Adacolumn® mechanism of action on the immune system

Dr. Rubén Francés

EXPERT COMMENTARY

Dr. Eugeni Domènech

Dr. Iago Rodríguez Lago

Instructions for use available at: **www.adacyte.com**

Adacyte
Therapeutics

ES-CEN-ADY-50320-CC

INDEX

Adacolumn® mechanism of action on the immune system

Dr. Rubén Francés

WHAT DOES IT DO?

1.1. Inflammation and receptors in monocytes and neutrophils

Inflammation is part of the immune response that is triggered by different physio-pathological processes. In immune-mediated inflammatory diseases (IMID), the inflammatory activity and its resolution are altered, generating an excess of cells and molecules that contribute to the progression and aggravation of these conditions.

A fundamental part of the inflammatory response is determined by our **innate immunity**, by all those cells and receptors with immune activity that are found in tissues and that conduct local immune surveillance. These cells secrete signals that enable the recruitment of new cell types to the site of injury. Among the cells recruited, there are **monocytes and neutrophils, two cell types from the myeloid lineage with a high inflammatory capacity when their receptors are activated** with certain signals.

Fc-gamma (FcgR) and complement component C3 (CR3) are, among others, two such receptors and recognize, respectively, immunoglobulins and complement fraction 3b (C3b), a cleaved fragment of C3 in the presence of calcium. In response to their ligands, **monocytes/macrophages and granulocytes secrete inflammatory mediators such as cytokines and increase oxidative stress**, which promotes the formation of free radicals.

1.2. Cooperation in the immune system

One of the main characteristics of the immune system is its complex cooperative activity. In addition to cell recruitment, these cells and receptors with immune surveillance activity in the tissues also indicate the guidelines for **continuing the immune response towards an adaptive, specific activity**, which completes the inflammatory process and its resolution. This activity includes the **activation and expansion of such important cells as T and B lymphocytes**, as well as the **deployment of** one of the immune system's most powerful and specific arsenals by the latter, **antibodies**.

Many IMID have an autoimmune component. In these cases, the products and residues generated in the inflamed areas constitute self antigens for the effector lymphocytes that are being recruited. This self-reactivity **becomes harmful when it feeds back inflammation**. On the other hand, the adaptive response also has the task of generating **memory immunity**, which allows for a faster secondary response in the case of antigenic re-exposure. The accumulation of memory T-cells in the tissue of IMID patients is common in advanced stages of inflammatory damage, and poses an additional problem by **facilitating outbreaks and inflammatory activity in exposed** tissues.

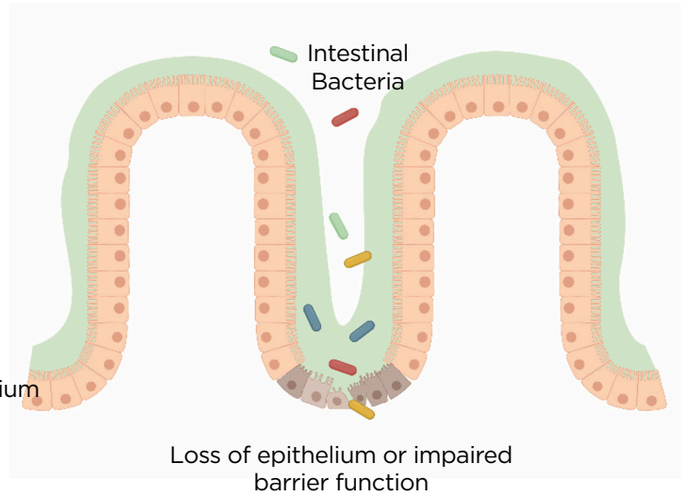
The **adaptive response profile is therefore dependent on the innate inflammatory signal and can be polarised as a result towards maintaining a pro-inflammatory state, or on the contrary, acquire a tolerogenic phenotype and resolution of inflammation**. In **IMID, constant pro-inflammatory signalling** from innate immunity also compromises the development of the tolerogenic response at the adaptive level, and **over time sustains the progression of a pathogenic pro-inflammatory environment**.

Adacolumn® mechanism of action on the immune system

WHAT DOES IT DO?

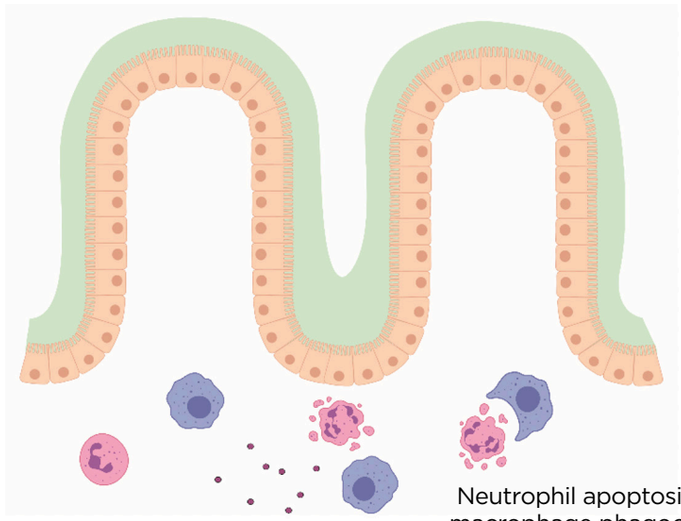
Phases of inflammation

FASE 1: INITIAL DAMAGE



Loss of epithelium or impaired barrier function

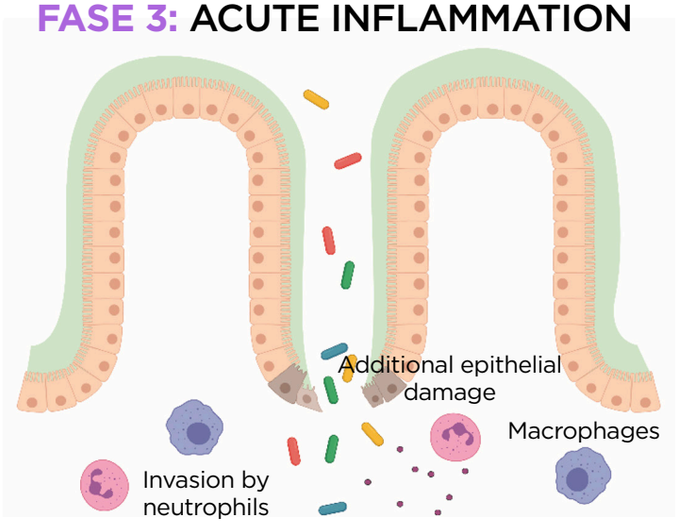
FASE 2: RESOLUTION MECHANISM



Secretion of lipoxins, resolvins, secretins and other resolution mediators

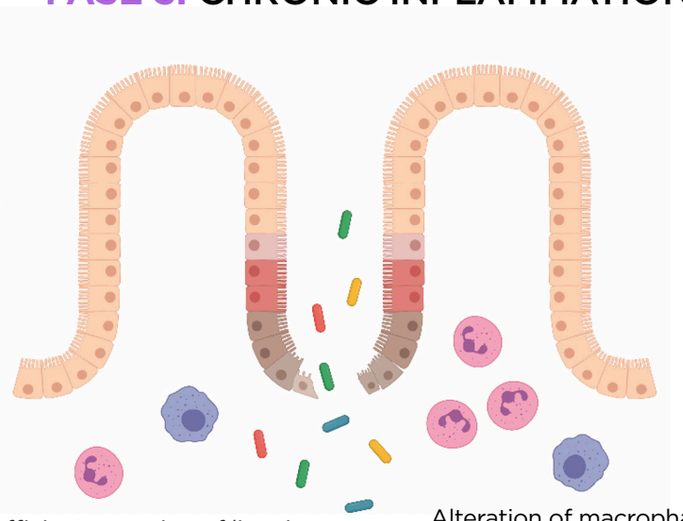
Neutrophil apoptosis and macrophage phagocytosis

