Abstract: Granulocyte-monocyte apheresis is a relatively new therapy that has been proposed, sometimes with controversial results, for the treatment of inflammatory bowel disease, particularly ulcerative colitis. The aim of the present study was to perform a thorough review of the literature on the application of this type of treatment in ulcerative colitis and discuss the results, in order to provide an opinion on its use which is shared by the involved experts. The review of the literature was performed by searching PubMed with appropriate key words. The results obtained suggest that the major role for this treatment at this moment is for those patients with steroid dependency or with major contraindications to use of steroids. However, promising, albeit very preliminary, results have also been observed in steroid-naïve subjects, and this is of particular interest in consideration of the safety profile of this therapeutic method. As such, the Adacolumn may prove useful in specific subgroups of patients. Future phenotypic, genotypic, and molecular characterization of patients with inflammatory bowel disease might prove useful in defining better those subjects who might benefit most from this treatment modality.

Keywords: ulcerative colitis, inflammatory bowel disease, guidelines, apheresis

Introduction
The treatment of chronic inflammatory bowel disease (IBD) is always a challenge for gastroenterologists dealing with this type of condition.\textsuperscript{1,2} Indeed, the variability and complexity of the clinical picture, the possibility that other organs and systems may be involved, and the possible toxicity caused by drugs make both the diagnosis and treatment of this condition particularly complex. In recent years, considerable progress has been made, both in diagnostic techniques and in the range of therapeutic options available. However, with regard to the latter, it has been shown that greater treatment potential is often accompanied by an increased risk of adverse events.\textsuperscript{3,4}

The development of granulocyte-monocyte apheresis (GMA)\textsuperscript{5} appears to be an innovative approach, comprising both treatment safety and therapeutic potential. The Adacolumn\textsuperscript{®} is the most diffuse device of this type and consists of a column packed with cellulose acetate beads capable of adsorbing granulocytes and monocytes and through which the blood of the patients is run. Extremely positive results have been reported using this method for the treatment of ulcerative colitis in Japan,\textsuperscript{6-13} but results obtained in Europe and the US have been more contradictory.\textsuperscript{14-19} Nevertheless, a recent meta-analysis\textsuperscript{20} pooling data from seven randomized controlled trials 6,9,17,21-24 clearly demonstrated the benefits of this method with respect to control treatments for the induction of remission or response at week 12. On the other hand, the only sham-controlled randomized controlled trial, in a slightly to moderately ill population, did
not show a statistically significant difference between sham and active treatment.24

In this report, the current knowledge related to GMA in the treatment of IBD has been reviewed by means of an extensive research aimed at retrieving all papers regarding the clinical efficacy and safety of the Adacolumn in the treatment of ulcerative colitis. This research was done by means of a Medline search using specific key words, including Medical Subjects Headings (MeSH) for papers published since 1995. Additional references were also obtained by hand searches and cross-referencing. In all, only abstracts written in English were retrieved. The most meaningful papers regarding other aspects of the treatment, ie, mechanism(s) of action, identification of ideal patient profile, and pharmacoeconomics were also retrieved and included in the analysis by the authors. Thus, on the basis of each author’s personal experience, an “expert opinion” on this therapeutic approach was drawn up.

**Mechanism of action**

The underlying mechanism of action in GMA comprises the selective removal of cell populations taking part in the induction and perpetuation of intestinal inflammation in IBD. GMA is highly selective for granulocytes, monocytes, and macrophages5 and, in accordance with this finding, it has been shown that the outflow from GMA columns has a low (40/60%) monocyte and granulocyte cell count, while the lymphocyte and erythrocyte populations are almost unchanged. Interestingly, a reduction of monocytes and granulocytes can also be seen in the colonic mucosa of patients who respond to treatment.25 In particular, a recent study reported that inflammatory CD14+CD16+ monocytes are considerably reduced after 10 sessions of GMA in ulcerative colitis, as well as in Crohn’s disease.26

A marked reduction in proinflammatory cytokines also accompanies this effect, which is probably triggered by a dual mechanism of action, ie, by their direct adsorption on the column and via reactive immune regulation of nonabsorbed leukocytes.27 In fact, interleukin-6 mRNA and interleukin-8 mRNA return to normal levels following GMA.28 Moreover, the clinical efficacy of GMA in IBD appears to be associated with an increase in circulating T regulatory lymphocytes, with a higher expression of FoxP3 in CD4+ T cells29 and with a reduction of both myeloid and plasmocytoid dendritic populations.30 Generally speaking, several elements indicate that, in addition to removal of activated cells, a reactive immunomodulatory effect is one of the mechanisms of action of GMA.

