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Role of Autologous Bone Marrow Stem Cell Transplantation in the Treatment of Active Ulcerative Colitis

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Abstract

Background: Stem cell therapy was suggested to improve the quality of life to patients of UC through its powerful immunomodulatory effects and its ability to stimulate regeneration of intestinal mucosa.

Aim of the work: To evaluate autologous bone marrow stem cells transplantation as a treatment option for cases of active ulcerative colitis in comparison with the conventional treatment, and to evaluate its safety and feasibility.

Patients and methods: 10 patients of active ulcerative colitis were intravenously injected with autologous bone marrow mononuclear layer containing stem cell and continued on their conventional treatment. Clinical, laboratory and endoscopic assessment of disease severity were done before and after 3 months after SCT.

Results: There was statistically significant improvement in the number of diarrheal motions, heart rate, ESR, CRP, disease extent and severity after SCT with p value0.026, 0.009, 0.006, 0.012, 0.038 respectively with no recorded side effects or complications.

Conclusion: Bone marrow stem Cell transplantation for patients of ulcerative colitis is a safe and feasible procedure. It can improve the quality of life of the patients as well as the disease activity assessed by clinical assessment, laboratory tests, endoscopic extent and severity.

Keywords: Ulcerative colitis; IBD; Autologous; Bone marrow stem cells; Transplantation

Abbreviations: 5-ASA: 5 Amino Salicylic Acid; AZA: Azathioprine; BM: Bone Marrow; BMA: Bone Marrow Aspirate; BMI: Body Mass Index; CDAI: Crohn's Disease Activity Index; COX-2: Cyclooxygenase 2; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate GMSCs: Gingiva-derived Mesenchymal Stem Cells; GVHD: Graft-Versus-Host Disease; IBD: Inflammatory Bowel Disease; IFN-γ: Interferon γ; IL-10: Interleukin 10

Introduction

Ulcerative colitis is a chronic disease leading to diffuse mucosal inflammation of the colon, characterized by a relapsing & remitting course [1]. It is a lifelong disease arising from an interaction between genetic and environmental factors. It is characterized by a deregulated mucosal immune response to luminal antigens that leads to chronic inflammation of the intestine [2]. The precise etiology is unknown and therefore medical therapy to cure the disease is not yet available [3]. There is evidence that in addition to genetic susceptibility and environmental stimuli, abnormal T-cell responses and overwhelming secretion of pro-inflammatory mediators disturb the homeostatic defenses of the gut, resulting in epithelial injuries [2].

Currently, therapy is most often implemented in a stepwise fashion, progressing through amino salicylates, corticosteroids, immunosuppressive medications including ciclosporin, tacrolimus, and finally biological therapy [4]. They attempt to modulate the immune processes to induce remissions of active disease, maintain remission, and prevent relapse [2].

Primary and secondary failure to respond to approved therapies and, in some cases, inability to provide a surgical solution to a particular patient due to extension and/or location of lesions represents unmet needs in the treatment of IBD [5].

A novel and exciting approach could be offered through the current development in the field of stem cell biology [6]. This is due to thebiological properties of these cells and their capacity to self-renew and regenerate tissue and organ systems beside the immunomodulatory ability of stem cell therapy [5].

This has led to the concept of regenerative medicine, which is based on their potential for therapies aimed to facilitate the repair of degenerating or injured tissues [7].

SCs can be obtained from various sources, including embryos, fetal tissues, umbilical cord blood, and also terminally differentiated organs. Once isolated, these cells may be forced - *ex vivo* or *in vivo* - to expand and differentiate into functional progenies suitable for cell replacement and tissue engineering [8].

Recent progress in cell biology resulting in the isolation and characterization of bone marrow SCs and progenitor cells further increases the expectation for a new approach to the treatment of genetic and chronic diseases [9].

There are at least two types of SCs in the human BM; mesenchymal SCs, and hematopoietic SCs. HSC are continuously moving between the bone marrow and peripheral blood. This movement is critical for hematopoietic homeostasis and is hypothesized to contribute to homeostasis and tissue repair [10].

