

Ulcerative Colitis, a Debilitating Inflammatory Bowel Disease: How to Treat Without Drugs

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SUMMARY

Colonoscopy provides a unique opportunity to view intestinal lesions, inflammation, ulcers and make diagnostic assessment in patients with Ulcerative Colitis (**UC**). Further, cytokines like Tumour Necrosis Factor (**TNF**)- α have a validated role in the immunopathogenesis of UC, and intercepting inflammatory cytokines is currently the best hope for maximizing treatment efficacy, but the therapeutic impact of anti-TNF biologics is compromised by serious adverse side effects and loss of response. However, major sources of inflammatory cytokines include myeloid lineage leucocytes (granulocytes, monocytes), which in patients with UC are elevated with activation behaviour and increased survival time. Hence, selective depletion of myeloid leucocytes by adsorptive Granulocyte, Monocyte Apheresis (**GMA**) with an Adacolumn, which reduces the circulating level as well as the mucosal concentrations of myeloid leucocytes should be therapeutic in UC. In spite of this view, efficacy outcomes have been encouraging as well as disappointing, reflecting different demographic variables at entry. In line with this thinking, in a cohort of 120 patients with active UC, we identified responders and non-responders to GMA as follows. Most patients with a fair level of intact mucosal tissue appeared to respond well. Specifically, all patients with the first UC episode and short duration of disease responded well. The second best responders were steroid naïve patients, most were spared from corticosteroids. Patients with deep colonic lesions together with extensive loss of the mucosal tissue and those with a long history of exposure to multiple pharmacologics were identified as unlikely responders

to GMA. Further, one of the most favoured features of GMA is its safety profile, which is in sharp contrast to multiple severe adverse effects associated with most conventional pharmacologics 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. **Keywords:** Ulcerative Colitis; Neutrophils And Monocytes; Mucosal Biopsy; Loss Of Mucosal Tissue; Granulocyte And Monocyte Apheresis; Neutrophil Infiltration; Colonoscopy.

INTRODUCTION

Ulcerative Colitis (**UC**) is one of the two major phenotypes of the Idiopathic Inflammatory Bowel Diseases (**IBD**) of the intestine; Crohn's Disease (**CD**) the other major phenotype of IBD [1], which is not featured in this review. Ulcerative Colitis (**UC**) is a disease of mucosal inflammation and is limited to the large intestine, often characterized by bloody diarrhoea, tenesmus, abdominal discomfort, fever, anaemia, and weight loss. However, in spite of landmark progress in medical therapy of IBD, factor(s) associated with the dysregulated or otherwise exuberant immune profile in patients with active IBD is not understood well at present. UC was the first phenotype of IBD to be characterized as a distinct disease entity. Therefore, the early history of IBD has featured UC, but this is not to say that UC appeared before CD [1-3]. Both conditions were likely afflicting humans long before modern medicine was able to distinguish them. However, 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. In clinical settings UC is seen to be confined to the large intestine (colon and rectum), while CD may be seen in any part of the digestive tract, from the mouth to the perianal, and up to 70% of CD patients may have small intestinal involvement [2]. Both UC and CD tend to run a remitting-relapsing course affected by diverse environmental factors [1,2].

From here on this article focuses 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 article). However, in this article, our endeavours were supported by the diagnostic power of colonoscopy to identify patients with an active flare of UC who were most likely to respond to selective, but therapeutic removal of elevated/activated myeloid lineage leucocytes (granulocytes and monocytes/macrophages) by extracorporeal adsorption as a non-pharmacologic treatment intervention. This strategy is known as GMA, which stands for granulocyte and monocyte adsorption [4]. In Figure 1 colonoscopic photographs from the colonic mucosa of a healthy human subject and from patients with UC are presented. 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. However, in patients with IBD, the vascular patterns may be lost due to inflammation or ulcers (Figure 1).

