Chapter

Inhibitors of Tumoral Necrosis Factor Alpha in Inflammatory Bowel Disease

Carlos Walter Sobrado, Natália Sousa Freitas Queiroz and Caio Almeida Perez

Abstract

The treatment of inflammatory bowel disease (IBD) has undergone a major paradigm shift in the last two decades with the introduction of biological drugs. Tumoral necrosis factor (TNF) antagonists were the first monoclonal antibodies available for treatment of IBD. New emerging concepts as early initiation of treatment during the "opportunity window," and "treat to target" with a tight control strategy have contributed to optimum utilization of these drugs allowing better long-term outcomes for treated patients. This chapter aims to review all current pivotal data regarding efficacy and safety of infliximab, adalimumab, certolizumab pegol, and golimumab, as long as real life experience with these agents. Comparative efficacy among anti-TNF agents and the role of therapeutic drug monitoring in the management of IBD will also be discussed. Last, the authors present future perspectives with the drugs and position anti-TNF agents as viable therapeutic options in the current IBD therapeutic armamentarium.

Keywords: biologics, TNF inhibitors, therapy, Crohn's disease, ulcerative colitis

1. Introduction

The treatment of inflammatory bowel disease (IBD) has remained a challenge for physicians involved in disease care because of its chronic nature and the impact on patient's quality of life. Traditionally, the pharmacological arsenal for the treatment of Crohn's Disease (CD) includes the aminosalicylates (sulfasalazine, mesalazine), immunosuppressants (e.g., azathioprine, 6-mercaptopurine, and methotrexate), corticosteroids (e.g., prednisone, hydrocortisone, methylprednisolone, and budesonide), and antibiotics. This therapeutic armamentarium, regarded as "conventional," does not seem to interfere with the natural history of the disease, while improving the symptoms of many patients [1–3].

In the last two decades, there has been a major paradigm shift in the treatment of IBD, with the introduction of biological drugs (monoclonal antibodies) [4, 5]. Biological drugs were the only class of drugs that alter the natural course of the disease, reducing the risk of hospitalizations, and surgeries [6]. However, insights into the importance of early and optimized therapy have prompted interest in a 'treat to target' approach to achieve good disease control. This strategy involves treating to a pre-defined target that is associated with optimal long-term outcomes. Regular

monitoring of objective measures of disease is required, and treatment is optimized based on these findings to ensure the target is achieved and maintained.

The natural course of inflammatory bowel disease is characterized by periods of remission and exacerbation and, over time, patients can develop irreversible damage such as stenosis and fistulas in Crohn's disease shortening and lead pipe appearance of colon in UC. However, it has been shown that early diagnosis with identification of severity predictors factors [7] and the early initiation of treatment with biological drugs during the "opportunity window," where symptoms are mainly derived from the diseases inflammatory activity in its initial phase, significantly reduces the rate of surgical complications, such as fistula stenosis in CD, as well as the need for colectomy in patients with UC who present severe acute colitis or chronic colitis refractory to corticoid, aminosalicylates, and immunosuppressive therapy [8–10].

The current IBD treatment goals include not only symptoms control, mainly but also sustained control of inflammation, through the mucosal healing and complication prevention (fistulae, abscesses, stenoses, dysmotility, and dysplasia), which may lead to hospitalization, surgery and substantial impact in quality of life [1, 11, 12]. In 2015, the International Organization for the Study of Inflammatory Bowel Diseases for the Study of Inflammatory Bowel Diseases (IOIBD) published the

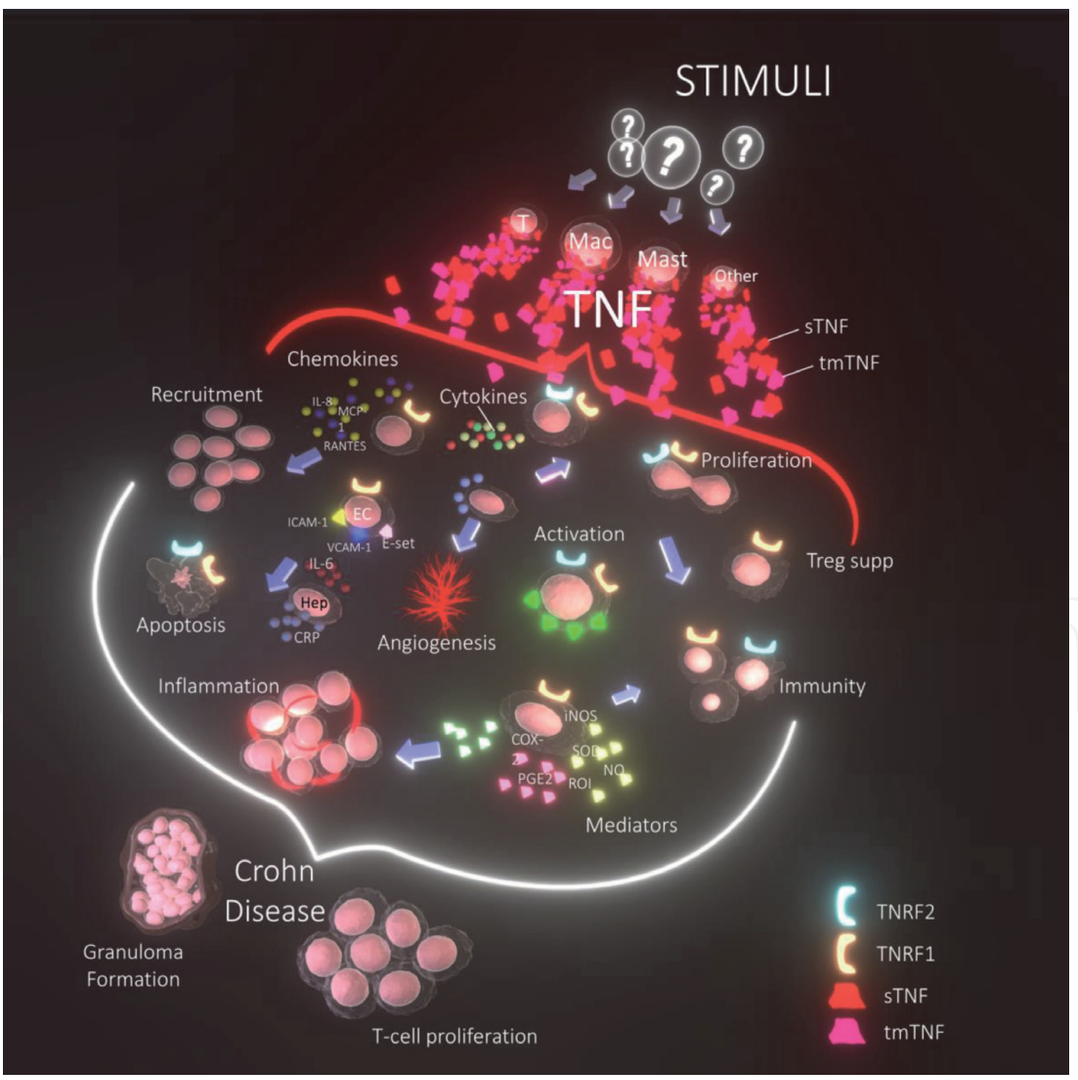

Figure 1.
TNF's mechanisms of action - In the pathophysiology of Crohn's disease, TNF is produced at high concentrations by a variety of cell types, presumably induced by endogenous or microbial stimuli. A cascade and network of cellular responses mediated by TNF are shown in the the diagram.

selecting therapeutic targets in inflammatory bowel disease (STRIDE), where 28 experts in IBD developed recommendations based on a systematic literature review and expert opinion proposing the strategy "treat to target" in IBD. In this publication, the recommended therapeutic targets were clinical remission defined by improvement in bowel movements and the resolution of the associated rectal bleeding for UC or abdominal pain for Crohn's disease. Furthermore, endoscopic remission with no ulcerations in CD and an endoscopic Mayo score 0-1 in UC should be confirmed [11].

