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REVIEW ARTICLE

Novel cell-based therapies in inflammatory bowel diseases: the established concept, promising results

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Abstract

Inflammatory bowel diseases (IBDs) are chronic and relapsing disorders that affect the quality of life in many individuals around the world. Over the past few years, the prevalence of IBDs is substantially rising which might pose a considerable social and economic burden on health systems. Progresses in the management of chronic inflammatory diseases lead to prolonged remission phase and decreased hospitalization rate. However, during treatment, many patients become refractory to conventional therapies. Recently, advanced approaches using somatic cell therapy medicinal products (SCTMPs) including immune and stem cell-based therapies have drawn many researchers' attentions. Promising results from recent trials, alongside with the emerging market indicated that these therapeutic approaches could be an alternative and promising treatment to conventional therapies. In this review, we will discuss recent advances in cell-based therapies, which have been developed for treatment of IBDs. In addition, the global emerging market and the novel products in this field are highlighted.

Keywords Inflammatory bowel diseases · Cell therapy · Immune therapy · Cell-based products

Introduction

Inflammatory bowel diseases (IBDs) are chronic inflammatory conditions that affect the gastrointestinal tract. IBDs mainly encompass Crohn's disease (CD) and ulcerative colitis (UC) [1]. UC is characterized by mucosal inflammation and usually limited to the colon. However, CD commonly affect any part of the gastrointestinal tract (like the terminal ileum or the perianal region) and is associated with transmural inflammation, abscesses, fistulas and strictures [2]. It appears that environmental factors, disruption of intestinal microflora, deregulated host immune responses and individual's genetic predisposition contribute to IBDs initiation, progression and severity of symptoms [3, 4]. In the gastrointestinal tract, the balance of the innate and adaptive immunity is critical for promoting immune tolerance and avoiding the specific immune response against normal enteric bacterial flora. Injury or genetic predisposed due to dysregulated innate and adaptive immune responses and breakage of self-antigens tolerance in the intestinal mucosa could have a leading role in the epithelial cell damage and IBDs initiation and development [5]. IBDs are characterized by chronic inflammation resulted from cytokine secretion by intestinal flora and a large number of immune cells migrate

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into the lamina propria including T cells, B cells, macrophages, dendritic cells (DCs), and neutrophils. Cytokines derived from immune cells like T helper 2 (Th2) cells play an important role in UC development, while CD is a Th1/Th17-mediated disorder [6, 7]. High levels of inflammatory cytokines including tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), IL-6, IL-17, IL-22 and IL-23 can drive intestinal inflammation [8].

Conventional therapies for IBDs include corticosteroids, immunosuppressant medicines and surgery. Recently, biological agents, such as anti-TNF-α, anti-α4β7, and anti-interleukin 12/23 (IL-12/23) antibodies, have been developed for IBDs treatment [9, 10]. However, despite the use of biological agents, these interventions still have some limitations and many patients encounter multidrug resistance and finally become refractory to treatment protocols [11]. Thus, it is of paramount importance to develop novel and innovative approaches for improving the treatment of IBDs (Fig. 1), enabling mucosal healing and avoiding potentially invasive surgeries in refractory IBDs patients. Effective and curative advanced therapy medicinal products (ATMPs) including somatic cell therapy medicinal products (SCTMPs) are one of those promising therapies and are currently in preclinical and clinical development.

Cell-based therapy in IBDs patients

Cell-based therapy for IBDs treatment has been developed in recent years. The main goal of this approach is replacing damaged cells, enabling mucosal tissues healing and limiting the inflammatory responses [12, 13]. Several types of