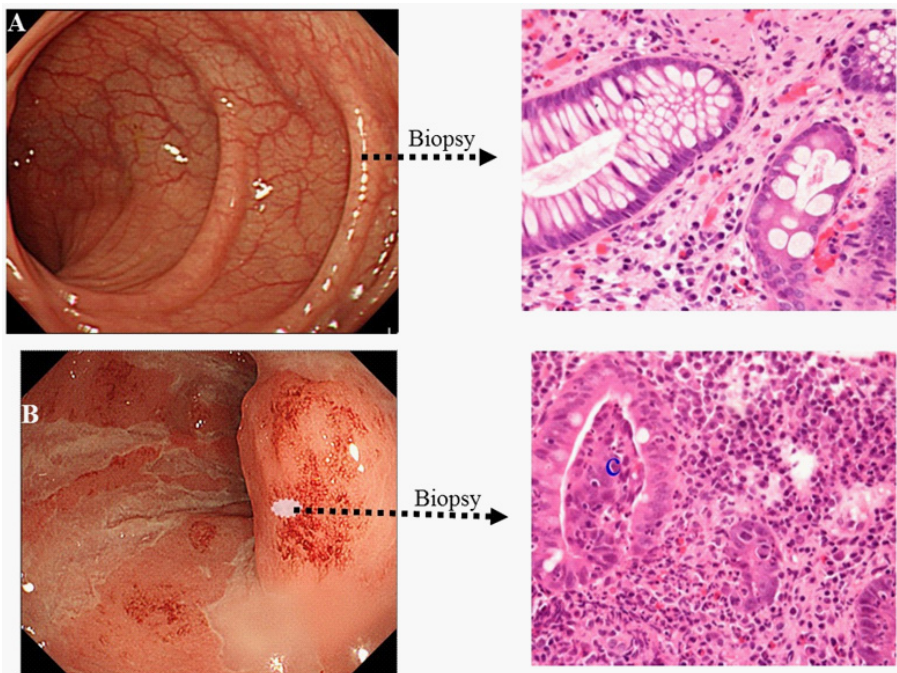


Figure 1: The colonic mucosa in a healthy individual or in a patient with quiescent UC is well vascularised for efficient absorption of water and nutrients from the gut. Accordingly, leucocyte accumulation and crypt abscess formation is not seen in the biopsy. B, in patients with active ulcerative colitis, the mucosa may be inflamed, vascular patterns are lost, and absorption of water and nutrients can be impaired. This may lead to erosions and ulcers. In B, biopsy from the colonic mucosa shows vast numbers of myeloid leucocytes in the inflamed mucosa and the formation of the so-called crypt abscess (**c**). This patient had a long history of exposure to multiple pharmacologics and had failed to respond to optimal doses of conventional medications. Likewise, such patients may not readily respond to adsorptive Granulocyte/Monocyte Apheresis (**GMA**).

The symptoms of UC are due to the ulceration and 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 compromised. In Figure 2, typical colonoscopy photographs from the surface of the colon or the rectum of patients with severe, fulminant UC are seen. Extensive and deep ulcers together with near total loss of the mucosal tissue are not uncommon in patients with severe UC even in the presence of optimum conventional medications. This condition is debilitating, 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 ulcers. Such patients are not likely to respond to any drug based medication or even to therapeutic

depletion of myeloid leucocytes by the Adacolumn GMA, they have fulminant UC (disease persists in the presence of optimum medication) and often must opt for 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 resources.