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SC-based therapies could be used to cure inherited or genetic degenerative alterations associated with the loss of adult SC functions, such as cancers, immune system and hematopoietic disorders, cardiovascular, muscular and neurological diseases, gastrointestinal pathologies, diabetes and chronic hepatopathies [8].

Medical researches reflect that SCT has made improvement in the quality of life to patients of UC. The mechanism for the effect isn't clear but it interpreted through the powerful immunomodulatory effects of SCs and its ability to stimulate regeneration of intestinal mucosa. This study was designed to evaluate the autologous bone marrow stem cells intravascular injection as a treatment option for cases of active ulcerative colitis in comparison with the conventional treatment, and to evaluate its safety and feasibility.

Patients and Methods

This study was conducted on 10 patients with confirmed diagnose of ulcerative colitis. Cases were collected from Internal Medicine, Tropical departments and outpatient clinics of Ain Shams University, Electricity Hospitals and Nasser Institute, during the period from April 2013 till March 2014.

Inclusion criteria

Adult subjects diagnosed as ulcerative colitis patients clinically, by the characteristic endoscopic features and confirmed by biopsy.

Exclusion criteria

Patients with other inflammatory diseases rather than UC, patients with any malignancies or blood diseases, patients with other autoimmune diseases or with any other system affection.

All patients were subjected to following:

1. Written consents were obtained from all patients after detailed explanation of the procedure and its suspected benefits and possible risks. The study was approved by the ethical committee of Ain Shams University.
2. Clinical assessment including complete history taking, thorough medical examination and nutritional status evaluation with the calculation of BMI.
3. Investigations including: hemoglobin level, ESR, CRP, total proteins and serum albumin.
4. Colonoscopy with assessment of the extent of the disease according to the Montreal classification of UC [1].
5. Endoscopic and clinical activity assessment and scoring was done according to Mayo Endoscopic Scoring of Ulcerative Colitis Table 1a and b [11].

Stem cells transplantation

Stem cells transplantation was done in Nozha International Hospital. All steps were performed withincomplete sterile fieldas follow: Preparation and characterization of BMSC in accordance with the faculty ethical regulations and after obtaining patients' informed consent, the procedure of harvesting bone marrow for re-administration of selected cells was performed in a closed system. Autologous bone marrow aspirated from the posterior iliac crest was drawn in heparin-coated syringes after the induction of anesthesia. The procedure is complete after 120 ml of bone marrow has been aspirated from four penetrations of the left ileum and four penetrations of the right ileum. Then the concentration procedure by Harvest centrifuge

Extent		Anatomy
E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC	Involvement extends proximal to the splenic flexure

Table 1a: Montreal classification of extent of ulcerative colitis (UC).

Mayo index	0	1	2	3
Stool frequency	Normal	1-2/day > normal	3-4/day > normal	5/day > normal
Rectal bleeding	None	Obvious	Streaks	Mostly blood
Mucosa	Normal	Mild friability	Moderate friability	Spontaneous bleeding
Global assessment	Normal	Mild	Moderate	Severe

Table 1b: Patients with a Mayo score of6 or more have moderately to severely active disease and may be uncontrolled.

was performed outside the sterile field; upon completion of the processing cycle, excess plasma was removed by aspiration until no further volume could be aspirated. Using the 20 ml syringe with the blunt cannula, the remaining volume was removed from the chamber; 2-3 ml was aspirated into the syringe and gently expressed backinto the chamber in order to re-suspend the cellular components back into the plasma. This action was repeated four or five times until the volume has a uniform consistence, and then the entire volume was aspirated intothe syringe, and the cannula was removed and attached to a sterile syringe cap and saved in a syringe labeled "BMC". A blunt needle was attached to the syringe to transfer the BMC back into the sterile field for infusion. The enriched mononuclear cells were ready intravenous injection.