The "treat to target" strategy defines the therapeutic goals that professionals should aim for, although it is important to emphasize which treatment strategy should be adopted in order to achieve the desired outcome. With that purpose, in 2017 the effect of tight control management on Crohn's disease (CALM) trial was published, a multicenter phase 3, randomized controlled trial designed to evaluate the safety and effectiveness of two treatment strategies in patients with CD scaling to biological therapy based on predefined criteria of treatment failure. The primary endpoint was the mucosal healing, defined by a CDEIS <4 score and the absence of deep ulcers at the end of 48 weeks, patients were randomized into two groups: the "tight control," where therapy was scaled based on clinical evaluation and biomarkers (fecal calprotectin and CRP), and the clinical management group, in which only the symptom assessment was considered. It was observed that a significantly higher proportion of patients in the "tight control" group reached the primary endpoint compared to the clinical management group, showing that the escalation of biological therapy guided by targets in patients with early CD is associated with better clinical and endoscopic outcomes when there is an association of clinical evaluation and biomarkers for decision-making [13].

The first group of biological medicines was composed by tumoral necrosis factor (TNF) antagonists, approved for use in Crohn's disease patients in 1998. The currently available anti-TNFs for treatment of CD are infliximab, adalimumab, and certolizumab pegol (**Figure 1**).

2. Infliximab (Remicade®)

The infliximab (IFX), a chimeric monoclonal IgG1 antibody, was the first biological used in CD. In 1997, Targan et al. published a randomized controlled trial demonstrating the superiority of the drug in inducing clinical remission in moderate to severe CD compared to placebo. Four groups were defined, involving 108 patients, to receive doses of 5, 10, 20 mg/kg, or placebo. The primary outcome was clinical response after 4 weeks, defined by a decrease of 70 points, or more in CDAI score after a single infusion. It was observed that 81% of patients receiving 5 mg/kg, 50% of those who received 10 mg/kg, and 64% receiving 20 mg/kg achieved the goal, compared to only 17% in the placebo group ($p < 0.001$). This was the first comparative, randomized, placebo-controlled trial involving IFX in the treatment of CD. It is a landmark in biological therapy because it has demonstrated superiority of this drug over placebo in a single infusion and guided the currently adopted dose of 5 mg/kg [14]. Subsequently, Present et al. published a longer lasting study with 18 weeks of follow-up involving patients with penetrating CD that had active fistulas. In addition of the initial dose at week 0, IFX was administered at weeks 2 and 6 in two groups with 5 or 10 mg/kg compared to the placebo group. The primary endpoint was the 50% reduction in the drainage of fistula, which occurred in 68, 56, and 26% in the groups 5, 10 mg/kg, and placebo, respectively, with statistical significance [15].

With the efficacy of IFX in inducing clinical remission established, in order to evaluate its efficacy in maintain clinical response in CD, in 2002 the ACCENT I study was published, the most relevant publication related to IFX in CD; a multicenter study (US, Europe, and Israel), controlled trial involving 573 patients with moderate to severe Crohn's disease (CDAI between 220 and 400). All patients received a dose of IFX 5 mg/kg and were assessed after 2 weeks. Of these, 325 (58%) had clinical response (CDAI decrease of 70 points or more at baseline) and were randomized at week 2 into 03 groups: 5, 10 mg/kg, and placebo. Following treatment regimen suggested by Present et al., doses were administered at weeks 0, 2, and 6, and subsequently administered every 8 weeks. The primary endpoint was clinical remission (CDAI <150 points) maintained after 30 and 54 weeks of initiating therapy. It was observed that those who responded to induction dose had higher remission rate at weeks 30 and 54. The maintenance of clinical remission rates at 54 weeks were significantly higher in the groups that received IFX 5 and 10 mg/kg (28.3 and 38.4%, respectively) compared with placebo (13.6%), showing the effectiveness of maintenance therapy with IFX. No statistical significance was observed in the difference between 5 and 10 mg/kg groups. In addition, in the placebo group, there was no mucosal healing at week 10, whereas patients receiving IFX in doses of 5 and 10 mg/kg, healing was observed in 31% of cases [16]. Following this line of reasoning, ACCENT II was published in 2004, a phase III randomized, double-blind, placebo-controlled study that included 306 patients with penetrating CD (enterocutaneous and perianal fistula), of which 282 were randomized at week 14 after the induction therapy (weeks 0, 2, and 6) for receiving infusions of 5 mg/kg or placebo every 8 weeks, aiming to evaluate the loss of IFX response in both groups after 54 weeks of treatment. It was observed that the time to loss of response was significantly higher in the IFX group over placebo (>40 weeks vs. 14, $p < 0.001$), and after 54 weeks, only 19% of the patients in the placebo group did not have fistulas in compared to 36% in the IFX group ($p = 0.009$) [17].

In order to assess the IFX therapy effectiveness in induction and maintenance of clinical response in moderate to severe UC two phase III placebo-controlled studies were subsequently published: the ACT I and II. With a total of 364 patients involved in each study, they were randomized to receive placebo, 5 or 10 mg/kg at weeks 0, 2, and 6, followed by infusions every 8 weeks through weeks 46 (ACT I) and 22 (ACT II). The primary endpoint was to evaluate clinical response (defined as decrease of three points in Mayo score and, at least, one point in the sub-item for rectal bleeding) at week 8, having as secondary endpoints the clinical response or remission after corticosteroid withdrawal and mucosal healing at weeks 8, 30 in both studies, and at week 54 in ACT I. In this last study, only 37% of patients in placebo group had clinical response at week 8 versus 69% ($p < 0.001$) in the 5 mg/kg group and 62% ($p < 0.002$) in the 10 mg/kg group. In ACT II, 64% of patients receiving IFX 5 mg/kg and 69% of those who received 10 mg/kg had clinical response at week 8 compared to 29% of those receiving placebo ($p < 0.001$ for both comparisons). In both studies, clinical response was more frequently observed at week 30 among patients who received IFX ($p < 0.002$ for all comparisons). In ACT I, after 54 weeks, more patients receiving IFX 5 or 10 mg/kg (45 and 44%, respectively) showed clinical response compared to placebo (20%, $p < 0.001$) [18].

The pivotal studies mentioned consolidated IFX use as induction and maintenance therapy in CD and UC. However, in general, the clinical trials inclusion criteria are too restrictive, restricting the participation of most patients in daily clinical practice. One of the biggest real-life studies evaluating the effectiveness of treatment of CD with IFX was published in 2009 by Schnitzler et al. from Leuven group. Six hundred fourteen patients were evaluated with a median of

55 months follow-up, in which approximately 11% were primary non-responders. Of the 547 remaining, 63.3% of patients had sustained clinical benefit. Treatment was discontinued in 31.7% of cases due to complete remission, 12.8% due to adverse events, and 21.6% due to loss of response to the drug. This study demonstrated that good results can be obtained with IFX treatment in the real world, when the requirements of controlled studies are often not attained [19].

In order to evaluate the safety profile and long-term repercussions of IFX treatment based on real life clinical experience, Sandborn et al. published in 2012 a study involving 492 CD patients treated between 1998 and 2002 at the Mayo Clinic and followed until 2009. It was shown that approximately 80% of patients showed clinical response to induction therapy, of which 25% with partial and 75% with complete response, in agreement with previously reported data [16, 17]. Dose escalation or shortening of the interval between infusions occurred in approximately 57% of patients who received maintenance dose with a cumulative probability of a therapeutic adjustment of 19% in the first year, 57% in 5 years, and 74% in 10 years of follow-up, reflecting that there is a loss of response over time. Note that 10% of the 182 patients who received maintenance therapy, discontinued its use because of loss of response. The cumulative probability of adverse events was around 35% in the first year, increasing to 86% after 10 years of therapy. Approximately 5% of patients developed cancer, with a cumulative probability of 9.1% in 10 years, though it was unclear if this increased incidence of cancer was related to the CD itself, the use of IFX or because this study was performed at a reference center with a specific profile of patients. The most common infectious complications were bacterial infection (intra-abdominal abscesses and pneumonia) and viral [20].

Long-term studies have demonstrated that, despite its effectiveness, IFX shows loss of response over time, with frequent need for dose escalation due to their immunogenicity. Then was raised the possibility of association of anti-TNF with immunosuppressive agents such as azathioprine (AZA) and 6-mercaptopurine, as synergists agents. In this context, the SONIC study was published in 2010 evaluating 508 patients with CD randomized to three different treatment strategies: IFX monotherapy, AZA monotherapy, or combination therapy with the two drugs. After 30 weeks of treatment, approximately 57% of patients treated with the combination therapy achieved corticosteroid free clinical remission (primary endpoint), compared to 44.4% in IFX monotherapy group ($p = 0.02$) and 30% in AZA monotherapy group ($p < 0.001$ for combination therapy; $p = 0.006$ for IFX). The mucosal healing rate was also higher in the combination therapy and IFX monotherapy groups compared to isolated AZA ($p < 0.001$ and $p = 0.02$, respectively). The difference between the IFX monotherapy and combination therapy groups in this outcome was not statistically significant ($p = 0.06$) [21]. With a similar study design, the SUCCESS was published in 2014, analyzing 239 patients with moderate to severe UC who were randomized to treatment with the combination therapy (IFX + AZA), IFX monotherapy, or AZA alone. Steroid-free clinical remission at week 16 was achieved by 39.7% of patients treated with the combination therapy compared to 22.1% in the IFX group ($p = 0.017$) and 23.7% in the AZA group ($p = 0.032$). Similarly, the difference in mucosal healing was only statistically significant when the combination therapy was compared to AZA monotherapy (62.8 and 36.8%, respectively, $p = 0.001$) [22].

