Received: 21 August 2019 | Revised: 22 March 2020 | Accepted: 21 April 2020

DOI: 10.1002/jca.21787

RESEARCH ARTICLE

Journal of Clinical Apheresis ASFA WILEY

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

Na Li MD | Jingwei Mao PhD | Haiying Tang PhD | Lei Zhu PhD | Xiaoyan Tan PhD | Jian Bi MD | Hao Wu MD | Xiuli Chen MD | Yingde Wang MD

Department of Gastroenterology, First Affiliated Hospital of Dalian Medical University, Dalian, China

Correspondence
Yingde Wang, MD, Department of Gastroenterology, First Affiliated Hospital of Dalian Medical University, 222 Zhongshan Road, Dalian, China.
Email: albertwyd@163.com

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 $\leq$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 non-pharmacological treatment options. Accordingly, UC patients were spared from pharmaceuticals after applying GMA therapy.

KEYWORDS
adsorptive granulomonocytapheresis, albumin, hemoglobin, myeloid lineage leucocytes, ulcerative colitis

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.[1] 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.[2,3] 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.[2,3]

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.[4] Additionally, neutrophils in patients with UC show activated behaviors and prolonged survival times,[5] 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.[6] 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.[2,3] 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.[7-9]

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.[10] 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

TABLE 1 Baseline demographic variables of the 50 UC patients

Variable	Value
Age, year	46.31 ± 15.34
Male: female	27:23
Duration of UC, month	44.06 ± 66.72
Location of lesions	
Entire colon	34
Rectum and sigmoid colon	3
Left colon	13
Clinical course	
First episode	12
Chronic continuous	38
UC severity level	
Mild	9
Moderate	33
Severe	8
Past steroid therapy	
Steroid naïve, n (%)	36 (72.0%)
Steroid dependent/refractory, n (%)	14 (18.0%)
Number of GMA sessions	
5 sessions	13
10 sessions	35
Withdraw	2

Note. Data are presented as the mean ± SD, number or percentage.
Abbreviations: GMA, granulomonocytapheresis; UC, ulcerative colitis.

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.[11] 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,[12] and UC severity according to Truelove and Witts,[13] 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.[14-16] 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,[15] patients with moderately active UC or a steroid-naïve 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),[17] 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)[18] 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[17]

	Score		Score
(1) No. of stools weekly		(5) Abdominal pain/cramps	
<18	0	None	0
18-35	1	Mild	1
36-60	2	Moderate	2
>60	3	Sever	3
(2) Blood in stools(based on weekly average)		(6) Extraintestinal manifestations	
None	0	Iritis	3
Little	2	Erythema nodosum	3
A lot	4	Arthritis	3
(3) Investigator's global assessment of symptomatic state		(7) Laboratory findings	
Good	0	Sedimentation rate >50 mm in first hour	1
Average	1	Sedimentation rate >100 mm in first hour	2
Poor	2	Hemoglobin <100 g/L	4
Very poor	3		
(4) Temperature due to colitis (°C)			
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 (χ^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 ($\chi^2 = 1.067$, $P = .302$).

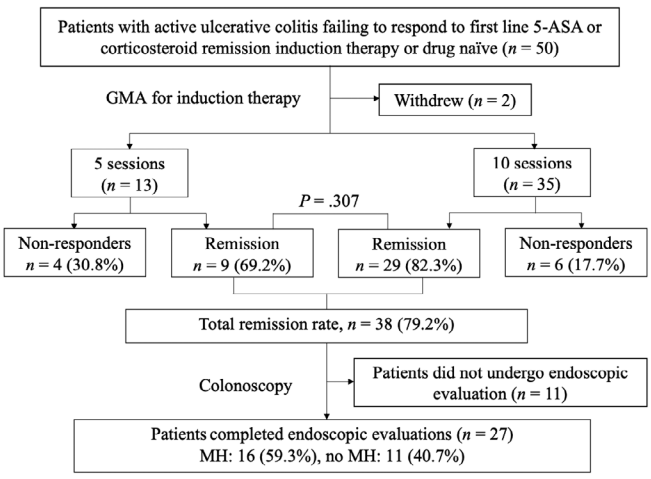

FIGURE 1 The overall therapeutic outcomes in all 50 patients of this study. Two patients withdrew, and among the remaining 48 patients, 13 finished 5 GMA sessions, and 35 finished 10 sessions. The overall clinical remission rate was 79.2%, while the overall mucosal healing (MH) rate was 59.3% of those who achieved clinical remission. GMA, granulomonocytapheresis

