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CASE SERIES

Granulocyte and monocyte/macrophage apheresis in paediatric patients with ulcerative colitis: a case series in Spain

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Abstract

Paediatric ulcerative colitis (UC) can cause malnutrition and growth retardation but its treatment can be limited by the potential adverse events of corticosteroids and anti-TNF agents in children. However, adsorptive granulocyte monocyte/macrophage apheresis (GMA) using Adacolumn® reduces intestinal inflammation through multiple immunomodulatory effects. This case series shows the safety and efficacy of GMA in paediatric UC, illustrating several GMA uses: in chronically active UC, for corticosteroid reduction in steroid-dependent UC, in UC with secondary loss of response to anti-TNF therapy, as bridge therapy in UC with failure of anti-TNF therapy, and to substitute toxic drug treatments.

Keywords: adolescent, azathioprine, child, corticosteroids, granulocyte-monocyte apheresis, leukocytapheresis, paediatric ulcerative colitis, tumour necrosis factor inhibitors.

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Introduction

Ulcerative colitis (UC) is a chronic debilitating inflammatory disease of unknown aetiology that has an intermittent course with remissions and relapses.[1] The incidence of paediatric UC is increasing all over Europe,[2,3] with an annual incidence of up to 15.0 per 100,000 persons.[2] In Spain, data from the SPIRIT registry showed that the incidence of paediatric UC duplicated within 14 years (between 1996 and 2009), from 0.39 to 0.88 per 100,000 persons.[4] The prevalence of the disease in Europe ranges between 8.3 and approximately 30 per 100,000 persons depending on the different European countries.[3]

Presentation of UC in children can be atypical, with features different from those seen in adults.[5,6] In addition, UC in children can cause malnutrition, growth retardation (more common in Crohn's disease) and delayed puberty by the effects of inflammation on hormone pathways or on the growth plate of long bones.[7] Therefore, it is of the utmost importance to control the disease and to achieve mucosal healing.[7] UC management in children also has some particularities, especially in the use of corticosteroids and anti-TNF agents. Corticosteroids can impair growth,[7] whilst the long-term safety of anti-TNF agents is poorly known, including the potential risk of infections and malignancies.[8] Generally, effective drugs for the treatment of paediatric UC can induce adverse effects that limit their use.[9]

The granulocyte monocyte/macrophage apheresis

An effective alternative to drug therapy in paediatric UC can be the adsorptive granulocyte monocyte/macrophage apheresis (GMA)[9,10] using Adacolumn*. It is a Class IIb medical device licensed in Europe for the treatment of inflammatory bowel disease (IBD) (both Crohn's disease and UC) and other inflammatory and immune diseases.[11] The device is basically a polycarbonate column with a capacity of 335 mL that contains 220 g of 2 mm cellulose acetate beads in 130 mL sterile saline.[11] Patient blood passes through the column, where two mechanisms occur. One mechanism is the linking of blood immunoglobulin G (IgG) or immunocomplexes as well as complement iC3b to the bead surface. The other mechanism is the retention of myeloid lineage cells (granulocytes and activated monocytes) that are elevated and potentially

*Adacolumn is a registered trademark of JIMRO Co. Ltd., Takasaki, Japan/Adacyte Therapeutics, Sant Cugat del Vallés, Barcelona, Spain.

activated: these cells express Fcγ receptors or complement receptors that bind to IgG or iC3b, respectively. As a result, the column retains granulocytes (65%) and activated monocytes (35%, with more than 50% being macrophages),[12,13] thus reducing intestinal inflammation.[10] Blood is then reinfused to the patient.