The data presented above have reassured that IFX, marketed for over 20 years, are efficient and have a satisfactory safety profile, being considered as a first-line biological treatment of IBD, especially in the management of perianal Crohn's disease and severe acute colitis. Moreover, it plays an important

role in the management of extra intestinal manifestations and the prevention of postoperative recurrence [23].

3. Adalimumab (Humira®)

Adalimumab, a fully humanized monoclonal antibody IgG1, was the second anti-TNF antibody released for treating IBD. The first paper published on the efficacy of ADA in induction of remission in CD was the CLASSIC I trial in 2006. Aiming the assessment of clinical response after 4 weeks of treatment (CDAI <150 points), 299 patients naïve to anti-TNF therapy were randomized to receive, respectively, at weeks 0 and 2, a dose of ADA 40/20, 80/40, 80/160 mg, or placebo. The results showed major clinical remission rate at a dose of 160/80 mg (36%) compared to placebo (12%, $p < 0.001$). Secondary endpoints were to evaluate the partial clinical improvement, defined by a decrease of 70 or 100 points in the CDAI. The first one was obtained with the three therapeutic regimens and the last only by the 160/80 mg dose, which has defined this regimen as the best option for ADA induction therapy [24].

In order to establish the efficacy of ADA in maintaining clinical response, CLASSIC II was subsequently published evaluating 55 patients from the CLASSIC I who were in clinical that were further randomized to three different treatment regimens: ADA 40 mg every other week, 40 mg weekly, or placebo until completing 56 weeks. In addition, 204 patients from CLASSIC I who were not in clinical remission were enrolled in an open label arm to use ADA 40 mg every other week. The primary endpoint was to evaluate the clinical remission (CDAI <150 points) among randomized patients and it was observed that 79% of patients receiving ADA every other week and 83% of those who received ADA weekly were in clinical remission against 44% in the placebo group ($p < 0.05$) Among the 204 patients assigned to treatment with ADA 40 mg every other week, 46% achieved clinical remission at the end of the 56 weeks. It is noteworthy that this is a study with a low randomized sample [25].

In order to emphasize the sustained efficacy of ADA in CD therapy, in 2007 Colombel et al. published the CHARM trial, a phase III study involving 854 patients who initially were subjected to induction with ADA, of which 499 (58%) had initial clinical response (CDAI decrease in ≥70 basal line) and were randomized to maintenance therapy with ADA 40 mg every other week, 40 mg weekly, or placebo with assess of clinical remission (CDAI <150) after 26 and 56 weeks of therapy. Analyzing the randomized groups, it was noted that clinical remission was significantly greater in the groups using ADA than to placebo at week 56, with 41% in the group receiving the drug weekly, 36% in the group receiving every other week, and 12% in the placebo group ($p < 0.001$). There was no statistically significance in the difference observed between the groups treated with ADA, confirming that the best initial regimen therapy with ADA is 40 mg every other week. It was noted that the superior results observed in CLASSIC II may be due to the fact that patients randomized in this study were in clinical remission, while in CHARM patients with a partial clinical response were included, giving a difference in population of the two studies, preventing direct comparison between them [26]. Analyzing the subgroup of patients who had been previous treated with IFX and discontinued therapy due to loss of response or intolerance it was also observed a higher remission rate compared to placebo, confirming that ADA therapy is a plausible alternative in this group of patients.

In order to properly evaluate the effectiveness of ADA as a rescue therapy in patients with CD who have intolerance or loss of response to IFX, GAIN study was

further published in 2006. Similarly to CLASSIC I, clinical remission was assessed at the end of 4 weeks after the randomization of 325 patients to receive induction therapy (160 and 80 mg at weeks 0 and 2) or placebo. It was observed that 21% of patients with ADA therapy reached the primary endpoint compared to only 7% in the placebo group ($p < 0.001$). This study has demonstrated that ADA is indeed an alternative for patients with refractory CD or is intolerant to IFX [27].

The therapy with ADA in UC was described later, when, in 2010, ULTRA 1 was published evaluating the drug efficacy in induction of clinical remission in patients naive for biological drugs. The study included 390 patients randomized into three groups to receive ADA in induction regimen with 160/80 mg at weeks 0 and 2, followed by 40 mg at weeks 4 and 6; 80/40 mg at weeks 0 and 2, followed by 40 mg every other week and the placebo group. At the end of 8 weeks, approximately 19% of patients in group 160/80 mg showed clinical remission compared with 9.2% of patients in the placebo group ($p = 0.031$), showing modest efficacy of this therapeutic regimen in UC patients who failed therapy with corticosteroids and/or immunosuppressant. The induction regimen with ADA 80/40 mg compared to placebo did not present statistical significance [28].

To analyze the efficiency in the induction of remission and also the maintenance of clinical response ULTRA 2 was sequentially published, studying 494 patients with UC who were initially stratified by prior use or not of anti-TNF alpha and randomized for induction therapy with ADA 160/80 mg at weeks 0 and 2 followed by ADA 40 mg every other week or placebo. The primary endpoint was clinical remission at weeks 8 and 52. Analyzing the group as a whole, there was no statistically significant difference at week 8, however, at week 52, 17.3% of patients with ADA achieved clinical remission superior to placebo group (8.5%, $p = 0.004$). The superiority was also observed at the end of 52 weeks (12.4 vs. 22%, respectively; $p = 0.029$). In the subgroup previously experienced with anti-TNF alpha, a statistically significant superiority was observed at the end of 52 weeks (10.2% in the ADA group vs. 3% in the placebo group, $p = 0.039$) [29].

Even though data in pivotal studies for ADA in UC are not as robust, Tursi et al. published in 2018 the results of a real-life study involving 102 UC patients demonstrating drug efficacy and safety more consistently. The primary outcome was the induction and maintenance of remission, defined by a Mayo score ≤ 2. At 3 months, 54.9% of patients achieved clinical remission and during an average follow-up of 18 months, 56.6% of the patients were in this same situation. Secondarily, clinical response and mucosal healing was achieved by 89.2 and 76.7% of the patients, respectively. Only three patients underwent colectomy (two because of primary therapeutic failure and one for secondary loss) and one patient discontinued treatment due to leukopenia [30].

In relation to real life experience in CD, Loftus et al. recently published the results of PYRAMID registry, evaluating the efficacy and safety of ADA in patients naive to biological therapy followed for 6 years. Taking into consideration the Physician's Global Assessment (PGA) and clinical remission (Harvey Bradshaw index <5), 2057 patients were analyzed with an improvement baseline PGA from 7.5 to 3.9 in the first year and 3.3 in the sixth year. The rate of patients in clinical remission increased from 29 to 68% and 75% after 1 and 6 years, respectively. As related to adverse events, 11.1% of patients had severe infections and the incidence of malignancy was relatively low (1.9%) [31].

ADA has demonstrated superiority to placebo for induction and maintenance of remission in patients with CD and UC. Its subcutaneous administration seems to be a more convenient approach to patients who prefer to self-administer. It is also considered a first-line agent in the management of moderate to severe CD and UC patients refractory to conventional therapy with a satisfactory safety profile.

4. Certolizumab pegol (Cimzia®)

Certolizumab pegol (CZP), a pegylated humanized Fab fragment of IgG1 was also studied in CD. Although the initial induction trial did not demonstrate statistically significant difference in clinical remission after 6 weeks of treatment compared to placebo, PRECISE 2 study was further published assessing maintenance of clinical response in 213 patients that responded to induction phase with 400 mg at weeks 0, 2, and 6 and had values of CRP ≥ 10 mg/L (50% of 428 patients with a reduction in CDAI >100 points after induction phase). These patients were randomized into two groups to receive either 400 mg of CZP or placebo. At the end of 26 weeks of follow-up, 62% of patients treated with the drug maintained clinical response, showing superiority over placebo (34%, $p < 0.001$). Second, it was observed that this superiority was maintained even for patients with CRP < 10 mg/L after the induction phase [32]. Subsequently, analyzing CD patients treated with CZP and followed for 7 years, it was seen that it showed a comparable safety profile to the others anti-TNF drugs [33].

