Efficacy and safety of adsorptive granulomonocytapheresis in Chinese patients with ulcerative colitis: A retrospective analysis of 50 cases with focus on factors impacting clinical efficacy

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Abstract

Background: Myeloid-derived leucocytes, a major source of inflammatory cytokines, play an important role in the exacerbation of ulcerative colitis (UC). Selective depletion of myeloid leucocytes by adsorptive granulomonocytapheresis (GMA) with an Adacolumn should alleviate inflammation and promote remission. However, there are discrepancies among the reported efficacy outcomes. This study aimed to evaluate the efficacy and safety of GMA in UC patients with a focus on factors affecting clinical efficacy.

Methods: This was a retrospective analysis of 50 patients with active UC who had received GMA therapy. GMA efficacy was evaluated based on the Rachmilewitz's clinical activity index (CAI) and Mayo endoscopic score for mucosal healing. Laboratory findings were analyzed to demonstrate any relationship with the GMA-responder or nonresponder feature. Adverse events were recorded during and after GMA therapy.

Results: The overall clinical remission rate (CAI ≤ 4) was 79.2%, and among these, the mucosal healing rate was 59.2%. The clinical remission rate was 69.2% in patients who received 5 GMA sessions and 82.3% in patients who received 10 sessions. Significantly higher baseline CAIs and lower albumin and hemoglobin levels were observed in nonremission cases compared with those who achieved remission. Four patients (8%) experienced transient adverse events, but none were severe.

Conclusions: GMA was favored by patients because of its safety and nonpharmacological treatment options. Accordingly, UC patients were spared from pharmaceuticals after applying GMA therapy.
1 | INTRODUCTION

Ulcerative colitis (UC) is one of the two major phenotypes of inflammatory bowel disease (IBD), with a chronic relapsing-remitting course involving mucosal inflammation in the colon and the rectum. The other major IBD phenotype is Crohn’s disease. These conditions afflict millions of individuals throughout the world with debilitating symptoms such as bloody diarrhea, fever, abdominal discomfort, and weight loss, which impair their daily activities and quality of life. Currently, the precise etiology of UC is not fully understood; therefore, while curative medical therapy is not available, the aim of medical therapy is to suppress the symptoms. Dysregulated immunologic profiles triggered by interactions between host genetic and environmental factors have been considered the major pathophysiological alteration leading to UC.

Furthermore, currently, the medical treatment of mild to moderate UC considers adsorptive granulomonocytapheresis (GMA) as a second-line treatment option based on the available evidence in the literature. Immunologic abnormalities together with extensive infiltration of leucocytes of the myeloid lineage (granulocytes and monocytes) into the colonic mucosa have been observed through histological examination of mucosal biopsies in patients with active UC. Additionally, neutrophils in patients with UC show activated behaviors and prolonged survival times, producing an array of cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-12, and IL-23, which are strongly pro-inflammatory with a major role in the exacerbation and perpetuation of UC. Accordingly, selective depletion of these leucocytes thereby lowering the pro-inflammatory cytokine profile using GMA with an Adacolumn has been applied as a nonpharmacological treatment option for patients with active UC. Since the publication of the first clinical trial on GMA in patients with UC, a large number of publications, primarily from Japan, Europe, and the United States, have reported varying efficacy outcomes ranging from 85% to a statistically insignificant level.

GMA therapy for IBD was not approved in China until 2013, and very few articles on GMA have been published in China. The first multicenter study on the efficacy and safety of GMA therapy involving 34 Chinese patients with UC was published in 2017. Currently, clinical experience on the efficacy and safety of GMA in Chinese patients with IBD is still inadequate. Our hospital is one of the first few medical centers in China to undertake GMA therapy for patients with UC. Herein we report the outcomes of a retrospective study after analyzing the efficacy and safety of GMA therapy in 50 Chinese patients with active UC.