FASE 3: ACUTE INFLAMMATION



Secretion of tissue-degrading enzymes, oxidative stress and inflammatory mediators

FASE 3: CHRONIC INFLAMMATION



Insufficient secretion of lipoxins, resolvins and other resolution mediators

Alteration of macrophage differentiation and phagocytosis

Adacolumn® mechanism of action on the immune system

1.3. Reduction of activated monocytes and neutrophils

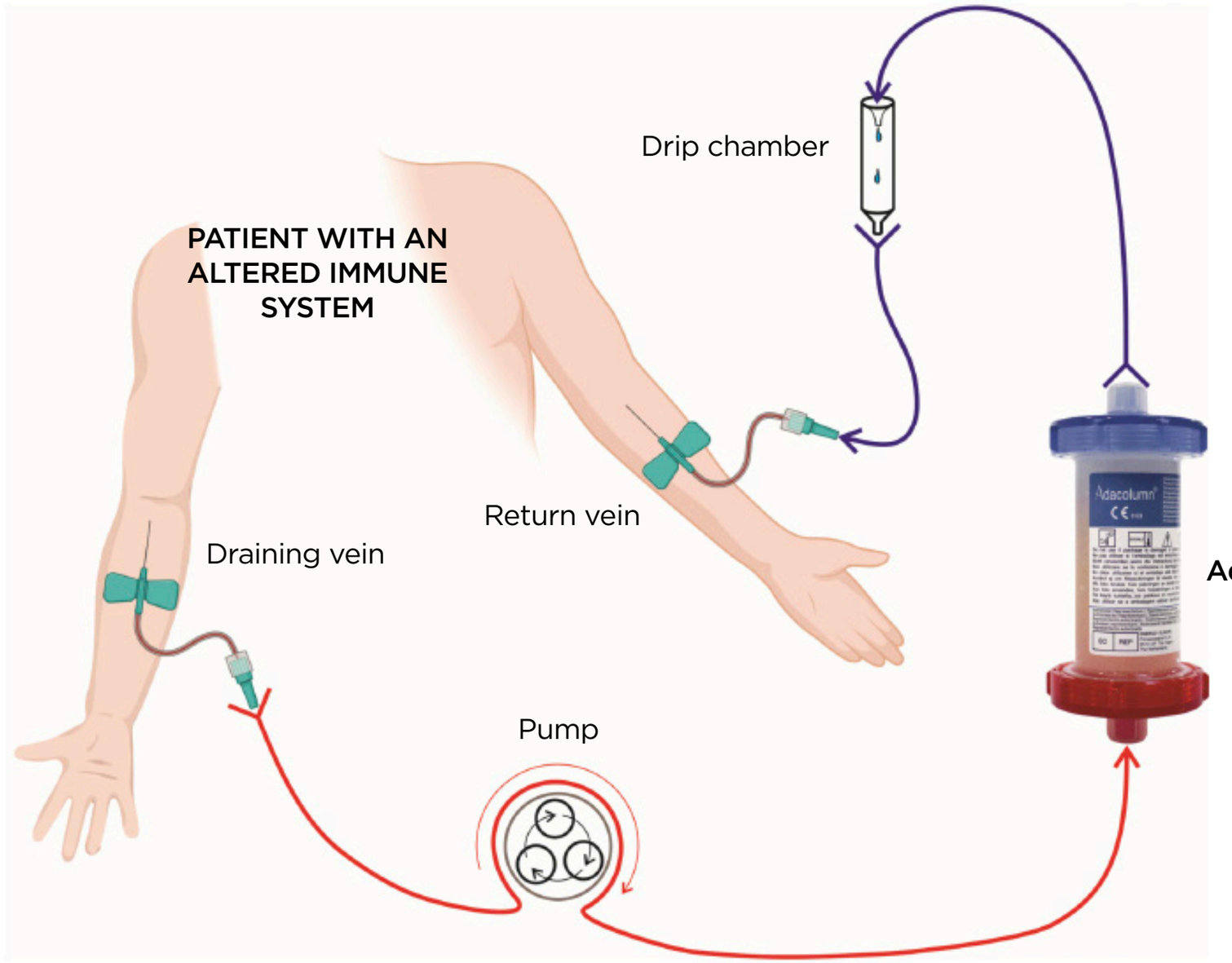
Granulocyte apheresis (GMA) therapy allows the fixation of circulating monocytes/macrophages and granulocytes to the beads which become coated with immunoglobulin G (IgG) and C3b through the specific receptors that these cells express on their surface. The fixation of these cell types that are capable of generating mediators that perpetuate inflammation **prevents their recruitment in injured sites,** to which they are normally directed by chemokines and other signals.

The result is a **decrease in the contribution of these inflammatory cell types in the damaged tissue, and consequently, of the pro-inflammatory mediators that they secrete, primarily at a local level, but also systemic**. This implies an overall **modulation of the inflammatory response**.

Additionally, the cooperative activity of the immune system facilitates that the **intensity of the inflammatory signals of the environment are modulated** due to the reduction in the cellular contribution to the tissue. Thus, the constant decompensation towards the usual pro-inflammatory profile in these diseases is limited and a **partial recovery of homeostasis is favoured**.

WHAT DOES IT DO?

