Original Article
The combined efficacy of adalimumab with GMA method on the treatment of ulcerative colitis and repair of intestinal mucosal lesion

Ailing Song, Hai Jiang, Liang Guo, Shanshan Wu

Department of Gastroenterology, The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Ji'nan 250001, Shandong, China

Abstract: Objectives: The study discussed and analyzed the combined efficacy of adalimumab with granulocyte and monocyte adsorption apheresis (GMA) method on patients with ulcerative colitis (UC) and the repair of intestinal mucosal lesion. Methods: 60 UC patients in moderate-to-severe active phase that hospitalized from January 2017 to March 2020 were chosen and randomly classified into observation group (n=30) and control group (n=30). The control-group patients received GMA treatment, and the observation-group patients received combination therapy of GMA and adalimumab. The therapeutic efficacy, laboratory indicators, changes of serum inflammatory factors, and intestinal mucosal barrier impairment in two sets of participants were compared. Results: The comprehensive effective rate of clinical treatment was remarkably higher in observation group than that in control group (*P<0.05*). CRP and ESR of the two groups in post- treatment were notably lower than those before treatment (*P<0.05*), while Hb and ALB in post-treatment increased significantly than in pre-intervention (*P<0.05*); CRP in observation group after treatment was remarkably lower than that in control group (*P<0.05*), while no significant difference was noticed in ESR, ALB and Hb between the two groups (*P>0.05*). The serum inflammatory factors in observation group in post-treatment were significantly lower than those in the control group (*P<0.05*). The scores of PCT, DAO and intestinal mucosa in two sets of participants in post-treatment were dramatically lower than those in pre-treatment (P<0.05), and the scores in observation group after treatment were notably lower than those in the control group (*P<0.05*). Conclusion: The combined efficacy of adalimumab with GMA on UC patients can improve the clinical curative efficacy, effectively reduce the inflammatory factors, which is beneficial to the repair of intestinal mucosal barrier function, and worthy of clinical application.

Keywords: Adalimumab, Granulocyte and Monocyte Adsorption Apheresis (GMA), Ulcerative Colitis (UC), repair of intestinal mucosal damage

Introduction

Ulcerative colitis (UC) is a chronic non-specific inflammatory disease of intestinal tract, with characteristics of chronic and life-long recurrence due to a variety of reasons. The illness can occur at any age, but is much more frequent in people between 20 to 49 years old [1, 2]. The etiology of UC is still unclear. It may be related to factors such as genetics, environment or immunity. Moreover, the disease has long course, high relapse, and currently lacks of effective treatment in clinic [3]. In recent years, the application of granulocyte and monocyte adsorption apheresis (GMA) has made a new path for the clinical treatment of UC, which becomes a hot spot in non-drug treatment strqategy [4]. GMA takes leukocytes as therapeutic targets, selectively adsorb granulocytes and monocytes/macrophages, so that production of pro-inflammatory factors could be effectively reduced [5, 6]. In addition, with molecular targeted research on the pathogenesis of UC, the prevention of cascade reaction of immune inflammation has become a new direction for UC treatment. The preparation of anti-tumor necrosis factor TNF-α can promote the apoptosis of inflammatory cells by combining with the proinflammatory factor TNF-α in the immune response, and block its pro-inflammatory

effect. Adalimumab is a new type of anti-TNF-α preparation [7, 8]. This study searched and analyzed the combination efficacy of adalimumab with GMA on UC patients and its repair effect on intestinal mucosal damage.

Materials and methods

Clinical materials

60 UC patients that hospitalized from January 2017 to March 2020 were chosen as research subjects, and randomly classified into observation group (n=30) and control group (n=30) in accordance with random number table. The patients met the inclusive criteria for patients in moderate-to-severe active phase. The study acquired approval from the hospital ethics committee.

