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# The Diagnostic Value of Colonoscopy in Understanding Inflammatory Mucosal Damage in Patients with Ulcerative Colitis and Predicting Clinical Response to Adsorptive Leucocytapheresis as a Non-Pharmacologic Treatment Intervention

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## 1. Introduction

The gastrointestinal system consists of a hollow muscular tube starting from the oral cavity, where food enters the mouth, continuing through the pharynx, oesophagus, stomach and intestines to the rectum and anus, where faeces pass out. The primary purpose of the gastrointestinal system is to break down food into nutrients, which together with water can be absorbed to feed the body cells. In the case of gastrointestinal disease or disorders, these functions of the gastrointestinal tract are not achieved successfully, discussed in the subsequent sections of this chapter. The innermost layer of the gastrointestinal system is the mucosa, which is lined with specialised epithelial cells, supported by an underlying connective tissue layer called the lamina propria, where infiltrating leucocytes, in particular, myeloid lineage leucocytes are often seen.

## 2. The natural history of ulcerative colitis

Ulcerative colitis (UC) is one of the two major phenotypes of the idiopathic inflammatory bowel diseases (IBD) of the intestine; the other major phenotype is Crohn's disease (CD). UC and CD are both debilitating chronic disorders that afflict millions of individuals throughout the world with symptoms which impair function and quality of life. However, whereas UC is confined to the colon and the rectum, CD may affect any part of the gut from the mouth to the perianal (1,2). A multitude of clinical manifestations represent the expressions of IBD. These include diarrhoea, rectal bleeding, abdominal discomfort, fever, anaemia, and weight loss; both UC and CD tend to run a remitting-relapsing course affected

by diverse environmental factors (2). From here on, we shall focus only on UC. The severity of UC is often presented by clinical activity index (CAI). Another, but complementary parameter is endoscopic activity index, not used in this chapter.

### **3. Colonoscope, the gastroenterologist's eye and arms in modern times**

Colonoscopy is a revolutionary development in gastroenterology, now days like both arm and eyes for specialist gastroenterologists that can reach the inside of the large and distal segment of the small intestine. Introduced in the late 1960s (3), the term, colonoscopy refers to the endoscopic examination of the bowel with a charge-coupled device (CCD) camera or a fiber optic camera on a flexible tube passed through the rectal opening. As the name implies, colonoscopy allows a visual diagnosis of intestinal wall lesions like inflammation, ulceration, polyps and provides the opportunity for biopsy or removal of suspected cancerous lesions. Colonoscopy can remove polyps as small as one millimetre or less. Once polyps are removed, they can be studied with the aid of a microscope to determine if they are precancerous or not. Retrograde colonoscopy of the entire colon, and endoscopic excision of polyps from anywhere in the colon, began in 1969 (4). Momentous advances have occurred over the past two decades, and the two procedures are now widely accepted and practiced. Development and perfection of the methodology were, at first, fraught with many difficulties, both procedural and technical, which had to be overcome. Significant opposition was engendered in the early years by some who claimed that the methods were both unnecessary and unduly dangerous. Time has proven otherwise. Progress came about as the result of a steady stream of publications from a number of centres documenting the successful and safe application of the methodology.

More advanced versions include virtual colonoscopy, which uses 2D and 3D imagery reconstructed from computed tomography (CT) scans or from nuclear magnetic resonance (MR) scans, is also possible, as a totally non-invasive medical test. However, unlike standard colonoscopy, virtual colonoscopy does not allow for therapeutic maneuvers such as polyp/tumour removal or biopsy nor visualization of lesions smaller than 5 millimeters. If a growth or polyp is detected by using CT colonography, a standard colonoscopy would still need to be performed. Further, colonoscopy is similar to, but not the same as, sigmoidoscopy, the difference being related to which parts of the colon each can examine. A colonoscopy allows an examination of the entire colon (measuring more than 1.5m in length). A sigmoidoscopy allows an examination of only the final 60cm of the colon. A sigmoidoscopy is often used as a screening procedure for a full colonoscopy to be followed in many instances in conjunction with a faecal occult blood test, which can detect the formation of cancerous cells throughout the colon. At other times, a sigmoidoscopy is preferred to a full colonoscopy in patients having an active flare of ulcerative colitis (UC) or Crohn's disease (CD) to avoid a perforation of the colon. Additionally, surgeons use the term pouchoscopy to refer to a colonoscopy of the ileo-anal pouch. Conditions that call for diagnostic colonoscopy include gastrointestinal haemorrhage, unexplained changes in bowel habit and suspicion of malignancy. Colonoscopies are often used to diagnose colon cancer, but are also frequently used to diagnose and assess inflammatory bowel disease (IBD). In older patients (sometimes even younger ones) an unexplained drop in haematocrit (one sign of anaemia) is an indication that calls for a colonoscopy, usually along with an oesophagogastroduodenoscopy, even if no obvious blood has been seen in the stool (faeces).