GMA has different immunomodulatory effects apart from the depletion of pro-inflammatory monocytes and neutrophils; amongst the currently known effects are the decrease in plasma cytokine levels, the modification of leukocyte morphology (surface receptors), the induction of myeloid-derived suppressor cells that reduce inflammatory responses and the induction of regulatory T and B cells.[14] GMA has long-term anti-inflammatory effects, probably mediated by IL-10-producing regulatory B cells.[15] Figure 1 summarizes the different phenomena that are involved in the GMA mode of action.[16]

According to the results of many studies in adult patients, GMA is effective and safe for the treatment of moderate to severe UC. It is especially useful in patients that do not respond to or are dependent on corticosteroids because GMA can help their tapering or withdrawal.[17] GMA is also effective after the loss of response to immunosuppressants[18] or anti-TNF agents.[19] Experience with GMA in paediatric UC is not as extensive as in adult patients. However, several studies have suggested that GMA can be effective and safe in children and adolescents with IBD and especially in UC.[20–26] In our experience, the benefits of GMA can be particularly evident in some situations (Box 1). In addition, GMA in UC with extraintestinal manifestations has been found useful in adult patients,[27,28] but no experience in children is available.

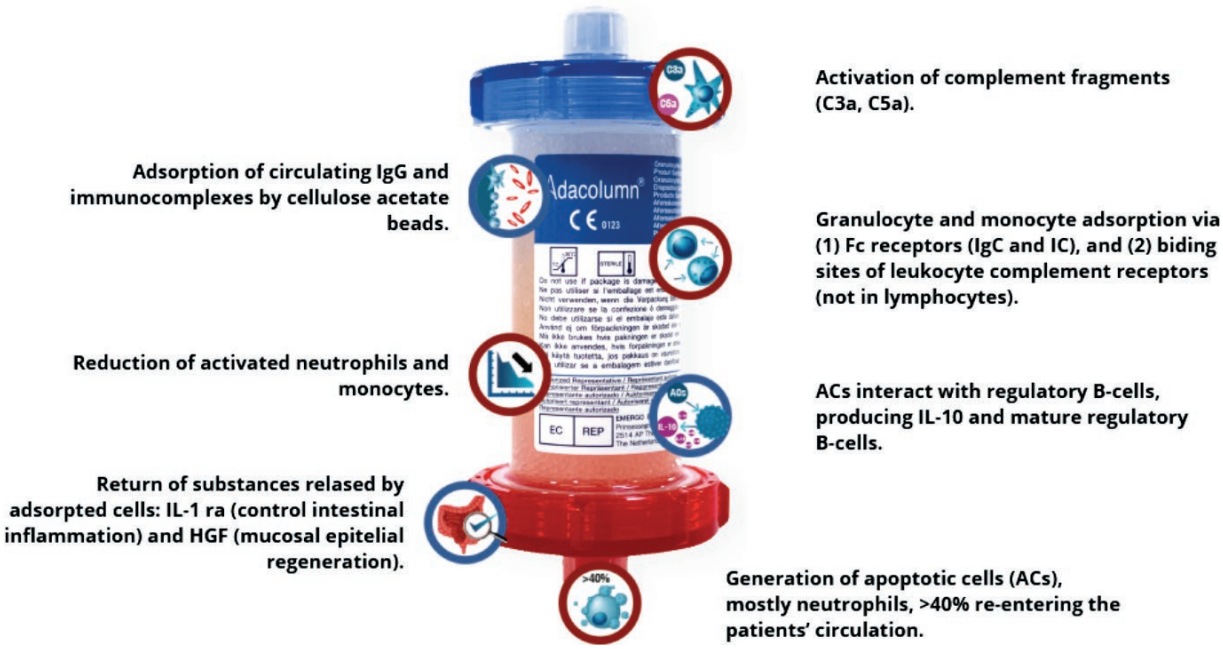
A case series is presented below to illustrate the use and benefits of GMA in paediatric patients with UC managed in the San Joan de Déu Hospital, Barcelona, Spain. Case reports have been totally anonymized to hide patients' identities; therefore, signed patient consent was not required.