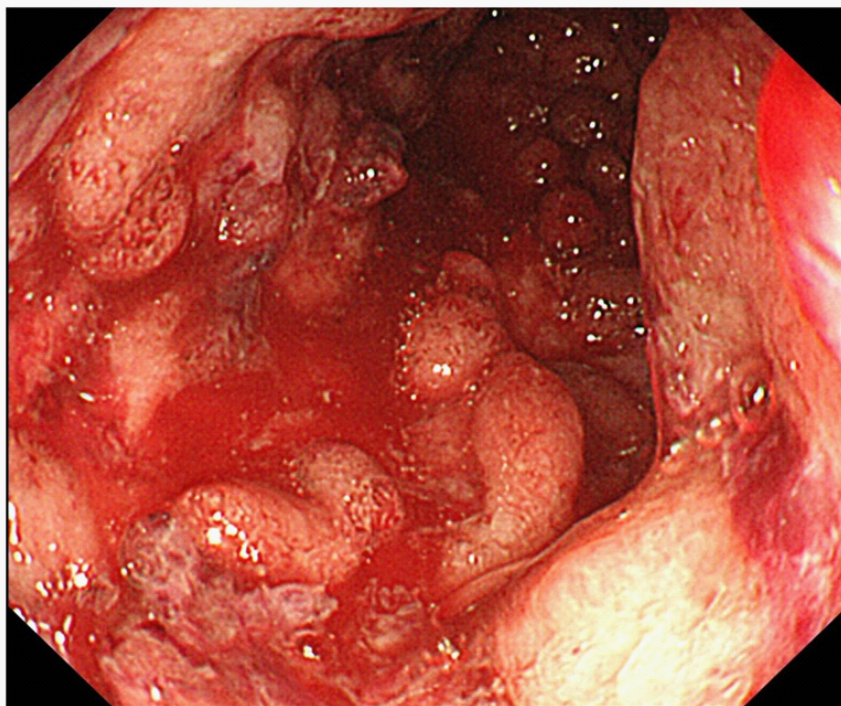


Figure 2: Colonoscopy image showing extensive and deep ulcers together with near total loss of the mucosal layer seen in a patient with fulminant ulcerative colitis. This condition is debilitating, and the patient may show weight loss, and experience an impaired quality of life.

Surgery known as colectomy may be an option in such cases.

LIMITATIONS OF CURRENT PHARMACOLOGIC OPTIONS FOR ULCERATIVE COLITIS PATIENTS

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 [1-3,5-7], 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 a 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 [8,9]. 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 [3,10-15]. Treatment failure in patients with severe disease has often been an indication for colectomy in up to 40% of steroid refractory patients [3,16] although in recent years, cyclosporin A (**CsA**) has been introduced for corticosteroid refractory UC [14,17]. Despite being moderately effective in this clinical setting in reducing colectomy rate, there remain serious concerns over long-term efficacy and toxicity of CsA [18]. However, this is not to say that drugs have 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.

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 [8,9]. 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 [19-21].

MYELOID LINEAGE LEUCOCYTES, CYTOKINES AND ULCERATIVE COLITIS.

It is now known that UC is exacerbated by inflammatory cytokines like Tumour Necrosis Factor (**TNF**)- α , interleukin IL)-1 β , IL-6, IL-8 and others [22]. 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 [23,24]. Indeed, the efficacy of IFX in patients with CD [24] as well as in UC [23] 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 of biologics [25,26].

There is growing evidence for the role of myeloid lineage leucocytes in the immunopathogenesis of IBD [3,4,27]. Patients with active IBD harbour elevated and activated myeloid lineage leucocytes in the presence of compromised lymphocytes [27-32]. 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 [3,20,31]. When activated, myeloid leucocytes produce an array of pleiotropic cytokines like TNF- α , IL-1 β , IL-6, IL-12, IL-23, which are strongly pro-inflammatory [33]. Therefore, targeting leucocytes as key players in the exacerbation of IBD is what lies behind GMA with the Adacolumn [4]. Likewise, neutrophils in patients with IBD show activation behaviour [27] and prolonged survival time [34]. Factors that are known to promote neutrophil survival in IBD include inflammatory cytokines [35] and paradoxically corticosteroids [36], which are commonly used to treat IBD patients. Myeloid leucocytes, like the CD14(+) CD16(+) monocytes are major sources of TNF- α [37,38], 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% [29,39] to a statistically insignificant level [40], indicating that certain subpopulations of patients respond to GMA while others not so, suggesting that patients' baseline demographic variables might determine clinical response to this non-pharmacologic mode of therapy (reviewed below).