Due to the high mortality associated with colon cancer and the high effectiveness and low risks associated with colonoscopy, it is now becoming a routine screening test for people 50 years of age or older. Subsequent re-screenings are then scheduled based on the initial results found, with a five or ten-year recall being common for colonoscopies that produce normal results (5). Patients with a family history of colon cancer are often first screened during their teenage years. A recent study found that among people who have had an initial colonoscopy that found no polyps, the risk of developing colorectal cancer within five years is extremely low. Therefore, there is no need for those people to have another colonoscopy sooner than five years after the first screening (6). In this chapter, the authors endeavour to describe the potential diagnostic power of colonoscopy potentially to identify patients with an active flare of UC who are most likely to respond to selective, but therapeutic removal of circulating myeloid lineage leucocytes (granulocytes and monocytes/macrophages) by extracorporeal adsorption, as a new and non-pharmacologic treatment intervention for patients with IBD, better known as GMA, which stands for granulocyte and monocyte adsorption (7).

#### 4. Colonoscopy in inflammatory bowel diseases

Figure 1 shows colonoscopy photographs from the surface of the colonic mucosa of healthy human subjects or patients with UC following full remission in association with GMA therapy. The mucosa is the surface through, which nutrients and water from the food in the intestine are absorbed into the blood stream. Accordingly, healthy mucosa is typically well vascularised for adequate absorption. Colonoscopy has a unique position in viewing and assessing intestinal integrity.

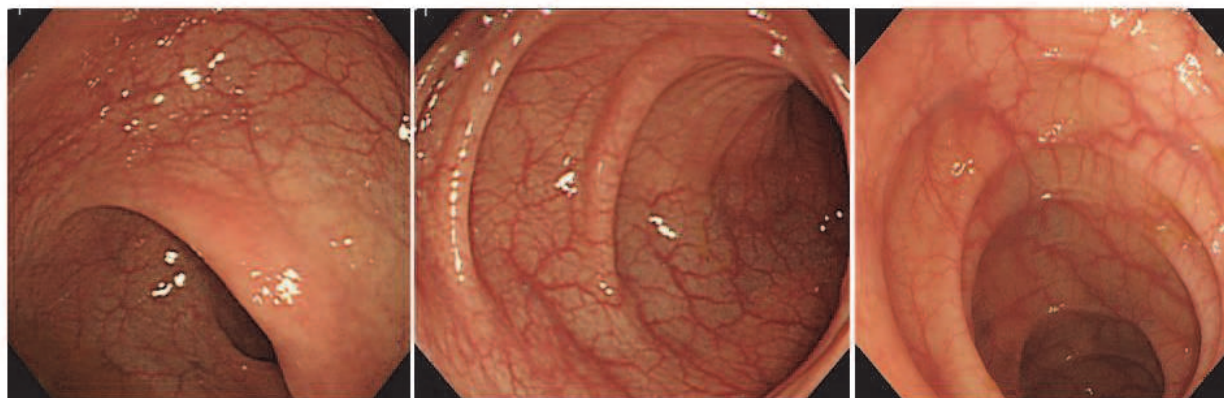


Fig. 1.

Most symptoms of UC are due to the ulceration and the loss of the mucosal layer covering the inner wall of the large intestine (colon and the rectum). As the mucosal layer is involved in the absorption of nutrients and water from the gut, during severely active UC, absorption of nutrients and water is seriously impaired. In Figure 2, typical colonoscopy photographs from the surface of the colon or the rectum of patients with severe and fulminant UC are seen. There is extensive and deep ulcers together with near total loss of the mucosal tissue. This condition is debilitating, the patients may suffer from weight loss, and impaired quality of life. For example unabsorbed food and water will pass as watery diarrhoea, or bloody diarrhoea due to bleeding. Such patients are not likely to respond to any drug based



medication or even to therapeutic depletion of myeloid leucocytes by GMA, they have fulminant (disease persists in the presence of optimal medication) UC and often must opt for surgery known as colectomy. Needless to say that only an initial diagnostic colonoscopy can identify such patients as non-responders to drug based interventions so that the patient can opt for colectomy at an early stage. This should significantly shorten morbidity time and save medical cost.

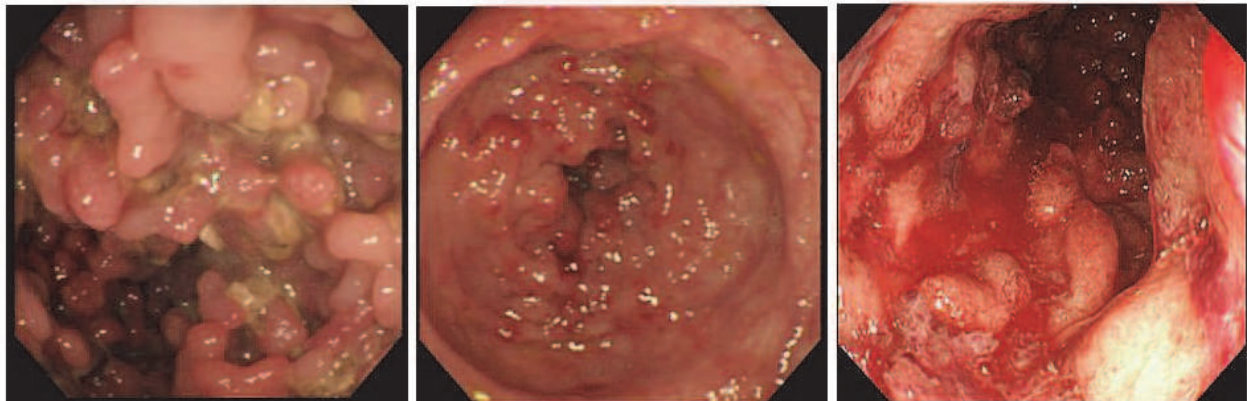


Fig. 2.