Since chronic inflammatory diseases usually have a higher incidence and prevalence in females, there is much discussion about what would be the best therapeutic strategy to be adopted during pregnancy, once treatment suspension may be associated with "flares" of the underlying disease with deleterious effects for both the mother and fetus, in addition to the fact that anti-TNF alpha present variables degrees of placental transfer that can influence the immune response of the newborn. Due to its molecular conformation devoid of the Fc region, which prevents recognition by the FcRn receptor and consequently the active placental transfer, certolizumab pegol was evaluated as a safe treatment option during pregnancy [34].

In 2017, a prospective pharmacokinetic study (CRIB study) was published evaluating 16 patients with at least 30 weeks pregnancy who were treated with CZP (three of them with CD) to assess the degree of placental transfer to the fetus via the dosage of the serum level of the drug in the newborn plasma. Patients were required to receive the last dose of CZP within a maximum of 35 days before delivery to be included. It was observed that even with maternal plasma levels within the therapeutic range of CZP, 13 of the 16 neonates had no detectable levels of CZP in plasma and one shows minimum levels (0.09% concentration in maternal plasma), which hardly had any clinical consequences [34]. In accordance with previous studies, it was shown that CZP presents minimal to no placental transfer even when used in the third trimester of pregnancy, unlike IFX, or ADA [35]. In the same year, CRADLE study analyzed breast milk from 17 mothers who were treated with the CZP (five of them with CD), showing that the drug concentration in breast milk is minimal, with a relative dose transferred to the newborn well below the 10% limit considered safe. Besides that, adverse events in patients exposed to CZP were consistent with the known safety profile and newborns had an adverse event profile that could be expected in an untreated population of similar age [36].

The CZP presents itself as another subcutaneously administered anti-TNF option for CD with a suitable safety profile, especially in women in the reproductive phase.

5. Golimumab (Simponi®)

Golimumab (GOLI), a fully humanized antibody anti-TNF alpha administered subcutaneously, has been described as effective in induction of clinical response and remission in ulcerative colitis in 2014, with the publication of PURSUIT-SC. This

study combined the analysis of a phase 2 study (used to evaluate the appropriate dose of induction therapy) and phase 3, demonstrating the superiority of the drug over placebo. After determining the doses of 200/100 and 400/200 mg at the weeks 2 and 0 as the most appropriate induction regimen, 761 patients were randomized 1:1:1 to receive said regimens or placebo. At the end of 6 weeks, it was observed that the groups randomized to receive the golimumab 200/100 and 400/200 mg had better clinical response (51 and 54.9%, respectively) than placebo (30.3%; $p < 0.0001$ for both comparisons), with no statistically significant differences between the dosing schedules. Second, GOLI also demonstrated superiority to placebo regarding clinical remission and mucosal healing [36].

Having 464 patients who responded to induction therapy with GOLI in previous studies (PURSUIT-SC and PURSUIT-IV), PURSUIT-M evaluated the efficacy of the drug in maintaining clinical response. Patients were randomized to receive 50, 100 mg, or placebo every 4 weeks and evaluated after 52 weeks of treatment at week 54. As a result, 47% of patients receiving 50 mg and 49.7% of those who received 100 mg had sustained clinical response, while 31.2% of those receiving placebo had the same result ($p = 0.01$ and $p < 0.001$, respectively). Second, it was observed that about 28% of the patients who had received 100 mg of golimumab were in clinical remission and 42.4% in endoscopic remission, reinforcing its superiority over placebo, in which 15.6% were in clinical remission ($p = 0.004$) and 26.4% achieved mucosal healing ($p = 0.002$) [37].

Thus, GOLI is presented as another subcutaneous anti-TNF therapy option for ulcerative colitis. Due to its recent approval, more data on its long-term safety and real life experience are needed (**Table 1**).

Main studies	Objective	Primary end point	Results	Conclusion
Infliximab				
Cohort de Targan et al.	Assess the efficacy of IFX in inducing clinical response in patients with moderate to severe CD	Reduction of CDAI ≥ 70 points after 4 weeks of single induction dose	Placebo: 17% had clinical response IFX 5 mg/kg: 81% had clinical response IFX 10 mg/kg: 50% had clinical response IFX 20 mg/kg: 64% had clinical response	A single induction dose is superior to placebo to induce clinical response in patients with moderate to severe CD
ACCENT I	Assess the benefit of maintenance therapy with infliximab in patients with active CD who responded to a single initial infusion of infliximab	Clinical remission at week 30 (CDAI < 150) and time to loss of clinical response by week 54	Placebo: 21% in remission at week 30; mean time to loss of response of 19 weeks IFX 5 mg/kg at weeks 2 and 6, followed by 5 mg/kg every 8 weeks: 39% in remission at week 30; mean time to loss of response of 38 weeks IFX 5 mg/kg at weeks 2 and 6, followed by 10 mg/kg every 8 weeks: 45% in remission at week 30; mean time to loss of response >54 weeks	Patients who initially responded to IFX are most commonly in remission at week 30 and 54, when a dose of IFX is maintained every 8 weeks

Main studies	Objective	Primary end point	Results	Conclusion
ACCENT II	Assess the efficacy of maintenance treatment with IFX in the closure of fistulas in patients with CD having one or more fistulas who have responded to the induction therapy with IFX	Time to loss of response during 54 weeks of follow-up among patients who had a response at week 14 and were randomized	Placebo: mean time of 14 weeks to loss of response IFX: mean time to loss of response of over 40 weeks	Patients with penetrating CD responding to induction therapy are more likely to have a sustained clinical response to maintenance therapy over a 54-week period
ACT I	Assess the efficacy of IFX in induction and maintenance therapy in patients with moderate to severe UC	Clinical response at week 8 and secondarily, clinical remission and mucosal healing at weeks 8, 30, and 54 (among other secondary end points)	Clinical response at week 8: • Placebo: 37.2% • IFX 5 mg/kg: 69.4% • IFX 10 mg/kg: 61.5% Clinical remission at weeks 8, 30, and 54: • Placebo: 14.9, 15.7, and 16.5% • IFX 5 mg/kg: 38.8, 33.9, and 34.7% • IFX 10 mg/kg: 32, 36.9, and 34.4% Mucosal healing at weeks 8, 30, and 54: • Placebo: 33.9, 24.8, and 18.2% • IFX 5 mg/kg: 62, 50.4, 45.5% • IFX 10 mg/kg: 59%, 49.2, 46.7%	Patients with moderate to severe UC treated with IFX at weeks 0, 2, and 6, followed by maintenance every 8 weeks, more commonly have a clinical response at weeks 8, 30, and 54 than those who received placebo
ACT II	Assess the efficacy of IFX in induction and maintenance therapy in patients with moderate to severe UC	Clinical response at week 8 and secondarily, clinical remission and mucosal healing at weeks 8 and 30 (within other secondary end points)	Clinical response at week 8: • Placebo: 29.3% • IFX 5 mg/kg: 64.5% • IFX 10 mg/kg: 69.2% Clinical remission at weeks 8 and 30: • Placebo: 5.7 and 10.6% • IFX 5 mg/kg: 33.9 and 25.6% • IFX 10 mg/kg: 27.5 and 35.8% Mucosal healing at weeks 8 and 30: • Placebo 30.9 and 30.1% • IFX 5 mg/kg: 60.3 and 46.3% • IFX 10 mg/kg: 61.7 and 56.7%	Patients with moderate to severe UC treated with IFX at weeks 0, 2, and 6, followed by maintenance every 8 weeks, more commonly have a clinical response at weeks 8 and 30 than those receiving placebo