Diagnostic criteria

Participants should conform to the diagnostic criteria of Consensus on Diagnosis and Treatment of Inflammatory Bowel Disease (Beijing, 2018) [9], including the clinical types of the disease, range of lesions, severity and stage of the disease, and whether there is a combination of parenteral manifestations. According to colonoscopy results, the range of lesions was evaluated upon the Montreal classification. E1: the inflammation distributed in rectum, and the inflammatory lesions were confined to the rectum and yet form into sigmoid colon; E2: the inflammation distributed in left colon, and the inflammatory lesions affected the left colon (beyond the spleen area); E3: the inflammation widely distributed in colon, and the inflammatory lesions were widely accumulated in spleen area or even entire colon. The severity of the disease was scored according to the modified Mayo scoring system. The scores of 3-5 points were mild activity, 6-10 points were moderate activity, and 11-12 points were severe activity.

Pathological staining

The pathological tissues were taken under colonoscopy, fixed with 4% paraformaldehyde fixative, routinely embedded in paraffin and sectioned. Subsequently, we stained the pathological tissues and observed the lesions under light microscope.

Inclusive and exclusive criteria

Inclusive criteria: (1) The patient met the diagnostic criteria of UC; (2) Patients belong to moderate to severe activity; (3) Patients aged between 18-60 years old; (4) Patients who were willing to receive GMA treatment and signed the informed consent for specialized treatment.

Exclusive criteria: (1) Patients with coagulation dysfunction: (2) Patients who cannot tolerate GMA therapy or were allergic to heparin; (3) Patients with mild disease or in remission stage; (4) Patients who were afraid of leukocyte therapy or had a psychical diseases history; or (5) Patients in pregnancy, breast-feeding or planning a pregnancy.

Methods

Both groups of participants received GMA treatment. Before treatment, the patents' VS, including blood pressure, pulse, heart rate, breathing, etc., were measured. The GMA treatment was performed under stable condition of patients. During treatment, the patient was placed in supine position, a circulation pathway was established in the patient's median cubital vein. The blood discharged from the left (right) vein, passed through the Adacolumn adsorption column, and then returned to body from the right (left) vein. The system was pre-immersed in 1 L normal saline, followed by 400 IU of heparin sodium. The filtration rate was 30 ml/min, and the whole circulation process was about 60 min. A total of 1800 ml blood was processed, and 2000 IU heparin sodium was continuously pumped through the input port. The patient rested in the intensive care unit for 2 hours after the treatment, and returned to the ward without any discomfort. After the GMA treatment, the patients were given 5-ASA maintenance treatment with a dose of 2-3 g/d, and the dosage was adjusted according to the patient's condition. The observation group patients, after the completion of GMA treatment, were given Adamumab (40 mg/ml) subcutaneous injection by 40 mg/ml once every two weeks, and 4 times in total; while the control-group-patients received same volume of saline subcutaneous injection by once every two weeks for 4 times totally.

Table 1. Comparison of clinical data between the two groups

Group	Number of Cases	Gender		Age (years old, $\bar{x} \pm s$)	Diseases course (years, $\bar{x} \pm s$)	Disease Condition	
		Male	Female			Moderate	severe
Observation group	30	23	7	29.83±7.42	1.25±0.36	19	11
Control group	30	21	9	30.16±6.95	1.33±0.40	17	13
t/X^2	-	0.341		0.178	0.814	0.278	
P	-	0.559		0.860	0.419	0.598	

Evaluation criteria for clinical efficacy

According to literature standards [10], the remission was defined as: the patient's clinical symptoms completely disappeared, the mucosal healing was prompted by colonoscopy or the modified Mayo score was ≤2 points, and there was no single sub-item score >1 point; Effective: the symptoms of participants basically disappeared, mild mucosal inflammation was observed by colonoscopy or the modified Mayo score was reduced by ≥30% or ≥3 points relative to the decrease of baseline, and scores of the blood stool decreased by ≥1 point or was scored at 0 or 1 point; Invalid: The patient's clinical symptoms and colonoscopy were not improved. The comprehensive effective rate of treatment = (remission + effective)/total number of cases × 100%.

