Clinical and endoscopic features of responders and non-responders to adsorptive leucocytapheresis: A report based on 120 patients with active ulcerative colitis

Caractéristiques cliniques et endoscopiques des sujets répondeurs et non répondeurs à la leucopherèse : un rapport basé sur 120 patients ayant une colite ulcéreuse

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Abstract

Background and Objective. — Elevated/activated myeloid leucocytes, like the CD14(+)CD16(+) monocytes are sources of TNF-α, and therefore, selective depletion of these cells by granulocyte/monocyte (GM) adsorption (GMA) should promote remission or enhance drug efficacy. However, studies in ulcerative colitis (UC) reported contrasting efficacy, from an 85% to statistically insignificant level. We investigated patients’ demography in responders and non-responders.

Methods. — In 120 UC patients, 61 steroid naive and 59 steroid dependent, we looked for entry clinical or endoscopic features to identify responders (or non-responders) to GMA. Patients received up to an 11 Adacolumn GMA sessions over 12 weeks. Patients were clinically and endoscopically evaluated, allowing each patient to serve as her/his own control. Immunohistochemistry on colonic biopsies was to reveal the impact of GMA on leucocyte infiltration of the mucosa.
Results. — Entry average clinical activity index (CAI) was 12.6, 10–16. An 80 of 120 patients responded (CAI ≤ 4); 45 steroid naïve (73.8%) and 35 steroid dependent (59.3%). Over 900 biopsies were processed. Infiltrating leucocytes were overwhelmingly polymorphonuclear and macrophages around and within crypt abscesses. There was a marked reduction of infiltrating leucocytes in responders. Most non-responders had extensive colonic lesions with virtually no mucosal tissue left at the lesions.

Conclusions. — Steroid naïve patients with short duration of UC were the best responders, while patients with deep colonic lesions and extensive loss of the mucosal tissue were non-responders.

Introduction

Ulcerative colitis (UC) together with Crohn’s disease (CD) are the major phenotypes of chronic inflammatory bowel disease (IBD) that has a relapsing-remitting feature. Relapses are manifested as increased inflammatory activity and symptoms. The latter include abdominal discomfort, diarrhoea, fever, and weight loss [1,2]. During a relapse, patients with IBD are treated with drugs like corticosteroids, 5-aminosalicylates (5-ASA), azathioprine, 6-mercaptopurines, methotrexate, cyclosporine, biologics, notably infliximab (IFX), and antibiotics (in some patients), with surgery being a common option if drug therapy fails and severe IBD continues [1—5].

However, recently, the efficacy of IFX has validated the role of inflammatory cytokines like tumour necrosis factor (TNF)-α in the immunopathogenesis of IBD. Further, patients with IBD often present with elevated or activated leucocytes of myeloid lineage (granulocytes, monocytes) and during active disease, vast numbers of these cells are seen in the colonic mucosa in patients with UC [2,6,7]. Myeloid leucocytes, like the CD14(+)CD16(+) monocytes are major sources of TNF-α [8—10], and it could be valid to say that selective depletion of myeloid leucocytes by granulocyte and monocyte (GM) adsorption (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% [11] to a statistically insignificant level [12], indicating that certain subpopulations of patients benefit from GMA while others not so; could this reflect different demographic features (Discussion)?

In light of the afore reviewed background, the Adacolumn medical device has been developed for selective depletion of excess and activated leucocytes [13], which are suspected to promote IBD [14—16], and in the past few years, a large number of authors have reported on the clinical efficacy of GMA [17—28]. Further, in spite of the very poor clinical trial outcome in one study [12], treatment of IBD by GMA has been expanding in Europe and in Japan, unimaginable if, in fact, GMA therapy was not associated with clinical efficacy and in our view being without steroid sparing effect [17]. Our view is that GMA will remain as a non-pharmacologic strategy to treat IBD, very much favoured by patients for its safety profile. The major focus of this investigation was to identify patient demographic factors, which could label a patient a responder, or otherwise a non-responder to GMA. We found patients with the first UC episode and short duration of disease being the best responders, while patients with deep-colonic lesions and extensive loss of the mucosal tissue as unlikely responders.

Methods

Objectives

In view of the inherent diversity of demographic factors in patients with UC together with the aforementioned inconsistent clinical efficacy reports, in this investigation, we were interested to find patient background factor(s), which could be markers of clinical response (or lack of response) to the Adacolumn GMA. As the treatment cost with this medical device is very expensive, this work was expected to benefit cost-saving endeavours as well.

Patients’ demography at entry

One hundred and twenty consecutive patients, 57 male and 63 female with moderate to severe UC, average clinical activity index (CAI) 12.6, range 10—16 [30] were included (Table 1). Patients’ average age was 45.8 years, range 11—84 years. Of the 120 patients, 61 were steroid-naïve, and 59 steroid-dependent as defined by Hanai et al. [18,28]. The extent of UC was total colitis in 68 patients,

Table 1 Main baseline demographic features of the 120 patients with active ulcerative colitis (UC) who received Adacolumn granulocyte and monocyte adsorption (GMA) therapy.

