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OBSERVATIONAL STUDY

Granulo-monocyto apheresis is more effective in mild ulcerative colitis than in moderate to severe disease

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Abstract

AIM: To evaluate whether the effectiveness of Granulo-monocyto apheresis (GMA), a technique that consists of the extracorporeal removal of granulocytes and monocytes from the peripheral blood, might vary according to the severity of ulcerative colitis (UC) in patients with mild to moderate-severe disease UC activity.

METHODS: We retrospectively reviewed prospectively collected data of patients undergoing GMA at our inflammatory bowel disease centre who had at least a 6 mo of follow-up. The demographics, clinical and laboratory data were extracted from the patients' charts and electronic records. The severity of UC was scored according to the Modified Truelove Witts Severity Index (MTWSI). A clinical response was defined as a decrease from baseline of $\geqslant$ 2 points or a value of MTWSI $\leqslant$ 2 points.

RESULTS: A total of 41 (24 males/17 females; mean age 47 years) patients were included in the study. After GMA cycle completion, 21/28 (75%) of mild UC patients showed a clinical response compared with 7/13 (54%) of patients with moderate to severe disease (P = 0.27). At 6-mo, 14/28 (50%) of the mild UC patients maintained a clinical response compared with 2/13 (15%) of the patients with moderate to severe disease (P = 0.04). After the GMA cycle completion and during the 6-mo follow up period, 13/16 (81%) and 9/16 (56%) of mild UC patients with intolerance, resistance and contraindications to immunosuppressants and/or biologics showed a clinical response compared with 2/6 (33%) and 0/6 (0%) of patients with moderate to severe disease activity with these characteristics (P = 0.05 and P = 0.04, respectively).

CONCLUSION: Patients with mild UC benefit from GMA more than patients with moderate to severe disease in the short-term period. GMA should be considered a valid therapeutic option in cases of contraindications to immunosuppressants, corticosteroids and/or biologics.

Key words: Ulcerative colitis; Granulo-monocyto-apheresis; Inflammatory bowel disease; Therapy; Severity

Core tip: Several studies evaluating granulo-monocyto apheresis in ulcerative colitis have been previously conducted, and these studies have shown conflicting results. We performed a retrospective study evaluating granulo-monocyto apheresis effectiveness according to disease severity. Granulo-monocyto-mpheresis was found to be more effective in patients with mild disease activity than in patients with moderate to severe disease activity.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that exclusively involves the colonic mucosa[1]. Several treatment methods have been adopted according to the severity of inflammation and disease localisation; the treatments aim to induce and maintain clinical remission[2]. The treatments of choice in mild to moderate disease are 5-aminosalicylate based compounds (5-ASA)[3,4]; these agents are also used to maintain remission. Systemic corticosteroids are used in cases of no response to 5-ASA and in cases of extensive and/or moderate to severe disease[5-7]. Immunosuppressants, such as thiopurines and cyclosporine, should be used in cases of steroid dependent and resistant disease[8,9,10], whereas anti-tumour necrosis factor (TNF)-α treatment is indicated in cases of steroid and/or immune-modulator refractory disease[11]. The majority of these drugs present several side effects, requiring careful attention in drug dosage and duration[12-15]. Apheresis has emerged as a non-pharmacological treatment with few side effects[16]. The mechanism of action consists of the removal of the cell population involved in the induction and perpetuation of bowel inflammation from the peripheral blood, without affecting other cells such as erythrocytes[17]. Two apheresis systems are available: granulomonocyto-apheresis (GMA) acts through a system of cellulose acetate beads (Adacolumn®, Otsuka Pharmaceuticals, Milan, Italy) and selectively removes granulocytes and monocyte/macrophages with only a small fraction of lymphocytes[18,19], whereas leukocytapheresis (LCAP) acts through a polyester fibre filter (Cellsorba®, Asahi Medical Company) and removes neutrophils and monocytes with up to 60% of lymphocytes[20]. Immunemodulation is thought to occur from the reduction of pro-inflammatory cytokines[21] or from the increase in anti-inflammatory cytokines[22] and increase in circulating T regulatory cells[23].