**Current evidence of efficacy in ulcerative colitis**

Many experimental demonstrations of the efficacy of GMA in IBD have been derived from uncontrolled studies7,13–17,25,31–34 performed in patients who do not respond to conventional pharmacological treatment. In this setting, the data are fairly homogeneous, showing favorable responses (remission or partial response) at percentages varying from 60% to 84% of patients treated. Treatment with GMA also appears to be more advantageous compared with extension or intensification of conventional pharmacological treatment, which has involved steroids in most studies. In those papers, use of GMA has led to a rapid reduction in the steroid dose and/or withdrawal of steroid administration. Furthermore, GMA is associated with a good safety profile.20 Evaluation of efficacy has been primarily performed using clinical and/or biohumoral parameters, while the healing of the intestinal mucosa has rarely been taken into consideration. According to the very limited amount of data available, mucosal healing would appear to take place in about 25% of cases.35

In ulcerative colitis, the efficacy of GMA and leukocyte apheresis, the other apheresis technique currently used to treat IBD, appears to be comparable, with a slight advantage for GMA, as shown in a prospective study that compared the two methods.36 While bearing in mind the statistical limits associated with the small number of patients recruited in this study (39 patients), the clinical response for the two procedures was similar (72.2% for GMA versus 66.6% for leukocyte apheresis). Due to the obvious difficulty of carrying out double-blind randomized studies with inactive columns, results are available from only two studies of this type (one using leukocyte apheresis and one using GMA). In the leukocyte apheresis study, the response to active treatment was significantly higher than in control subjects (80% versus 33%, respectively).37 Surprisingly, in the other study, carried out in more than 200 patients treated with GMA or an inactive column,24 no significant difference was found (clinical response for 44% versus 39%, respectively). In spite of the theoretically adequate strength of the study, the large number of cases rejected during recruitment or lost to follow-up during the study, together with debatable inclusion criteria, have given rise to some doubts regarding the reliability of these results. Furthermore, a recent meta-analysis20 of the seven randomized, controlled studies performed using the Adacolumn, which also included the afore-mentioned sham-controlled study,24 nevertheless demonstrated the greater efficacy of GMA in reducing clinical and endoscopic activity
in ulcerative colitis compared with comparator treatment. Results in over 1000 patients treated in the previously mentioned uncontrolled cohorts would appear to support the efficacy of GMA further.

The suggestion that the efficacy of GMA would appear to continue beyond the actual treatment period, with a “carryover” effect, is certainly interesting, although controversial. A lower probability of recurrence in the 6–12 months following effective GMA than after pharmacological treatment was documented in other studies. This proved true also in one randomized study showing that GMA reduced the probability of relapse of the disease. This study, carried out in patients in remission but at a high risk of recurrence (patients with fecal calprotectin > 5 times the upper limit of normal), demonstrated the efficacy of preventive treatment with GMA. In fact, 67.7% of patients treated with conventional pharmacological treatment showed a relapse of the disease within 6 months, while a preventive cycle of five sessions of GMA reduced the risk by more than half (27.6%).

Evidence of differing efficacy using different treatment schedules

The most commonly used GMA treatment schedule consists of one weekly session for 5 weeks. Each apheresis session lasts for 60 minutes and the volume of filtered blood amounts to 1800 mL each session. Alternative schedules have been proposed with the use of “intensive” GMA comprising two sessions per week for a total of 10 sessions, or “longer” GMA, ie, an increase in the duration of each session or in the total number of sessions. It is somewhat difficult to establish whether these latter approaches are more efficacious compared with standard treatment, given that the evidence available so far concerns only open studies, each with a limited number of cases.

In a study by Sakuraba et al, an intensive GMA program was found to be more efficacious than the conventional schedule in achieving remission (71% versus 54%), and was also achieved in a shorter time period (14.9 ± 9.5 days versus 28.1 ± 16.9 days). An even more intensive treatment schedule of daily GMA (five sessions in five consecutive days) has been reported, with favorable therapeutic results and good safety, so that this type of schedule is now used in several Japanese institutions. Therefore, a frequency-dependent or dose-dependent response is possible. On the other hand, the safety profile of the procedure remains unchanged when the frequency of the sessions is increased.

In another study, increasing the number of sessions was more effective in achieving remission in patients undergoing steroid treatment compared with an increase in the steroid dose. However, recent data from a large number of European steroid-dependent or steroid-resistant patients treated openly with either the classic or an extended procedure demonstrate comparable efficacy, as far as both achievement of remission (40% versus 44%) and clinical response (59% versus 56%) are concerned. In both cases, the treatment was well tolerated without significant differences in the frequency of adverse events.