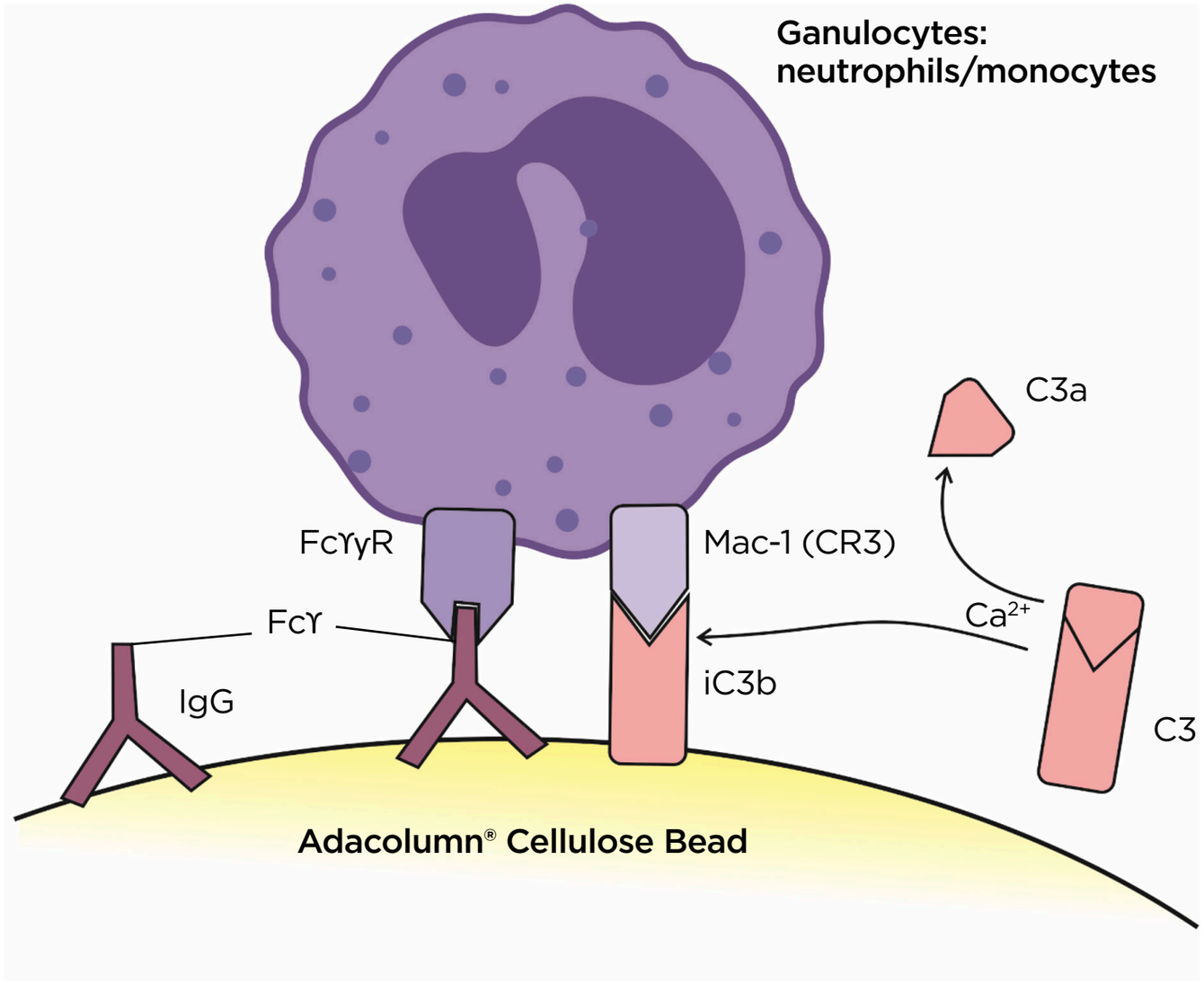
Granulocyte/monocyte apheresis circuit



Adacolumn® mechanism of action on the immune system

WHAT DOES IT DO?

Diagram of the binding mechanism of activated leukocytes in contact with Adacolumn® cellulose beads



Adacolumn® mechanism of action on the immune system

IS IT EFFECTIVE?

2.1. Modulation of cell recruitment and decrease in cytokine load

Recruitment of monocytes/macrophages and granulocytes increases in IMID. **GMA has been described to reduce monocytes/macrophages and granulocytes by 55-65%** in patients with active ulcerative colitis (UC) [1,2]; with Crohn's disease (CD), including those resistant to conventional treatments [3-6], and with psoriasis [7].

Different clinical trials have more recently confirmed these results [8-10]. Decreased concentration of circulating monocytes/macrophages and granulocytes has the direct result of **increasing the ratio of lymphocytes to myeloid cells**. Given the importance of neutrophils in IMID, such as rheumatoid arthritis, the use of this technology is also suitable for this pathology [11] and may be useful in others such as psoriatic arthritis.

Most studies show a reduction of systemic concentration of monocytes/macrophages and neutrophils with a weekly GMA regimen. However, some with **intensified treatment protocols** for patients with CD have shown **earlier remission** compared to non-intensified therapy, and no increase in the occurrence of adverse effects [12,13]. However, the non-inferiority of weekly versus intensified treatment in patients with UC has also been discussed [14]. Therefore, this aspect constitutes a point of scientific interest that requires further research.

IS IT EFFECTIVE?

2.1. Modulation of cell recruitment and decrease in cytokine load

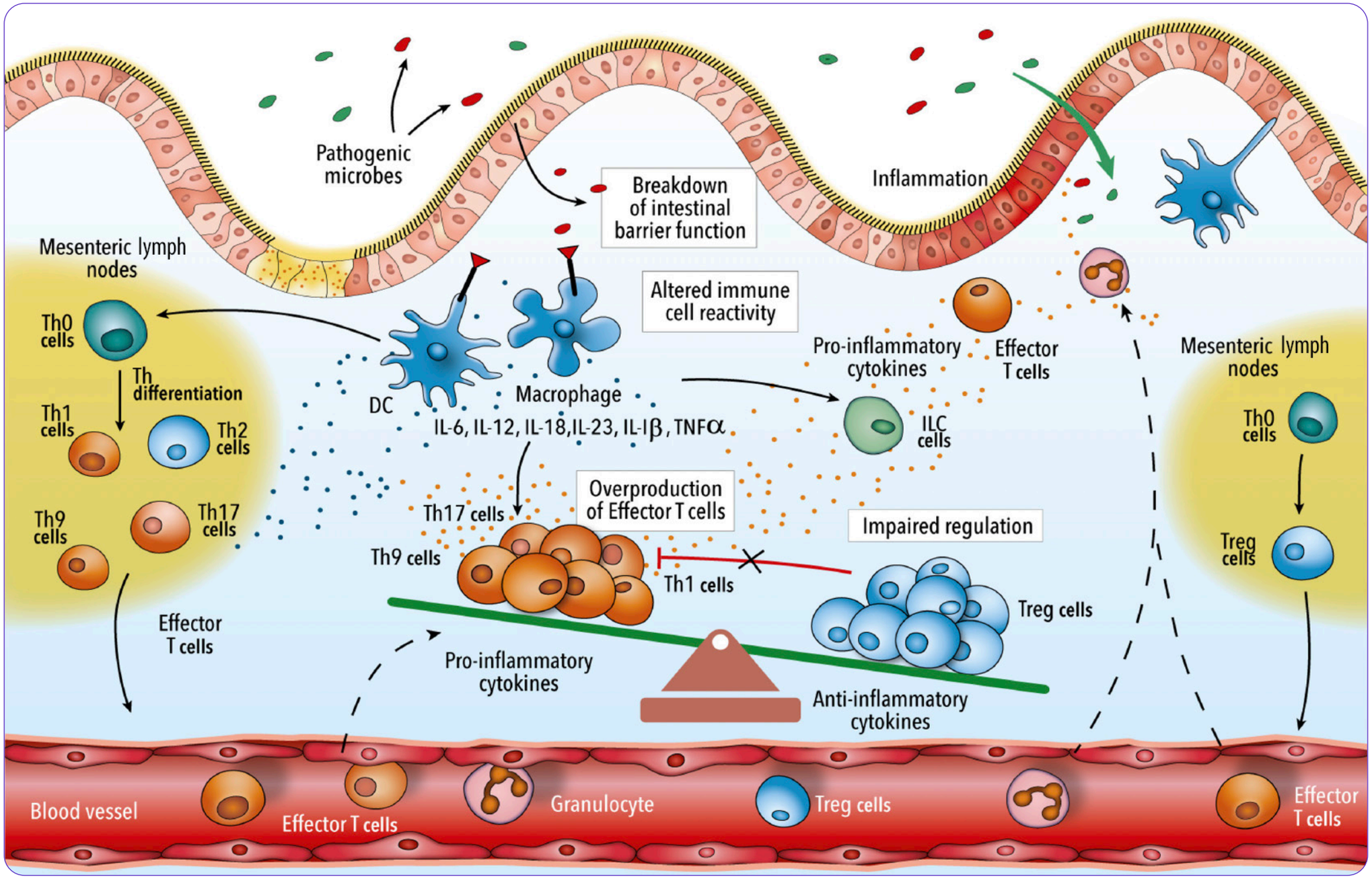
Activated monocytes/macrophages and neutrophils are producers of pleiotropic cytokines, such as tumour necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), 12 (IL-12), and 23 (IL-23). All these mediators are very important in the progression of the inflammatory response and expansion of an adaptive activity that is pathogenic in the case of patients with IMID, since they perpetuate the pro-inflammatory cascade and thus facilitate tissue damage.

