REFERENCES

1. Sairenji T, Collins KL, Evans DV. An update on inflammatory bowel disease. *Prim Care*. 2017;44(4):673–692. doi: 10.1016/j.pop.2017.07.010

2. Guindi M, Riddell RH. Indeterminate colitis. *J Clin Pathol*. 2004;57(12):1233–1244. doi: 10.1136/jcp.2003.015214

3. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature*. 2011;474(7351):307–317. doi: 10.1038/nature10209

4. The facts about inflammatory bowel diseases. The Crohn's & Colitis Foundation of America (CCFA); 2014. Avalable from: https://www.crohnscolitisfoundation.org/sites/default/files/2019-02/Updated%20IBD%20Factbook.pdf

5. GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020;5(1):17–30. doi: 10.1016/S2468-1253(19)30333-4

6. Magro F, Portela F. Management of inflammatory bowel disease with infliximab and other anti-tumor necrosis factor alpha therapies. *BioDrugs*. 2010;24(Suppl 1):3–14. doi: 10.2165/11586290-000000000-00000

7. Ocansey DK, Qiu W, Wang J, et al. The Achievements and Challenges of Mesenchymal Stem Cell-Based Therapy in Inflammatory Bowel Disease and Its Associated Colorectal Cancer. *Stem Cells Int*. 2020;2020:7819824. doi: 10.1155/2020/7819824

8. Tolar J, Le Blanc K, Keating A, et al. Concise review: hitting the right spot with mesenchymal stromal cells. *Stem Cells*. 2010;28(8):1446–1455. doi: 10.1002/stem.459

9. Williams JT, Southerland SS, Souza J, et al. Cells isolated from adult human skeletal muscle capable of differentiating into multiple mesodermal phenotypes. *Am Surg*. 1999; 65:22–26.

10. Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implication for cell-based therapies. *Tissue Engl*. 2001;7(2):211–228. doi: 10.1089/107632701300062859

11. Gronthos S, Arthur A, Bartold PM, et al. A method to isolate and culture expand human dental pulp stem cells. *J Methods Mol Biol*. 2011;698:107–121. doi: 10.1007/978-1-60761-999-4_9

12. Prockop D. Repair of tissues by adult stem/progenitor cells [MSCs]: controversies, myths, and changing paradigms. *Mol Ther*. 2009;17(6):939–946. doi: 10.1038/mt.2009.62

13. Lv FJ, Tuan RS, Cheung KM, et al. Concise review: the surface markers and identity of human mesenchymal stem cells. *Stem Cells*. 2014;32(6):1408–1419. doi: 10.1002/stem.1681

14. Caplan AI, Correa D. The MSC: an injury drugstore. *Cell Stem Cell*. 2011;9(1):11–15. doi: 10.1016/j.stem.2011.06.008

15. Wang S, Miao Z, Yang Q, et al. The dynamic roles of mesenchymal stem cells in colon cancer. *Can J Gastroenterol Hepatol*. 2018;2018:7628763. doi: 10.1155/2018/7628763

16. Caplan AI. MSCs: The sentinel and safe-guards of injury. *J Cell Physiol*. 2016;231(7):1413–1416. doi: 10.1002/jcp.25255

17. Bernardo ME, Fibbe WE. Mesenchymal stromal cells: sensors and switchers of inflammation. *Cell Stem Cell*. 2013;13(4):392–402. doi: 10.1016/j.stem.2013.09.006

18. Spaggiari GM, Capobianco A, Abdelrazik HF, et al. Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2, 3-dioxygenase and prostaglandin E2. *Blood*. 2008;111(3):1327–1333. doi: 10.1182/blood-2007-02-074997

19. Terai S, Tsuchiya A. Status of and candidates for cell therapy in liver cirrhosis: overcoming the "point of no return" in advanced liver cirrhosis. *J Gastroenterol*. 2017;52(2):129–140. doi: 10.1007/s00535-016-1258-1