Use of a combined regimen of intensive extended apheresis (two sessions per week for the first 3 weeks and one session per week for another 8 weeks) in a study by Hanai et al in 70 patients, provided responses, as far as percentages are concerned, that were comparable with steroids administered intravenously (83% versus 65%). In particular, the GMA response appears to be slower but longer-lasting in time (the percentage of response at 2 weeks is 40% for GMA and 50% for steroids, whereas at 6 and 12 weeks, it is 77% and 65%, respectively, and 82% and 61%, respectively). Prolonging the duration of each session to 90 minutes, together with an increase in the number of sessions (one per week for 10 weeks), appears to increase the percentage of remissions (83%) and to reduce the need for steroids.

In conclusion, the data available on more intensive and/or extended use of GMA differ considerably and need to be confirmed in controlled studies. In the meantime, it would seem reasonable to adhere to the recommended treatment schedule of one session per week for 5 weeks.

Patient profiles for ideal treatment candidates

Treatment of ulcerative colitis is characterized by a well defined flow chart with the following sequence: mesalazine (mild and moderate active disease and maintenance treatment); steroids (moderate to severe active disease); and immunosuppressants and biological treatment (steroid-dependent and steroid-resistant disease).

Severe forms of the disease are not a major priority indication for GMA treatment, because a very rapid response is needed in these cases, as will occur in many cases when using steroids and/or biological drugs. Negative evidence is present in the literature in support of this consideration.

On the other hand, evaluation of GMA in 163 patients with mild to moderate ulcerative colitis, for whom simultaneous treatment with mesalazine and/or azathioprine was permitted, showed a high rate of clinical remission (62.4%). A randomized study even showed a trend in favour of GMA compared with steroids in mild to moderate forms.
of the disease (90% versus 75% of remission-response, respectively) with a reduction in side effects but with higher costs. In one single report, GMA appeared to be more effective in steroid-naïve patients and patients treated with low doses and for a short time only, but the data must still be confirmed in larger and more homogeneous studies. Other possible predictors of response found in these studies are low steroid doses and high basal granulocyte levels.

In this type of patient, GMA could be an alternative option to steroid treatment and become a first-line option in conditions for which contraindications to the use of steroids are greater, eg, diabetes, high blood pressure, and glaucoma.

However, steroid resistance with mild to moderate activity or steroid dependence appear, at present, to be the main indications for GMA. As confirmation of this, in a Japanese post-marketing surveillance study of 697 patients treated at 53 centers in the period 1999–2006, 489 patients were found to be resistant to conventional forms of treatment, especially steroids. This report confirmed, in a larger number of cases, the previous retrospective review of the first 100 Scandinavian patients (which grouped together ulcerative colitis, Crohn’s disease, and indeterminate colitis), who were almost all steroid-resistant or steroid-dependent and the data contained in the Italian Registry (92% steroid-resistant/steroid-dependent patients). Further, the duration of clinical response to GMA treatment, although differing in the various studies, would appear to be long enough to allow the delayed response of azathioprine to be reached, thus suggesting a possible role for GMA in bridge therapy as an alternative to infliximab. In addition, because GMA has no significant side effects (see Safety section), it could be preferable in patients with contraindications to biological treatment (intolerance to infliximab, carriers of specific antibodies, hepatitis B virus carriers, multidrug immunosuppression, or a history of tumors).

As far as its possible use in prolonging remission is concerned, the efficacy of GMA used monthly has also been reported in a small group of 10 patients. The possible role of GMA in preventing relapses in high-risk patients, identified by high levels of fecal calprotectin, was reported by Maiden et al. No comparative studies of treatment with biological drugs and GMA or associated treatment using the two methods are available.

Safety
GMA has been demonstrated to be very safe, with a low percentage of side effects. The first important study assessing the efficacy and safety profile of GMA in the treatment of active ulcerative colitis carried out in Japan at the end of the 1990s reported side effects in only 8% of cases treated with apheresis compared with 43% of adverse events recorded in a group of patients treated with traditional drugs, ie, steroids and/or mesalazine.

Later studies confirmed this excellent safety profile. In fact, the percentage of side effects occurring with GMA in the main clinical trials ranged from 5% to 33%, with almost total absence of serious adverse events. The main adverse events reported were shivering, nausea, headaches, “flushing”, and fever. These problems can last a few minutes to a few hours. Use of painkillers before starting the procedure may prevent onset of headaches, while fever can easily be treated with common antipyretics. In extremely rare circumstances, infection of the upper airways has been reported. Some alterations in hematochemical tests, consisting of an increase in transaminases and leucopenia, have also been very rarely observed.