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

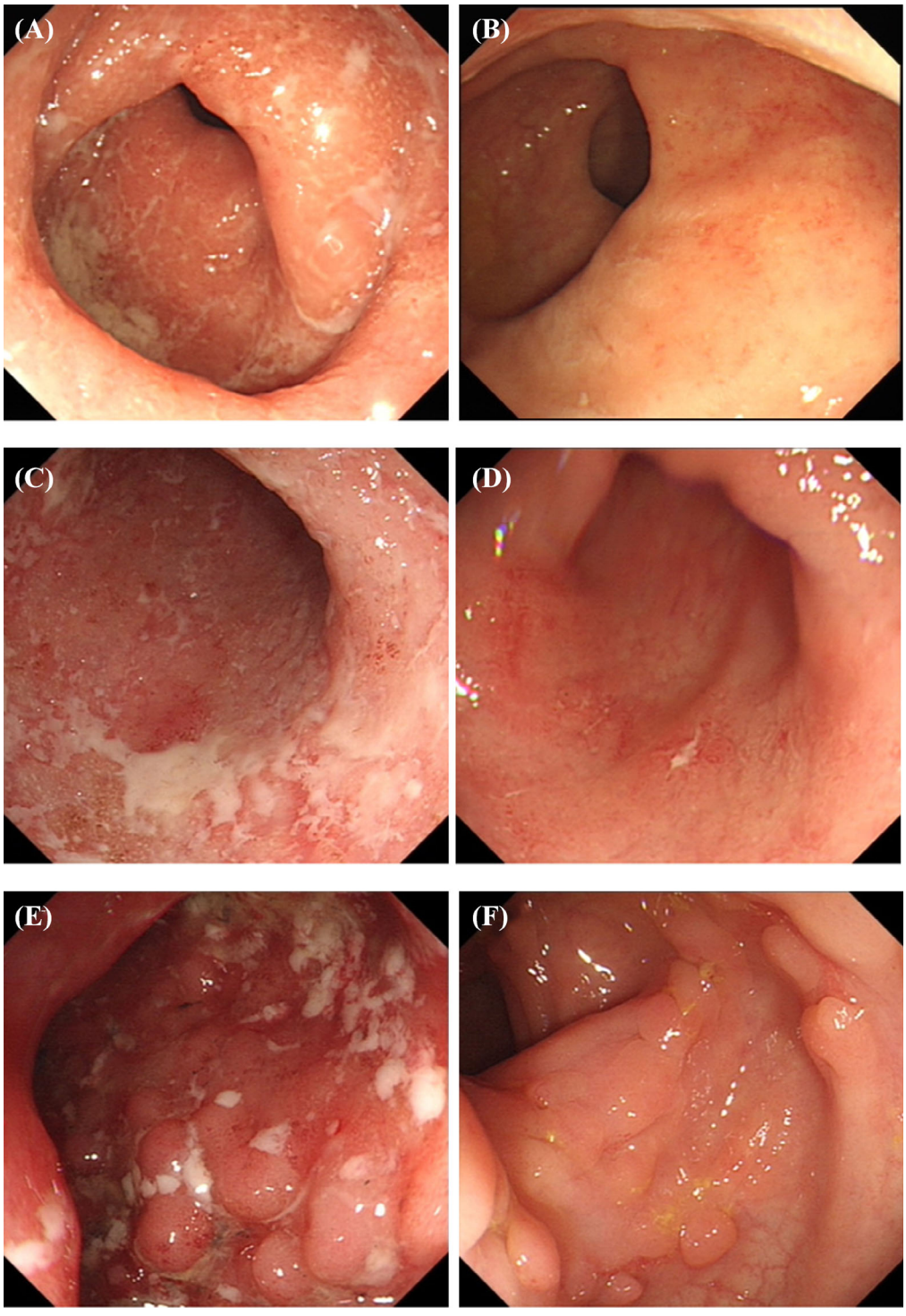

FIGURE 2 Representative colonoscopic findings before (A,C,E) and after (B,D,F) granulomonocytapheresis (GMA) therapy

