

Critical analysis of anti-TNF use in the era of new biological agents in inflammatory bowel disease

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ABSTRACT – Background – Inflammatory bowel diseases (IBD), both Crohn's disease and ulcerative colitis, are chronic immune-mediated diseases that present a relapsing and remitting course and requires long-term treatment. Anti-tumor necrosis factor (anti-TNF) therapy has changed the management of the disease by reducing the need for hospitalizations, surgeries and improving patient's quality of life. **Objective** – The aim of this review is to discuss the role of anti-TNF agents in IBD, highlighting the situations where its use as first-line therapy would be appropriate. **Methods** – Narrative review summarizing the best available evidence on the topic based on searches in databases such as MedLine and PubMed up to April 2020 using the following keywords: “inflammatory bowel disease”, “anti-TNF agents” and “biologic therapy”. **Conclusion** – Biological therapy remains the cornerstone in the treatment of IBD. In the absence of head-to-head comparisons, the choice of the biological agent may be challenging and should take into account several variables. Anti-TNF agents should be considered as first line therapy in specific scenarios such as acute severe ulcerative colitis, fistulizing Crohn's disease and extra-intestinal manifestations of IBD, given the strong body of evidence supporting its efficacy and safety in these situations.

HEADINGS – Inflammatory bowel diseases. Tumor necrosis factor-alpha, antagonists & inhibitors. Biologic therapy. Crohn disease, drug therapy. Ulcerative colitis, drug therapy.

INTRODUCTION

In the last two decades anti-tumor necrosis factor (anti-TNF) therapy has been widely used for the treatment of inflammatory bowel disease (IBD) changing the management of the disease. Data have been accumulated demonstrating the efficacy of these agents in inducing mucosal healing, reducing the need for hospitalizations, surgeries and improving patient's quality of life^(1,2). Unfortunately, roughly one third of patients are primary non responders and, among responders, dose intensification is needed in 23%–46% of patients and drug discontinuation occurs in 5%–13% of patients yearly^(3,4). With the advances in the understanding of the pathological mechanisms involved in IBD, new biologic agents with different mechanisms of action or small molecules targeting intracellular pathways were recently approved. Within this scenario, the aim of this review is to discuss the role of anti-TNF agents (infliximab, adalimumab, certolizumab and golimumab) in IBD as a therapeutic option in the era of biologics with other mechanisms of action highlighting the situations where its use as first line therapy would be appropriate.

CROHN'S DISEASE

Anti-TNF inducing remission

The great landmark in biological therapy occurred in 1997,

when Targan et al.⁽⁵⁾ published the first study (multicenter, double-blind) involving 108 patients with moderate to severe Crohn's disease (CD) refractory to steroids and aminosalicilates. Patients received infliximab (IFX) single doses of 5 mg/kg, 10 mg/kg, 20 mg/kg or placebo. Comparing IFX with placebo up to four weeks, the clinical response rate, as well as remission rate, was superior in the placebo group (65% IFX vs 17% placebo; 33% IFX vs 4% placebo, respectively). According to CLASSIC I study⁽⁶⁾ (double-blind, placebo-controlled RCT) the efficacy of adalimumab (ADA) was demonstrated in a group of 299 patients with moderate to severe CD naïve to anti-TNF. At week 4, higher rates of clinical remission were observed in ADA group (dose of 160 mg at week 0; 80 mg at week 2) than in the placebo group (36 % vs 12%, respectively). Additionally, improvement of symptoms was observed in 59% of patients on ADA treatment vs 37% in placebo group.

Anti-TNF inducing maintenance of remission

The efficacy of IFX in maintaining clinical response in CD was demonstrated in ACCENT I⁽⁷⁾ (multicenter, double-blind, randomized controlled trial) that involved 335 patients with luminal CD which responded to a single infusion of IFX within 2 weeks. At week 30, clinical remission was achieved in 39% of patients (IFX 5 mg/kg every 8 weeks) as compared to 21% in the placebo group. After week 54, 40% of the biological group achieved clinical remis-

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sion with corticosteroid withdrawal vs 15.0% in the placebo group. This data shows the effectiveness of IFX therapy in maintaining response for a longer period of time.

The long-term effectiveness of IFX treatment was assessed in a real-life cohort⁽⁸⁾ including 614 patients followed for a median of 55 months. The study demonstrated that approximately 11% of patients were primary non-responders and that the majority of responders had sustained clinical benefit with biological therapy (63.4%). The treatment was discontinued in 31.7% of patients due to complete remission, in 21.6% due to loss of response and in 12.8% due to adverse events. Thus, this study reinforced preliminary pivotal data in the real world setting.

