Adacolumn® mechanism of action on the immune system (II)

EXPERT COMMENTARY

Prof. Giorgos Bamias

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INDEX

Adacolumn® mechanism of action on the immune system (II)

Prof. Giorgos Bamias

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PROF. GIORGOS BAMIAS

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1. Presentation

At present, **a significant unmet therapeutic need exists for patients with ulcerative colitis** (UC), despite the recent approval of several biologics and small molecules with diverse modes of action. Indeed, the percentage of patients in clinical remission after one year of treatment, is less than 50% for most currently available therapies, whilst more demanding outcomes, **such as endoscopic or histological healing, are accomplished by even less patients**. In addition, biologics and small molecules are associated with certain safety concerns that may compromise their applicability to specific subpopulations with UC. **Taken together, novel therapeutic approaches that will demonstrate adequate efficacy combined with acceptable safety profiles are continually needed**.

Extracorporeal granulocyte monocyte/macrophage adsorption (GMA) by use of the Adacolumn offers a different perspective for the treatment of inflammatory bowel diseases (IBD), particularly for UC, where most studies have been done so far.

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2. How does Adacolumn work?

The concept behind Adacolumn function lies in the adsorption of plasma immunoglobulin G and immune complexes to the column carriers, which enforces circulating cells that recognize them via expression of Fcγ receptors (FcγR) to be trapped within the column.[1] As neutrophils and myeloid cells (monocytes/macrophages) are the primary expressers of FcγR, these are mostly removed by the Adacolumn. In addition, localized complement activation also takes place, leading to the release of complement fragments C3a, C5a, and, most importantly, opsonins C3b/C3bi, which are absorbed onto the carriers.[2] Binding of those fragments to their respective complement receptors [CR1, CR2, CR3] further attracts neutrophils and myeloid cells. The end result of such phenomena is that, **during passage through the Adacolumn, peripheral blood is depleted from granulocytes and monocytes/macrophages. At the same moment, lymphocytes** avoid getting entrapped as they lack receptors for IgG or complement binding; hence, they **remain almost unaffected** during passage. Indeed, almost all lymphocytes, along with >40% of myeloid leucocytes pass through the Adacolumn and return to the circulation.

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PROF. GIORGOS BAMIAS

3. Why are Adacolumn effects relevant to IBD?

Granulocytes and myeloid cells highly contribute to the pathogenesis of IBD, especially during acute exacerbations of inflammatory activity. During such phases, intestinal mucosa is highly populated with extravasated neutrophils and macrophages. Once inside the inflamed area, those cells further accelerate tissue injury through the secretion of a variety of inflammatory mediators, including proteolytic enzymes, reactive oxygen species (ROS) and cytokines. In fact, active inflammation in histology reports is defined by the detection of intestinal neutrophils, which are excluded from the mucosal in the homeostatic state. Accordingly, a recent publication reported that the **complete resolution of mucosal neutrophils was an indicator of improved long-term clinical outcomes of patients with ulcerative colitis**.[3] Likewise, a published meta-analysis reported a **60%–70% relative reduction in the risk of relapse in patients without mucosal neutrophils at baseline**.[4] Similarly, detection in the stools of the granulocyte product calprotectin is considered the most reliable marker of ongoing inflammatory activity in IBD and its absence/low concentration an indication of clinical remission and mucosal healing.[5] These data show that neutrophils/myeloid cells are important pro-inflammatory factors in IBD and insinuate that their depletion by Adacolumn may be of therapeutic benefit in patients. In fact, it was shown recently that the **neutrophil-to-lymphocyte ratio (NLR) is a useful biomarker of inflammatory activity in UC and**, more importantly, **may predict adverse outcomes and response to therapy**.[6] This further emphasizes the therapeutic potential of **Adacolumn as the latter depletes neutrophils without affecting lymphocytes, thus, decreasing the NLR ratio**.

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3. Why are Adacolumn effects relevant to IBD?

In addition to neutrophils, monocytes are also known to mediate inflammatory effects in IBD, thus, their depletion by Adacolumn is also of benefit. The number of CD14+CD16+ monocytes was shown to be significantly reduced by GMA in patients with IBD.[7] This may have pathophysiological implications, as it was shown that those monocytes are proinflammatory via the secretion of cytokines such as TNF-α and IL-1β.

Besides the cellular depletion of the relevant populations, **GMA exerts additional immunological effects** that may be of benefit to patients with IBD.