Case series

Case 1. GMA in chronically active UC

A 9-year-old male patient was diagnosed with UC involving the entire colon. Induction therapy with intravenous (IV) methylprednisolone was started and the patient evolved favourably. Treatment was changed to oral corticosteroids, with progressive tapering, and then azathioprine (AZA) was initiated as maintenance therapy. After 14 months, the patient had several episodes of rectal bleeding; although he was in good condition, he had a slight increase of acute-phase reactants. These episodes were successfully treated by adding oral and/or rectal 5-aminosalicylic acid (5-ASA). However, symptoms reappeared after changing back to AZA monotherapy.[29]

Figure 1. Mode of action of adsorptive granulocyte monocyte/macrophage apheresis (GMA).[16] Reproduced with permission from www.adacyte.com



AC, apoptotic cell; C, complement; Fc, fragment crystallizable region; HGF, hepatocyte growth factor; Ig, immunoglobulin.

Box 1. GMA in paediatric UC. Based on authors' opinions.

- Chronically active ulcerative colitis (UC)
- Steroid-dependent UC
- UC with secondary loss of response to an anti-TNF agent
- UC with failure to an anti-TNF agent (bridge therapy)
- UC with toxicity of efficacious maintenance treatments
- UC with extraintestinal manifestations

After 2 years of chronically active UC treated with AZA and 5-ASA, a colonoscopy showed moderately active extensive UC. Two therapeutic options were considered: infliximab *versus* GMA. Because of the maintained clinical situation, it was decided to start with weekly GMA for 5 weeks and then a GMA session every 8 weeks as maintenance therapy. Dose of 5-ASA could be reduced after the third session and the drug was discontinued after the fifth session. A colonoscopy after the tenth maintenance session showed complete endoscopic and histological remission. The patient received AZA monotherapy but, at 8 months, GMA was added again due to recurrence of bleeding episodes. GMA was always well tolerated and no adverse events were reported. The patient was on remission with AZA plus GMA until his referral to the adult gastroenterology service.[29]

Use of GMA in paediatric corticosteroid-resistant UC has been reported by other authors. Thus, an 8-year-old female patient, who had UC resistant to corticosteroids, infliximab and cyclosporine A, received six GMA sessions within 2 weeks. GMA results allowed the avoidance of colectomy.[30]

This case shows the usefulness of adjunctive therapy with GMA in children with chronically active UC, as shown in other cases in the literature.[31] In patients already on different treatments in whom the activity of the disease remains, adjunctive GMA can add a beneficial effect without increasing adverse events or complications of other therapies.

Case 2. GMA for corticosteroid reduction in steroid-dependent UC

A 16-year-old female patient presented with a 4-week history of episodes of rectal bleeding. Findings in colonoscopy were compatible with UC with rectal preservation. Her disease was controlled with oral and/or rectal 5-ASA. After 4 months of 5-ASA monotherapy (2 g/d), she had an episode of diarrhoea and rectal bleeding that did not improve with adding topical therapy or with changing to prolonged-release mesalamine (4.8 g/d). The colonoscopy showed moderately active pancolitis. Beclomethasone dipropionate (10 mg/d) was added, but the response was not complete and important cosmetic adverse events occurred (cushingoid facies, truncal obesity and purple striae).

The therapeutic strategy was to initiate systemic corticosteroids and to concomitantly (apart from starting AZA) administer 10 sessions of GMA (2 sessions/week) to facilitate posterior corticosteroid tapering. Response to systemic corticosteroid was good; after the fifth GMA session, the corticosteroid dose began to be reduced. Corticosteroid tapering was well tolerated. Moreover, oral and topical 5-ASAs were progressively reduced. GMA was safe and well tolerated, with no adverse events.

One month after the last GMA session, corticosteroids were withdrawn and the patient was treated with AZA monotherapy until transition to an adult IBD unit 10 months later.

