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

**de la Cal AIF *et al.* Stem cell in inflammatory bowel disease**

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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.

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**Key words:** Mesenchymal stem cell; Hematopoietic stem cell; Inflammatory bowel disease; Crohn’s disease; Ulcerative colitis; Amniotic fluid stem cells; Induced Pluripotent stem cells; Intestinal stem cells; Endothelial progenitor cells; Tolerogenic immune cell therapies

**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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**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 (GWAS) 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].**

***Hemapoietic stem cells transplantation***

**Use of hemapoietic 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 IL-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 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 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, Kfl4, 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 days 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 mutipotency capabilities, i.e. they are able to divide and later differentiate into all intestinal subtypes (enterocytes, globet cells, Paneth cells and neuroendocrine cells). Recently, research in the ISCs field has advanced greatly and many ISCs 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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**REFERENCES**

1 **Martínez-Montiel MP**, Muñoz-Yagüe MT. Biologic therapies for chronic inflammatory bowel disease. *Rev Esp Enferm Dig* 2006; **98**: 265-291 [PMID: 16792456]

2 **Neurath MF**, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut* 2012; **61**: 1619-1635 [PMID: 22842618]

3 **Tysk C**, Lindberg E, Järnerot G, Flodérus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. *Gut* 1988; **29**: 990-996 [PMID: 3396969]

4 **Orholm M**, Binder V, Sørensen TI, Rasmussen LP, Kyvik KO. Concordance of inflammatory bowel disease among Danish twins. Results of a nationwide study. *Scand J Gastroenterol* 2000; **35**: 1075-1081 [PMID: 11099061]

5 **Orholm M**, Munkholm P, Langholz E, Nielsen OH, Sørensen TI, Binder V. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991; **324**: 84-88 [PMID: 1984188]

6 **Peeters M**, Nevens H, Baert F, Hiele M, de Meyer AM, Vlietinck R, Rutgeerts P. Familial aggregation in Crohn's disease: increased age-adjusted risk and concordance in clinical characteristics. *Gastroenterology* 1996; **111**: 597-603 [PMID: 8780562]

7 **Roth MP**, Petersen GM, McElree C, Feldman E, Rotter JI. Geographic origins of Jewish patients with inflammatory bowel disease. *Gastroenterology* 1989; **97**: 900-904 [PMID: 2777043]

8 **Yang H**, McElree C, Roth MP, Shanahan F, Targan SR, Rotter JI. Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews. *Gut* 1993; **34**: 517-524 [PMID: 8491401]

9 **Jostins L**, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, Lee JC, Schumm LP, Sharma Y, Anderson CA, Essers J, Mitrovic M, Ning K, Cleynen I, Theatre E, Spain SL, Raychaudhuri S, Goyette P, Wei Z, Abraham C, Achkar JP, Ahmad T, Amininejad L, Ananthakrishnan AN, Andersen V, Andrews JM, Baidoo L, Balschun T, Bampton PA, Bitton A, Boucher G, Brand S, Büning C, Cohain A, Cichon S, D'Amato M, De Jong D, Devaney KL, Dubinsky M, Edwards C, Ellinghaus D, Ferguson LR, Franchimont D, Fransen K, Gearry R, Georges M, Gieger C, Glas J, Haritunians T, Hart A, Hawkey C, Hedl M, Hu X, Karlsen TH, Kupcinskas L, Kugathasan S, Latiano A, Laukens D, Lawrance IC, Lees CW, Louis E, Mahy G, Mansfield J, Morgan AR, Mowat C, Newman W, Palmieri O, Ponsioen CY, Potocnik U, Prescott NJ, Regueiro M, Rotter JI, Russell RK, Sanderson JD, Sans M, Satsangi J, Schreiber S, Simms LA, Sventoraityte J, Targan SR, Taylor KD, Tremelling M, Verspaget HW, De Vos M, Wijmenga C, Wilson DC, Winkelmann J, Xavier RJ, Zeissig S, Zhang B, Zhang CK, Zhao H, Silverberg MS, Annese V, Hakonarson H, Brant SR, Radford-Smith G, Mathew CG, Rioux JD, Schadt EE, Daly MJ, Franke A, Parkes M, Vermeire S, Barrett JC, Cho JH. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 2012; **491**: 119-124 [PMID: 23128233 DOI: 10.1038/nature11582]

10 **Fiocchi C**. Genes and 'in-vironment': how will our concepts on the pathophysiology of inflammatory bowel disease develop in the future? *Dig Dis* 2012; **30 Suppl 3**: 2-11 [PMID: 23295686 DOI: 10.1159/000342585]