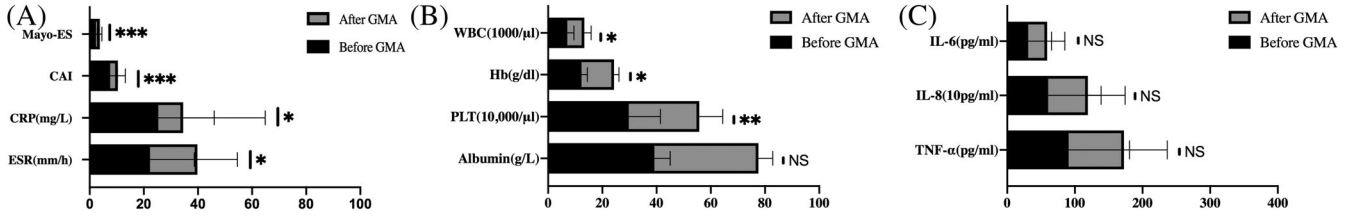

FIGURE 3 A-C, Comparison of CAI, Mayo-ES and laboratory measures before and after GMA therapy. *$P < .05$, **$P < .00$, ***$P < 0.000$. CAI, clinical activity index; GMA, granulomonocytapheresis; NS, not statistical significant

TABLE 3 Comparison of demographic variables at baseline and after GMA therapy between patients who achieved clinical remission and those who did not following a course of GMA therapy

Variable	Before GMA			After GMA		
	Clinical remission group (n = 38)	Non-remission group (n = 10)	*P* value	Clinical remission group (n = 38)	Nonremission group (n = 10)	*P* value
Age, year	45.47 ± 16.26	49.50 ± 11.30	.31	-	-	-
Duration of UC, month	41.24 ± 59.55	54.80 ± 88.42	.57	-	-	-
ESR (mm/h)	19.84 ± 13.46	33.2 ± 20.30	.15	15.69 ± 12.08	23.9 ± 21.37	.12
WBC (1000/μL)	7.10 ± 2.53	6.99 ± 1.87	.90	6.35 ± 2.65	6.02 ± 2.04	.72
Hb (g/dL)	12.90 ± 1.52	10.38 ± 2.70	.00*	12.48 ± 1.43	10.29 ± 2.21	.01*
PLT (10 000/μL)	28.61 ± 8.09	34.52 ± 19.16	.14	26.31 ± 8.92	25.12 ± 9.51	.71
IL-6 (pg/mL)	27.81 ± 34.56	28.05 ± 16.16	.99	23.55 ± 25.64	43.24 ± 24.01	.12
IL-8 (pg/mL)	504.94 ± 739.60	665.00 ± 608.44	.62	528.60 ± 522.41	703.80 ± 721.16	.52
TNF-α (pg/mL)	84.78 ± 88.47	60.32 ± 54.27	.52	75.35 ± 60.27	102.26 ± 80.40	.39
Albumin (g/L)	41.12 ± 4.97	33.96 ± 4.67	.00*	40.25 ± 4.19	33.42 ± 4.83	.00*
CAI	6.84 ± 1.82	10.40 ± 3.63	.04*	1.66 ± 1.05	7.60 ± 2.32	.00*
Mayo-SE	2.39 ± 0.55	2.40 ± 0.52	.226	1.33 ± 0.73	2.6 ± 0.55	.01*

*$P < .05$.

Note. Data are presented as the mean ± SD values, compared by one-way analysis of variance statistic.

Abbreviations: CAI, clinical activity index; ESR, erythrocyte sedimentation rate; HB, haemoglobin; IL, interleukin; PLT, platelet; UC, ulcerative colitis; WBC, white blood cell.

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.[18] The incidence of UC in Asian countries, including China, has increased dramatically in recent decades probably due to changes in diet and environmental triggers.[19-21] 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.[22] Additionally, cyclosporin A (CsA), tacrolimus, or an anti-TNF-α biologic has been indicated for patients with corticosteroid refractory UC.[23,24] 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.[25-30] Since patients with active UC harbor elevated and activated granulocytes and monocytes/macrophages both in the peripheral blood as well as in the colonic mucosa that are related to the severity of clinical relapse.[5,31] Hence, elevated myeloid lineage leucocytes appear as logical targets for UC treatment by selective leucocytapheresis such as GMA.[9,32,33]

Experience with GMAs for the treatment of patients with IBD in China has been very limited.[10] 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%.[10] 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.[10] This discrepancy may be attributed to the higher number of steroid-naïve patients in our cohort (72%) who were known to respond better to GMA therapy than patients with steroid refractory backgrounds.[31,34] Furthermore, the efficacy rates of steroid-naïve and steroid-dependent or refractory subgroups were 83.33% and 66.67%, respectively, in our study. Unfortunately, due to the large sample size difference

