

Stem cell therapy in inflammatory bowel disease: A promising therapeutic strategy?

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Core tip: Inflammatory bowel diseases are inflammatory, chronic and progressive diseases of the intestinal tract. A limited experience is available with hematopoietic and mesenchymal stem cell transplantation for the treatment of these conditions. Research is ongoing with other cell lines which have been used in conditions alike to inflammatory bowel disease and which will possibly have a therapeutic role in this condition.

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Abstract

Inflammatory bowel diseases are inflammatory, chronic and progressive diseases of the intestinal tract for which no curative treatment is available. Research in other fields with stem cells of different sources and with immunoregulatory cells (regulatory T-lymphocytes and dendritic T-cells) opens up new expectations for their use in these diseases. The goal for stem cell-based therapy is to provide a permanent cure. To achieve this, it will be necessary to obtain a cellular product, original or genetically modified, that has a high migration capacity and homes into the intestine, has high survival after transplantation, regulates the immune reaction while not being visible to the patient's immune system, and repairs the injured tissue.

INTRODUCTION

Inflammatory bowel disease (IBD) mainly consists of two clinical conditions, Crohn's disease (CD) and ulcerative colitis (UC). It is mainly characterized by chronic, destructive inflammation of the gastrointestinal tract for which no curative treatment is currently available.

Its etiology is unknown, but it is accepted that it could be the result of loss of tolerance to intraluminal bowel antigens^[1]. Genetic, environmental, and microbiological factors are involved in its development,

together with morphological and functional changes in the intestinal barrier associated to an impaired immune response^[2]. Early data supporting genetic involvement in the pathogenesis of IBD come from familial clinical studies showing a greater incidence in twins^[3,4], first-degree relatives^[5,6] and given ethnic groups^[7,8]. Genome-wide association scan studies have allowed for identification of more than 163 loci associated to IBD^[9], 73 genes associated to CD and 47 to UC^[10], and overlapping genes for both conditions have also been found^[11]. Genetic factors would however account for less than 25% of cases^[12]. The exception is represented by a monogenic disorder referred to as IBD-like diseases, which are associated with severe colitis in childhood and have at most three loci alternatives^[13]. On the other hand the increase of the incidence of IBD suggests that environmental factors are more important than genetic factors in the development of IBD^[14].

Since IBD etiology is currently unknown, current treatment is intended to control the inflammatory intestinal process, thus avoiding irreversible structural damage. However, current therapeutic results are discouraging. Thirty-three percent of patients with CD do not respond to anti-TNF alfa therapy^[15-18], and one third of responders loss the response^[19]. Based on all the foregoing and on advances in understanding of the pathophysiological mechanisms involved in IBD development, new biological drugs and cell therapies are being investigated.

Future of the cellular-based therapy in IBD: Lessons from preclinical and clinical studies

Cell therapies are promising candidates for the treatment of IBD. However, inconsistent results have emerged from current clinical trials using both, hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). To establish the best stem cell type, the administration route and optimal dose of cells to achieve an effective therapy and to guarantee the safety of the patient, in-depth basic research is necessary. Therefore, preclinical studies using different animal models are necessary to understand the pathogenesis of IBD. These studies will facilitate a better design of preclinical stem cell therapies that will eventually become a suitable clinical therapy for IBD patients.

ADULT STEM CELLS

At present, HSCs and MSCs have been used in several clinical trials. However, up to now, the results are unpredictable. For additional information, the reader is referred to the recent review published by our group in 2014^[20].

Hematopoietic stem cells transplantation

Use of hematopoietic stem cells transplantation (HSCT) in IBD is restricted to severe CD with few therapeutic

options. These are patients who do not respond to standard treatment in whom surgery is not an option due to extent of disease. HSCT may also be used in monogenic diseases, such as interleukin-10 deficiency, where allogenic bone marrow transplant would correct the disease by reconstituting a new immune system.

Allogenic HSCT is not currently accepted for the treatment of CD because of its high mortality rate. Current studies focus on autologous HSCT, which is intended to "reset" the immune system of the patient. Once reactive T-lymphocytes and memory cells of the patient are eliminated by chemotherapy (lymphoablation), administration of autologous HSCs generates an immunotolerant system^[21-23]. Unfortunately, this effect will probably be transient until the patient cells start the inflammatory mechanisms again.