20. Yabana T, Arimura Y, Tanaka H, et al. Enhancing epithelial engraftment of rat mesenchymal stem cells restores epithelial barrier integrity. *J Pathol*. 2009;218:350–359. doi: 10.1002/path.2535

21. Dias CB, Milanski M, Portovedo M, et al. Defective apoptosis in intestinal and mesenteric adipose tissue of Crohn's disease patients. *PLoS One*. 2014;9(6):e98547. doi: 10.1371/journal.pone.0098547

22. Akiyama K, Chen C, Wang D, et al. Mesenchymal-stem cell-induced immunoregulation involves FAS-ligand-/FASmediated T cell apoptosis. *Cell Stem Cell*. 2012;10(5):544–555. doi: 10.1016/j.stem.2012.03.007

23. Sisakhtnezhad S, Alimoradi E, Akrami H. External factors influencing mesenchymal stem cell fate in vitro. *Eur J Cell Biol*. 2017;96(1):13–33. doi: 10.1016/j.ejcb.2016.11.003

24. Chen Q, Yan L, Wang CZ, et al. Mesenchymal stem cells alleviate TNBS-induced colitis by modulating inflammatory and autoimmune responses. *World J Gastroenterol*. 2013;19(29):4702–4717. doi: 10.3748/wjg.v19.i29.4702

25. Hidalgo-Garcia L, Galvez J, Rodriguez-Cabezas ME, Anderson PO. Can a conversation between mesenchymal stromal cells and macrophages solve the crisis in the inflamed intestine? *Front Pharmacol*. 20186;9:179. doi: 10.3389/fphar.2018.00179

26. Jo H, Eom YW, Kim HS, et al. Regulatory dendritic cells induced by mesenchymal stem cells ameliorate dextran sodium sulfate-induced chronic colitis in mice. *Gut Liver*. 2018;12(6):664–673. doi: 10.5009/gnl18072

27. Liu J, Liu Q, Chen X. The immunomodulatory effects of mesenchymal stem cells on regulatory B cells. *Front Immunol*. 2020;11:1843. doi: 10.3389/fimmu.2020.01843

28. Самойлова Е.М., Кальсин В.А., Беспалова В.А., и др. Экзосомы — от биологии к клинике // *Гены и клетки*. 2017. Т. 12, № 4. С. 7–19. [Samoilova EM, Kalsin VA, Bespalova VA, et al. Exosomes — from biology to the clinic. *Genes & Cells*. 2017;12(4):7–19. (In Russ).] doi: 10.23868/201707024

29. Zhao T, Sun F, Liu J, et al. Emerging role of mesenchymal stem cell-derived exosomes in regenerative medicine. *Curr Stem Cell Res Ther*. 2019;14(6):482–494. doi: 10.2174/1574888X14666190228103230

30. Mianehsaz E, Mirzaei HR, Mahjoubin-Tehran M, et al. Mesenchymal stem cell-derived exosomes: a new therapeutic approach to osteoarthritis? *Stem Cell Res Ther*. 2019;10(1):340. doi: 10.1186/s13287-019-1445-0

31. Mendt M, Rezvani K, Shpall E. Mesenchymal stem cell-derived exosomes for clinical use. *Bone Marrow Transplant*. 2019;54(Suppl 2):789–792. doi: 10.1038/s41409-019-0616-z

32. Mao F, Yunbing Wu, Xudong Tang, et al. Exosomes derived from human umbilical cord mesenchymal stem cells relieve inflammatory bowel disease in mice. *Biomed Res Int*. 2017;2017:5356760. doi: 10.1155/2017/5356760

33. Yang R, Huang H, Cui S, et al. IFN-γ promoted exosomes from mesenchymal stem cells to attenuate colitis via miR-125a and miR-125b. *Cell Death Dis*. 2020;11(7):603. doi: 10.1038/s41419-020-02788-0

https://doi.org/10.17816/clinpract64530

journal of clinical practice 2021 Том 12 №1

34. Ko JZ, Johnson S, Dave M. Efficacy and safety of mesenchymal stem/stromal cell therapy for inflammatory bowel diseases: an up-to-date systematic review. *Biomolecules*. 2021;11(1):82. doi: 10.3390/biom11010082