Despite no head-to-head trial is available, indirect comparisons suggest that IFX or ADA may be preferred first-line agents for induction of remission in patients with moderate to severe CD. A recent meta-analysis by Singh et al.⁽⁹⁾ showed that all agents (IFX, ADA, Vedolizumab and Ustekinumab), except Certolizumab pegol, were superior to placebo for induction of clinical remission and effect size was strongest for IFX and ADA. In biologic-naïve patients and patients with response to induction therapy, IFX and ADA were ranked highest for induction of clinical remission and maintenance of remission.

Fistulizing Crohn's disease

The importance of anti-TNF therapies in fistulizing disease (abdominal or perianal) comes from one positive study (multicenter, double-blind-placebo-controlled trial) headed by Present et al.⁽¹⁰⁾, which enrolled 94 patients who had draining abdominal or perianal fistulas for at least three months. Patients received IFX (5 mg/kg or 10 mg/kg at weeks 0, 2 and 6) and the primary outcome was a 50% reduction in the drainage of fistula. At 18 weeks follow-up, fistula healing occurred in 68% (5 mg/kg), 56% (10 mg/kg) and 26% (placebo) of patients. The ACCENT II⁽¹¹⁾ (multicenter, double-blind, randomized, placebo-controlled trial) enrolled 306 patients with CD and one or more fistulas with active drainage. Patients responding to induction therapy (IFX 5 mg/kg at weeks 0, 2, 6) had an increased likelihood of a sustained response over a 54-week period compared with placebo (36% vs 19%, respectively), reinforcing the role of IFX maintenance therapy in fistulizing CD.

Regarding ADA therapy, there are no trials investigating fistula closure as primary endpoint. However, the subgroup analysis of the maintenance trial with ADA (CHARM)⁽¹²⁾ observed that complete fistula closure was achieved in a greater percentage of ADA-treated patients vs those receiving placebo (30% vs 13%, at week 26; 33% vs 13%, at week 56; respectively).

Prevention of postoperative clinical recurrence

Despite developments in medical therapy, surgical intervention may be required in up to 75% of CD patients 10 years from diagnosis^(13,14). Since surgery is not curative, clinical recurrence is reported in 50% of patients and endoscopic recurrence in 80% of patients in the first year after surgery.⁽¹⁵⁾ Anti-TNF agents, specifically IFX and adalimumab ADA, seem to be the most effective therapy for preventing postoperative recurrence.

Regueiro et al.⁽¹⁶⁾, in 2009, demonstrated in the first placebo-controlled randomized trial that endoscopic recurrence was significantly lower in the IFX group compared with controls at the first year after surgery (9.1% vs 84.6%). Similarly, the PREVENT trial⁽¹⁷⁾ (multicenter, placebo-controlled RCT) enrolled 297 patients undergoing ileocolonic resection within 45 days before randomiza-

tion and observed that before or at week 76 a significantly lower proportion of patients in the IFX group (5 mg/kg, every 8 weeks) had endoscopic recurrence compared with the placebo group (30.6% vs 60.0%, respectively).

Different strategies for prevention of postoperative recurrence were assessed in the POCER study⁽¹⁸⁾ which enrolled 101 patients at high risk of disease recurrence, after a three months trial of antibiotics. High-risk patients (smoker, penetrating disease, ≥ second operation) received thiopurine (or every other week ADA if thiopurine intolerant). At 6 months, endoscopic recurrence was demonstrated in 39% of patients in the thiopurine group and in 13% of patients in the ADA group. Similarly, Savarino et al. compared the efficacy of ADA, mesalamine and azathioprine in prevention of recurrence⁽¹⁹⁾. After 2 years, endoscopic recurrence was significantly lower in the ADA group (6.3%) as compared with the AZA patients (64.7%) and mesalamine group (83.3%). Clinical recurrence was also lower in the ADA group (12.5%) compared with AZA (64.7%) and mesalamine patients (50%). This data highlights that anti-TNF treatment exhibits higher efficacy in prevention of postoperative recurrence as compared with conventional therapy (FIGURE 1).

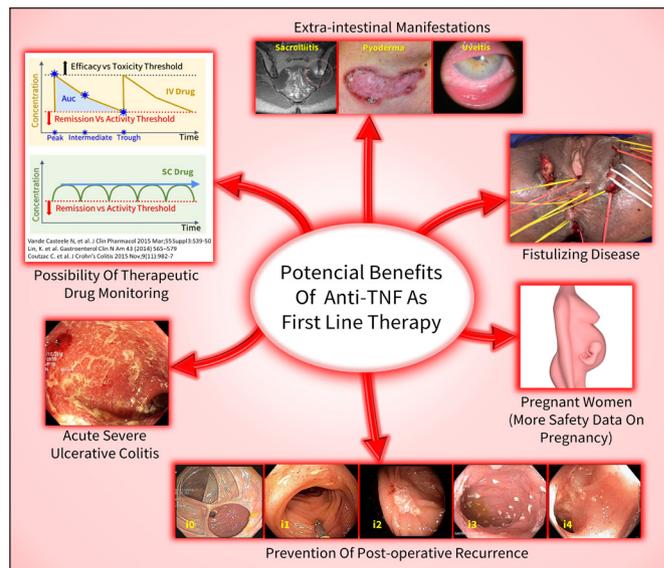


FIGURE 1. The role of anti-TNF agents in the setting of inflammatory bowel disease.