Main studies	Objective	Primary end point	Results	Conclusion
SONIC	Comparatively assess the efficacy of IFX monotherapy, AZA monotherapy or combined therapy in patients with moderate to severe CD naïve for biological therapy	Clinical remission free of corticoid and, secondarily, mucosal healing at week 26	Clinical remission at week 26: • AZA: 30% • IFX: 44.4% • IFX + AZA: 56.8% Mucosal healing at week 26: • AZA: 16.5% • IFX: 30.1% • IFX + AZA: 43.9% Note: the observed difference in mucosal healing between the IFX and IFX + AZA groups was not statistically significant	Patients with moderate to severe CD treated with IFX or IFX + AZA are more likely to achieve clinical remission free of corticosteroids than those treated with AZA alone
SUCCESS	Comparatively evaluate the efficacy of IFX monotherapy, AZA monotherapy, or combined therapy in patients with moderate to severe UC naïve for biological therapy	Clinical remission free of corticoid and secondarily mucosal healing at week 16	Clinical remission at week 16: • AZA: 23.7% • IFX: 22.1% • IFX + AZA: 39.7% Mucosal healing at week 16: • AZA: 36.8% • IFX: 54.6% • IFX + AZA: 62.8% Note: the difference in mucosal healing observed in IFX and IFX + AZA groups was not statistically significant	Patients naive for biological drugs with UC treated with combined therapy are more likely to achieve clinical remission than those treated with monotherapy drugs. Combined therapy is associated with better mucosal healing rates when compared to AZA monotherapy
Adalimumab				
CLASSIC I	Assess ADA's efficacy in inducing clinical remission in patients with moderate to severe CD naive for biological therapy	Clinical remission at week 4 after initial induction therapy	Placebo: 12% of the patients achieved remission ADA 40/20 mg: 18% of the patients achieved remission 18% (p = 0.36) ADA 80/40 mg: 24% of the patients achieved remission (p = 0.06) ADA 160/80 mg: 36% of the patients achieved remission (p = 0.001)	The ADA was superior to placebo in clinical remission induction in patients naive for biological therapy with moderate to severe CD, with a dose of 160 mg at week 0 followed by 80 mg at week 2 as the recommended regimen
CLASSIC II	Assess the efficacy and safety of ADA in maintenance therapy in	Maintenance of clinical remission at week 56 in the group of patients randomized after	Placebo: 44% of the patients had clinical remission ADA 40 mg every other week: 79% of	ADA was more effective than placebo in maintain remission after 56 follow-up

Main studies	Objective	Primary end point	Results	Conclusion
	patients with moderate to severe CD	responding to induction therapy	the patients maintained clinical remission ADA 40 mg weekly: 83% of the patients maintained clinical remission	
ULTRA I	Assess the effectiveness of ADA in clinical remission induction in patients with moderate to severe UC naive for biological therapy	Clinical remission at week 8 after initial induction therapy	Placebo: 9.2% of the patients achieved remission ADA 80/40 mg: 10% of the patients achieved remission ($p = 0.833$) ADA 160/80 mg: 18.5% of the patients reached remission ($p = 0.031$)	The 160/80 mg dose of ADA was effective and safe in inducing clinical remission in patients with moderate to severe UC who failed to corticoid or immunosuppressive therapy
ULTRA II	Assess the efficacy and safety of ADA in maintenance therapy of patients with moderate to severe UC	Maintenance of clinical remission at week 8 and week 52 after induction therapy	Placebo: 9.3% at week 8 and 8.5% at week 52 ADA: 16.5% at week 8 and 17.3% at week 52	ADA was effective and safe in maintaining clinical remission in patients with moderate to severe UC who failed to corticoid or immunosuppressive therapy
CHARM	Assess the efficacy and safety of ADA in maintenance therapy in patients with moderate to severe CD who responded to induction therapy	Percentage of patients who responded to induction and achieved clinical remission at weeks 26 and 56	Placebo: 17% at week 26 and 12% at week 56 ADA 40 mg every other week: 40% at week 26 and 36% at week 56 ADA 40 mg weekly: 47% at week 26 and 41% at week 56	ADA maintenance therapy in patients with moderate to severe CD who responded to induction therapy was more effective than placebo in maintaining clinical remission after 56 weeks of follow-up
GAIN	Assess the efficacy of ADA in inducing clinical remission in patients with moderate to severe CD who lost response or were intolerant to IFX	Clinical remission at week 4 after ADA induction therapy	Placebo: 7% achieved clinical remission at week 4 ADA: 21% achieved clinical remission in week 4	ADA was more effective than placebo in inducing clinical remission in patients who lost or were intolerant to IFX
Certolizumab pegol				
PRECISE 2	Assess the efficacy and safety of CTZ in inducing and maintaining	Clinical response rates in patients with baseline CRP ≥10 mg/L at week 26	Placebo: 36% of patients maintained clinical response CTZ: 62% of patients	Among patients who responded to the initial induction dose, maintenance of CTZ was more

Main studies	Objective	Primary end point	Results	Conclusion
	response and clinical remission in patients with moderate to severe CD who have responded to induction therapy		maintained clinical response	effective in maintaining clinical response than placebo
Golimumab				
PURSUIT	Assess the efficacy of golimumab in maintaining clinical response in patients with moderate to severe UC who responded to induction therapy	Maintenance of clinical response at week 54	Placebo: 31.2% of the patients maintained clinical response Golimumab 50 mg: 47% of the patients maintained clinical response Golimumabe 100 mg: 49.7% of the patients maintained clinical response	Golimumab maintenance therapy was more effective than placebo in maintaining clinical response after 54 weeks of follow-up

Table 1.
Main studies with Anti-TNF in inflammatory bowel disease.

6. Comparative efficacy among anti-TNF agents

As stated above, the treatment of IBD with the advent of anti-TNF alpha and more recently, other classes of biological drugs (anti-integrin, anti-IL 12/23 etc.) has dramatically changed the natural history of the disease and the incidence of complications. However, no head to head studies directly compared the efficacy of different drugs. Lacking such data, the decision on which treatment regimen to be used is mainly based on reported clinical experience, proposed algorithms by clinical trials, patient preference and safety profile [38].

Although imperfect, indirect comparative analyses, such as network meta analyses are available evidence to assess efficacy of different drugs. In 2018, Singh et al., through a systematic review and network meta-analysis, compared the efficacy and safety of treatment with various biological drugs in CD in naive patients for biological therapy (first-line therapy) and in patients previously tested with some anti-TNF (second-line therapy). Comparing direct and indirect evidence from 18 randomized controlled trials (RCT's) involving patients with moderate to severe CD, it was observed that anti-TNF alpha, particularly IFX and ADA, were the options with strongest evidence in the induction of clinical remission and response as well as maintenance therapy. Ustekinumab and vedolizumab appear to have similar efficacy in the first-line therapy and were not higher when compared to IFX or ADA. The CZP at the standardized dose has been reported as inferior to the other agents.

As second-line therapy (non-RCT using IFX or CZP as a second biological drug was identified), in the specific subgroup of patients who lost response or were intolerant to IFX, ADA seems to be superior compared to other agents. It is noteworthy that, for patients with primary nonresponse to IFX, the effectiveness of the ADA is uncertain, scenario in which ustekinumab seems to gain prominence. The safety profile and the incidence of major adverse events were assessed in

maintenance studies, not being seen clear superiority of one agent over the other, although the risk of adverse events appears to be low to IFX and ustekinumab. However, RCT's involved in the analysis were not powered to determine this difference, so this result should be evaluated with caution. Vedolizumab, a gut-selective anti-integrin, has not been clearly associated with an increased risk of serious infections in RCT's analysis and longitudinal cohorts. It is noteworthy that the risk factors most associated with severe infections were concomitant use of corticosteroids, narcotics and severe disease activity [38].

The same group published a meta-analysis evaluating the therapy in UC, where, besides the efficacy of induction/maintenance of clinical remission and safety profile of the drug, mucosal healing was also assessed. Combining direct and indirect evidence of 14 RCT's including 4212 patients with moderate to severe disease, the group concluded that, as first-line therapy, all evaluated agents (IFX, ADA, golimumab, and vedolizumab tofacitinibe) were superior to placebo, with IFX and vedolizumab considered the most effective in the inducing of clinical remission and mucosal healing. In general, ADA was considered the least effective agent for both outcomes. Comparing IFX to ADA, data obtained favor IFX for induction of remission, however, as maintenance therapy, it appears to be no significant difference between the two drugs [39]. Superiority of IFX can be associated with pharmacokinetics and bioavailability of the drug since its dosage is variable according to the weight of the patient, unlike ADA with a fixed dose.