35. Panés J, García-Olmo D, Van Assche G, et al; ADMIRE CD Study Group Collaborators. Long-term efficacy and safety of stem cell therapy (Cx601) for complex perianal fistulas in patients with Crohn's disease. *Gastroenterology*. 2018;154(5):1334–1342.e4. doi: 10.1053/j.gastro.2017.12.020

36. Herreros MD, Garcia-Olmo D, Guadalajara HT, et al. Stem cell therapy: a compassionate use program in perianal fistula. *Stem Cells Int*. 2019;2019:6132340. doi: 10.1155/2019/6132340

37. Garcia-Olmo D, Garcia-Arranz M, Herreros D, et al. A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. *Dis Colon Rectum*. 2005;48(7):1416–1423. doi: 10.1007/s10350-005-0052-6

38. McNevin MS, Lee PY, Bax TW. Martius flap: an adjunct for repair of complex, low rectovaginal fistula. *Am J Surg*. 2007;193(5):597–599. doi: 10.1016/j.amjsurg.2007.01.009

39. Cho YB, Park KJ, Yoon SN, et al. Long-Term results of adipose-derived stem cell therapy for the treatment of Crohn's fistula: ASCs for the treatment of Crohn's fistula. *Stem Cells Transl Med*. 2015;4(5):532–537. doi: 10.5966/sctm.2014-0199

40. Scott LJ. Darvadstrocel: a review in treatment-refractory complex perianal fistulas in Crohn's disease. *BioDrugs*. 2018;32(6):627–634. doi: 10.1007/s40259-018-0311-4

41. Cao Y, Su Q, Zhang B, et al. Efficacy of stem cells therapy for Crohn's fistula: a meta-analysis and systematic review. *Stem Cell Res Ther*. 2021;12(1):32. doi: 10.1186/s13287-020-02095-7

42. Hu J, Zhao G, Zhang L, et al. Safety and therapeutic effect of mesenchymal stem cell infusion on moderate to severe ulcerative colitis. *Exp Ther Med*. 2016;12(5):2983–2989. doi: 10.3892/etm.2016.3724

43. Zhang J, Lv S, Liu X, et al. Umbilical cord mesenchymal stem cell treatment for Crohn's disease: a randomized controlled clinical trial. *Gut and Liver*. 201812(1):73–78. doi: 10.5009/gnl17035

44. Knyazev OV, Parfenov AI, Konoplyannikov AG, Boldyreva ON. The use of mesenchymal stromal cells in the complex therapy of ulcerative colitis. *Therapeutic archive*. 2016;88(2):44–48. (In Russ).

45. Knyazev OV, Kagramanova AV, Fadeeva NA, et al. Bone marrow mesenchymal stromal cells and azathioprine in the treatment of Crohn's disease. *Therapeutic archive*. 2018;90(2):47–52. (In Russ). doi: 10.26442/terarkh201890247-52

46. Knyazev OV, Fadeeva NA, Kagramanova AV, et al. Cell therapy of the perianal manifestations of Crohn's disease. *Therapeutic archive*. 2018;90(3):60–66. (In Russ). doi: 10.26442/terarkh201890360-66

AUTHORS INFO

The author responsible for the correspondence:
Mikhail A. Konoplyannikov, Cand. Sci. (Biol.); address: 28, Orekhovy blvd, Moscow, 115682, Russia;
e-mail: mkonopl@mail.ru; eLibrary SPIN: 9211-6391; ORCID: https://orcid.org/0000-0003-1180-2343

Co-authors:
Oleg V. Knyazev, Dr. Sci. (Med.); e-mail: oleg7@bk.ru; eLibrary SPIN: 3268-0360;
ORCID: https://orcid.org/0000-0001-7250-0977

Vladimir P. Baklaushev, Dr. Sci. (Med.); e-mail: serpoff@gmail.com; eLibrary SPIN: 3968-2971;
ORCID: https://orcid.org/0000-0003-1039-4245