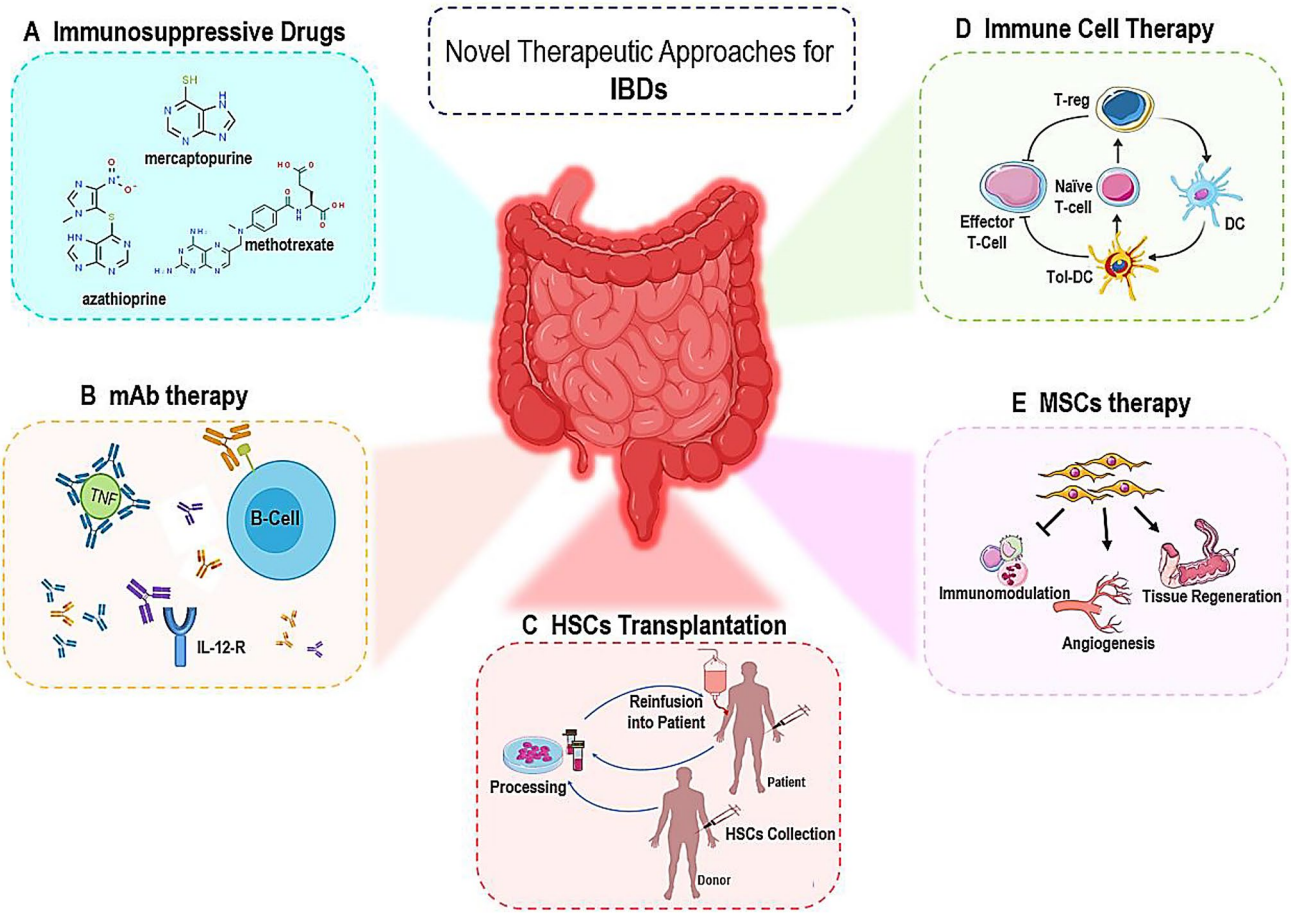

Fig. 1 New therapeutic avenues in inflammatory Bowel Diseases (IBDs). **A** immunosuppressive therapies, such as 6-mercaptopurine (6-MP), azathioprine (AZA), and methotrexate (MTX), induce anti-inflammatory effects through suppression of T cell function and natural killer cell activity. **B** Monoclonal Antibody (mAb) -Based Biological Therapies against prototypical pro-inflammatory cytokines, chemokines and receptors, such as TNF-α, IL-12-R and CD19. **C** Allogeneic or autologous Hematopoietic Stem Cells can migrate to damaged tissues and differentiate to epithelial or immune-modulatory cells to restore normal mucosa and tissue integrity. **D** specialized immune cells, such as Regulatory T cell (Treg) and Tolerogenic Dendritic cells (Tol-DCs), help to repair intestinal mucosal tissues by damping inflammation and effector T cells activity. **E** Mesenchyme stromal cells (MSCs) can control IBD through facilitating tissue regeneration, supporting angiogenesis and limiting inflammation

stem cells, such as hematopoietic stem cells (HSCs), antigen-presenting cells (APCs), and mesenchyme stem cells (MSCs), have been used in cell-based therapy approaches. The considerable results of published clinical trials and the growing number of ongoing clinical studies have indicated that cell-based therapy could be a promising approach for the treatment of these disorders [14]. Tables 1 and 2 summarize completed and ongoing clinical trials, respectively. In general, cell-based therapeutic strategies are divided into two subtypes; immune cell therapy and stem cell therapy.