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-naïve patients from exposure to steroids.[15,34-36] Additionally, as mentioned previously, steroid-naïve 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.[37] Therefore, GMA was considered an effective first-line therapy for steroid-naïve patients.[38]

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.[15,39] It had also been reported that intensive GMA therapy (two sessions per week) induces significantly more rapid clinical remission, with higher mucosal healing rate.[35] Additionally, Hanai et al[39] reported that patients with steroid-naïve 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.[40,41] Likewise, Kanke et al[16] 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,[15] 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.[31,33,35,38] According to previous clinical reports, most patients with UC respond well to GMA therapy, but a minority do not benefit.[38,42-46] 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.[31,35,45,46] Yokoyama et al[44] 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.[43,47] 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 indictors, 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.[41,48,49] 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.

ORCID

Yingde Wang https://orcid.org/0000-0002-1131-238X

REFERENCES

1. Selby W. The natural history of ulcerative colitis. *Baillieres Clin Gastroenterol*. 1997;11:53-64.
2. de Souza HS, Fiocchi C. Immunopathogenesis of IBD: current state of the art. *Nat Rev Gastroenterol Hepatol*. 2016;13:13-27. https://doi.org/10.1038/nrgastro.2015.186.
3. Fiocchi C. Inflammatory bowel disease: etiology and pathogenesis. *Gastroenterology*. 1998;115:182-205.
4. Muthas D, Reznichenko A, Balendran CA, et al. Neutrophils in ulcerative colitis: a review of selected biomarkers and their potential therapeutic implications. *Scand J Gastroenterol*. 2017; 52:125-135. https://doi.org/10.1080/00365521.2016.1235224.
5. Brannigan AE, O'Connell PR, Hurley H, et al. Neutrophil apoptosis is delayed in patients with inflammatory bowel disease. *Shock*. 2000;13:361-366.
6. Monteleone G, MacDonald TT. Manipulation of cytokines in the management of patients with inflammatory bowel disease. *Ann Med*. 2000;32:552-560.
7. Cohen RD. Treating ulcerative colitis without medications—"look mom, no drugs!". *Gastroenterology*. 2005;128:235-236.
8. Sands BE, Sandborn WJ, Feagan B, et al. A randomized, double-blind, sham-controlled study of granulocyte/monocyte apheresis for active ulcerative colitis. *Gastroenterology*. 2008; 135:400-409. https://doi.org/10.1053/j.gastro.2008.04.023.
9. Saniabadi AR, Tanaka T, Yamamoto T, Kruis W, Sacco R. Granulomonocytapheresis as a cell-dependent treatment option for patients with inflammatory bowel disease: concepts and clinical features for better therapeutic outcomes. *J Clin Apher*. 2019;34:51-60. https://doi.org/10.1002/jca.21670.
10. Lai YM, Yao WY, He Y, et al. Adsorptive granulocyte and monocyte apheresis in the treatment of ulcerative colitis: the first multicenter study in China. *Gut Liver*. 2017;11:216-225. https://doi.org/10.5009/gnl15408.
11. PJ H. The consensus for the diagnosis and treatment of inflammatory bowel disease. *Chin J Dig* 2012; 32: 796–813.
12. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006;55:749-753. https://doi.org/10.1136/gut.2005.082909.
13. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J*. 1955;2:1041-1048. https://doi.org/10.1136/bmj.2.4947.1041.
14. Fukunaga K, Nagase K, Kusaka T, et al. Cytapheresis in patients with severe ulcerative colitis after failure of intravenous corticosteroid: a long-term retrospective cohort study. *Gut Liver*. 2009;3:41-47. https://doi.org/10.5009/gnl.2009.3.1.41.
15. Hanai H, Watanabe F, Takeuchi K, et al. Leukocyte adsorptive apheresis for the treatment of active ulcerative colitis: a prospective, uncontrolled, pilot study. *Clin Gastroenterol Hepatol*. 2003;1:28-35. https://doi.org/10.1053/jcgh.2003.50005.
16. Kanke K, Nakano M, Hiraishi H, Terano A. Clinical evaluation of granulocyte/monocyte apheresis therapy for active ulcerative colitis. *Dig Liver Dis*. 2004;36:811-817. https://doi.org/10.1016/j.dld.2004.08.004.
17. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ*. 1989;298:82-86. https://doi.org/10.1136/bmj.298.6666.82.
18. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317: 1625-1629. https://doi.org/10.1056/NEJM198712243172603.
19. Yang H, Li Y, Wu W, et al. The incidence of inflammatory bowel disease in Northern China: a prospective population-