The trials that assessed the efficacy of anti-TNF agents in CD patients are summarized in TABLE 1.

ULCERATIVE COLITIS

Anti-TNF inducing remission

Definitive evidence for the efficacy of IFX in the treatment of ulcerative colitis (UC) was offered by the two large placebo-controlled clinical trials ACT-1 and ACT-2. In these studies, Rutgeerts et al.⁽²⁰⁾ assessed the IFX effectiveness in induction and maintenance of clinical response obtained at 8 weeks with IFX (weeks 0, 2, 6 followed by infusions every 8 weeks) in patients with Mayo score 6–12. At week 8, clinical response was superior in both groups (5 mg/kg or 10 mg/kg) when compared to placebo. The efficacy of ADA in induction of clinical remission in UC patients was also assessed in ULTRA I Trial⁽²¹⁾ that included patients with moderate

TABLE 1. Characteristics of included trials comparing different biologic agents for patients with moderate-severe Crohn's disease.

Trial (year)	Design; n	Population	Primary outcome	Follow-up duration	Medication	Results
Targan et al. ⁽⁵⁾ (1997)	Multicenter, double-blind, placebo-controlled RCT. n=108	Patients with moderate to severe CD refractory to 5-ASA and steroids.	Reduction of CDAI \geq 70 points after 4 weeks of single induction dose.	12 weeks	Placebo (n=25) IFX 5 mg/kg (n=27) IFX 10 mg/kg (n=28) IFX 20 mg/kg (n=28)	Clinical response (week 4) 17% 81% 50% 64%
CLASSIC I ⁽⁶⁾ (2006)	Multicenter, double-blind, placebo-controlled RCT. n=299	Patients with moderate to severe CD naive to anti-TNF therapy.	Clinical remission (CDAI <150) at week 4 after initial induction therapy.	4 weeks	Placebo (n=74) ADA 40 mg/ 20 mg (n=74) ADA 80 mg/ 40 mg (n=75) ADA 160 mg/ 80 mg (n=76)	Clinical remission (week 4) 12% 18% 24% 36%
ACCENT I ⁽⁷⁾ (2002)	Multicenter, double-blind, randomized controlled RCT. n=335	Patients with luminal CD that responded to a single infusion of IFX within 2 weeks.	Clinical remission (defined as a CDAI score <150) at week 30.	54 weeks	Placebo (n=110) IFX 5 mg/kg (n=113) IFX 10 mg/kg (n=112)	Clinical remission (week 30) 21% 39% 45%
Schnitzler et al. ⁽⁸⁾ (2009)	Single centre, real-life cohort. n=614	CD patients (treated for luminal, perianal or extraintestinal manifestations).	Assess the patients with initial response to IFX who had sustained clinical benefit at the end of follow-up.	55 months	IFX 5 mg/kg – single dose (n=432) IFX 5 mg/kg 0, 2 and 6 (n=182)	Clinical response (week 10) 87.7% 92.3%
Present et al. ⁽¹⁰⁾ (1999)	Randomized, multicenter, double-blind, placebo-controlled RCT. n=94	Patients who had draining abdominal or perianal fistulas of at least three months' duration.	Reduction of \geq 50% from base line in the number of draining fistulas.	18 weeks	Placebo (n=31) IFX 5 mg/kg (n=31) IFX 10 mg/kg (n=32)	Achieved primary endpoint 26% 68% 56%
ACCENT II ⁽¹¹⁾ (2004)	Multicenter, double-blind, randomized, placebo-controlled. n=306	Patients with CD and one or more fistulas, with active drainage, abdominal or perianal, of at least three months duration.	Time to loss of response during follow-up among patients who had a response at week 14 and were randomized.	54 weeks	Placebo IFX 5 mg/kg Placebo IFX 5 mg/kg	Absence of draining fistulas (week 54) 19% 36% Median time to loss of response 14 weeks >40 weeks
CHARM ⁽¹²⁾ (2007)	Multicenter, randomized, double-blind, placebo-controlled. n=854	Patients with moderate to severe luminal and fistulizing CD for at least 4 months.	Percentage of randomized responders who achieved clinical remission (CDAI <150) at weeks 26 and 56.	56 weeks	Placebo (n=170) ADA 40mg w (n=157) ADA 40mg eow (n=172) Placebo (n=47) ADA-treated patients (n=70)	Clinical remission at week 26 56 17% 12% 47% 41% 40% 36% Complete fistula closure at week 26 56 13% 13% 30% 33%