Immune cell therapy in IBDs

Specialized immune cells that dampen inflammation like T regulatory cells (Tregs) and tolerogenic dendritic cells (Tol-DCs) play a crucial role in sustaining immune homeostasis and stimulating the appropriate immune responses by modulating cells of both the innate and adaptive immune systems. Interestingly, several protocols have been established to produce clinical grade Tol-DCs and Treg in vitro, opening the possibility to restore the intestinal homeostasis to bacterial flora by immune cell therapy [15, 16].

T regulatory cells in IBDs

Cell-based therapy using regulatory T (Treg) cells could be a promising approach for regulation of the immune responses in autoimmune diseases [14]. Treg cells are usually secrete potent anti-inflammatory cytokines including TGF-β and IL-10 [17]. They also develop antigen-specific, long-lasting immunological memory and inhibit proliferation and function of activated CD4 + T cells. Several studies have shown a dramatic increment of Treg cell population in IBDs patients [18]. During intestinal inflammation, Treg cells migrate to the colon and inhibit proliferation of lymphocytes [19]. Studies showed that Treg cell therapy could be used as a potential treatment in inflammatory disorders such as IBDs [19, 20]. Moreover, clinical trials which used autologous Treg cells, showed safety and efficacy of these cells for the treatment of CD [21]. A major issue in Treg-based therapy is safety since the systemic immunosuppression followed by Treg infusion is a crucial concern[22]. Recent studies have presented a subset of Treg cells called Tr1, which produce large amounts of IL-10 and IL-22. These cytokines play an important role in healing process of epithelial barrier. It was reported that immune therapy with Treg cells for CD patients was well tolerated and induced remission in 38% of patients[23]. Therefore, it has been suggested that these cells could be developed as a potential cell-based therapy for IBDs[23, 24].

Tolerogenic dendritic cells in IBDs

Dendritic cells (DCs) are specialized antigen-presenting cells that connect innate immunity to adoptive immune system [25]. DCs can either enhance or inhibit immune responses based on their maturity status and antigen properties [26]. Several studies demonstrated that DCs stimulate immune reactions and could be potential therapeutic tools for the treatment of infectious diseases and cancers [27, 28]. Depending on tolerogenic properties, DCs could be a promising approach for the treatment of inflammatory and autoimmune disorders including type I diabetes, multiple sclerosis and CD [29–31]. Tolerogenic DCs (Tol-DCs) are able to induce tolerance through producing IL-10 and shift naïve T cells towards Treg phenotype and hypo responsiveness of TH1 cells [32, 33].

Using Tol-DCs in animal models of colitis has shown that Tol-DCs could successfully decrease inflammation and ameliorate the complications of the disease, as well as improvement in clinical symptoms and prevention of the establishment of the diseases, were reported [34, 35]. Moreover, intraperitoneal injection of Tol-DCs is more efficient than intravenous administration, as mesenteric lymph nodes are the main home to TH1 and TH17 differentiation. To investigate the role of Tol-DCs in CD, peripheral mononuclear cells (PBMCs) were isolated and Tol-DCs were generated using a cytokines cocktail (IL-1β, IL-6, TNF-α and dexamethasone) and then injected to the patients. Results showed that the administration of autologous Tol-DCs was safe, improved lesions in 33% and induced remission in 11% of CD patients [35]. It seems that Tol-DCs possess an anti-inflammatory phenotype and could be a potential therapeutic tool against IBDs[34, 35].

Human stem cell therapy in IBDs

Hematopoietic stem cells (HSCs) and mesenchyme stem cells (MSCs) are two common stem cell types, which have been used for treatment of IBDs [12]. Encouraging results from experimental and clinical studies suggested that stem cell therapy could be a potential candidate for those whom suffer from active, uncontrolled or refractory IBD [12].