based study. *PLoS One*. 2014;9:e101296. https://doi.org/10.1371/journal.pone.0101296.
20. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2018;390:2769-2778. https://doi.org/10.1016/S0140-6736(17)32448-0.
21. Zeng Z, Zhu Z, Yang Y, et al. Incidence and clinical characteristics of inflammatory bowel disease in a developed region of Guangdong Province, China: a prospective population-based study. *J Gastroenterol Hepatol*. 2013;28:1148-1153. https://doi.org/10.1111/jgh.12164.
22. Hanauer SB. Medical therapy for ulcerative colitis 2004. *Gastroenterology*. 2004;126:1582-1592.
23. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353:2462-2476. https://doi.org/10.1056/NEJMoa050516.
24. Ikeya K, Sugimoto K, Kawasaki S, et al. Tacrolimus for remission induction in ulcerative colitis: Mayo endoscopic subscore 0 and 1 predict long-term prognosis. *Dig Liver Dis*. 2015;47:365-371. https://doi.org/10.1016/j.dld.2015.01.149.
25. Kornbluth A, Marion JF, Salomon P, Janowitz HD. How effective is current medical therapy for severe ulcerative and Crohn's colitis? An analytic review of selected trials. *J Clin Gastroenterol*. 1995;20:280-284.
26. Garcia-Vidal C, Rodriguez-Fernandez S, Teijon S, et al. Risk factors for opportunistic infections in infliximab-treated patients: the importance of screening in prevention. *Eur J Clin Microbiol Infect Dis*. 2009;28:331-337. https://doi.org/10.1007/s10096-008-0628-x.
27. Johannesdottir SA, Horvath-Puho E, Dekkers OM, et al. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. *JAMA Intern Med*. 2013;173:743-752. https://doi.org/10.1001/jamainternmed.2013.122.
28. Toruner M, Loftus EV Jr, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology*. 2008;134:929-936. https://doi.org/10.1053/j.gastro.2008.01.012.
29. Naganuma M, Kunisaki R, Yoshimura N, Takeuchi Y, Watanabe M. A prospective analysis of the incidence of and risk factors for opportunistic infections in patients with inflammatory bowel disease. *J Gastroenterol*. 2013;48:595-600. https://doi.org/10.1007/s00535-012-0686-9.
30. Hwang JL, Weiss RE. Steroid-induced diabetes: a clinical and molecular approach to understanding and treatment. *Diabetes Metab Res Rev*. 2014;30:96-102. https://doi.org/10.1002/dmrr.2486.
31. McCarthy DA, Rampton DS, Liu YC. Peripheral blood neutrophils in inflammatory bowel disease: morphological evidence of in vivo activation in active disease. *Clin Exp Immunol*. 1991;86:489-493.
32. Saniabadi AR, Hanai H, Takeuchi K, et al. Adacolumn, an adsorptive carrier based granulocyte and monocyte apheresis device for the treatment of inflammatory and refractory diseases associated with leukocytes. *Ther Apher Dial*. 2003;7:48-59.
33. Saez-Gonzalez E, Moret I, Alvarez-Sotomayor D, et al. Immunological mechanisms of adsorptive cytapheresis in inflammatory bowel disease. *Dig Dis Sci*. 2017;62:1417-1425. https://doi.org/10.1007/s10620-017-4577-z.
34. Domenech E, Hinojosa J, Esteve-Comas M, et al. Granulocyteaphaeresis in steroid-dependent inflammatory bowel disease: a prospective, open, pilot study. *Aliment Pharmacol Ther*. 2004;20:1347-1352. https://doi.org/10.1111/j.1365-2036.2004.02288.x.
35. Sakuraba A, Motoya S, Watanabe K, et al. An open-label prospective randomized multicenter study shows very rapid remission of ulcerative colitis by intensive granulocyte and monocyte adsorptive apheresis as compared with routine weekly treatment. *Am J Gastroenterol*. 2009;104:2990-2995. https://doi.org/10.1038/ajg.2009.453.
36. Tanaka T, Sugiyama S, Goishi H, Kajihara T, Akagi M, Miura T. Treatment of children and adolescents with ulcerative colitis by adsorptive depletion of myeloid lineage leucocytes as monotherapy or in combination with low dose prednisolone after failure of first-line medications. *BMC Gastroenterol*. 2013;13:130. https://doi.org/10.1186/1471-230X-13-130.
37. Yamamoto T, Umegae S, Matsumoto K. Long-term clinical impact of early introduction of granulocyte and monocyte adsorptive apheresis in new onset, moderately active, extensive ulcerative colitis. *J Crohns Colitis*. 2012;6:750-755. https://doi.org/10.1016/j.crohns.2011.12.009.
38. Suzuki Y, Yoshimura N, Saniabadi AR, Saito Y. Selective granulocyte and monocyte adsorptive apheresis as a first-line treatment for steroid naive patients with active ulcerative colitis: a prospective uncontrolled study. *Dig Dis Sci*. 2004;49:565-571.
39. Hanai H, Iida T, Takeuchi K, et al. Intensive granulocyte and monocyte adsorption versus intravenous prednisolone in patients with severe ulcerative colitis: an unblinded randomised multi-centre controlled study. *Dig Liver Dis*. 2008;40:433-440. https://doi.org/10.1016/j.dld.2008.01.007.
40. Kikuyama R, Fukunaga K, Kawai M, et al. Relevance of the processed blood volume per granulocyte and monocyte apheresis session to its clinical efficacy in patients with ulcerative colitis. *Ther Apher Dial*. 2011;15:360-366. https://doi.org/10.1111/j.1744-9987.2011.00968.x.
41. Yoshimura N, Yokoyama Y, Matsuoka K, et al. An open-label prospective randomized multicenter study of intensive versus weekly granulocyte and monocyte apheresis in active Crohn's disease. *BMC Gastroenterol*. 2015;15:163. https://doi.org/10.1186/s12876-015-0390-3.
42. Suzuki Y, Yoshimura N, Fukuda K, Shirai K, Saito Y, Saniabadi AR. A retrospective search for predictors of clinical response to selective granulocyte and monocyte apheresis in patients with ulcerative colitis. *Dig Dis Sci*. 2006;51:2031-2038. https://doi.org/10.1007/s10620-006-9199-9.
43. Tanaka T, Okanobu H, Kuga Y, et al. Clinical and endoscopic features of responders and non-responders to adsorptive leucocytapheresis: a report based on 120 patients with active ulcerative colitis. *Gastroenterol Clin Biol*. 2010;34:687-695. https://doi.org/10.1016/j.gcb.2010.08.007.
44. Yokoyama Y, Kawai M, Fukunaga K, et al. Looking for predictive factors of clinical response to adsorptive granulocyte and monocyte apheresis in patients with ulcerative colitis: markers