Continuation →

Trial (year)	Design; n	Population	Primary outcome	Follow-up duration	Medication	Results
Regueiro et al. ¹⁵ (2009)	Randomized, double-blind, placebo-controlled RCT. n=24	Patients with CD who had undergone ileocolonic resection and were allocated to receive intravenous IFX or placebo administered within 4 weeks of surgery and continued for 1 year.	Proportion of patients with endoscopic recurrence at 1 year after surgery.	1 year	Placebo (n=13)	Endoscopic recurrence (1 year) 84.6%
					IFX 5 mg/kg (n=11)	9.1%
PREVENT ¹⁷ (2016)	Multicenter, randomized, double-blind, placebo-controlled RCT. n=297	Patients with CD which had undergone ileocolonic resection within 45 days before randomization.	Clinical recurrence prior to or at week 76 and evidence of endoscopic recurrence.	76 weeks	Placebo (n=150)	Endoscopic recurrence (≤76 weeks) 60.0%
					IFX 5 mg/kg (n=147)	30.6%
POCER ¹⁸ (2015)	Part of multicenter, randomized, double-blind, placebo-controlled RCT. n=101	Patients with CD undergoing intestinal resection of all macroscopic disease, with an endoscopically accessible anastomosis.	Presence and severity of endoscopic recurrence 6 months after surgery.	6 months	Colonoscopy at 6 month post-operatively Thiopurine (n=62) ADA 160/80 (followed by 40 mg eow) (n=24)	Endoscopic recurrence 39% 13%
Savarino et al. ¹⁹ (2013)	Randomized, prospective, three-armed, unblinded. n=51	Patients with ileal or ileocolonic CD undergoing resection to receive after 2 weeks from surgery ADA, AZA or Mesalamine.	Proportion of patients with endoscopic and clinical recurrence at 2 years after surgery.	2 years	ADA 160/80 mg (followed by 40 mg eow) (n=16) AZA 2 mg/kg/day (n=17) Mesalamine 3g/day (n=18)	Endoscopic recurrence 6.3% 64.7% 83.3%

ADA: adalimumab; IFX: infliximab; RCT: randomized controlled trials; CDAI: Crohn's Disease Activity Index; eow: every other week; w: weekly.

to severe UC which were treated with ADA 160/80 mg or 80/40 mg or placebo at weeks 0 and 2. At week 8, clinical remission was achieved in 18.5% of patients on ADA 160/80 mg, 10.0% on ADA 80/40 mg, and 9.2% in the placebo group. It has been speculated that higher loading doses of ADA could improve clinical outcomes in CD and, specifically, in UC. However, preliminary data from SERENE-UC Trial⁽²²⁾ has not proven this hypothesis through the evaluation of clinical and endoscopic response after 8 weeks induction period with loading doses of ADA (160 mg at weeks 0, 1, 2, and 3, followed by 40 mg at weeks 4 and 6) compared to standard dose (160 mg at week 0 and 80 mg at week 2, followed by 40 mg at weeks 4 and 6). Data regarding long term outcomes are still awaited.

Anti-TNF inducing maintenance of remission

The effect of maintenance therapy with IFX over placebo was also demonstrated in ACT I and ACT II trials⁽²⁰⁾. At week 30, clinical response rates of 48.8% (5 mg/kg group), 45.9% (10 mg/kg group) and 23.1% (placebo group) were observed in ACT I; and 41.3% (5 mg/kg), 53.3% (10 mg/kg) and 15.4% (placebo) in ACT II. (10 mg/kg group) and 23.1% (placebo group) in ACT I; and 41.3% (5 mg/kg), 53.3% (10 mg/kg) compared 15.4% (placebo) in ACT II.

The ULTRA 2 study⁽²³⁾ (multicenter, randomized, double-blind, placebo-controlled, phase III) was conducted to further investigate the long-term efficacy of ADA in patients with moderate to severe UC that had previously been exposed or not to anti-TNF therapy. At week 52, clinical remission was documented in 17.3% of patients treated with ADA (40 mg every other week) vs 8.5% of patients treated with placebo. Accordingly, real-life data⁽²⁴⁾ demonstrate higher rates of induction and maintenance of remission in with ADA treatment. A recent Italian study⁽²⁴⁾ showed that 54,9% of patients achieved clinical remission and the drug was maintained in 56,6% of the patients during a median follow-up of 18 months.

According to PURSUIT- M study⁽²⁵⁾, which analyzed maintenance therapy with Golimumab (GOL) in responders to induction therapy, clinical response, at week 54, was seen in 47.0% of patients on GOL 50 mg every 4 weeks and 49.7% of patients on GOL 100 mg administered in the same interval. Comparing to placebo, 31.2% had clinical response, reinforcing the superiority of this drug over placebo in the maintenance of remission in UC.