As second line therapy, tofacitinib (JAK-2 inhibitor) seems to be the best choice for induction of remission and mucosal healing. A direct meta-analysis further demonstrated that vedolizumab and ADA were not superior to placebo, conferring a low level of evidence to indicate these drugs as a therapeutic alternative in this scenario. Importantly however, the studies that assessed ADA included only patients who lost response or were intolerant to IFX as part of the patients treated with vedolizumab were not primary responders to IFX, which may be linked to a specific population with a more aggressive form of the disease, disadvantaging vedolizumab in this analysis. This information was not clear in studies with tofacitinib and no study using IFX or golimumab as a second biological drug was identified [39].

As a maintenance therapy, because of differences in the design of studies, RCT's involving IFX and ADA were considered separately from those involving golimumab, vedolizumab, and tofacitinib. As stated earlier, IFX and ADA appear to be equally effective in maintaining remission in naive treatment patients. The other drugs were also superior to placebo in patients who responded to induction therapy and did not seem to differ from each other. Regarding the safety profile, none of the options was significantly worse compared to placebo in the incidence of adverse events. Taking into account the incidence of serious infections, vedolizumab seems to be the safer drug, since there was no difference compared to placebo, while golimumab and tofacitinib were associated to higher risk of infection [39].

In an innovative way, the preliminary results of VARSITY, the first head to head trial in IBD were presented in a specific event. It is a phase 3b double-dummy, controlled and randomized trial, comparing ADA and vedolizumab in the treatment of moderate to severe UC. With a total of 769 patients who had failed conventional therapy (25% had been exposed to any anti-TNF), which were randomized into four groups to receive vedolizumab vs. placebo or adalimumab vs. placebo, clinical remission (primary endpoint), and mucosal healing were assessed after 52 weeks. It has been observed that patients treated with vedolizumab achieved clinical remission rates of 31.3% and mucosal healing of 39.7%, significantly better than patients treated with ADA (22.5% $p = 0.0061$ and 27.7% $p = 0.0005$, respectively), with no statistically significant difference in the incidence of infections and adverse events [40].

7. Safety of anti-TNF agents

The use of TNF-alpha inhibitors and their combination with thiopurines has proved to be more effective in controlling severe forms of CD and UC compared to monotherapy [21, 22]. However the use of these drugs is associated to a higher risk of adverse events, particularly infections and malignancies [41, 42].

The analysis of a cohort study involving a large number of patients [43], showed a higher risk of serious and opportunistic infections in combination therapy than with the use of anti-TNF or thiopurines alone. Comparing anti-TNF and thiopurines in monotherapy, there was a higher incidence of serious infections and mycobacterial infections associated with anti-TNF, however, there is no difference in the incidence of opportunistic infections in general, since thiopurines were associated with higher chance of viral opportunistic infections and anti-TNF to bacterial infections. It is noteworthy that the results of a previous meta-analysis showed an increased incidence of opportunistic infections by bacteria and mycobacteria in patients treated with the combination therapy compared to monotherapy with anti-TNF, inferring that the use of thiopurines adds an extra risk for developing infections [44]. There was a higher incidence of viral opportunistic infections when combination therapy was compared to monotherapy with anti-TNF, but it did not differ when compared to monotherapy with the thiopurines, suggesting that the risk of this complication in the combination therapy is due to the use of thiopurines [45].

It should be considered that not only therapeutic option is linked with a higher risk of infectious complications, but also the patient's age, disease severity, and concomitant use of corticosteroids, all those associated with a worse outcome [46].

Classically, therapy with thiopurines is associated with an increased risk of malignancy in patients with IBD, particularly non-Hodgkin's lymphoma, hepatosplenic lymphoma associated with EBV, cervical cancer associated with HPV, urinary tract cancer, and non-melanoma skin cancer, both as monotherapy and in combination therapy with an anti-TNF agent [42]. However, the association between malignancy and anti-TNF alpha use remains uncertain. In prior meta-analysis involving 21 placebo-controlled trials including more than 5000 patients with CD, treatment with anti-TNF was not associated with an increased risk of cancer development [47].

Through the analysis of the TREAT™ Registry database, a prospective cohort study that evaluated the outcomes of long-term treatment regimens in DC involving 6237 patients in with more than half used the IFX sometime in the follow-up, it was found that, in general, the incidence of cancers (benign or malignant) was similar between the group treated with IFX and with the other therapeutic options [48]. In this study, age, disease duration and smoking were associated with increased risk of cancer. In a more recent meta-analysis including 44 RCT's and more than 14,000 patients, and the incidence of malignancy as a secondary outcome, it was not possible to conclude that the use of anti-TNF significantly affect the risk of cancer. However, the data were scarce and periods of exposure and follow-up were too short to allow conclusions [41]. The incidence of melanoma is described as higher in patients with IBD in general, however, some studies suggest a possible association with the use of anti-TNF [49] while others do not [50].

A recent French cohort gathered data from nearly 190,000 patients to assess risk of lymphoma in patients with IBD that used azathioprine and/or anti-TNF agents. Surprisingly, not only the use of thiopurines but also the use of anti-TNF monotherapy was associated with a small but statistically significant increased risk of lymphoma among patients exposed. The risk was greater in the combination therapy than either drug alone [51].

Other adverse events associated with anti-TNF therapy are described and should also be remembered. Since there are reported the reactivation of tuberculosis and hepatitis B virus after initiation of therapy, the pretreatment screening, in order to guide the treatment of latent tuberculosis and prophylaxis with antiretroviral, is indicated [52, 53]. In those patients who are in triple immunosuppression, *Pneumocystis jirovecii* prophylaxis may be considered [54]. Infusion reactions (relatively frequent), angioedema, anaphylaxis, lupus-like syndrome, psoriasis induced by anti-TNF, eczematous lesions, demyelinating syndromes, and heart failure are also described [54].

8. The role of therapeutic drug monitoring in the management of IBD with anti-TNF agents

Although effective in the induction and maintenance of clinical remission and mucosal healing, the therapeutic fail of anti-TNF is not uncommon in IBD, occurring in patients which are considered as primary non-responders (10–40% approximately) or lose the response in the first year of treatment (24–46%), and those who have some adverse effect that lead to treatment interruption [24, 26]. An understanding of the factors involved in therapeutic failure, as the patient's profile, the presentation of the disease and the relationship between the concentration of the drug and its interaction with the anti-drug antibodies (ADAbs), are useful tools to guide the best strategy to be followed [55].

The concentration of drug in the site of action is directly linked to the magnitude of the expected pharmacological response and its monitoring in specific scenarios can assist in therapeutic decision. For example, the patient may experience an inadequate response due to the low concentration of the drug secondary to increased clearance, differing completely from one that has inadequate response with therapeutic trough levels, suggesting mechanistic failure. In the first situation, dose escalation can be effective, while the second would most benefit from exchange to a medication with a distinct mechanism of action (**Figure 2**) [56].

Based on these assumptions, in 2017, the American Gastroenterological Association has published a technical review on the role of therapeutic drug monitoring (TDM) as an auxiliary tool in decision-making regarding treatment of IBD. In the absence of adequate response, the dosage of the trough level of the drug has been suggested as a first step (reactive approach): if the serum levels of anti-TNF are within the therapeutic range, it is characterized the failure to the mechanism of action and class exchange is possibly the best option. However, if serum levels are below the appropriate, dosage of ADAbs can bring additional information: if they are high, it is likely that the clearance of the drug is being immune-mediated, and it is plausible the exchange of medication for a drug of the same class, besides the association with immunomodulator. If the ADAbs level is undetectable or low, it is likely that the clearance is increased due to mechanisms not immune-mediated, such as severe inflammatory burden leading to rapid use of anti-TNF and/or excessive loss in feces (indicated by hypoalbuminemia, CRP, and high fecal calprotectin), which would allow the optimization of the dosage instead of changing the biological agent. This strategy seems to be more effective than making decisions empirically, despite the low level of evidence further described [56]. In patients with the disease in remission, the dosage of the trough level and ADAbs as an auxiliary tool in decision-making (proactive proposal) is still uncertain, with few studies that corroborate its effectiveness, mainly regarding cost savings [57, 58].

In order to examine predictors of therapeutic failure to anti-TNF, PANTS study has been recently published, a randomized clinical trial involving patients with luminal CD naive for biological therapy who started treatment with IFX or ADA.