Hematopoietic stem cell therapy

Hematopoietic stem cells (HSCs) are multi-potent cells that have self-renewal properties and can differentiate into different types of blood and immune cells. Several studies showed that transplantation of HSCs in the treatment

Table 1 Published human studies of stem cell therapy in IBDs

Reference	Type of study/ phase	Patients No IBDs type	Type of stem cell	Route of administration	Intervention	Results
Panes [98]	Double blind/ phase III	212/CD	Allogenic AD-MSC	Local/Intrafistular	Single dose of 120 million cells	59.2% clinical remission
Dhere [82]	Phase I	12/CD	Autologous BM-MSC	Intravenously	10 million/kg	Clinical improvement/BM-MSC express IDO and inhibited allogenic PBMC
Forbes [89]	Open labeled/ phase II	16/luminal CD	Allogenic BM-MSC	Intravenously	2×10^6cell/kg	12/12 reduction in CDAI, 8/12 clinical remission, 7/12 endoscopy improvement
Homes [40]	ND	3	Autologous HSC	Intravenously	5.9×10^6–3.5×10^6/kg	Remission achieve
Ciccocioppo [81]	ND	12/CD	Autologous BM-MSC	Local/ Intrafistular	20×10^6	Reduction of CDAI/ increased T reg cells
Duijvestein [76]	Phase I	10/ refractory CD	Autologous BM-MSC	Intravenously	1e23106 cells/kg	MSC were safe and feasible, CDAI decreased in 2 patients
Hu [93]	Phase I/II	40/UC	Allogenic UC-MSC	Intravenously	$3.8\pm1.6\times10^7$	Improved Mayo score, No significant change in IL-6, TNF-α and IFN-γ
Zhang [99]	Randomized Controlled Clinical Trial	82/CD	Allogenic UC-MSC	Intravenously	1×10^6 /kg	Improvement CDAI/ endoscopic index/ improving fistula/ No complete remission
Mayer [100]	Phase I	12/CD	Allogenic Placenta-derived MSC	Intravenously	2×10^8–8×10^8	Remission achieve in low dose groups/ no permanent adverse effects/
Olmo [84]	Phase I	5/CD	Autologous AD-MSC	Local/ Intrafistular	3–30×10^6	Fistula healing/ decreasing discharge
Olmo [87]	Phase II	50/CD	Autologous AD-MSC	Local/ Intrafistular		Stem cell therapy were more effective than fibrin glue in fistula healing
Cho [85]	Phase I	10/CD	Autologous AD-MSC	Local/ Intrafistular	2–4×10^7	Complete closure of fistula/ decreased inflammation
Lee [101]	Phase II	43/ CD	Autologous AD-MSC	Local/ Intrafistular	3×10^7	Complete fistula healing
Wainstein [102]	Phase I	9/CD	AD-MSC + PRP	Local/ Intrafistular	100–120 million	Complete fistula healing/ activity index improved
Guadalajara [83]	Phase II	49/ CD	Autologous AD-MSC + fibrin glue	Local/ Intrafistular		Long-term follow-up indicated safety and 7 patients didn't relapse

Table 1 (continued)

Reference	Type of study/ phase	Patients No IBDs type	Type of stem cell	Route of administration	Intervention	Results
De la Portilla [92]	Phase I/IIa	24/CD	Allogenic AD-MSC	Local/ Intrafistular	20 million	Complete closure of fistula/MRI index improvement
Herreros [103]	Phase III	200/ CD	Autologous AD-MSC	Local/ Intrafistular	20 million	The treatment was safe and 40% of patients achieved fistula healing
Liang [68]	Phase I	7/ CD, UC	Allogenic BM-MSC/UC-MSC	Intravenously	1×10^6/kg	The treatment was safe, clinical improvement achieved
Molendijk [91]	randomized, double-blind, dose -escalating clinical trial	21/CD	Allogenic BM-MSC	Local/ Intrafistular	1×107 3×10^7 9×107	No adverse effect, fistula healing in 85.6% in patients who received 3×10^7 cells
Cho [96]	Phase II	43/CD	Autologous AD-MSC	Local/ Intrafistular	3×10^7	No adverse reaction/ Complete healing and closure of fistulas

of autoimmune and inflammatory diseases such as IBDs could be useful [36–38].

Autologous administration of HSCs

Autologous HSCs transplantation has been reported in both animal and human studies. Mobilization and conditioning are the two principal phases in autologous HSC transplantation. In the mobilization phase, HSCs are stimulated to migrate into peripheral blood. Then, isolated using apheresis and cryopreserved. In the conditioning phase, the patient receives doses of a lymphoablative conditioning regimen followed by autologous cell infusion [39]. Studies indicated that HSCs transplantation induced clinical remission in refractory CD [40]. Autologous HSCs therapy in refractory CD, resulted in clinical remission and endoscopic scores improvement [41]. Despite a marked beneficial effect in promoting remission in IBDs patients, autologous HSCs engraftment still encounters major limitations due to its serious side effects [42]. HSCT may enhance the risk of infections, especially, during the aplasia of mobilization and conditioning. Additionally, intestinal stomas in CD can increase the risk of morbidity in immunocompromised patients [43].