11 **Franke A**, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, Lees CW, Balschun T, Lee J, Roberts R, Anderson CA, Bis JC, Bumpstead S, Ellinghaus D, Festen EM, Georges M, Green T, Haritunians T, Jostins L, Latiano A, Mathew CG, Montgomery GW, Prescott NJ, Raychaudhuri S, Rotter JI, Schumm P, Sharma Y, Simms LA, Taylor KD, Whiteman D, Wijmenga C, Baldassano RN, Barclay M, Bayless TM, Brand S, Büning C, Cohen A, Colombel JF, Cottone M, Stronati L, Denson T, De Vos M, D'Inca R, Dubinsky M, Edwards C, Florin T, Franchimont D, Gearry R, Glas J, Van Gossum A, Guthery SL, Halfvarson J, Verspaget HW, Hugot JP, Karban A, Laukens D, Lawrance I, Lemann M, Levine A, Libioulle C, Louis E, Mowat C, Newman W, Panés J, Phillips A, Proctor DD, Regueiro M, Russell R, Rutgeerts P, Sanderson J, Sans M, Seibold F, Steinhart AH, Stokkers PC, Torkvist L, Kullak-Ublick G, Wilson D, Walters T, Targan SR, Brant SR, Rioux JD, D'Amato M, Weersma RK, Kugathasan S, Griffiths AM, Mansfield JC, Vermeire S, Duerr RH, Silverberg MS, Satsangi J, Schreiber S, Cho JH, Annese V, Hakonarson H, Daly MJ, Parkes M. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet* 2010; **42**: 1118-1125 [PMID: 21102463 DOI: 10.1038/ng.717]

12 **Park JH**, Wacholder S, Gail MH, Peters U, Jacobs KB, Chanock SJ, Chatterjee N. Estimation of effect size distribution from genome-wide association studies and implications for future discoveries. *Nat Genet* 2010; **42**: 570-575 [PMID: 20562874 DOI: 10.1038/ng.610]

13 **Uhlig HH**. Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease. *Gut* 2013; **62**: 1795-1805 [PMID: 24203055 DOI: 10.1136/gutjnl-2012-303956]

14 **Cho JH**. The genetics and immunopathogenesis of inflammatory bowel disease. *Nat Rev Immunol* 2008; **8**: 458-466 [PMID: 18500230 DOI: 10.1038/nri2340]

15 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549 [PMID: 12047962 DOI: 10.1016/S0140-6736(02)08512-4]

16 **Colombel JF**, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132**: 52-65 [PMID: 17241859 DOI: 10.1053/j.gastro.2006.11.041]

17 **Sandborn WJ**, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, Bloomfield R, Schreiber S. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007; **357**: 228-238 [PMID: 17634458 DOI: 10.1056/NEJMoa067594]

18 **Schreiber S**, Khaliq-Kareemi M, Lawrance IC, Thomsen OØ, Hanauer SB, McColm J, Bloomfield R, Sandborn WJ. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007; **357**: 239-250 [PMID: 17634459 DOI: 10.1056/NEJMoa062897]

19 **Yanai H**, Hanauer SB. Assessing response and loss of response to biological therapies in IBD. *Am J Gastroenterol* 2011; **106**: 685-698 [PMID: 21427713 DOI: 10.1038/ajg.2011.103]

20 **Martínez-Montiel Mdel P**, Gómez-Gómez GJ, Flores AI. Therapy with stem cells in inflammatory bowel disease. *World J Gastroenterol* 2014; **20**: 1211-1227 [PMID: 24574796 DOI: 10.3748/wjg.v20.i5.1211]

21 **Clerici M**, Cassinotti A, Onida F, Trabattoni D, Annaloro C, Della Volpe A, Rainone V, Lissoni F, Duca P, Sampietro G, Fociani P, Vago G, Foschi D, Ardizzone S, Deliliers GL, Porro GB. Immunomodulatory effects of unselected haematopoietic stem cells autotransplantation in refractory Crohn's disease. *Dig Liver Dis* 2011; **43**: 946-952 [PMID: 21907652 DOI: 10.1016/j.dld.2011.07.021]

22 **García-Bosch O**, Ricart E, Panés J. Review article: stem cell therapies for inflammatory bowel disease - efficacy and safety. *Aliment Pharmacol Ther* 2010; **32**: 939-952 [PMID: 20804451 DOI: 10.1111/j.1365-2036.2010.04439.x]

23 **van Deen WK**, Oikonomopoulos A, Hommes DW. Stem cell therapy in inflammatory bowel disease: which, when and how? *Curr Opin Gastroenterol* 2013; **29**: 384-390 [PMID: 23666365 DOI: 10.1097/MOG.0b013e328361f763]

