Immunotherapy of inflammatory bowel disease (IBD)

by Turnitin.com ®

Submission date: 09-Apr-2022 04:49PM (UTC+0700)
Submission ID: 1806002880
File name: Immunotherapy_of_inflammatory_bowel_disease_IBD.pdf (1.79M)
Word count: 9264
Character count: 53538

International Immunopharmacology 107 (2022) 108698

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Immunotherapy of inflammatory bowel disease (IBD) through mesenchymal stem cells

Huldani Huldani [a], Ria Margiana [b,i,j,k], Fawad Ahmad [c], Maria Jade Catalan Opulencia [d], Mohammad Javed Ansari [e], Dmitry Olegovich Bokov [f,l], Nargiza N. Abdullaeva [g,m], Homayoon Siahmansouri [h,*]

[a] Department of Physiology, Lambung Mangkurat University, Banjarmasin, South Kalimantan, Indonesia
[b] Department of Anatomy, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[c] Lahore General Hospital, Lahore, Pakistan
[d] College of Business Administration, Ajman University, Ajman, United Arab Emirates
[e] Department of Pharmaceutics, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-kharj, Saudi Arabia
[f] Institute of Pharmacy, Sechenov First Moscow State Medical University, 8 Trubetskaya St., bldg. 2, Moscow 119991, Russian Federation
[g] Research Scholar, Department of Scientific Affairs, Tashkent State Dental Institute, Makhtumkuli Street 103, Tashkent 100047, Uzbekistan
[h] Department of Immunology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[i] Master's Programme Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[j] Andrology Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[k] Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[l] Laboratory of Food Chemistry, Federal Research Center of Nutrition, Biotechnology and Food Safety, 2/14 Ustyinsky pr., Moscow 109240, Russian Federation
[m] Associate Professor, Doctor of Medical Sciences, Vice-rector for Therapeutic Affairs, Chief Physician of the 1st Clinic of Samarkand State Medical Institute, Amir Temur Street 18, Samarkand, Uzbekistan

ARTICLE INFO

Keywords:
Mesenchymal stem cells
Inflammatory bowel disease
Crohn's disease
Ulcerative colitis

ABSTRACT

Many pathophysiologic pathways and immune-pathologic etiologies are addressed as Inflammatory bowel disease (IBD) causes. Moreover, dysfunction of the immune system leads to inflammatory responses against intestinal components that boost disease severity. The use of routine treatments has limitations. Besides, patients may experience drug resistance. Therefore, the use of novel and effective therapies is essential. Relying on the immune regulatory functions of Mesenchymal Stem Cells (MSCs), researchers have suggested possible benefits of MSCs administration for IBD, both in experimental and clinical studies. Experimental animal models of IBD have shown effects of MSCs, MSC-derived exosomal micro RNAs, and MSC-based drug delivery systems on the regulation of the immune system (Th17 suppression versus T-regular cell biased responses). These studies have suggested MSCs' benefits on intestinal integrity, improved smooth cell function, and tissue repair. On the other hand, various clinical trials have been registered for MSCs application in IBD patients that show reliable safety in humans. Most clinical trials have used MSCs of bone marrow, umbilical cord, and adipose tissue that have been administered by intravenous or intra-tissue injection. Studies have evaluated clinical outcomes, patient symptoms, or healing processes; while immunological studies in the clinical era are missing. As we reviewed, huge shreds of experimental shreds of evidence have led to the inception of multiple clinical trials in phase I/II, showing promising results for IBD treatment. We suggest that further clinical investigation should be more focused on in-vitro/in-vivo assessed outcomes as well as the immunological endpoints to have more reliable results with more support for laboratory evidence.

1. Introduction

"Inflammatory bowel disease (IBD)" refers to two diseases (ulcerative colitis/Crohn's disease) in which the gastrointestinal (GI) tract is inflamed for a long time [1]. This prolonged inflammation damages the gastrointestinal tract and mainly presents at a young age (between 15 and 30 years old) [2]. It is divided into Crohn's disease and ulcerative colitis. There are no specific clinical manifestations for IBD and certain

* Corresponding author at: Department of Immunology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
E-mail address: Homayoon_siyahmansoori@yahoo.com (H. Siahmansouri).

https://doi.org/10.1016/j.intimp.2022.108698
Received 24 January 2022; Received in revised form 2 March 2022; Accepted 10 March 2022
Available online 17 March 2022

symptoms for it. Abdominal pain and chronic or recurrent diarrhea are symptoms making physicians suspected of IBD, and colonoscopy and biopsy are used to diagnose it [3]. Tissue ulcers caused by IBD can be painful and sometimes debilitating and life-threatening. Crohn's disease can appear anywhere in the gastrointestinal tract in different people. In some patients, the end of the small intestine (ileum) and others might be presented throughout the large intestine (colon) [4]. The most common areas of inflammation in Crohn's disease are the end of the small intestine and the colon. The main etiology for Crohn's is still unknown [5]. Stress and dietary factors are known to be causes of IBD exacerbation but are not described as an etiologic factor [6]. Immune system dysfunctions and heredity genetic factors are possible causes of the disease: Family history, white ethnicity, smoking, use of non-steroidal anti-inflammatory medications, which could lead to intestinal inflammation and exacerbation of the disease, living in industrial cities, living in more northern climates, high-fat diets are risk factors for the disease [7].

Ulcerative colitis (UC) is the second medical condition defined in the IBD category. Ulcerative colitis is a disease of the rectum and upper areas of the colon, and the inflammation is usually superficial and limited to the mucosa but is continuous [8]. Diarrhea, rectal bleeding, phlegm, and abdominal cramping are the main symptoms of UC [9]. The exact cause of ulcerative colitis remains unknown. Previously, diet and stress were suspected to be the etiology of this condition, but as well as Crohn's disease, these factors remain only as triggers of the inflammation exacerbation [10]. One possible cause is thought to be immune system dysfunction. The immune system trying to fight off viruses or invading bacteria might trigger an abnormal immune response that can lead to autoimmune responses against the gastrointestinal tract. UC is more common in people with a positive family history of IBD [11].

Many immune-pathologic etiologies, as well as immune system dysfunction resulting in inadequate inflammatory responses against intestinal components or oxidative stress repercussions, are addressed to contribute to IBD. Researchers have proposed prospective advantages of MSC treatment for IBD in both experimental and clinical investigations, based on the immune regulatory activities of MSCs. They have shown that the use of MSCs in the treatment of IBD is not only safe but also as a multifunctional-cell-based drug, they have significant positive clinical outcomes, such as overcoming drug resistance, high efficacy, deletion of steroid drugs from the treatment protocol, and reduce their complications in patients. So, we aimed to review the current pieces of evidence about the MSC application in IBD treatment.

2. Pathophysiology

Based on previous studies, the role of genetics, immune dysregulation, luminal, and environmental factors in the pathogenesis of these diseases have been investigated. In inflammatory processes of the intestinal mucosa, several immunological factors are involved, all leading to chronic activation and inflammation of the gastrointestinal tract [12]. Histologically, intestinal inflammation is characterized by the secretion of polymorphonuclear leukocytes, monocytes, and macrophages [13]. There are many hypothesizes trying to find the pathophysiologic etiology of the disease. Naturally, due to a phenomenon known as oral tolerance, the mucosal immune system does not react with the contents of the intestinal duct as well as food and microbial flora [14]. The reduction of immunological response to a protein previously exposed via the oral route is known as oral tolerance [15]. When food is being consumed orally, protein antigens can be absorbed via the mucosal surfaces of the gastrointestinal system and make physical contact with immune cells in the intestinal lamina propria [16]. Numerous mechanisms are involved in the development of oral tolerance, including the removal of CD4+ lymphocyte T cells, which secrete anti-inflammatory cytokines such as IL-10 and TGF-B, which contribute to suppressing the inflammation of the intestine [17]. Oral tolerance may be responsible for the lack of an immune response to food antigens and microbial flora in the intestinal tract. In IBD, oral tolerance dysfunction due to inflammatory triggers may lead to uncontrolled inflammation of the intestine [16]. Activation of T helper 1, 17, and 22 cells (Th1, Th17, and Th22) as well as NK, and NKT cells are known to have roles in immune tolerance dysfunction [18]. Th22 cells secret IL-22 that perform its actions through a receptor named IL-1R-22 and IL-10R2 that triggers JAK1 molecules pathways and STAT system. This cytokine mainly acts on epithelial cells and hepatocytes, is involved not only in antimicrobial defense but also in the production of acute-phase proteins and chemokines [19]. Various studies in mice lacking the IL-22 gene have shown an important role for this cytokine in the development of IBD [20].