However, in most cases, side effects have been mild to moderate, almost never requiring discontinuation of treatment. The excellent tolerability of GMA reported in clinical studies has also been confirmed in observational studies carried out in large numbers of unselected patients, reflecting the real use of GMA in daily clinical practice. In particular, in the recent post-marketing surveillance study carried out in Japan, adverse events, including complications related to the procedure (eg, difficulty in finding venous access, difficulty in preventing coagulation in the apheresis system, difficulty in maintaining a suitable venous return) occurred in 2.3% of treatment sessions and in 8.18% of patients. The most frequent events were headache (1.58%) and fever (1.29%), but no serious adverse events were found. No statistically significant differences in the rate of side effects were found between patients undergoing few procedures (fewer than five) and patients undergoing more than six treatments. A relatively higher rate of side effects occurred in women and in hospitalized patients (P < 0.05).

With regard to the Italian experience, the National Register of Therapeutic Apheresis (online at http://www. afersi.it) shows that almost 95% of GMA procedures (94.9%) produced no adverse events, with headaches being reported in 3.9% of cases.

GMA has also been used in the treatment of pediatric forms of IBD, in spite of the lack of data currently available. From the limited evidence so far, which mainly comes from Japan, the treatment has proved to be extremely safe also in this context. Recently, the results of some European studies have also been published, which confirm the safety
of GMA in the treatment of pediatric patients with IBD.\textsuperscript{52,53} In particular, a small Spanish study of nine pediatric patients did not report any adverse events (either early or late), despite placement of a central venous catheter,\textsuperscript{52} while the most frequent side effects found in a larger study in Scandinavia (37 patients with chronic IBD), all slight and not long-lasting, were tiredness (reported in most children) and headache (in 30% of subjects undergoing treatment).\textsuperscript{53}

**Pharmacoeconomics**

GMA has proved to be an effective and safe procedure in the treatment of steroid-dependent and chronically active ulcerative colitis. The main limitations to its use lie in the relatively high cost compared with traditional forms of treatment, and also in the need to carry out this treatment in a hospital environment. A recent Spanish pharmacoeconomic study, which evaluated GMA in patients suffering from steroid-dependent ulcerative colitis in terms of cost efficacy in comparison with traditional azathioprine treatment showed that the costs involved in the two different approaches were comparable.\textsuperscript{54}

In fact, despite an increase in cost of €5377 per year per patient treated (€11,436 versus €6059), the higher response rate obtained using GMA (61% versus 38.5%) as well as reduction in side effects and need for surgery indicate that the cost required to obtain remission is not very different between the two types of treatment (€18,748 versus €15,738).

The results of a recent Scandinavian study, published at present only in abstract form, confirm that GMA can be considered to be a cost-effective treatment if compared with traditional treatment approaches, given that the increase in cost, calculated by quality-adjusted life-years gained (€55,426), is in keeping with that of treatments considered to be cost-effective.\textsuperscript{55}

Unfortunately, no pharmacoeconomic study comparing all the treatment approaches used for steroid-dependent/steroid-resistant forms of ulcerative colitis, including biological drugs, is available as yet. However, if we consider the high cost of this latter type of treatment, GMA may in comparison still prove to be economical. However, without the results of appropriate pharmacoeconomic studies, no final conclusions can be drawn on this issue at present.

**Conclusion**

According to published data, GMA is a useful technique among the various treatment options available for ulcerative colitis. In this setting, GMA has been used primarily in steroid-dependent or steroid-resistant patients. However, promising preliminary results have also been obtained in steroid-naïve patients or when GMA is used as an alternative treatment to steroids during the acute phases of the disease. Thus, on the basis of the available data, and also due to the fact that the treatment is still rather expensive, we believe that its current use should be restricted mainly to steroid-dependent or steroid-resistant patients. However, GMA should also be considered for those patients in whom standard treatment cannot be used, due to lack of efficacy, toxicity, or personal intolerance. These possible indications are also based on the safety profile of GMA, which has now been confirmed both in clinical trials and in post-marketing surveillance, and probably also by some pharmacoeconomic data which do not appear to be particularly negative.

Although some observations suggest that diversified GMA schedules (more intensive and prolonged treatment) may in some instances offer better results, it is advisable at present to adhere to traditional treatment schedules, with one session per week for 5 weeks. We believe that, in the future, as long as research progresses towards an increasing recognition of specific disease patterns, it will become possible to select patient subgroups likely to respond better to specific therapeutic approaches, such as GMA.

**Disclosure**

The authors report no conflicts of interest in this work.

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