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Anti-Integrins, Anti-Interleukin 12/23p40, and JAK Inhibitors for the Inflammatory Bowel Disease Treatment

Karine Mariane Steigleder, Fernando Lopes Ponte Neto, Cristiane Kibune Nagasako and Raquel Franco Leal

Abstract

Inflammatory bowel diseases (IBD) present a broad inflammatory cascade that is sometimes difficult to control. Patients with ulcerative colitis (UC) and Crohn's disease (CD) are exposed to intense and harmful effects that compromise their quality of life. There is a constant need for new classes of drugs that act on different fronts of inflammation control. Initially, biologics revolutionized inflammatory bowel disease treatment. Anti-tumor necrosis factor (anti-TNF) agents and infliximab, followed by adalimumab and certolizumab pegol, have been proven to induce clinical and endoscopic remission. However, some patients are primary nonresponders, and a significant proportion of initial responders lose response throughout the treatment. The emergence of new therapies, such as anti-integrins, anti-interleukins, and inhibitors of Janus kinase (JAK), can become an alternative option for patients with previous therapeutic failures, besides offering greater safety than other biological therapies up to now. Among anti-integrins, vedolizumab is the drug with proven efficacy in both induction and maintenance of remission and has local and selective action in the intestine. Ustekinumab represents the group of anti-interleukins, acting to control interleukin-12 (IL12) and interleukin-23 (IL23). JAK inhibitors (tofacitinib) act on intracellular inflammatory mediators and have the advantage of being orally administered.

Keywords: ulcerative colitis, Crohn's disease, vedolizumab, ustekinumab, tofacitinib

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the main inflammatory bowel diseases (IBD) [1]. Inappropriate inflammatory response is multifactorial and involves environmental, genetic, immune-mediated, and gut microbial factors [2].

IBDs were previously more prevalent in North America, Europe, and Oceania, but since 1990 the incidence rate is stable or decreasing in those areas. In contrast, increasing incidence was observed in developing regions, such as Latin and South America, Asia, and Africa, making it a rising global disease [3].

For years, the therapeutic management of IBD has been restricted to local action medications with mild anti-inflammatory power, such as amino salicylates and corticosteroids. Adverse effects of prolonged use of corticosteroids include infections, diabetes, osteoporosis, cataracts, metabolic syndrome, and esthetic changes that further raise morbidity and mortality [4].

Immunomodulators initially used in rheumatologic conditions have also been applied in IBD treatment. Thiopurines (azathioprine and 6-mercaptopurines) and methotrexate were widely used against both UC and CD, but these medications alone failed to induce and maintain clinical and endoscopic remission in a significant percentage of cases. Failure to control the disease increases the risk of complications, like strictures, abscesses, fistulas, and the need for surgical approaches. Additionally, worse quality of life and an increase in clinical complications like anemia and malnutrition [5] may occur.

The therapeutic revolution of IBDs began with biological therapy containing anti-tumor necrosis factor (anti-TNF) agents such as infliximab, which was widely used in the management of rheumatologic, dermatological, and inflammatory bowel diseases. Subsequently, other drugs of the same class emerged, such as adalimumab, a fully human monoclonal antibody, and certolizumab, which does not have the Fc portion, making it less immunogenic [5].

Anti-TNF treatment (alone or in combination with immunomodulators) can induce clinical and endoscopic remission. However, only 10–30% will have a primary no-response, and over 50% will, after an initial response, have a secondary loss [6].

New classes of immunobiological therapies are available to treat patients with loss of response to anti-TNF treatment, since the response to a second anti-TNF is low [4, 5]. Integrins and interleukins are the main targets of the available drugs to treat IBD. They act on receptors of cells involved in the inflammatory process and on proinflammatory cytokines, respectively. Furthermore, the intracellular inhibition of kinases by JAK inhibitors acts on intracellular inflammatory mediators. Each of these action pathways will be detailed in this chapter.

2. Anti-integrins and anti-interleukin 12/23p40

2.1 Anti-integrins

Integrins are cell surface glycoprotein receptors that play a role in leukocyte adhesion, signaling, proliferation, and migration [7]. Migration of circulating leukocytes from blood to intestinal tissue is a key step for intestinal inflammation. $\alpha 4\beta 7$ integrin expressed on the surface of the leukocyte binds to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) expressed on endothelial cells. Anti-integrin blocks the action of integrins, inhibiting leukocyte trafficking from the systemic circulation to the gastrointestinal endothelial cells [8].

