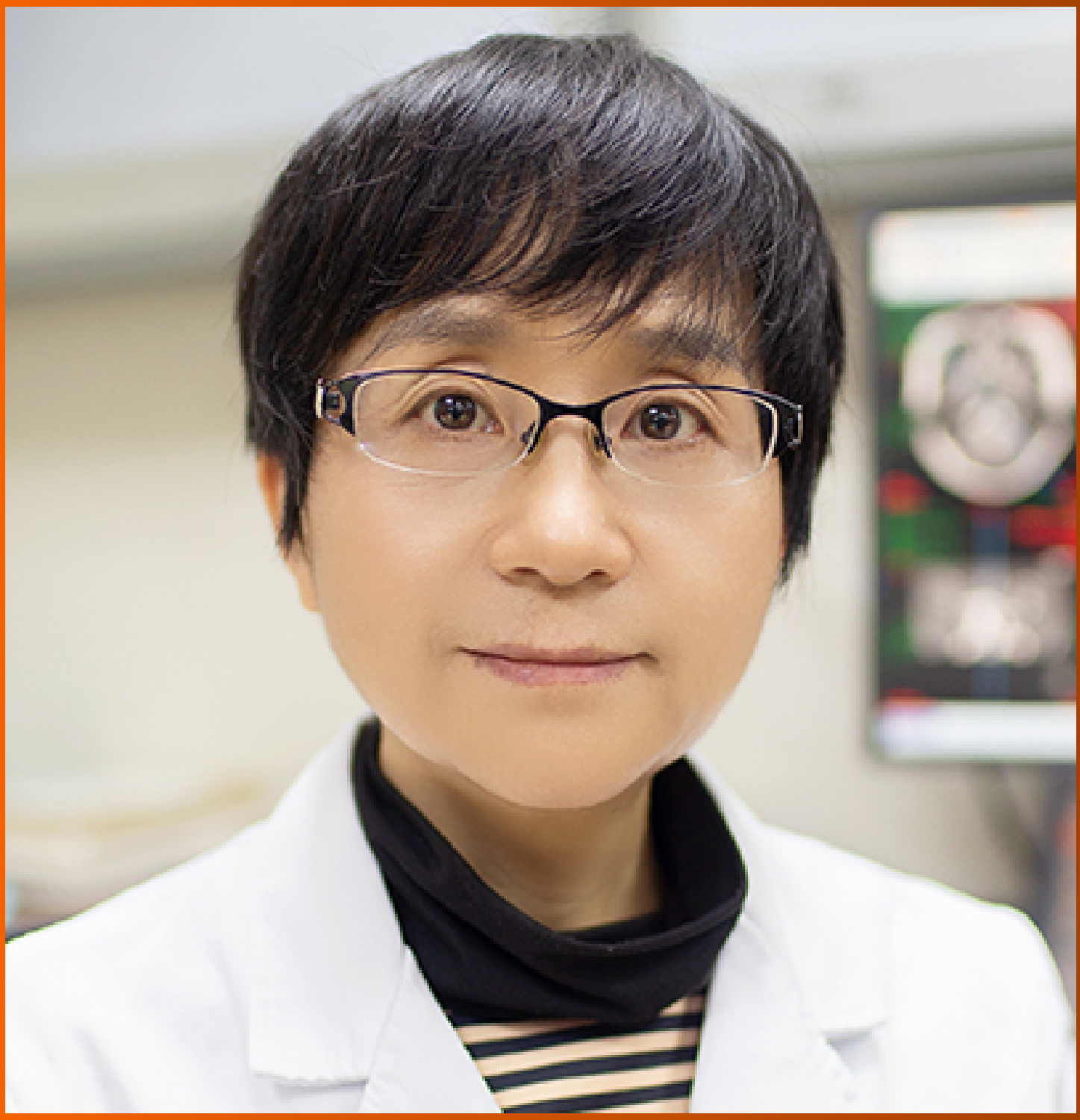
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2021 March 14; 27(10): 908-989



Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 27 Number 10 March 14, 2021

OPINION REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

Clinical Trials Study

Observational Study

World Journal of Gastroenterology

Weekly Volume 27 Number 10 March 14, 2021

Contents

ABOUT COVER

Qi Xie, MD, PhD, Chief Doctor, Professor, Director, Department of Medical Imaging, Nansha Hospital, Guangzhou First People's Hospital, School of Medicine, South China University of Technology, No. 105 Fengzedong Road, Guangzhou 511457, Guangdong Province, China. eyqixie@scut.edu.cn

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for *WJG* as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2. The *WJG*'s CiteScore for 2019 is 7.1 and Scopus CiteScore rank 2019: Gastroenterology is 17/137.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
March 14, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2021 March 14; 27(10): 908-918

DOI: 10.3748/wjg.v27.i10.908

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

OPINION REVIEW

Use of granulocyte/monocytapheresis in ulcerative colitis: A practical review from a European perspective

Eugeni Domènech, Joan-Ramon Grífols, Ayesha Akbar, Axel U Dignass

ORCID number: Eugeni Domènech 0000-0002-2315-7196; Joan-Ramon Grífols 0000-0001-5573-9740; Ayesha Akbar 0000-0002-3924-6505; Axel U Dignass 0000-0002-9724-054X.

Author contributions: Domènech E conceived the idea of the manuscript; all the authors were involved in reviewing the literature and drafting the manuscript.

Conflict-of-interest statement: Domènech E has served as a speaker or has received research or education funding or advisory fees from Samsung, MSD, AbbVie, Takeda, Kern Pharma, Pfizer, Janssen, Celgene, Adacyte Therapeutics, Roche, Otsuka Pharmaceuticals, Ferring, Shire Pharmaceuticals, Tillots, ThermoFisher, Grifols, Gebro, and Gilead. Akbar A has received speaker fees or advisory fees from Takeda, Dr Falk, Abbvie, Janssen, Otsuka Pharmaceuticals, Adacyte therapeutics and MSD. Dignass AU has received research support or acted as a principal investigator for Abbvie, Dr. Falk Pharma, Celgene/BMS, Gilead/Galapagos, Janssen, Otsuka and Takeda; he has acted as a consultant for AbbVie, Amgen, Boehringer Ingelheim, Celgene/BMS, Celltrion, Dr Falk Pharma, Ferring, Fresenius Kabi, Janssen, MSD,

Eugeni Domènech, Department of Gastroenterology, Hospital Universitari Germans Trias i Pujol, Badalona 08916, Catalonia, Spain

Eugeni Domènech, Department of Medicine, Universitat Autònoma de Barcelona, Badalona 08916, Catalonia, Spain

Eugeni Domènech, Centro de Investigaciones Biomédicas en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Badalona 08916, Catalonia, Spain

Joan-Ramon Grífols, Blood and Tissue Bank, Hospital Universitari Germans Trias i Pujol, Badalona 08916, Catalonia, Spain