Administration of allogeneic HSCs

In allogeneic HSCT, the host bone marrow stem cells are ablated and replaced with donor-derived stem cells. Several studies demonstrated that allogeneic transplantation of HSCs has beneficial effects for treatment of IBDs. These investigations showed that allogeneic HSCs could improve IBDs complications and patients experienced clinical remission. However, due to the risks of allogeneic HSCs transplantation, e.g., G*v*HD, limited number of studies supported the use of allogeneic HSCT for IBDs [42].

Mesenchymal stromal cells therapy

Mesenchymal stromal cells (MSCs) are multi-potent stromal cells that have great homing and immunomodulatory capabilities [44]. These cells adhere to plastic surfaces, express CD90, CD105 and CD73 markers, lack CD34, CD45, CD19 and CD11b markers and differentiate into different cell types including adipocytes, chondrocytes and osteoblasts [13, 45–47]. The ex vivo cultured MSCs are heterogeneous population and only a fraction of cells meet generally approved biologic properties of stem cells including potency and self-renewal. Thus, the term 'mesenchymal stromal cells' was proposed by ISCT, the International Society for Cellular Therapy [48, 49]. MSCs can be isolated from a variety of tissues including bone marrow, adipose tissue, dental tissues, cord blood, etc. [50]. These cells can migrate into the sites of inflammation and induce regeneration by producing trophic and anti-inflammatory factors. The characteristics of MSCs make them a promising tool for the treatment of autoimmune and inflammatory disorders including IBDs [51]. MSCs represent different characteristics due to different sources and microenvironment. It was demonstrated that Wharton's Jelly derived MSCs (WJ-MSCs) and (AD-MSCs)

Table 2 Ongoing clinical trials using MSCs in IBDs

CT number	Disease	MSC source	Country	Recruitment Status	phase
NCT02150551	Pediatric Inflammatory Bowel Disease	Allogenic BM-MSC	United States	Suspended	I
NCT03299413	UC	Allogenic Warton's jelly MSC	Jordan	Active, not recruiting	I II
NCT01659762	CD	Autologous BM-MSC	United States	Completed	I
NCT03901235	CD	MSC	Belgium	Recruiting	I II
NCT01090817	CD	MSC	Australia	Completed	II
NCT01540292	CD	Allogenic BM-MSC	Belgium	Recruiting	I II
NCT03056664	CD	MSC	China	Not yet recruiting	II III
NCT02445547	CD	UC-MSC	China	Completed	I II
NCT03449069	CD	Autologous MSC	United States	Recruiting	I
NCT03000296	CD	Autologous HSC	Brazil	Recruiting	Not Applicable
NCT01144962	CD	Allogenic BM-MSC	Netherlands	Completed	I II
NCT03609905	UC	Allogenic AD-MSC	China	Recruiting	I II
NCT02442037	UC	Allogenic UC-MSC	China	Unknown Was recruiting	1 II
NCT01874015	CD	Autologous BM-MSC	Iran	Unknown Was recruiting	I
NCT00294112	CD	Allogenic BM-MSC	United States	Completed	II
NCT02403232	CD	Autologous AD-MSC	Italy	Unknown Was recruiting	II
NCT00482092	CD	Allogenic MSC (PROCHYMAL)	United States	Completed	III
NCT01914887	UC	Allogenic AD-MSC	Spain	Unknown Was recruiting	I II
NCT01157650	CD	Autologous AD-MSC	Spain	Completed	I II
NCT00543374	CD	Allogenic MSC (PROCHYMAL)	United States	Completed	III
NCT03183661	CD	Allogenic AD-MSC	Korea	Enrolling by invitation	I
NCT01221428	UC	Allogenic UC-MSC	China	Was active, no recruiting	I II
NCT01541579	CD	Allogenic AD-MSC	Austria	Completed	III
NCT01233960	CD	Allogenic MSC (PROCHYMAL)	United States Australia New Zealand	Completed	III
NCT02580617	CD	Allogenic AD-MSC	S. Korea	Recruiting	I
NCT02403232	CD	Autologous AD-MSC	United States	Recruiting	II

had higher proliferation capacity in comparison with (BM-MSCs) [52, 53]. In terms of differentiation ability, BM-MSC possess high osteogenic and chondrogenic differentiation potential [54, 55]. Moreover, WJ-MSCs had marked immunosuppressive activities and were more efficient to suppress allogeneic T cells proliferation and activation than BM-MSCs due to their massive immuno-regulatory mediator production and low immunogenicity [50, 52, 56].