- *Firstly*, **increases in regulatory/anti-inflammatory populations has been reported, following treatment with Adacolumn**. On the one hand, GMA was shown to **increase total lymphocyte numbers**, which, most importantly, included elevations in the number of **$CD4^+CD25^+$ regulatory T cells (Tregs)**.[8] Interestingly, the effects of GMA on lymphocyte numbers were sustained after the last apheresis session. Aditionally, an **increase in the number of regulatory B cells (Bregs)** was also noted in patients subjected to GMA. The mechanism behind this effect initially involves the generation of **apoptotic neutrophils**, which then interact with $CD19^+$ B-cells. Following such **interaction, B cells become IL-10 producing Bregs, or $CD19^{hi}CD1D^{hi}$ B-cells**.[9] Additional Bregs are derived from immature B-cells, when the latter phagocytose GM-produced apoptotic cells.

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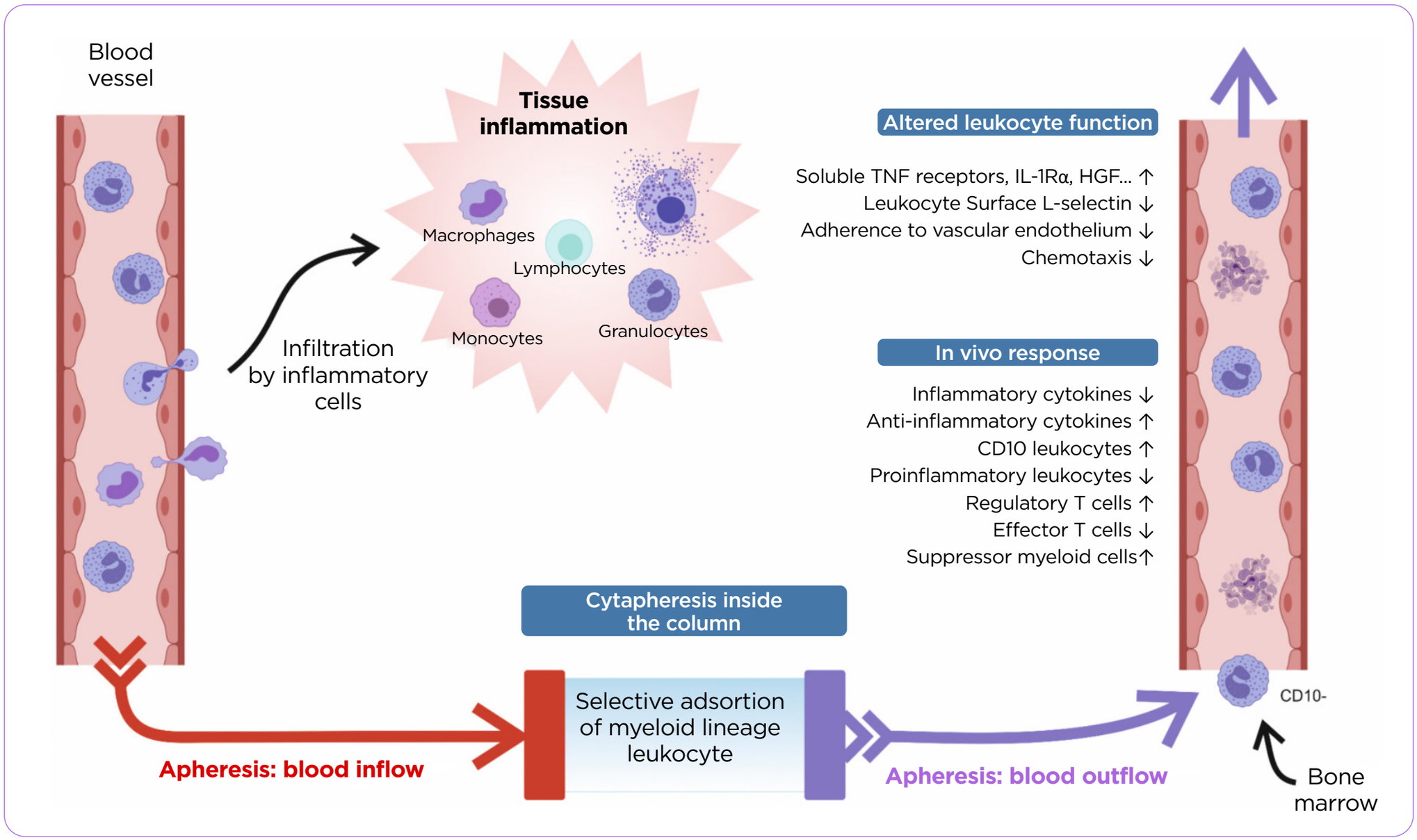
3. Why are Adacolumn effects relevant to IBD?