Related to cellular modulation, different studies have documented a **decrease in the systemic levels of different pro-inflammatory cytokines, primarily in active UC** [2,15,16]. Despite dispersed results and a lack of differences in the levels of multiple cytokines before and after treatment with GMA, different studies have also shown a **decrease in pro-inflammatory cytokines in mucosa of UC patients** treated with GMA [17,18].

IS IT EFFECTIVE?

2.1. Modulation of cell recruitment and decrease in cytokine load

Inflammatory bowel process



Adacolumn® mechanism of action on the immune system

2.2. Improved environmental signalling

In an inflammatory environment, the signals that outline the monocyte/macrophage phenotypes define their pro-inflammatory character. These signals are made up of some of the cytokines mentioned above, as well as chemokines and other signalling molecules.

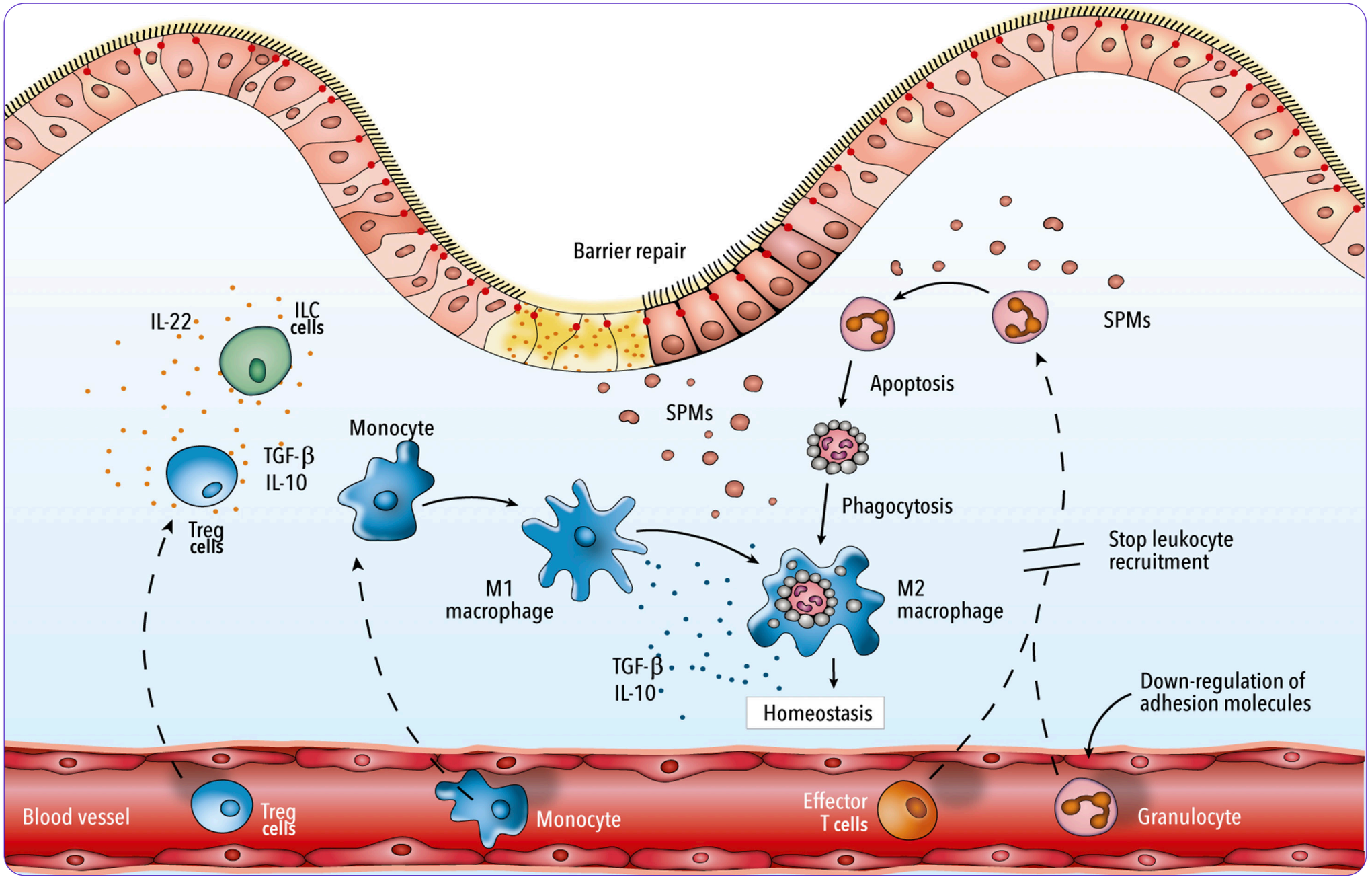
A decrease in pro-inflammatory mediators leads to a **change in signalling molecules, which acquire tolerogenic or tissue repair profiles**. In this environment, the **cytokines** released into the environment become mostly **anti-inflammatory, such as tumour growth factor beta (TGF-β) and interleukin-10 (IL-10)** .

The change in the signalling profile and increased concentrations of anti-inflammatory mediators leads to the **mobilization of *immature* CD10-** neutrophils and **expansion of T lymphocytes with tolerogenic activity**, which help to balance the excess inflammation and which are reduced in patients with IMID. Treatment with GMA has shown an **increase in the concentration of these regulatory T cells** (identified by their **CD4+ and CD25+** markers) and in the levels of the *forkhead box* protein P3 (**FoxP3**), the transcription factor that polarizes them [19].

IS IT EFFECTIVE?

2.2. Improved enviromental signalling

Resolution of intestinal inflammation



SPMs = specialized pro-resolving mediators.

Adacolumn® mechanism of action on the immune system

2.3. Relationship between efficacy, progression and location of the disease

The innate response that dominates the initiation of inflammatory progression in IMID is rapidly amplified by adaptive immunity. This sequential and cyclical activity of the immune system allows for increased inflammation, and associated tissue injury as a result of sustained damage. This means that, from an immunological point of view, IMID is completely different in its initial stages than during the more advanced stages, in which effector and memory lymphocytes can be found in the tissues.

