Introduction

Inflammatory bowel disease (IBD) represents a group of idiopathic chronic inflammatory intestinal conditions. The two main disease categories are **Crohn's disease** (CD) and **ulcerative colitis** (UC), with both overlapping and distinct clinical and pathological features ***(Charles, et al., 2009).***

Ulcerative colitis is a chronic disease leading to inflammation of the colon and in more severe degrees even causing painful ulcers in the colon which can bleed, cause mucous production and infection. Symptoms can recur or be minimal for months and years. Common symptoms include bloody diarrhea, abdominal pain and weight loss which may be mild to severe and affect individual's quality of life ***(Lakatos PL, et al., 2007).***

In a meta-analysis performed by Mayo Clinic, incidence of ulcerative colitis was reported as 2 to 14 per thousand person-years ***(Mahid, et al., 2006).***

The disease pathogenesis is still incompletely understood. The genetic and environmental factors such as altered luminal bacteria and enhanced the intestinal permeability play a role in the dysregulation of intestinal immunity, leading to the gastrointestinal injury ***(Ricart E, et al., 2010).***

Standard medical therapy is directed against the inflammatory and immune processes that are known to play an important role in the disease process. Medical therapy is of variable success in ameliorating cardinal symptoms of the disease (diarrhea, abdominal pain), in treating extra intestinal manifestations, and in preventing complications ***(Ricart E, et al., 2010).***

Currently, therapy is most often implemented in a stepwise fashion, progressing through amino salicylates [sulfasalazine, mesalazine (mesalamine)], corticosteroids, immunosuppressive medications including tioguanine (thioguanine) compounds (mercaptopurine, azathioprine), methotrexate, and ciclosporin, and finally anti-TNF drugs. This common approach is predicated on the addition of more potent medications to agents that are believed to be safer but that may also be less effective ***(Ricart E, et al., 2010).***

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 ***(Ricart E, et al., 2010).***

A novel and exciting approach could be offered through the current development in the field of stem cell biology ***(Masson, et al, 2004).***

Consequently, bone marrow stem cells have been sought of as a promising new approach capable of addressing mostly unmet medical needs ***(Weissman, 2000).***

The considerable excitement surrounding the stem cell field is based on the unique biological properties of these cells and their capacity to self-renew and regenerate tissue and organ systems, a flurry of studies reported bone marrow derived stroma to brain, bone marrow to liver, skin to brain, brain to heart and other such stem cells differentiation ***(Morrison, 2000).***

Two streams of research, experimental and clinical, are the origin of the increasing utilization of stem cell therapies for severe immune-mediated diseases (IMIDs) including IBD. The considerable excitement surrounding the stem cell field was initially based on the unique biological properties of these cells; later, the immunomodulatory ability of stem cell therapy has become also apparent ***(Ricart E, et al., 2010).***

Aim of the Work

To **investigate** the role of autologous bone marrow stem cells intravenous injection in treatment for cases of ulcerative colitis disease.

Ulcerative Colitis

❖ *Inflammatory bowel disease:*

Inflammatory bowel disease (IBD) commonly refers to ulcerative colitis (UC) and Crohn's disease (CD), which are chronic inflammatory diseases of the GI tract of unknown etiology ***(Hyams, 2002).***

Ulcerative colitis is characterized by diffuse mucosal inflammation limited to the colon. It is classified according to the maximal extent of inflammation observed at colonoscopy, while Crohn's disease is characterized by patchy, trans mural inflammation, which may affect any part of the gastrointestinal tract, it may be defined by: age of onset, location, or behavior ***(Silverberg, et al., 2005).***

In particular, the definitions of ulcerative colitis and Crohn's disease acknowledge the revised Montreal classification which attempts to more accurately characterize the clinical patterns of IBD ***(Satsangi, et al., 2006).***

Unclassified (IBDU) is the term best suited for the minority of cases where a definitive distinction between UC, CD, or other cause of colitis cannot be made after considering clinical, radiological, endoscopic and pathological criteria, because they have some features of both conditions. **Indeterminate colitis** (IC) is a term reserved for pathologists to describe overlapping features in IBDU ***(Satsangi, et al., 2006).***

❖ ***Ulcerative colitis:***

Ulcerative colitis is a lifelong disease arising from an interaction between genetic and environmental factors, observed predominantly in the developed countries of the world. The precise etiology is unknown and therefore medical therapy to cure the disease is not yet available ***(Dignass, et al., 2012).***

It is a chronic inflammatory condition causing continuous mucosal inflammation of the colon without granulomas on biopsy, affecting the rectum and a variable extent of the colon in continuity, which is characterized by a relapsing & remitting course ***(Silverberg, et al., 2005).***