Ayesha Akbar, IBD Unit, St. Mark's Hospital and Academic Institute, London HA1 3UJ, United Kingdom

Axel U Dignass, Department of Medicine I, Agaplesion Markus Hospital, Goethe-University, Frankfurt am Main 60431, Germany

Corresponding author: Eugeni Domènech, MD, PhD, Chief Physician, Professor, Department of Gastroenterology, Hospital Universitari Germans Trias i Pujol, Carretera del Canyet s/n, Badalona 08916, Catalonia, Spain. eugenidomenech@gmail.com

Abstract

Half of the patients with ulcerative colitis require at least one course of systemic corticosteroids in their lifetime. Approximately 75% of these patients will also require immunosuppressive drugs (*i.e.*, thiopurines or biological agents) in the mid-term to avoid colectomy. Immunosuppressive drugs raise some concerns due to an increased risk of serious and opportunistic infections and cancer, particularly in elderly and co-morbid patients, underlining the unmet need for safer alternative therapies. Granulocyte/monocytapheresis (GMA), a CE-marked, non-pharmacological procedure for the treatment of ulcerative colitis (among other immune-mediated diseases), remains the only therapy targeting neutrophils, the hallmark of pathology in ulcerative colitis. GMA has proven its efficacy in different clinical scenarios and shows an excellent and unique safety profile. In spite of being a first line therapy in Japan, GMA use is still limited to a small number of centres and countries in Europe. In this article, we aim to give an overview from a European perspective of the mechanism of action, recent clinical data on efficacy and practical aspects for the use of GMA in ulcerative colitis.

Otsuka, Pfizer, Roche, Takeda, Tillotts, Pharmacosmos and Vifor; and has participated in speaker bureaus for AbbVie, Falk Foundation, Ferring, Janssen, Med Update, MSD, Otsuka, Pfizer, Roche, Takeda, Tillotts, and Vifor.

Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Spain

Peer-review report's scientific quality classification

Grade A (Excellent): A, A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 12, 2020
Peer-review started: December 12, 2020
First decision: December 27, 2020
Revised: January 3, 2021
Accepted: February 11, 2021
Article in press: February 11, 2021
Published online: March 14, 2021

P-Reviewer: Lankarani KB, Matsui T
S-Editor: Gao CC
L-Editor: Webster JR
P-Editor: Liu JH

Key Words: Granulocyte; Monocyte; Ulcerative colitis; Inflammatory bowel disease; Apheresis; Safety

Core Tip: Approximately 30%-40% of patients with ulcerative colitis will require immunosuppressive therapies, including immunomodulators and biological agents. Unfortunately, none of these therapies achieve more than 40% of steroid-free clinical remission in the middle term; moreover, most immunosuppressive therapies increase the risk of infections and some malignancies, raising the unmet need for therapeutic alternatives in ulcerative colitis. Granulocyte/monocytapheresis (GMA) remains the only therapy targeting neutrophils, the hallmark of pathology in ulcerative colitis. GMA has proven its efficacy in different clinical scenarios and shows an excellent and unique safety profile.

Citation: Domènech E, Grífols JR, Akbar A, Dignass AU. Use of granulocyte/monocytapheresis in ulcerative colitis: A practical review from a European perspective. *World J Gastroenterol* 2021; 27(10): 908-918
URL: https://www.wjgnet.com/1007-9327/full/v27/i10/908.htm
DOI: https://dx.doi.org/10.3748/wjg.v27.i10.908

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory condition of unknown origin and has a relapsing-remitting clinical course. Approximately half of the patients present a mild course of the disease and are easily managed with aminosalicylates, while the other half require at least one course of oral or intravenous corticosteroids[1,2]. Among the latter, immunosuppressive drugs (including thiopurines and/or biological agents) are required in up to 75% of cases for steroid-refractoriness, steroid-dependency or chronic disease activity. Even with the more potent available drugs, only 30% to 40% of those patients achieve an appropriate disease control (*i.e.*, clinical remission) in the medium-term as assessed in randomized controlled trials (RCT)[3-5], and a large proportion of them lose the initial therapeutic benefit in the long-term[6]. In addition, immunosuppressive drugs increase the risk of serious and opportunistic infections and neoplasia, as well as other adverse outcomes, *e.g.*, worsening of chronic heart failure and thromboembolic complications[7,8], particularly in elderly patients with elderly-onset or long-lasting UC and those with other co-morbidities. For all these reasons, there is an unmet need for safe therapeutic alternatives in UC.

From a pathogenic point of view, neutrophils seem to play a key role in tissue damage. As in other chronic inflammatory conditions, dysregulation of neutrophil apoptosis has been observed in UC[9]. Neutrophilic infiltration is a hallmark of UC as emphasized by the fact that it is a crucial component of UC severity grading in several histological scores[10]. Moreover, the presence of neutrophils in mucosal colonic biopsies has been associated with a risk of clinical relapse and even dysplasia, leading some authors to pose histologic remission as the ultimate therapeutic goal in UC[11]. Accordingly, modulating the activity and numbers of mucosal neutrophils may be a viable therapeutic approach in UC[12], although no drug targeting these cells is available as yet.

The therapeutic effect of granulocyte/monocytapheresis (GMA) is based on the removal of the activated neutrophils from the bloodstream without increasing the risk of infections, given that immature cells are moved from the hematopoietic pools. In Japan, GMA has been covered by National Health Insurance for the treatment of active UC since April 2000 and it is widely used in clinical practice, even as a first line therapy for moderate-to-severe active UC in monotherapy; however, although GMA is CE-marked for the treatment of UC, Crohn's disease, pustular psoriasis and Behçet's disease in the European Union, it has hardly been used in Europe. Although other apheresis techniques focusing on lymphocyte removal have been studied in the past, they are currently not commercially available; thus, this review will focus on GMA. Given that a number of differences in genetic, epidemiologic and clinical features

between Western and Asian UC have been reported[13-16] and that these could lead to differences in response to therapies, we aim to give an overview of the mechanism of action, recent clinical data and practical aspects of GMA use in UC from a European perspective.