Clinical experience is limited (Table 1), with the Burt study^[25] reporting complete remission in all their 24 patients. We are currently waiting for the results of the ASTIC study^[28]. This is a phase III clinical trial comparing two treatment arms intended to clarify whether improvement is due to reset of the immune system or to transplantation. The first arm uses chemotherapy followed by early transplantation (30 d), and the second arm chemotherapy with late transplantation (13 mo). Results reported to date include a high adverse effect rate and appear to suggest efficacy of transplantation.

Mesenchymal stem cell transplantation

MSCs seem to be a promising therapeutic strategy for IBD because of their ability to selectively home in to injury/inflammation areas after systemic administration, and their immunosuppressive and tissue healing properties^[30,31]. However, the clinical data published about MSCs transplantation in IBD patients showed conflicting results. An explanation for these inconsistent results could be the different sources used to obtain the MSCs that could have distinct differentiation and regeneration capabilities and the variety of protocols used for their isolation and culture. A better understanding of the MSCs biology and mechanisms of action and the exploration of other sources of stem cells in preclinical models of IBD are necessary.

Bone marrow and adipose tissue are the main sources of MSCs for both experimental and clinical studies. However, these sources have several disadvantages such as the invasive procedure used for their isolation, the small number of MSCs isolated, and the low proliferation and differentiation capacities related to donor age. For this reason, in the last few years the search for alternative tissue sources for MSCs has become of vital importance. Placental tissues, both fetal (amniotic fluid, Wharton's jelly, amniotic membrane, chorionic villi) and maternal (decidua) represent an important source of MSCs with some advantages including the isolation of large number of cells in a non invasive way^[32,33]. In addition, like

Table 1 Autologous hemopoietic stem cells transplantation studies in Crohn's disease

| Ref. | Patients (n) | Follow up (mo) | Deaths | Remission (number of patients, time of evaluation in months) | Recurrence (number of patients or %, time of evaluation in months) |
|---|--|----------------------|--|--|---|
| Oyama <i>et al</i> ^[24] | 12 | 18.5 mo (7-37) | No | Clinical 11 (12 mo) | 1% (18.5 mo) |
| Burt <i>et al</i> ^[25] | 24 | 60 mo | 1 not related | Clinical 24 (6-12 mo) | 9% (12 mo) 37% (24 mo) 43% (36 mo) 61% (48 mo) 81% (60 mo) |
| Cassinotti <i>et al</i> ^[26] | 10 | 56 mo (23-68) | No | Clinical 10 (3 mo) Endoscopic 5 (3 mo) | 20% (12 mo) 50% (24 mo) 60% (36 mo) 70% (48 mo) 70% (60 mo) |
| Hasselblatt <i>et al</i> ^[27] | 12 | 37 mo (IQR 6-123) | No | Clinical 4/8 (6 mo) Endoscopic 5/9 (9.1 mo) 3/9 mild disease | 7% (10.9 mo) |
| Hawkey ^[28] | Data from 30 out of 45 patients 16 mobilisation + HCST (A) 16 mobilisation (B) | | 1 death after HCST | NA A: CDAI fell 162 (IQR 0-190) B: CDAI fell 82 (IQR 41-137) | NA |
| Jauregui-Amezaga <i>et al</i> ^[29] | 21 evaluable | 12 mo | 1 after CMV infection and multiorganic failure | NA | NA |

NA: Not available; CDAI: Crohn's disease activity index; IQR: Interquartile range; CMV: Cytomegalovirus.

bone marrow MSCs, placenta-derived MSCs are non-immunogenic and immunomodulatory stem cells with high expansion and differentiation capacity^[32-35].

An important issue in using MSCs is their safety. Although some studies supported that there is a risk of MSCs malignant transformation^[36,37], several recent studies using different types of MSCs supported that there is neither *in vitro* risk of development chromosomal aberrations after long term culture nor *in vivo* induction of tumors^[30,32,38,39].