The latter cell types are capable of amplifying the inflammatory response and causing tissue/mucosal damage quickly, regardless of the circulatory supply of myeloid cells. Therefore, this suggests that **the efficacy of the treatment would be greater in new patients and in environments of mild or moderate inflammation** [20,21].

On the other hand, a **decrease in the levels of L-selectin** [22] has been associated with treatment with GMA**. This adhesion molecule** is involved, along with integrins expressed in the vascular endothelium, in the **anchoring of leukocytes recruited for extravasation into the damaged tissue**. The expression of L-selectin ligands is higher in intestinal colonic sections, for example, suggesting that **GMA activity may be higher in colonic involvement** of patients with chronic inflammatory bowel disease (CIBD).

IS IT SAFE?

3.1. Immunosuppression

The selective reduction of the monocyte/macrophage and granulocyte populations in the peripheral blood of patients with IMID involves a modulation of the immune system that enables, on the one hand, functional maintenance of the immune cell population within the tissues, and on the other hand, the activity of the lymphoid cell population, which is responsible for adaptive immunity.

The innate cell population with immune capacity residing in tissues **retains its immune surveillance capacity and is able to respond rapidly** through the multiple receptors of natural immunity existing in them, which remain intact during the use of GMA.

T and B lymphocytes and the products with immunological activity derived from them, including antibodies, which participate in all immune system functions (from defence against infection to the generation of immunological memory), **are not a target**, therefore, the use of GMA does not increase the risk of suffering infections by keeping the immune response intact.

Adacolumn® mechanism of action on the immune system

3.2. Immunogenicity

One of the most common problems in biological treatments has historically been the **loss of secondary response as a result of the appearance of biological anti-drug antibodies**. **This situation directly affects the efficacy of treatments** and delays the restoration of vital immune homeostasis for IMID patients.

The immunomodulatory strategy of GMA does not require the infusion of molecules that can generate immunogenicity in patients. Preventing the formation of immunocomplexes is also relevant from an immunological standpoint, since they can be deposited in the blood vessels and cause vasculitis. The deposited immunocomplexes induce inflammation by attracting and activating leukocytes. For example, immunoglobulins 1 (IgG1) and 3 (IgG3) can bind to the macrophage and granulocyte Fc receptors (FcR) and activate the complement system by the classical pathway, causing an inflammatory response that includes the release of free radicals and other tissue-damaging products.

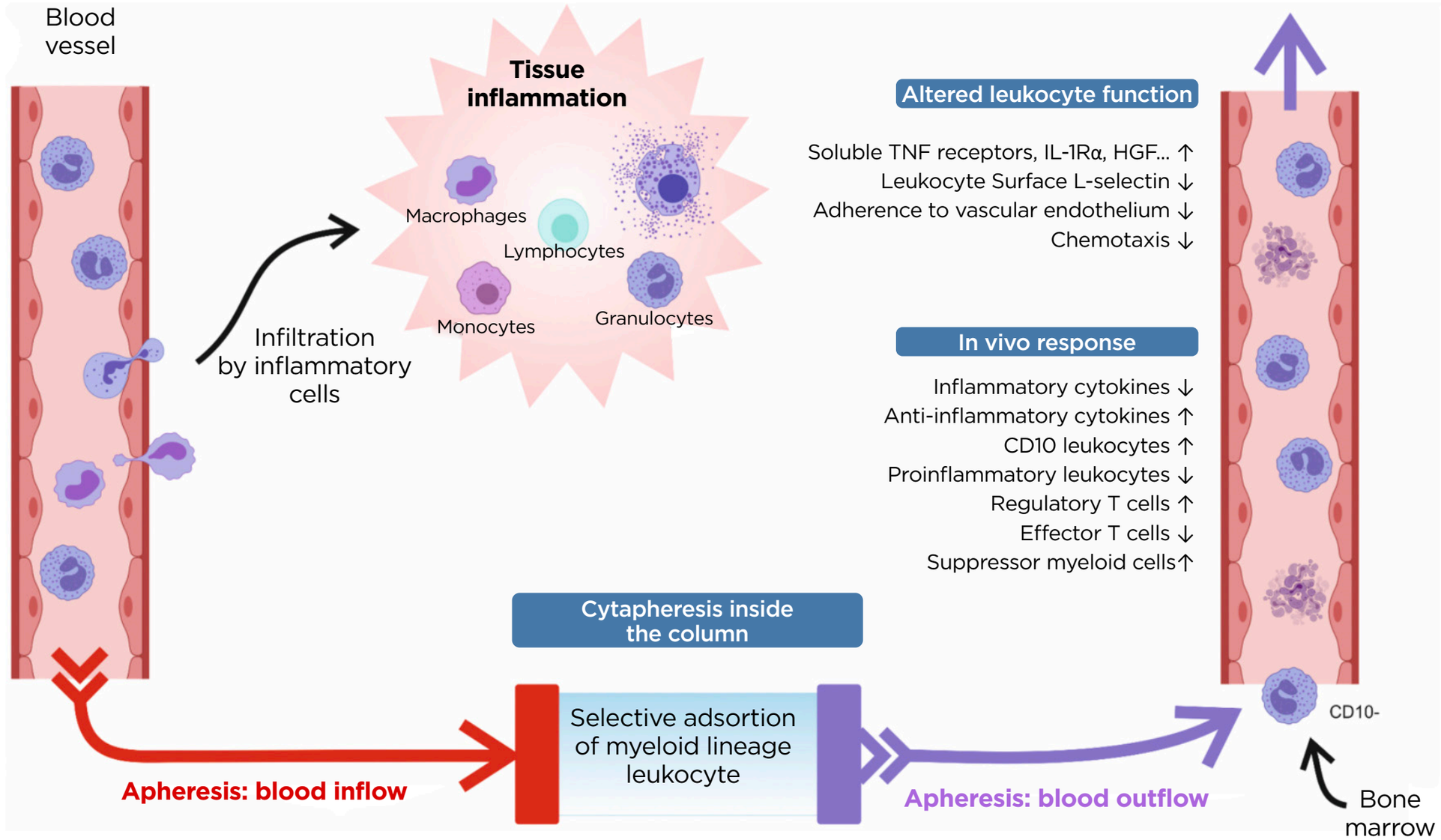
Unlike biological treatments, GMA does not induce immunogenic reactions.

Adacolumn® mechanism of action on the immune system

DOES IT DO IT SAFELY?

3.2. Inmunogenicity

Granulocytopaheresis: An overview of its immunomodulatory effects



Adacolumn® mechanism of action on the immune system

3.3. Combined use with other strategies

The above safety features raise the **possibility of using GMA in combination with other therapeutic strategies**. Although there are some studies in patients with loss of response to infliximab [23,24], the results are preliminary and the potential of this possibility has yet to be explored in general. In particular, combined use with anti-integrins that prevent the extravasation of circulating leukocytes into the damaged tissue may be beneficial.