Granulocytopaheresis: An overview of its immunomodulatory effects



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3. Why are Adacolumn effects relevant to IBD?

- *Secondly*, the process of **GMA enriches the outflow blood composition in anti-inflammatory mediators**. Besides IL-10 that is produced by the aforementioned Bregs, **entrapped leukocytes also secrete several soluble factors with anti-inflammatory properties**. Those include **soluble TNF receptors I & II**, that neutralize TNF, **IL-1 receptor antagonist (IL-1ra)** that was shown to neutralize IL1-β and control intestinal inflammation, and **hepatocyte growth factor (HGF)** that was shown to promote mucosal epithelial cell regeneration, which are all relevant to IBD pathogenesis.[10,11]. The translational importance of such effects was highlighted by reports of **significantly reduced mucosal and systemic expression of inflammatory cytokines [IFN-γ, TNF-α, IL-1β, IL-6, IL-8]** in patients treated and responding to GMA.[2]

- *Finally*, **GMA may also affect the capability of circulating immunocytes (leukocytes) for entry into the inflamed bowel by affecting their expression of adhesion molecules**. For example, it was shown in vitro that incubation with cellulose acetate beads significantly **reduced the concentration of soluble cell adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1)** in blood samples.[12] As those molecules are upregulated and correlate with intestinal inflammation in IBD patients, their decrease by GMA may also contribute to its anti-inflammatory effects.