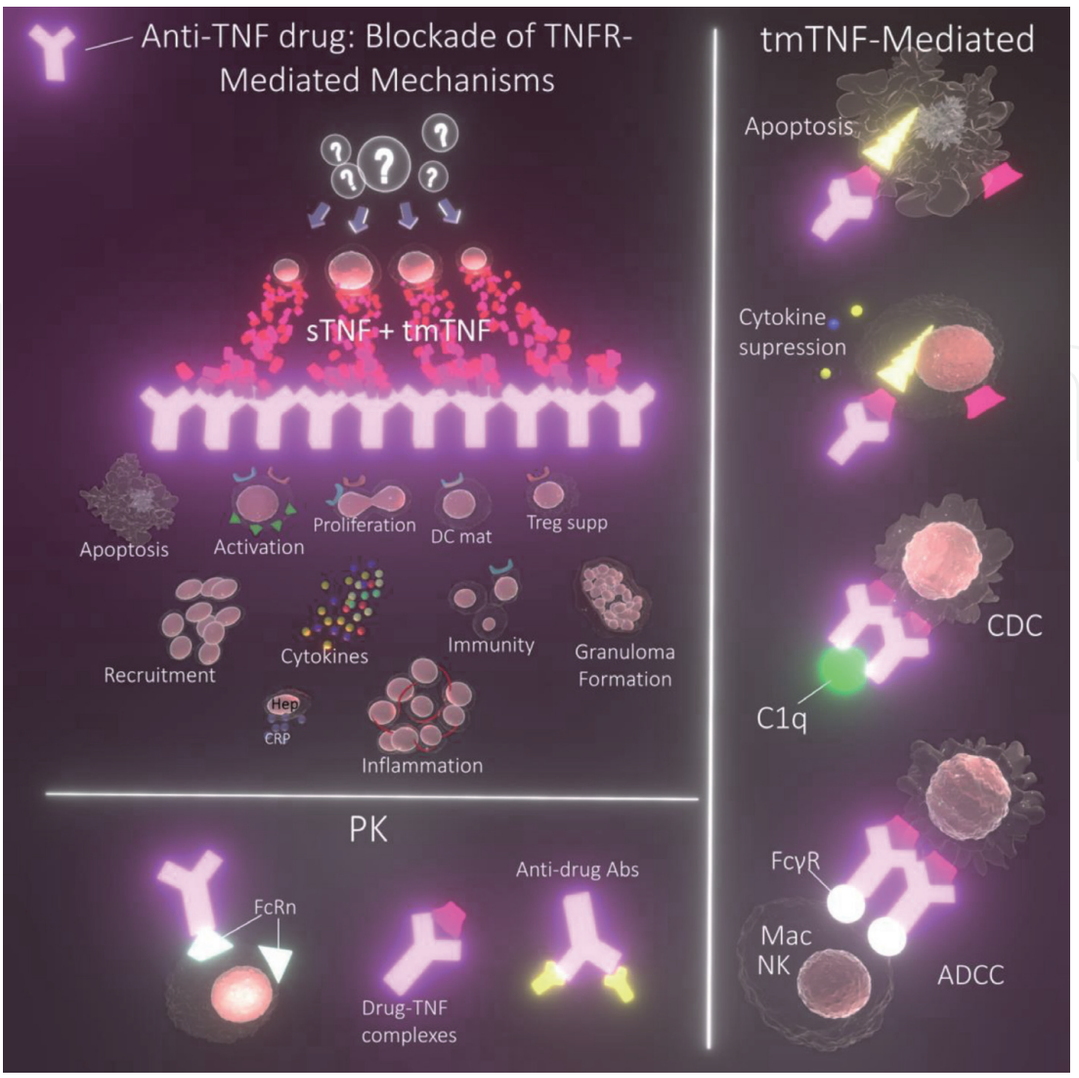

Figure 2.
anti TNF's mechanisms of action are illustrated above. The inflammatory cascade triggered by TNFR is disrupted by anti TNF-mediated direct blockade, which prevents binding of sTNF and tmTNF to specific receptors. On the right are the results of tmTNF antagonization by the drug, which include cytotoxicity of the CDC (complement – dependent cytotoxicity) or ADCC (antibody-dependent cellular cytotoxicity), as well as reverse signaling via tmTNF. The pharmacokinetics-related are illustrated at the bottom of the image.

Through regression logistic, it was identified that only low trough level in week 14 (IFX < 7 mg/L and ADA < 12 mg/L) was associated to the absence of primary response. Obesity, smoking, hypoalbuminemia, high levels of inflammatory markers, and the development of immunogenicity were associated with lower serum levels of the drug. It was also observed that low levels at week 14 were independently associated to non-clinical remission at week 54, and were associated with increased formation of ADAbs. The combination with immunomodulators (azathioprine or methotrexate) was associated with lower immunogenicity for both IFX and ADA, and in the group of patients with IFX, combination therapy was associated with higher clinical remission rate at week 54 compared to monotherapy with IFX, unlike ADA, which was not more effective in maintaining remission when associated with immunomodulators [55].

9. Final considerations

The initiation of therapy with tumor necrosis factor inhibitors certainly was a milestone in the treatment of inflammatory bowel disease, drastically changing the natural course of the disease and offering better quality of life to treated patients.

With an acceptable safety profile, anti-TNF agents are excellent therapeutic options in severe forms of the disease, with proven efficacy in both Crohn's disease and ulcerative colitis. The association with immunomodulators, particularly to infliximab is associated with better outcomes. A lack of head to head trials that compares the biological drugs limits the assessment of superiority among them to indirect comparisons, making it crucial that such evidence come to light. Therapeutic drug monitoring seems to be useful tools in decision-making and can increase the therapeutic success rates obtained. However, in the face of current evidence, it has not yet been consolidated as a cost effective strategy.

Future perspectives involving anti-TNF agents include the development of new molecules of this class. Currently, several new TNF-alpha inhibitors have been studied in patients with CD. The DLX 105 (esbat Tech) is an anti-TNF antibody that has been studied specifically in patients with fistulizing CD, trough a local injection in a phase II trial (ClinicalTrials.gov NCT01624376), but no results are available to date. Other two anti-TNF-alpha oral therapies, V565 (VHsquared) and OPRX-106 (Bio Protalix) are in the pipeline. The V565 is currently recruiting patients with moderate to severely active CD to a phase II study (NCT02976129) after favorable results in a phase Ib (NCT03010787). The OPRX-106 demonstrated efficacy in clinical improvement of biomarkers in a phase II study of patients with mild to moderate UC. It is worth to wait for these promising therapies, since the oral mode of administration may be more convenient for some patients [59, 60].

In the era of the new mechanisms of action, this critical analysis consolidates the anti-TNF agents as viable therapeutic options in the current IBD therapeutic armamentarium.

Author details

Carlos Walter Sobrado*, Natália Sousa Freitas Queiroz and Caio Almeida Perez
Department of Gastroenterology, University of São Paulo School of Medicine, Brazil

*Address all correspondence to: cwsobrado@hotmail.com

References

[1] Sandborn WJ. Crohn's disease evaluation and treatment: Clinical decision tool. Gastroenterology. 2014; **147**:702-703

[2] De Azevedo MFC, De Sousa Carlos A, Milani LR, Oba J, Cintra Damião AOM. Doença inflamatória intestinal. Revista Brasileira de Medicina. 2014;**71**:46-58

[3] Cosnes J et al. Long-term evolution of disease behavior of Crohn's disease. Inflammatory Bowel Diseases. 2002;**8**: 244-250

[4] Ungar B, Kopylov U. Advances in the development of new biologics in inflammatory bowel disease. Annals of Gastroenterology. 2016;**29**: 243-248

[5] Löwenberg M, D'Haens G. Next-generation therapeutics for IBD. Current Gastroenterology Reports. June 2015;**17**(6):21

[6] Khanna R et al. Early combined immunosuppression for the management of Crohn's disease (REACT): A cluster randomised controlled trial. Lancet. 2015;**386**: 1825-1834

[7] Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of crohn's disease. Gastroenterology. 2006;**130**(3):650-656

[8] Sands BE, Arsenault JE, Rosen MJ, Alsahli M, Bailen L, Banks P, et al. Risk of early surgery for Crohn's disease: Implications for early treatment strategies. The American Journal of Gastroenterology. 2003;**98**:2712-2718

[9] Lakatos PL, Czegledi Z, Szamosi T, Banai J, David G, Zsigmond F, et al. Perianal disease, small bowel disease, smoking, prior steroid or early azathioprine/biological therapy are predictors ofdisease behavior change in patients with Crohn's disease. World Journal of Gastroenterology. 2009; **15**(28):3504-3510

[10] Allez M, Lemann M, Bonnet J, et al. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. American Journal of Gastroenterology. 2002;**97**:947-953