4 FUTURE OUTLOOK

The anti-inflammatory effect induced by GMA may be favoured by the reintroduction of apoptotic cells induced by the generation of reactive oxygen species after contact with the spine and **with potential capacity to produce tolerogenic mediators, such as IL-10** [25]. However, the studies carried out so far to this effect, in experimental models, are still preliminary and must be confirmed in future research. On the other hand, **increases in anti-inflammatory mediators, such as interleukin-1 receptor antagonist (IL-1Ra)** ***or hepatocyte growth factor*** **(HGF)**, have been depicted *in vitro* in whole blood from healthy volunteers cultured with GMA *carriers* [26]. Likewise, these experiments have shown **changes in the concentration of soluble receptors of TNF-α** [27]. Although a number of patients with active UC in immunosuppressive treatment show similar results [28,29], it is essential to elaborate on the concentration changes of these and other anti-inflammatory mediators in new patient cohorts. These studies would allow for an evaluation **of the additional anti-inflammatory potential of GMA in the systemic environment**.

BIBLIOGRAPHY

1. Yamamoto T, Umegae S, Kitagawa T, Yasuda Y, Yamada Y, Takahashi D, et al. Granulocyte and monocyte adsorptive apheresis in the treatment of active distal ulcerative colitis: a prospective, pilot study. Aliment Pharmacol Ther. 2004;20:783-92.
2. Aoki H, Nakamura K, Yoshimatsu Y, Tsuda Y, Irie M, Fukuda K, et al. Adacolumn selective leukocyte adsorption apheresis in patients with active ulcerative colitis: clinical efficacy, effects on plasma IL-8, and expression of Toll-like receptor 2 on granulocytes. Dig Dis Sci. 2007;52:1427-33.
3. Fukuda Y, Matsui T, Suzuki Y, Kanke K, Matsumoto T, Takazoe M, et al. Adsorptive granulocyte and monocyte apheresis for refractory Crohn's disease: an open multicenter prospective study. J Gastroenterol. 2004;39:1158-64.
4. Martín de Carpi J, Vilar P, Prieto G, García Novo MD, Ribes C, Varea V. Safety and efficacy of granulocyte and monocyte adsorption apheresis in paediatric inflammatory bowel disease: a prospective pilot study. J Pediatr Gastroenterol Nutr. 2008;46:386-91.
5. 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.
6. Sacco R, Romano A, Mazzoni A, Bertini M, Federici G, Metrangolo S, et al. Granulocytapheresis in steroid-dependent and steroid-resistant patients with inflammatory bowel disease: a prospective observational study. J Crohn Colitis. 2013;7:e692-7.
7. Ikeda S, Takahashi H, Suga Y, Eto H, Etoh T, Okuma K, et al. Therapeutic depletion of myeloid lineage leukocytes in patients with generalized pustular psoriasis indicates a major role for neutrophils in the immunopathogenesis of psoriasis. J Am Acad Dermatol. 2013;68:609-17.
8. Fukunaga K, Yokoyama Y, Kamokozuru K, Nagase K, Nakamura S, Miwa H, et al. 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;6:427-33.
9. Matsuda K, Ohno K, Okada Y, Yagi T, Tsukamoto M, Fukushima Y, et al. Adsorptive Granulocyte and Monocyte Apheresis Is Effective in Ulcerative Colitis Patients Both with and without Concomitant Prednisolone. Inflamm Intest Dis. 2020;5:36-41.
10. Naganuma M, Yokoyama Y, Motoya S, Watanabe K, Sawada K, Hirai F, et al.; 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.
11. Sanmartí R, Marsal S, Valverde J, Casado E, Lafuente R, Kashiwagi N, et al. Adsorptive granulocyte/monocyte apheresis for the treatment of refractory rheumatoid arthritis: an open pilot multicentre trial. Rheumatology (Oxford). 2005;44:1140-4.
12. Sakuraba A, Motoya S, Watanabe K, Nishishita M, Kanke K, Matsui T, et al. An open-label prospective randomized multicenter study shows very rapid remission of ulcerative colitis by intensive granulocyte and monocyte adsorptive apheresis as compared with routine weekly treatment. Am J Gastroenterol, 2009;104:2990-5.
13. Yoshimura N, Yokoyama Y, Matsuoka K, Takahashi K, Iwakiri R, Yamamoto T, et al. An open-label prospective randomized multicenter study of intensive versus weekly granulocyte and monocyte apheresis in active crohn's disease. BMC Gastroenterol. 2015;15:163.
14. Dignass AU, Eriksson A, Kilander A, Pukitis A, Rhodes JM, Vavricka S. Clinical trial: five or ten cycles of granulocyte-monocyte apheresis show equivalent efficacy and safety in ulcerative colitis. Aliment Pharmacol Ther. 2010;31:1286-95.
15. Toya Y, Chiba T, Mizutani T, Sato K, Kasugai S, Matsuda N, et al. The effect of granulocyte and monocyte adsorptive apheresis on serum cytokine levels in patients with ulcerative colitis. Cytokine. 2013;62:146-50.
16. Hanai H, Iida T, Yamada M, Sato Y, Takeuchi K, Tanaka T, et al. Effects of adacolumn selective leukocytapheresis on plasma cytokines during active disease in patients with active ulcerative colitis. World J Gastroenterol. 2006;12:3393-9.

BIBLIOGRAPHY

17. Yamamoto T, Saniabadi AR, Umegae S, Matsumoto K. Impact of selective leukocytapheresis on mucosal inflammation and ulcerative colitis: cytokine profiles and endoscopic findings. Inflamm Bowel Dis. 2006;12:719-26.

18. Muratov V, Lundahl J, Ulfgren AK, Elvin K, Fehrman I, Ahlborg N, et al. Down-regulation of interferon-gamma parallels clinical response to selective leukocyte apheresis in patients with inflammatory bowel disease: a 12-month follow-up study. Int J Colorectal Dis. 2006;21:493-504.

19. Kamikozuru K, Fukunaga K, Hirota S, Hida N, Ohda Y, Yoshida K, et al. The expression profile of functional regulatory T cells, CD4+CD25high+/forkhead box protein P3+, in patients with ulcerative colitis during active and quiescent disease. Clin Exp Immunol. 2009;156:320-7.

20. Suzuki Y, Yoshimura N, Fukuda K, Shirai K, Saito Y, Saniabadi AR. A retrospective search for predictors of clinical response to selective granulocyte and monocyte apheresis in patients with ulcerative colitis. Dig Dis Sci. 2006;51:2031-8.

21. Tanaka T, Okanobu H, Kuga Y, Yoshifuku Y, Fujino H, Miwata T, et al. Clinical and endoscopic features of responders and non-responders to adsorptive leucocytapheresis: a report based on 120 patients with active ulcerative colitis. Gastroenterol Clin Biol. 2010;34:687-95.

22. D'Arrigo C, Candal-Couto JJ, Greer M, Veale DJ, Woof JM. Human neutrophil Fc receptor mediated adhesion under flow: a hollow fibre model of intravascular arrest. Clin Exp Immunol. 1994;100:173-9.

23. Yokoyama Y, Sawada K, Aoyama N, Yoshimura N, Sako M, Hirai F, et al. Efficacy of Granulocyte and Monocyte Adsorptive Apheresis in Patients with Inflammatory Bowel Disease Showing Lost Response to Infliximab. J Crohn Colitis. 2020;jjaa051.

24. Rodriguez-Lago I, Sempere L, Gutiérrez A, Núñez A, Leo Carnerero E, Hinojosa E, et al. Granulocyte-monocyte apheresis: an alternative combination therapy after loss of response to anti-TNF agents in ulcerative colitis. Scand J Gastroenterol. 2019;54:459-64.