For IBD treatment it is essential to increase the number of cells that migrate and home in to the intestine. A preclinical model of radiation enteritis treated with MSCs genetically modified to express the CXCR-4 receptor showed an increase of MSCs migration to intestinal site of injury and an improvement of symptoms^[40]. In the same way, MSCs coated with antibodies against vascular cell adhesion molecule VCAM-1 showed an increased cell migration of MSCs to inflamed colon and thereby an increased tissue repair capacity^[41]. A different strategy is to select a subpopulation of MSCs within the bone marrow that expresses high levels of EphrinB2. This subpopulation has an increased migration capacity to intestinal injury areas, and as a consequence, these MSCs would help to improve healing of intestinal injury^[42]. Once MSCs engraft in the intestinal damaged tissue they can proliferate and transdifferentiate into intestinal stem cells, or secrete cytokines and growth factors that will promote the proliferation and differentiation of intestinal stem cells in order to repair the injured areas of the intestinal tissue^[43].

Besides the migration, homing and tissue repair capabilities of MSCs, they also have an important function in modulating the inflammation and high

immune response within the injured tissues. These immunomodulatory properties of MSCs are of special importance in the treatment of IBD. Systemic administration of bone marrow MSCs in a mouse model of chemical-induced colitis^[43] and in a pig model of radiation-induced proctitis^[44], down-regulated autoimmune and inflammatory responses, and as a consequence, facilitated tissue regeneration.

The experience in luminal CD is limited (Table 2). Experience in UC is even smaller, and was mainly obtained in Russian studies about response of clinical activity^[50], changes in the pattern of systemic cytokines^[51] and elimination of cytomegalovirus after Mesenchymal stem cell transplantation (MSCT)^[52]. The most important work in this field is a phase III study^[48] that plans to include 330 patients who will be treated with MSCs at different doses, but final results are not expected until 2018. According to data reported to date, the safety profile appears to be favorable, and formation of aberrant tissue has not been detected.

As regards local treatment for perianal CD (Table 3), a single study using bone marrow cells is available^[55], and there is an 11-year experience of the Spanish group with MSCs taken from fat tissue (ASCs)^[53,54,56], initially autologous, except for a phase I / II trial using donor cells^[56]. We are currently waiting for completion of a phase III trial using donor cells which is planned to recruit a large patient sample. Two Korean studies using autologous ASCs have more recently been published. The first was carried out to evaluate the safety of the treatment^[57]. The second is a phase II study^[58]. A total of 43 patients were injected with ASCs. Among these, 33 were included in the modified per protocol analysis. The results showed complete sealing of 27 patients 8 wk after the final injection of

Table 2 Mesenchymal stem cell transplantation studies in luminal inflammatory bowel diseases

| Ref. | Patient (n) | Procedence | Follow up (d, mo or wk) | SAEs | Response/remission (number of patients, time of evaluation) | Recurrence (number of patients, time of evaluation) |
|--|----------------------|--------------------------------|-------------------------|----------------------------|---|---|
| Onken <i>et al</i> ^[45] | 10 CD (9 evaluable) | BM Allogenic | 28 d | No SAEs | Clinical 3/1 (28 d) | NA |
| Duijvestein <i>et al</i> ^[46] | 10 CD (9 evaluable) | BM Autologous | 14 wk | No SAEs | Clinical 3/0 (6 wk) Endoscopic 0/2 (6 wk) | NA |
| Liang <i>et al</i> ^[47] | 7 (4 CD/3UC) | BM/umbilical cord Allogenic | 19 mo (range 6-32) | No SAEs | Clinical 7/3 (12 wk) Endoscopic 3/0 (3-5 mo) | 1-3 |
| Osiris Therapeutics ^[48] | Estimated 330 CD | BM Allogenic | NA | NA | NA | NA |
| Forbes <i>et al</i> ^[49] | 16 CD (15 evaluable) | BM Allogenic | 42 d | 1 SAE probably not related | Clinical 12/8 (42 d) Endoscopic 7/0 (42 d) | NA |
| Lazebnik <i>et al</i> ^[50] | 39 UC 11 CD | BM Allogenic | 4-8 mo | NA | Clinical response UC 39/39 CD 11/11 | NA |

BM: Bone marrow; SAEs: Serious adverse events; NA: Not available; CD: Crohn’s disease; UC: Ulcerative colitis.