THE SELECTIVE MECHANISM OF ACTION OF GMA

GMA is an extracorporeal vein-to-vein apheresis technique. The available GMA device (Adacolumn™, JIMRO, Takasaki, Japan) is a column that contains 35000 beads of cellulose diacetate (2 mm diameter) as GMA carriers soaked in isotonic saline within a 335 mL polycarbonate housing. The blood flows into the column and returns to the patient from the column outflow, usually through two peripheral venous catheters. Many clinical, *in vitro* and *ex vivo* studies have been performed to ascertain the mechanisms of action of GMA (Table 1). The main effect is the selective removal of granulocytes, monocytes, along with a smaller number of platelets from the bloodstream, which can be seen by comparing their number in the inflow and outflow column lines. The cellulose beads adsorb circulating immunoglobulin (Ig) G and immunocomplexes and trigger the activation of complement fragments C3a and C5a, allowing for the removal of granulocytes and monocytes through the interaction of IgG and immunocomplexes with the Fc gamma receptor and the binding sites of leukocyte complement receptors (not present in lymphocytes). Hence, the GMA carriers selectively adsorb the leukocytes from peripheral blood, with the granulocytes exhibiting the highest affinity towards the carrier beads[17]. Despite granulocyte removal, the total number of circulating granulocytes after GMA remains stable. In fact, flow cytometry studies in the inflow and outflow column lines observed a decrease in CD10(+) (mature and activated) and an increase in CD10(-) (immature, naïve) granulocytes, indicating an increased turnover of these cells in the circulation[18]. Similarly, a significant reduction in peripheral CD14(+) CD16(+) monocytes (pro-inflammatory phenotype) has been observed in patients with inflammatory bowel disease treated with GMA[19]. Finally, a significant increase in circulating levels of the $CD^{4+}CD^{25high+/FoxP3}$ phenotype (functional regulatory T cells) following a course of GMA has also been reported in UC patients[20,21].

In addition to these changes in the phenotypical pattern of peripheral leukocytes, *in vitro* studies using human whole blood incubated with the GMA carriers measured significant amounts of interleukin (IL)-1 receptor antagonist, hepatocyte growth factor, and soluble tumor necrosis factor (TNF) receptors I and II released from granulocytes and monocytes that adhered to the carriers. Interestingly, the amounts of these anti-inflammatory cytokines were directly proportional to the number of cells that adhered to the carriers[17]. Some of these cytokines may reach the patient's circulation, exerting beneficial effects on the inflammatory process[22]. Finally, the exposure of neutrophils to cellulose beads results in the generation of apoptotic cells and over 40% of these apoptotic cells re-enter the patient's bloodstream[22] and can interact with B-cells, inducing IL-10 producing regulatory B-cells[23].

ROLE OF GMA IN THE MANAGEMENT OF UC IN EUROPE

The initial controlled European trials of GMA took place in the early 2000s (in the pre-biologic era of UC), yielding promising results, although most trials were too small to allow robust conclusions to be drawn. However, the negative results of an American double-blind, sham-controlled RCT for moderate-to-severe active UC[24] and the licensing of anti-TNF agent use for UC, led to a consequent loss of interest in GMA in Europe. However, safety concerns regarding anti-TNF agents and their lower efficiency in the medium-term (as compared to Crohn's disease), as well as an increasing concern for finding therapeutic alternatives for frail patients (elderly, comorbidities), reawakened interest in GMA[25].

The first systematic review on the efficacy of GMA in UC performed in 2010 concluded that, though it appeared to be of some benefit, high-quality RCTs comparing GMA with conventional medical therapy and sham procedures in Western populations with endoscopically confirmed disease activity were required[26]. Two European prospective controlled trials addressing the role of GMA in other clinical scenarios have recently been published. The ATTICA study, a RCT promoted by the Spanish Working Group in Inflammatory Bowel Disease (GETECCU) involving five European countries (Spain, Portugal, Italy, Germany and Austria), aimed to evaluate

Table 1 Main drivers of the mechanism of action of granulocyte/monocytapheresis

Within the apheresis filter	In the patient's bloodstream
(1) Absorption of circulating IgG and immunocomplexes by cellulose beads; (2) Activation of complement fragments (C3a, C5a); (3) Granulocyte and monocyte absorption *via* Fcγ receptors (IgG and immunocomplexes), and binding sites of leukocyte complement receptors (not in lymphocytes); and (4) Generation of apoptotic cells	(1) Reduction of activated neutrophils and pro-inflammatory monocytes (CD14+CD16+); (2) Apoptotic cells interact with regulatory B-cells, producing IL-10 and mature regulatory B-cells; and (3) Return of substances released by adsorbed cells: IL-1ra and HGF

IgG: Immunoglobulin G; IL: Interleukin; HGF: Hepatocyte growth factor.

the efficacy of GMA in steroid-dependent active UC (as defined by the inability to withdraw corticosteroids within three months after starting treatment or clinical relapse within three months after withdrawal)[27]. This study included 123 patients who were randomized to a 9-wk tapering schedule of oral prednisone alone or in combination with 7 GMA sessions. The main endpoint was steroid-free clinical and endoscopic remission at wk 24, which was achieved in 13% of the subjects (95% confidence interval: 6-24) in the GMA group and 7% [95% confidence interval: 2-16] in the control group (P = 0.11). The results were hampered by the lack of a final endoscopic assessment in two patients in the GMA group who were in steroid-free clinical remission, leading to a non-significant statistical difference due to the non-response imputation for missing values. However, time to relapse was significantly longer and steroid-related adverse events were significantly lower in the GMA group. Moreover, in patients naïve to thiopurines, GMA resulted in a significantly higher rate of steroid-free clinical and endoscopic remission as compared to the patients in the control group. The second study is the ART trial, a multicentre controlled trial for ultra-refractory UC conducted in three European countries (Germany, United Kingdom and France) that included patients with steroid-dependency or refractory moderate-to-severe active UC with insufficient response or intolerance to thiopurines and/or anti-TNF agents[28]. Of note, thiopurines had previously failed in 90% of the patients, anti-TNF agents as monotherapy in 40%, and combination therapy in 32%. Patients were treated with 5 to 10 GMA weekly sessions (at the discretion of the treating physician) and efficacy was assessed at 12, 24 and 48 wk. At wk 12, 47.8% of the patients had a steroid-free clinical response, of whom 28.7% were in steroid-free clinical remission; it is noteworthy that these figures remained almost identical at wk 24 and 48. Finally, the cumulative colectomy rate at wk 96 was 23.4%.

Given the excellent safety profile of GMA, its use in combination with biological agents in order to increase efficacy without increasing the risk of adverse effects seems appealing. To date, a number of small case-series reporting combination therapy with GMA have been published for patients showing primary non-response or secondary loss of response to biologicals[29,30]. Up to one third of those patients regained response and avoided dose-escalation, switching therapy and colectomy in the medium-term. Moreover, in a small study with patients treated for secondary loss of response, a decrease in anti-drug antibodies was observed in responders following GMA therapy[31].

The economic burden of GMA may also be taken into account in decision-making. In the early times of anti-TNF agents, a cost-effectiveness analysis using a decision tree model for patients with moderate-to-severe UC showed that incorporating GMA in the therapeutic management of UC was cost-effective and implied savings related to the reduction of adverse effects derived from corticosteroid use and to the decreased number of surgical interventions[32]. Of course, the availability of biosimilars has reduced the costs of anti-TNF agents, but GMA still has a cost slightly below the new biologicals (*i.e.*, ustekinumab and vedolizumab) with an even better safety profile.