THE LOGICS OF THERAPEUTIC GMA IN ULCERATIVE COLITIS

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, patients with active IBD are found to have compromised lymphocytes [28-30]. With this in mind, certain sub-populations of lymphocytes like the CD4(+) CD25(+) phenotype, known as the regulatory T cells (**Treg**) have essential immune regulatory roles and therefore, are indispensable to the host [41-46]. Based on these understandings, the Adacolumn leucocytapheresis system (Figure 3) is designed to spare lymphocytes. It is filled with specially designed cellulose acetate beads of 2mm in diameter as the column leucocytapheresis carriers [47]. The carriers remove from the blood in the column most of the granulocytes, monocytes/macrophages together with a significant fraction of platelets [4,48]. Surprisingly, the procedure has been associated with a sustained increase in absolute lymphocyte counts in the post treatment phase [29,30,47,48] including the regulatory phenotype, CD4(+)CD25(+) Treg [46]. The mechanisms for sparing lymphocytes are briefly described here. Patients with immune dysfunction may have Immune Complexes (**IC**) in their plasma [4,48,49]. Cellulose acetate adsorbs immunoglobulin G (**IgG**) and IC from the plasma [49,50]. Upon adsorption, the binding sites on IgG and IC become available for the Fcγ receptors (FcγRs) on myelocytes [4,48-50]. Further, cellulose acetate with adsorbed IgG and IC generates complement activation fragments including C3a and C5a [4,49,50]. 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 [4,50]. 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 [4,48]. These basic phenomena proceed well on the carriers and lend the Adacolumn GMA selectivity.

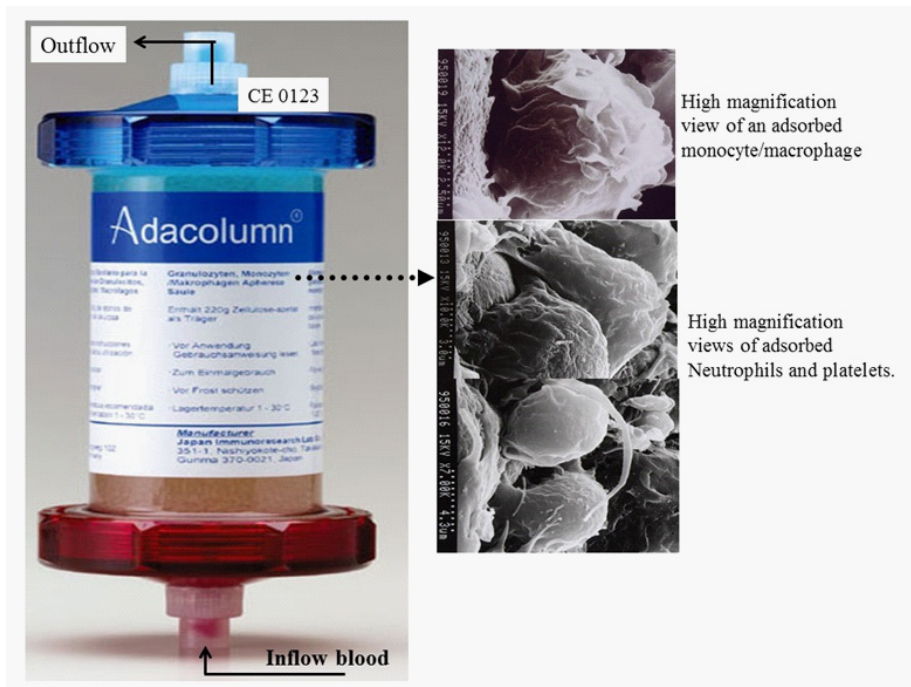


Figure 3: This figure shows the Adacolumn medical device developed to treat patients with inflammatory bowel disease like ulcerative colitis by depleting elevated and activated myeloid lineage leucocytes from patients' peripheral blood. The column is filled with cellulose acetate beads of 2 mm in diameter as adsorptive leucocytapheresis carriers. The Adacolumn is the first and the only adsorptive type leucocytapheresis medical device in clinical use. Also seen in this figure are scanning electron photomicrographs of leucocytes adsorbed onto an Adacolumn carrier. The high magnification views show that no lymphocyte was adsorbed to the carrier. Further, as seen, adsorbed leucocytes undergo extensive release reaction. Up to now, interleukin (IL)-1 receptor antagonist, hepatocyte growth factor, IL-10 and soluble TNF receptors have been measured (all have anti-inflammatory effects, reviewed in ref. [51]). Accordingly, during Granulocyte/Monocyte Apheresis (**GMA**), the blood, which returns to patients from the Adacolumn outflow may be likened to a biologic cocktail containing a vast number of soluble substances released by the adherent leucocytes.