Recently, through a systematic review and network meta-analysis, Singh et al.⁽²⁶⁾, assessed the comparative efficacy and safety of different therapies as first-line (biologic-naïve) and second-line (prior exposure to anti-tumour necrosis factor) therapy through the analysis of randomized controlled trials

(RCTs) in adults with moderate-severe UC treated with anti-TNF agents, anti-integrin agents and janus kinase (JAK) inhibitors. In biologic-naïve patients, it was observed that all agents (IFX, ADA, GOL, vedolizumab and tofacitinibe) were superior to placebo for induction of mucosal healing and effect size was strongest for IFX and vedolizumab. As compared to IFX and ADA as first-line therapy, data have shown superiority of IFX over ADA for inducing clinical response and decreasing the risk of hospitalisation.

Acute severe ulcerative colitis

Sands et al.⁽²⁷⁾ conducted the first trial in the setting of acute severe UC (ASUC), which enrolled which enrolled 11 steroid-refractory patients. After a 2 week follow-up, patients that received a single infusion of IFX (5, 10 or 20 mg/kg) achieved 50% of response to treatment compared to no response in the placebo group. Subsequently, in 2005, Jarnerot et al.⁽²⁸⁾ evaluated 45 patients with ASUC refractory to high doses of intravenous corticosteroids. Greater efficacy was observed in patients that undergone a single dose of IFX (5 mg/kg) when compared to

placebo at 3 months of follow-up. Regarding colectomy rates, 29% of patients required surgery in the IFX group vs 67% in the placebo group. In a long-term follow-up (3 years)⁽²⁹⁾, biological therapy showed sustained benefit with colectomy rates of 50% in the IFX group compared to 76% in the placebo group.

Many studies have highlighted the importance of accelerated IFX induction regimen in ASUC. In this context, Gibson et al.⁽³⁰⁾ demonstrated that, at 3 months of follow-up, 6.7% of patients in the accelerated regimen group (three doses of IFX over 2 weeks) demanded colectomy vs 40% of patients that received IFX induction in a standard dose of 6 weeks, showing that IFX intensified dosing induction regimen could improve the efficacy of this drug in decreasing the need for early colectomy.

However, a recent metanalysis⁽³¹⁾ have not confirmed this initial data and found no association between accelerated IFX induction therapy and lower rates of colectomy in patients with ASUC compared to standard induction therapy.

The summary of studies evaluating efficacy of anti-TNF agents in UC patients are listed in TABLE 2.

TABLE 2. Characteristics of included controlled trials comparing different biologic agents for patients with for moderate-severe ulcerative colitis.

Trial (year)	Design; n	Population	Primary outcome	Follow-up duration	Medication	Results	
ACT 1 ⁽²⁰⁾ (2005)	Multicenter, randomized, double-blind, placebo-controlled RCT. n=364	Patients with moderate-to-severe active ulcerative colitis despite treatment with concurrent medications.	Clinical response at week 8 and secondarily, clinical response or remission and mucosal healing at weeks 8, 30, and 54.	54 weeks	Placebo (n=121)	Clinical response at week 8 37.2%	54 19.8%
					IFX 5 mg/kg (n=121)	69.4 %	45.5%
					IFX 10 mg/kg (n=122)	61.5 %	44.3%
ACT 2 ⁽²⁰⁾ (2005)	Multicenter, randomized, double-blind, placebo-controlled RCT. n=364	Patients with moderate-to-severe active ulcerative colitis despite treatment with concurrent medications.	Clinical response at week 8 and secondarily, clinical response or remission and mucosal healing at weeks 8 and 30.	30 weeks	Placebo (n=123)	Clinical response at week 8 29.3%	30 26.0%
					IFX 5 mg/kg (n=121)	64.5 %	47.1%
					IFX 10 mg/kg (n=120)	69.2 %	60.0%
ULTRA I ⁽²¹⁾ (2011)	Multicenter, randomized, double-blind, placebo-controlled RCT. n=390	Anti-TNF naive patients with moderate-to-severe active ulcerative colitis.	Clinical remission at week 8 after initial induction therapy.	8 weeks	Placebo (n=130)	Clinical response (week 8) 9.2%	
					ADA 80/40 (followed by 40 mg EOW) (n=130)	10.0%	
					ADA 160/80 (followed by 40 mg EOW) (n=130)	18.5%	
SERENE- UC ⁽²²⁾ (2019)	Multicenter, randomized, double-blind. n=852	Patients with moderate-to-severe active ulcerative colitis.	Clinical remission at week 8.	8 weeks	ADA 160 mg at week 0, 80 mg at week 2 (followed by 40 mg eow) (n=340)	Clinical remission (week 8) 10.9%	
					ADA 160 mg at weeks 0, 1, 2, and 3 (followed by 40 mg EOW) (n=512)	13.3%	