## 5. Therapeutic options for patients with ulcerative colitis

Despite the recognition of a genetic background together with environmental factors, which at present are thought to translate into an inappropriate inflammatory response in patients with UC (2, 8-10), currently our understanding on the immunopathogenesis of UC is inadequate. Hence, up to now drug therapy of UC has been empirical rather than based on sound understanding of disease aetiology. Accordingly, while drug therapy initially appears successful in the majority of patients, it comes at the cost of significant side effects (11,12). Further, up to now, first line medications for exacerbation of UC include 5-aminosalicylic acid (5-ASA) or sulphasalazine in combination with a corticosteroid with consideration of azathioprine (or 6-mercaptopurine) and nutritional support for some patients (2,14-18). Treatment failure in patients with severe disease has often been an indication for colectomy in up to 40% of steroid refractory patients (2,19, 20) although in recent years, cyclosporin A (CsA) has been introduced for corticosteroid refractory UC (18,21). Despite being moderately effective in this clinical setting in reducing colectomy rates, there remain serious concerns over long-term efficacy and toxicity of CsA (22).

However, this is not to say that drug has no place in the treatment of UC. In fact, no one can deny the role of medicines in the elimination of most disease that our ancestors were left defenseless against. However, even in today's era of modern medicine, it is essential to bear in mind that drug therapy by its very nature, involves adding a foreign substance to the body system and although initially effective, may lead to the disease becoming drug dependent or refractory. Additionally, many drugs are associated with toxic side effects which can add to the disease complexity. Hence, a therapeutic strategy based on a non-drug intervention, a correction or support of body's natural processes like GMA (which takes away from the body instead of adding to it), if effective, should have advantages over drugs, long term adverse side effects and refractoriness are unlikely (23, 24).

## 6. Myeloid leucocytes, cytokines and ulcerative colitis

It is now known that UC is exacerbated by inflammatory cytokines like tumour necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$ , IL-6, IL-8 and others (25). Accordingly, anti-cytokine antibodies, notably anti-TNF antibodies like infliximab (IFX) are being used and new antibodies are being developed for the treatment of IBD (26). Indeed, the efficacy of anti-TNF, notably IFX, in patients with CD (27) as well as in UC (26) has validated the role of this cytokine in the immunopathogenesis of IBD. However, the enthusiasm towards biologicals is increasingly being dampened by concerns about their long-term efficacy and in particular, the safety profiles (28,29). However, patients with active IBD harbour elevated and activated myeloid lineage leucocytes (granulocytes and monocytes) in the presence of compromised lymphocytes (1,30-33). Further, histologic examinations of mucosal biopsies from patients with active IBD reveals a spectrum of pathologic manifestations among which an abundance of neutrophils accounts not only for the morphologic lesions in IBD, but also for the prevailing patterns of mucosal inflammation (2,34,35). When activated, myeloid leucocytes produce an array of pleiotropic cytokines like TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-12, IL-23, which are strongly pro-inflammatory (25,36). Therefore, targeting leucocytes as key players in the exacerbation of IBD is what lies behind extracorporeal granulocyte monocyte/macrophage adsorption (GMA) with the Adacolumn (7). Likewise, neutrophils in patients with IBD show activation behaviour (30) and prolonged survival time (37). Factors that are known to promote neutrophil survival in IBD include inflammatory cytokines (38) and paradoxically corticosteroids (39), which are commonly used to treat IBD patients. Myeloid leucocytes, like the CD14(+)CD16(+) monocytes are major sources of TNF- $\alpha$  (40,41), and it could be valid to say that selective depletion of myeloid leucocytes by GMA should alleviate inflammation and promote remission or at least enhance the efficacy of pharmacologics. However, clinical studies in patients with UC have reported unmatched efficacy outcomes, ranging from an 85% (42) to a statistically insignificant level (43), indicating that certain subpopulations of patients benefit from GMA while others not so, suggesting that patients' baseline demographic variables determine clinical response to this non-pharmacologic mode of therapy (23,24).