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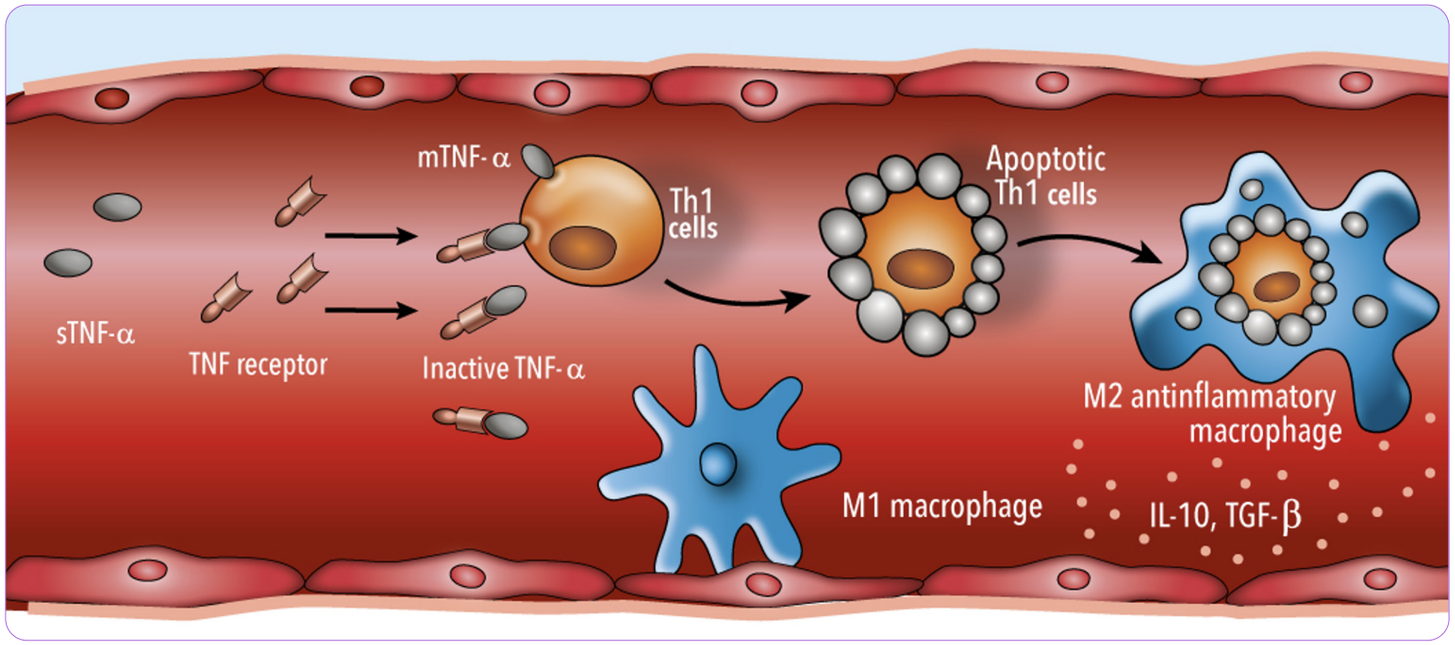
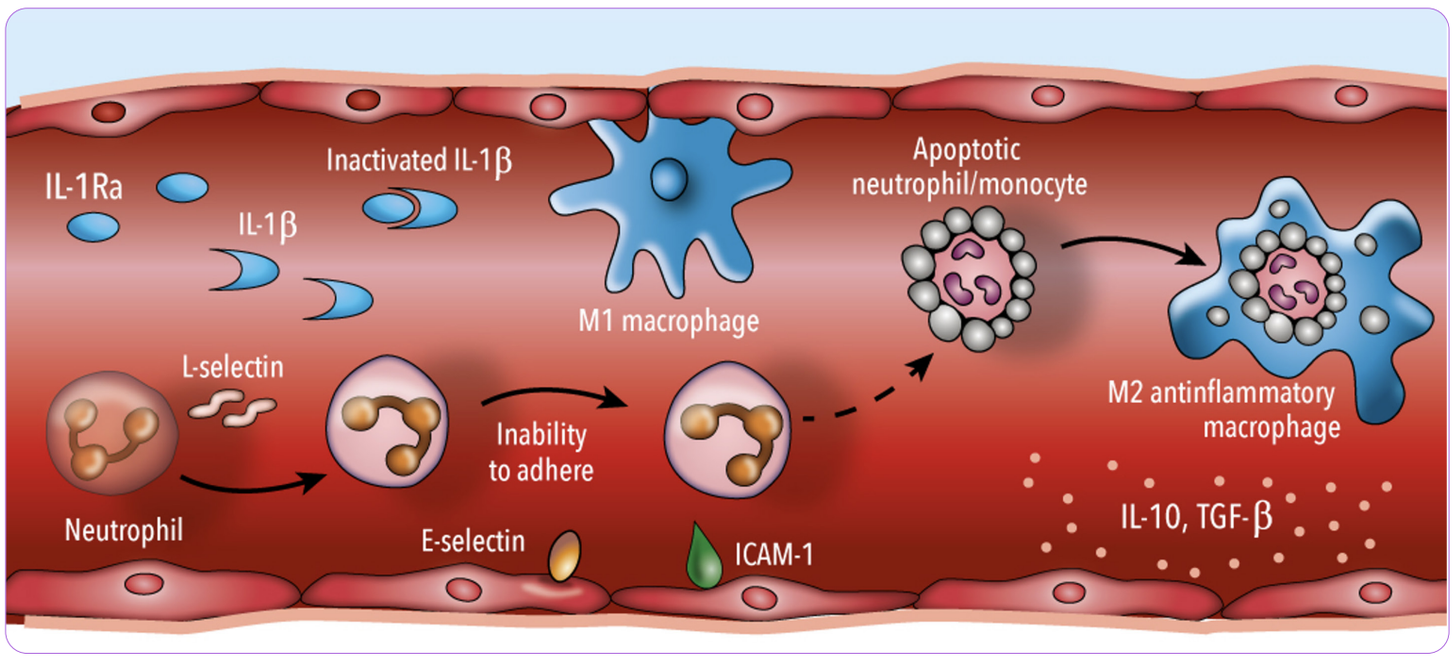
3. Why are Adacolumn effects relevant to IBD?





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4. How does Adacolumn fit in the treatment of IBD?

The majority of clinical studies on Adacolumn were done in patients with UC. Although most of the original studies were reported in Japanese patients, there are, nowadays, several reports from other patient populations as well. Those studies have established the high efficacy of GMA in patients with UC and have also defined predictors of better response to this therapy.