Continuation →

Trial (year)	Design; n	Population	Primary outcome	Follow-up duration	Medication	Results
ULTRA 2 ⁽²³⁾ (2012)	Multicenter, randomized, double-blind, placebo-controlled RCT. n=494	Patients with moderate-to-severe ulcerative colitis who received concurrent treatment with oral corticosteroids or immunosuppressants.	Clinical remission at week 8 and week 52 after initial induction therapy.	52 weeks	Placebo (n=246) ADA160/80 (followed by 40 mg EOW) (n=248)	Clinical remission at week 8 52 9.3% 8.5% 16.5% 17.3%
Tursi et al. ⁽²⁴⁾ (2018)	Real-life, multicenter, retrospective, observational. n=107	Patients with ulcerative colitis unresponsive to standard treatments and treated with ADA.	Induction and maintenance of remission in UC, defined as Mayo score ≤2.	24 months	ADA160/80 (followed by 40 mg EOW)	Clinical remission (at 3-month) 54.9%
PURSUIT-M ⁽²⁵⁾ (2014)	Multicenter, randomized, double-blind, placebo-controlled RCT. n=464	Patients with moderate-to-severe ulcerative colitis who responded to induction therapy with GOL.	Clinical response maintained through week 54.	54 weeks	Placebo (n=156) GOL 50 mg every 4 weeks (n=154) GOL 100 mg every 4 weeks (n=154)	Clinical remission (week 54) 31.2% 47.0% 49.7%
Sands et al. ⁽²⁷⁾ (2001)	Randomized, double-blind, placebo-controlled RCT. n=11	Severe ulcerative colitis for at least 2 weeks and receiving at least 5 days of intravenous corticosteroids.	Treatment failure at 2 weeks after infusion.	10 weeks	Placebo (n=3) IFX 5 mg/kg (n=3) IFX 10mg/kg (n=3) IFX 20mg/kg (n=2)	Treatment success (week 2) 0% 66.7% 33.3% 50.0%
Järnerot et al. ⁽²⁸⁾ (2005)	Randomized, double-blind, placebo-controlled RCT. n=45	Patients with an acute severe or moderately severe ulcerative colitis that did not respond quickly to intravenous corticosteroids.	Colectomy or death 3 months after randomization.	6 months	Placebo (n=21) IFX 5 mg/kg (n=24)	Colectomy rates (90 days after) 67% 29%
Gustavsson et al. ⁽²⁹⁾ (2010)	Randomized, double-blind, placebo-controlled RCT. n=45	patients with an acute severe or moderately severe ulcerative colitis that did not respond quickly to intravenous corticosteroids.	Determine the number of patients escaping a colectomy at follow-up.	3 years	Placebo (n=21) IFX 5 mg/kg (n=24)	Colectomy rates (3 years after) 76% 50%

ADA: adalimumab; IFX: infliximab; GOL: golimumab; RCT: randomized controlled trials; EOW: every other week.

SPECIFIC SITUATIONS

Pregnancy

Many studies have evaluated the safety profile of anti-TNF drugs in the setting of pregnancy. With exception of Certolizumab (CZP), which has minimal placental transfer, others anti-TNF agents (IFX and ADA) are actively transported across the placenta since the 13th week⁽³²⁾.

Preliminary data from the PIANO registry⁽³³⁾, an extensive database that evaluated pregnant women using biologics, concluded that

there were no differences in the rate of congenital malformations, preterm births, or other adverse events in pregnant women exposed to anti-TNF compared to patients exposed to thiopurines and the control group. Conversely, data from the EVASION study⁽³⁴⁾ have demonstrated an increased risk of maternal complication, mainly infections, in pregnant women exposed to anti-TNF. However, exposition to biologics during pregnancy was not associated with increased risk of infection in the offspring during the first year of life. Regarding the risk of complications, no differences were reported between women treated during the third trimester and those

which stopped anti-TNF at, or before 24 weeks of amenorrhea (as recommended by guidelines)⁽³⁵⁾.

No data showed increased rate of spontaneous miscarriages, stillbirths, preterm deliveries or congenital malformations with the use of ADA during pregnancy. Even though anti-TNF therapy can be considered safe in the early stages of pregnancy, the guidelines recommend temporary discontinuation of treatment around gestational week 24-26 in patients presenting sustained remission⁽³⁵⁾.

Extraintestinal manifestations

Extraintestinal manifestations (EIM) in IBD are most frequently reported in joints (peripheral and axial arthropathies), skin, hepatobiliary tract, and eyes. In this setting, the frequencies of involvement range from 6% to 47%⁽³⁶⁻³⁸⁾. Anti-TNF drugs have significantly changed the management of EIM in IBD patients. A study headed by Caspersen and colleagues⁽³⁹⁾ observed that patients with CD on IFX presented 80% of improvement or remission in skin or joint symptoms with biological therapy. Similarly, in an open-label study, Barreiro-de-Acosta et al.⁽⁴⁰⁾ concluded that 66.7% of CD patients with at least one EIM that received ADA on standard dose achieved remission (38.1%) or any response (28.5%) of the EIM.