## 7. Therapeutic leucocytapheresis in ulcerative colitis – logics and mechanisms

For an extracorporeal intervention to be a novel non-drug therapeutic option, it should be able to selectively deplete leucocytes, which in patients with UC are thought to contribute to the disease pathogenesis. For example, we have already said that patients with active IBD are found to have compromised lymphocytes (31-33). With this in mind, certain subpopulations of lymphocytes like the CD4(+)CD25(+) phenotype, known as the regulatory T cells (Treg) have essential immunoregulatory roles and therefore, are indispensable to the host (44-49). Based on these understandings, the Adacolumn leucocytapheresis system is designed to spare lymphocytes. It is filled with specially designed cellulose acetate beads of 2mm in diameter as the column leucocytapheresis carriers that are bathed in physiologic saline (50). The carriers remove from blood in the column most of the granulocytes, monocytes/macrophages together with some platelets (7,51). Surprisingly, the procedure has been associated with a sustained increase in absolute lymphocyte

counts in the post treatment phase (32,33,50) including the regulatory phenotype, CD4(+)CD25(+) Treg (7,49,50). The Adacolumn is an adsorptive type and leucocytapheresis with this column is often abbreviated as GMA. The mechanisms for sparing lymphocytes are briefly described here. Patients with immune dysfunction may have immune complexes (IC) in their plasma (7,51,52). Cellulose acetate adsorbs immunoglobulin G (IgG) and IC from the plasma (52,53). Upon adsorption, the binding sites on IgG and IC become available for the Fcγ receptors (FcγRs) on myelocytes (7,51-53). Further, cellulose acetate with adsorbed IgG and IC generates complement activation fragments including C3a and C5a (7,52,53). The opsonins C3b/C3bi and others derived from the activation fragments also adsorb onto the carriers and serve as binding sites for the leucocyte complement receptors, CR1, CR2, CR3 (Mac-1, CD11b/CD18). Hence, leucocyte adsorption to the GMA carriers in the Adacolumn is governed by the opsonins, FcγRs and the leucocytes complement receptors (7,53). The expressions of these sets of receptors are common features of myeloid lineage leucocytes. Lymphocytes are not known to express complement receptors except on small subsets of B, T and natural killer (NK) cells. Similarly, FcγRs are not widely expressed on lymphocytes except on small populations of CD19+B cells and CD56+NK cells (7,51). These basic phenomena proceed well on the carriers and lend the Adacolumn GMA selectivity.

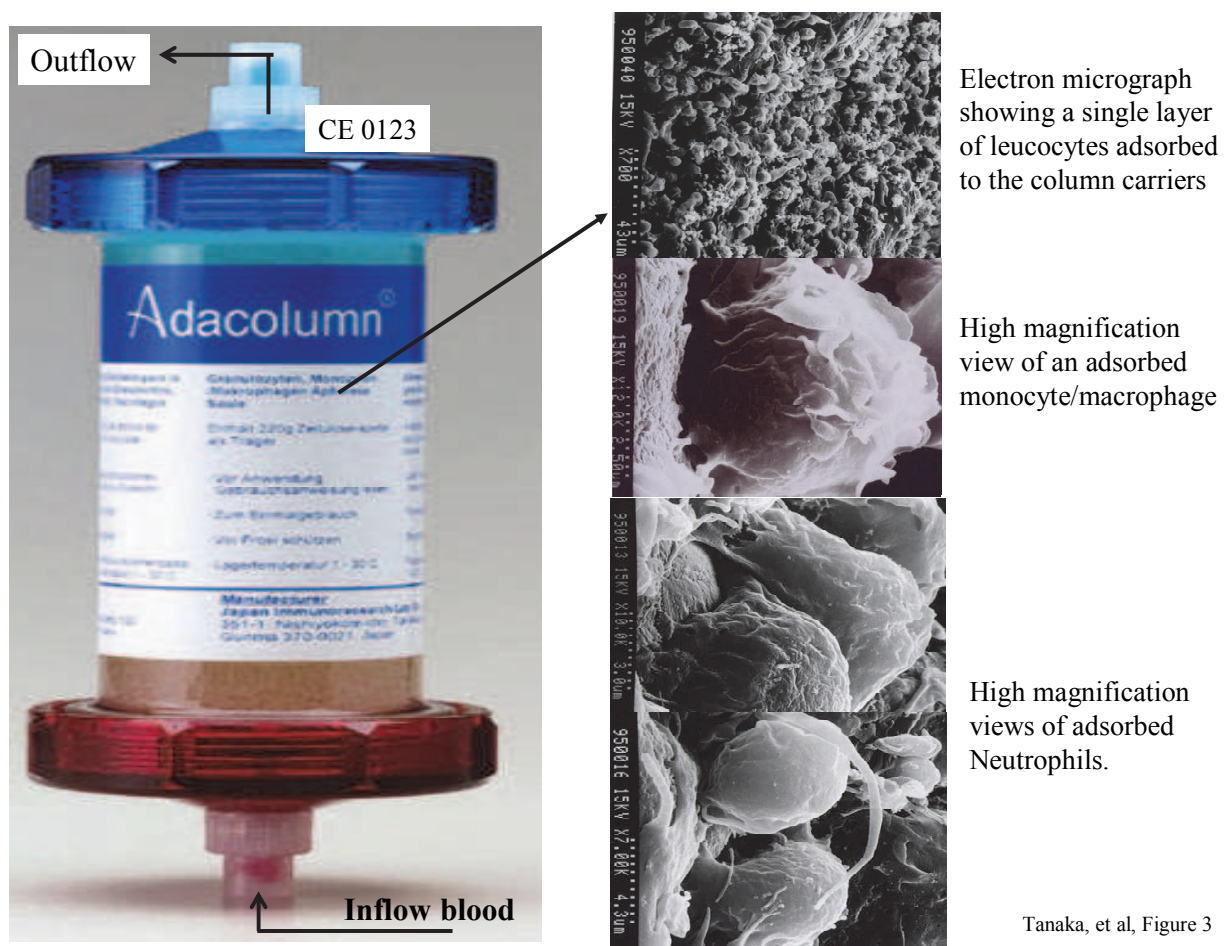


Fig. 3.