Use of GMA in paediatric corticosteroid-dependent UC has been reported by other authors. In 23 patients aged 8–16 years with moderate-to-severe steroid-resistant UC, GMA was effective and corticosteroid dose was reduced from 1.1 ± 0.4 mg/kg to 0.8 ± 0.5 mg/kg.[32] In 25 patients aged between 8 and 17 years with moderate active UC, corticosteroid dose decreased from a mean 12.4 mg/d to 10 mg/d after GMA therapy.[26]

Steroid dependency can be a problem in UC, especially in children, in whom long treatment with steroids can have severe adverse effects on growth and sexual maturation. Steroid-sparing treatments as GMA must be used in the paediatric population in order to avoid these effects.

Case 3. GMA in UC with secondary loss of response to anti-TNF agents

This case has been previously presented in the literature as a clinical case.[33] A female patient was diagnosed with IBD-unclassified at 13 years of age. Two years later, she presented with a flare-up that was treated with oral prednisone (1 mg/kg/d). After upper and lower endoscopy and an image study, the diagnosis of ulcerative colitis was confirmed. As the patient became dependent on steroids, adalimumab was initiated. However, coinciding with the third induction dose, she had a severe flare-up. She then received IV methylprednisolone, cefotaxime and metronidazole in addition to adenosine deaminase (ADA) at increased doses. Furthermore, GMA was started.

After five GMA sessions, clinical remission and a decrease of faecal calprotectin level from 2376 to 107 µg/g were seen. GMA was continued until achieving serum ADA levels of 8–12 mg/L. In addition, corticosteroids could be tapered from the second session. Three months after the last GMA session, clinical and analytical remission was maintained and the patient received ADA (80 mg every 2 weeks) but no corticosteroids.[33] No GMA adverse events were reported.

Box 2. Clinical scenarios where granulocyte monocyte/macrophage apheresis should be considered. Based on Ito et al.,[38] Rodríguez-Lago et al.,[19] Maiden et al.,[39] and Domènech et al.[1]

- Corticosteroid-dependent inflammatory bowel disease
- Previous or as bridging therapy to immunomodulators
- Patients with a previous failure of thiopurines or anti-TNF agents
- Maintenance or prevention of relapse
- Paediatric inflammatory bowel disease
- Frail patients (elderly, patients with comorbidities such as cancer, infections and heart failure)
- Combination with biologics:
  - Partial response
  - Loss of response
  - Concomitant
- Partial response to corticosteroids
- Patients at risk:
  - Frequent relapsers
  - Early need for steroids

This case is an example of GMA use to induce remission and recover the previous efficacy of other therapies such as an anti-TNF agent.

Case 4. GMA as bridge therapy in UC with failure to anti-TNF agents

A 15-year-old male patient was hospitalized to assess 2-week mucous bloody stools. Colonoscopy showed images of ulcerative pancolitis and IV corticosteroid therapy was initiated. However, the patient did not improve. Fifteen days later, another colonoscopy showed active disease and associated cytomegalovirus infection. Despite treatment with antiviral drugs and disappearance of cytomegalovirus, active disease remained. Infliximab (10 mg/kg, at accelerated schedule) was then started. Maintenance treatment was composed of infliximab (10 mg/kg every 4 weeks), AZA, and oral and rectal 5-ASA. However, faecal calprotectin levels intermittently increased. Eleven months after UC diagnosis, active colitis was present in a new colonoscopy. Treatment with vedolizumab (VDZ) and GMA sessions as bridging therapy were initiated. The patient experienced a good response to combined treatment, and seven months later, faecal calprotectin level was between normal ranges. After 12 months of VDZ and GMA initiation, the patient is currently doing well with scheduled VDZ and GMA sessions every 2 months. GMA has been safe and well tolerated.

There is no published experience in paediatric patients with UC treated with GMA as bridge therapy to VDZ. However, GMA has been useful in adult patients with UC and inadequate response to VDZ. In eight adult patients with UC, with primary or secondary loss of response to VDZ, and previously treated with anti-TNF agents, partial Mayo score improved after 1 and 6 months of combining GMA and VDZ.[34] In another adult patient with refractory UC and no response to VDZ, clinical remission was achieved with the combination of GMA and VDZ.[35]

Paediatric patients with failure of induction treatment are at special risk of clinical deterioration before the full effect of second-line therapies is achieved. Bridging therapy with GMA can help to shorten the time lapse before the therapeutic effect of drugs with a slow onset of action such as VDZ.