Natalizumab is a chimeric recombinant human IgG4 antibody that blocks the $\alpha 4$ subunits in $\alpha 4\beta 7$ and $\alpha 4\beta 1$ integrins on leukocytes, inhibits binding to vascular cell adhesion molecule 1 (VCAM-1), and decreases inflammatory cells in affected gastrointestinal tissue, contributing to induction and maintenance of remission in CD [9]. Natalizumab also blocks lymphocyte infiltration in the central nervous system and is also approved for multiple sclerosis treatment [10]. However, association with progressive multifocal leukoencephalopathy (PML), a rare disabling and potentially fatal neurological syndrome caused by reactivation of the John Cunningham virus (JCV), has limited its use in treating CD patients [11].

Etrolizumab is a humanized IgG1 monoclonal antibody against the $\beta 7$ subunit of the $\alpha 4\beta 7$ and $\alpha E\beta 7$ integrins that blocks binding to MAdCAM-1 and E-cadherin, respectively [12]. Still under study, it is not part of the IBD therapeutic arsenal, and studies failed to demonstrate an advantage when compared to placebo [13].

Vedolizumab is an anti-integrin currently used to treat IBD. It is a humanized monoclonal antibody composed of two light chains of kappa subclass and two heavy chains linked by two disulfide bridges, which form an immunoglobulin that targets $\alpha 4\beta 7$ integrin, selectively blocking gut lymphocyte trafficking [14]. Its inhibitory effect on T-lymphocyte recruitment is reversible with its suspension. Renal elimination occurs after drug degradation into peptides and amino acids in the liver. The drug half-life was estimated at 25.5 days, being the potential predictors of poor response to therapy: albumin < 3.2 g/dl and weight > 120 kg [15].

The currently recommended dosage is 300 mg vedolizumab with intravenous administration at weeks 0, 2, and 6 and then every 8 weeks. The interval can be shortened to every 4 weeks when the patient's response is not satisfactory [15].

Studies showed no difference in serious adverse events resulting in death, life-threatening conditions, hospitalization, or disability, comparing vedolizumab and placebo [14]. However, possible adverse events can occur such as nasopharyngitis, headache, arthralgia, and other less uncommon events. Among the contraindications, we can highlight the presence of active infections, such as tuberculosis, sepsis, cytomegalovirus, listerioses, and opportunistic infections such as PML [16, 17].

There are no controlled studies of vedolizumab during pregnancy and breastfeeding, and current data are based on observational cases. FDA classified this drug as category B, being safe for use in pregnancy. During breastfeeding, caution is required because it is not known if the medication is transferred to the newborn [4].

In 2013, the randomized, double-blind, placebo-controlled phase 3, GEMINI I study showed the efficacy of vedolizumab in induction and maintenance of remission in patients with UC. For induction, a 300 mg-day intravenous dose repeated at 15 days was used. For maintenance, both groups received the medication after 4 or 8 weeks; therapeutic serum levels were obtained with 95% saturation of the $\alpha 4\beta 7$ receptor and proven clinical remission for 52 weeks. The intestinal selectivity of vedolizumab gives the drug greater safety, especially in countries with a marked presence of mycobacteria. No cases of PML were documented during the GEMINI I study [14].

Also, in 2013, the GEMINI II placebo-controlled, randomized, double-blind, phase 3 study evaluated induction and maintenance remission in patients with moderately to severely active CD for 4 years in 39 countries. The study analyzed patients aged 18–80 years, diagnosed for at least 3 years, with active CD. Compared to placebo, patients treated with vedolizumab had better response in both induction and remission maintenance at week 52. The rates were discrete and may be justified by patient selection bias, since a significant part of the group had severe disease, difficult to control and refractory to anti-TNF treatment [18].

Of the 1434 patients who used vedolizumab for 52 weeks evaluated in the GEMINI I and GEMINI II studies, 56 (4%) had anti-drug antibodies, of which only 9 (0.6%) had persistent positivity after two or more consecutive dosages. Immunogenicity increases with exposure time reaching 10% at week 66. However, it is believed that the presence of antibodies in low to moderate-titer does not affect drug response, as therapeutic failure occurred in only nine patients and elevated antibody levels were maintained for a prolonged period [15].