In summary, recent controlled studies suggest a therapeutic effect of GMA on steroid-dependent UC and on patients with a previous failure of thiopurines or anti-TNF agents. Moreover, there are promising preliminary data using an add-on strategy with GMA in patients not responding or losing response mainly to anti-TNF agents. These data support considering the use of GMA, particularly in frail patients for whom safety has become a major issue or in those for whom colectomy seems to be the only available alternative.

SAFETY PROFILE OF GMA

One of the strengths of GMA is its safety profile. Beyond controlled trials, data from clinical practice have confirmed that no serious adverse events are observed in patients treated with GMA. In a post-marketing surveillance undertaken in Japan on 697 patients (for a total of 5287 GMA sessions) in 53 medical institutions over seven years (from 1999 to 2006), all reported events were of mild to moderate severity[33]. More than half of the reported events were related to the difficulty in performing blood access and adequate flow rate, elevation of venous pressure, coagulation and blood return problems. Among clinically adverse events, headache, fever and chills were the most common, occurring in less than 2% in each case. More recently, another Japanese study including a total of 894 GMA treatment courses in 593 patients, observed similar findings, with headache occurring in 13%, fever in 8%, and fatigue in 4%[34]. Importantly, in spite of being a therapy targeting neutrophils, concerns about an increased risk of infections have never been raised, strengthening the suitability of GMA for combination strategies. This excellent safety profile seemed to remain the same when it was assessed in a recent retrospective series including a subgroup of elderly patients, despite a higher baseline rate of co-morbidities[35].

Finally, patients' perceptions are also positive and agree with the convenience of the procedure. In a survey of patients treated with GMA in Spain, 82% of participants said they would agree to be treated with this technique again in the future, regardless of their response to the treatment[36].

PRACTICAL ASPECTS REGARDING THE USE OF GMA IN DAILY CLINICAL PRACTICE

Technical issues of GMA

GMA is usually performed in Blood Banks or haemodialysis units, but as the procedure is simple it can even be performed in dedicated GI units. The procedure is contraindicated when there is a suspicion of general infection, hypersensitivity to heparin, anaemia, hypercoagulability, the use of angiotensin-converting enzyme inhibitors (in this case, cancel the treatment 24 h before the process), pregnancy or lactation, paediatric patients of less than 30 kg body weight, and treatment with oral anticoagulants (unless switched to heparin for the duration of the apheresis procedures).

The procedure involves processing 1800 mL of blood that circulate through sterile non-reusable equipment (Adacircuit™), placed in a machine (Adamonitor™), to achieve an established flow rate of 30 mL/min with an overall process duration of 60 min, according to the specifications provided by the supplier (Figure 1). Higher flows might provoke a decrease in the column's adsorption capacity. In order to minimize the risk of severe hypovolaemia or anaemia in the patients undergoing the adsorption processes with Adacolumn®, it is recommended that the extracorporeal volume during any apheresis process should not surpass 13% of the volaemia; with Adacolumn® and Adacircuit®, the residual volume is 335 mL.

The guidelines for a correct apheresis procedure are based on the vein access through which the procedure is carried out, an appropriate previous count of the component to be adsorbed and good anticoagulation of the system. Antecubital vein access is recommended, as are 18-16G locking-handle needles with a side window or Abbocaths® of the same calibre. There is the option of inserting a tunnelled double-light central vein catheter, with lumens not inferior to 11F and Hickman®-type thick walls[37,38] *via* the subclavian for those patients with insufficient vein access, but a proper risk-benefit seems to be appropriate in this selected patient population. The manipulation and care of the central vein access must follow the established protocols in place at each centre. Currently, there is the also the possibility of carrying out the procedures through unipuncture[39,40].

The appropriate anticoagulation of Adacircuit® and Adacolumn® is obtained by an initial priming of both with 1 L of saline solution at a flow rate of 100 mL/min, and repeating the procedure with another saline solution of 1 L heparinized with 0.8 mL of 5% sodium heparin. This also allows for the removal of air from the column and promotes an increase in the surface area of the blood exposed to the Adacolumn® beads, favouring greater efficiency of the procedure. Additionally, intravenous low molecular weight heparin (at a dose of 0.8-1 mg/kg) must be administered between 10 to 30 min before the process or, alternatively, a continuous perfusion of 5000 IU of

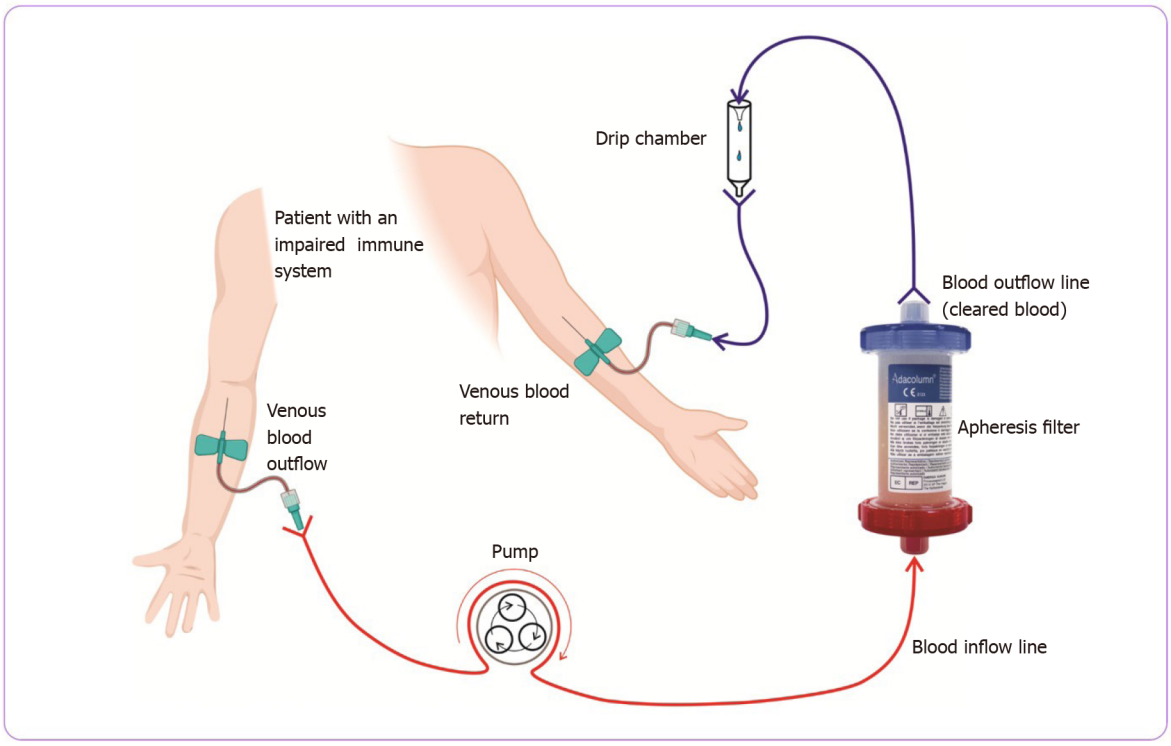


Figure 1 Basic scheme of the granulocyte/monocytapheresis procedure.

sodium heparin in 50 mL of physiological saline serum during the apheresis procedure. The anticoagulant effect of heparin disappears a few hours thereafter, its average life being one and a half hours, approximately. Using citrate as an anticoagulant solution is not advised, as it may interfere with the mechanism of action of GMA by acting as an ionic calcium chelator. Using nafamostat mesylate may be an alternative to heparin, although it is not available in some countries.