Oxidative stress also plays an essential role in the pathogenesis of associated intestinal damage. Significant imbalances in total antioxidant activity have been identified in colonic mucosal biopsies as oxidative stress increases and antioxidant protection decreases [21]. If the free radicals quantity increased or the antioxidant protection decreased, a state of oxidative stress occurs, which may cause chronic or permanent damage to the cells [22]. One of the markers of oxidative stress is the increment of lipid peroxidation in cells, which is determined by measuring the number of reactants with thiobarbituric acid. Previous studies have shown the presence of oxidative stress in biological fluids such as saliva and plasma in IBD patients. The effectiveness of various therapies in treatment may be attributed to their antioxidant function. Compounds, such as sulfasalazine and its metabolites, 5-aminosalicylic acid, which are used in IBD treatment, are extremely effective in the depletion of reactive oxygens [23–25]. Neutrophils play a major role in inflammatory and immune responses. The enzyme myeloperoxidase is able to form a large number of oxidants by catalyzing the oxidation of electron donor compounds (such as halides) by hydrogen peroxide [26].

Genetically, IBD is a multigene disorder that can cause UC and Crohn's disease. Nucleotide-binding domain oligomerization protein (NOD 2) and autophagy-dependent gene (ATG) functioning in innate immune cells (both parenchymal and hematopoietic) are involved in immune defense against bacteria, mycobacteria, and viruses; although, variations in these genes are known to be associated with Crohn's disease [27,28].

In subjects with Crohn's disease, the mucosal T cells have a faster cell cycle, which increases the number of these cells compared to healthy subjects. Subjects with UC also have increased expression of a caspase-8 inhibitor called FLIP, which inhibits cell death through death receptors. Resistance to apoptosis of mucosal T cells has also been observed in patients with Crohn's disease. An increase in Bcl2/BAX ratio in lamina propria T cells enhances resistance to programmed cell death. The Bcl2 family plays an important role in this mechanism [29–31].

3. Treatment methods

The first-line treatment of IBD with mild/or moderate severity is sulfasalazine and other aminosalicylic acid compounds. The extent and severity of the disease should be determined before starting treatment. In mild to moderate disease, treatment can be provided on an outpatient basis, but patients with a severe fever, high heart rate, anemia, increased white blood cell count, and abdominal pain should be hospitalized [32,33]. In general, in the treatment of patients with inflammatory bowel disease, various drug groups are used including corticosteroids, Aminosalicylates, immunomodulators, antibiotics, and supportive medications. For many years, treatment for these patients has been limited to sulfasalazine and corticosteroids, but various oral Aminosalicylates are now used as the first line of treatment. Corticosteroids are still used as effective agents in improving symptoms in patients with moderate to severe severity, including antibiotics such as metronidazole, quinolones (such as ciprofloxacin), amoxicillin, and clarithromycin in the maintenance and maintenance of Crohn's patients [34–36]. Immunosuppressive drugs are widely used in individuals who are resistant to these treatments or patients getting highly dependent on corticosteroids. 6-Mercaptopurine and azathioprine are the most widely used. But methotrexate, cyclosporine, and anti-TNF agents are also used

Table 1
Some examples of traditional and biological DMARDs in IBD treatment.

Drug name	Mechanism of Action	Side effects	Reference
Traditional DMARDs Drugs			
Methotrexate	• Inhibition of T cell activation • suppression of intercellular adhesion molecule • down-regulation of B Lymphocytes • Inhibition of methyltransferase activity • Inhibition of the binding of interleukin 1-beta	• Hepatotoxicity • Ulcerative stomatitis • Abdominal pain • Leukopenia • Nausea • Acute pneumonitis • Fever • Kidney failure • Fatigue	[80,81]
Sulfasalazine	• Suppression of IL-1 • Suppression of TNF-alpha • Apoptosis of inflammatory cells • Increase chemotactic factors	• Depression • Oligospermia • Infertility • Thrombocytopenia • Megaloblastic anemia • Hemolytic anemia • Kidney stones • Headache	[82–84]
Hydroxychloroquine	• Inhibits stimulation of the toll-like receptor • Induce apoptosis of inflammatory cells • Decrease chemotaxis • TNF-alpha	• Stomach cramps • Headache • Retinopathy • Agitation • Paranoia and depression • Stevens–Johnson syndrome • Lymphopenia • Liver failure • Weakness	[85,86]
Biological DMARDs Drugs			
Abatacept	• Inhibitor of T-cells costimulatory signal	• Anaphylactic reactions • Upper respiratory tract infections • Urinary tract infections • Herpes infections • High blood pressure • Fatigue • Upset stomach	[87,88]
Adalimumab	• TNF inhibitor	• Tuberculosis • Risk of Cancer • Liver injury • Demyelinating central nervous system • Anaphylaxis	[89,90]
Certolizumab pegol	• TNF inhibitor	• Serious infections • Heart failure • Urinary tract infections • Diarrhea • Stomach pain • Stuffy nose	[91,92]
Etanercept	• TNF inhibitor	• Sepsis • Reactivation of latent tuberculosis and hepatitis B	[93]
Golimumab	• TNF inhibitor • Reduction of IL-6, ICAM-1, MMP-3, VEGF	• Upper respiratory infections • Viral infections	[94,95]
Sarilumab	• IL-6 receptor antagonist	• Neutropenia • Thrombocytopenia • Hyperlipidaemia • Infections of the upper respiratory tract	[96]
Ustekinumab	• Inhibitor of IL-23, and IL-12	• upper respiratory tract infections • tuberculosis • risk of cancer • headache	[97]

DMARD: Disease-modifying anti-rheumatic drugs.

in selective cases; While all these medications have side effects as well as immune system dysfunction, gastrointestinal disorders, skin disorders, avesicular necrosis, kidney diseases, liver dysfunction, allergic reactions, and so on. Therefore, the use of alternative therapies is inevitable. With the advancement of MSC science, UC has also been treated with a variety of MSC-based drugs [35–38]. There are several DMARDs in order to IBD treatment; we summarized some of them in Table 1.

4. Mesenchymal stem cells

In recent years, there has been a great deal of interest in the use of stem cells in the treatment of various diseases. One type of these fatal diseases is COVID-19; Alveolar type II cells can be infected by the SARS-CoV-2 through the expression of ACE2 and cause dysfunction of these cells, apoptosis, and the spread of lung tissue damage [39,40]. One group of these stem cells that are currently undergoing extensive studies are the Mesenchymal Stem Cells (MSCs), which due to the regulatory function of these immune systems, are highly repulsive. Consider the use

of MSCs as a means of regulating the immune system in the treatment of autoimmune diseases and also their role in the clinical application [41,42]. For a cell to be defined as a mesenchymal cell, it must have several characteristics. First of all, they must have the following phenotype CD105+, CD73+, CD90+, CD34-, CD14-CD11b-, CD45-, CD79a-, and CD19-. Secondly, they must be able to differentiate into adipocytes, osteoblasts, and chondroblasts. Mesenchymal cells produce and secrete a variety of immune-modulating factors, such as indoleamine 2,3-dioxygenase, prostaglandin E2, exosomes, FasL, PD-L2, PD-L1, and IL-6 [43,44]. MSCs are known as multipotent stromal cells. These cells have the ability to differentiate into different types of mesenchymal cells, including fat, bone, cartilage, and muscle in the intracellular and extracellular environment. Recent studies have shown that these cells can also obtain the germ cell phenotype under appropriate induction conditions. Using proper induction methods, MSCs can differentiate into many other types of cells and tissues as well as skeletal muscle, adipose tissue, synovial membrane, umbilical cord blood, and placenta [45,46]. Mesenchymal stem cells are known to have a regulatory function altering the immune system by affecting T lymphocytes. A unique feature of these cells is the ability to suppress and moderate immune responses [47]. MSCs have an inhibitory effect on various immune system cells such as T cells, B cells, natural killer cells (NK) and dendritic cells (CD11), CD + 11 which reduce and regulate immune responses [48–50]. Moreover, this type of immunomodulatory cells can reduce the expression of monocytes stimulus-assisting molecules, so MSCs are potent to adjust pro-inflammatory cytokines, including TNF-α and IL-12 [51,52]. The anti-inflammatory effect of MSCs is described in Fig. 1, briefly.

5. Mesenchymal stem cells in IBD treatment

Some researchers have shown that MCSs in IBD patients are dysfunctional. Grim et al. anticipated that MSCs of IBD patients contribute to the induction of pathogenic myofibroblasts in IBD patients. In UC, but not Crohn's disease, expression of two stem cell markers, Oct4 and ALDH1A was enhanced in the inflamed IBD colonic mucosa and linked with an increase in the mesenchymal lineage marker Grem1. These cells proliferated more and differentiated abnormally in UC, but not in Crohn's disease colonic mucosa. Crohn's disease MSCs, in contrast to normal and UC-derived MSCs, lose most of their clonogenic and differentiation abilities. Their findings also imply that the pathogenic PD-L1 low phenotype of Crohn's disease myofibroblasts may be due to significant damage to these cells in Crohn's disease. However, in UC, abnormal MSC differentiation appears to be implicated in the formation of pathogenic partly differentiated PD-L1high myofibroblasts inside the inflamed colonic mucosa. For the first time, their findings reveal that MSC progenitor activities are affected differently in Crohn's disease versus UC [53]. Due to these findings, some researchers have tried to solve this problem using MCS driven from other tissues such as adipose, bone marrow, and placenta. The characteristics of MSCs, especially their immunomodulatory function, have led to the use of these cells as immune system regulators for the treatment of IBD, as Gao et al.'s showed that Adipose-derived mesenchymal stem cell helped Crohn's disease treatment through the Wnt signaling pathway, and T cell immunoregulation [54].