<table>
<thead>
<tr>
<th>Demography</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>120</td>
</tr>
<tr>
<td>Mean age (range), years</td>
<td>45.8 (11—84)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>57/63</td>
</tr>
<tr>
<td>Use of corticosteroid</td>
<td></td>
</tr>
<tr>
<td>Steroid-naïve</td>
<td>61</td>
</tr>
<tr>
<td>Steroid-dependent</td>
<td>59</td>
</tr>
<tr>
<td>Location of lesion</td>
<td></td>
</tr>
<tr>
<td>Total colitis</td>
<td>68</td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>52</td>
</tr>
<tr>
<td>Clinical activity index, average (range) according to Rachmilewitz [30]</td>
<td>12.6 (10—17)</td>
</tr>
</tbody>
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and left-sided colitis in 52. All patients were on 5-ASA, 1.5–2.25 g/day for more than 8 weeks prior to entry, while the dose of prednisolone (PSL) in steroid-dependent group was 15–30 mg/day for at least 2 weeks prior to entry.

**GMA procedures**

GMA with the Adacolumn was as described previously [18,27]. In Japan, GMA is approved by the Ministry of Health for funding in the national health insurance scheme to treat patients with active IBD. Accordingly, all Adacolumns used in our hospital were purchased from JIMRO Co., Ltd. (Takasaki, Japan). Each patient could receive up to an 11 GMA sessions over 12 weeks. GMA therapy was added to the patients’ ongoing medication following a relapse or worsening UC. No additional medication was given. At entry and prior to each GMA session, the patients’ CAI scores were determined. In this study, GMA responder was defined as CAI inferior or equal to 4 at week 12.

**Colonoscopy and biopsy processing**

In all patients, during colonoscopy, mucosal biopsy specimens at baseline and post Adacolumn GMA treatment (week 12) were taken and processed precisely as described by Gironella et al. [31] to see the impact of GMA on mucosal leucocyte level. In each case, biopsy specimens were taken from the colonoscopically detectable inflamed mucosa and each patient served as her/his own control (entry vs. week 12, post GMA therapy).

**Ethical considerations**

As stated above, GMA with the Adacolumn is a Japan Ministry of Health approved treatment option for patients with active IBD. Additionally, the investigation was carried out in accordance with the principle of good clinical practice and the declaration of Helsinki at all times. Initially, patients were advised that they could choose between conventional medication and GMA with the Adacolumn. In under-age cases, consent from one of the patient’s parents was necessary.

**Statistics**

Where appropriate average values together with ranges are presented. CAI values at baseline and post GMA are compared by the Student’s t-test. \( P < 0.05 \) was considered statistically significant.

**Results**

**Clinical efficacy outcomes**

At entry, the average CAI score was 12.6, range 10—16 (\( n = 120 \)). Based on CAI, an 80 of the 120 patients (66.7%, \( P < 0.001 \)) responded to GMA (CAI inferior or equal to 4, our clinical response criteria for GMA in this investigation). These included 45 of 61 steroid-naive patients (73.8%, \( P < 0.001 \)) and 35 of 59 steroid-dependent (59.3%, \( P < 0.001 \)). In Figs. 1 A and B, the changes in CAI from baseline to week 12 are presented separately for steroid-naive and dependent groups, respectively. Based on this presentation, each patient served as her/his own control (entry vs. week 12). However, there was no relationship between entry CAI level and the clinical response to GMA.

**Colonoscopic features of GMA responders and non-responders**

Colonoscopy was done in all patients together with biopsy at entry and within 2 weeks following the last GMA session or week 12 for all responders. Colonoscopic photographs from typical GMA responder patients and typical GMA non-responder cases are presented in Figs. 2—4. Fig. 2 shows mostly erosions (case A), ulcers and erosions (case B) at entry and the restoration of mucosal vascular patterns at post GMA. Such cases readily responded to GMA. In contrast, Fig. 3 shows deep and extensive colonic lesions with virtually no mucosal tissue left at the lesion sites in two typical GMA non-responder patients. Even patients with a near-equal CAI score had very different mucosal damage status. Some patients without deep-colonic lesions or extensive loss of the mucosal tissue did not respond to GMA as well. Typical colonoscopy photographs from such patients are presented in Fig. 4, showing inflammation, but without extensive ulcers (entry CAI, 15). This case was a 70-year-old patient with a long history of multiple drug therapy. However, no patient with the entry colonoscopy features seen in Fig. 3 did show any significant fall in CAI score.