A recent systematic review⁽⁴¹⁾ has further corroborated the benefits of anti-TNF treatment in EIM through the analysis of 9 interventional studies and 13 non-interventional studies. Regarding patients with pyoderma gangrenosum under anti-TNF therapy, complete response was observed in 21%–25% of patients in interventional studies and in 92%–100% patients in non-interventional studies. Similar results were observed for other cutaneous manifestations, such as erythema nodosum. Complete response after anti-TNF treatment was also observed in patients with joints involvement with a reduction in arthralgia prevalence from 47.1% to 26.8% and arthritis prevalence from 8.7% to 2.1%.

LIMITATIONS OF ANTI-TNF USE

Safety and adverse events

Although the overall safety profile of anti-TNF is considered satisfactory, there are some concerns about the higher risk of adverse events with these agents, including infection, malignancy, metabolic and immunological disorders, specially when used in combination with thiopurines. Susceptibility to infection is of significant concern following the long-term treatment with anti-TNF. Analysis from the CD TREAT registry⁽⁴²⁾ found that IFX treatment was associated with a significant increased risk of serious infections (unadjusted rates of 2.06 per 100 patient-years) compared with the other treatments-only group (1.42 per 100 patient-years). The risk of opportunistic infections is also clearly increased with anti-TNF treatment. Due to the role of TNF in the formation of granulomas, anti-TNF-a therapy has been associated with increased risk of tuberculosis reactivation⁽⁴³⁾. It is important to emphasize that disease activity itself and treatment with steroids and narcotic analgesics were also linked with infectious complications. Despite the increased risk of serious infection with IFX, mortality rate was similar between IFX and other-treatments-only-treated CD patients⁽⁴²⁾.

An important adverse event reported with anti-TNF treatment is the occurrence of skin lesions⁽⁴⁴⁾. A retrospective cohort⁽⁴⁵⁾ analyzed skin lesions of 917 patients associated with the use of anti-TNF therapy. It was shown that 29% of patients developed drug-induced skin lesions as follows: psoriasiform eczema (30.6%),

eczema (23.5%), xerosis cutis (10.6%), palmoplantar pustulosis (5.3%), psoriasis (3.8%) and others (26.1%). All the lesions reported occurred between the 3rd and 4th infusion of IFX and discontinuation of therapy was rarely required.

A great concern with the use of anti-TNF is related to the increased risk for malignancy. A retrospective study comparing patients on ADA monotherapy with those on combination therapy with immunosuppressants conducted by Osterman et al.⁽⁴⁶⁾ demonstrated no increase in lymphoma risk with ADA monotherapy. On the other hand, the authors observed an eightfold increase in lymphoma risk in patients on combination therapy with immunosuppressant compared with the general population, suggesting that the increased risk is likely attributable to the immunomodulator. Similarly, the REFURBISH study⁽⁴⁷⁾ found that the risk of T-cell non-Hodgkin's lymphoma in IBD patients is not increased with the use of anti-TNF monotherapy, however, when anti-TNF is used in combination with thiopurine therapy this risk is higher.

On the other hand, a recent French cohort study⁽⁴⁸⁾ analyzed the risk of lymphoma in patients with IBD which were exposed to thiopurines and anti-TNF agents (alone or in combination). The use of thiopurine or anti-TNF monotherapy was associated with a small but statistically significant increased risk of lymphoma. However, the risk was higher with combination therapy.

Loss of response and therapeutic drug monitoring (TDM)

Although anti-TNF agents are effective in treating IBD, primary failures of anti-TNF induction therapy occur in up to 40% of patients in clinical trials and in 10%–20% in clinical series^(7,49,50). Moreover, almost half of patients with initial response develop secondary loss of response within the first year⁽⁵¹⁾. Part of this failure to anti-TNF is mediated by pharmacokinetic issues related to undetectable or subtherapeutic drug concentrations with or without antidrug antibodies⁽⁵²⁾.

A recent prospective real-life study (PANTS)⁽⁵³⁾ involving 1601 CD patients naive for biological therapy treated with IFX or ADA concluded that immunogenicity is significantly associated with non-remission at week 54. Moreover, concomitant therapy with immunomodulators can reduce immunogenicity in IFX and also in ADA therapy, suggesting better outcomes when these drugs are used in association.