In recent years, the therapeutic performance of MSCs on animal models of IBD or in-vitro models has been studied. Some studies have used MSCs or their productions as the medication; while some have used it as a vehicle for other medications or used in the drug delivery methods of IBD treatment. Interestingly, research in an animal model has shown that allogeneic mesenchymal stem cell transplantation could improve medical treatment with steroids. Cristóbal et al.'s study showed that after adipose-derived mesenchymal stem cells infusion, the steroid dosage can be greatly lowered or eliminated. Cristóbal et al. found positive long-lasting treatment outcomes [55]. These effects are attributed to the multipotential abilities of MSCs as it has been shown that bone marrow-derived MSCs can migrate to the bowel after being injected intraperitoneally in murine models and reduce the onset of colitis. Also, MSCs inhibit tumor cell growth and promoted apoptosis in tumor cells of the colon. In addition, previous studies demonstrated

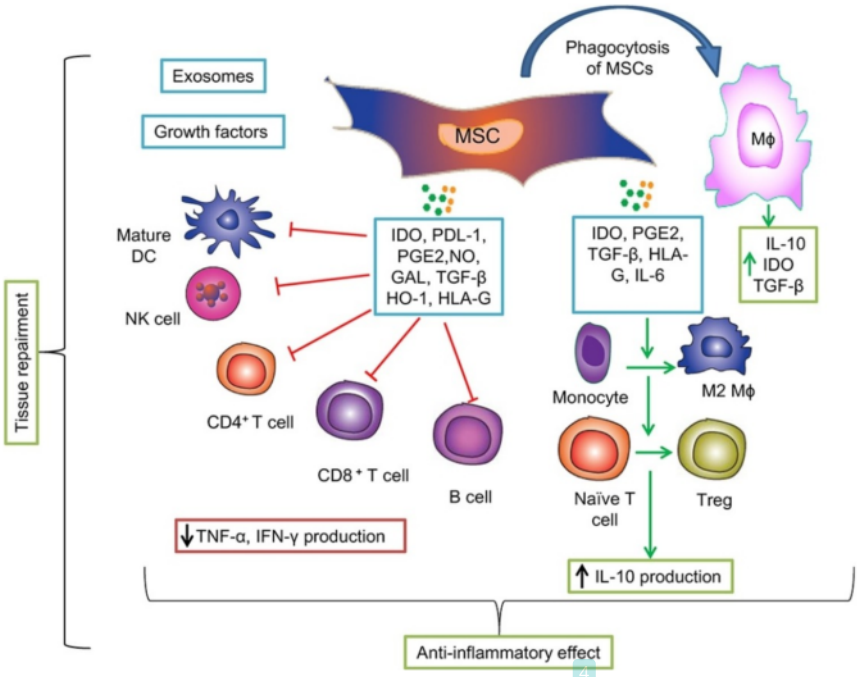

Fig. 1. Schematic of the anti-inflammatory mechanisms of mesenchymal stem cells. Figure is reused from Elsevier publisher [79].

Table 2
Completed clinical trial studies on MSCs and IBD. (https://www.clinicaltrials.gov).

	NCT Number	Title	Conditions	Characteristics	Locations
1	NCT00294112	Prochymal™ Adult Human Mesenchymal Stem Cells for Treatment of Moderate-to-severe Crohn's Disease	• Crohn's Disease	Outcome Measures: • Number of Participants with Reduction in Crohn's Disease Activity Index (CDAI) of at Least 100 Points • Number of Participants with Reduction in CDAI of at Least 70 points • Improvement as Assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ) • Time to Improvement in IBDQ • Number of Participants with Reduction of at Least 50% in Fistulas in Participants with Fistulas Draining Under Moderate Compression • Number of Participants with Induction of Remission as Defined by Reduction of CDAI to Below 150 • Time to Reduction in CDAI of at Least 100 Points • Time to Reduction in CDAI of at Least 70 Points • Time to Induction of Remission as Defined by Reduction of CDAI to Below 150. • Number of Participants with Adverse Events	• Osiris Clinical Site, Baton Rouge, Louisiana, United States • Osiris Clinical Site, Charlotte, North Carolina, United States • Osiris Clinical Site, Pittsburgh, Pennsylvania, United States • Osiris Clinical Site, Richmond, Virginia, United States
2	NCT01144962	Dose-escalating Therapeutic Study of Allogeneic Bone Marrow Derived Mesenchymal Stem Cells for the Treatment of Fistulas in Patients With Refractory Perianal Crohn's Disease	• Crohn's Disease • Fistula	Outcome Measures: • Safety and efficacy (fistula closure) • Clinical scores • Endoscopic scores • Quality of life • C-reactive protein (CRP) • Safety	• Leiden University Medical Center (LUMC), Leiden, Zuid Holland, Netherlands
3	NCT01157650	Treatment of Fistulous Crohn's Disease by Implant of Autologous Mesenchymal Stem Cells Derived From Adipose Tissue	• Crohn Disease	Outcome Measures: • Security and tolerance • therapeutic effect	• Clínica Universitaria de Navarra, Pamplona, Spain • Hospital Provincial de Navarra, Pamplona, Spain • Hospital Virgen del Camino, Pamplona, Spain
4	NCT02445547	Umbilical Cord Mesenchymal Stem Cell Treatment for Crohn's Disease	• Crohn Disease	Outcome Measures: • Crohn's disease activity index • Harvey-Bradshaw index • Corticosteroid dosage	• Shaanxi Provincial People's Hospital, Xi Ail, Shaanxi, China
5	NCT00543374	Extended Evaluation of PROCHYMAL® Adult Human Stem Cells for Treatment-Resistant Moderate-to- Severe Crohn's Disease	• Crohn's Disease	Outcome Measures: • Duration of clinical benefit (Crohn's disease activity index) • Re-induction of clinical benefit (Crohn's disease activity index) • Improvement in quality of life (Inflammatory Bowel Disease Questionnaire [IBDQ] instrument)	• Advanced Clinical Research Institute, Anaheim, California, United States • Veteran's Administration Medical Center (does not require vet status), Long Beach, California, United States • University of Southern California University Hospital, Los Angeles, California, United States • University of California, San Francisco, San Francisco, California, United States • Western States Clinical Research, Wheat Ridge, Colorado, United States • Gastroenterology Center of Connecticut, Hamden, Connecticut, United States • Clinical Research of West Florida, Clearwater, Florida, United States • Borland-Groover Clinic, Jacksonville, Florida, United States • Venture Research Institute, Miami, Florida, United States • Shafran Gastroenterology Center, Winter Park, Florida, United States • and 48 more
6	NCT00482092	Evaluation of PROCHYMAL® Adult Human Stem Cells for Treatment-resistant Moderate-to-severe Crohn's Disease	• Crohn's Disease	Outcome Measures: • Disease remission (CDAI at or below 150) • Disease improvement (Reduction by at least 100 points in CDAI) • Improvement in quality of life (IBDQ) • Reduction in number of draining fistulas	• University of Southern California University Hospital, Los Angeles, California, United States • University of California, San Francisco, San Francisco, California, United States • Western States Clinical Research, Wheat Ridge, Colorado, United States

(continued on next page)

Table 2 (*continued*)