ENDOSCOPIC FEATURES OF TYPICAL RESPONDERS TO GMA

In Figure 4, colonoscopic images from a typical GMA responder patient are presented. 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 [19,20,29]. Therefore, published data [19,20,29,31,51] 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. [29] was an 85%. Similarly, Tanaka et al. [31] 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 ≤ 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 [20,31] echo those of Suzuki et al. [29] a few years earlier [29], 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. [52], 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 cases was just 3.4 months compared with 40.2 months for all 28 patients and 65.4 months for another 8 patients who did not respond. 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 [19,20,29,52].

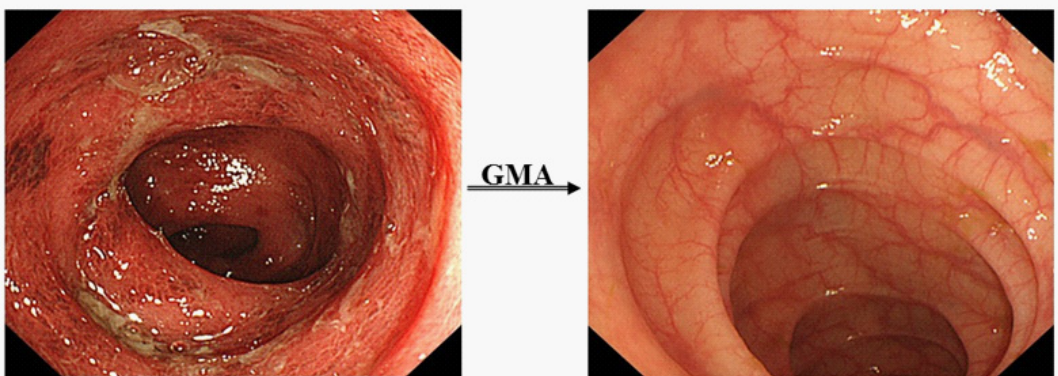


Figure 4: Typical colonoscopy photographs from an ulcerative colitis (UC) patient who achieved complete remission following a course of Adacolumn GMA to deplete elevated/activated myeloid lineage leucocytes. The major colonoscopic findings seen at baseline in this patient are widespread ulcers, but without extensive loss of the mucosal tissue seen in Figure 2.

GMA REDUCES THE MUCOSAL LEVELS OF MYELOID LINEAGE 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 an inhibitory effect on neutrophil trafficking [20,31].