### 8. Colonoscopic features of typical responders to GMA

Clinical experience has shown that GMA in patients with steroid dependent or steroid refractory UC was associated with significant efficacy as assessed by measuring the fall in UC clinical activity index (CAI) and tapering or discontinuation of steroids, while in steroid naïve patients, GMA spared patients from exposure to steroids (23,24). Therefore, published data (23,24,32,34,55) suggest that steroid naïve patients respond particularly well. Characteristically they respond faster with fewer GMA sessions and have a high cumulative rate of remission. Thus, the remission rate in steroid naïve patients reported by Suzuki et al. (32) was an 85%. Similarly, Tanaka et al. (34) treated a cohort of 45 patients, 26 steroid naïve and 19 steroid dependent. Each patient could receive up to a maximum of 11 GMA sessions (or until CAI decreased to 4 or less). At week 12, the response rate (CAI  $\leq$ 4) in steroid naïve subgroup was 22 of 26 patients (84.6%) and in steroid dependent sub-group was 11 of 19 (57.9%). Colonoscopy revealed that most non-responders in both groups had deep colonic ulcers and extensive loss of the mucosal tissue. Further, this is the only study that looked at the impact of GMA on leucocyte level in the colonic mucosa. Biopsies taken during colonoscopy revealed massive infiltration of the colonic mucosa by neutrophils and GMA was associated with a striking reduction of neutrophils in the mucosa (Figure 5). Tanaka's colonoscopic observations (23,34) echo those of Suzuki et al. a few years earlier (32), who also reported that the only 3 non-responders in their cohort of 20 steroid naïve patients had deep colonic ulcers. In a very thorough study by Suzuki et al. (56), the authors aimed at determining the responders to GMA. Their major findings are as follows. Seven days after the last GMA session, 20 of 28 patients (71.4%) achieved clinical remission including all 8 patients who had their first UC episode. The mean duration of UC in the 8 first episode

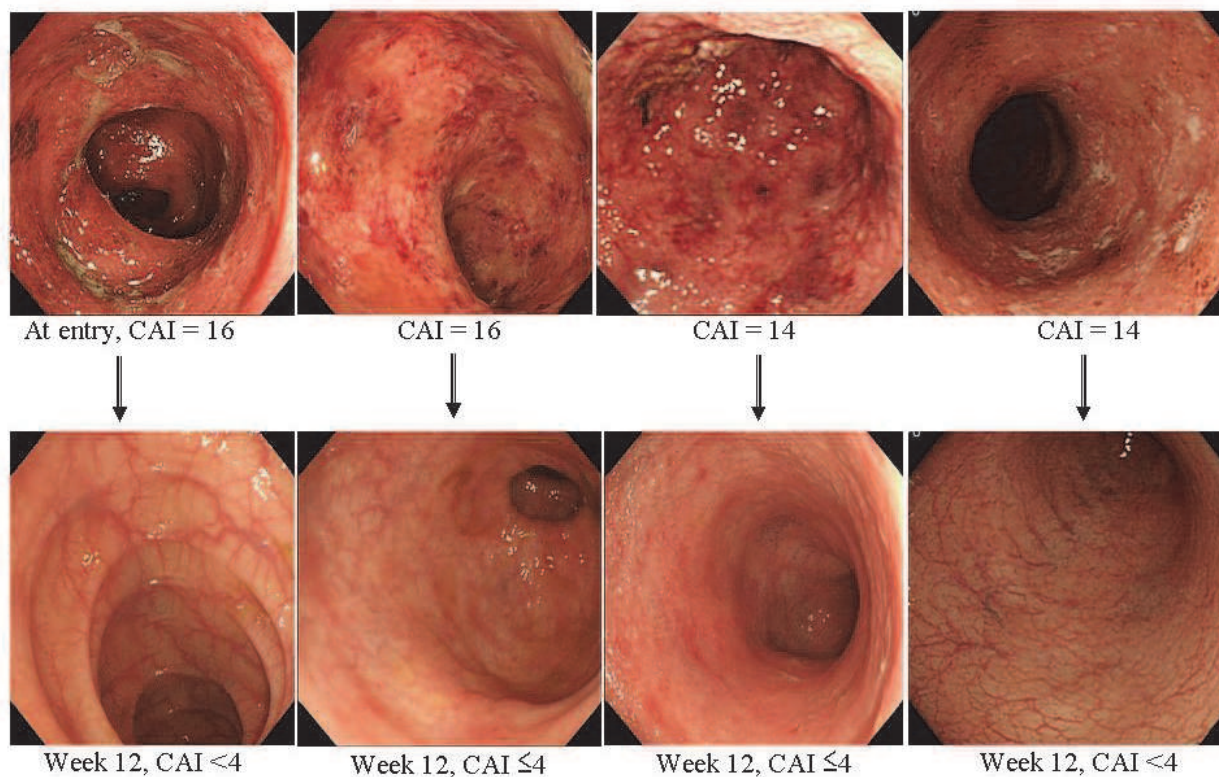


Fig. 4.



cases was just 3.4 months compared with 40.2 months for all 28 patients and 65.4 months for the 8 patients who did not respond at all. The response to GMA seemed to be independent of baseline CAI. The authors concluded that first UC episode and short disease duration might be good predictors of response to GMA in that clinical setting. Further, they stated that GMA could be an effective first line medication for steroid naïve patients (23,32,56).