25. Ansary MM, Ishihara S, Oka A, Kusunoki R, Oshima N, Yuki T, et al. Apoptotic cells ameliorate chronic intestinal inflammation by enhancing regulatory B-cell function. Inflamm Bowel Dis. 2014;20:2308-20.

26. Takeda Y, Shiobara N, Saniabadi AR, Adachi M, Hiraishi K. Adhesion dependent release of hepatocyte growth factor and interleukin-1 receptor antagonist from human blood granulocytes and monocytes: evidence for the involvement of plasma IgG, complement C3 and beta2 integrin. Inflamm Res. 2004;53:277-83.

27. Hiraishi K, Takeda Y, Shiobara N, Shibusawa H, Jimma F, Kashiwagi N, et al. Studies on the mechanisms of leukocyte adhesion to cellulose acetate beads: an in vitro model to assess the efficacy of cellulose acetate carrier-based granulocyte and monocyte adsorptive apheresis. Ther Apher Dial. 2003;7:334-40.

28. Hanai H, Watanabe F, Takeuchi K, Iida T, Yamada M, Iwaoka Y, et al. Leukocyte adsorptive apheresis for the treatment of active ulcerative colitis: a prospective, uncontrolled, pilot study. Clin Gastroenterol Hepatol. 2003;1:28-35.

29. Hanai H, Watanabe F, Yamada M, Sato Y, Takeuchi K, Iida T, et al. Correlation of serum soluble TNF-alpha receptors I and II levels with disease activity in patients with ulcerative colitis. Am J Gastroenterol. 2004;99:1532-8.

EXPERT COMMENTARY

Dr. Eugeni Domènech

Gastroenterology & Hepatology Department

Germans Trias i Pujol University Hospital, Badalona, Barcelona, Spain

From a pathogenic point of view, **neutrophils seem to play a key role in direct tissue damage and in perpetuating the inflammatory response** in ulcerative colitis (UC). As in other chronic inflammatory conditions, a deregulation of neutrophil apoptosis has been observed in UC[1]. Mucosal **infiltration by neutrophils** is a key event in UC, as demonstrated by the fact that it is a **crucial and constant component for its classification of severity and histological activity in various histological indices** [2]. Additionally, the **presence of neutrophils in colon biopsies** from the mucosa of patients with UC has been **associated with an increased risk of clinical recurrence and even dysplasia**, which leads some authors to propose histological remission as the final therapeutic objective in UC [3]. Consequently, **modulation of mucosal neutrophil activity and number has been postulated as an attractive therapeutic approach** in UC, although no drug targeting these cells is yet available, mainly because of fears of increased risk of bacterial infection [4].

Currently, granulocytapheresis (**GMA**) **is the only approved treatment for UC, whose main target is**

EXPERT COMMENTARY

Dr. Eugeni Domènech

the neutrophil. Beyond the results in efficacy of the multiple published studies, the validity of the GMA mechanism of action was demonstrated in the study by Maiden et al. [5], in which patients with UC in clinical remission, but with levels of **faecal calprotectin** (**protein produced almost exclusively by neutrophils**) higher than 250 g/kg, were randomised to be treated or not with 5 sessions of GMA without another therapeutic intervention. After a 6-month monitoring period, the group treated with GMA showed a significantly higher clinical relapse-free survival. **Faecal calprotectin has been shown to be the most useful biological marker in the clinical management of UC. It is produced almost exclusively by neutrophils**, which make up 80% of the cytosolic proteins in these cells. Its **presence is thus synonymous with neutrophils** in the environment where it is determined. **In faeces, calprotectin has been shown to be the best prognostic marker of relapse in patients with UC**; additionally, **its healthy state reveals an excellent correlation with both endoscopic and histological remission**, and its use is recommended in the follow-up of patients with UC [6].

BIBLIOGRAPHY

1. Brannigan AE, O'Connell PR, Hurley H, O'Neill A, Brady HR, Fitzpatrick JM, et al. Neutrophil apoptosis is delayed in patients with inflammatory bowel disease. Shock. 2000;13:361-6.
2. Mosli MH, Feagan BG, Sandborn WJ, D'haens G, Behling C, Kaplan K, et al. Histologic evaluation of ulcerative colitis: a systematic review of disease activity indices. Inflamm Bowel Dis. 2014;20:564-75.
3. Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? Clin Gastroenterol Hepatol. 2014;12:929-34.
4. Muthas D, Reznichenko A, Balendran CA, Böttcher G, Clausen IG, Mårdh CK, et al. Neutrophils in ulcerative colitis: a review of selected biomarkers and their potential therapeutic implications. Scand J Gastroenterol. 2017;52:125-35.
5. Maiden L, Takeuchi K, Baur R, Bjarnason I, O'Donohue J, Forgacs I, et al. Selective white cell apheresis reduces relapse rates in patients with IBD at significant risk of clinical relapse. Inflamm Bowel Dis. 2008;14:1413-8.
6. Guardiola J, Lobatón T, Cerrillo E, Ferreiro-Iglesias R, Gisbert JP, Domènech E, et al.; on behalf of GETECCU. Recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) on the utility of the determination of faecal calprotectin in inflammatory bowel disease. Gastroenterol Hepatol. 2018;41:514-29.

EXPERT COMMENTARY

Dr. Iago Rodríguez-Lago

Gastroenterology Department: Inflammatory Bowel Disease Unit
Hospital Galdakao-Usansolo, Galdakao, Biscay, Spain

Leukocyte apheresis or granulocyte apheresis (GMA) with Adacolumn is a non-pharmacological treatment option for ulcerative colitis that eliminates certain cell populations. As its name suggests, its mechanism of action is based on adsorption (A), distribution (D) and apheresis (A). This filtration column contains approximately 35,000 spheres of cellulose acetate with a diameter of 2 mm, which enable the **elimination of 65% of granulocytes, 55% of circulating monocytes/macrophages and, to a lesser extent, lymphocytes (2%)** [1]. In addition, it has also been **associated with changes in both circulating and intestinal mucosal cytokines, immunoglobulins and complement components**.

Unlike most pharmacological therapies used in UC, granulocyte apheresis (GMA) allows for a more comprehensive and varying level of treatment of the immunological alterations present in these patients. **Its activity involves some key cytokines in the inflammatory process, such as tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), 6 (IL-6), 12 (IL-12) or 23 (IL-23), which are only selectively blocked by other drugs, such as biologicals**. On the other hand, there are also important **differences compared to thiopurine derivatives, as they exercise their effect by blocking the proliferation of T-lymphocytes**. This means that **the activity on the cellular component of GMA, and especially on neutrophils, is an added value and unique within the current treatment** options for inflammatory bowel disease. Its different effects allow this technique to **reduce the inflammatory load, both at a systemic level and in the intestinal mucosa, creating a less pro-inflammatory environment**. This makes it necessary **to consider the use of immunosuppressants or biologicals, as well as concurrently**, since there are no significant overlaps or relevant direct interaction between them.