Index observation

(1) Patients underwent monitoring of erythrocyte sedimentation rate (ESR), albumin (ALB), hemoglobin (Hb), and CRP before and after treatment. ALB and Hb were detected by automatic biochemical analyzer (Beckman, USA), ESR by erythrocyte sedimentation rate analyzer (Beijing Putian Xinqiao Technology Co., Ltd.), and C-reactive protein (CRP) by enzyme-linked immunoassay (ELISA).

(2) The peripheral venous blood of the two groups was drawn in prior - and post-therapy, the serum was separated after centrifugation, and the interleukin-1β (IL-1β), IL-6, IL-8 and TNF-α were detected.

(3) The damage indexes of intestinal mucosal in two groups were tested in pre- and post-therapy, which including procalcitonin (PCT), diamine oxidase (DAO) and change in mucosal scores under colonoscopy. PCT was detected by chemiluminescent method, DAO was by ELISA and intestinal mucosa was evaluated on the basis of colonoscopy results. The normal, mild, moderate and severe fragile with exudation were marked by 0, 1, 2 and 3 points respectively.

Statistical analysis

Data processing and analysis were conducted by the researcher via statistical tool SPSS 22.0. The comparison of measurement data was by t test, and the enumeration data was by X^2 test. The difference with statistical criteria was settled by $P<0.05$.

Results

Clinical data

The comparison of clinical data in two groups showed none statistical criteria (P>0.05), as shown in **Table 1**. HE pathological staining is shown in **Figure 1**, the ulcerative colitis can be observed through staining of pathological tissues, the mucosal structure partially disappeared, the crypt structure partially destroyed, the epithelial cells partially retained, and the infiltration of inflammatory cell can be seen.

Comparison of clinical efficacy

The comprehensive effective rate of clinical therapy in observation group was critically higher than that in control group (*P<0.05*), as stated in **Table 2**.