	NCT Number	Title	Conditions	Characteristics	Locations
					• Clinical Research of West Florida, Clearwater, Florida, United States • Borland-Groover Clinic, Jacksonville, Florida, United States • Shafran Gastroenterology Center, Winter Park, Florida, United States • Atlanta Gastroenterology Associates, Atlanta, Georgia, United States • University of Chicago Medical Center, Chicago, Illinois, United States • Carle Clinic Association, Urbana, Illinois, United States • Indiana University Medical Center, Indianapolis, Indiana, United States • and 46 more
	NCT Number	Title	Conditions	Characteristics	Locations
7	NCT01541579	Adipose Derived Mesenchymal Stem Cells for Induction of Remission in Perianal Fistulizing Crohn's Disease	• Crohn's Disease	Outcome Measures: • Combine remission of perianal fistulising Crohn's • Efficacy Assessment by week 24 • Efficacy Assessment by week 52 • Efficacy Assessment by week 104 • Safety analysis throughout the study:	• Univ.-Klinik Innsbruck, Innsbruck, Austria • Krankenhaus, St. Veit/Glan, Austria • Medizinische Universität, Wien, Austria • Hospital Oost-Limburg, Genk, Belgium • Gent University Hospital, Gent, Belgium • Leuven University Hospital, Leuven, Belgium • Hospital Hartziekenhuis, Roeselare, Belgium • CHU d'Amiens, Amiens, France • CHU de Bordeaux, Bordeaux, France • CHU de Caen, Caen, France • and 42 more
8	NCT01233960	Evaluation of PROCHYMAL® for Treatment- refractory Moderate-to-severe Crohn's Disease	• Crohn's Disease	Outcome Measures: • Disease remission • Disease Improvement • Improvement in Quality of Life (IBDQ) • Number of Adverse events as a measure of safety • Infusional toxicity as a measure of safety and tolerability	• University of California, San Francisco, San Francisco, California, United States • Clinical Research of West Florida, Clearwater, Florida, United States • Shafran Gastroenterology Center, Winter Park, Florida, United States • University of Chicago, Chicago, Illinois, United States • Cotton-O'Neil Clinical Research Center, Topeka, Kansas, United States • University of Maryland, Baltimore, Baltimore, Maryland, United States • Chevy Chase Clinical Research, Chevy Chase, Maryland, United States • Saint Louis Center for Clinical Research, Saint Louis, Missouri, United States • St. Louis Center for Clinical Studies, Saint Louis, Missouri, United States • Dartmouth HItchcock Medical Center, Lebanon, New Hampshire, United States • and 10 more
9	NCT03220243	Stem Cell Coated Fistula Plug in Patients With Crohn's RVF	• Fistula Vagina • Crohn Disease	Outcome Measures: • Number of participants with treatment-related adverse events (safety and toxicity). • Number of participants with response to the treatment regarding potential cessation of drainage from their fistula.	• Mayo Clinic in Rochester, Rochester, Minnesota, United States
10	NCT01915927	Stem Cell Fistula Plug in Perianal Crohn's Disease	• Perianal Crohn's Disease	Outcome Measures: • To determine the safety and toxicity of using autologous MSC coated fistula plug in patients with fistulizing Crohn's Disease. • To assess in preliminary fashion the response of fistula healing induced by the GORE plug containing MSC	• Mayo Clinic, Rochester, Minnesota, United States

MSCs were found to be able to migrate into the colon, reduce chronic inflammation, and regulate gut microbiome dysbiosis; all of these functions helped to prevent the development of colitis-associated colon cancer [56]. Completed clinical trial studies are listed in Table 2.

6. MSCs-derived exosomes in IBD research

In an experimental UC model, Gu et al. focused on the impact of "MSC-derived exosomal miR-181a" on intestinal barrier function, gut microbiota, and immunological responses. This MSCs product might help treat experimental colitis by improving intestinal barrier task. It acted as an anti-inflammatory and influenced the gut microbiome. This suggested that MSCs exosomal miR-181a could be useful as an effective treatment for UC [57].

Yang et al. evaluated a theory that says exosomes from MSCs stimulated by IFN-γ can reduce colitis via micro-RNA-125a and micro-RNA-125b. This study shows that IFN-γ treatment increased MSC exosomes that contribute to reducing colitis by increasing the levels of micro-RNA-125a and micro-RNA-125b, which bind to the 3′ untranslated region of Stat3 and suppress Th17 cell development [58]. In another study, in a Dextran sodium sulfate (DSS)-induced colitis model, MSC-derived exosomal miR-181a reduced TNF- and IL-17 levels while improving intestinal barrier integrity [59].

Micro RNAs are a new class of non-coding and endogenous single-stranded RNAs that are abundant in plants and animals, and their immature variants become functional under several nuclear and cytoplasmic stages. Micro RNAs play a vital role in controlling various dimensions of the innate immune system, for example, controlling the ability to kill microbes, stimulate the production of cytokines, and provide antigen by MHC proteins. Micro RNAs play an important role in the proliferation of Th17 cells [60,61]. Induction and suppression of micro RNA expression in response to inflammation can affect various biological functions and cause pro-inflammatory or anti-inflammatory effects. Thus, micro RNAs are central regulators of inflammation. The balance between Th1 and Th2 cells plays a key role in causing inflammation. Th17 cells are characterized by the production of IL-17A and other cytokines such as IL-17F, IL-21, and IL-22. Recently, many studies have reported the role of Th17 cell pathogenesis in the development or progression of IBD. Some important regulatory pathways based on micro RNAs prevent lymphocyte accumulation and the autoimmune process, thus highlighting the vital role of micro RNA regulation in Treg function. This issue was addressed by Heidari et al. study in which the immune response regulatory effects of MSCs-derived exosomes in the acute phase of DSS-induced colitis were investigated and in the lymph node and spleen of mice treated via exosomes, the levels of TNF-β, IFN-γ, IL-17, and IL-12 were reduced, while the levels of TGF-β, IL-10, and IL-4 were elevated due to Treg cell induction. The results demonstrated that exosome delivery reduced colon shortening, bodyweight loss, hemorrhage, and colon damage [62–64]. The immunomodulatory effects of exosomes derived from MSCs are shown in Fig. 2.

7. MCSs effect on smooth cell function and intestine integrity

In Crohn's disease ileum, intrinsic myogenic changes occur in smooth muscle cells, which probably lead to stricture development. This process is widely associated with the TGF-β function. Smooth muscle cells produced more IL-6 in Crohn's disease patients with stricture segments. Furthermore, IL-6 induces TGF-1 synthesis by Crohn's disease patients' intestinal smooth muscle cells by activating the STAT3 pathway [65,66]. Duan et al. study showed that in mice with trinitrobenzene sulfonic acid (TSA)-induced colitis, Extracellular vesicles derived from human placental mesenchymal stem cells significantly reduced clinical symptoms by suppressing inflammation and oxidative stress and promoting mucosal repair [67].

In colitis mice, Xu et al. produced phenotypically homogenous MSCs from human embryonic stem cells and investigated the molecular processes that promote mucosal integrity and regeneration. This study showed that MSCs from human embryonic stem cells infusions reduced colitis in rats by increasing the level of circulating IGF-1. Increased IGF-1 helps epithelial cells maintain their integrity as well as muscular repair and regeneration [68]. Liyun & Xiaocang have worked on a hypothesis that stated extracellular vesicles produced from human placental MSCs can influence collagen deposition in the intestinal mucosa of mice models of colitis. The findings of their study imply that these types of MCSs can significantly lower the severity of colon damage and intestinal mucosa collagen deposition in mice [69].

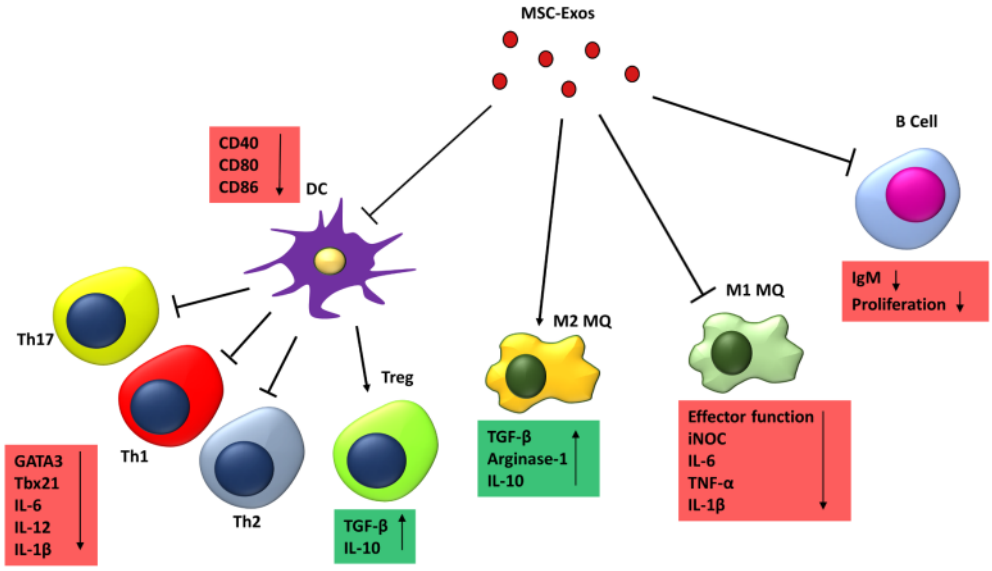

Fig. 2. Exosomes and immunomodulation mechanisms.

8. MCSs effect on IBD through oxidative stress pathways

Regmi et al. devised an approach to improve the microenvironment of MSCs by combining MSCs with quercetin (QUR)-loaded microspheres (MSCHS) in a mouse model of colitis, resulting in local medication delivery to the cells. MSCHS, in comparison to 3D-cultured MSCs (MSC3D) and 2D-cultured cells (MSC2D) in vitro, showed resistance to senescence-associated phenotype and oxidative stress-induced apoptosis. MSCHS and MSC3D had a greater anti-inflammatory effect than MSC2D in a mouse model of colitis by reducing neutrophil infiltration and regulating Th polarization into Th17 and Th1 cells, correspondingly. MSCHS outperformed MSC3D in terms of therapeutic results, owing to their higher in vivo survival capability. Furthermore, Regmi S et al. discovered that prostaglandin E2 (PGE2), a paracrine substance produced from MSCs, can directly drive epithelial regeneration by generating specialized tissue-repairing cell production using intestinal organoid culture. Interestingly, MSC3D and MSCHS had much higher regeneration-inducing potency than MSC2D because of their higher PGE2 production. Altogether, they propose a convergent MSCHS production approach using the ROS (reactive oxygen species) scavenger, which can maximize MSCs' inflammation-attenuating and tissue-repairing capacity, as well as implantation efficiency after transplantation [70].