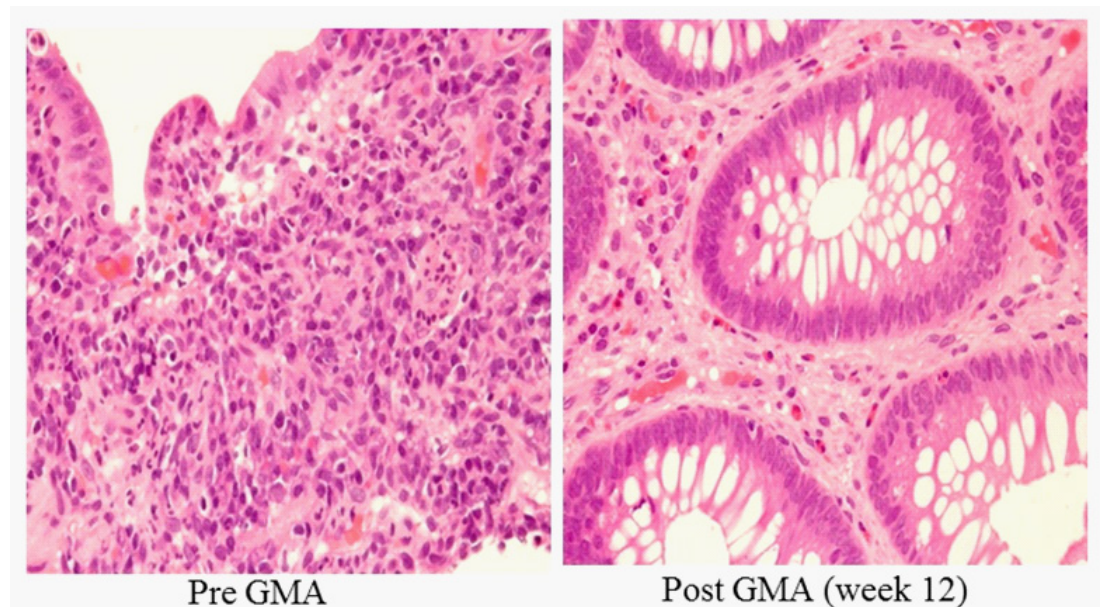


Figure 5: Typical immunohistochemical images taken from colonic biopsy specimens in a patient with active ulcerative colitis showing mucosal tissue is densely infiltrated by myeloid leucocytes and Adacolumn GMA therapy has reduced the concentration of the leucocytes in the mucosa. The specimens seen in this figure are from a patient with severe total colitis and corticosteroid naïve, baseline CAI score 15.

ENDOSCOPIC FEATURES OF TYPICAL NON-RESPONDERS TO GMA

As reviewed above, several studies have reported that any patient with a fair level of intact colonic mucosa is a potential responder to GMA. With this in mind, 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. Even patients with a near equal CAI score may have 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 colonoscopic images from the colonic mucosa of a steroid dependent patient who showed partial response to GMA. We tried to treat a few such patients because there are patients who do not wish to have colectomy like young ladies for social reasons or they fear colectomy may reduce their chance of conceiving a child. At baseline, the major colonoscopic findings seen are deep ulcers with multiple polyp-like protrusions. Following a course of GMA therapy, inflammation has alleviated, suggesting a fair level of mucosal tissue was left prior to the initiation of GMA therapy. Based on the CAI, this patient might be in clinical remission, but has not achieved endoscopic remission, and the patient soon may experience reactivation of UC. Also, a small minority of patients without deep colonic lesions or extensive loss of the mucosal tissue may not respond to GMA. Colonoscopy photographs from one such patient is presented in Figure 1, showing strong inflammation, but without extensive ulcers, entry CAI, 15, while on conventional medication. Such cases are likely to have a long history of exposure to multiple conventional drugs. However, no patient with the entry colonoscopy features seen in Figure 2 may show any significant fall in CAI score in response to GMA or drug based therapy, they are candidates for colectomy.