24 **Oyama Y**, Craig RM, Traynor AE, Quigley K, Statkute L, Halverson A, Brush M, Verda L, Kowalska B, Krosnjar N, Kletzel M, Whitington PF, Burt RK. Autologous hematopoietic stem cell transplantation in patients with refractory Crohn's disease. *Gastroenterology* 2005; **128**: 552-563 [PMID: 15765390 DOI: 10.1053/j.gastro.2004.11.051]

25 **Burt RK**, Craig RM, Milanetti F, Quigley K, Gozdziak P, Bucha J, Testori A, Halverson A, Verda L, de Villiers WJ, Jovanovic B, Oyama Y. Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with severe anti-TNF refractory Crohn disease: long-term follow-up. *Blood* 2010; **116**: 6123-6132 [PMID: 20837778 DOI: 10.1182/blood-2010-06-292391]

26 **Cassinotti A,** Annaloro C, Sampietro G, Fociani P, Fichera1 M, Maconi1 G, M. Lombardini1, Bezzio1 C, Foschi D, Lambertenghi Deliliers G, Bianchi Porro1 G, De Franchis1 R, Ardizzone S. Autologous haematopoietic stem cell transplantation without CD34 cell selection for refractory Crohn’s disease: The Milan experience after 5 years. *J Crohns Colitis* 2012; **6:** S153-S154 [DOI: 10.1016/S1873-9946(12)60381-X]

27 **Hasselblatt P**, Drognitz K, Potthoff K, Bertz H, Kruis W, Schmidt C, Stallmach A, Schmitt-Graeff A, Finke J, Kreisel W. Remission of refractory Crohn's disease by high-dose cyclophosphamide and autologous peripheral blood stem cell transplantation. *Aliment Pharmacol Ther* 2012; **36**: 725-735 [PMID: 22937722 DOI: 10.1111/apt.12032]

28 **Hawkey C**, Allez M, Ardizzone S, Clark M, Clark L, Colombel J-F, Danese S, Farge-Bancel D, Labopin M, Lindsay J, Norman A, Onida F, Ricart E, Rogler G, RoviraM, Russell N, Satsangi J, Travis S, Tyndall A, VermeireS. Clinical and endocopic improvement following hemopoietic stem cell transplantation in the ASTIC trial. *J Crohns Colitis* 2013; **7**: S4 [DOI: 10.1016/S1873-9946(13)60010-0]

29 **Jauregui-Amezaga A**, Rovira M, Pin´o Donnay S, Marín PJ, Feu F, Elizalde JI, Fernández-Avilés F, Martínez C, Rosiñol L, Suarez-Lledó M, Masamunt MC, Ramírez-Morros A, Gallego M, Ordás I, Panés J, Ricart E. Hematopoietic stem cell transplantation in refractory Crohn’s disease: Feasibility and toxicity. *J Crohns Coliti* 2014; **8**: S263 [DOI: 10.1016/S1873-9946(14)60591-2]

30 **Vegh I**, Grau M, Gracia M, Grande J, de la Torre P, Flores AI. Decidua mesenchymal stem cells migrated toward mammary tumors in vitro and in vivo affecting tumor growth and tumor development. *Cancer Gene Ther* 2013; **20**: 8-16 [PMID: 23037810 DOI: 10.1038/cgt.2012.71]

31 **Griffin MD**, Elliman SJ, Cahill E, English K, Ceredig R, Ritter T. Concise review: adult mesenchymal stromal cell therapy for inflammatory diseases: how well are we joining the dots? *Stem Cells* 2013; **31**: 2033-2041 [PMID: 23766124 DOI: 10.1002/stem.1452]

32 **Macias MI**, Grande J, Moreno A, Domínguez I, Bornstein R, Flores AI. Isolation and characterization of true mesenchymal stem cells derived from human term decidua capable of multilineage differentiation into all 3 embryonic layers. *Am J Obstet Gynecol* 2010; **203**: 495.e9-495.e23 [PMID: 20692642 DOI: 10.1016/j.ajog.2010.06.045]

33 **Parolini O**, Alviano F, Bagnara GP, Bilic G, Bühring HJ, Evangelista M, Hennerbichler S, Liu B, Magatti M, Mao N, Miki T, Marongiu F, Nakajima H, Nikaido T, Portmann-Lanz CB, Sankar V, Soncini M, Stadler G, Surbek D, Takahashi TA, Redl H, Sakuragawa N, Wolbank S, Zeisberger S, Zisch A, Strom SC. Concise review: isolation and characterization of cells from human term placenta: outcome of the first international Workshop on Placenta Derived Stem Cells. *Stem Cells* 2008; **26**: 300-311 [PMID: 17975221]

34 **Haddad R**, Saldanha-Araujo F. Mechanisms of T-cell immunosuppression by mesenchymal stromal cells: what do we know so far? *Biomed Res Int* 2014; **2014**: 216806 [PMID: 25025040]