of response to GMA. *BMC Gastroenterol*. 2013;13:27. https://doi.org/10.1186/1471-230X-13-27.

45. Yokoyama Y, Watanabe K, Ito H, et al. Factors associated with treatment outcome, and long-term prognosis of patients with ulcerative colitis undergoing selective depletion of myeloid lineage leucocytes: a prospective multicenter study. *Cytotherapy*. 2015;17:680-688. https://doi.org/10.1016/j.jcyt.2015.02.007.
46. Yamamoto T, Iida T, Ikeya K, et al. A multicenter retrospective study aiming to identify patients who respond well to adsorptive granulomonocytapheresis in moderately to severely active ulcerative colitis. *Clin Transl Gastroenterol*. 2018;9:170. https://doi.org/10.1038/s41424-018-0037-0.
47. Yamamoto T, Umegae S, Matsumoto K. Mucosal healing in patients with ulcerative colitis during a course of selective leukocytapheresis therapy: a prospective cohort study. *Inflamm Bowel Dis*. 2010;16:1905-1911. https://doi.org/10.1002/ibd.21260.
48. Rodriguez-Lago I, Benitez JM, Garcia-Sanchez V, et al. Granulocyte and monocyte apheresis in inflammatory bowel disease: the patients' point of view. *Gastroenterol Hepatol*. 2018;41:423-431. https://doi.org/10.1016/j.gastrohep.2018.04.007.
49. Hibi T, Sameshima Y, Sekiguchi Y, et al. Treating ulcerative colitis by Adacolumn therapeutic leucocytapheresis: clinical efficacy and safety based on surveillance of 656 patients in 53 centres in Japan. *Dig Liver Dis*. 2009;41:570-577. https://doi.org/10.1016/j.dld.2008.11.020.

How to cite this article: Li N, Mao J, Tang H, et al. 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. *J Clin Apher*. 2020;35:271–280. https://doi.org/10.1002/jca.21787