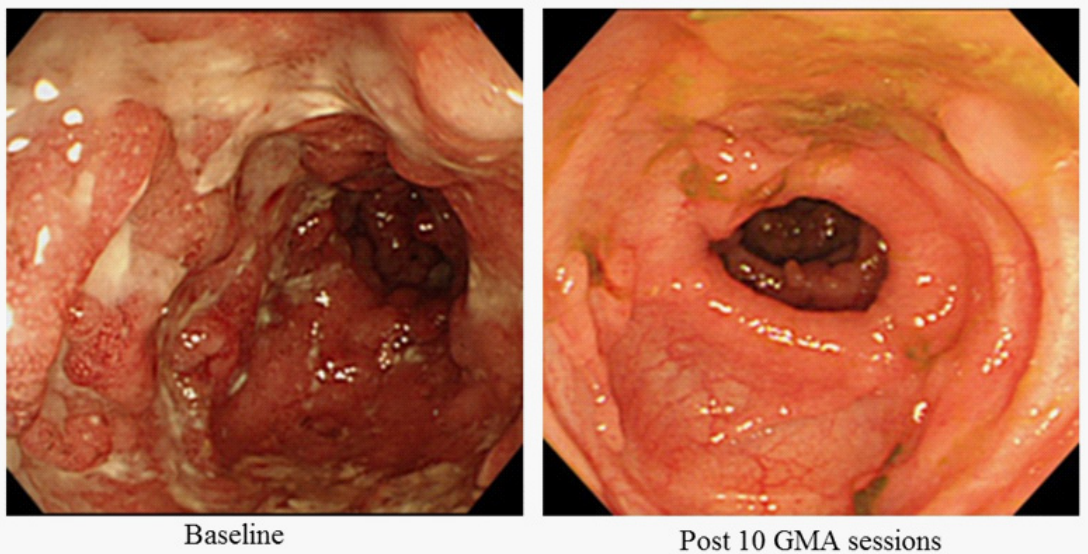


Figure 6: Colonoscopy photographs from a patient with deep ulcers showing partial response to GMA. The clinical outcome in this case was not very encouraging except that colonic ulcers stopped bleeding, but active colitis may return.

ENDOSCOPIC FEATURES OF THE MOST LIKELY GMA RESPONDER PATIENTS

As stated above, drug naïve patients without deep UC lesions, usually first episode cases are the best responders to GMA [29,52-56]. These patients respond soon after a few GMA sessions and can be spared from multiple drug therapy. Further, by avoiding corticosteroids from an early stage of IBD, patients who respond to GMA attain a favourable long term disease course [19,57]. Typical colonoscopic features in these patients are seen in Figure 7. Therefore, GMA should have maximum therapeutic impact if applied immediately after a flare up ,and be most effective in first episode cases [29,52,54,56].

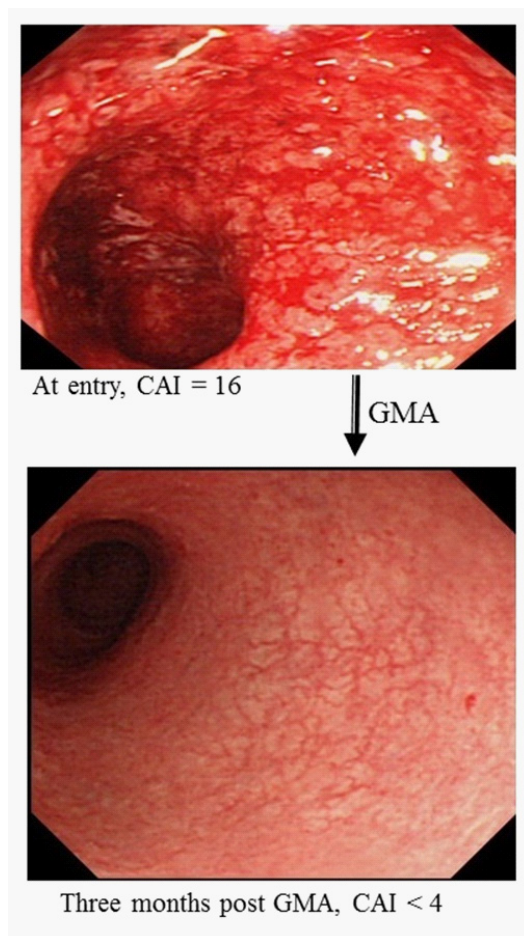


Figure 7: Typical colonoscopy photographs from a patient who may readily respond to GMA. This case was from a subgroup of patients who have been identified as good responders by colonoscopy. The patient was steroid naïve, but with total colitis and severe based on CAI, yet a good responder to GMA because, firstly, the mucosal tissue was preserved and secondly, the patient was not exposed to multiple drugs prior to GMA.