Adacolumn® mechanism of action on the immune system

EXPERT COMMENTARY

Dr. Iago Rodríguez-Lago

According to its data sheet, GMA is indicated for use in patients with certain immune-mediated diseases, such as ulcerative colitis and Crohn's disease, as well as for the treatment of ocular Behçet's disease, systemic lupus erythematosus and pustular psoriasis.

The recommended guideline for use is one 60-minute session per week for 5 consecutive weeks. However, prospective studies and clinical practice experience suggest that **increasing the number and frequency of sessions may increase their effectiveness, even in patients resistant to other therapies**. In this **pattern, termed intensive**, the treatment is carried out at a rate of **2 sessions per week**. Additionally, **it is possible to increase the volume filtered in each session**, from a fixed 1,800 ml in all patients (standard guideline), and to adjust it **according to the weight**, having observed that the effectiveness can improve by filtering 60 ml/kg of weight and session. Similarly, this same trend has been found by **extending the duration** of the sessions to 90 minutes – and thus the filtered volume. These findings are explained by the observation that the apheresis column maintains its adsorption capacity after the first 60 minutes which is the usual pattern.

The results of two recent clinical trials have shown that GMA can be used in patients with ulcerative colitis who have previously received other treatments such as thiopurine or biological drugs [2,3]. Generally speaking, in view of the development of corticodependence, the recommended strategy in ulcerative colitis is treatment with thiopurine drugs [4]. In any case, the **association of leukocyte apheresis with corticoids has been shown to increase the time to clinical relapse** [2], and may constitute a treatment option in some of these patients. Both options should also not be considered mutually exclusive, since **apheresis can also be used concurrently with thiopurines** and may be considered, for example, **as a bridge therapy** until the onset of action of the latter [5].

EXPERT COMMENTARY

Dr. Iago Rodríguez-Lago

It is also important to note that experience with this technique has shown that its **efficacy does not seem to be as influenced by concomitant treatments** as with other pharmacological therapies [6]. This may be because no adsorption of some of the most common active ingredients used in ulcerative colitis has been observed, despite their mechanism of action. This aspect, along with the fact that medical treatment options are still limited, has raised **interest in possible combinations with other treatments, such as biological drugs [7]. The association with both anti-tumour necrosis factor (anti-TNF) and vedolizumab has shown promising results, demonstrating clinical improvement, along with reduction in faecal calprotectin in a group of difficult-to-treat patients** [8-11].

Given the special characteristics of the technique, it is also important to understand the perspective of the patients who have be treated with it. Although its non-pharmacological mechanism of action involves a change in the usual concept of treatment, it is an **accepted and well-tolerated technique by most patients, even in guidelines with a greater number of sessions [12,13]. The fact that its safety profile is taken into account** also makes it a technique that should be considered in certain situations.

Currently, **its main application is in corticodependent ulcerative colitis**, with increasing experience following an insufficient response or a loss of response to certain immunosuppressants or biologics. One should also bear in mind that **its efficacy can be increased with earlier use** within the evolution of the disease **and by adopting more intensive treatment guidelines**. In addition to this, it remains to be seen whether **maintenance therapy** can play a role in this pathology. Finally, within all these aspects, leukocyte apheresis also stands due to the possibility of **adjusting to different situations** according to the indication in which it is applied, the course of the disease and its severity, as well as the individual situation and characteristics of each patient.

EXPERT COMMENTARY

Dr. Iago Rodríguez-Lago

BIBLIOGRAPHY

1. Hanai H, Takeda Y, Eberhardson M, Gruber R, Saniabadi AR, Winqvist O, et al. The mode of actions of the Adacolumn therapeutic leucocytapheresis in patients with inflammatory bowel disease: a concise review. Clin Exp Immunol. 2011;163(1):50-8.
2. Domenech E, Panes J, Hinojosa J, Annese V, Magro F, Sturniolo GC, et al. Addition of granulocyte/monocyte apheresis to oral prednisone for steroid-dependent ulcerative colitis: A randomized, multicentre, clinical trial. J Crohns Colitis. 2018;12(6):687-94.
3. Dignass A, Akbar A, Baumgart DC, Bommelaer G, Bouguen G, Cadiot G, et al. Granulocyte/monocyte adsorptive apheresis for the treatment of therapy-refractory chronic active ulcerative colitis. Scand J Gastroenterol. 2018;53(4):442-8.
4. Harbord M, Eliakim R, Bettenworth D, Karmiris K, Katsanos K, Kopylov U, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. J Crohns Colitis. 2017;11(7):769-84.
5. Cabriada JL, Domenech E, Ibargoyen N, Hernandez V, Clofent J, Ginard D, et al. Leukocytapheresis for steroid-dependent ulcerative colitis in clinical practice: results of a nationwide Spanish registry. J Gastroenterol. 2012;47(4):359-65.
6. Yokoyama Y, Matsuoka K, Kobayashi T, Sawada K, Fujiyoshi T, Ando T, et al. A large-scale, prospective, observational study of leukocytapheresis for ulcerative colitis: treatment outcomes of 847 patients in clinical practice. J Crohns Colitis. 2014;8(9):981-91.
7. Cabriada JL, Rodríguez-Lago I. Granulocitoaféresis en 2017: Puesta al día. Enfermedad Inflamatoria Intestinal al Día. 2017;16:62-9.
8. Rodriguez-Lago I, Gomez-Irwin L, Fernandez E, Higuera R, Cabriada JL. Granulocyte-Monocyte Apheresis as an Adjuvant Therapy to Anti-Tumor Necrosis Factor Drugs for Ulcerative Colitis. Ther Apher Dial. 2017;21(1):26-30.
9. Rodriguez-Lago I, Sempere L, Gutierrez A, Nunez A, Leo Carnerero E, Hinojosa E, et al. Granulocyte-monocyte apheresis: an alternative combination therapy after loss of response to anti-TNF agents in ulcerative colitis. Scand J Gastroenterol. 2019;54(4):459-64.
10. Saez-Gonzalez E, Aguas M, Huguet JM, Nos P, Beltran B. Combination therapy with cytapheresis plus vedolizumab in a corticosteroid-dependent patient with ulcerative colitis and previous ANTI-TNF-alpha drug failure. Dig Liver Dis. 2018;50(4):415-7.
11. Yokoyama Y, Sawada K, Aoyama N, Yoshimura N, Sako M, Hirai F, et al. Efficacy of Granulocyte and Monocyte Adsorptive Apheresis in Patients with Inflammatory Bowel Disease Showing Lost Response to Infliximab. J Crohns Colitis. 2020;jjaa051.
12. Rodriguez-Lago I, Benitez JM, Garcia-Sanchez V, Gutierrez A, Sempere L, Ginard D, et al. Granulocyte and monocyte apheresis in inflammatory bowel disease: The patients' point of view. Gastroenterol Hepatol. 2018;41(7):423-31.
13. Nagase K, Fukuanga K, Yokoyama Y, Kamikozuru K, Miwa H, Nakamura S. Questionnaire based assessment of patients' acceptability of leukocytapheresis for the treatment of inflammatory bowel disease. Ther Apher Dial. 2013;17(5):490-7.

Adacolumn® mechanism of action on the immune system

Adacyte
Therapeutics

Instructions for use available at: **www.adacyte.com**

CE certificate: CE 0123 by TÜV SÜD, risk class IIb.

ES-ADA-0920031