**The impact of GMA on mucosal leucocytes**

We were particularly interested to see if GMA, in fact, does impact the mucosal level of infiltrating-myeloid leucocytes. Over 900 biopsies were processed. Figs. 5 A and B show representative histology photographs from GMA responder patients. The specimens taken at baseline show 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 specimens taken at week 12 show very striking reduction in inflammatory-cell infiltrate. Surprisingly, the density of leucocytes was stronger in steroid-naive patients vs. patients on steroids.

**Steroid sparing effect of GMA**

All steroid-naive patients who achieved remission avoided corticosteroid therapy. At week 12, the average daily dose of PSL in the 35 steroid-dependent patients who achieved remission was 8.6 mg, range 0—20 mg.
Figure 1  Clinical efficacy outcomes of granulocyte and monocyte adsorption (GMA) therapy in 61 steroid-naïve (A) and 59 steroid-dependent (B) patients. Based on clinical activity index (CAI), an 80 patients (66.7%, \( P < 0.001 \)) from the total of 120 patients responded to GMA (CAI inferior or equal to 4: the clinical response criteria set for GMA in this study). In this figure, the changes in CAI from baseline to week 12 are presented allowing each patient to serve as her/his own control. It can be seen that there was no relationship between entry CAI score and the clinical response to GMA.

Figure 2  Colonoscopic features of granulocyte and monocyte adsorption (GMA) responder patients. Colonoscopy was done in all patients together with biopsy at entry and within 2 weeks following the last GMA session or week 12 for all responders. Here, colonoscopy photographs from typical GMA responder patients are presented. The photographs show mostly erosions (A) or extensive ulcers (B) at entry and a complete restoration of the mucosal vascular patterns at post GMA. Almost all such cases readily responded to GMA (further information on the colonoscopic features of responders and non-responders is presented in the legends to Figs. 3 and 4).
Responders and non-responders to GMA

Figure 3  Colonoscopic features of granulocyte and monocyte adsorption (GMA) non-responder patients. Here, colonoscopy photographs from typical GMA non-responder patients, at entry and at week 12 are presented. The colonoscopy at entry revealed deep and extensive colonic lesions with virtually no mucosal tissue left at the lesion sites. Even patients with a near-equal clinical activity index (CAI) score had a very different mucosal damage status. In case A, some fall in CAI was seen, but still far from inferior or equal to 4 we had set for the clinical response to GMA. In case B, there was absolutely no fall in CAI. However, no patient with the entry mucosal damage seen in this figure showed any significant fall in CAI (see below).

Figure 4  A very small minority of patients without deep-colonic lesions or extensive loss of the mucosal tissue did not respond to granulocyte and monocyte adsorption (GMA) as well. In this figure, colonoscopy photographs from a typical GMA non-responder without deep ulcers and extensive loss of the mucosal tissue are presented. As seen, inflammation in the colonic mucosa appears strong, but without extensive ulcers. This case was a 70-year-old male with total colitis and therefore, a long history of exposure to multiple drugs.
Safety of GMA

Neither during the procedure nor in the follow-up time any serious adverse side effect associated with GMA was observed. Transient flushing and light-headedness were seen in a small number of patients during or towards the end of the 60-minutes GMA session. These observations are in line with the reports in previous studies with GMA in patients with UC [17–28]. The safety profile of the Adacolumn GMA is in sharp contrast to pharmacologics, which are often associated with serious side effects that further complicate the ongoing IBD [2,3,32,33].

Discussion.

The major focus of this investigation was to determine mucosal features, which could identify patients as responders or otherwise as non-responders to the Adacolumn GMA. For this intention, we retrospectively treated 120 patients with active UC who visited our IBD centre to receive treatment for a flare-up. At the end of the GMA treatment course, the clinical response rates based on CAI were 73.8% in steroid-naïve patients and 59.3% in steroid-dependent patients, a very marked difference. At present, the underlying mechanism(s) associated with low GMA induced response rate in steroid-dependent patients is not clear to us. One factor could be a tendency for UC to exacerbate in the absence of an adequate corticosteroid. The steroid-naïve patients had not taken any steroid for that flare-up, while steroid-dependent patients were those who would improve upon administration of a corticosteroid or otherwise relapse when the corticosteroid dose was tapered [28]. In Japan, most patients are very reluctant to take corticosteroids and with this culture in mind, we avoid including corticosteroids in their medications if at all possible and this is a significant factor for our interest in GMA as a non-pharmacologic treatment option. Accordingly, all 45 steroid-naïve patients who achieved remission avoided corticosteroids and the dose of PSL in the majority of the 35 steroid-dependent patients who achieved remission had been tapered to 0. Further, a minority of patients were those who had their first UC episode, hence with a short duration of UC and steroid-naïve. The first-episode cases were the best responders to GMA and this could have contributed to a higher remission rate in the steroid-naïve group.