Li et al. also showed immunosuppressive and anti-inflammatory effects of MCS therapy on the DSS-induced colitis model [71]. The goal of Wu et al. was to observe if and how flavonoid therapy improved the therapeutic efficacy of MSCs in dextran sulfate sodium (DSS)-induced colitis. The MSC treatment with Wogonin (a flavonoid) dramatically reduces enteric inflammation in IBD mice by increasing IL-10 expression, according to conducted research. Wogonin increases IL-10 and ROS levels in MSCs in vitro in a dose-associated system. Wogonin enhances IL-10 secretion by boosting HIF-1 expression as a transcript factor via the GSK3/AKT signaling pathway, according to western blot data. Finally, an in vivo IL-10 blockage experiment verified Wogonin's beneficial effects on MSCs. Flavonoid therapy significantly raises IL-10 release and improved the therapeutic results of MSCs in DSS-induced colitis, according to their findings. Thus, flavonoid therapy was proposed as a potential ideal method for MSC clinical application [72].

9. Randomised clinical TRIALs

Studies in recent years have contributed to our understanding of MSCs to some extent and have provided clues to the use of these cells as a promising tool for the treatment of diseases, especially autoimmune diseases. For example, the first phase I clinical trial report of a treatment cell using MSCs derived from autologous adipose tissue was published in 2005 in which topical injection of MSCs improved fistulas in the intestine. This result was confirmed in 2009 by the same research group in the Phase II clinical trial. Vieujean et al. evaluated the safety and efficacy of injecting local MSCs into strictures caused by Crohn's disease. They concluded that the injection of local MSCs into a non-passable Crohn's disease stricture was well tolerated in the short term, although there were multiple occlusions described in the follow-up. Combining the benefits of MSCs with the proven benefits of endoscopic balloon dilatation may enhance the result of CD stricture [73,74]. In the study of Dhere et al. (NCT01659762), in individuals experiencing Crohn's disease, an IV infusion of fresh autologous bone marrow mesenchymal stromal cells was found to be safe and effective at dosages of up to 10 million cells/kg BW. In their study (Dhere et al.), in individuals experiencing Crohn's disease, an IV infusion of fresh autologous bone marrow mesenchymal stromal cells was found to be safe and effective at dosages of up to 10 million cells/kg BW [75]. Based on Molendijk et al. trial, in individuals with perianal fistulizing Crohn's disease, local injection of allogeneic MSCs was not linked with serious adverse effects [76]. Forbes et al.'s [77] trial showed a reduced Crohn's disease activity score (NCT01090817). In a more recent study in 2021, Cabalza-Wondberg et al. evaluated the efficiency, safety, and feasibility of an MCS application in the clinical trial, in form of case series. This study shows that allogeneic expanded adipose-derived mesenchymal stem cells could be helpful in the treatment of the perianal fistulas in Crohn's disease. This new treatment approach for complex perianal fistulas offers a potential therapeutic option [78].

10. Conclusion

MSCs, MSC-driven exosomal microRNAs and MSC-based drug delivery systems have been demonstrated to affect immune system modulation in experimental animal models of IBD (Th17 suppression versus T-regular cell biased responses). MSCs have been shown to enhance intestinal integrity and smooth cell function in several studies. Various clinical trials for MSCs administration in IBD patients have been filed with reliable safety in humans mostly including infusion of MCSs generated from bone marrow adipose tissue and the umbilical cord. Clinical research has looked at patient symptoms or the healing process while immune-pathologic studies have been lacking in the clinical period. As we've seen a slew of experimental data has prompted the start of a slew of phase I/II clinical trials all of which have yielded encouraging findings for IBD therapy. Overall our study shows that the use of MSCs in the treatment of IBD is not only safe but also the dangerous side effects of conventional and DMARDs drugs can be avoided and gives rise to enhancing the quality of treatment. We believe that future clinical research should focus more on in-vitro/in-vivo outcomes as well as immunological endpoints in order to provide more trustworthy results with more laboratory proof.

Funding

There is no financial support for this study.

Data availability

Not applicable

Ethical approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Credit authorship contribution statement

Writing original draft: Huldani Huldani. Editing: Ria Margiana and Maria Jade Catalan Opulencia. Investigation: Fawad Ahmad and Mohammad Javed Ansari. Resources and revision: Dmitry Olegovich Bokov and Nargiza N. Abdullaeva. Conceptualization, Supervision, writing original draft: Homayoon Siahmansouri.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A. Sturm, C. Maaser, M. Mendall, D. Karagiannis, P. Karatzas, N. Ipenburg, et al., European Crohn's and Colitis Organisation topical review on IBD in the elderly, J. Crohn's Colitis 11 (3) (2017) 263–273.
[2] S.S. Seyedian, F. Nokhostin, M.D. Malamir, A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease, J. Med. Life 12 (2) (2019) 113.
[3] D. Duricova, M. Fumery, V. Annese, P.L. Lakatos, L. Peyrin-Biroulet, C. Gower-Rousseau, The natural history of Crohn's disease in children: a review of population-based studies, Eur. J. Gastroenterol. Hepatol. 29 (2) (2017) 125–134.

[4] D. Lauritano, E. Boccalari, D. Di Stasio, F. Della Vella, F. Carinci, A. Lucchese, et al., Prevalence of oral lesions and correlation with intestinal symptoms of inflammatory bowel disease: a systematic review, Diagnostics 9 (3) (2019) 77.

[5] M. Gajendran, P. Loganathan, A.P. Catinella, J.G. Hashash, A comprehensive review and update on Crohn's disease, Dis. Mon. 64 (2) (2018) 20–57.

[6] F. Carbonnel, P. Jantchou, E. Monnet, J. Cosnes, Environmental risk factors in Crohn's disease and ulcerative colitis: an update, Gastroenterol. Clin. Biol. 33 (2009) S145–S157.

[7] A.N. Ananthakrishnan, Epidemiology and risk factors for IBD, Nat. Rev. Gastroenterol. Hepatol. 12 (4) (2015) 205–217.

[8] U. Colitis-Pathophysiology, Inflammatory bowel disease part I: ulcerative colitis-pathophysiology and conventional and alternative treatment options, Altern. Med. Rev. 8 (3) (2003) 247–283.

[9] R.C. Langan, P.B. Gotsch, M.A. Krafczyk, D.D. Skillinge, Ulcerative colitis: diagnosis and treatment, Am. Fam. Phys. 76 (9) (2007) 1323–1330.

[10] L. Lakatos, G. Mester, Z. Erdelyi, G. David, T. Pandur, M. Balogh, S. Fischer, P. Vargha, P.L. Lakatos, Risk factors for ulcerative colitis–associated colorectal cancer in a Hungarian cohort of patients with ulcerative colitis: results of a population-based study, Inflamm. Bowel Dis. 12 (3) (2006) 205–211.

[11] R.P. Macdermott, W.F. Stenson, Alterations of the immune system in ulcerative colitis and Crohn's disease, Adv. Immunol. 42 (1988) 285–328.

[12] R.P. MacDermott, Chemokines in the inflammatory bowel diseases, J. Clin. Immunol. 19 (5) (1999) 266–272.

[13] D. Lissner, M. Schumann, A. Batra, L.-I. Kredel, A.A. Kühl, U. Erben, C. May, J.-D. Schulzke, B. Siegmund, Monocyte and M1 macrophage-induced barrier defect contributes to chronic intestinal inflammation in IBD, Inflamm. Bowel Dis. (2015) 1.

[14] T.A. Kraus, L. Mayer, Oral tolerance and inflammatory bowel disease, Curr. Opin. Gastroenterol. 21 (6) (2005) 692–696.

[15] T.A. Kraus, L. Toy, L. Chan, J. Childs, L. Mayer, Failure to induce oral tolerance to a soluble protein in patients with inflammatory bowel disease, Gastroenterology 126 (7) (2004) 1771–1778.

[16] T.A. Kraus, A. Cheifetz, L. Toy, J.B. Meddings, L. Mayer, Evidence for a genetic defect in oral tolerance induction in inflammatory bowel disease, Inflamm. Bowel Dis. 12 (2) (2006) 82–88.

[17] Y. Chen, J.-i. Inobe, H.L. Weiner, Induction of oral tolerance to myelin basic protein in CD8-depleted mice: both CD4+ and CD8+ cells mediate active suppression, J. Immunol. 155 (2) (1995) 910–916.