1. Bone marrow stem cells injection: a wide pore cannula is applied to a peripheral vein. 100 ml of autologous BM mononuclear cell layer containing SCsis infused intravenously viaan infusion set that connects the cannula to the plastic bag. Lastly, the cannula is flushed with 10 ml of normal saline and the procedure is finished and the cannula is removed. The patients received 500 ml of normal saline that contains 1 g cefoperazone before starting the injection. They were kept under medical observation for their vital data for 6 hours after that they were discharged.
2. Full clinical, laboratory and endoscopic examinations were performed to the patients at the beginning of the study and after 3 months after the autologous bone marrow stem cells transplantation with observation of the changes in the patient's clinical condition, nutritional status, biochemical profile, endoscopic findings, medication requirements, and quality of life (Table 2).
3. The patients of this study continued on the same medications they were on before the stem cell transplantation including aminosalisylates, corticosteroids and immunosuppressive drugs (azathioprine or mercaptopurine). Changes in the doses or types of the drugs were done according to the clinical assessment throughout the study period and following the latest guidelines of management of ulcerative colitis.
4. Assessment of the clinical disease severity was done in the beginning of the study and after the SCT during the follow up period according to Truelove and Witts severity index [12].

	Mild	Moderate	Severe
Bowel movements (no. per day)	Fewer than 4	6-Apr	6 or more plus at least one of the features of systemic upset (marked with * below)
Blood in stools	No more than small amounts of blood	Between mild and severe	Visible blood
Temperature>37.8°C	No	No	yes
Pulse >90 bpm	No	No	yes
Hb< 10g %	No	No	yes
ESR (mm/hour)	30 or below	30 or below	above 30

Table 2: Biochemical profile.

Statistical methods

Statistical analysis of the results of the present study was conducted, using the mean, standard deviation, Paired t-test, Chi-square by SPSS V17.

Results

The patients included in this study were 4 males (40%) and 6 females (60%). Their ages ranged from 24-50 years with mean of (39.2 ± 10.2) and their BMI ranged from 20-33 with mean of (25.0 ± 4.7). All the patients underwent autologous bone marrow stem cell transplantation, and all the patients tolerated the treatment protocol well without any complications or side effects related to the procedure.

The 10 patients complained of diarrhea of 5-10 motions/day associated with mucus and bloody in the initial clinical assessment, but after the stem cell transplantation all patients had diarrheal motions that decreased to 3-5 motions/day during the follow up period with statistically significant difference as shown in Figure 1.

As regard the presence of rectal bleeding, 6 patients complained of rectal bleeding in the initial clinical assessment, 4 of them become free of rectal bleeding in the final clinical assessment after the procedure during the follow up period with none statistically significant difference as shown in Table 3.

There were statistically significant differences as regard the disease extent and severity before and after the procedure. 5 patients were classified as moderate, moderate to severe and severe pan colitis and 5 cases of moderate and moderate to severe left sided colitis in the initial endoscopic assessment. After 3 month of the SCT only 2 cases were found to have moderate left sided colitis while the other 8 cases showed endoscopic picture ranging between mild proctitis and mild to moderate left sided colitis as shown in Table 4 and Figure 2.

The heart rate, ESR and CRP showed statistically significant

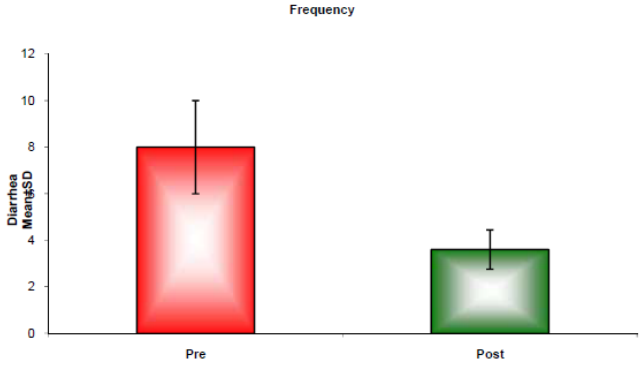

Figure 1: Showing the diarrheal motion frequency in patients pre and post the SCT procedure.