Clinical disease activity is grouped into **remission**, **mild**, **moderate** and **severe**. This refers to biological activity and not to treatment responsiveness ***(Rice-Oxley and Truelove, 1950).***

The term **severe colitis** (or 'acute severe colitis') is preferred to 'fulminant' colitis, because the term 'fulminant' is ill-defined. Severe colitis as defined according to Truelove and Witt's' criteria is easy to apply in outpatients, mandates hospital admission for intensive treatment and defines an outcome (only 70% respond to intensive therapy) ***(Dignass, et al., 2012).***

Response is defined as clinical and endoscopic improvement, depending on the activity index used. In general, this means a decrease in the activity index of >30%, plus a decrease in the rectal bleeding and endoscopy sub scores, but there are many permutations ***(D'Haens, et al., 2007).***

The term **relapse** is used to define a flare of symptoms in a patient with established UC who is in clinical remission, either spontaneously or after medical treatment. It is considered when a combination of rectal bleeding with an increase in stool frequency and abnormal mucosa at sigmoidoscopy are present. It may be **infrequent** (≤1/year), **frequent** (≥2 relapses/year), or **continuous** (persistent symptoms of active UC without a period of remission) ***(D'Haens G et al., 2007).***

The term 'chronic active disease' has been used in the past to define a patient who is dependent on, refractory to, or intolerant of steroids, or who has disease activity despite immunomodulators. Since this term is ambiguous it is best avoided. Instead, arbitrary, but more precise definitions are preferred, including steroid-refractory or steroid-dependence ***(Van Assche, et al., 2010).***

Steroid-refractory colitis if patients have active disease despite prednisolone up to 0.75 mg/kg/day over a period of 4 weeks. **Steroid-dependent colitis** patients who are either unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, without recurrent active disease, or who have a relapse within 3 months of stopping steroids ***(Van Assche, et al., 2010).***

Immunomodulator-refractory colitis patients who have active disease or relapse in spite of thiopurines at an appropriate dose for at least 3 months (i.e. azathioprine 2–2.5 mg/kg/day or mercaptopurine 1– 1.5 mg/kg/day in the absence of leucopenia) ***(Dignass, et al., 2012).***

❖ *Classifications:*

A. Classification according to disease extent

The preferred classification is an endoscopic classification as outlined in the **Montréal classification** into **ulcerative proctitis** (limited to the rectum), **left-sided colitis** (up to the splenic flexure) and **extensive colitis**, and by maximal extent upon follow up ***(Dignass, et al., 2012).***

There are several reasons why patients with UC should be classified according to disease extent. The extent of inflammation will influence the patient's management and the choice of delivery system for a given therapy. For instance, topical therapy in the form of **suppositories** (for proctitis) or **enemas** (for left-sided colitis) is often the first line choice, but **oral** therapy often combined with **topical** therapy is appropriate for extensive colitis. Also, it influences start and frequency of surveillance ***(Dignass, et al., 2012).***

Table (1): The Montreal classification of UC ***(Silverberg, et al., 2005).***

E1	**Proctitis**	Involvement limited to the rectum (i.e. proximal extent of inflammation is distal to recto-sigmoid junction)
E2	**Left-sided**	Involvement limited to the proportion of the colon distal to the splenic flexure (analogous to 'distal' colitis)
E3	**Extensive**	Involvement extends proximal to the splenic flexure, including pan colitis

B. Classification according to disease severity

Classification of UC based on disease severity is useful for clinical practice and dictates the patient's management. Many disease activity indices or criteria have been proposed, but none have been adequately validated. Although modifications of the original Truelove and Witts' criteria are used in daily practice, the modified Mayo score is used more frequently in current clinical trials. For clinical practice a combination of clinical features, laboratory findings, imaging modalities and endoscopic parameters including histopathology will all assist physicians in their patients' management ***(Dignass, et al., 2012).***

A distinction should be made between disease activity at a point in time (remission, mild, moderate, severe) and the response of disease to treatment. Moderate colitis has become necessary to distinguish from mildly active disease, because the efficacy of some treatments may differ. The simplest clinical measure to distinguish moderate from mildly active colitis is the presence of mucosal friability (bleeding on light contact with the rectal mucosa at sigmoidoscopy) ***(D'Haens, et al., 2007).***

There is no fully validated definition of remission. The best way of defining remission is a combination of clinical parameters (i.e. stool frequency $\leq$ 3/day with no bleeding) and a normal mucosa at endoscopy. Absence of an acute inflammatory infiltrate at histology is helpful ***(Dignass, et al., 2012).***