35 **Bornstein R**, Macias MI, de la Torre P, Grande J, Flores AI. Human decidua-derived mesenchymal stromal cells differentiate into hepatic-like cells and form functional three-dimensional structures. *Cytotherapy* 2012; **14**: 1182-1192 [PMID: 22900961 DOI: 10.3109/14653249.2012.706706]

36 **Rubio D**, Garcia-Castro J, Martín MC, de la Fuente R, Cigudosa JC, Lloyd AC, Bernad A. Spontaneous human adult stem cell transformation. *Cancer Res* 2005; **65**: 3035-3039 [PMID: 15833829]

37 **Røsland GV**, Svendsen A, Torsvik A, Sobala E, McCormack E, Immervoll H, Mysliwietz J, Tonn JC, Goldbrunner R, Lønning PE, Bjerkvig R, Schichor C. Long-term cultures of bone marrow-derived human mesenchymal stem cells frequently undergo spontaneous malignant transformation. *Cancer Res* 2009; **69**: 5331-5339 [PMID: 19509230 DOI: 10.1158/0008-5472.CAN-08-4630]

38 **Tarte K**, Gaillard J, Lataillade JJ, Fouillard L, Becker M, Mossafa H, Tchirkov A, Rouard H, Henry C, Splingard M, Dulong J, Monnier D, Gourmelon P, Gorin NC, Sensebé L. Clinical-grade production of human mesenchymal stromal cells: occurrence of aneuploidy without transformation. *Blood* 2010; **115**: 1549-1553 [PMID: 20032501 DOI: 10.1182/blood-2009-05-219907]

39 **Bernardo ME**, Zaffaroni N, Novara F, Cometa AM, Avanzini MA, Moretta A, Montagna D, Maccario R, Villa R, Daidone MG, Zuffardi O, Locatelli F. Human bone marrow derived mesenchymal stem cells do not undergo transformation after long-term in vitro culture and do not exhibit telomere maintenance mechanisms. *Cancer Res* 2007; **67**: 9142-9149 [PMID: 17909019]

40 **Zhang J**, Gong JF, Zhang W, Zhu WM, Li JS. Effects of transplanted bone marrow mesenchymal stem cells on the irradiated intestine of mice. *J Biomed Sci* 2008; **15**: 585-594 [PMID: 18763056 DOI: 10.1007/s11373-008-9256-9]

41 **Ko IK**, Kim BG, Awadallah A, Mikulan J, Lin P, Letterio JJ, Dennis JE. Targeting improves MSC treatment of inflammatory bowel disease. *Mol Ther* 2010; **18**: 1365-1372 [PMID: 20389289 DOI: 10.1038/mt.2010.54]

42 **Colletti E**, El Shabrawy D, Soland M, Yamagami T, Mokhtari S, Osborne C, Schlauch K, Zanjani ED, Porada CD, Almeida-Porada G. EphB2 isolates a human marrow stromal cell subpopulation with enhanced ability to contribute to the resident intestinal cellular pool. *FASEB J* 2013; **27**: 2111-2121 [PMID: 23413357]

43 **Chen QQ**, Yan L, Wang CZ, Wang WH, Shi H, Su BB, Zeng QH, Du HT, Wan J. Mesenchymal stem cells alleviate TNBS-induced colitis by modulating inflammatory and autoimmune responses. *World J Gastroenterol* 2013; **19**: 4702-4717 [PMID: 23922467 DOI: 10.3748/wjg.v19.i29.4702]

44 **Linard C**, Busson E, Holler V, Strup-Perrot C, Lacave-Lapalun JV, Lhomme B, Prat M, Devauchelle P, Sabourin JC, Simon JM, Bonneau M, Lataillade JJ, Benderitter M. Repeated autologous bone marrow-derived mesenchymal stem cell injections improve radiation-induced proctitis in pigs. *Stem Cells Transl Med* 2013; **2**: 916-927 [PMID: 24068742]

45 **Onken J**, Gallup D, Hanson J, Pandak M, Custer L. Sucessful outpatient treatment of refractory Cron’s disease using adult mesenchymal stem cells. American College of Gastroenterology Annual Meeting. Las Vegas, 2006. Available from: URL: http: //universe.gi.org/contentitem.asp?c=1047

46 **Duijvestein M**, Vos AC, Roelofs H, Wildenberg ME, Wendrich BB, Verspaget HW, Kooy-Winkelaar EM, Koning F, Zwaginga JJ, Fidder HH, Verhaar AP, Fibbe WE, van den Brink GR, Hommes DW. Autologous bone marrow-derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: results of a phase I study. *Gut* 2010; **59**: 1662-1669 [PMID: 20921206 DOI: 10.1136/gut.2010.215152]