Comparison of laboratory indexes

No statistical difference in two groups with respect to the levels of ESR, ALB, Hb and CRP before treatment (*P>0.05*). CRP and ESR in two groups after treatment were notably lower than those in prior-treatment (*P<0.05*), while Hb and ALB increased significantly than in pre-intervention (*P<0.05*); The CRP in observation group after treatment was remarkably lower than that of in group (*P<0.05*), while no statistical difference revealed in ESR, ALB and Hb between the two groups (*P>0.05*), as illustrated in **Table 3**.
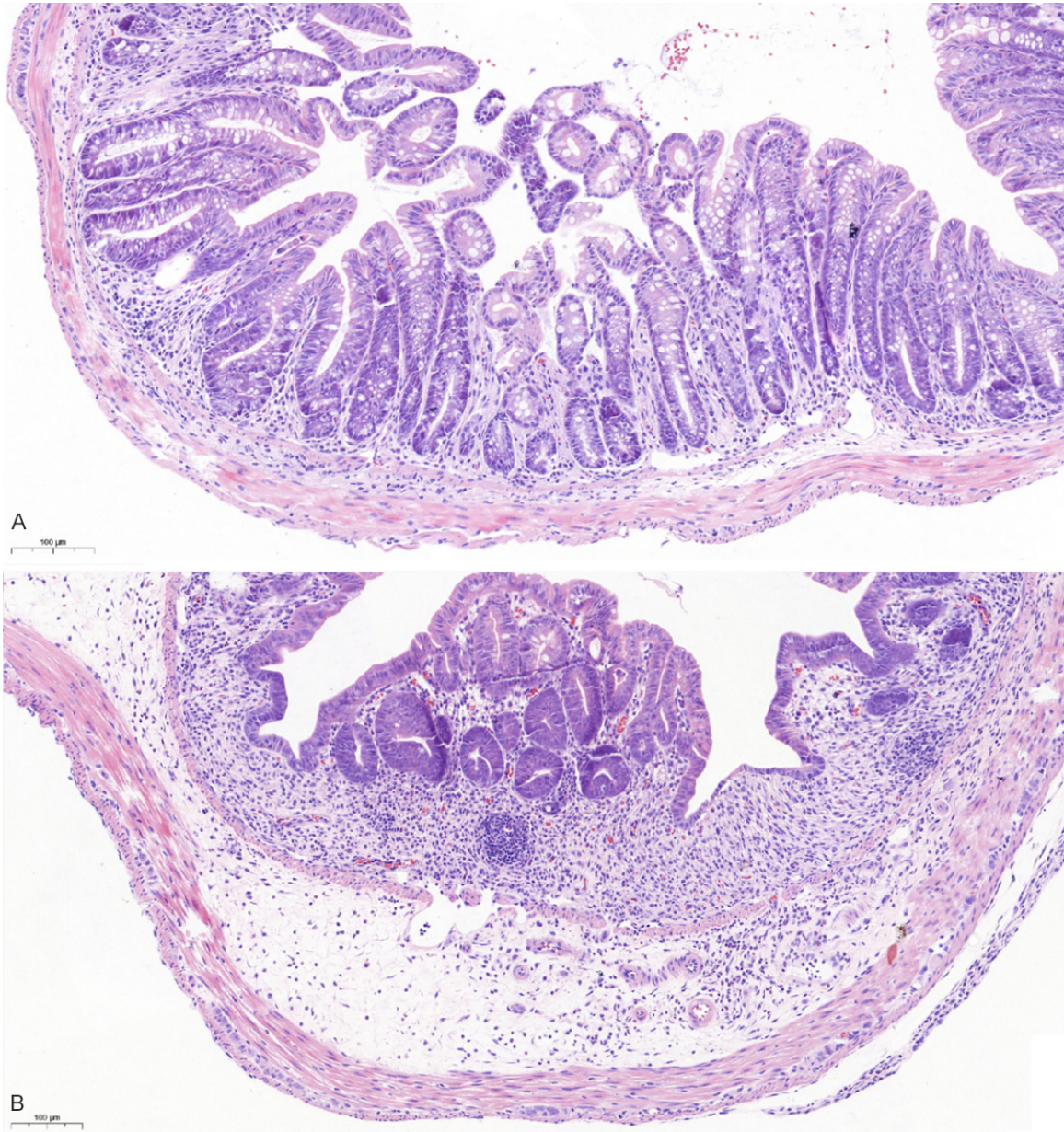
Figure 1. HE pathological staining. A: Observation group; B: Control group. The ulcerative colitis can be observed through staining of pathological tissues, the mucosal structure partially disappeared, the crypt structure partially destroyed, the epithelial cells partially retained, and the infiltration of inflammatory cell can be seen.

Table 2. Comparison of clinical efficacy between the two groups [n (%)]

Group	Number of Cases	Remission	Effective	Invalid	comprehensive effective rate (%)
Observation group	30	19 (63.33)	10 (33.33)	1 (3.33)	29 (96.67)
Control group	30	13 (43.33)	9 (30.00)	8 (26.67)	22 (73.33)
X^2	-	-	-	-	4.706
P	-	-	-	-	0.030

Comparison of serum inflammatory factors

No statistical difference in two groups with respect to the inflammatory factors IL-1β, IL-6, IL-8 and TNF-α in pre-treatment ($P>0.05$); the indexes of the two groups in post-treatment were decreased significantly than in pre-treatment ($P<0.05$), and the inflammatory factors of

Table 3. Comparison of laboratory indexes between the two groups ($\overline{x}\pm s$)

Group	Time	ESR (mm/h)	ALB (g/L)	Hb (g/L)	CRP (mg/L)
Observation group (n=30)	Before treatment	30.18±13.46	30.02±3.21	105.28±20.93	22.38±7.02
	After treatment	13.27±4.02	36.28±6.40	119.83±15.64	8.36±2.10*
	t	6.593	4.789	3.050	10.480
	P	0.000	0.000	0.003	0.000
Control group (n=30)	Before treatment	30.75±11.07	30.17±4.06	107.31±22.03	23.19±6.49
	After treatment	14.03±3.97	35.95±5.37	120.74±17.48	12.51±1.98
	t	7.787	4.703	2.616	8.621
	P	0.000	0.000	0.011	0.000

Note: Compared with the control group, *P<0.05.