2 | MATERIALS AND METHODS

2.1 | Patients

From August 2015 to October 2018, a total of 50 patients (27 males and 23 females) with active UC received GMA therapy.
therapy. The average age was 46 ± 15 years, and the average UC duration was 44 ± 66 months. The diagnosis of UC was based on the Consensus on Diagnosis and Treatment of Inflammatory Bowel Disease, 2012 Guangzhou, China. Furthermore, based on the past exposure to corticosteroids, the patients were divided into two groups: steroid-naive (n = 36) and steroid-refractory or dependent (n = 14). Likewise, based on the UC disease course, the patients were divided into two groups: first episode cases (n = 12) and chronic continuous cases (n = 38). Other demographic variables including the location of lesions defined according to the Montreal classification, and UC severity according to Truelove and Witts, are presented in Table 1.

2.2 GMA procedures

All patients received GMA therapy using an Adacolumn (JIMRO, Takasaki, Japan) twice a week as previously described. In brief, the Adacolumn and blood circuit lines were primed with sterile saline to remove air bubbles from the column void volume and flow lines, and then the system was primed with heparinized saline. Intravenous access via the antecubital vein was initiated in one arm and the column outflow was returned via the antecubital vein in the contralateral arm. The duration of one GMA session was 60 minutes at a flow rate of 30 mL/min according to our protocol. Conventional medications that the patients had begun well in advance of the first GMA session could be continued during the entire course of GMA therapy without any change in dosage. Furthermore, according to a previous study by Hanai et al, patients with moderately active UC or a steroid-naive background received 5 GMA sessions, while those with severe UC responded well to 10 sessions. Therefore, 13 patients received 5 GMA sessions and 35 received 10 sessions. Two patients discontinued treatment due to lack of efficacy or adverse events.

2.3 Evaluation of efficacy and safety

The clinical and laboratory data of the patients before and after GMA therapy were collected and analyzed to evaluate their efficacy and safety. Disease severity in all patients was evaluated according to Rachmilewitz's clinical activity index (CAI), as shown in Table 2. Clinical remission was defined as CAI ≤4, while endoscopic UC severity was assessed using the Mayo endoscopic score (Mayo-ES) as follows: normal or inactive disease (score 0); erythema, decreased vascular patterns and mild friability (score 1); marked erythema, invisible vascular patterns, friability and erosions (score 2); spontaneous bleeding and ulceration (score 3). Mucosal healing was defined as Mayo-ES 0 or 1. Colonoscopic

| TABLE 2 | Rachmilewitz's clinical activity index |
|---------|---------------------------------------|
| (1) No. of stools weekly | Score | (5) Abdominal pain/cramps |
| <18 | 0 | None |
| 18-35 | 1 | Mild |
| 36-60 | 2 | Moderate |
| >60 | 3 | Sever |
| (2) Blood in stools (based on weekly average) | Score | (6) Extraintestinal manifestations |
| None | 0 | Iritis |
| Little | 2 | Erythema nodosum |
| A lot | 4 | Arthritis |
| (3) Investigator’s global assessment of symptomatic state | Score | (7) Laboratory findings |
| Good | 0 | Sedimentation rate >50 mm in first hour |
| Average | 1 | Sedimentation rate >100 mm in first hour |
| Poor | 2 | Hemoglobin <100 g/L |
| Very poor | 3 | |
| (4) Temperature due to colitis (°C) | Score |
| 37-38 | 0 |
| >38 | 3 |
findings were reevaluated in 32 patients 1 day after the 5th or 10th GMA session.

### 2.4 Statistical analysis

When appropriate, measurement data were displayed as means ± SD, while count data were displayed as relative numbers (n %). The chi-squared ($\chi^2$) test was used for the comparison of clinical remission rates between different subgroups. A $t$ test was used for the comparison of laboratory measurements before and after GMA therapy. One-way analysis of variance (ANOVA) was applied to determine the indicators for nonresponders to GMA therapy (IBM, SPSS statistics 22.0 for Windows). $P < .05$ was considered statistically significant.