### 9. The impact of GMA on mucosal leucocytes

It is of particular interest to see if GMA, in fact does impact the mucosal level of infiltrating myeloid leucocytes. As stated above, colonic biopsies were taken from active disease sites before and after GMA induced remission in patients with active UC. Figure 5 shows representative histology photographs from a GMA responder patient. The specimen taken at baseline shows the colonic mucosa is infiltrated by a vast number of inflammatory leucocytes, primarily granulocytes and monocytes/macrophages; the density of the infiltrating cells was strongest in or around the glandular lumen (crypt abscesses). The specimen taken when the patient had achieved remission shows very striking reduction in inflammatory cell infiltrate. Surprisingly, the density of leucocytes was reported to be stronger in steroid naïve patients vs patients on steroids, suggesting that corticosteroids have inhibitory effects on neutrophils (23).

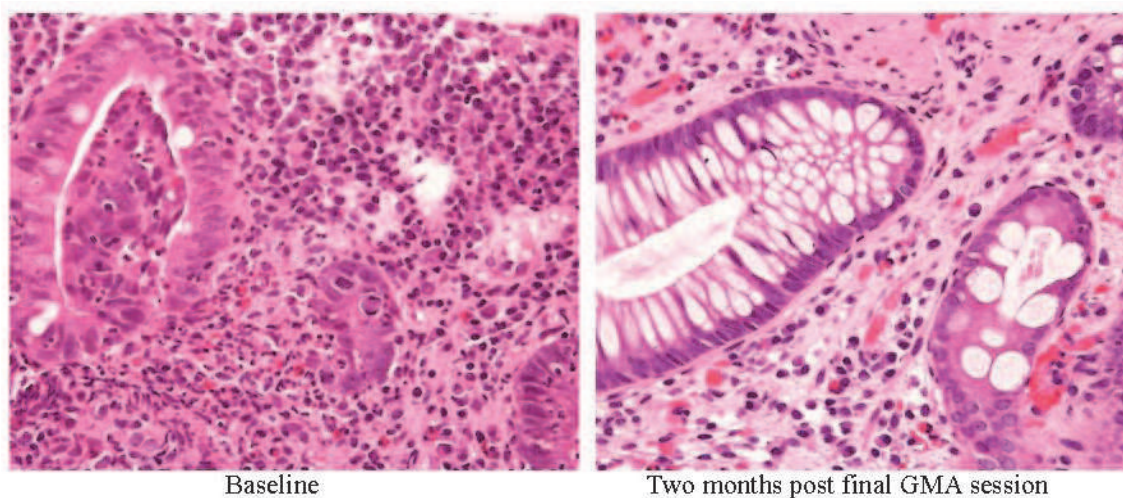


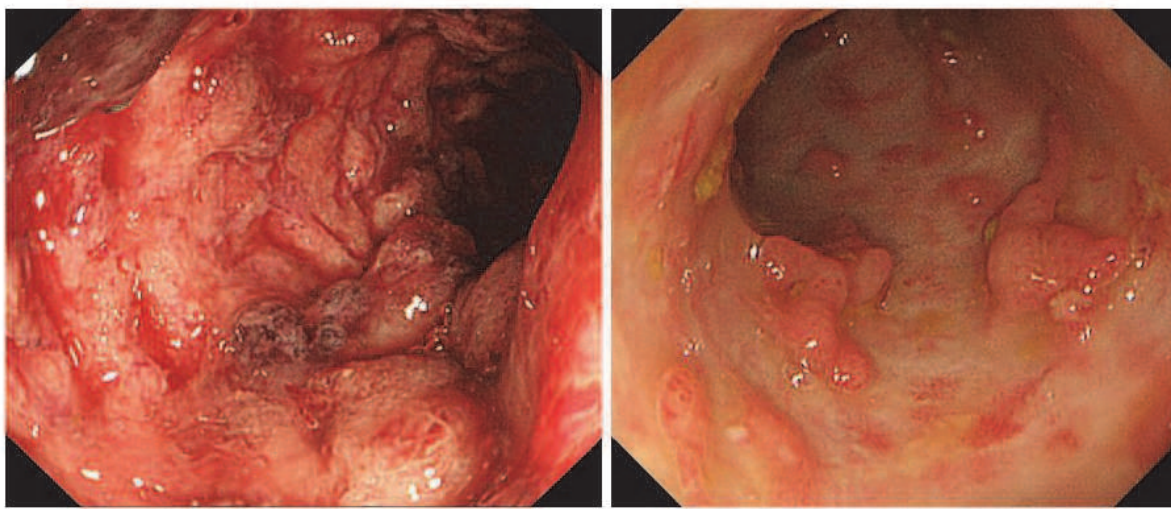
Fig. 5.