Table 4. Comparison of serum inflammatory factors between the two groups (pg/ml, $\overline{x}\pm s$)

Group	Time	IL-1β	IL-6	IL-8	TNF-α
Observation group (n=30)	Before treatment	5.49±0.63	22.07±3.79	268.20±45.28	58.94±6.33
	After treatment	4.37±0.73*	13.12±2.16	201.93±40.64	45.03±5.27
	t	6.362	11.237	5.966	9.250
	P	0.000	0.000	0.000	0.000
Control group (n=30)	Before treatment	5.33±0.95	21.85±3.17	275.64±48.30	58.25±7.21
	After treatment	4.85±0.66	16.44±2.08	233.71±38.74	49.33±6.02
	t	2.273	7.815	3.709	5.202
	P	0.027	0.000	0.001	0.000

Note: Compared with the control group, *P<0.05.

observation group in post-treatment were critically lower than those of control group (*P<0.05*), as shown in **Table 4** and **Figure 2**.

Comparison of intestinal mucosal barrier damage

No statistical difference in two groups with respect to the scores of PCT, DAO and intestinal mucosa before treatment (*P>0.05*); The scores of PCT, DAO and intestinal mucosa of the two groups in post-treatment were dramatically lower than those in prior-treatment (P<0.05), and the scores of observation group in post-treatment were notably lower than those of control group (*P<0.05*), as shown in **Table 5**.

Discussion

The specific pathogenesis of UC so far has yet been clarified, and researchers consider that the disease may be related to factors such as genetics, food allergies, infections, breeding, depression, and anxiety. In recent years, the function of cytokines in pathogenesis of UC has been recognized by an increasingly number of scholars [11]. Cytokines can be divided into