### 3 RESULTS

#### 3.1 Clinical efficacy of GMA therapy

Based on the CAI score, the overall clinical remission rate was 79.2% in all patients who finished 5 to 10 GMA sessions (Figure 1). The clinical remission rate was 69.2% in 13 patients who finished 5 GMA sessions and 82.3% in 35 patients who completed 10 sessions ($P = .307$).

In relation to the UC disease course, the remission rate in the 12 first episode cases was 91.67% (11 out of 12 patients), and 75% (27 out of 36 patients) in patients with chronic continuous UC ($\chi^2 = 1.067$, $P = .302$).

Additionally, the clinical remission rate in the steroid-naïve subgroup was 83.33% (30 out of 36 patients) and 66.67% (8 out of 12 patients) in the steroid-dependent or refractory subgroup ($\chi^2 = 1.516$, $P = .218$).

In 38 patients with clinical remission, 27 were reevaluated by colonoscopies after their 5th or 10th GMA session. The mucosal healing rate was 59.3% (16 out of 27 patients) according to the Mayo-ES. Figure 2 presents representative colonoscopic findings before and after GMA therapy.

#### 3.2 Comparison of laboratory measurements before and after GMA treatment

As shown in Figure 3, a significant decrease in the CAI as well as in the Mayo-ES, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell counts (WBC), hemoglobin (Hb), and platelet (PLT) counts were observed after GMA therapy. However, the WBC, PLT, and Hb levels were still within the normal range. Furthermore, plasma cytokines including IL-6, IL-8, and TNF-α, before and after GMA therapy, showed no statistically significant differences ($P > .05$).

#### 3.3 Indicators of nonresponders to GMA

We attempted to detect factors that could identify a patient as a GMA non-responder by relying on one-way ANOVA applied to the patients’ demographic variables before GMA, including disease duration, age, ESR, CRP, CAI, Mayo-ES, WBC, Hb, PLT, albumin, and cytokines (IL-6, IL-8, and TNF-α). The results showed significantly higher CAIs, and lower albumin and Hb levels in patients with no clinical remission (Table 3).

#### 3.4 Safety findings

All adverse events in the 50 patients were recorded. One patient experienced headaches during the first GMA session, but the symptoms gradually decreased without any medical treatment. Another patient experienced precordial discomfort at the end of a GMA session; electrocardiogram (ECG) showed first-degree atrioventricular block and an abnormal Q wave in the V1 and V2 lead, but the myocardial enzymes were normal. The symptoms spontaneously relieved after approximately 5 minutes and the ECG returned to normal after GMA therapy. However, another patient developed fevers with coughs...
FIGURE 2
Representative colonoscopic findings before (A,C,E) and after (B,D,F) granulomonocytapheresis (GMA) therapy.

FIGURE 3
A-C, Comparison of CAI, Mayo-ES and laboratory measures before and after GMA therapy. *P < .05, **P < .00, ***P < 0.000. CAI, clinical activity index; GMA, granulomonocytapheresis; NS, not statistical significant.
after every GMA session. Chest computed tomography showed pneumonia, which was relieved after antibiotic administration. Two patients withdrew from the treatment, one due to severe dizziness and light-headedness and one due to lack of efficacy who ultimately underwent a colectomy.

No other serious adverse events such as opportunistic infections, venous catheter-related complications, infections, or thromboses during and after GMA therapy were reported. Likewise, liver and kidney function tests showed no significant changes after GMA therapy.