[18] A.A. Kühl, N.N. Pawlowski, K. Grollich, C. Loddenkemper, M. Zeitz, J.C. Hoffmann, Aggravation of intestinal inflammation by depletion/deficiency of γδ T cells in different types of IBD animal models, J. Leukoc. Biol. 81 (1) (2007) 168–175.

[19] S. Zundler, M.F. Neurath, Integrating immunologic signaling networks: the JAK/STAT pathway in colitis and colitis-associated cancer, Vaccines 4 (1) (2016) 5.

[20] A. Mizoguchi, A. Yano, H. Himuro, Y. Ezaki, T. Sadanaga, E. Mizoguchi, Clinical importance of IL-22 cascade in IBD, J. Gastroenterol. 53 (4) (2018) 465–474.

[21] A. Piechota-Polanczyk, J. Fichna, The role of oxidative stress in pathogenesis and treatment of inflammatory bowel diseases, Naunyn-Schmiedeberg's Arch. Pharmacol. 387 (7) (2014) 605–620.

[22] T. Tian, Z. Wang, J. Zhang, Pathomechanisms of Oxidative Stress in Inflammatory Bowel Disease and Potential Antioxidant Therapies, Oxid. Med. Cell. Longevity 2017 (2017) 1–18.

[23] F. Ebrahimi, H. Esmaily, M. Baeeri, A. Mohammadirad, S. Fallah, M. Abdollahi, Molecular evidences on the benefit of N-acetylcysteine in experimental colitis, Open Life Sci. 3 (2) (2008) 135–142.

[24] I.-A. Lee, Y.-J. Hyun, D.-H. Kim, Berberine ameliorates TNBS-induced colitis by inhibiting lipid peroxidation, enterobacterial growth and NF-κB activation, Eur. J. Pharmacol. 648 (1–3) (2010) 162–170.

[25] B. Peskar, K. Dreyling, B. Peskar, B. May, H. Goebell, Enhanced formation of sulfidopeptide-leukotrienes in ulcerative colitis and Crohn's disease: inhibition by sulfasalazine and 5-aminosalicylic acid, Agents Actions 18 (3) (1986) 381–383.

[26] G. Zhou, L. Yu, L. Fang, W. Yang, T. Yu, Y. Miao, M. Chen, K. Wu, F. Chen, Y. Cong, Z. Liu, CD177+ neutrophils as functionally activated neutrophils negatively regulate IBD, Gut 67 (6) (2018) 1052–1063.

[27] M.T. Abreu, K.D. Taylor, Y.-C. Lin, T. Hang, J. Gaiennie, C.J. Landers, E. A. Vasiliauskas, L.Y. Kam, M. Rojany, K.A. Papadakis, J.I. Rotter, S.R. Targan, H. Yang, Mutations in NOD2 are associated with fibrostenosing disease in patients with Crohn's disease, Gastroenterology 123 (3) (2002) 679–688.

[28] Y. Leung, M. Geddes, J. Storek, R. Panaccione, P. Beck, Hematopoietic cell transplantation for Crohn's disease; is it time, World J. Gastroenterol.: WJG 12 (41) (2006) 6665.

[29] H.S.P. de Souza, G.A. West, N. Rebert, C. de la Motte, J. Drazba, C. Fiocchi, Increased levels of survivin, via association with heat shock protein 90, in mucosal T cells from patients with Crohn's disease, Gastroenterology 143 (4) (2012) 1017–1026.e9.

[30] K. Ina, J. Itoh, K. Fukushima, K. Kusugami, T. Yamaguchi, K. Kyokane, et al., Resistance of Crohn's disease T cells to multiple apoptotic signals is associated with a Bcl-2/Bax mucosal imbalance, J. Immunol. 163 (2) (1999) 1081–1090.

[31] J.B. Seidelin, M. Coskun, B. Vainer, L. Riis, C. Soendergaard, O.H. Nielsen, ERK controls epithelial cell death receptor signalling and cellular FLICE-like inhibitory protein (c-FLIP) in ulcerative colitis, J. Mol. Med. 91 (7) (2013) 839–849.

[32] A. Oussalah, L. Evesque, D. Laharie, X. Roblin, G. Boschetti, S. Nancey, J. Filippi, B. Flourié, X. Hebuterne, M.-A. Bigard, L. Peyrin-Biroulet, A multicenter experience with infliximab for ulcerative colitis: outcomes and predictors of response, optimization, colectomy, and hospitalization, Off. J. Am. College Gastroenterol.| ACG. 105 (12) (2010) 2617–2625.

[33] L.R. Sutherland, G.R. May, E.A. Shaffer, Sulfasalazine revisited: a meta-analysis of 5-aminosalicylic acid in the treatment of ulcerative colitis, Ann. Intern. Med. 118 (7) (1993) 540–549.

[34] S. Ben-Horin, Y. Chowers, loss of response to anti-TNF treatments in Crohn's disease, Aliment. Pharmacol. Ther. 33 (9) (2011) 987–995.

[35] M. Boeri, K. Myers, C. Ervin, A. Marren, M. DiBonaventura, J.C. Cappelleri, et al., Patient and physician preferences for ulcerative colitis treatments in the United States, Clin. Experim. Gastroenterol. 12 (2019) 263.

[36] G. Bouguen, B.G. Levesque, B.G. Feagan, A. Kavanaugh, L. Peyrin–Biroulet, J. Colombel, S.B. Hanauer, W.J. Sandborn, Treat to target: a proposed new paradigm for the management of Crohn's disease, Clin. Gastroenterol. Hepatol. 13 (6) (2015) 1042–1050.e2.

[37] M. Fakhoury, R. Negrulj, A. Mooranian, H. Al-Salami, Inflammatory bowel disease: clinical aspects and treatments, J. Inflammat. Res. 7 (2014) 113.

[38] S. Singh, K. Yadav, A.K. Varma, Inflammatory bowel disease: an overview of immune mechanisms and biological treatments, Int. J. Pharm. Life Sci. 10 (6) (2019).

[39] B. Ruaro, F. Salton, L. Braga, B. Wade, P. Confalonieri, M.C. Volpe, E. Baratella, S. Maiocchi, M. Confalonieri, The history and mystery of alveolar epithelial type II cells: focus on their physiologic and pathologic role in lung, Int. J. Mol. Sci. 22 (5) (2021) 2566.

[40] F. Salton, B. Ruaro, P. Confalonieri, M. Confalonieri, Epithelial–Mesenchymal Transition: A Major Pathogenic Driver in Idiopathic Pulmonary Fibrosis? : Multidisciplinary Digital Publishing Institute, 2020, p. 608.

[41] F. Dazzi, M. Krampera, Mesenchymal stem cells and autoimmune diseases, Best Pract. Res. Clin. Haematol. 24 (1) (2011) 49–57.

[42] G. Ren, X. Chen, F. Dong, W. Li, X. Ren, Y. Zhang, Y. Shi, Concise review: mesenchymal stem cells and translational medicine: emerging issues, Stem Cells Translat. Med. 1 (1) (2012) 51–58.

[43] M. Dauletova, H. Hafsan, N. Mahhengam, A.O. Zekiy, M. Ahmadi, H. Siahmansouri, Mesenchymal stem cell alongside exosomes as a novel cell-based therapy for COVID-19: A review study, Clin. Immunol. 226 (2021) 108712.

[44] W. Suksatan, S. Chupradit, A.V. Yumashev, S. Ravali, M.N. Shalaby, Y.F. Mustafa, A. Kurochkin, H. Siahmansouri, Immunotherapy of multisystem inflammatory syndrome in children (MIS-C) following COVID-19 through mesenchymal stem cells, Int. Immunopharmacol. 101 (2021) 108217.

[45] M. Dominici, K. Le Blanc, I. Mueller, I. Slaper-Cortenbach, F.C. Marini, D.S. Krause, R.J. Deans, A. Keating, D.J. Prockop, E.M. Horwitz, Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement, Cytotherapy 8 (4) (2006) 315–317.

[46] B.L. Larson, J. Ylöstalo, D.J. Prockop, Human multipotent stromal cells undergo sharp transition from division to development in culture, Stem Cells 26 (1) (2008) 193–201.

[47] W. Li, G. Ren, Y. Huang, J. Su, Y. Han, J. Li, X. Chen, K. Cao, Q. Chen, P. Shou, L. Zhang, Z.-R. Yuan, A.I. Roberts, S. Shi, A.D. Le, Y. Shi, Mesenchymal stem cells: a double-edged sword in regulating immune responses, Cell Death Differ. 19 (9) (2012) 1505–1513.

[48] W. Deng, Q. Han, L. Liao, S. You, H. Deng, R.C. Zhao, Effects of allogeneic bone marrow-derived mesenchymal stem cells on T and B lymphocytes from BXSB mice, DNA Cell Biol. 24 (7) (2005) 458–463.