In 2014, Sands et al. (GEMINI III) evaluated the response of vedolizumab in patients with previous anti-TNF treatment. The study showed an advantage of

anti-integrin when compared to placebo only after 10 weeks, concluding that in patients who fail anti-TNF treatment, longer time is required to achieve clinical remission with vedolizumab [16].

The VARSITY study presented in 2019 was the first study that compared two biological drugs (vedolizumab and adalimumab). The randomized, double-blind phase 3 study evaluated clinical and endoscopic response at week 52 in patients with moderate-to-severe active UC treated with standard drug doses. Vedolizumab was more effective in inducing clinical remission and mucosal healing. There was no statistically significant difference between the drugs when the outcome evaluated was steroid-free remission. Both drugs were safe and well tolerated for treatment of moderate-to-severe UC [19].

No studies compared the efficacy of different biological agents in patients with CD.

2.2 Anti-interleukin 12/23p40

IBD presents a large infiltration of leukocytes, especially T lymphocytes. When activated, these cells produce a high concentration of cytokines that have an important role in the inflammatory process of the disease [20]. However, there seems to be a distinction in the profile of cytokines produced in CD and UC. While in CD there is a predominant synthesis of type 1 helper T-cell (Th1) cytokines, such as interferon- γ (IFN- γ) and TNF- α ; in UC, Th2 cytokines, such as interleukin-5 and interleukin-13, are more relevant [20, 21].

CD mucosa has an increased production of interleukin-12 (IL-12), a pro-inflammatory cytokine that induces IFN- γ production and promotes Th1 cell differentiation [22, 23]. IL-12 is a heterodimeric cytokine produced by macrophages, monocytes, and dendritic cells, with two covalently linked subunits: p40 and p35 [23].

The IL-12p40 subunit can be combined with another cytokine, derived of IL-6 subfamily structures, the p19 protein, to form the p19p40 complex, also nowed like interleukin-23 cytokine (IL-23) [24]. The natural function of IL-23 is to coordinate inflammatory responses within peripheral tissues. However, unregulated expression of IL-23 may promote detrimental immune pathology at these sites [25]. In IBD, IL-23 may play the role of initiating and perpetuating innate T cell-mediated intestinal inflammation [26], thus leaving the place to IL-12/IFN- γ /T-cell pathway in the late phase [20].

A systematic review published by MacDonald et al. evaluated the use of ustekinumab (CNTO 1275) and briakinumab (ABT-874), monoclonal antibodies that target the standard p40 subunit of the cytokines IL-12 and IL-23 (IL-12/23p40), in patients with CD [27]. In this review two studies that compared briakinumab to placebo and four studies that compared ustekinumab to placebo were analyzed.

In 2004, Mannon et al. investigated two different doses of briakinumab. This was a multisite, randomized, double-blind, placebo-controlled study where 79 CD patients received 1 or 3 mg of anti-IL-12p40 monoclonal antibody subcutaneous injections versus placebo. The results showed that the use of anti-IL-12p40 might induce clinical responses and remissions in patients with active CD, with responses in 75% of CD patients compared with 25% in the placebo group. These results were associated with decreases in Th1-mediated inflammatory cytokines (IFN- γ and TNF- α) at the site of disease. There were no significant differences in the rate of adverse effects between placebo and anti-IL-12, except a higher rate of local reactions at injection sites in the former group [28].

The other study testing the use of briakinumab was published in 2015 and evaluated the efficacy and safety of this drug [29]. This was a phase 2b, multicenter,

double-blind, parallel group study, conducted with 246 patients with moderate-to-severe CD stratified by prior TNF- α antagonist use and response to anti-TNF- α therapy, who were randomly given placebo and 200, 400, or 700 mg briakinumab over the period of 0, 4, and 8 weeks. On week 12, patients who got clinical response in the placebo or 400-mg induction groups proceeded to the maintenance phase with the same protocol. Those who responded clinically with 700 mg were randomized to receive placebo and 200 or 700 mg briakinumab at weeks 12, 16, and 20 during the maintenance phase. Patients in remission stopped receiving the study drug at week 24. During the induction and maintenance phase of this study, briakinumab was well tolerated and had a safety profile similar to placebo. However, the authors pointed out that infusion reactions were observed in a higher percentage of patients treated with briakinumab than placebo during the induction phase (up to week 12). After week 12, adverse events and severe reactions occurred at a higher rate, mainly due to the increase in serious infusion reactions. The sponsor stopped the study during the open-label phase due to poor induction of remission results.