pro-inflammatory factors and anti-inflammatory factors, The pathogenesis of UC is primary related to the role of pro-inflammatory factors, including IL-1, IL-5, IL-6, IL-8, TNF- and interferon [12]. IL-1 is primary secreted by monocytes, macrophages, endothelial cells and neutrophils. IL-1β can stimulate to generate inflammatory mediators, such as IL-6, IL-8 and TNF-α, induce expression of immune molecules on the surface of antigen presenting cells, so that the second signal for the activation of T lymphocytes can be provided. It also promotes the hyperplasia and differentiation of B cells, mediates the exudation of immunoglobulins, activates complement, and enhances tissue damage mediated by cellular and humoral immunity. Meanwhile, with the increased degree of inflammation and gradually strengthened expression of IL-1β and mRNA, chemotactic neutrophils, monocytes and other inflammatory cells in concentrated lesions release many active substances, which lead to tissue damage and trigger a cascade of inflammation. Therefore, UC patients in active stage are generally accompanied by abundant granulocytes and monocytes/cells infiltrating into the intesti-
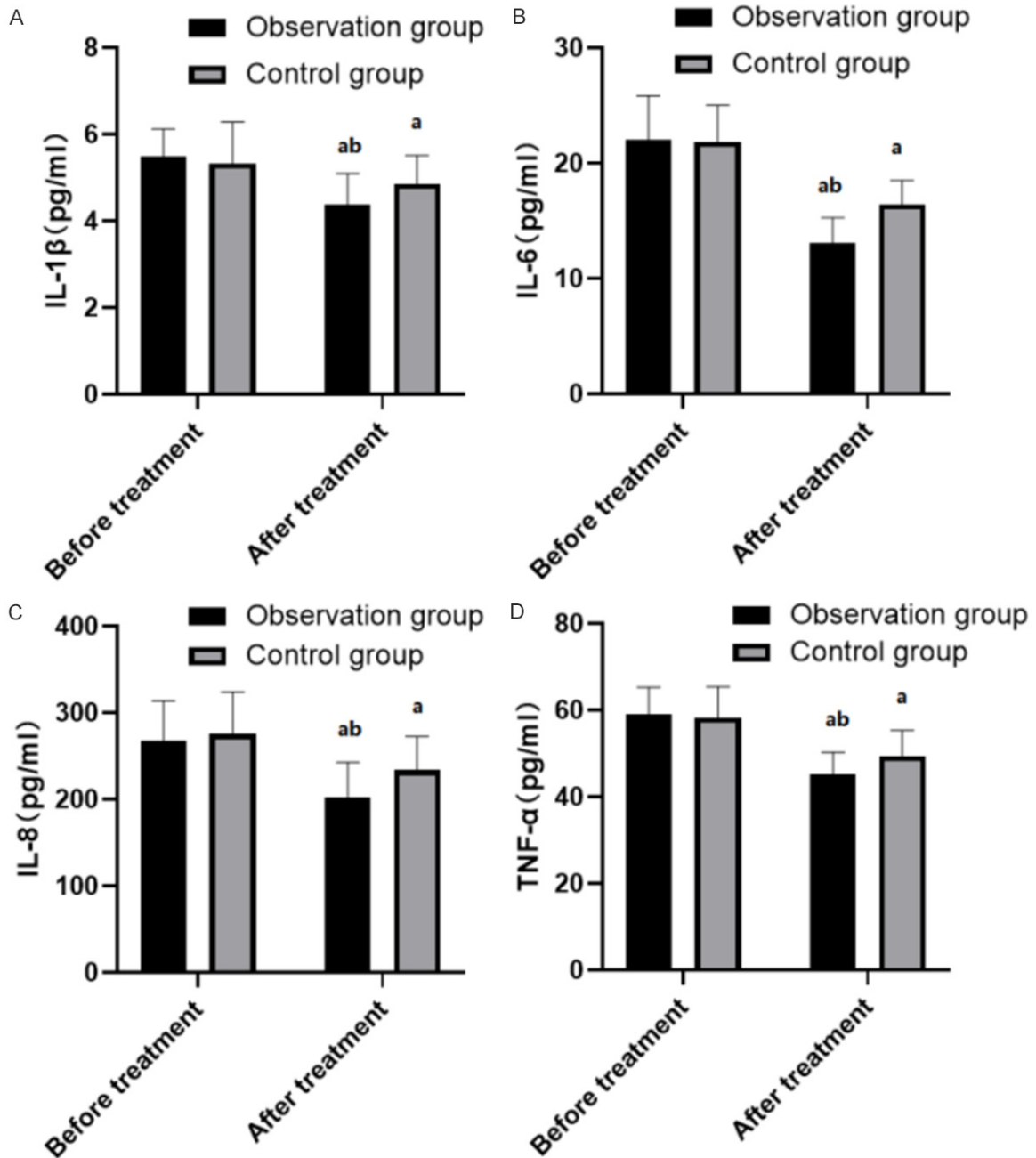
Figure 2. Comparison of IL-1β, IL-6, IL-8 and TNF-α levels between the two groups before and after treatment. Note: Compared with before treatment, $^{a}P<0.05$; compared with the control group, $^{b}P<0.05$. A: IL-1β; B: IL-6; C: IL-8; D: TNF-α.

nal mucosa, resulting in a series of clinical symptoms [13-15].

The Adacolumn device is filled with cellulose acetate microbeads that selectively adsorb circulating granulocytes and mononuclear/ opportunistic cells on the basis that these cells have expression of Fcγ receptor (CD16) [16].

Adacolumn adsorbs IgG fragments and immune complexes in plasma, and then produces active complement fragments, such as C3a, C5a, C3bi, etc.; and neutrophils and monocytes will expose Fcγ receptors when they meet IgG and immune complexes and combine with C3bi to bind to the complement on Adacolumn surface [17, 18]. On the contrary, most lymphocytes do

Table 5. Comparison of intestinal mucosal barrier damage between the two groups ($\bar{x}\pm$s)

Group	Time	PCT (ng/ml)	DAO (mmol/L)	Score of Intestinal Mucosa (Score)
Observation group (n=30)	Before treatment	3.18±0.45	10.28±2.19	1.85±0.25
	After treatment	1.56±0.27*	4.89±0.85*	1.06±0.21*
	t	16.908	12.567	13.253
	P	0.000	0.000	0.000
Control group (n=30)	Before treatment	3.06±0.56	10.36±2.33	1.91±0.30
	After treatment	2.13±0.37	6.28±1.56	1.25±0.26
	t	7.589	7.970	9.106
	P	0.000	0.000	0.000

Note: Compared with the control group, *P<0.05.

not have Fcy receptor (CD16), thus will not be bound.