One of the most common procedural problems is the pressure problem in the access flow. The exposure of blood to the Adacircuit™ activates the coagulation cascade (a process that can be slowed by prior anticoagulation of the patient); for this reason, it is recommended to set in motion the blood retained in the Adacircuit™ by establishing a closed circuit.

At the end of the procedure, it is necessary to return the maximum amount of red blood cells retained in the Adacolumn® to ensure a minimum loss of blood. This is achieved by administering 300-500 mL of physiological saline to cause entrainment of the blood retained in the cartridge.

The monitoring of vital signs, blood pressure, pulse, breathing rate and temperature should be carried out at the beginning, midway through and at the end of the procedure. Before starting a round of treatment, it is necessary to analyze the clotting process and red blood cell and leukocyte counts. Although there are preliminary studies which indicate that better clinical results would be obtained if the procedure was carried out over 90 min, this has not been entirely proven. Therefore, the recommended flow rate is 30 mL/min. It must be noted that the complete recovery of the previous values of the different haematological cell lines takes place a few hours before the end of the procedure.

How many sessions should be performed and how often?

Most clinical trials involving GMA used 5 to 10 sessions, and this is the usual clinical practice. The choice to perform more than five sessions remains at the discretion of the treating physician; additional sessions are usually performed if the patient has not achieved clinical remission after the first five sessions. In the ATTICA study[27], patients in the GMA arm received a total of seven sessions. Interestingly, unlike what happened in the control group, in which a steady rate of relapse was observed, clinical relapses in the GMA group took place mainly once the scheduled regimen of GMA had finished, suggesting a therapeutic benefit of GMA and raising the question of whether a higher number of sessions would have resulted in greater efficacy.

Another controversial aspect regarding the GMA schedule is the number of sessions

per week. In 2009, Sakuraba *et al*[41] reported the results of a randomized, open study comparing the conventional (once per week) *vs* an intensive (twice per week) GMA regimen in 163 patients with mild-to-moderate active UC. Patients received at least five sessions with a maximum of 10 (once again, at the discretion of the treating physician). The intensive regimen resulted in a strikingly higher rate of clinical remission (71.2% *vs* 54%; $P = 0.029$) and a significantly shorter time to remission (14.9 ± 9.5 *vs* 28.1 ± 16.9 days; $P < 0.0001$). Although a similar trial in Crohn's disease found a significantly shorter time to clinical remission but a similar remission rate[42], no other controlled trial assessing the efficacy of intensive regimens has been performed for UC. Moreover, it remains to be assessed whether these differences would be the same in patients with a more severely active disease.

In summary, most centres use the schedule of five initial sessions. The decision to perform up to five additional sessions often relies on the clinical activity at the end of this schedule; additional sessions are usually added in cases of clinical response without remission. Similarly, the initial regimen is often intensive (two sessions per week) until clinical response or a decrease in inflammatory markers (C-reactive protein, faecal calprotectin) is achieved, moving thereafter to a conventional weekly schedule.

GMA also for maintenance therapy?

Whether or not GMA should be maintained once a patient has achieved clinical remission is still under debate. An initial, small-sized, randomized, sham-controlled trial reported promising, although confusing results on the usefulness of monthly GMA sessions for one year after achieving clinical remission with the same procedure[43]. Another pilot open-label, randomized study compared the efficacy of GMA every two weeks with mercaptopurine for two years to maintain remission of UC that was induced by GMA, corticosteroids or cyclosporine, and observed similar efficacy[44]. The results of the largest study assessing the efficacy of maintenance therapy with leukocytapheresis in UC have been published recently[45]. In this open, randomized trial, 163 UC patients in clinical remission induced by apheresis were randomized (stratified by the concomitant use of thiopurines) to receive two monthly sessions of leukocytapheresis or no additional treatment for one year. At the end of the study, the apheresis group showed a higher rate of endoscopic remission (42.5% *vs* 25.9%; $P = 0.048$) and a clear but non-significant trend towards a beneficial effect of apheresis was observed for clinical remission (47.5% *vs* 32.1%; $P = 0.054$) and complete endoscopic remission (33.8% *vs* 19.8%; $P = 0.051$). Unfortunately, in this trial two different leukocytapheresis devices (with supposed different mechanisms of action) were used with respect to the one that was used for inducing clinical remission.

Furthermore, the clinical outcomes of UC patients who respond to a first course of five to 10 GMA sessions suggest that a long-term therapeutic effect holds for most of them, as observed in the ART trial in which the rate of steroid-free clinical remission at 12 wk remained almost the same at 24 and 48 wk in spite of a lack of additional treatment[29]. Additionally, patients who responded once to GMA, seemed to regain response with GMA in the case of relapse[46,47]. Therefore, once remission has been achieved with GMA, patients are usually monitored and if relapse occurs, a new course of GMA is often successful. Given the mechanism of action of GMA and despite the lack of data on this, it makes sense to monitor patients by means of periodical faecal calprotectin. However, in patients at a high risk of relapse (*i.e.*, in clinical remission but increased faecal calprotectin levels or in patients intolerant or for whom no maintenance drug therapies are possible), monthly GMA sessions might be an option.

Prediction of response to GMA

The possibility of predicting the response to GMA could help the decision-making on when and how to treat UC patients with GMA and the positioning of this non-pharmacological therapy in UC. A retrospective study including 894 treatment courses in 593 patients treated with GMA for moderate-to-severe active UC from 2008 to 2017 at three Japanese referral centres aimed to identify the baseline factors that determined the efficacy of GMA (clinical remission)[33]. In the multivariate analysis, age below 60 years, and duration of UC less than one year were independently associated with clinical remission; endoscopic severity and prior exposure to steroids or biologics were independently associated with lower efficacy. Interestingly, the rate of clinical remission increased with the number of factors of good response to GMA. Short disease duration has been previously identified as a predictor of response to GMA in a large study[48]. However, this is unlikely to be practical for patient selection in Europe as GMA is not considered a first line therapy for UC. Previous corticosteroid exposure

has also been identified in other studies as a predictor of a worse response[48,49], and a European registry observed that the response rate was significantly higher among steroid-dependent UC as opposed to steroid-refractory patients[50]. Moreover, the ATTICA study also found that patients naïve to thiopurines had a significantly better response to GMA[27]. From this point of view, the worse response in patients with previous exposure to corticosteroids, thiopurines or biological agents should facilitate the use of GMA in frail patients, not only because of an expected higher efficacy but also because of its much better safety profile as compared to those drugs. Unfortunately, there is a lack of data on the usefulness for early detection of responders by means of the change or early normalization of faecal calprotectin levels, a potentially ideal biomarker for a therapy that targets the main source of this protein.