These investigations did not find severe side effects comparing briakinumab and placebo. However, there were common reactions to the site of injection and some secondary infections produced by briakinumab therapy. Due to these results, the production of briakinumab was interrupted [27].

Sandborn et al. conducted a phase IIa study of ustekinumab comparing clinical effects to placebo [30]. They made a double-blind, crossover design with 104 patients with moderate-to-severe CD, including both TNF- α antagonist naive patients and those who had previously failed one or more of these agents. These patients were divided into four groups: two groups received subcutaneous treatment doses, of which one group received placebo at weeks 0–3 and then 90 mg ustekinumab at weeks 8–11, while the other group received 90 mg ustekinumab at weeks 0–3 and then placebo at weeks 8–11. The other two groups followed the same weekly protocol, but the pathway was intravenous, and the dose was 4.5 mg/kg ustekinumab. Furthermore, a sub study like open-label trial evaluated the effects of four weekly subcutaneous injections of 90 mg or one intravenous infusion of 4.5 mg/kg ustekinumab in 27 patients who were primary or secondary nonresponders to infliximab, but it was not placebo-controlled. They showed that ustekinumab induced a clinical response in CD patients, who were previously treated infliximab, with the best effect in weeks 4–6 [30].

In 2012, Sandborn et al. published another study that evaluated ustekinumab therapy in patients with moderate-to-severe CD which was resistant to anti-TNF- α . This was a double-blind, placebo-controlled phase 2b trial with 526 patients who were randomized to receive intravenous ustekinumab (1, 3, or 6 mg/kg) or placebo at week 0. After 6 weeks, the clinical response was measured, and 145 patients who responded to ustekinumab were randomized to receive subcutaneous injections of ustekinumab (90 mg) or placebo at weeks 8 and 16 in the maintenance phase. Patients who used ustekinumab as an induction therapy had a higher response than the placebo group but did not differ in remission. These patients, during the maintenance phase with ustekinumab administration, had a significant increase in response and remission rates when compared to placebo. It is noteworthy that some serious infections occurred during the study, which affected 7 patients (6 receiving ustekinumab) in the induction phase and 11 (4 receiving ustekinumab) in the maintenance phase [31].

According to MacDonald et al., strong evidence indicates that ustekinumab is efficient for remission induction and that it improves symptoms in patients with moderate-to-severe CD. Moderate- to high-quality evidence implies that the optimal dose of ustekinumab is 6 mg/kg [27].

In addition to the improvement in patients' clinical condition and symptomatology, positive responses were also observed in histological examinations of patients who used maintenance therapy with ustekinumab every 8 weeks [32]. When analyzing histological data from participants in phase 3 induction and maintenance studies, significant histological improvement was observed in patients receiving ustekinumab compared to placebo [32].

Indeed, in 2016, with phase III UNITI trial program's positive results [33], the US Food and Drug Administration (FDA) approved ustekinumab for the treatment of moderate-to-severe CD [34]. Although there is no increased risk of serious adverse events, further studies are needed to assess the long-term benefit of their use in patients with CD [27].

Recently a study was published evaluating the use of ustekinumab to treat patients with moderate-to-severe active UC who do not respond well or were unable to tolerate conventional treatment or biological therapies [35]. It was a randomized, double-blind, placebo-controlled phase 3 study. Patients receiving a single intravenous ustekinumab dose of 130 mg or 6 mg/kg body weight (320 and 322 patients respectively) achieved clinical remission, endoscopic healing, clinical response, and mucosal healing at week 8, significantly better than placebo. It has been shown to be effective not only for the treatment of CD but also for the induction and maintenance of remission in patients with moderate-to-severe UC [35].

Serious infections were the most common side effects in the ustekinumab studies [27]. The therapeutic target of this drug is the p40 subunit, and it is not selective for IL-12 or IL-23. IL-12 is known to mediate protective systemic antimicrobial immunity, so this immune suppression may be responsible for these secondary opportunistic infections [23].