Adalimumab is a humanized monoclonal antibody against human tumor necrosis factor (TNF), which can specifically integrate to TNF- and prevent its interaction with TNF receptors on P55 and P75 cell surface, thus reducing TNF activity and achieving therapeutic effect [19]. The biological agents, compared with traditional drug therapy, have the characteristics of specific immunity and inflammatory molecular targeting. Biological agents have been officially approved in foreign countries for the treatment of UC and other diseases, and have been officially marketed in China in August 2010 [20]. In order to further promote the clinical curative effect of UC patients, this study discussed and analyzed the combined curative effect of Adamumab with GMA on UC patients and its repair effect of intestinal mucosal damage.

The study outcomes demonstrated that the comprehensive effective rate of clinical treatment in observation group was dramatically higher than that in control group, indicating that the combination of Adamumab with GMA therapy improve the total effective rate of clinical treatment in UC patients. The comparison of laboratory indicators showed that two sets of participants' CRP and ESR in post-treatment were notably lower than those in prior-treatment, while Hb and ALB increased significantly than in pre-intervention; The CRP of observation group after treatment was remarkably lower than that of control group, while no statistical difference was observed in ESR, ALB and Hb between the two groups. Serum inflammatory factors IL-1β, IL-6, IL-8 and TNF-α levels after treatment in two groups of participants were decreased significantly than in pre-treatment, and the above index in observation group

after treatment were critically lower than those in control group. GMA therapy combined with adalimumab therapy, which results were similar to scholars' [21, 22], can further improve the clearance of inflammatory factors, while has no difference in indicators of erythrocyte sedimentation rate or albumin.

In addition, there was no statistical difference in two groups in scores of PCT, DAO and intestinal mucosa before treatment; while PCT, DAO and intestinal mucosa scores of the two groups in post-treatment were dramatically lower than those in prior-treatment, and the scores of observation group after treatment were notably lower than those of control group. The normal intestinal defense system includes intestinal mucosal epithelial barrier, intestinal flora barrier, mucus barrier, chemical barrier, intestinal mucosal immune barrier and hepatointestinal axis, which effectively prevent the occurrence of bacterial overgrowth and endotoxemia in small intestine [23]. DAO is a high-lively intracellular enzyme in cytoplasm of intestinal mucosal upper villus of human and mammals, which is high in content and strong in activity in the intestinal mucosal upper villus, but low in content and other tissues [24]. Intestinal mucosal cells can cause DAO to be released into the blood after damage and necrosis, or enter the intestinal lumen with intestinal mucosal cells shed with necrosis, resulting in the increased activity of DAO in plasma and intestinal lumen [25, 26]. PCT is a hormone-free glycoprotein molecule that amplifies and enhances endotoxin-induced inflammation and damage to the intestinal mucosal barrier [27, 28]. The study results suggested that the combination of GMA with Adamumab can further promote the repair of intestinal mucosal barrier function in UC patients, and improve intestinal mucosa under gastroscopy.

However, due to the specificity of the treatment methods in this study and the small sample size included, it is necessary to expand the sample quantity in following studies to obtain more reliable clinical research data and provide a basis for clinical treatment.

In summary, the combined therapy of Adalimumab with GMA on UC patients can improve the clinical treatment efficacy and further reduce the inflammatory factors, which is beneficial to the repair of intestinal mucosal barrier function, and is worthy of clinical promotion.

Disclosure of conflict of interest

None.

Address correspondence to: Shanshan Wu, Department of Gastroenterology, The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, No. 1 Jingba Road, Shizhong District, Ji'nan 250001, Shandong, China. Tel: +86–0531-82436006; E-mail: sdzyydxdefy@163.com

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