However, studies performed using apheresis present conflicting results. Efficacy of the treatment has been shown in several uncontrolled studies[21,24-34], where the percentage of responses and remissions vary between 60% to 84% of treated patients[17]. The main advantage compared with conventional treatments is represented by the steroid-sparing effect. The results are conflicting, even in randomised controlled trials (RCTs); some studies have shown apheresis to be effective in inducing and maintaining clinical remission[35-42], whereas the study by Sands *et al*[43] failed to demonstrate any substantial benefit in inducing clinical remission or response. These studies were carried out in heterogeneous cohorts of patients with active disease; however, in some of the cases, disease severity was not clearly defined[35,42]. Thus, it is reasonable to hypothesise that the observed conflicting results might be due to the inclusion of patients with different degrees of disease activity at baseline. Moreover, data on the therapeutic benefit of this type of treatment in patients with mild UC are lacking, especially in patients refractory to immunosuppressants and biologics.

The aim of our study was to evaluate whether GMA effectiveness varies according to the severity of UC and if patients with mild disease refractory to 5-ASA and steroids and with contra-indications to immunosuppressants and biologics might benefit from GMA.

MATERIALS AND METHODS

Subjects

We performed a retrospective study of prospectively collected data of patients who presented to our IBD centre between June 2009 and March 2013. We included consecutive patients with histologically proven UC of at least 6 mo who underwent a complete cycle of GMA and who underwent an endoscopy documenting active disease during the 6 mo prior to the GMA; the patients were required to have a follow-up visit after the end of treatment and a subsequent follow-up visit at 6 mo. The exclusion criteria were a diagnosis of Crohn's disease and indeterminate colitis, previous ileo-colonic surgery or biologic treatment within 2 years in cases of patients with clinically mild UC.

GMA was initiated in steroid-dependent or steroid-resistant patients with active disease. Steroid dependency was defined as the inability to taper steroids without a relapse of UC symptoms. Steroid refractoriness was defined as active disease despite prednisone up to 0.75-1.00 mg/kg per day over a period of at least 2 wk[44]. Patients were required to be on stable treatment with topical and oral 5-ASA agents (≥ 2.4 g/d) and/or immunosuppressants. GMA was proposed for patients with important impairments of their quality of life who presented intolerance or contraindications to immunosuppressants and/or biologics or in patients who refused step up treatment.

Study protocol

All of the consecutive subjects who agreed to undergo GMA were evaluated at the Transfusional Unit, Azienda Ospedaliera di Padova; if the patients were judged suitable for the extracorporeal procedure, GMA was performed with Adacolumn® (Otsuka Pharmaceuticals, Italy). The GMA consisted of 5 sessions (one session per week for 5 consecutive weeks), during which the patient's blood was pumped out from the antecubital vein at 30 mL/min, introduced through the column of cellulose acetate beads and then returned to the patient *via* the contralateral antecubital vein. Each session lasted one hour, and 1.8 L of blood was processed. The demographic and clinical characteristics of the patients were prospectively recorded.

Table 1 Clinical and demographic characteristics of the enrolled population

	Total population (n = 41)	Mild (n = 28)	Moderate to severe (n = 13)	P value
Sex: M	24	14	10	0.17
Age: mean (range)	47 (16-82)	48 (19-73)	44 (16-82)	0.44
Disease duration before apheresis: median (range)	8 (1-31)	10 (1-31)	4 (1-11)	0.02
Disease localisation:		1	0	
Proctitis	1	9	1	
Left	10	18	12	
Extensive	30			
Steroid experience:				
Steroid resistance	6	2	4	0.06
Steroid dependence	33	26	7	0.007
Steroid intolerance	2	0	2	0.09
Previous treatments:			6	1
Immunosuppressants	20	14	2	0.64
Biologics	5	3		
Concomitant treatments:				
Steroids	15	10	5	1
Immunosuppressants	8	5	3	0.69
Biologics	0	0	0	1
Reasons for apheresis:				
Immunosuppressants resistance/intolerance/contraindications	15	12	3	0.3
Biologics resistance/intolerance/contraindications	1	1	0	1
Biologics and immune suppressors resistance/intolerance/contraindications	6	3	3	0.3
Others	19	12	7	0.7
Mean CRP (range) at study entry (normal if < 5 mg/dL)	13.6 (1-73)	11.6 (0.1-73)	15.2 (1.22-61)	0.67
Mean Lactoferrin (range) at study entry (normal if < 7 μg/g faeces)	84.55 (13-100)	80.71 (13-100)	85.9 (28-100)	0.7