Table 3 Mesenchymal stem cell transplantation studies in perianal Crohn's disease

| Ref. | Patients (n) | Procedence | Follow up (mo) | SAEs related | Response/closure (number of patients or fistulas, time of evaluation) | Recurrence (number of patients, time of evaluation in months) |
|---|--|-----------------------|---------------------|---|---|---|
| García-Olmo <i>et al</i> ^[53] | 4 patients (8 fistulas) | Adipose Autologous | 22 mo (range 12-30) | No | 2/6 (2 mo) | NA |
| García-Olmo <i>et al</i> ^[54] | 49 (14 CD) 25 (7 CD) fibrin glue (group A) 24 (7CD) ASCs (group B) | Adipose Autologous | 12 mo | No | Group A: NA/1 (7 CD) Group B: 2/5 (7 CD) | 3/17 global recurrence in group B (12 mo) Data for CD NA |
| Ciccocioppo <i>et al</i> ^[55] | 10 | BM Autologous | 12 mo | No | 3/7 (12 mo) | 0/7 (12 mo) |
| de la Portilla <i>et al</i> ^[56] | 22 per protocol | Adipose Allogenic | 6 mo | 2 SAEs possibly related Pyrexia Abscess | Closure: 5/18 fistulas (6 mo) | NA |
| Cho <i>et al</i> ^[57] | 10 | Adipose Autologous | 6 mo | No SAEs | 1/3 (2 mo) | 0/3 (8 mo) |
| Lee <i>et al</i> ^[58] | 33 per protocol | Adipose Autologous | 12 mo | No SAEs | 5/27 (2 mo) Per protocol | 3/26 (12 mo) |

BM: Bone marrow; CD: Crohn’s disease; NA: Not available.

ASCs. No serious adverse effects were reported.

It is obvious that MSCs are a promising tool in the treatment of IBD. However, a large amount of work remains to be done to understand the mechanisms through which MSCs regulate the immune system, homeostasis and tissue repair. This knowledge will provide us with new tools to implement an effective MSCs-based treatment for IBD.

AMNIOTIC FLUID STEM CELLS

Amniotic fluid stem cells (AFSCs) are isolated from the excess of second-trimester amniotic fluid obtained during routine amniocentesis for prenatal diagnosis.

Recently, AFSCs were used in a neonatal rat model of necrotizing enterocolitis, one of the primary causes of morbidity and mortality in neonates, showed a decrease in intestinal damage, an increase in gut tissue repair and a higher survival^[59,60]. A better understanding of the AFSCs biology and mechanisms of action may help to develop strategies for their use in other IBD.

INDUCED PLURIPOTENT STEM CELLS

These are pluripotent cells derived from somatic cells by the introduction of reprogramming factors (Oct-4, Sox2, Klf4, c-Myc, Nanog and Lin28). These pluripotent cells can be differentiated to any

tissue specific cells to generate autologous cells for cell-replacement therapy^[61]. Human intestinal organoids have recently been generated from these cell lines^[62]. This will allow in the future for studying the pathophysiology of the disease and for testing new therapies, including generation of potentially viable tissues. Induced pluripotent stem cells (iPSCs) have been derived from somatic cells obtained from patients suffering a variety of diseases and important progress has been made in establishing preclinical iPSC-based disease models including IBD^[63]. Although iPSCs do not have the ethical problems of embryonic stem cells, there are many similarities between them and, as a consequence, iPSCs could develop teratomas following transplantation, hindering their use in clinical trials.