[49] P. Mafi, S. Hindocha, R. Mafi, M. Griffin, W. Khan, Suppl 2: adult mesenchymal stem cells and cell surface characterization-a systematic review of the literature, Open Orthopaed. J. 5 (2011) 253.

[50] M. Moloudizargari, A. Govahi, M. Fallah, M.A. Rezvanfar, M.H. Asghari, M. Abdollahi, The mechanisms of cellular crosstalk between mesenchymal stem cells and natural killer cells: Therapeutic implications, J. Cell. Physiol. 236 (4) (2021) 2413–2429.

[51] M. Gazdic, V. Volarevic, N. Arsenijevic, M. Stojkovic, Mesenchymal stem cells: a friend or foe in immune-mediated diseases, Stem Cell Rev. Rep. 11 (2) (2015) 280–287.

[52] W. Zhang, W. Ge, C. Li, S. You, L. Liao, Q. Han, W. Deng, R.C.H. Zhao, Effects of mesenchymal stem cells on differentiation, maturation, and function of human monocyte-derived dendritic cells, Stem Cells Dev. 13 (3) (2004) 263–271.

[53] C. Grim, R. Noble, G. Uribe, K. Khanipov, P. Johnson, W.A. Koltun, T. Watts, Y. Fofanov, G.S. Yochum, D.W. Powell, E.J. Beswick, I.V. Pinchuk, Impairment of tissue resident mesenchymal stem cells in chronic ulcerative colitis and Crohn's disease, J. Crohn's Colitis 15 (8) (2021) 1362–1375.

[54] J.-G. Gao, M.-S. Yu, M.-M. Zhang, X.-W. Gu, Y. Ren, X.-X. Zhou, D. Chen, T.-L. Yan, Y.-M. Li, X.i. Jin, Adipose-derived mesenchymal stem cells alleviate TNBS-induced colitis in rats by influencing intestinal epithelial cell regeneration, Wnt signaling, and T cell immunity, World J. Gastroenterol. 26 (26) (2020) 3750–3766.

[55] J.I. Cristóbal, F.J. Duque, J.M. Usón-Casaús, P. Ruiz, E.L. Nieto, E.M. Pérez-Merino, Effects of allogeneic mesenchymal stem cell transplantation in dogs with inflammatory bowel disease treated with and without corticosteroids, Animals 11 (7) (2021) 2061.

[56] R. He, C. Han, Y. Li, W. Qian, X. Hou, Cancer-preventive role of bone marrow-derived mesenchymal stem cells on colitis-associated colorectal cancer: roles of gut microbiota involved, Front. Cell Dev. Biol. 9 (2021) 610.

[57] L. Gu, F. Ren, X. Fang, L. Yuan, G. Liu, S. Wang, Exosomal MicroRNA-181a derived from mesenchymal stem cells improves gut microbiota composition, barrier function, and inflammatory status in an experimental colitis model, Front. Med. 8 (2021) 898.

[58] R. Yang, H. Huang, S. Cui, Y. Zhou, T. Zhang, Y. Zhou, IFN-γ promoted exosomes from mesenchymal stem cells to attenuate colitis via miR-125a and miR-125b, Cell Death Dis. 11 (7) (2020) 1–12.