In the largest multicenter study so far, 656 patients with severe or refractory UC were followed-up for more than seven years. The clinical response rates for severe, moderate and mild cases were 63.2%, 65.7% and 80.4%, respectively, whereas **lower recurrence rates and longer periods of sustained remission were demonstrated in patients treated with GMA**.[13]

Analysis of the factors associated with improved GMA efficacy have reported that the best candidates are patients with short duration of UC, patients that are naïve to steroids, and patients who received Adacolumn as their first therapy.[14] Such results indicate that GMA should not only be considered a treatment option for failures of medical therapies for UC, but, rather, incorporated early in treatment algorithms. In fact, it was reported that higher doses of prednisolone at commencement of GMA and a larger cumulative dose of prednisolone administered before entry were independently associated with suboptimal response to GMA.[15]

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PROF. GIORGOS BAMIAS

4. How does Adacolumn fit in the treatment of IBD?

It should be noted, however, that GMA is also effective in steroid-dependent or steroid-refractory UC, as almost half of those patients also respond,[16] **making it a highly efficacious steroid-sparing treatment** and establishing its therapeutic position across a wide spectrum of indications. Patients who do not respond to treatment with 5-ASA, also appear to benefit from GMA monotherapy, thus, bypassing the need for concomitant therapy with steroids, which is traditionally associated with serious adverse effects. In fact, GMA was found superior to methylprednisolone therapy in a population of 5-ASA-resistant, active UC.[17]

Recently, the therapeutic cornerstone for moderate to severe UC have been biological therapies, mainly anti-TNF and anti-integrin monoclonal antibodies. Nevertheless, almost half of the patients do not respond to induction regimens and even less maintain a long-term remission with these agents, the most frequent reason being the secondary loss of response (LOR). In several cases the latter is associated with immunogenicity mechanisms through the development of anti-drug antibodies. Recent studies have showed that GMA may act as salvage therapy in such cases and re-establish the lost response to biologics. This was shown for both patients with anti-TNF and anti-integrin secondary failures, who regained response to their biological therapy after application of GMA sessions.[18, 19]

Taken together, existing data clearly points to a multifaceted role of GMA via Adacolumn in various subpopulation of patients with UC, including 5-ASA refractory/steroid-naïve, steroid dependent/refractory patients, as well as patients with loss of response to anti-TNF or anti-integrin biologics.

Adacolumn® mechanism of action on the immune system

PROF. GIORGOS BAMIAS

4. How does Adacolumn fit in the treatment of IBD?

Technical and protocol improvements of GMA, such as increasing number of sessions, higher per-session volumes and body-weight adjustments may also offer additional benefits for patients and sustain the initial response to GMA.

In addition, GMA has demonstrated **an excellent safety profile**, and due to its **non-pharmacologic nature, adverse effects are minimal and temporary**. These characteristics make GMA an excellent choice for specific subpopulations of patients with IBD, in whom safety is of the highest priority. Such groups include pregnant women, children and older patients, studies in whom also support a role for GMA.

Finally, the pathophysiological properties of GMA make it a **much suitable therapy not only for UC but also CD**, as well as several immunological extra-intestinal manifestations that affect the joints, the skin or other organs.

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DR. JOANA TORRES

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1. Presentation

Inflammatory bowel disease (IBD) is a chronic disease in which multiple pathways and inflammatory processes are unregulated. A central mechanism in the physiopathology of the disease is a lesion of the intestinal barrier that leads to an exaggerated immune response triggered by exposure to luminal microflora. The result is the activation of several cells of the innate and adaptive immune compartment, with overexpression of multiple pathways and pro-inflammatory cytokines.

Despite many recent therapeutic advances, with a growing number of drugs with new mechanisms of action to be approved or studied in phase 3 trials, there is **still an unmet need in IBD**, as a significant proportion of patients depend on corticosteroids to maintain remission, lose the response or become refractory to the approved treatments. Additionally, **many of the treatments used in IBD have associated infectious or neoplastic risks**.

Adacolumn® mechanism of action on the immune system

DR. JOANA TORRES

2. What is Adacolumn and how does it work?

Adacolumn® is a medical device that enables leukocyte apheresis, a therapeutic process that consists of “filtering” the blood through a column that performs selective adsorption of inflammatory cells, particularly granulocytes (neutrophils) and monocytes/macrophages.

A central process in the perpetuation of the inflammatory response is related to the recruitment and activation of granulocytes and monocytes in the intestine. When activated, these cells produce a wide range of pleiotropic cytokines, such as TNF-α, IL-1β, IL-6, IL-12 and IL-23, which are potent proinflammatories, as well as reactive oxygen species (ROS) and proteases that contribute to the lesion of the mucosa.[1]

The granulocytes and monocytes/macrophages express Fc gamma receptors (FcγR) and the complement component C3 receptor (C3R). The leukocyte apheresis column consists of spheres of cellulose acetate that become coated with IgG and iC3b when the blood goes through the column, which function as ligands for the FcγR and C3R expressed in the activated leukocytes, respectively, allowing selective adsorption of these cells.[1,2]