MSCs and immunomodulation

MSCs possess great immunomodulation features and interact with almost all cells of innate and adoptive immune systems [57]. Immunomodulatory effects of MSCs is a result of cell–cell communications and secretion of soluble factors. MSCs produce various soluble factors including TGF-β, IL-10, prostaglandin E2 (PGE2), hepatocyte growth factor

(HGF), indoleamine 2,3-dioxygenase (IDO), heme-oxygenase-1 (HO-1) and nitric oxide (NO) [58]. They can also inhibit proliferation and function of T helper cells, impede their differentiation to Th1 and Th17 and suppress proliferation and activation of cytotoxic T cells (CTLs) [51, 59, 60]. Additionally, in-vitro and in-vivo investigations demonstrated that MSCs could induce Treg cell differentiation from naïve T cells, which in turn, suppresses inflammatory responses through secretion of IL-10 and TGF-β [51, 61, 62]. MSCs also have a considerable impact on DCs and force them towards an immature phenotype. In this regard, they downregulate expression of co-stimulatory molecules and increase expression of IL-10 [57, 63]. Moreover, MSCs interfere with NK cells cytotoxicity and proliferation through down regulation of IL-2 and IL-15, and induce M2 phenotype in macrophages, which results in excessive secretion of anti-inflammatory mediators [64].

Several studies have shown that an inflammatory stimuli like IFN-γ or TNF-α, induces secretion of high levels of anti-inflammatory cytokines from MSCs [65]. Pre-stimulation of MSCs with IFN-γ can increase their suppressive ability and therapeutic effects in an experimental colitis model [51]. MSCs can maintain their immunomodulatory features even after differentiation to other cell types such as osteoblasts [66]. Recently, it was indicated that one of the crucial factors for immunomodulatory activities of MSCs is perforin mediated apoptosis by host TCD8 + cells. It seems that generation of *ex-vivo* apoptotic MSCs could also be an alternative treatment option [67].

MSCs derivatives and immunomodulation

Several reports demonstrated that there is a direct relation between paracrine factors released by MSCs and their immunomodulatory and regenerative properties [68–71]. MSCs derivatives including conditioned medium and extracellular vehicles (EVs), are new cell-free tools that have drawn considerable attention in novel therapies [72]. MSCs derived EVs are classified as microvesicles (MVs) and exosomes. Exosomes are vesicles of endocytic origin, 30–150 nm in diameter that deliver many types of biomolecules, such as mRNA, proteins, microRNA and lipids [68, 73]. Exosomes downregulate inflammatory responses through promoting M2 macrophages polarization (by up regulating CD163), inhibiting the proliferation of Th1 cells and inducing Treg cells differentiation [74]. Studies reported that exosomes have cyto-protective effects in various diseases including myocardial ischemia, neurodegenerative disorders, autoimmune hepatitis and IBDs [68]. These secreted organelles ameliorate the clinical complications of IBDs patients and improve healing process in chemically induced animal models [73, 75]. Exosomes also exert anti-inflammatory effects in UC animal models. Although MSC-derived exosomes have been used in clinical trials for various diseases, such as Type I diabetes mellitus (T1D), stroke, periodontitis, wound healing and coronavirus pneumonia, there has been no report of their application for the treatment of IBD.

Autologous MSCs transplantation for treatment of IBDs

The long-term safety and efficacy of both autologous and allogeneic MSCs have since been evaluated in IBDs treatment. Autologous administration of MSCs was used in several human studies [76–80]. Local injection of autologous BM-MSCs in patients with perianal fistula was safe, well tolerated and following resolution of inflammation, decreased CD activity index (CDAI) score and induced mucosal healing in patients [81]. Also, improvement of CDAI and endoscopic evaluation results were observed in refractory patients following systemic injection of BM-MSCs. It was proven that MSCs isolated from IBDs patients, have immunomodulatory properties comparable to those from healthy donors including inhibition of proliferation of PBMCs in-vitro [76]. Nonetheless, after BM-MSCs engraftment some serious side effects including appendicitis and *C. difficile* colitis were reported that might be due to the infusion of BM-MSCs [82].