### 10. Colonoscopic features of non-responders to GMA

As reviewed above, several studies have reported that any patient with a fair level of colonic mucosa is a potential responder to GMA. In contrast, Figure 2 (above) shows deep and extensive colonic lesions with virtually no mucosal tissue left at the lesion sites in two typical GMA non-responder patients. Such patients are unlikely to respond to any medication except colectomy. Even patients with a near equal CAI score had very different mucosal damage status, indicating that CAI per se does not reflect the full extent of mucosal damage in patients with UC. Figure 6 shows colonoscopy photographs from the colonic mucosa of a 60-year-old steroid dependent patient who showed partial response to GMA. At baseline, the major colonoscopic findings seen are strong inflammation with multiple polyp-like protrusions in the mucosa. Following a course of GMA therapy, inflammation

has alleviated, but multiple polyps are exposed and apparently seem not to be affected by GMA, but the mucosa appears to be regenerating once again, suggesting a fair level of mucosal tissue was left prior to the initiation of GMA therapy. Based on CAI, this patient might be in clinical remission, but has not achieved endoscopic (colonoscopic) remission, which could require a long observation time.

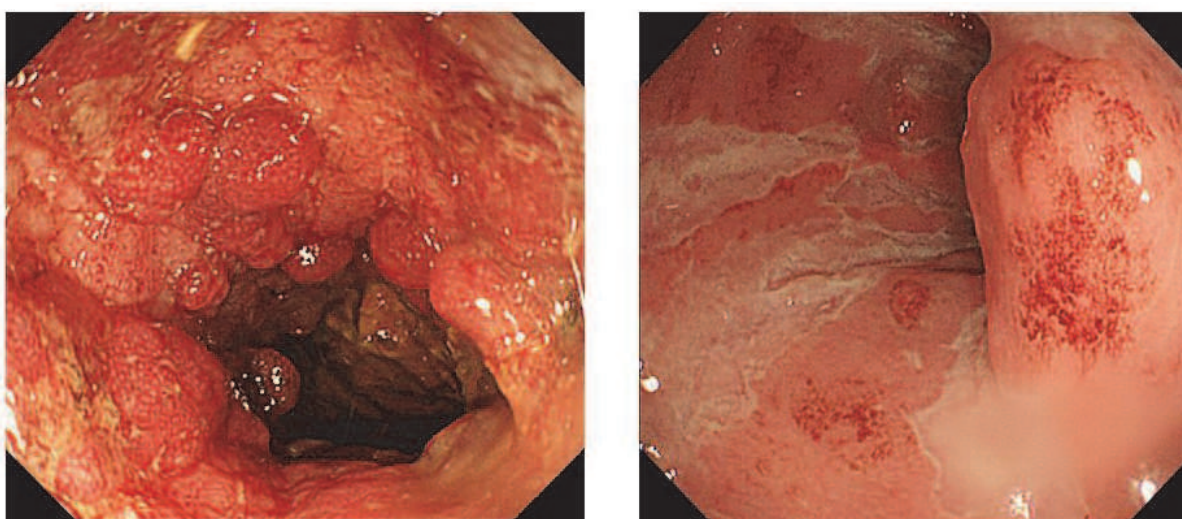
A small minority of patients without deep colonic lesions or extensive loss of the mucosal tissue do not respond to GMA as well. Colonoscopy photographs from such patients are presented in Figure 7, showing inflammation, but without extensive ulcers (entry CAI, 15). These cases are likely to have a long history of multiple drug therapy. However, no patient with the entry colonoscopy features seen in Figure 2 did show any significant fall in CAI score.



A 60-year-old patient with left-sided colitis, steroid dependent with severe UC in the presence of optimal corticosteroid, baseline CAI = 16.

Four months post last GMA (partial response)

Fig. 6.



Case A, GMA non-responder due to lack of adequate mucosal tissue.

Case B, GMA non-responder defined by patient's demography

Fig. 7.



### 11. Colonoscopic features of patients who are most likely to respond to GMA

From the plethora of published clinical observations, it appears that drug naïve patients with superficial lesions, usually first episode cases are the best responders to GMA, respond soon after a few GMA sessions and can be spared from multiple drug therapy. Typical colonoscopic features in these patients are seen in Figure 8. Accordingly, GMA should have maximum impact if applied immediately after a flare up, and be most effective in first episode cases.