Rectal bleeding Pre		Rectal bleeding Post		
		Negative	Positive	Total
Negative	N	4	0	4
	%	40	0	40
Positive	N	4	2	6
	%	40	20	60
Total	N	8	2	10
	%	80	20	100
Chi-square	X2	2.37		
	P-value	0.124		

Table 3: Showing comparison between patients before and after the SCT as regard the rectal bleeding.

Outcome Pre		Outcome Post					
		mild proctitis	mild to moderate proctitis	mild left sided colitis	mild to moderate left sided colitis	moderate left sided colitis	Total
Moderate active left sided colitis	N	1	0	1	0	0	2
	%	10	0	10	0	0	20
Moderate active pancolitis	N	0	1	0	1	0	2
	%	20	10	0	10	0	20
Moderate to severe active left sided colitis	N	1	0	1	0	1	3
	%	10	0	10	0	10	30
moderate to severe active pancolitis	N	0	1	0	0	0	1
	%	0	10	0	0	0	10
Sever active pancolitis	N	0	0	0	1	1	2
	%	0	0	0	10	10	20
Total cases (after)	N	2	2	2	2	2	10
	%	20	20	20	20	20	100
Wilcoxon Signed Ranks Test	Z	17.27					
	P-value	0.038*					

Table 4: Showing comparison between patients before and after the SCT as regard the disease extent and severity.

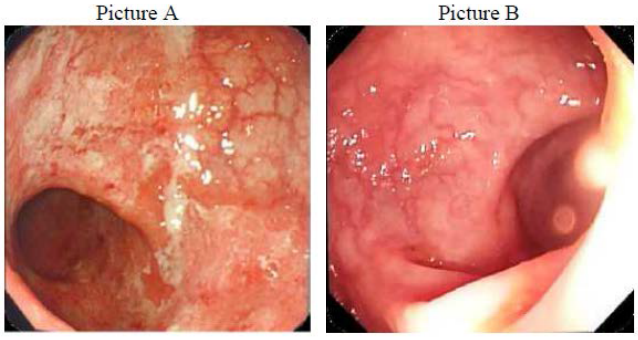

Figure 2: Endoscopic picture of patient before (picture A) and after SCT procedure (picture B).

	Mean ± SD Before	Mean ± SD After	Paired t-test t	Paired t-test P value
Body temprature (degree celsius)	37.440 ± 0.381	37.220 ± 0.262	1.354	0.209
Pulse rate (beat/min)	86.600 ± 10.679	80.400 ± 8.809	3.321	0.009*
Hemoglobin(gm%)	10.840 ± 2.688	11.340 ± 2.744	-0.739	0.479
ESR (mm/hour)	75.400 ± 49.332	49.200 ± 32.913	3.628	0.006*
CRP(mg/L)	20.667 ± 3.724	14.500 ± 12.124	3.273	0.012*
Activity score	7.800 ± 0.789	5.800 ± 0.789	6.708	0.000*

Table 5: Showing comparison as regard the body temperature, pulse rate, hemoglobin concentration, ESR, CRP and activity score before and after SCT.

Mean ± SD Before	Mean ± SD After	Paired t-test t	Paired t-test P value
Serum Albumin	4.000 ± 0.772	4.040 ± 0.659	-0.309	0.764
BMI	25.040 ± 4.739	24.980 ± 4.468	0.178	0.863

Table 6: Shows comparison as regard the BMI and serum albumin before and after SCT.