47 **Liang J**, Zhang H, Wang D, Feng X, Wang H, Hua B, Liu B, Sun L. Allogeneic mesenchymal stem cell transplantation in seven patients with refractory inflammatory bowel disease. *Gut* 2012; **61**: 468-469 [PMID: 21617158 DOI: 10.1136/gutjnl-2011-300083]

48 **Osiris Therapeutics**. A phase III, multicenter, placebo-controlled, randomized, double-blind study to evaluate the safety and efficacy of Prochimaltm (ex vivo cultured adult human mesenchymal stem cells) intravenous infusion for induction of remission in subjects experiencing treatment-refractory moderate-to-severe Crohn’s disease. ClinicalTrials. Gov2010, NCTO0482092. Available from: http: //www.clinicaltrials.gov/ct2/show/NCT00482092

49 **Forbes GM**, Sturm MJ, Leong RW, Sparrow MP, Segarajasingam D, Cummins AG, Phillips M, Herrmann RP. A phase 2 study of allogeneic mesenchymal stromal cells for luminal Crohn's disease refractory to biologic therapy. *Clin Gastroenterol Hepatol* 2014; **12**: 64-71 [PMID: 23872668 DOI: 10.1016/j.cgh.2013.06.021]

50 **Lazebnik LB**, Konopliannikov AG, Kniazev OV, Parfenov AI, Tsaregorodtseva TM, Ruchkina IN, Khomeriki SG, Rogozina VA, Konopliannikova OA. [Use of allogeneic mesenchymal stem cells in the treatment of intestinal inflammatory diseases]. *Ter Arkh* 2010; **82**: 38-43 [PMID: 20387674]

51 **Kniazev OV**, Parfenov AI, Ruchkina IN, Lazebnik LB, Sagynbaeva VÉ. [Immune response to biological therapy of inflammatory bowel diseases]. *Ter Arkh* 2013; **85**: 55-59 [PMID: 24640669]

52 **Knyazev O**, Ruchkina I, Konoplyannikov A, Schakhpazyan3 N, Parfenov A. The elimination of cytomegalovirus in patients with ulcerative colitis without antiviral therapy. *J Crohns Colitis* 2014; **8:** S202-S203 [DOI: 10.1016/S1873-9946(14)60451-7]

53 **García-Olmo D**, García-Arranz M, Herreros D, Pascual I, Peiro C, Rodríguez-Montes JA. A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. *Dis Colon Rectum* 2005; **48**: 1416-1423 [PMID: 15933795 DOI: 10.1007/s10350-005-0052-6]

54 **Garcia-Olmo D**, Herreros D, Pascual I, Pascual JA, Del-Valle E, Zorrilla J, De-La-Quintana P, Garcia-Arranz M, Pascual M. Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial. *Dis Colon Rectum* 2009; **52**: 79-86 [PMID: 19273960 DOI: 10.1007/DCR.0b013e3181973487]

55 **Ciccocioppo R**, Bernardo ME, Sgarella A, Maccario R, Avanzini MA, Ubezio C, Minelli A, Alvisi C, Vanoli A, Calliada F, Dionigi P, Perotti C, Locatelli F, Corazza GR. Autologous bone marrow-derived mesenchymal stromal cells in the treatment of fistulising Crohn's disease. *Gut* 2011; **60**: 788-798 [PMID: 21257987 DOI: 10.1136/gut.2010.214841]

56 **de la Portilla F**, Alba F, García-Olmo D, Herrerías JM, González FX, Galindo A. Expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of complex perianal fistula in Crohn's disease: results from a multicenter phase I/IIa clinical trial. *Int J Colorectal Dis* 2013; **28**: 313-323 [PMID: 23053677 DOI: 10.1007/s00384-012-1581-9]

57 **Cho YB**, Lee WY, Park KJ, Kim M, Yoo HW, Yu CS. Autologous adipose tissue-derived stem cells for the treatment of Crohn's fistula: a phase I clinical study. *Cell Transplant* 2013; **22**: 279-285 [PMID: 23006344 DOI: 10.3727/096368912X656045]

58 **Lee WY**, Park KJ, Cho YB, Yoon SN, Song KH, Kim do S, Jung SH, Kim M, Yoo HW, Kim I, Ha H, Yu CS. Autologous adipose tissue-derived stem cells treatment demonstrated favorable and sustainable therapeutic effect for Crohn's fistula. *Stem Cells* 2013; **31**: 2575-2581 [PMID: 23404825 DOI: 10.1002/stem.1357]

59 **Zani A**, Cananzi M, Lauriti G, Fascetti-Leon F, Wells J, Siow B, Lythgoe MF, Pierro A, Eaton S, De Coppi P. Amniotic fluid stem cells prevent development of ascites in a neonatal rat model of necrotizing enterocolitis. *Eur J Pediatr Surg* 2014; **24**: 57-60 [PMID: 23852724 DOI: 10.1055/s-0033-1350059]