Autologous engraftment of AD-MSCs for perianal fistula in CD patients was found safe and efficient. AD-MSCs administration could help healing and closure of fistula [83]. After cell therapy, the discharge from fistula was decreased and the epithelialization of fistula opening happened [84]. Furthermore, complete healing occurred during 8 weeks after cell transplantation [85, 86]. Also, it was revealed that autologous AD-MSCs are more effective than fibrin glue in patients with perianal fistula [87]. Some evidences suggested that combination therapy with AD-MSCs and platelet-rich plasma (PRP) has remarkable benefits including complete remission and improvement of perianal and vaginal fistulas[87].

Allogeneic MSCs transplantation for treatment of IBDs

MSCs are less immunogenic and they are better tolerated by host immune system [88]. Systemic infusion of allogenic BM-MSCs in refractory luminal CD indicated safety and efficacy, decrease of the mean CDAI score and improvement of endoscopic index after the injection [89]. Local injection of allogenic BM-MSCs into perianal fistula demonstrated enhanced healing process [89, 90]. Data showed local administration of MSCs promoted fistula relive and ameliorated clinical complications such as fistula discharge. Following intra-fistula administration, the total number of active fistulas and the amount of discharge decreased [91].

Investigations of allogeneic AD-MSCs also showed encouraging results. Allogeneic AD-MSCs were found safe

and efficient and could reduce the number of draining fistula [92]. Long-term follow-up of refractory CD patients that underwent allogeneic AD-MSCs transplantation, showed safety and efficacy and resulted in clinical remission [92]. Encouraging results were also obtained following treatment of CD patients with placenta-derived MSCs. It was demonstrated that the infusion of allogeneic placenta-derived MSCs in CD patients was safe and well tolerated. Moreover, MSCs infusion decreased CDAI score and complete remission reported [64]. Furthermore, in refractory UC, application of allogeneic umbilical cord MSCs (UC-MSCs) showed safety, feasibility, and no serious adverse effects. Moreover, clinical symptoms and histological findings improved and remission was achieved [93]. Although patients showed good response to MSCs therapy, there were no significant changes in the levels of inflammatory cytokines in blood [93, 94].

IBDs may have negative impacts on the regenerative and immunomodulatory properties of autologous MSCs. Therefore, using allogenic source of MSCs could provide a ready-to-use and off the shelf cell-based product from young and healthy donors for immediate treatment of IBDs [92].

IBDs cell therapy market

Over the past few years, the introduction of ATMPs to the global pharma market has been revolutionizing the pharmaceutical industry and has opened new windows for treatment of various types of complicated diseases. In recent decades, stem cell science and related market size have been grown in parallel with the development of novel stem cell therapy approaches [95]. Polaris Market Research reported that stem cell therapy market size was 105.24 million USD in 2017 and estimated that stem cell industry will reach 2518.5 million USD by the year 2026. North America will be the most dominating region, however, Asia Pacific is the fastest growing region. Among different cell therapy approaches, allogeneic stem cells therapies are growing very fast for a wide spectrum of applications and will reach the highest compound annual growth rate (CAGR) until 2025 [52]. In general, we depict an overall perspective of approved ATMP products for the treatment of IBDs patients (Fig. 2), while reflecting the degree of their success in a clinical point of view and highlighting their main safety concerns and effectiveness.

Cupistem®, is the first approved autologous AD-MSCs product, which has been developed by Anterogen Company (South Korea) and was approved by South Korea Ministry of Food and Drug Safety (MFDS) in 2012 for treatment of fistula in CD. This product is packaged into single use vials containing 3.0×10^7 AD-MSCs in 1 ml for fistula diameter ≤ 1 cm and 6.0×10^7 AD-MSCs in 2 ml for fistula diameter $1 < X < 2$ cm. Treatment with Cupistem® seemed to be safe and efficient according to the results of phase II trial in 41 patients during 2 years follow-up. Long-term follow-up of 24 patients with Crohn's fistula showed that AD-MSCs therapy helped complete closure in 80% of the patients after 12 months. Complete fistula closure observed in 83.3% of the patients at the eighth week after injection. Moreover, 80% of patients had complete fistula healing two years after injection [96].