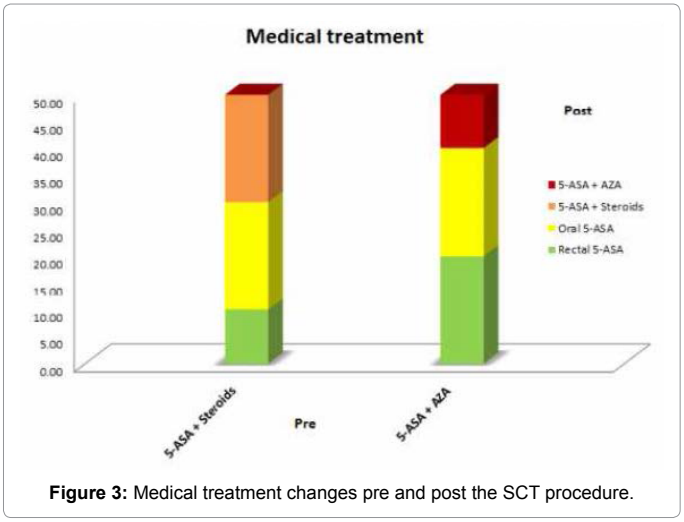

Figure 3: Medical treatment changes pre and post the SCT procedure.

difference before and after the SCT with P values <0.05. On the other hand, the body temperature and hemoglobin concentration showed statistically non-significant differences before and after the SCT with P values >0.05. The disease activity score according to Mayo Endoscopic Scoring of Ulcerative Colitis showed statistical significant improvement after the SCT as shown in Table 5.

There was statistically none significant difference as regard the serum albumin and BMI before and after SCT as shown in Table 6.

Also there were statistically none significant differences as regard the medical treatment modifications as patients were divided in two groups, one group treated by 5-ASA with steroids and other treated by 5-ASA with AZA in the initial assessment, but by the end of the study there were 7 patients treated with 5-ASA alone while 3 patients continued on steroids and AZA but with lower doses than the initial ones as shown in Figure 3.

Discussion

Whatever deserves to exist deserves to be known (Francis Bacon) So much has been written and rewritten on stem cells, their potentials, their properties, their possible uses and their risks. Protagonists of a new scientific era, SCs are promising tools for treating diseases of any sort, from degenerative disorders to inborn errors of metabolism. This study hypothesized that intravascular infusion of bone marrow stem cells may help to reverse the inflammatory process in patients with ulcerative colitis. Thus, we conducted a human trial to evaluate safety and feasibility of autologous bone marrow SC transplantation in Egyptian patients with ulcerative colitis and to evaluate stem cell transplantation as a therapeutic option compared to the conventional treatment. There are some data suggesting that stem cell transplantation may either worsen or at least not prevent inflammatory bowel disease in some patients. Three patients have been reported to develop ulcerative colitis or colonic ulceration after allogeneic stem cell transplantation. All of the cases of colitis were atypical of ulcerative colitis and an element of graft versus host disease may have been involved [13]. All the patients in the current study underwent autologous bone marrow stem cell transplantation, and all the patients tolerated the treatment protocol well without any complications or side effects related to the procedure. In autologous bone marrow stem cell transplantation, the stem cells are taken from the same subject with the same HLA with no risk of transplant rejection or GVHR. On the other hand, in allogenic stem cell transplantation, the donor's immune cells are transplanted and may attack the patient in a reverse kind of rejection causing graft-versus-host disease (GVHD) [14]. The studied patients showed statistically significant improvement regarding the frequency of thediarrheal motion after SCT. Although the exact mechanism is not clear, this may reflect the activation of genes corresponding to an enterocyte differentiation program in the transplanted SCs upon exposure to injured colon environment. Clinically wise, there was statistical improvement in the heart rate of the patients after SCT. Although changes in the body temperature were statistically in significant after the SCT, there was obvious clinical improvement on the individual assessment. Body temperature and heart rate are components of the scoring systems of UC severity but they are considered as supporting factors in assessment and are not calculated alone as they might be affected by other several factors. Although there was statistically none significant difference regarding the hemoglobin concentration levels of patients before and after the SCT, patient 3 showed elevation in her HB% levels from 7.3gm% before the procedure to 9.5gm% after it without blood transfusion. These results goes with results of Lazebnik, et al., who conducted a human clinical study on patients with inflammatory bowel disease receiving allogenic mesenchymal stem cells in 2010 and observed statistically significant decrease in the indices of the clinical and morphological activities of the inflammatory process in most of the studied patients [15]. CRP and ESR showed statistically significant improvement in their levels after SCT. This could be explained by the immunomodulatory properties of SCT porved by several reseaches. For example, gingiva-derived mesenchymal stem cells (GMSCs) were capable of immunomodulatory functions, specifically via suppressing peripheral blood lymphocyte proliferation, inducing expression of a wide panel of immunosuppressive factors including IL-10, inducible NO synthase (iNOS), and cyclooxygenase 2 (COX-2) in response to the inflammatory cytokine, IFN-γ. Cell-based therapy using systemic infusion of GMSCs in experimental colitis significantly ameliorated both clinical and histopathological severity of the colonic inflammation, restored the injured gastrointestinal mucosal tissues, reversed diarrhea and weight loss, and suppressed the overall disease activity [16].