60 **Zani A**, Cananzi M, Fascetti-Leon F, Lauriti G, Smith VV, Bollini S, Ghionzoli M, D'Arrigo A, Pozzobon M, Piccoli M, Hicks A, Wells J, Siow B, Sebire NJ, Bishop C, Leon A, Atala A, Lythgoe MF, Pierro A, Eaton S, De Coppi P. Amniotic fluid stem cells improve survival and enhance repair of damaged intestine in necrotising enterocolitis via a COX-2 dependent mechanism. *Gut* 2014; **63**: 300-309 [PMID: 23525603 DOI: 10.1136/gutjnl-2012-303735]

61 **Wu SM**, Hochedlinger K. Harnessing the potential of induced pluripotent stem cells for regenerative medicine. *Nat Cell Biol* 2011; **13**: 497-505 [PMID: 21540845 DOI: 10.1038/ncb0511-497]

62 [**Watson CL**](http://www.ncbi.nlm.nih.gov/pubmed?term=Watson%20CL%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Mahe MM](http://www.ncbi.nlm.nih.gov/pubmed?term=Mahe%20MM%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Múnera J](http://www.ncbi.nlm.nih.gov/pubmed?term=M%C3%BAnera%20J%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Howell JC](http://www.ncbi.nlm.nih.gov/pubmed?term=Howell%20JC%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Sundaram N](http://www.ncbi.nlm.nih.gov/pubmed?term=Sundaram%20N%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Poling HM](http://www.ncbi.nlm.nih.gov/pubmed?term=Poling%20HM%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Schweitzer JI](http://www.ncbi.nlm.nih.gov/pubmed?term=Schweitzer%20JI%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Vallance JE](http://www.ncbi.nlm.nih.gov/pubmed?term=Vallance%20JE%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Mayhew CN](http://www.ncbi.nlm.nih.gov/pubmed?term=Mayhew%20CN%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Sun Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Sun%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Grabowski G](http://www.ncbi.nlm.nih.gov/pubmed?term=Grabowski%20G%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Finkbeiner SR](http://www.ncbi.nlm.nih.gov/pubmed?term=Finkbeiner%20SR%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Spence JR](http://www.ncbi.nlm.nih.gov/pubmed?term=Spence%20JR%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Shroyer NF](http://www.ncbi.nlm.nih.gov/pubmed?term=Shroyer%20NF%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Wells JM](http://www.ncbi.nlm.nih.gov/pubmed?term=Wells%20JM%5BAuthor%5D&cauthor=true&cauthor_uid=25326803), [Helmrath MA](http://www.ncbi.nlm.nih.gov/pubmed?term=Helmrath%20MA%5BAuthor%5D&cauthor=true&cauthor_uid=25326803). An in vivo model of human small intestine using pluripotent stem cells. *Nat Med* 2014 [PMID: 25326803 DOI: 10.1038/nm.3737]

63 **Wagnerova A**, Gardlik R. In vivo reprogramming in inflammatory bowel disease. *Gene Ther* 2013; **20**: 1111-1118 [PMID: 24025994 DOI: 10.1038/gt.2013.43]

64 **Moossavi S**, Zhang H, Sun J, Rezaei N. Host-microbiota interaction and intestinal stem cells in chronic inflammation and colorectal cancer. *Expert Rev Clin Immunol* 2013; **9**: 409-422 [PMID: 23634736 DOI: 10.1586/eci.13.27]

65 **Yan KS**, Chia LA, Li X, Ootani A, Su J, Lee JY, Su N, Luo Y, Heilshorn SC, Amieva MR, Sangiorgi E, Capecchi MR, Kuo CJ. The intestinal stem cell markers Bmi1 and Lgr5 identify two functionally distinct populations. *Proc Natl Acad Sci U S A* 2012; **109**: 466-471 [PMID: 22190486 DOI: 10.1073/pnas.1118857109]

66 **Basak O**, van de Born M, Korving J, Beumer J, van der Elst S, van Es JH, Clevers H. Mapping early fate determination in Lgr5+ crypt stem cells using a novel Ki67-RFP allele. *EMBO J* 2014; **33**: 2057-2068 [PMID: 25092767]

67 **Philpott A**, Winton DJ. Lineage selection and plasticity in the intestinal crypt. *Curr Opin Cell Biol* 2014; **31C**: 39-45 [PMID: 25083805 DOI: 10.1016/j.ceb.2014.07.002]

68 **Mohamed MS**, Chen Y, Yao CL. Intestinal stem cells and stem cell-based therapy for intestinal diseases. *Cytotechnology* 2014 [PMID: 24981313]