CONCLUSION

GMA is the only available therapy for UC directly targeting neutrophils. Two controlled, multicentre, European studies and a number of recent cases series found a potential therapeutic benefit of GMA in different clinical scenarios of UC with a still unmet need for optimal treatment. Moreover, GMA has an excellent safety profile and is perceived as a convenient procedure by patients, making this non-pharmacological therapy a suitable alternative or add-on therapy in UC, particularly for frail or co-morbid patients.

REFERENCES

1 **Romberg-Camps MJ**, Dagnelie PC, Kester AD, Hesselink-van de Kruijs MA, Cilissen M, Engels LG, Van Deursen C, Hameeteman WH, Wolters FL, Russel MG, Stockbrügger RW. Influence of phenotype at diagnosis and of other potential prognostic factors on the course of inflammatory bowel disease. *Am J Gastroenterol* 2009; **104**: 371-383 [PMID: 19174787 DOI: 10.1038/ajg.2008.38]

2 **Jess T**, Riis L, Vind I, Winther KV, Borg S, Binder V, Langholz E, Thomsen OØ, Munkholm P. Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen, Denmark. *Inflamm Bowel Dis* 2007; **13**: 481-489 [PMID: 17206705 DOI: 10.1002/ibd.20036]

3 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476 [PMID: 16339095 DOI: 10.1056/NEJMoa050516]

4 **Reinisch W**, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, Panaccione R, Fedorak RN, Tighe MB, Huang B, Kampman W, Lazar A, Thakkar R. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011; **60**: 780-787 [PMID: 21209123 DOI: 10.1136/gut.2010.221127]

5 **Feagan BG**, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Van Assche G, Axler J, Kim HJ, Danese S, Fox I, Milch C, Sankoh S, Wyant T, Xu J, Parikh A; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013; **369**: 699-710 [PMID: 23964932 DOI: 10.1056/NEJMoa1215734]

6 **O'Donnell S**, Stempak JM, Steinhart AH, Silverberg MS. Higher Rates of Dose Optimisation for Infliximab Responders in Ulcerative Colitis than in Crohn's disease. *J Crohns Colitis* 2015; **9**: 830-836 [PMID: 26116556 DOI: 10.1093/ecco-jcc/jjv115]

7 **Beaugerie L**, Rahier JF, Kirchgesner J. Predicting, Preventing, and Managing Treatment-Related Complications in Patients With Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol* 2020; **18**: 1324-1335. e2 [PMID: 32059920 DOI: 10.1016/j.cgh.2020.02.009]

8 **Beaugerie L**, Kirchgesner J. Balancing Benefit *vs* Risk of Immunosuppressive Therapy for Individual Patients With Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol* 2019; **17**: 370-379 [PMID: 30031174 DOI: 10.1016/j.cgh.2018.07.013]

9 **Brannigan AE**, O'Connell PR, Hurley H, O'Neill A, Brady HR, Fitzpatrick JM, Watson RW. Neutrophil apoptosis is delayed in patients with inflammatory bowel disease. *Shock* 2000; **13**: 361-366 [PMID: 10807010 DOI: 10.1097/00024382-200005000-00003]

10 **Mosli MH**, Feagan BG, Sandborn WJ, D'haens G, Behling C, Kaplan K, Driman DK, Shackelton LM, Baker KA, Macdonald JK, Vandervoort MK, Geboes K, Levesque BG. Histologic evaluation of ulcerative colitis: a systematic review of disease activity indices. *Inflamm Bowel Dis* 2014; **20**: 564-575 [PMID: 24412993 DOI: 10.1097/01.MIB.0000437986.00190.71]

11 **Peyrin-Biroulet L**, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? *Clin Gastroenterol Hepatol* 2014; **12**: 929-34.e2 [PMID: 23911875 DOI: 10.1016/j.cgh.2013.07.022]

12 **Muthas D**, Reznichenko A, Balendran CA, Böttcher G, Clausen IG, Kärrman Mårdh C, Ottosson T,

Uddin M, MacDonald TT, Danese S, Berner Hansen M. Neutrophils in ulcerative colitis: a review of selected biomarkers and their potential therapeutic implications. *Scand J Gastroenterol* 2017; **52**: 125-135 [PMID: 27610713 DOI: 10.1080/00365521.2016.1235224]

13 **Ye BD**, Choi H, Hong M, Yun WJ, Low HQ, Haritunians T, Kim KJ, Park SH, Lee I, Bang SY, Kim TH, Shin HD, Kang D, Youn HS, Li Y, Liu J, McGovern DP, Yang SK, Song K. Identification of Ten Additional Susceptibility Loci for Ulcerative Colitis Through Immunochip Analysis in Koreans. *Inflamm Bowel Dis* 2016; **22**: 13-19 [PMID: 26398853 DOI: 10.1097/MIB.0000000000000584]

14 **Yang SK**. Personalizing IBD Therapy: The Asian Perspective. *Dig Dis* 2016; **34**: 165-174 [PMID: 26982286 DOI: 10.1159/000443134]

15 **Park SH**, Kim YJ, Rhee KH, Kim YH, Hong SN, Kim KH, Seo SI, Cha JM, Park SY, Jeong SK, Lee JH, Park H, Kim JS, Im JP, Yoon H, Kim SH, Jang J, Kim JH, Suh SO, Kim YK, Ye BD, Yang SK; Songpa-Kangdong Inflammatory Bowel Disease [SK-IBD] Study Group. A 30-year Trend Analysis in the Epidemiology of Inflammatory Bowel Disease in the Songpa-Kangdong District of Seoul, Korea in 1986-2015. *J Crohns Colitis* 2019; **13**: 1410-1417 [PMID: 30989166 DOI: 10.1093/ecco-jcc/jjz081]

16 **Cha JM**, Park SH, Rhee KH, Hong SN, Kim YH, Seo SI, Kim KH, Jeong SK, Lee JH, Park SY, Park H, Kim JS, Im JP, Yoon H, Kim SH, Jang J, Kim JH, Suh SO, Kim YK, Ye BD, Yang SK. Long-term prognosis of ulcerative colitis and its temporal changes between 1986 and 2015 in a population-based cohort in the Songpa-Kangdong district of Seoul, Korea. *Gut* 2020; **69**: 1432-1440 [PMID: 31822581 DOI: 10.1136/gutjnl-2019-319699]

17 **Hanai H**, Takeda Y, Eberhardson M, Gruber R, Saniabadi AR, Winqvist O, Lofberg R. The mode of actions of the Adacolumn therapeutic leucocytapheresis in patients with inflammatory bowel disease: a concise review. *Clin Exp Immunol* 2011; **163**: 50-58 [PMID: 21078086 DOI: 10.1111/j.1365-2249.2010.04279.x]