Adacolumn® mechanism of action on the immune system

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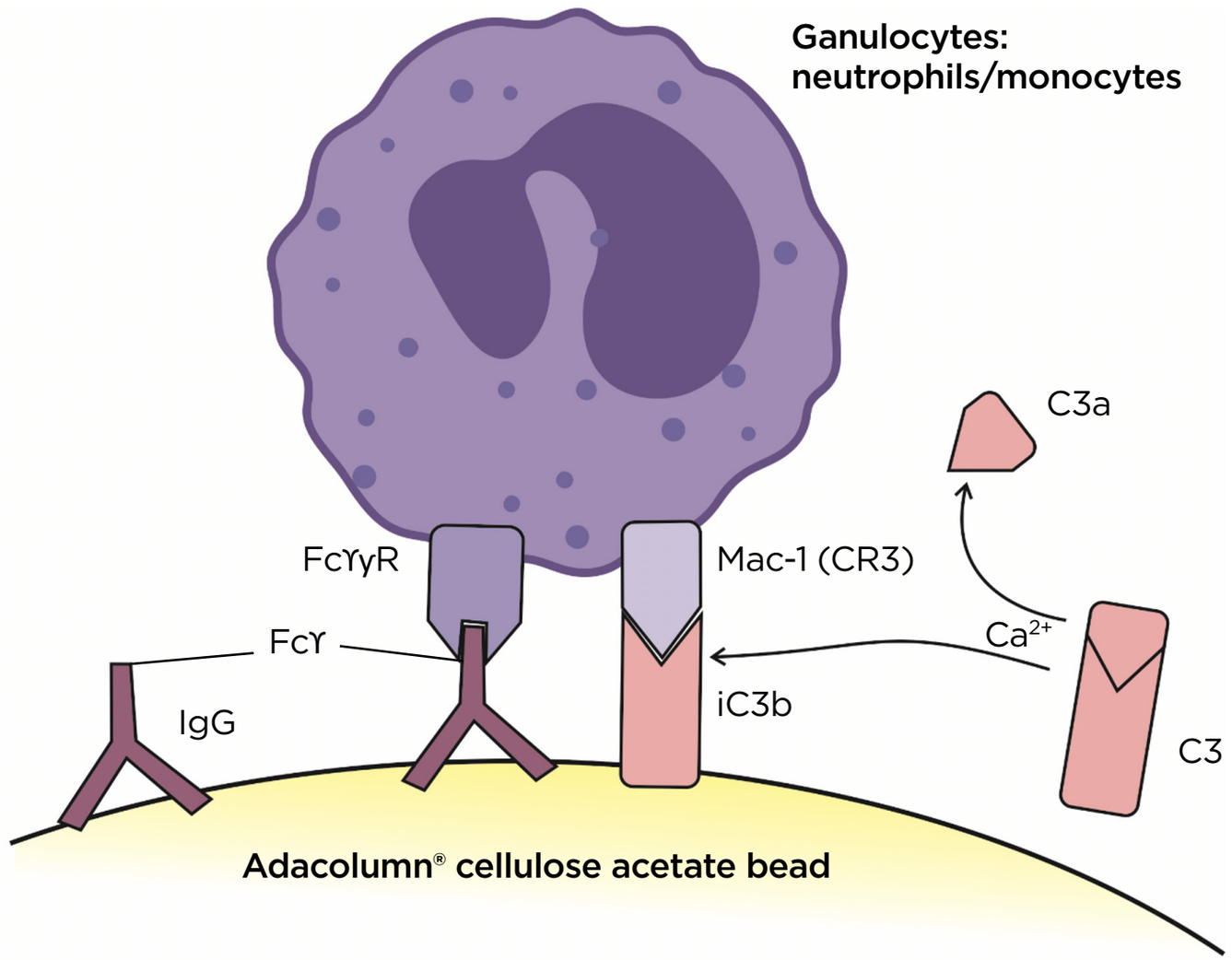
2. What is Adacolumn and how does it work?

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



Adacolumn® mechanism of action on the immune system

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2. What is Adacolumn and how does it work?

Clinical studies have demonstrated that through this procedure, a 55-65% reduction in circulating granulocytes and monocytes/macrophages occurs.[1,2]

Given the central role of these cells in the activation and perpetuation of the inflammatory response in the intestinal mucosa, there is a consequent decrease in proinflammatory monocytes and cytokines and an increase in anti-inflammatory cytokines, CD10- leukocytes, and regulatory T cells.[1] Overall, **these effects contribute to a reduction in inflammatory activity at both systemic and mucosa levels**.