Studies support the specific blockade of IL-23, for its blockade may be as effective as the blockade of both cytokines but may result in fewer infectious problems [26]. A recently published review study evaluated the use of two drugs as a specific antagonist of the p19 subunit [34]. Risankizumab and brazikumab are the first anti-IL23p19 whose results were positive in randomized placebo-controlled phase II study to induction and maintenance therapy for moderate-to-severe CD patients. This review showed that both adverse events and serious adverse events did not differ between the treated groups and placebo. These results were observed in phase II studies with risankizumab and brazikumab, to treat not only IBD but also psoriasis. Based on symptomatic, endoscopic, and positive biomarker results, as well as treatment safety and efficacy during phase II trials, phase III studies are ongoing. These studies will help answer questions about the optimal dosage of drugs and their action at other levels of CD involvement [34].

3. JAK inhibitors

Despite advances in the therapeutic arsenal of IBDs, significant numbers of patients do not achieve mucosal healing. Janus kinase (JAK) inhibitors already used in oncological, rheumatological, and dermatological disease treatment are being studied as a new therapeutic resource against IBDs.

Many cytokines involved in IBD act on the JAK/signal transducer and activator of transcription (STAT) cell signaling pathway, generating cellular responses through gene expression [36]. By binding to specific membrane receptors, cytokines activate JAK, which catalyzes the phosphorylation of the complex enabling STAT binding [37]. After phosphorylation, STATs dimerize, leave the receptor, and go to the cell nucleus to activate the transcription of the target gene [38].

Some JAKs, like JAK1, JAK2, and JAK3, play an important role in the growth, differentiation, and survival of immune system cells in general. Unlike the others, JAK3 is present in hematopoietic cells, acting mediated signaling pathways by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 [38]. According to Lovato et al., patients with CD have an overactivation of STAT3 and STAT4 in intestinal T cells [39]. Therefore, despite the importance in diverse cellular activities, changes in the JAK/STAT signaling pathways have been related to various immune disorders [38].

JAK inhibitors have been developed and are under clinical investigation to assess their ability to attenuate the inflammation process in UC [40]. Tofacitinib (CP-690,550), a first-class JAK360 inhibitor, works by inhibiting JAK1/JAK3 and has a lower side effect on JAK2 and TYK2 [41]. This JAK inhibitor was tested in clinical trials to verify its potential treatment for some immune system disorders, including CD and UC [42].

To test the efficacy of tofacitinib in UC, a double-blind, placebo-controlled, phase 2 trial study was conducted [40]. Patients with moderately to severely active UC (n = 194) randomly received placebo or tofacitinib at a dose of 0.5, 3, 10, or 15 mg twice daily for 8 weeks. Significant clinical remission (Mayo score ≤ 2 , with no subscore >1) at 8 weeks occurred in patients who received 10 mg (48%, $p < 0.001$) and 15 mg (41%, $p < 0.001$), compared with 10% in placebo group. Endoscopic remission at 8 weeks occurred in patients receiving 10 mg (30%, $p < 0.001$) and 15 mg (27%, $p < 0.001$), compared with 2% in placebo group.

OCTAVE Induction 1 and 2 were phase 3, randomized, double-blind, placebo-controlled studies in patients with moderately to severely active UC [43]. Patients randomly received tofacitinib (10 mg twice daily) or placebo for 8 weeks. In the OCTAVE Induction 1 (n = 598 patients), remission occurred in 18.5% of the patients in tofacitinib group and in 8.2% in placebo group ($p = 0.007$). In OCTAVE Induction 2 (n = 541 patients), remission occurred in 16.6 versus 3.6%, respectively ($p < 0.001$). According to the results, tofacitinib use showed remission induction after 8 weeks of use in patients with moderate-to-severe UC compared with placebo [43].

In OCTAVE sustain study, the rate of maintenance of clinical remission was evaluated. The patients with clinical response to induction therapy in OCTAVE Induction 1 and 2 were followed for 52 weeks. The patients were randomized into three groups (placebo, 10 mg and 5 mg, 2 times daily). The clinical remission at 52 weeks occurred in 34.3% (n = 68/198) of patients taking 5 mg; 40.6% (n = 80/197) with 10 mg; and 11.1% (n = 22/198) in the placebo group. The mucosal healing rate at 52 weeks was 37.4% (n = 74/198) in patients on 5 mg; 45.7% (n = 90/197) in those who used 10 mg; and 13.1% in the placebo group (26/198) [43].