Table (2): Disease severity index of UC ***(Truelove and Witts, 1995).***

	Mild	Moderate	Severe
Bloody stools/day	< 4	4 - 6	≥ 6
Pulse	< 90 bpm	≤ 90 bpm	> 90 bpm
Temperature	< 37.5 °C	≤ 37.8 °C	> 37.8 °C
Hemoglobin	> 11.5 g/dL	≥ 10.5 g/dL	< 10.5 g/dL
ESR	< 20 mm/h	≤ 30 mm/h	> 30 mm/h
CRP	Normal	≤ 30 mg/L	> 30 mg/L

Table (3): Mayo activity scoring index ***(D'Haens, et al., 2007).***

	0	1	2	3
Stool frequency	Normal	1-2/day > normal	3-4/day > normal	5/day > normal
Rectal bleeding	None	Streaks	Obvious	Mostly blood
Endoscopic finding	Normal	Mild friability	Moderate friability	Spontaneous bleeding
Global assessment	Normal	Mild	Moderate	Severe
The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.			• 0 to 1: Remission • 2 to 5: Mild disease • 6 to 9: Moderate disease • 10 to 12: Severe disease	

Table (4): Endoscopic scores for UC ***(Dignass, et al., 2012).***

Baron Score *(Baron JH, et al., 1964)*	
0	Normal: matt mucosa, ramifying vascular pattern clearly visible, no spontaneous bleeding, no bleeding to light touch
1	Abnormal, but non-hemorrhagic: appearances between 0 and 2
2	Moderately hemorrhagic: bleeding to light touch, but no spontaneous bleeding seen on initial inspection
3	Severely hemorrhagic: spontaneous bleeding seen ahead of instrument at initial inspection and bleeds to light touch
Schroeder Score *(Schroeder KW, et al., 1987)*	
0	Normal or inactive disease
1	Mild (erythema, decreased vascular pattern, mild friability)
2	Moderate (marked erythema, absent vascular pattern, friability, erosions)
3	Severe (spontaneous bleeding, ulceration)
Feagan Score *(Feagan BG, et al., 2005)*	
0	Normal, smooth, glistening mucosa, with vascular pattern visible; not friable
1	Granular mucosa; vascular pattern not visible; not friable; hyperemia
2	As 1, with a friable mucosa, but not spontaneously bleeding
3	As 2, but mucosa spontaneously bleeding

❖ ***Pathophysiology:***

Increasing evidence suggests that there is **a defect in the function of the intestinal immune system**. As a consequence, there is a breakdown of the defense barrier of the gut, which, in turn, results in exposure of the mucosa to microorganisms or their products. The result is **a chronic inflammatory process mediated by T-cells**. Hence, therapy should be directed at improving the intestinal immune system. It has been postulated that genetic factors may predispose certain individuals to developing a "leaky gut" ***(William Tremaine, et al., 2008).***

In ulcerative colitis, inflammation always begins in the **rectum**, extends proximally a certain distance, and then abruptly stops. A clear demarcation exists between involved and uninvolved mucosa and no "skip areas" are present. It primarily involves the mucosa and submucosa, with formation of crypt abscesses and mucosal ulceration. The mucosa typically appears granular and friable. The small intestine is never involved, except when the distal terminal ileum is inflamed in a superficial manner, referred to as backwash ileitis ***(William Tremaine, et al., 2008).***

In severe cases, pseudo polyps form, consisting of areas of hyperplastic growth with swollen mucosa surrounded by inflamed mucosa with shallow ulcers. Necrosis can extend below the lamina propria to involve the submucosa and the circular and longitudinal muscles, although this is unusual. As the disease becomes chronic, the colon becomes a rigid foreshortened tube that lacks its usual haustral markings, leading to the lead pipe appearance observed on barium enema ***(William Tremaine, et al., 2008).***

❖ ***Etiology:***

The etiology of IBD is **unknown**. **Environmental**, **infectious**, **genetic**, **autoimmune**, and **host factors** have been suspected. Interactions among these factors may be more important ***(Buhner, et al., 2006).***

A. Genetic Factors

IBD is seen two to four times greater in the Jewish population as compared with other ethnic groups. Ashkenazi Jews have the greatest risk within the Jewish population. Other epidemiologic studies have shown higher rates in whites, lower rates in African Americans, and the lowest rates in Asians ***(Ahmad, et al., 2001).***

The prevalence of IBD is also increased in relatives of those who have CD and UC. For patients who have UC, the occurrence of IBD in their offspring was 6.26%; for patients who have CD, the occurrence was 9.2% ***(Orholm, et al., 1999).***