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3. What is the rationale for its use in IBD?

Neutrophils and monocytes/macrophages play a central role in the physiopathology of IBD. Specifically, in ulcerative colitis they appear to perform a direct role in lesion of the mucosa, which incidentally, is represented by the fact that the degree of infiltration of these cells is used in several histological scores to determine severity. The presence of neutrophils in colon biopsies is associated with a greater risk of recurrence and faecal calprotectin, a faecal biomarker of disease activity, is produced almost exclusively by the neutrophils, correlating with the degree of infiltration of these cells in the mucosa. Thus, **modulation of neutrophil activity in the mucosa appears to be an attractive therapeutic target, although no pharmacological treatment is currently directed specifically at these cells**.

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4. What does the treatment consist of?

The usual treatment consists of 5-10 apheresis sessions performed over 5-10 consecutive weeks, i.e. once a week. However, there are situations in which more intense treatment (2 sessions per week) may be advisable to increase therapeutic effectiveness. Leukocyte apheresis functions by means of an extracorporeal circulation system. To that end, 2 venous accesses are obtained that are connected to a closed circuit such that the blood passes through the column and is filtered, removing the granulocytes and monocytes. Each session can last from 60 to 90 minutes, with a total of around 1800 to 2700 mL of blood being processed.

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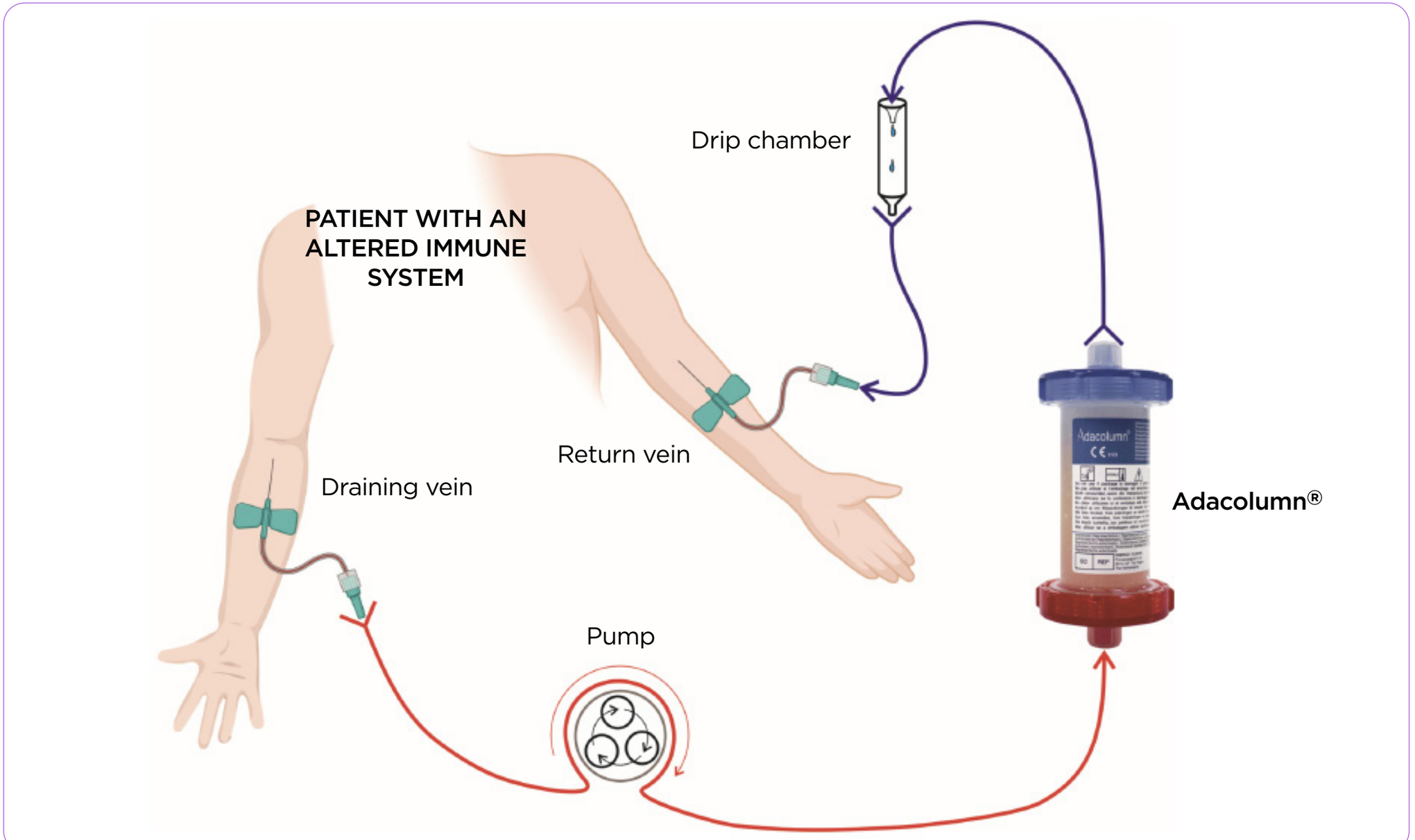
4. What does the treatment consist of?