These characteristics included age, gender, disease anatomic distribution according to Montreal classification, duration of disease before GMA, prior and concomitant treatments, indication for GMA, clinical severity, endoscopic activity and laboratory data such as the C-reactive protein (CRP) and lactoferrin levels.

Disease severity was classified according to the Modified Truelove Witts Severity Index (MTWSI). The MTWSI is a composite activity score calculated as the sum of stool frequency, rectal bleeding, nocturnal diarrhoea, faecal incontinence or soiling, abdominal pain, definition of general well-being, need for anti-diarrhoeals or narcotics and abdominal tenderness on the physical examination. The MTWSI score, ranging from 0-21 (higher scores indicate more active disease), was calculated. Active disease was defined as an MTWSI score > 3; active disease was classified as mild (4 ⩽ MTWSI ⩽ 8), moderate (9 ⩽ MTWSI ⩽ 14) or severe (15 ⩽ MTWSI ⩽ 21)[45]. Given the small number of patients with severe disease, the patients with moderate to severe disease were grouped together. A clinical response was defined as a decrease from the baseline MTWSI value of at least 2 points. A clinical and laboratory evaluation was performed at the end of the GMA cycle and 6 mo thereafter. No improvement in the MTWSI score ⩾ 2 points was considered as a non-response. All of the patients who did not respond to GMA at one month received a step-up treatment (increased steroid-dosage or immunosuppressants/biologics).

Statistical analysis

Descriptive statistics were used to analyse the baseline characteristics. Means with ranges were calculated for the continuous data, and percentages were computed for the discrete data. $P < 0.05$ was considered significant.

RESULTS

Clinical and demographic characteristics of the enrolled population

Details on the clinical and demographic features of the enrolled patients are shown in Table 1. Overall, 41 consecutive patients (mean age 47, range: 16-82, 17 women) met the enrolment criteria and were entered into the study. According to the Montreal classification, 30 patients (72.5%) presented with extensive colitis, 10 patients (25%) had left colitis and one patient (2.5%) had proctosigmoiditis. The mean disease duration before GMA was 8 years (1-31). According to the MTWSI at baseline, 28 (68%) patients presented with mild disease, 12 (29%) patients had moderate disease and 1 (3%) patient had severe disease. The groups were similar regarding the sex, age, disease localisation, previous or concomitant treatments and laboratory findings at baseline. Patients with mild disease had a longer disease duration (median duration: 10 years, range: 1-31 years) compared with the patients with moderate to severe disease (median duration: 4 years, range: 1-11 years) ($P < 0.05$). All of the patients had been treated with corticosteroids, which resulted in resistance in 6 patients (15%), dependency in 33 patients (80%) and intolerance in the remaining 2 patients (5%). Twenty-two patients (54%), 16 with mild disease and 6 with moderate to severe disease previously experienced intolerance, resistance or contraindications