[59] S.M. Hammond, An overview of microRNAs, Adv. Drug Deliv. Rev. 87 (2015) 3–14.
[60] D.P. Bartel, MicroRNAs: genomics, biogenesis, mechanism, and function, Cell 116 (2) (2004) 281–297.
[61] A.E. Pasquinelli, S. Hunter, J. Bracht, MicroRNAs: a developing story, Curr. Opin. Genet. Dev. 15 (2) (2005) 200–205.
[62] N. Heidari, H. Abbasi-Kenarsari, S. Namaki, K. Baghaei, M.R. Zali, S. Ghaffari Khaligh, S.M. Hashemi, Adipose-derived mesenchymal stem cell-secreted exosome alleviates dextran sulfate sodium-induced acute colitis by Treg cell induction and inflammatory cytokine reduction, J. Cell. Physiol. 236 (8) (2021) 5906–5920.
[63] E. Sonkoly, A. Pivarcsi, microRNAs in inflammation, Int. Rev. Immunol. 28 (6) (2009) 535–561.
[64] E. Sonkoly, M. Ståhle, A. Pivarcsi, MicroRNAs: novel regulators in skin inflammation, Clin. Experim. Dermatol.: Continuing Profess. Devel. (CPD). 33 (3) (2008) 312–315.
[65] C. Li, A. Iness, J. Yoon, J.R. Grider, K.S. Murthy, J.M. Kellum, J.F. Kuemmerle, Noncanonical STAT3 activation regulates excess TGF-β1 and collagen I expression in muscle of stricturing Crohn's disease, J. Immunol. 194 (7) (2015) 3422–3431.
[66] C. Severi, R. Sferra, A. Scirocco, A. Vetuschi, N. Pallotta, A. Pronio, R. Caronna, G. Di Rocco, E. Gaudio, E. Corazziari, P. Onori, Contribution of intestinal smooth muscle to Crohn's disease fibrogenesis, Eur. J. Histochem.: EJH (2014).
[67] L. Duan, H. Huang, X. Zhao, M. Zhou, S. Chen, C. Wang, Z. Han, Z.-C. Han, Z. Guo, Z. Li, X. Cao, Extracellular vesicles derived from human placental mesenchymal stem cells alleviate experimental colitis in mice by inhibiting inflammation and oxidative stress, Int. J. Mol. Med. (2020).
[68] J. Xu, X. Wang, J. Chen, S. Chen, Z. Li, H. Liu, Y. Bai, F. Zhi, Embryonic stem cell-derived mesenchymal stem cells promote colon epithelial integrity and regeneration by elevating circulating IGF-1 in colitis mice, Theranostics 10 (26) (2020) 12204–12222.
[69] D. Liyun, C. Xiaocang, Human placenta mesenchymal stem cells-derived extracellular vesicles regulate collagen deposition in intestinal mucosa of mice with colitis, Chin. J. Tissue Eng. Res. 25 (7) (2021) 1026.
[70] S. Regmi, Y. Seo, J.-S. Ahn, S. Pathak, S. Acharya, T.T. Nguyen, S. Yook, J.-H. Sung, J.-B. Park, J.O. Kim, C.S. Young, H.-S. Kim, J.-H. Jeong, Heterospheroid formation improves therapeutic efficacy of mesenchymal stem cells in murine colitis through immunomodulation and epithelial regeneration, Biomaterials 271 (2021) 120752.
[71] Y. Li, J. Altemus, A.L. Lightner, Mesenchymal stem cells and acellular products attenuate murine induced colitis, Stem Cell Res. Ther. 11 (1) (2020) 1–11.
[72] Q. Wu, S. Xie, Y. Zhu, J. Chen, J. Tian, S. Xiong, C. Wu, Y. Ye, Y. Peng, D. Trombetta, Wogonin strengthens the therapeutic effects of mesenchymal stem cells in DSS-induced colitis via promoting IL-10 production, Oxid. Med. Cell. Longevity 2021 (2021) 1–14.
[73] D. García-Olmo, M. García-Arranz, D. Herreros, I. Pascual, C. Peiro, J.A. Rodríguez-Montes, A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation, Dis. Colon Rectum. 48 (7) (2005) 1416–1423.
[74] S. Vieujean, J.P. Loly, L. Boutaffala, B. Pariente, C. Reenaers, A. Briquet, C. Lechanteur, Y. Beguin, E. Louis, P293 Local Mesenchymal Stem Cells injection in Crohn's disease strictures: a phase I-II, open-label clinical study, J. Crohn's Colitis 15 (Supplement_1) (2021) S323–S324.
[75] T. Dhere, I. Copland, M. Garcia, K.Y. Chiang, R. Chinnadurai, M. Prasad, J. Galipeau, S. Kugathasan, The safety of autologous and metabolically fit bone marrow mesenchymal stromal cells in medically refractory Crohn's disease - a phase 1 trial with three doses, Aliment Pharmacol. Ther. 44 (5) (2016) 471–481.
[76] I. Molendijk, B.A. Bonsing, H. Roelofs, K.C.M.J. Peeters, M.N.J.M. Wasser, G. Dijkstra, C.J. van der Woude, M. Duijvestein, R.A. Veenendaal, J.-J. Zwaginga, H.W. Verspaget, W.E. Fibbe, A.E. van der Meulen-de Jong, D.W. Hommes, Allogeneic bone marrow–derived mesenchymal stromal cells promote healing of refractory perianal fistulas in patients with Crohn's disease, Gastroenterology 149 (4) (2015) 918–927.e6.
[77] G.M. Forbes, M.J. Sturm, R.W. Leong, M.P. Sparrow, D. Segarajasingam, A. G. Cummins, M. Phillips, R.P. Herrmann, A phase 2 study of allogeneic mesenchymal stromal cells for luminal Crohn's disease refractory to biologic therapy, Clin. Gastroenterol. Hepatol. 12 (1) (2014) 64–71.
[78] D. Cabalzar-Wondberg, M. Turina, L. Biedermann, G. Rogler, P. Schreiner, Allogeneic expanded adipose-derived mesenchymal stem cell therapy for perianal fistulas in Crohn's disease: A case series, Colorectal Dis. 23 (6) (2021) 1444–1450.
[79] S. Regmi, S. Pathak, J.O. Kim, C.S. Yong, J.-H. Jeong, Mesenchymal stem cell therapy for the treatment of inflammatory diseases: challenges, opportunities, and future perspectives, Eur. J. Cell Biol. 98 (5-8) (2019) 151041.
[80] T. AlAmeel, E. Al Sulais, T. Raine, Methotrexate in inflammatory bowel disease: A primer for gastroenterologists, Saudi J. Gastroenterol.: Off. J. Saudi Gastroenterol. Associat. 0 (0) (2022) 0.
[81] E. Gromnica-Ihle, K. Kruger, Use of methotrexate in young patients with respect to the reproductive system, Clin. Experim. Rheumatol.-Incl Suppl. 28 (5) (2010) S80.
[82] L. Cantarini, I. Tinazzi, D. Biasi, A. Fioravanti, M. Galeazzi, Sulfasalazine-induced immune thrombocytopenia, Postgrad. Med. J. 83 (980) (2007) e1.
[83] K.M. Das, Sulfasalazine therapy in inflammatory bowel disease, Gastroenterol. Clin. North Am. 18 (1) (1989) 1–20.
[84] S.J. Dixon, D.N. Patel, M. Welsch, R. Skouta, E.D. Lee, M. Hayano, A.G. Thomas, C. E. Gleason, N.P. Tatonetti, B.S. Slusher, B.R. Stockwell, Pharmacological inhibition of cystine–glutamate exchange induces endoplasmic reticulum stress and ferroptosis, elife 3 (2014) e02523.
[85] D.N. Juurlink, Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection, CMAJ 192 (17) (2020) E450–E453.
[86] E. Louis, J. Belaiche, Hydroxychloroquine (Plaquenil) for recurrence prevention of Crohn's disease after curative surgery, Gastroentérologie clinique et biologique 19 (2) (1995) 233–234.
[87] S. de Germay, H. Bagheri, F. Despas, V. Rousseau, F. Montastruc, Abatacept in rheumatoid arthritis and the risk of cancer: a world observational post-marketing study, Rheumatology 59 (9) (2020) 2360–2367.
[88] W.J. Sandborn, J. Colombel, B.E. Sands, P. Rutgeerts, S.R. Targan, R. Panaccione, B. Bressler, K. Geboes, S. Schreiber, R. Aranda, S. Gujrathi, A. Luo, Y. Peng, L. Salter–Cid, S.B. Hanauer, Abatacept for Crohn's disease and ulcerative colitis, Gastroenterology 143 (1) (2012) 62–69.e4.
[89] F. AlborziAvanaki, N. Moghbel, N. Aletaha, N.E. Daryani, M.J. Farahvash, A. Miroliaii, N. Shayegan, N. Anjidani, P364 Comparison of two treatment strategies in IBD: Biosimilar adalimumab (CinnoRA®) in monotherapy and in combination with azathioprine, J. Crohn's Colitis 16 (Supplement_1) (2022) i370–i371.
[90] Y. Chen, M. Friedman, G. Liu, A. Deodhar, C.-Q. Chu, Do tumor necrosis factor inhibitors increase cancer risk in patients with chronic immune-mediated inflammatory disorders? Cytokine 101 (2018) 78–88.
[91] F.S. Fousekis, K. Papamichael, G. Kourtis, E.N. Albani, A. Orfanidou, M. Saridi, et al., The efficacy of immunomodulators in the prevention and suppression of anti-drug antibodies to anti-tumor necrosis factor therapy in inflammatory bowel disease, Ann. Gastroenterol. 35 (1) (2022) 1.
[92] V.R. Garcia, A. Burls, J.B. Cabello, P.V. Casasempere, S. Bort-Marti, J.A. Bernal, Certolizumab pegol (CDP870) for rheumatoid arthritis in adults, Cochrane Database System. Rev. 9 (2017).
[93] W.J. Sandborn, S.B. Hanauer, S. Katz, M. Safdi, D.G. Wolf, R.D. Baerg, W. J. Tremaine, T. Johnson, N.N. Diehl, A.R. Zinsmeister, Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial, Gastroenterology 121 (5) (2001) 1088–1094.
[94] M. Flamant, S. Paul, X. Roblin, Golimumab for the treatment of ulcerative colitis, Expert Opin. Biol. Ther. 17 (7) (2017) 879–886.
[95] J.S. Smolen, R. Landewé, J. Bijlsma, G. Burmester, K. Chatzidionysiou, M. Dougados, J. Nam, S. Ramiro, M. Voshaar, R. van Vollenhoven, D. Aletaha, M. Aringer, M. Boers, C.D. Buckley, F. Buttgereit, V. Bykerk, M. Cardiel, B. Combe, M. Cutolo, Y. van Eijk-Hustings, P. Emery, A. Finckh, C. Gabay, J. Gomez-Reino, L. Gossec, J.-E. Gottenberg, J.M.W. Hazes, T. Huizinga, M. Jani, D. Karateev, M. Kouloumas, T. Kvien, Z. Li, X. Mariette, I. McInnes, E. Mysler, P. Nash, K. Pavelka, G. Poór, C. Richez, P. van Riel, A. Rubbert-Roth, K. Saag, J. da Silva, T. Stamm, T. Takeuchi, R. Westhovens, M. de Wit, D. van der Heijde, EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update, Ann. Rheum. Dis. 76 (6) (2017) 960–977.
[96] M. Allocca, M. Jovani, G. Fiorino, S. Schreiber, S. Danese, Anti-IL-6 treatment for inflammatory bowel diseases: next cytokine, next target, Curr. Drug Targets 14 (12) (2013) 1508–1521.
[97] M.J. Fobelo Lozano, R. Serrano Giménez, F.M. Castro, Emergence of inflammatory bowel disease during treatment with secukinumab, J. Crohn's Colitis 12 (9) (2018) 1131–1133.

Immunotherapy of inflammatory bowel disease (IBD)

ORIGINALITY REPORT

18%	13%	17%	4%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	"Digestive System Diseases", Springer Science and Business Media LLC, 2019 Publication	3%
2	ClinicalTrials.gov Internet Source	3%
3	www.clinicaltrials.gov Internet Source	2%
4	Wanich Suksatan, Supat Chupradit, Alexei Valerievich Yumashev, Sahithya Ravali et al. "Immunotherapy of multisystem inflammatory syndrome in children (MIS-C) following COVID-19 through mesenchymal stem cells", International Immunopharmacology, 2021 Publication	2%
5	Clinicaltrials.gov Internet Source	1%
6	Submitted to Rhodes University Student Paper	1%

7	Pooneh Khoshakhlagh, Mina Bahrololoumi-Shapourabadi, Azadeh Mohammadirad, Leila Ashtaral-Nakhai et al. "Beneficial Effect of Phosphodiesterase-5 Inhibitor in Experimental Inflammatory Bowel Disease; Molecular Evidence for Involvement of Oxidative Stress", Toxicology Mechanisms and Methods, 2008 Publication	1 %
8	Shobha Regmi, Yoojin Seo, Ji-Su Ahn, Shiva Pathak et al. "Heterospheroid formation improves therapeutic efficacy of mesenchymal stem cells in murine colitis through immunomodulation and epithelial regeneration", Biomaterials, 2021 Publication	1 %
9	Meera Nair, Pooja Saxena. "Recent Patents on Mesenchymal Stem Cell Mediated Therapy in Inflammatory Diseases", Recent Patents on Inflammation & Allergy Drug Discovery, 2013 Publication	1 %
10	"Stem Cells: Current Challenges and New Directions", Springer Science and Business Media LLC, 2013 Publication	1 %
11	Wei Zhang, Wei Ge, Changhong Li, Shengguo You, Lianming Liao, Qin Han, Weimin Deng, Robert C.H. Zhao. "Effects of Mesenchymal Stem Cells on Differentiation, Maturation, and	1 %

Function of Human Monocyte-Derived Dendritic Cells", Stem Cells and Development, 2004
Publication

12	Medical Therapy of Ulcerative Colitis, 2014. Publication	1 %
13	Huldani Huldani, Saade Abdalkareem Jasim, Dmitry Olegovich Bokov, Walid Kamal Abdelbasset et al. "Application of extracellular vesicles derived from mesenchymal stem cells as potential therapeutic tools in autoimmune and rheumatic diseases", International Immunopharmacology, 2022 Publication	1 %
14	"Crohn's Disease and Ulcerative Colitis", Springer Science and Business Media LLC, 2017 Publication	1 %

Exclude quotes	Off	Exclude matches	Off
Exclude bibliography	Off		

Immunotherapy of inflammatory bowel disease (IBD)

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10