In patients with CD, initial studies with JAK inhibitors have shown unsatisfactory results in inducing clinical and endoscopic remission of the disease. In a, multicenter, randomized, double-blind, placebo-controlled phase 2 study, patients with severe CD (CDAI between 220 and 450) were randomized to receive placebo or 1 mg, 5 mg, and 15 mg tofacitinib, twice daily for 4 weeks. Clinical response and remission were similar between both groups. However, this outcome could be associated with a selection bias in the control group [44].

Another multicenter phase IIb, randomized, double-blind, placebo-controlled study evaluated patients with moderate-to-severe CD. Patients were assigned randomly to receive placebo or tofacitinib 5 or 10 mg twice daily for 8 and 26 weeks. The rates of clinical response (decrease in CDAI ≥ 100 from baseline) and clinical remission (CDAI <150) at week 8 and 26 were not significantly different from the placebo [45].

In 2018, tofacitinib was the first JAK inhibitor to be approved by the US FDA and the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) to treat moderate-to-severe active UC. According to EMA it should be used in patients who have tried conventional therapy or biological agents and failed or did not progress positively.

There is another small molecule, still in the testing phase, which selectively acts on important specific pathways in UC and CD, thus limiting some of the side effects such as bacterial and viral infections [41].

Indeed, tofacitinib therapy in rheumatoid arthritis showed an increased risk of infection, including herpes zoster [46]. Herpes zoster infection, among others, was also observed in the OCTAVE study comparing the use of 10 mg tofacitinib with placebo [43]. Vaccination against herpes zoster is indicated 3–4 weeks before starting tofacitinib treatment as a preventive strategy [47].

The other most common adverse effects of using JAK inhibitors are influenza, rhinopharyngitis, arthralgia, and headache. Studies in patients with rheumatologic diseases and psoriasis have not shown increased cardiovascular risk in patients treated with tofacitinib [43], although there may be an increase in HDL and LDL cholesterol serum levels [40].

In a cohort analysis, including OCTAVE I and II and Sustain, with UC patients exposed to tofacitinib, 25 cases of pregnancy occurred, but no definitive conclusions about maternal and fetal risks, due to methodological limitations (absence of control group, retrospective study, and small number of cases) [48]. Further studies are needed to assess medication safety in pregnant women. It is not currently approved for pregnant and breastfeeding women [47, 48]. In addition, information provided by the manufacturer itself showed preclinical trials with rabbits and rats that showed a risk of fetal malformations with the use of tofacitinib but at doses 10 times higher than recommended for humans [Pfizer Inc. Xeljanz prescribes information, <http://labeling.pfizer.com/ShowLabeling.aspx?id=959> (2014, accessed July 13, 2019)] [47].

Vermeire et al. evaluated the efficacy of filgotinib, a kind of selective JAK1 inhibitor [49]. This search was a randomized, double-blinded, placebo-controlled phase II FITZROY study, with CD patients with moderate-to-severe activity. The patients received 200 mg filgotinib once daily or placebo for 10 weeks. As a result, the number of patients who received the drug and went into remission was much larger than that of those who received placebo after 10 weeks of treatment. This study showed the first evidence for potential clinical efficacy and safety of a selective JAK1 inhibitor for the treatment of active CD [49]. Filgotinib might represent a new oral treatment to induce remission in patients with CD, but a phase III study will still be necessary [42]. According to Soendergaard et al., a combined phase IIb/III randomized, placebo-controlled study with filgotinib for the treatment of moderate-to-severe UC (the SELECTION1 study) is ongoing.

4. Conclusion

Inflammatory bowel diseases have very complex pathophysiological mechanisms, which makes treatment difficult. Advances in research presented here show new possibilities for alternative treatments, some already approved by the FDA (ustekinumab and tofacitinib) and others still under investigation.

The study of these alternative biological therapies is very important to help treat severe CD and UC patients with previous therapeutic failures, who no longer respond to or have not adapted to conventional treatments.

Conflict of interest

The authors declare no conflict of interest.

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