As our major interest was to find mucosal features, which could identify responders and non-responders to GMA, at entry as well as at the end of the GMA treatment course, colonoscopy together with biopsy were done in all patients. Colonoscopy showed deep and extensive colonic lesions with virtually no mucosal tissue left at the lesion sites in most GMA non-responders. Even patients with a near-equal CAI score had very different mucosal damage condition. A small number of patients without deep-colonic lesions or extensive loss of the mucosal tissue did not respond to GMA as
well, but most of such non-responders had a long duration of UC (see below). However, no patient with deep-colonic lesions and extensive loss of the mucosal tissue at entry showed any marked fall in CAI. It should be equally important to state here that entry CAI per se did not identify responders or non-responders to GMA because many GMA responders, even steroid-naïve patients had CAI scores equal or even higher than the CAI score in some patients who did not respond at all. As the treatment cost with this medical device is over $1000 per session, potentially the observations in this study should support endeavours to save resources and reduce morbidity time (patients may opt for alternative medications without waiting for several weeks to see the efficacy of a GMA).

We also wished to see if GMA treatment reduces the level of infiltrating-myeloid leucocytes in the colonic mucosa where they are suspected to exacerbate IBD and for this purpose, we processed a very large number of biopsies from all patients. Our investigations showed a striking reduction in infiltrating-myeloid leucocytes in responder patients. Paradoxically, during active disease, the density of the infiltrated neutrophils was stronger in steroid-naïve patients vs. patients on steroids. This could be taken as an inhibitory effect on neutrophils by corticosteroids [34].

Regarding the clinical efficacy of GMA, there is no shortage of contrasting efficacy outcome reports in the literature. In 2004, Suzuki, et al. reported an 85% efficacy rate or 17 of 20 patients they treated with GMA as the first-line medication [19]. Highlights of this report appeared in Gastroenterology as special summaries [11]. Then in 2008, a study in the US [12] reported no statistically significant difference between the sham arm and the GMA arm. However, the patients included in the latter study had very different demography vs. the former study in which all patients were steroid-naïve, most with a short UC duration and only needed first-line medication [19]. Interesting, Suzuki reported that the only three GMA non-responder patients in that study had defective mucosal tissue and deep ulcers. Likewise, in a subsequent study, Suzuki et al. [26] reported that all patients with a short duration of UC (first-episode cases) readily responded to GMA, while all of the eight GMA non-responders in that study had long duration of UC and a long history of exposure to corticosteroids. Our observations are in line with those reported by Suzuki et al. [26]. The bottom line is that there are subgroups of IBD patients who should benefit from GMA and subgroups that do not respond significantly, the patients’ demography should reflect these.

As stated above, the Adacolumn has been developed for selective depletion of elevated granulocytes and monocytes/macrophages, which are suspected to be significant factors in the exacerbation and perpetuation of IBD. Additionally, there is significant fall of platelets [13,29]. Lymphocytes are spares; in fact increase post GMA [13]. However, wary physicians have frequently asked “how selectivity is achieved and what is the advantage of sparing lymphocytes?” The GMA carriers adsorb FcγR and complement receptors bearing leucocytes [20]. These are granulocytes, monocytes and small subsets of B cells and natural killer (NK) cells [35,36]. The expression of these sets of receptors is not a feature of lymphocytes and therefore, Adacolumn spares lymphocytes [13,19,29,37]. Further, the role of lymphocytes in the relapse of IBD is uncertain. Indeed, indiscriminately removing lymphocytes might be unwarranted in patients with IBD [38,39]. To our knowledge, there is no published study showing elevated peripheral lymphocytes in patients with IBD [38,39]. To our knowledge, there is no published study showing elevated peripheral lymphocytes in patients with IBD. On the contrary, recent studies found that lymphocyte counts in patients with active UC were well below the standard laboratory levels, which increased significantly, in absolute number, following a course of GMA [13,19,29,37]. Additionally, one of the best controlled studies on lymphocytapheresis in IBD reported by Lerebours and colleagues [40], the authors selectively removed peripheral lymphocytes in patients with CD with the aim of suppressing clinical relapse. At the end of an 18-month follow-up, the clinical outcome in the lymphocytapheresis group was 21% inferior to that of control.

In conclusion, patients with UC have activated myeloid leucocytes, which infiltrate the colonic mucosa in vast numbers and potentially can exacerbate the inflammation and tissue injury. Accordingly, efficient depletion of myeloid leucocytes by GMA, which reduces the mucosal concentrations of these leucocytes, should benefit patients with active IBD. 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. Our experience over a decade in patients with UC suggests 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 should respond 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. Most side effects are transient flushing, and light-headedness. This is in sharp contrast to multiple severe side effects associated with most conventional pharmacologics and new biologics.

Conflict of interest statement

The authors have absolutely no conflict of interest in connection with the publication of this manuscript.

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