Alofisel (darvadstrocel), previously called Cx601 is the first allogeneic expanded AD-MSCs, which has been developed by TiGenix (USA) & Takeda (Japan) pharmaceutical companies for using in complex perianal fistulas in CD. This product was approved by EMA (European Medicines Agency) in 2018 and is packaged into 4 vials consists of 120 million MSCs/ml suspension. The full content of the 4 vials is administered for the treatment of up to 3 fistula tracts that

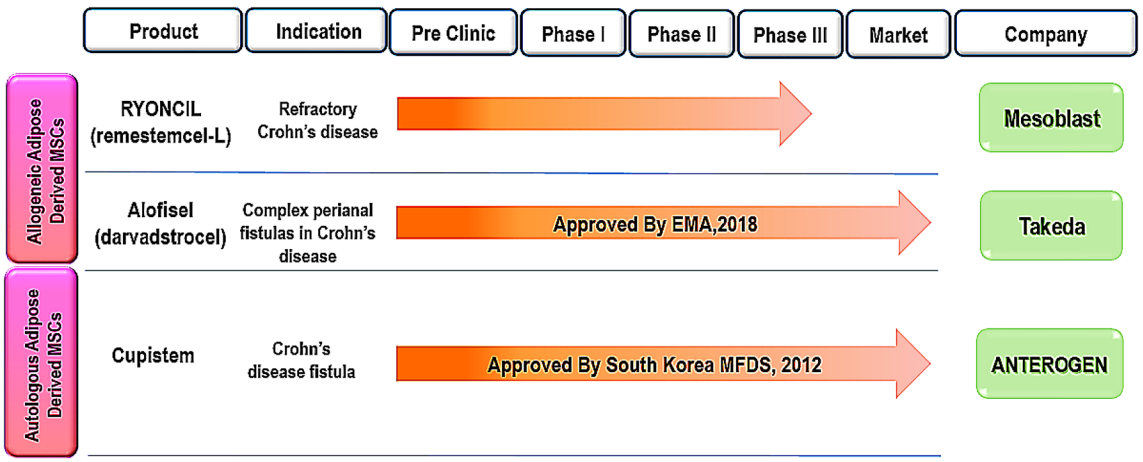

Fig. 2 Approved Mesenchyme Stromal Cells (MSCs) based products for treatment Refectory Crohn´s disease (CD)

open to the perianal area. Efficacy of Alofisel was evaluated in a phase I/II study of 24 patients with CD for 24 weeks. Data analysis indicated a reduced number of draining fistulas in 69.2% of patients and complete closure of the treated fistula in 56.3%. The FDA approval for Alofisel is currently under review [92].

RYONCIL (remestemcel-L) is another allogeneic AD-MSCs product that is developed by Mesoblast Co. and now is used in ongoing phase I/II clinical trial for the treatment of refractory CD. This product consists of 100–200 million MSCs delivered intravenously in a multiple dose regime. Remarkable increase of the stem cell market could be because of global growing prevalence of chronic, inflammatory disorders. This resulted in emerging new technologies and developing new products and adaptation of cell-based therapies in the treatment of diseases. Established governments funding, R&D activities and the number of cell-based clinical trials can change the future of the cell-based therapies and regenerative medicine market.

Conclusion and future prospect

Overall, preclinical and clinical studies on cell-based therapy in IBDs demonstrated that MSCs as direct mesenchymal progenitors, anti-inflammatory modulators, and tissue stromal cells are safe and beneficial for therapeutic applications. Studies revealed that MSCs are well tolerated and no malignancy or adverse effects reported [97]. However, some concerns should be addressed before using MSCs for treatment of IBDs. The major concern as already mentioned is safety [91]. During the long-term follow-up, the risk of transformation and malignancy should be considered. Besides, different sources of MSCs, and culture protocols should be defined. Moreover, inflammatory status and stage of the disease can greatly make an impact on the efficacy of grafted MSCs and final results [51]. Therefore, patient selection is a critical stage in clinical trials using MSCs.

Combination therapy using MSCs and biologicals may increase the efficacy of treatment; however, it can cause other complications too. Finally, for improving the efficacy, priming cells before injection may also be a smart option [88]. Dose escalation is another challenge for cell-based therapy, as some studies documented that using higher cell counts resulted in reduced cell viability and diminished beneficial effects. High-dose cell therapies may also increase immunogenicity and activate alloreactivity [81]. Thus, more studies are needed to define standards for stem and immune cell-based therapies in clinical applications.

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Declarations

Conflict of interest The authors declare that they have no known competing interests that could have appeared to influence the work reported in this paper.

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