69 **Yui S**, Nakamura T, Sato T, Nemoto Y, Mizutani T, Zheng X, Ichinose S, Nagaishi T, Okamoto R, Tsuchiya K, Clevers H, Watanabe M. Functional engraftment of colon epithelium expanded in vitro from a single adult Lgr5⁺ stem cell. *Nat Med* 2012; **18**: 618-623 [PMID: 22406745 DOI: 10.1038/nm.2695]

70 **Fordham RP**, Yui S, Hannan NR, Soendergaard C, Madgwick A, Schweiger PJ, Nielsen OH, Vallier L, Pedersen RA, Nakamura T, Watanabe M, Jensen KB. Transplantation of expanded fetal intestinal progenitors contributes to colon regeneration after injury. *Cell Stem Cell* 2013; **13**: 734-744 [PMID: 24139758 DOI: 10.1016/j.stem.2013.09.015]

71 **Kuratnik A**, Giardina C. Intestinal organoids as tissue surrogates for toxicological and pharmacological studies. *Biochem Pharmacol* 2013; **85**: 1721-1726 [PMID: 23623789 DOI: 10.1016/j.bcp.2013.04.016]

72 **Sato T**, Vries RG, Snippert HJ, van de Wetering M, Barker N, Stange DE, van Es JH, Abo A, Kujala P, Peters PJ, Clevers H. Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. *Nature* 2009; **459**: 262-265 [PMID: 19329995 DOI: 10.1038/nature07935]

73 **Belchior GG**, Sogayar MC, Grikscheit TC. Stem cells and biopharmaceuticals: vital roles in the growth of tissue-engineered small intestine. *Semin Pediatr Surg* 2014; **23**: 141-149 [PMID: 24994528 DOI: 10.1053/j.sempedsurg.2014.06.011]

74 **Costa C**, Incio J, Soares R. Angiogenesis and chronic inflammation: cause or consequence? *Angiogenesis* 2007; **10**: 149-166 [PMID: 17457680]

75 **Wood JA**, Colletti E, Mead LE, Ingram D, Porada CD, Zanjani ED, Yoder MC, Almeida-Porada G. Distinct contribution of human cord blood-derived endothelial colony forming cells to liver and gut in a fetal sheep model. *Hepatology* 2012; **56**: 1086-1096 [PMID: 22488442 DOI: 10.1002/hep.25753]

76 **Foussat A**, Cottrez F, Brun V, Fournier N, Breittmayer JP, Groux H. A comparative study between T regulatory type 1 and CD4+CD25+ T cells in the control of inflammation. *J Immunol* 2003; **171**: 5018-5026 [PMID: 14607898]

77 **Karlsson F**, Martinez NE, Gray L, Zhang S, Tsunoda I, Grisham MB. Therapeutic evaluation of ex vivo-generated versus natural regulatory T-cells in a mouse model of chronic gut inflammation. *Inflamm Bowel Dis* 2013; **19**: 2282-2294 [PMID: 23893082 DOI: 10.1097/MIB.0b013e31829c32dd]

78 **Cabezón R**, Benítez-Ribas D. Therapeutic potential of tolerogenic dendritic cells in IBD: from animal models to clinical application. *Clin Dev Immunol* 2013; **2013**: 789814 [PMID: 24319468 DOI: 10.1155/2013/789814]

79 **Pedersen AE**, Schmidt EG, Gad M, Poulsen SS, Claesson MH. Dexamethasone/1alpha-25-dihydroxyvitamin D3-treated dendritic cells suppress colitis in the SCID T-cell transfer model. *Immunology* 2009; **127**: 354-364 [PMID: 19019085 DOI: 10.1111/j.1365-2567.2008.02996.x]

80 **Pedersen AE**, Gad M, Kristensen NN, Haase C, Nielsen CH, Claesson MH. Tolerogenic dendritic cells pulsed with enterobacterial extract suppress development of colitis in the severe combined immunodeficiency transfer model. *Immunology* 2007; **121**: 526-532 [PMID: 17428312]

81 **Yamanishi H**, Murakami H, Ikeda Y, Abe M, Kumagi T, Hiasa Y, Matsuura B, Onji M. Regulatory dendritic cells pulsed with carbonic anhydrase I protect mice from colitis induced by CD4+CD25- T cells. *J Immunol* 2012; **188**: 2164-2172 [PMID: 22291189 DOI: 10.4049/jimmunol.1100559]

82 **Gonzalez-Rey E**, Delgado M. Therapeutic treatment of experimental colitis with regulatory dendritic cells generated with vasoactive intestinal peptide. *Gastroenterology* 2006; **131**: 1799-1811 [PMID: 17087944]