4 | DISCUSSION

UC is a debilitating chronic inflammatory disorder affecting mainly the colon and the rectum for which a complete cure has not yet been found. The incidence of UC in Asian countries, including China, has increased dramatically in recent decades probably due to changes in diet and environmental triggers. Regarding drug therapy, hitherto, 5-aminosalicylic acid (5-ASA) preparations have been the first-line medication for mild to moderately active UC, while a combination of corticosteroids and azathioprine (or 6-mercaptopurine) is recommended in cases with an inadequate response to 5-ASA. Additionally, cyclosporin A (CsA), tacrolimus, or an anti-TNF-α biologic has been indicated for patients with corticosteroid refractory UC. However, despite this plethora of pharmaceutical options, a significant proportion of patients with UC have active diseases due to a lack of response or ineffective medications in combination with drug-related adverse events, including opportunistic infections, reactivation of cytomegalovirus, osteoporosis, or steroid-related diabetes. Since patients with active UC harbor elevated and activated myeloid lineage leucocytes both in the peripheral blood as well as in the colonic mucosa that are related to the severity of clinical relapse. Hence, elevated myeloid lineage leucocytes appear as logical targets for UC treatment by selective leucocytapheresis such as GMA.

Experience with GMAs for the treatment of patients with IBD in China has been very limited. The first reported clinical efficacy rate for GMA therapy in Chinese patients with UC was 70.59% and the mucosal healing rate was 47.06%. In our study, the clinical GMA remission rate was 79.2%, while the mucosal healing rate in a subgroup who underwent colonoscopies was 59.5%, which is higher than the levels in the first multicenter study in China. This discrepancy may be attributed to the higher number of steroid-naive patients in our cohort (72%) who were known to respond better to GMA therapy than patients with steroid refractory backgrounds. Furthermore, the efficacy rates of steroid-naive and steroid-dependent or refractory subgroups were 83.33% and 66.67%, respectively, in our study. Unfortunately, due to the large sample size difference after every GMA session. Chest computed tomography showed pneumonia, which was relieved after antibiotic administration. Two patients withdrew from the treatment, one due to severe dizziness and light-headedness and one due to lack of efficacy who ultimately underwent a colectomy.

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between the two groups, no significant statistical difference was found. In previous clinical reports, it has been stated that GMA therapy showed significant efficacy in patients with active UC with steroid-dependent or steroid-refractory backgrounds and spared steroid-naive patients from exposure to steroids. Additionally, as mentioned previously, steroid-naive patients with UC showed significantly higher clinical remission and mucosal healing rates as well as longer durations of clinical remission than steroid-dependent or refractory patients. Therefore, GMA was considered an effective first-line therapy for steroid-naive patients.

In addition to the clinical efficacy, we measured and analyzed ESR, CRP, and PLT counts before and after the GMA sessions. All three measures decreased after GMA therapy, which favored the effectiveness of GMA therapy. Furthermore, it is clinically relevant to know the most effective frequency and the number of GMA sessions for patients with active UC since this can minimize the procedure associated costs. One session per week for up to 5 sessions was applied in the initial clinical trial of GMA, while others administered 2 sessions per week in the first 2 to 3 weeks followed by 1 session per week up to 10 or 11 sessions. It had also been reported that intensive GMA therapy (two sessions per week) induces significantly more rapid clinical remission, with higher mucosal healing rate. Additionally, Hanai et al reported that patients with steroid-naive UC responded well to 5 GMA sessions while steroid-refractory patients with severe UC responded better to 10 sessions. Regarding the determination of the optimal duration of each GMA session and an appropriately processed blood volume (PV) in one session, a positive relationship between the PV and the efficacy of GMA therapy has been reported. Likewise, Kanke et al found that 90 minutes per GMA session was significantly better in terms of efficacy rates than the 60 minutes which was routinely applied. In our study, GMA therapy was applied twice per week for 5 or 10 sessions with durations of 60 minutes and a PV of 1800 mL. The clinical remission rate was higher in patients who received 10 sessions (82.3%) than in patients who received 5 sessions (69.2%). There were no statistical differences between the 2 groups, but this may be due to the discrepancy in sample sizes between the 5 session group (13 patients) and the 10 session group (35 patients) which may lead to statistical error. In our clinical trial and based on a previous study, there was a tendency to utilize 10 session GMA therapies for patients with relatively severe UC conditions to achieve better efficacy.