The body mass index (BMI) and serum albumin can reflect the nutritional status of the patients with ulcerative colitis. They showed statistically non-significant differences in their levels before and after the SCT in the patients of the current study over the follow up period. Although, there was limited increase in the level of the serum albumin by about 0.5 gm/dl in patients 1 and 6 on analyzing the results of each patient individually. Serum albumin of the other patients did

not remarkably change with slight decrease in patient 2. On the other hand, BMI of the patients did not change throughout the follow up period except in patient 9 who gained around two kilograms in his final assessment which may be due to improved anorexia or from the effect of the corticosteroids therapy. Colonoscopic examination showed significant improvement in the extent and severity of the colonic inflammation and ulceration after 3 months of the SCT. Most of the patients were having moderate, moderate to severe left sided or extensive colitis in the initial assessment before SCT. Improvement to mild, mild to moderate proctitis or left sided colitis was noticed after 3 months after SCT. The activity score also showed significant improvement after the SCT with decreased scores to less than 6 in all studied patients. These results are also in parallel with the results of Lazebnik et al., who concluded that the use of MSC may be appreciated as a new strategic direction of therapy for IBD. The intravenously administered stem cells exert a potent immunomodulatory effect, reduce the activity of autoimmune inflammation, and stimulate a reparative process in the intestinal mucosa [16]. In another study that performed autologous bone marrow SCT for 10 patients with refractory Crohn's disease, there was improvement in the Crohn's disease activity index (CDAI) scores 6 weeks post-treatment [17]. Similarly, Ciccocioppo et al. performed autologous bone marrow SCT for 10 fistulizing Crohn's disease patients and observed sustained complete closure (seven cases) or incomplete closure (three cases) of fistula tracks with a parallel reduction of Crohn's disease and perianal disease activity indexes together with rectal mucosal healing without any adverse effects supporting the efficacy and regenerative properties of SC in treatment of inflammatory bowel disease [18].

The results of the current study also goes with the results of Ditschkowski et al who retrospectively analyzed the course of four patients with idiopathic ulcerative colitis and seven patients with Crohn's disease and who underwent allogeneic SCT for acute and chronic myeloid leukemia and myelodysplastic syndrome. None of those patients showed IBD activity after SCT, except for one patient who had mild persistent symptoms of Crohn's disease early after transplant. Colonoscopy after complete discontinuation of prophylactic post-transplant immunosuppression revealed no pathologic findings. These observations imply that host immune dysregulation may be influenced by the implementation of the new allogeneic immune system resulting from the transplantation of hematopoietic stem cells [2]. The results of the current study go with a former study in which two patients with a long history of psoriasis and ulcerative colitis underwent allogeneic stem cell transplantation for leukemia. The colitis, psoriasis, and leukemia remained in remission for four years following transplantation [19].

Conclusion

Bone marrow stem cell transplantation for patients of ulcerative colitis is a safe and feasible procedure without recorded complications. It can improve the quality of life of the patients as well as the disease activity assessed by laboratory tests, endoscopic extent and severity.

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