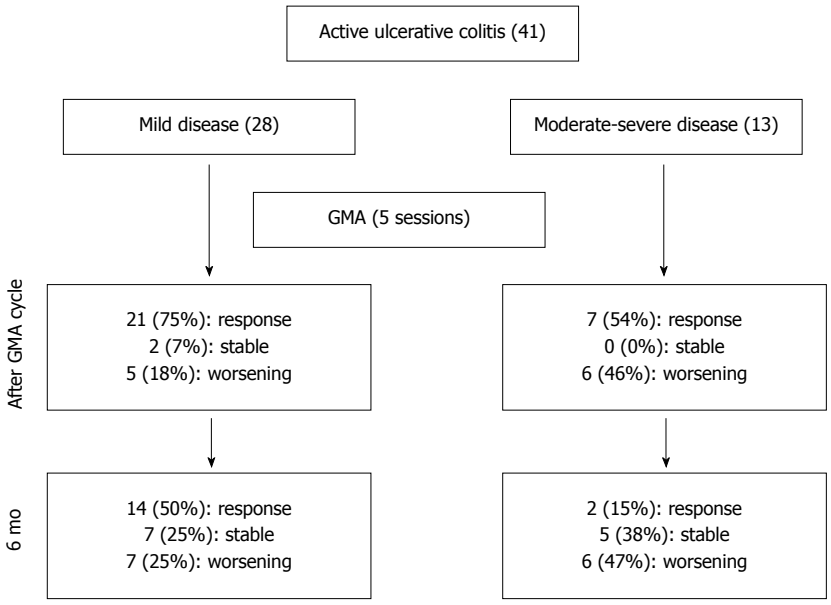

Figure 1 Study design and major results.

to immunosuppressants and/or biologics.

The mean CRP level before GMA was 13.6 (1-73) mg/dL (normal value < 5 mg/dL), and the mean lactoferrin level was 84.55 (13-100) μg (normal value < 7 μg/g faeces). No adverse events related to the treatment were reported. None of the patients underwent surgery during the study period.

GMA effectiveness according to disease severity

Figure 1 shows the flow diagram of the progression through the phases of this study. The proportion of patients who achieved a clinical response at the end of the GMA cycle was 75% (21/28) in the mild disease activity group and 54% (7/13) in the moderate-severe disease activity group, as shown in Figure 2A. No statistically significant difference was found between the two groups (P = 0.27). At 6 mo of follow-up, 50% (14/28) of the patients with mild disease activity showed a sustained response, 25% (7/14) had persistent disease activity and 25% (7/14) had worsened disease. In the moderate to severe group, the clinical response remained present in 15% (2/13) of the patients, whereas in 38% (5/13) of the cases, the disease remained active, and in 47% (6/13), the disease worsened. A clinical response at 6 mo occurred significantly more frequently in the patients with initial mild disease activity than in the patients with moderate to severe disease (P = 0.04), as illustrated in Figure 2A. At 6 mo after the GMA, the mean CRP level in the mild disease group significantly decreased from baseline [1.02 (0.1-5) mg/dL *vs* 11.6 (0.1-73) mg/dL, respectively; P = 0.01]. No statistically significant differences were reached in patients with moderate to severe disease [17.9 (2-65) mg/dL *vs* 15.02 (1.22-61) mg/dL; P = 0.7]. Similar results were obtained when comparing the faecal lactoferrin levels at 6 mo after the GMA with the baseline values in the mild disease patients [28.3 (5-50) *vs* 80.7 (13-100) μg/g; P < 0.01] and in the moderate to severe disease patients [73.8 (5-100) *vs* 85.9 (28-100) μg/g; P = 0.5].

GMA effectiveness according to intolerance, resistance or contraindications to immunosuppressants and/or biologics

Twenty-two patients were intolerant, resistant or had contraindications to immune suppressors/biologics. Sixteen of those patients were in the mild disease severity group, and 6 were in the moderate to severe group. In this population, GMA was effective at the end of the GMA cycle in 81% (13/16) of the patients with mild disease and in 33% (2/6) of the patients with moderate to severe disease (P = 0.05). At 6 mo, a clinical response was maintained in 56% (9/16) of the patients with mild disease and in none (0/6) of the patients with moderate to severe disease (P = 0.04) (Figure 2B).