Cases 5 and 6. Use of GMA with efficacious but toxic UC treatments

Case 5 corresponds to a 13-year-old female patient diagnosed with pancolitis and treated initially with corticosteroids. During treatment with steroids, cosmetic adverse effects were important and provoked anxiety, irritability and depression. After corticosteroid withdrawal, she was maintained on 5-ASA and AZA with maintenance of remission. However, 10 months after steroid cessation, the patient had a serious primary infection by Epstein–Barr virus and she had to be hospitalized for a long period, treated with antiviral treatment, and AZA was stopped. After discharge, the patient received oral and topical 5-ASA monotherapy. Faecal calprotectin was steadily increasing during follow-up, but the patient and her family were reluctant to try other treatments due to safety concerns. GMA was then proposed and accepted. The administration schedule was 1 session/week for 5 weeks, 1 session/month until 12 months, and thereafter 1 session/2 months. GMA treatment was administered for 2.5 years, until transition to adult care. During this time, faecal calprotectin levels were maintained between normal ranges and no GMA adverse events were reported.

Case 6 is a female patient that was diagnosed with UC at 5 years of age. Compliance was low until the patient was withdrawn from therapy and was lost to follow-up. In 2017, when she

was 12, she presented with moderate pancolitis that resolved with IV corticosteroids and 5-ASA. She was then treated with AZA and 5-ASA but compliance was irregular due to periods of emotional instability. In October 2018, AZA was substituted by mercaptopurine because of digestive intolerance. In March 2019, she had severe leukopenia (1.6×10^9/L) with neutropenia (0.5×10^9/L) and mercaptopurine was discontinued. As UC remained moderately active despite 5-ASA monotherapy, GMA was initiated. At first, GMA sessions were monthly for 1 year but they were bimonthly afterwards. Later, the patient was withdrawn from 5-ASA. Clinical and analytical UC remission was apparent from the first GMA session and maintained during the follow-up. In May 2021, after 2 years of GMA therapy, the patient reached the age of 18 and she was referred to an adult IBD unit. GMA compliance was good, as the therapy was administered at the hospital. Furthermore, no adverse events were reported throughout GMA therapy.

These two cases are of special interest because to our knowledge, there is no published literature on the efficacy of GMA as maintenance therapy in patients with previous complicated UC (i.e. need of systemic steroids to control the disease) in whom maintenance therapy with immunosuppressants has been stopped due to severe adverse effects. These patients are quite challenging because they are at high risk of UC relapse. Therefore, to initiate an effective therapy with a good safety profile, especially after discontinuing a previous treatment by a severe adverse effect, it is of extreme importance and well accepted by the patients and their families.

Conclusions

Patients with UC will require life-long treatment and therefore adverse events, secondary loss of response and drug dependence can occur at some time during their lifetime.[10] Hence, a non-pharmacological therapy such as GMA has its place in the treatment of UC in children and adolescents. In adult patients, GMA is used in IBD, mainly in UC treatment[36] but also in Crohn's disease[36] as well as in rheumatoid arthritis,[37] arthropathies and dermatological diseases such as psoriasis.[36] There is a series of clinical scenarios where GMA should be considered (Box 2).[1,19,38,39]

As expected by the results of clinical studies, GMA was found to be effective in the paediatric patients with UC included in this case series. In addition, no adverse events were reported, and the technique was well accepted by patients and their families. According to the experience in children and adolescents, this technique should be preferably used in specific profiles of patients. Finally, GMA should be part of an individualized approach to UC treatment, with an assessment of UC features, clinical status and preferences for each patient.

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