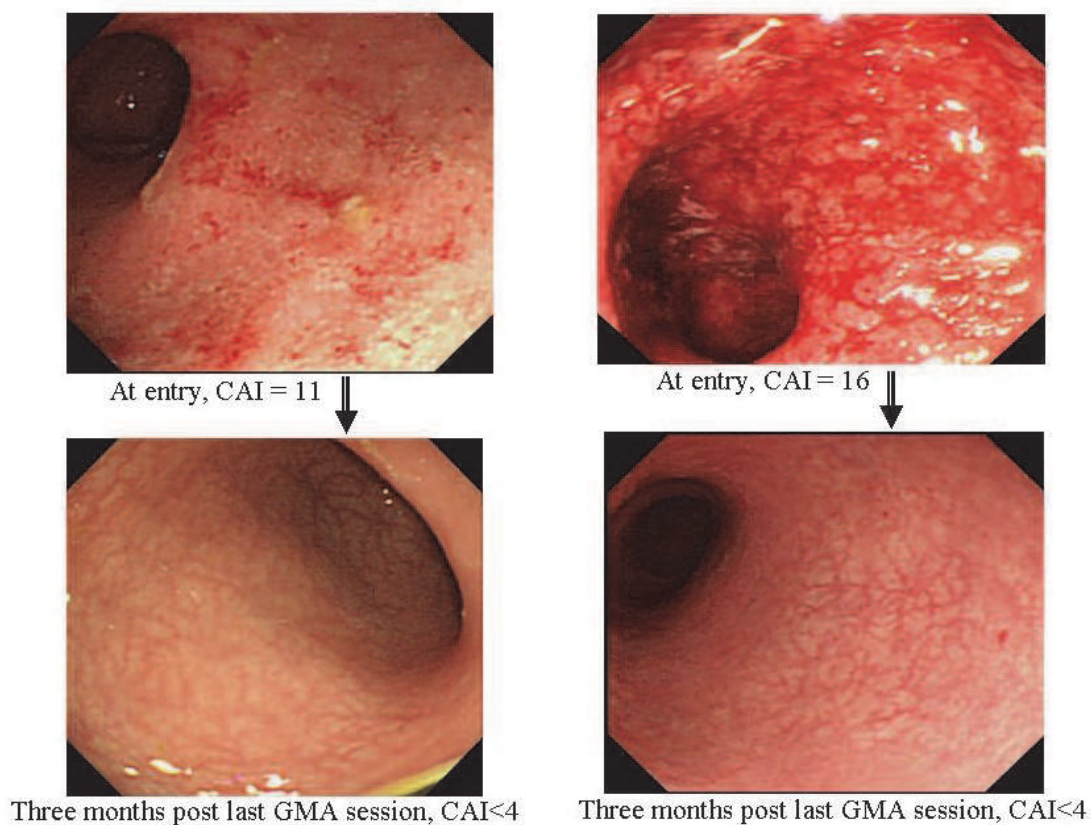


Fig. 8.

### 12. Concluding remarks

The gastrointestinal system is often affected by diseases which can impair its function and the individual's well being. The colonoscope may be regarded as the gastroenterologist's eyes and arms. Within limits, surgery can be achieved by the application of colonoscope like removing suspected cancerous lesions and excision of polyps which grow inside the large intestine in many individuals and can cause morbidity. Further, the large intestine is the main organ where IBD, in particular UC develops as a very debilitating health disorder. UC patients present with diverse clinical and endoscopic disease severity levels, and therefore, their clinical response to medical interventions can be complete remission, partial response or no response at all. Therefore, without colonoscopic evaluations of patients' relevant demographic variables, medical resources will be wasted together with prolonged morbidity time for many patients. Further, patients with UC have activated myeloid leucocytes, which infiltrate the colonic mucosa in vast numbers and potentially can



exacerbate the inflammation and perpetuate the disease. Accordingly, efficient depletion of myeloid leucocytes by GMA, which reduces the mucosal concentrations of myeloid leucocytes, should benefit patients with UC. In spite of this view, clinical efficacy outcomes are both encouraging as well as disappointing; the answer might lie in the patients' disease status at entry. By the power of colonoscopy over a decade in patients with UC we have learnt that all patients with the first UC episode and short duration of disease readily respond to GMA and can be spared from multiple drug therapy. Similarly, most steroid naïve or dependent patients who have a fair level of intact mucosal tissue are potential responders to GMA. Patients with extensive loss of the mucosal tissue and those with a long history of exposure to multiple drugs like corticosteroids are unlikely to respond to GMA. Further, one of the most favoured features of Adacolumn GMA is its safety profile. Serious side effects are very rare. This is in sharp contrast to multiple severe side effects associated with most conventional pharmacologicals and new biologics. Our view is that in patients with UC, there is an evolving scope for therapeutic opportunity based on taking away the sources of inflammatory cytokines.

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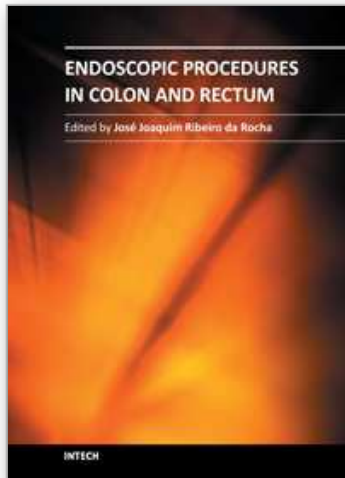
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## **Endoscopic Procedures in Colon and Rectum**

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Endoscopic procedures in colon and rectum presents nine chapters which start with introductory ones like screening by colonoscopy as the preparation and monitoring for this exam. In addition to these approaches the book aims in the last four chapters to explain endoscopic diagnostic and therapeutic aspects in the colon and rectum. The description of each text is very comprehensive, instructive and easy to understand and presents the most current practices on the topics described. This book is recommended for general and colorectal surgeons as it presents guidelines for diagnosis and treatment which are very well established.

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