18 **Kashiwagi N**, Sugimura K, Koiwai H, Yamamoto H, Yoshikawa T, Saniabadi AR, Adachi M, Shimoyama T. Immunomodulatory effects of granulocyte and monocyte adsorption apheresis as a treatment for patients with ulcerative colitis. *Dig Dis Sci* 2002; **47**: 1334-1341 [PMID: 12064810 DOI: 10.1023/a:1015330816364]

19 **Hanai H**, Iida T, Takeuchi K, Watanabe F, Yamada M, Kikuyama M, Maruyama Y, Iwaoka Y, Hirayama K, Nagata S, Takai K. Adsorptive depletion of elevated proinflammatory CD14+CD16+DR++ monocytes in patients with inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 1210-1216 [PMID: 18177452 DOI: 10.1111/j.1572-0241.2007.01714.x]

20 **Cuadrado E**, Alonso M, de Juan MD, Echaniz P, Arenas JI. Regulatory T cells in patients with inflammatory bowel diseases treated with adacolumn granulocytapheresis. *World J Gastroenterol* 2008; **14**: 1521-1527 [PMID: 18330941 DOI: 10.3748/wjg.14.1521]

21 **Yokoyama Y**, Fukunaga K, Fukuda Y, Tozawa K, Kamikozuru K, Ohnishi K, Kusaka T, Kosaka T, Hida N, Ohda Y, Miwa H, Matsumoto T. Demonstration of low-regulatory CD25High+CD4+ and high-pro-inflammatory CD28-CD4+ T-Cell subsets in patients with ulcerative colitis: modified by selective granulocyte and monocyte adsorption apheresis. *Dig Dis Sci* 2007; **52**: 2725-2731 [PMID: 17404876 DOI: 10.1007/s10620-006-9560-z]

22 **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 [PMID: 30407662 DOI: 10.1002/jca.21670]

23 **Ansary MM**, Ishihara S, Oka A, Kusunoki R, Oshima N, Yuki T, Kawashima K, Maegawa H, Kashiwagi N, Kinoshita Y. Apoptotic cells ameliorate chronic intestinal inflammation by enhancing regulatory B-cell function. *Inflamm Bowel Dis* 2014; **20**: 2308-2320 [PMID: 25358066 DOI: 10.1097/MIB.0000000000000240]

24 **Sands BE**, Sandborn WJ, Feagan B, Löfberg R, Hibi T, Wang T, Gustofson LM, Wong CJ, Vandervoort MK, Hanauer S; Adacolumn Study Group. A randomized, double-blind, sham-controlled study of granulocyte/monocyte apheresis for active ulcerative colitis. *Gastroenterology* 2008; **135**: 400-409 [PMID: 18602921 DOI: 10.1053/j.gastro.2008.04.023]

25 **Sacco R**, Romano A, Mazzoni A, Bertini M, Federici G, Metrangolo S, Parisi G, Nencini C, Giampietro C, Bertoni M, Tumino E, Scatena F, Bresci G. Granulocytapheresis in steroid-dependent and steroid-resistant patients with inflammatory bowel disease: a prospective observational study. *J Crohns Colitis* 2013; **7**: e692-e697 [PMID: 23870727 DOI: 10.1016/j.crohns.2013.06.012]

26 **Thanaraj S**, Hamlin PJ, Ford AC. Systematic review: granulocyte/monocyte adsorptive apheresis for ulcerative colitis. *Aliment Pharmacol Ther* 2010; **32**: 1297-1306 [PMID: 21050231 DOI: 10.1111/j.1365-2036.2010.04490.x]

27 **Domènech E**, Panés J, Hinojosa J, Annese V, Magro F, Sturniolo GC, Bossa F, Fernández F, González-Conde B, García-Sánchez V, Dignass A, Herrera JM, Cabriada JL, Guardiola J, Vecchi M, Portela F, Ginard D; ATTICA Study Group by the Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa [listed at the end of the article]. Addition of Granulocyte/Monocyte Apheresis to Oral Prednisone for Steroid-dependent Ulcerative Colitis: A Randomized Multicentre Clinical Trial. *J Crohns Colitis* 2018; **12**: 687-694 [PMID: 29490024 DOI: 10.1093/ecco-jcc/jjy023]

28 **Dignass A**, Akbar A, Baumgart DC, Bommelaer G, Bouguen G, Cadiot G, Gillessen A, Grimaud JC, Hart A, Hoque S, Makins R, Michiels C, Moreau J, Premchand P, Ramlow W, Schanz S, Subramanian S, von Tirpitz C, Bonaz B. Granulocyte/monocyte adsorptive apheresis for the treatment of therapy-refractory chronic active ulcerative colitis. *Scand J Gastroenterol* 2018; **53**: 442-448