Therefore, it appears that multiple factors could affect the clinical efficacy of GMA therapy in addition to the number and frequency of GMA sessions. According to previous clinical reports, most patients with UC respond well to GMA therapy, but a minority do not benefit. This finding might be due to differences in the patients’ demographic variables prior to the initiation of GMA therapy and, in clinical practice settings, can be used to identify potential responders and non-responders to GMA therapy. Based on current knowledge, the best responders to GMA therapy appear to be patients facing their first UC episode, followed by steroid-naïve patients since they respond after only a few GMA sessions and can be spared from steroid or multi-drug therapies. Yokoyama et al reported that patients with a shorter duration of active UC and a lower cumulative corticosteroid dosage in the past responded well to GMA therapy. In contrast, patients in whom colonoscopies revealed deep ulcers and extensive loss of mucosal tissue, together with those who had a long history of exposure to multiple conventional drugs, may not benefit from GMA therapy. Using this knowledge, we applied a one-way ANOVA to identify potential demographic variables between patients who responded well and those who did not achieve complete remission and found significantly higher baseline CAIs, and lower albumin and Hb levels as markers for a poor response to GMA therapy. These indicators, which reflect severe disease, may be relevant markers in predicting the clinical response to GMA therapy.

GMA therapy was relatively safe and was well tolerated. The overwhelming majority of our patients (48 out of 50) completed the planned treatment course with only four patients experiencing transient migraine-like headaches reported by other authors. Similarly, only two patients discontinued the treatment: one due to lack of efficacy, and the other because of intolerance to dizziness and light-headedness during the extracorporeal circulation time of GMA therapy. Therefore, we can confidently say that GMA therapy had a favorable safety profile in addition to good patient compliance.

There are several limitations of this study, which potentially could have affected the interpretation of the findings and the clinical relevance. First, GMA therapy did not have a parallel running control arm. We believe that inclusion of another group of patients treated with conventional pharmaceuticals could produce another set of efficacy and safety data for comparison with the GMA data. Second, the number of patients in this study was not large enough for subgroup analyses. Third, this study did not have a long-term follow-up.

5 | CONCLUSIONS

In conclusion, GMA is a nonpharmacological treatment option, which targets elevated and activated myeloid lineage leucocytes known to exacerbate and perpetuate IBD.
by releasing inflammatory cytokines. Since GMA therapy removes potential causes of active IBD from the patient's body, the loss of response or refractoriness experienced with pharmacological therapy is unlikely. However, our experience together with earlier clinical reports on GMA therapy indicates that its efficacy reflects patient demographic variables at entry. The best responders to GMA are first episodic cases, followed by patients with steroid-naïve UC. Additionally, and similar to previous studies, we found that patients with a high CAI (severe UC) at baseline in whom UC had become refractory to common pharmaceuticals were poor responders compared with patients with lower CAIs, while lower Hb and albumin levels were associated with lower efficacy. In clinical settings, such information should help to avoid futile use of medical resources and potentially shorten morbidity time by selecting an appropriate treatment at an earlier stage. Finally, the Adacolumn used in GMA therapy, has an unrivalled safety profile, which is very much favored by patients. In this study, no patient experienced a lasting adverse event. However, an overwhelming number of studies have focused on the efficacy of GMA as an induction therapy. With this in mind, future studies should focus on the long-term efficacy of GMA as a maintenance therapy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

N. L. was involved in the conception and design, collection, analysis, and interpretation of the data, drafting of the first draft of the article, and final approval of the article. M. J., H. T., L. Z., and X. T. were involved in initial drafting, critical revision of the article, and final approval of the article. J. B., H. W., and X. C. were involved in collection of the data, revision of the article, and final approval of the article. Y. W. was involved in conception and design, study supervision, analysis and interpretation of the data, initial drafting of the article, critical revision of the article for important intellectual content, and final approval of the article.

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