83 **Sakuraba A**, Sato T, Kamada N, Kitazume M, Sugita A, Hibi T. Th1/Th17 immune response is induced by mesenteric lymph node dendritic cells in Crohn's disease. *Gastroenterology* 2009; **137**: 1736-1745 [PMID: 19632232 DOI: 10.1053/j.gastro.2009.07.049]

84 **Neurath MF**. Animal models of inflammatory bowel diseases: illuminating the pathogenesis of colitis, ileitis and cancer. *Dig Dis* 2012; **30 Suppl 1**: 91-94 [PMID: 23075875 DOI: 10.1159/000341131]

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**Table 1 Autologus Hemapoietic stem cells transplantation studies in Crohn´s disease**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | Patients (***n***) | **Follow up** (mo) | **Deaths** | **Remision**(number of patients, time of evaluation in months) | **Recurrence**(number of patients or %, time of evaluation in months) |
| Oyama *et al*[24] 2005 | 12 | 18,5 mo (7-37) | No | Clinical11 (12 mo) | 1 (18.5 mo) |
| Burt *et al*[25] 2010 | 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 *et al*[26] 2012 | 10 | 56 mo (23-68) | No | Clinical10 (3 mo)Endoscopic 5 (3 mo) | 20% (12 mo)50% (24 mo)60% (36 mo)70% (48 mo)70% (60 mo) |
| HasselblatT *et al*[27] 2012 | 12 | 37 mo (IQR 6-123) | No | Clinical 4/8 (6 mo)Endoscopic5/9 (9.1 mo)3/9 mild disease | 7 (10.9 mo) |
| Astic[28]2012 | Data from 30 out of 45 patients16 mobilisation + HCST (A)16 mobilisation (B) |  | 1 Death after HCST | NAA: CDAI fell 162 (IQR 0-190)B: CDAI fell 82 (IQR 41-137) | NA |
| Jáuregui-Amenazaga *et al*[29] 2014 | 21 evaluable | 12 mo | 1 after CMV infection and multiorganic failure  | NA | NA |

NA: Not available; SAEs: Severe adverse events; CDAI: Crohn´s disease activity index; IQR: Intercuartile range; CMV: Cytomegalovirus.

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

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ref. | Patient (*n*) | Procedence | Follow up(days, months or weeks) | SAEs | Response/remision (number of patients, time of evaluation) | Recurrence(number of patients, time of evaluation) |
| Onken *et al*[45] 2006 | 10 CD (9 evaluable) | BMAllogenic | 28 d | No SAES | Clinical3/1 (28 d) | NA |
| Duijvestein *et al*[46] 2010 | 10 CD (9 evaluable) | BMAutologous | 14 wk | No SAEs  | Clinical3/0 (6 wk)Endoscopic0/2 (6 wk) | NA |
| Liang *et al*[47] 2012 | 7 (4 CD/3UC) | BM/Umbilical cordAllogenic | 19 mo (range 6-32) | No SAEs | Clinical7/3 (12 wk)Endoscopic3/0 (3-5 mo) | 1/3  |
| Osiris[48] 2007 | Estimated 330 CD | BMAllogenic | NA | NA | NA | NA |
| Forbes *et al*[49] 2014 | 16 CD (15 evaluable) | BMAllogenic | 42 d | 1 SAE probably not related | Clinical12/8 (42 d)Endoscopic7/0 (42 d) | NA |
| Lazebnik *et al*[50]2010 | 39 UC11 CD | BMAllogenic | 4-8 mo | NA | Clinical reponseUC 39/39CD 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) |
| Garcia Olmo *et al*[53] 2005 | 4 patients(8 fistulas) | AdiposeAutologus | 22 mo (range 12-30) | No  | 2/6 (2 mo) |  NA |
| Garcia Olmo *et al*[54] 2009 | 49 (14 CD)25 (7 CD) fibrin glue (group A)24 (7CD) ASCs (group B) | AdiposeAutologous | 12 mo | No  | Group A: NA/1 (7 CD)Group B2/5 (7 CD) | 3/17 global recurrence in group B (12 mo)Data for CD NA |
| Ciccocioppo *et al*[55] 2011 | 10 | BMAutologous | 12 mo | No  | 3/7 (12 mo) | 0/7 (12 mo) |
| De la Portilla *et al*[56] 2013 |  22 Per protocol | AdiposeAllogenic |  6 mo | 2 SAEs possibly related- Pyerxia- abscess | Closure:5/18 fistulas (6 mo) | NA |
| Cho *et al*[57] 2013  | 10 | AdiposeAutologous | 6 mo | No SAEs | 1/3 (2 mo) | 0/3 (8 mo) |
| Lee *et al*[58] 2013 | 33Per protocol | AdiposeAutologous | 12 mo | No SAEs | 5/27 (2 mo)Per protocol  |  3/26 (12 mo) |

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