Epidemiologic studies demonstrate familial similitude for disease type, extent and extra-intestinal manifestations for siblings with UC, but the concordance rates are smaller than for CD. All studies that included the evaluation of concordance rates between monozygotic and dizygotic twins indicate that the genetic contribution to disease susceptibility is smaller for UC than for CD ***(Halfvarson, et al., 2003).***

The region of the major histocompatibility complex (MHC) locus on chromosome 6p that contains the genes encoding the HLA Class I and II histocompatibility molecules has been implicated in susceptibility to UC by both association and linkage studies; however, the linkage

studies do not discriminate between risk for UC and CD. Specifically, UC has been most consistently associated with HLA Class II alleles ***(Satsangi, et al. 2003).***

For example, in some populations the HLA-DRB1*1502 allele (representing HLA-DR2) is positively associated with UC and the HLA-DR4 and DR6 alleles negatively associated; the differences in association among populations may be accounted for by racial and ethnic variability. The infrequent HLA-DRB1*0103 allele is associated with extensive and severe UC and often associated with the requisite for colectomy. Although there is conflicting data in differing populations, other potential genetic associations for UC include the interleukin-1 family of genes on chromosome 2q13. Another potential 'functional candidate gene' is the multidrug resistance gene (MDR1) that is located in an area of linkage on chromosome 7 ***(Pallone; Silverberg; Ahmad, et al. 2003).***

In addition, there is a strong likelihood that genetics also impact on the incidence of extra-intestinal complications of UC. In particular, the association between HLA-B27 and the development of ankylosing spondylitis and sacroiliitis in patients with UC has been reproduced and approaches 100%. Peripheral arthropathies (type I and II) accompanying UC are also associated with HLA polymorphisms that associate with erythema nodosum and uveitis ***(Orchard, et al. 2002).***

Of note, the association of UC with primary sclerosing cholangitis is also related to the presence of several HLA Class II alleles and is modified (prevented) by the environmental factor of cigarette smoking ***(Mitchell, et al. 2002).***

B. Environmental Factors

- *Cigarette smoking:*

There are several environmental clues to susceptibility and development of UC ***(Krishnan and Korzenik, 2002).***

The long-standing finding that cigarette smoking protects against the development of ulcerative colitis has withstood the test of time. Indeed, case series continue to demonstrate a protective effect of smoking on both the development and course of UC ***(Abraham, et al., 2003).*** Although smokers are less likely to develop UC, however, ex-smokers are more likely to develop extensive or severe colitis. Others believe that ex-smokers account for the preponderance of the second age peak for UC in patients > 40 years ***(Halme, et al., 2002).***

The protective effect of smoking also extends to the extra-intestinal manifestations and the post-surgical complications of UC. For example, smoking protects against the development of PSC, smoking, or non-smoking, accounts for the differing incidence of PSC associated with UC ***(Mitchell, et al., 2002).***

- *Appendectomy:*

Another consistent epidemiologic clue to the pathogenesis of UC is the observation that appendectomy, particularly at a younger age, both reduces the likelihood of developing and the severity of disease. It seems to be an additive protective factor to cigarette smoking against the development of UC. In contrast to UC, prior appendectomy does not seem to be protective against development of PSC ***(Feeney et al.; Cosnes, et al.; Mitchell, et al., 2002).***

- *Bacteria:*

One ubiquitous factor in animal models of colitis and in human disease is the relationship with bacteria. In experimental models of IBD, colitis does not develop in animals that are raised in germ-free environments ***(Sartor, 2004).***

Commensal bacteria, not pathogens, are sufficient to induce colitis, but this is determined by both host and bacterial specificities. Also, different phenotypic patterns of colitis are seen with specific bacterial species. Commensal bacteria can induce a protective effect that can be transmitted by bacteria-responsive regulatory CD4+ T-cells ***(Cong, et al. 2002).***

Although it has not been possible to identify bacterial strains that are specific to UC, there are increased numbers of mucosa-associated (adherent) Bacteroides species and Enterobacteriaceae species in patients with inflamed segments ***(Swidsinski, et al. 2002).***

Whether early exposure to common environmental microbes is protective against UC as it is with other autoimmune disorders, in line with the so-called **hygiene hypothesis**, remains to be determined ***(Weiss, 2002).***

Alternatively, functional activity of microbial strains may also lead to 'DYSBIOSIS' and affect the metabolic activity of colonocytes or enterocytes, leading to the development of UC. The potential inductive or protective role of bacteria has also led to considerable interest in prebiotic or probiotic therapies for UC and its complications ***(Sartor, 2004).***