INTESTINAL STEM CELLS

Intestinal stem cells (ISCs) are a rare population of fast-cycling Lgr5⁺ cells and slow-cycling Tert⁺/Bmi1⁺ cells situated above them at the crypt base. ISCs are in charge of the renewal of the intestinal epithelium which is changed every 4-5 d and in the regeneration of the intestinal epithelium after injury or inflammation^[64]. It has been suggested that Lgr5⁺ cells and Tert⁺/Bmi1⁺ cells are two functionally different populations of ISCs^[65]. Lgr5⁺ cells are responsible for the maintenance of the normal homeostatis conditions, whereas Tert⁺/Bmi1⁺ cells are more quiescent cells responsible for the intestinal epithelium regeneration under injury or inflammation conditions^[66,67]. ISCs have proliferation and multipotency capabilities, *i.e.*, they are able to divide and later differentiate into all intestinal subtypes (enterocytes, goblet cells, Paneth cells and neuroendocrine cells). Recently, research in the ISCs field has advanced greatly and many ISC markers have been identified^[68]. However, an exhaustive characterization of ISCs as well as the identification of specific markers still remains elusive^[64].

Transplantation of fetal and adult ISCs expanded *in vitro* presented a strong engraftment and healing potential in a colonic injury model in mice^[69,70]. However, ISCs in culture maintained as single cells have a very limited use in the study of the development of IBD and as a method for drug screening. Recently, intestinal organoids have been obtained from adult mouse and human ISCs^[66,71,72]. These organoids were able to engraft and repair murine and human epithelium and represent an important step forward in the treatment of IBD^[73]. Human organoids will be a very useful tool to study the pathological mechanisms of the disease from a specific patient and to test which is the best treatment to repair the intestinal epithelium for that patient. These organoids will be an important way to reach a more personalized medicine for IBD. These results highlight that those intestinal stem cells are a very promising source of stem cells for future patient-specific regeneration of the digestive tract^[68].

ENDOTHELIAL PROGENITOR CELLS

Besides local inflammation, IBD is characterized by anomalous angiogenesis/vasculogenesis and severe damage in epithelial cells^[74]. Important results have been obtained using endothelial progenitor cells (EPCs) for the treatment of hindlimb ischemia and myocardial ischemia. Recently, EPCs transplantation into fetal sheep showed an efficient migration and homing within the mucosal layer and a contribution to the vasculogenesis of the intestine^[75]. These results suggest that EPCs could represent an additional source of cells for IBD cellular therapy, on their own or in combination with other stem cells such as MSCs.

TOLEROGENIC IMMUNE CELL THERAPIES

In inflammatory disorders, special interest has been given to therapeutic strategies that could enhance the patient's tolerance response to intraluminal antigens. T-regulatory cells (Tregs) suppress immune responses of other cells and maintain tolerance to self-antigens. Tregs can be generated *ex vivo* by activation of both, murine and human CD4 T cells, suggesting that they could be an extra source of cells for cellular therapies in IBD. Intraperitoneal injection of induced Tregs in a mouse model of chronic colitis showed an attenuation of the preexisting gut inflammation response^[76,77].

Dendritic cells (DCs) are antigen-presenting cells involved in immunity and tolerance. DCs seem to be the most important regulators of immune tolerance in the gastrointestinal system, however, extensive studies are necessary to understand their role in this tissue and their mechanisms of action^[78]. Like MSCs, tolerogenic-DCs (tol-DCs) do not express neither MHCII nor the T-cell co-stimulatory molecules, and will not activate an immune response in the host. *Ex vivo* generated tolerogenic-DCs are available as a clinical grade product and used as therapeutic vaccines to restore antigen-specific tolerance in autoimmune diseases^[78]. Tol-DCs have been used in very few recent clinical studies such as rheumatoid arthritis and other not inflammatory diseases, and as a result conclusions about their clinical efficiency are still elusive. Several mouse models of colitis showed an important effect of tol-DCs in the prevention and reduction of symptoms of IBD^[79-83]. However, several questions must be resolved before tol-DCs can be used in IBD cellular therapy in humans, mostly due to the differences in IBD and tol-DCs between mice and humans^[84].

CONCLUSION

The goal for stem cell-based therapy is to provide a permanent cure for IBD. To achieve this, it will be necessary to obtain a cellular product (original or genetically modified) that has a high migration and homes into the intestine, has high survival after

transplantation, regulates the immune reaction which is not detectable to the patient's immune system, and will repair the injured tissue. Intestinal tissue is composed of several cell types and IBD are characterized by widespread damage. Cell-based therapies will probably be designed as a combination of several cell types that will produce a synergic therapeutic response.

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