DISCUSSION

Our study demonstrates that GMA is effective in inducing a clinical response in patients with mild and moderate to severe UC; patients with mild disease had better chances of obtaining and maintaining long term a clinical response. Up to 50% of patients with mild disease activity achieved and maintained a clinical response at 6 mo of follow-up compared with only a small percentage (15%) of patients with moderate to severe disease. In the mild disease group of patients, we observed a significant decrease in the CRP level, which is a well-known surrogate marker of disease activity. Furthermore, GMA effectiveness was evaluated in patients with active disease caused by intolerance, resistance or contraindications to immune suppressors and/or biologics, and we determined that GMA represents a good alternative therapeu-

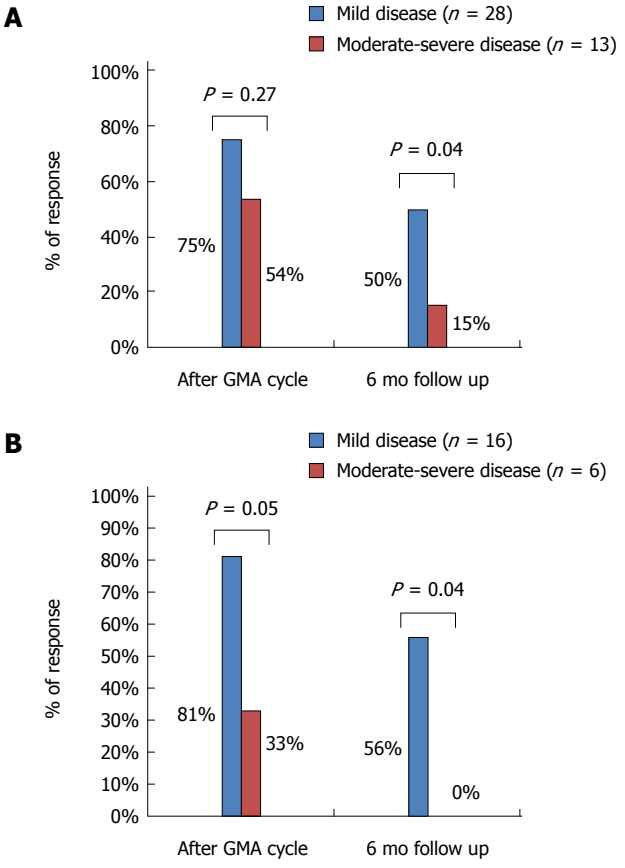

Figure 2 Percentage of patients. A: Percentage of patients achieving a clinical response after the Granulo-Monocyto Apheresis cycle and at 6 mo of follow-up; B: Percentage of patients with intolerance, resistance or contraindications to immunosuppressants and/or biologics who achieved a clinical response after the Granulo-Monocyto Apheresis cycle and at 6 mo of follow-up. Patients are classified according to disease severity.

tic approach for these patients.

Apheresis has been previously described as a therapeutic option in cases of corticosteroid dependent and resistant active UC. A recent meta-analysis demonstrated that this technique presents higher response and remission rates (OR = 2.88, 95%CI: 1.60-5.18 and 2.04, 95%CI: 1.36-3.07, respectively), increased steroid sparing effects (OR = 10.49, 95%CI: 3.44-31.93) and lower mild to moderate adverse effects (OR = 0.16, 95%CI: 0.04-0.60) compared with conventional treatments[16]. Similar results were shown in another meta-analysis, in which only RCTs with GMA were considered[46].

However, the majority of the RCTs previously conducted and included in the earlier analyses were performed in patients regardless their disease severity; data regarding the effectiveness of GMA in patients with different degrees of disease activity, in particular in cases of mild disease, are lacking. In a study conducted in 71 patients with moderate to severe steroid resistant disease, a lower Lichtiger's Colitis Activity Index (CAI) score at baseline was found by multivariate analysis to be a predictor of remission for more than 6 mo (OR = 0.74, 95%CI: 0.52-1.04, *P* value = 0.08). Other identified predictors were a rapid response to treatment (OR = 8.01, 95%CI: 1.08-59.37) and left-sided colitis (OR = 5.17, 95%CI: 0.77-34.63)[47]. Similar results emerged from the study by D' Ovidio *et al*[48] on 69 patients with mild to moderate steroid dependent or resistant disease; in that study, a lower CAI score at baseline was identified, on the univariate and multivariate analyses, to be an independent predictor of a clinical response at the short term follow up (OR = 0.770, 95%CI: 0.425-1.394). Other predictive factors of a clinical response on the multivariate analysis included steroid dependency (OR = 0.390, 95%CI: 0.176-0.865)[48]. However, none of the previous studies directly compared the efficacy of GMA in patients with mild or moderate to severe disease and in patients intolerant or resistant to immunosuppressants and/or biologics or with contraindications to these agents.