Measuring drug levels and determination of the presence of antidrug antibodies has been shown to be useful in guiding the treatment strategy once it has the potential of identifying those which will benefit from dose escalation and those which will be better managed by switching to an alternate drug within or outside the drug class. However, more data are needed to define the role of TDM into clinical practice specially regarding the definition the optimal thresholds to target^(54,55).

In this setting, therapeutic drug monitoring (TDM) has been implemented as an auxiliary tool for treatment decision-making. While reactive TDM has an established role for managing secondary loss of response and seems to be more cost-effective compared with empiric dose escalation, proactively monitoring of patients in stable remission remains controversial⁽⁵⁶⁾.

A retrospective observational cohort study⁽⁵⁷⁾ observed that reactive TDM to guide IFX dose adjustment compared with clinical decision making alone is associated with higher post adjustment clinical response, endoscopic remission and fewer hospitalizations.

However, recent data demonstrate that proactive TDM to potentially prevent future flare and loss-of-response in a treat-to-target

therapeutic approach may arise as a novel strategy to optimize anti-TNF therapy efficacy, safety, and cost⁽⁵⁸⁻⁶⁰⁾.

Preliminary studies indicate that drug titration to a target trough level, performed in patients with clinical response, can also improve the efficacy of anti-TNFs⁽⁶¹⁻⁶⁵⁾, preventing undetectable or low drug levels that consequently lead to immunogenicity and loss-of-response or infusion reactions⁽⁶⁶⁾.

Recently, the American Gastroenterological Association (AGA)⁽⁶⁷⁾ suggested the use of reactive TDM in the context of secondary loss of response to anti-TNF therapy aiming trough concentrations of IFX ≥ 5 $\mu\text{g/mL}$, ADA ≥ 7.5 $\mu\text{g/mL}$, and CTZ ≥ 20 $\mu\text{g/mL}$. However, the lack of data determining specific cut-offs and timepoints limit the overspread use of proactive TDM in clinical practice.

CONCLUSION

The use of drugs targeting anti-TNF has greatly advanced the therapeutic armamentarium for IBD and have become the cornerstone of treatment for moderate to severe UC and CD by improving quality of life and decreasing the risk of surgery and hospitalization, especially when used early in the treatment course.

Anti-TNFs agents have the best long-term evidence of efficacy in IBD with an acceptable safety profile with proven effectiveness for both induction and maintenance therapy, decreasing corticosteroid exposure and promoting mucosal healing.

The greatest concerns during the use of anti-TNF agents are mainly due to infectious events and immunogenicity. The concomitant use of immunomodulator can prevent the development of neutralizing anti-drug antibodies and increase trough levels of biologics, but, conversely, may increase the risk of infections and malignancies.

In the absence of head-to-head comparisons, the choice of the biological agent may be challenging and should take into account several variables. This comprehensive review highlights the specific scenarios in which the evidence supports the use of anti-TNFs as first-line agents, such as acute severe ulcerative colitis, fistulizing CD, and extra-intestinal manifestations of IBD. Moreover, these agents may be considered an appropriate treatment in the setting of pregnancy and prevention of post-operative recurrence.

Authors' contribution

All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

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RESUMO – Contexto – As doenças inflamatórias intestinais (DII), tanto a doença de Crohn (DC) como a retocolite ulcerativa (RCU), são doenças crônicas imunomediadas que se apresentam com períodos de surto e remissão e requerem terapia a longo prazo. A terapia com anti-fator de necrose tumoral (anti-TNF) tem mudado o manejo da doença reduzindo a necessidade de hospitalizações, cirurgias e melhorando a qualidade de vida dos pacientes. **Objetivo** – O objetivo do presente trabalho é apresentar uma revisão sobre a importância dos agentes anti-TNF no contexto da DII, levando em consideração situações em que essas drogas são usadas como terapia de primeira linha. **Métodos** – Revisão narrativa baseada nas melhores evidências disponíveis na literatura através de buscas feitas nas bases de dados MedLine e PubMed até abril de 2020, utilizando as seguintes palavras chaves: “doença inflamatória intestinal”, “agentes anti-TNF” e “terapia biológica”. **Conclusão** – A terapia biológica permanece sendo fundamental no tratamento da DII. Na ausência de estudos “head-to-head” comparando os biológicos entre si, a escolha do agente biológico pode ser um desafio na prática clínica e múltiplas variáveis devem ser levadas em consideração. Os agentes anti-TNF devem ser considerados terapia de primeira linha em situações específicas como na colite ulcerativa aguda grave, na doença de Crohn fistulizante e nas manifestações extra-intestinais da doença inflamatória intestinal, uma vez que há evidências científicas robustas que sustentam a sua eficácia e segurança nessas situações.

DESCRITORES – Doenças inflamatórias intestinais. Fator de necrose tumoral alfa, antagonistas & inibidores. Terapia biológica. Doença de Crohn, tratamento farmacológico. Colite ulcerativa, tratamento farmacológico.

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