[11] Peyrin-Biroulet L et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining therapeutic goals for treat-to-target. The American Journal of Gastroenterology. 2015;**110**:1324-1338

[12] Baert F et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010;**138**: 463-468

[13] Panaccione R, Colombel J-F, Hébuterne X, Bossuyt P, Robinson AM, Huang B, et al. Effect of tight control management on Crohn's disease (CALM): A multicentre, randomised, controlled phase 3 trial. The Lancet. 2017;**390**:2779-2789

[14] Targan SR, Hanauer SB, van Deventer SJH, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor α for Crohn's disease. The New England Journal of Medicine. 1997;**337**:1029-1035

[15] Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. The New England Journal of Medicine. 1999;**340**:1398-1405

[16] Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial. Lancet. 2002;**359**:1541-1549

[17] Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. The New England Journal of Medicine. 2004;**350**(9): 876-885

[18] Lichtenstein GR. Infliximab for induction and maintenance therapy for ulcerative colitis. Gastroenterology. 2008;**2006**:130-131

[19] Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: Results from a single-centre cohort. Gut. 2009;**58**(4):492-500

[20] Seminerio JL, Loftus EV, Colombel JF, Thapa P, Sandborn WJ. Infliximab for Crohn's disease: The first 500 patients followed up through 2009. Digestive Diseases and Sciences. 2013; **58**(3):797-806

[21] Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. The New England Journal of Medicine. 2010;**362**(15): 1383-1395

[22] Panaccione R, Ghosh S, Middleton S, Márquez JR, Scott BB, Flint L, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014;**146**(2):392-400.e3

[23] De Cruz P, Kamm MA, Hamilton AL, Ritchie KJ, Krejany EO, Gorelik A, et al. Crohn's disease management after intestinal resection: A randomised trial. Lancet. 2015; **385**(9976):1406-1417

[24] Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, Macintosh D, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial. Gastroenterology. 2006;**130**(2):323-333

[25] Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lulcas M, MacIntosh DG, et al. Adalimumab for maintenance treatment of Crohn's disease: Results of the CLASSIC II trial. Gut. 2007;**56**(9):1232-1239

[26] Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: The CHARM Trial. Gastroenterology. 2007;**132**(1):52-65

[27] Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: A randomized trial. Annals of Internal Medicine. 2007;**146**: 829-838

[28] Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: Results of a randomised controlled trial. Gut. 2011;**60**(6): 780-787

[29] Sandborn WJ, Van Assche G, Reinisch W, Colombel J, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;**142**(2):257-265.e3

[30] Tursi A, Elisei W, Faggiani R, Allegretta L, Della VN, Forti G, et al. Effectiveness and safety of adalimumab to treat outpatient ulcerative colitis: A real-life multicenter, observational study in primary inflammatory bowel disease centers. Medicine (Baltimore). 2018;**97**(34):e11897

[31] Loftus EV, D'Haens G, Reinisch W, Satsangi J, Panaccione R, Berg S, et al. Adalimumab long-term effectiveness in adalimumab-naive patients with Crohn's disease: Final data from PYRAMID registry. The American Journal of Gastroenterology. 2019;**112**: S363-S364

[32] Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. The New England Journal of Medicine. 2007;**357**(3):239-250

[33] Sandborn WJ, Lee SD, Randall C, Gutierrez A, Schwartz DA, Ambarkhane S, et al. Long-term safety and efficacy of certolizumab pegol in the treatment of Crohn's disease: 7-year results from the PRECiSE 3 study. Alimentary Pharmacology & Therapeutics. 2014;**40**(8):903-916

[34] Mariette X, Förger F, Abraham B, Flynn AD, Moltó A, Flipo RM, et al. Lack of placental transfer of certolizumab pegol during pregnancy: Results from CRIB, a prospective, postmarketing, pharmacokinetic study. Annals of the Rheumatic Diseases. 2018; **77**(2):228-233

[35] Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clinical Gastroenterology and Hepatology. 2013;**11**:286-292

[36] Clowse ME, Förger F, Hwang C, Thorp J, Dolhain RJ, Van Tubergen A, et al. Minimal to no transfer of certolizumab pegol into breast milk: Results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. Annals of the Rheumatic Diseases. 2017;**76**(11): 1890-1896

[37] Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;**146**(1):96-109.e1

[38] Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: First- and second-line biologic therapies for moderate-severe Crohn's disease. Alimentary Pharmacology & Therapeutics. 2018;**48**(4):394-409

[39] Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: First- and second-line pharmacotherapy for moderate-severe ulcerative colitis. Alimentary Pharmacology & Therapeutics. 2018;**47**(2):162-175

[40] Sands B, Peyrin-Biroulet L, Loftus EV Jr, et al. Vedolizumab shows superior efficacy versus adalimumab: Results of VARSITY: The first head-to-head study of biologic therapy for moderate-to-severe ulcerative colitis. In: Presented at Digestive Disease Week (DDW) San Diego, California (Oral Presentation—Sunday, May 19, 2019, 17:16–17:30 PDT)

[41] Bonovas S, Fiorino G, Allocca M, Lytras T, Nikolopoulos GK, Peyrin-Biroulet L, et al. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: A systematic review and network meta-analysis. Clinical Gastroenterology and Hepatology. 2016; **14**(10):1385-1397.e10

[42] Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. The New England Journal of Medicine. 2015;**372**(15): 1441-1452

[43] Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases.

Gastroenterology. 2018;**155**(2): 337-346.e10

[44] Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. Journal of Crohn's and Colitis. 2014;**8**(6):443-468

[45] Lorenzetti R, Zullo A, Ridola L, Diamanti AP, Laganà B, Gatta L, et al. Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: A systematic review of randomized controlled trials. Annals of Medicine. 2014;**46**(7):547-554

[46] Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, et al. Serious infection and mortality in patients with crohn's disease: More than 5 years of follow-up in the TREAT registry. The American Journal of Gastroenterology. 2012; **107**(9):1409-1422

[47] Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: Meta-analysis of placebo-controlled trials. Clinical Gastroenterology and Hepatology. 2008;**6**(6):644-653

[48] Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Langholff W, et al. Drug therapies and the risk of malignancy in crohn's disease: Results from the TREAT™ registry. The American Journal of Gastroenterology. 2014;**109**(2):212-223

[49] Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. YGAST. 2012;**143**(2):390-399.e1

[50] Singh S, Nagpal SJS, Murad MH, Yadav S, Kane SV, Pardi DS, et al. Inflammatory bowel disease is associated with an increased risk of melanoma: A systematic review and meta-analysis. Clinical Gastroenterology and Hepatology. 2014;**12**(2):210-218

[51] Lemaitre M et al. Association between use of tumor necrosis factor or thiopurines antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. JAMA. 2017;**318**:1679-1686

[52] López-serrano P, Pérez-calle JL, Sánchez-tembleque MD. Hepatitis B and inflammatory bowel disease: Role of antiviral prophylaxis. 2013;**19**(9):1342-1348

[53] Xie X, Li F, Chen J, Wang J. Risk of tuberculosis infection in anti-TNF-a biological therapy: From bench to bedside. Journal of Microbiology, Immunology, and Infection. 2013;**47**(4): 268-274. [Epub 2013 May 30]

[54] Quezada SM, McLean LP, Cross RK. Adverse events in IBD therapy: The 2018 update. Expert Review of Gastroenterology & Hepatology. 2018; **12**(12). DOI: 10.1080/17474124. 2018.1545574

[55] Kennedy NA, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: A prospective, multicentre, cohort study. The Lancet Gastroenterology & Hepatology. 2019;**1253**(19):1-13

[56] Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Technical Review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. Gastroenterology. 2017;**153**(3): 835-857.e6

[57] Vande CN, Ferrante M, Van AG, Ballet V, Compernolle G, Van SK, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 2015;1320-1329. [Epub 2015 Feb 24]

[58] D'Haens G, Vermeire S, Lambrecht G, Baert F, Bossuyt P, Pariente B, et al. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. Gastroenterology. 2018;**154**(5): 1343-1351.e1

[59] Almon E, Goldin E, Sbeit W, et al. A novel orally administered recombinant anti-TNF alpha fusion protein for the treatment of mild to moderate ulcerative colitis: Results of a phase 2A Clinical trials showing promissing results. Gastroenterology. 2018;**154**(6):S-153

[60] Cohen BL, Sachar DB. Update on anti-tumor necrosis factor agents and others new drugs for inflammatory bowel disease. BMJ. 2017;**357**:J2505