We should note that GMA is an expensive treatment. In a study by Panés *et al*[49] the average annual cost per UC patient was estimated to be €6959 when using GMA. In the same study, a cost-effectiveness analysis showed that GMA results in savings in steroid dependent patients with moderate to severe disease because there are reduced adverse events and reduced need for surgery[49]. There are no data regarding the average costs per patient with mild disease; however, it is important to consider that patients with mild disease suffer from an impaired quality of life compared with patients in clinical remission[50], that treatment-tolerability and acceptability are strong predictors of a better quality of life[51] and that good patient compliance reduces time spent in an active UC disease state[52].

Our study has some limitations. First, the retrospective nature of the study exposes it to selection bias. However, we included all of the consecutive UC patients who underwent GMA in our centre, thus reducing the risk of selection bias. Second, the number of patients was limited; however, the number was consistent for a single-centre study and was close to the numbers of patients involved in some of the RCTs evaluating the efficacy of GMA[30,37]. Moreover, the single centre design of the present study reduces the inter-observer variability related to clinical assessments and related to the indications for GMA treatment. Third, we did not have endoscopic data after the GMA treatment; this lack of data was caused by the short follow up period (6 mo).

We have demonstrated that patients with mild UC activity benefit from GMA more than patients with moderate to severe disease. Moreover, GMA was found to be effective in a significant number of patients with intolerance, resistance or contraindications to immune suppressors and/or biologics. Although GMA remains an expensive technique, our data demonstrate that GMA should be considered in patients with mild disease, especially in cases of severe impairment of quality of life, independent of disease severity. Our data also demonstrate that GMA represents a good alternative therapeutic approach for patients with intolerance, resistance or contraindications to standard treatments. Further randomised controlled data are needed to confirm if GMA is superior to

conventional treatment in inducing a clinical response in patients with mild UC and to assess the cost/effectiveness ratio of this approach.

COMMENTS

Background

Granulo-monocyto apheresis is a non-pharmacological treatment that is currently used in cases of moderate to severe ulcerative colitis; this treatment consists of removal of the cell population involved in the induction and perpetuation of bowel inflammation from the peripheral blood. Several studies evaluating the effectiveness of this treatment have been previously conducted, and the results of these studies are conflicting. This discrepancy in results is most likely caused by the heterogeneous cohorts of patients with different degrees of disease activity in the studies and by enrolling patients with overly severe disease in the studies.

Research frontiers

Some patients present contraindications to all immunosuppressive treatments, posing serious difficulties in their treatment. In this context, granulo-monocyto apheresis remains a valuable option because of its high safety profile.

Innovations and breakthroughs

In previous studies, granulo-monocyto apheresis was shown to be more effective in less severe cases. The authors performed a retrospective study evaluating GMA effectiveness according to disease severity. The authors evaluated if difficult to treat patients, such as patients with intolerance, resistance or contraindications to immune suppressors and/or biologics, could benefit from this apheresis.

Applications

Those results confirm the hypothesis that patients with mild disease benefit from GMA more than patients with moderate to severe disease. Moreover, GMA could be considered a valid alternative therapeutic approach in patients with intolerance, resistance or contraindications to immune suppressors and/or biologics.

Terminology

Granulo-monocyto apheresis is a non-pharmacological treatment consisting of the extracorporeal removal of granulocytes and monocytes through a selective filter.

Peer review

Several studies evaluating granulo-monocyto apheresis in ulcerative colitis have been previously conducted, and these studies show conflicting results. This research confirms the hypothesis that patients with mild disease benefit from GMA more than patients with moderate to severe disease.

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