[PMID: 29513111 DOI: 10.1080/00365521.2018.1447598]
29 **Rodríguez-Lago I**, Sempere L, Gutiérrez A, Núñez A, Leo Carnerero E, Hinojosa E, Mora M, Cañete F, Mañosa M, Herrera C, Beltrán B, Forés A, Arjona D, Barreiro-de Acosta M, Khorrami S, Aguirre U, Ginard D, Cabriada JL. Granulocyte-monocyte apheresis: an alternative combination therapy after loss of response to anti-TNF agents in ulcerative colitis. *Scand J Gastroenterol* 2019; **54**: 459-464 [PMID: 30982369 DOI: 10.1080/00365521.2019.1600715]
30 **Rodríguez-Lago I**, Benítez JM, Sempere L, Sáez-González E, Barreiro-de Acosta M, de Zárate JO, Cabriada JL. The combination of granulocyte-monocyte apheresis and vedolizumab: A new treatment option for ulcerative colitis? *J Clin Apher* 2019; **34**: 680-685 [PMID: 31518013 DOI: 10.1002/jca.21746]
31 **Yokoyama Y**, Sawada K, Aoyama N, Yoshimura N, Sako M, Hirai F, Kashiwagi N, Suzuki Y. Efficacy of Granulocyte and Monocyte Adsorptive Apheresis in Patients With Inflammatory Bowel Disease Showing Lost Response to Infliximab. *J Crohns Colitis* 2020; **14**: 1264-1273 [PMID: 32166331 DOI: 10.1093/ecco-jcc/jjaa051]
32 **Panés J**, Guilera M, Ginard D, Hinojosa J, González-Carro P, González-Lara V, Varea V, Domènech E, Badia X. Treatment cost of ulcerative colitis is apheresis with Adacolumn cost-effective? *Dig Liver Dis* 2007; **39**: 617-625 [PMID: 17531555 DOI: 10.1016/j.dld.2007.03.007]
33 **Hibi T**, Sameshima Y, Sekiguchi Y, Hisatome Y, Maruyama F, Moriwaki K, Shima C, Saniabadi AR, Matsumoto T. 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 [PMID: 19211314 DOI: 10.1016/j.dld.2008.11.020]
34 **Yamamoto T**, Iida T, Ikeya K, Kato M, Matsuura A, Tamura S, Takano R, Tani S, Osawa S, Sugimoto K, Shimoyama T, Hanai H. 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 [PMID: 29977035 DOI: 10.1038/s41424-018-0037-0]
35 **Ito A**, Omori T, Hanafusa N, Tsuchiya K, Nakamura S, Tokushige K. Efficacy and safety of granulocyte adsorption apheresis in elderly patients with ulcerative colitis. *J Clin Apher* 2018; **33**: 514-520 [PMID: 29687913 DOI: 10.1002/jca.21631]
36 **Rodríguez-Lago I**, Benítez JM, García-Sánchez V, Gutiérrez A, Sempere L, Ginard D, Barreiro-de Acosta M, Cabriada JL. Granulocyte and monocyte apheresis in inflammatory bowel disease: The patients' point of view. *Gastroenterol Hepatol* 2018; **41**: 423-431 [PMID: 29739692 DOI: 10.1016/j.gastrohep.2018.04.007]
37 **Golestaneh L**, Mokrzycki MH. Vascular access in therapeutic apheresis: update 2013. *J Clin Apher* 2013; **28**: 64-72 [PMID: 23420596 DOI: 10.1002/jca.21267]
38 **Kalantari K**. The choice of vascular access for therapeutic apheresis. *J Clin Apher* 2012; **27**: 153-159 [PMID: 22535654 DOI: 10.1002/jca.21225]
39 **Fukuchi T**, Koga H, Kaichi S, Ishikawa A, Horita T, Araki R, Yokota A, Namba Y, Kyo M, Eguchi T, Shimazu K. Single-Needle Intensive Granulocyte and Monocyte Adsorptive Apheresis Is Suitable for Elderly Patients With Active Ulcerative Colitis Taking no Corticosteroids or Biologics. *Ther Apher Dial* 2019; **23**: 224-232 [PMID: 31025824 DOI: 10.1111/1744-9987.12819]
40 **Shimazu K**, Fukuchi T, Kim I, Noguchi Y, Iwata M, Koyama S, Ubukata S, Tanaka A. Efficacy and Usefulness of New Single-Needle Intensive Granulocyte and Monocyte Adsorptive Apheresis in Active Ulcerative Colitis Patients Without Corticosteroids and Biologics. *Ther Apher Dial* 2016; **20**: 383-389 [PMID: 27523079 DOI: 10.1111/1744-9987.12470]
41 **Sakuraba A**, Motoya S, Watanabe K, Nishishita M, Kanke K, Matsui T, Suzuki Y, Oshima T, Kunisaki R, Matsumoto T, Hanai H, Fukunaga K, Yoshimura N, Chiba T, Funakoshi S, Aoyama N, Andoh A, Nakase H, Mizuta Y, Suzuki R, Akamatsu T, Iizuka M, Ashida T, Hibi T. 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 [PMID: 19724269 DOI: 10.1038/ajg.2009.453]
42 **Yoshimura N**, Yokoyama Y, Matsuoka K, Takahashi H, Iwakiri R, Yamamoto T, Nakagawa T, Fukuchi T, Motoya S, Kunisaki R, Kato S, Hirai F, Ishiguro Y, Tanida S, Hiraoka S, Mitsuyama K, Ishihara S, Tanaka S, Otaka M, Osada T, Kagaya T, Suzuki Y, Nakase H, Hanai H, Watanabe K, Kashiwagi N, Hibi T. 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 [PMID: 26585569 DOI: 10.1186/s12876-015-0390-3]
43 **Fukunaga K**, Yokoyama Y, Kamokozuru K, Nagase K, Nakamura S, Miwa H, Matsumoto T. Adsorptive granulocyte/monocyte apheresis for the maintenance of remission in patients with ulcerative colitis: a prospective randomized, double blind, sham-controlled clinical trial. *Gut Liver* 2012; **6**: 427-433 [PMID: 23170145 DOI: 10.5009/gnl.2012.6.4.427]
44 **Sakuraba A**, Sato T, Morohoshi Y, Matsuoka K, Okamoto S, Inoue N, Takaishi H, Ogata H, Iwao Y, Hibi T. Intermittent granulocyte and monocyte apheresis versus mercaptopurine for maintaining remission of ulcerative colitis: a pilot study. *Ther Apher Dial* 2012; **16**: 213-218 [PMID: 22607563 DOI: 10.1111/j.1744-9987.2012.01064.x]
45 **Naganuma M**, Yokoyama Y, Motoya S, Watanabe K, Sawada K, Hirai F, Yamamoto T, Hanai H, Omori T, Kanai T, Hibi T; CAPTAIN study Group. Efficacy of apheresis as maintenance therapy for patients with ulcerative colitis in an open-label prospective multicenter randomised controlled trial. *J Gastroenterol* 2020; **55**: 390-400 [PMID: 31811562 DOI: 10.1007/s00535-019-01651-0]
46 **Lindberg A**, Eberhardson M, Karlsson M, Karlén P. Long-term follow-up with Granulocyte and

Monocyte Apheresis re-treatment in patients with chronically active inflammatory bowel disease. *BMC Gastroenterol* 2010; **10**: 73 [PMID: 20604939 DOI: 10.1186/1471-230X-10-73]

47 **Takayama T**, Kanai T, Matsuoka K, Okamoto S, Sujino T, Mikami Y, Hisamatsu T, Yajima T, Iwao Y, Ogata H, Hibi T. Long-term prognosis of patients with ulcerative colitis treated with cytapheresis therapy. *J Crohns Colitis* 2013; **7**: e49-e54 [PMID: 22633997 DOI: 10.1016/j.crohns.2012.05.005]

48 **Yokoyama Y**, Watanabe K, Ito H, Nishishita M, Sawada K, Okuyama Y, Okazaki K, Fujii H, Nakase H, Masuda T, Fukunaga K, Andoh A, Nakamura S. 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 [PMID: 25804800 DOI: 10.1016/j.jcyt.2015.02.007]

49 **Iida T**, Ikeya K, Kato M, Abe J, Yamamoto M, Watanabe F, Sugimoto K, Hanai H. Adsorptive Depletion of Myeloid Lineage Leucocytes as Remission Induction Therapy in Patients with Ulcerative Colitis after Failure of First-Line Medications: Results from a Three-Year Real World, Clinical Practice. *Digestion* 2017; **96**: 119-126 [PMID: 28796990 DOI: 10.1159/000479502]

50 **D'Ovidio V**, Meo D, Viscido A, Bresci G, Vernia P, Caprilli R. Predictive factors of clinical response in steroid-refractory ulcerative colitis treated with granulocyte-monocyte apheresis. *World J Gastroenterol* 2011; **17**: 1831-1835 [PMID: 21528055 DOI: 10.3748/wjg.v17.i14.1831]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com