Granulocyte/monocyte apheresis circuit



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5. What are the data on clinical effectiveness?

Although there is limited experience with the use of Adacolumn® in Portugal, this device has been widely used in Japan, Germany, France, Sweden and Spain, among other European countries.

Several clinical studies have been conducted, sometimes with contradictory results.

A meta-analysis of randomized controlled studies that compared the use of Adacolumn® versus corticosteroids to induce remission in patients with moderate to severe ulcerative colitis revealed that **Adacolumn® is effective in inducing clinical remission in ulcerative colitis patients (OR 2.23; 95% CI: 1.38–3.60), with a lower rate of adverse effects (OR 0.24; 95% CI: 0.15–0.37) in relation to corticosteroids**.[3] However, the high heterogeneity (I2 59%) stands out in relation to the inclusion of heterogeneous populations, the use of different regimes for performing apheresis, etc.

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5. What are the data on clinical effectiveness?

A **promising indication for the use of Adacolumn® is corticosteroid-dependent ulcerative colitis. The ART study [Adacolumn in Refractory UC Patients Trial]** was an open-label, multicentre study in which 86 patients with moderate to severe corticosteroid-dependent ulcerative colitis and insufficient response or intolerance to immunosuppressants or biological drug were submitted to weekly sessions of Adacolumn®, over 5 consecutive weeks (with a possible extension to 10 weekly treatments). After treatment with Adacolumn®, 39.3% [95% CI (28.8, 50.6)] achieved remission and 56.0% [95% CI 44.7, 66.8]) clinical response. Clinical remission was achieved in a median time of 43 days [95% CI: 29-63], while a clinical response was achieved in a median time of 24 days [95% CI: 20-34]. In week 12, it was confirmed that 22.6% and 35.7% of patients achieved remission and corticosteroid-free response, respectively, highlighting the corticosteroid-sparing effect. These results were also obtained in patients who had previously failed immunosuppressant or anti-TNF treatment.[4]

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6. What are the main side effects?

Leukocyte apheresis has an excellent safety profile. The fact that adsorption is selective leads to a selective reduction in neutrophils and monocytes/macrophages, without reaching the erythroid line or leading to a decrease in circulating lymphocytes. Depletion of granulocytes and monocytes/macrophages does not result in a higher risk of infection. Due to its excellent safety profile, it can be used in pregnant women and children.

The main difficulty in performing the technique may be related to obtaining adequate venous access, which occurs in a small number of patients. Side effects, such as hypertension, headache, low-grade fever, general malaise, and dizziness are rarely described; these side effects occur in <2% of patients and are temporary and self-limiting.

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7. Perspectives

Several questions remain concerning the use of Adacolumn®.

One of the most important questions relates to the ideal patient profile for the use of Adacolumn®. The patient with corticosteroid-dependent ulcerative colitis seems to be the best candidate for this therapy. The presence of deep ulcerations is a poor prognostic response factor (similar to what is observed with pharmacological treatment).[5] Its earlier use in the therapeutic algorithm is probably more advantageous. In patients who respond to the therapy, the benefit of keeping Adacolumn® as maintenance therapy, and the regimen indicated in this circumstance, remain unclear.

The **use of Adacolumn® in combination with other drugs** is still to be defined. Preliminary results of Adacolumn® in combination with Anti-TNF[6] vedolizumab,[7] ustekinumab,[8] and tofacitinib[9] point to promising results, but confirmation is needed in larger studies.

Experience with Crohn's disease is also more limited than with ulcerative colitis. Some open-label studies in patients with refractory Crohn's disease have shown promising results,[10] but one randomised controlled study did not report any clinical benefits.[11]

Adacolumn® mechanism of action on the immune system

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