EFFECTIVE DOSAGE OF GMA IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

The evolution of modern medicine has relied on the outcomes of clinical trials to determine the dosage of drugs with maximum efficacy margin and minimum adverse side effect. Fortunately for GMA, which is a non-drug treatment strategy, reliance on clinical trial outcomes has been less demanding or at least lack of it has not caused serious concern partly because of its good safety profile, and partly for the fact that GMA removes from the body instead of adding to it. Accordingly, unlike drugs, loss of efficacy, dependency and refractoriness are not likely. Nonetheless, it is a basic requirement to know the most effective frequency and the number of GMA sessions for patients with mild, moderate or severe IBD as this can help to save time and cost. The reality is that up to now GMA treatment has been an empirical practice. Some institutes administer 2 GMA sessions per week in the first 2-3 weeks and then 1 session per week up to 10 or 11 sessions [20,29]. Hanai et al. [58] reported that although patients with steroid naïve UC responded well to 5 GMA sessions, steroid refractory patients with severe UC responded better to 10 sessions. In contrast, Suzuki et al. [29,52] administer 2 GMA sessions per week and cease when CAI decreases to 4 or less (clinical remission level); patients who do not improve after several sessions are classified as non-responders [52]. These treatment regimens are all contrary to the initial clinical trial in which 5 GMA sessions over five consecutive weeks were applied [48]. Regarding duration of one GMA session, Kanke, et al. [59] found that 90 minutes was significantly better than the routinely applied 60 minutes per GMA session. Likewise, Yoshimura et al. [60] increased the processed blood volume from the conventional 1800mL per GMA session to over 3000mL per session. In that study, the efficacy rate in the higher processed blood volume group was significantly greater than in the 1800mL per session group [60]. Further, in a prospective multicentre setting, Sakuraba et al. [61] found that intensive GMA at 2 sessions per week induced remission in shorter time and at a significantly higher rate when compared to weekly GMA. The authors assigned 112 patients with moderately active UC to 2 groups. Group 1 patients received one GMA session per week, while group 2 patients received 2 sessions per week, up to 10 sessions in both groups. The remission rate in group 1 was 46.7%, while in group 2 was 73.1%. Further, the mean time to remission was 28.1 days, in group 1 and 16.3 days in group 2. In spite of these outcomes, there is evidence to suggest that the efficacy of GMA is time dependent. As reviewed above, in patients with active IBD, large numbers of myeloid lineage leucocytes are found within the mucosal tissue [3,20], which may take several weeks to clear in spite of CAI showing clinical remission [32,53]. Additionally, the immunomodulatory actions of GMA are time dependent [51]. In line with this assertion, in rheumatoid arthritis patients, there was a sustained increase in the CD4+ T-lymphocytes up to 12 weeks following the last GMA session [47]. Similarly, there was a striking down-modulation of the inflammatory chemokine receptor CXCR3 on leucocytes several weeks after the last GMA session [48]. Accordingly, the full clinical efficacy of Adacolumn GMA may take several weeks to be seen, and should be higher at a higher processed blood volume [59,60].

CONCLUDING COMMENTS

Despite many triumphs, the aetiology of IBD is yet to be understood well. There is much to be optimistic about though, since more is known about UC than at any previous time point in history and this knowledge continues to increase. At present UC is still a very debilitating disease of dysregulated immune profile in the intestinal mucosa. Further, 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. However, it is now known that patients with UC have activated myeloid lineage leucocytes, which infiltrate the mucosa in vast numbers, potentially a pathologic factor. Accordingly, selective depletion of myeloid leucocytes by GMA should have therapeutic effect in these patients. In spite of this knowledge, efficacy outcomes from cohorts who received GMA are both encouraging as well as disappointing, reflecting different demographic variables potentially marking patients as responders or otherwise as non-responders. 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. Additionally, it is important to bear in mind that patients who respond to GMA and avoid pharmacologics from the initial stages of their UC continue to respond well and attain a favourable future clinical course. Patients with extensive loss of the mucosal tissue together with a long history of exposure to multiple pharmacologics are unlikely to respond to GMA. Further, GMA with the Adacolumn is very much favoured by patients for its safety profile. Serious side effects are very rare. This is in sharp contrast to multiple severe side effects associated with most conventional pharmacologics 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. However, selective depletion of activated and elevated myeloid lineage leucocytes to achieve IBD remission by applying GMA represents an intrigue, but this is yet to be achieved in all treated patients.

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