

Overview of Biological Therapy in Ulcerative Colitis: Current and Future Directions

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ABSTRACT

The treatment of ulcerative colitis (UC) has changed over the last decade. It is extremely important to optimize the therapies which are available nowadays and commonly used in daily clinical practice, as well as to stimulate the search for more powerful drugs for the induction and maintenance of sustained and durable remission, thus preventing further complications. Therefore, it is mandatory to identify the patients' prognostic variables associated with an aggressive clinical course and to test the most potent therapies accordingly.

To date, the conventional therapeutic approach based on corticosteroids, salicylates (sulfasalazine, 5-aminosalicylic acid) or immunosuppressive agents is commonly used as a first step to induce and to maintain remission. However, in recent years, knowledge of new pathogenetic mechanisms of ulcerative colitis have allowed us to find new therapeutic targets leading to the development of new treatments that directly target proinflammatory mediators, such as TNF-alpha, cytokines, membrane migration agents, cellular therapies. The aim of this review is to provide the most significant data regarding the therapeutic role of drugs in UC and to give an overview of biological and experimental drugs that will become available in the near future. In particular, we will analyse the role of these drugs in the treatment of acute flare and maintenance of UC, as well as its importance in mucosal healing and in treating patients at a high risk of relapse.

Key words: ulcerative colitis – therapy – biological therapy – infliximab – adalimumab.

Abbreviations: ADA: adalimumab; AZA: azathioprine; CyA: cyclosporine; EMA: European Medicines Agency; FDA: Food and Drug Administration; IBD: inflammatory bowel disease; IBDQ: inflammatory bowel disease questionnaire; IFX: infliximab; PGA: physician's global assessment; TNF- α : tumour necrosis factor alpha; UC: ulcerative colitis.

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INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by the alternation of acute and remission phases, affecting mainly young patients, whose quality of life may be strongly compromised by the disease progression.

In fact, over time, the progression of UC may lead to an impairment of the normal anatomy and physiology of the colon due to proximal extension, stricturing, dysmotility and

anorectal dysfunction (tenesmus, urgency, incontinence) [1]. All these aspects, together with the occurrence of extraintestinal manifestations and incidence of dysplasia and colorectal cancer, can impact on the working and overall ability of patients and ultimately on their quality of life [2, 3].

It should also be taken into consideration that only half of the patients with UC show a stable remission over time, whilst the remainder may have a more aggressive clinical course characterized by frequent relapses, severe onset of disease, refractoriness and steroid-dependency [4, 5]. Moreover, even in patients in clinical remission, the persistence of mucosal lesions may have a relevant negative impact on the clinical course of disease, with a significantly increased immunosuppression, hospitalization and colectomy rates [6].

The conventional approach to managing active UC is aimed at obtaining clinical response and at inducing and maintaining clinical and endoscopic corticosteroid-free remission.

Along with conventional therapeutic approaches currently used in the treatment of UC, advances in the understanding of pathophysiology of the disease have led to the detection of new therapeutic targets and the development of new drugs.

INFLIXIMAB

Infliximab (IFX) is a chimeric monoclonal antibody against tumour necrosis factor alpha (TNF- α), intravenously administered at a standard dose of 5 mg/Kg at week 0, 2, 6 and then every 8 weeks.

The first randomized double blind, placebo-controlled trials evaluating efficacy and safety of IFX for induction and maintenance therapy in ulcerative colitis were ACT 1 and

2 trials, which are summarised in Table I-a,b. Each study included 364 adult patients with moderate-to-severe UC. Patients received placebo or IFX infusions (5 or 10 mg/kg of body weight) intravenously until week 46 in ACT 1 and week 22 in ACT 2.

Acute UC. The treatment with IFX 5 mg or 10 mg was found to be significantly more effective than placebo in the induction of clinical remission, clinical response and mucosal healing at week 8 [7].

Maintenance of remission. Ulcerative colitis patients who obtain the clinical remission with IFX, benefit of IFX therapy as the maintenance treatment. ACT 1 and ACT 2 studies have shown that patients with acute UC who achieved benefit from IFX at 8 weeks can be successfully maintained in clinical

Table I-a. ACT 1 study (infliximab vs placebo)

Outcome	ACT 1					
	Placebo (n = 121)	IFX 5 mg/kg (n = 121)	p value	Placebo (n = 121)	IFX 10 mg/kg (n = 122)	p value
Clinical response, n (%)						
Week 8	45 (37.2)	84 (69.4)	< 0.001	45 (37.2)	75 (61.5)	< 0.001
Week 30	36 (29.8)	63 (52.1)	\leq 0.001	36 (29.8)	62 (50.8)	0.002
Week 54	24 (19.8)	55 (45.5)	\leq 0.001	24 (19.8)	54 (44.3)	\leq 0.001
Clinical remission, n (%)						
Week 8	18 (14.9)	47 (38.8)	< 0.001	18 (14.9)	39 (32.0)	0.002
Week 30	19 (15.7)	41 (33.9)	\leq 0.001	19 (15.7)	45 (36.9)	\leq 0.001
Week 54	20 (16.5)	42 (34.7)	\leq 0.001	20 (16.5)	42 (34.4)	0.001
Mucosal healing ^{††} , n (%)						
Week 8	41 (33.9)	75 (62.0)	< 0.001	41 (33.9)	72 (59.0)	< 0.001
Week 30	30 (24.8)	61 (50.4)	\leq 0.001	30 (24.8)	60 (49.2)	< 0.001
Week 54	22 (18.2)	55 (45.5)	\leq 0.001	22 (18.2)	57 (46.7)	< 0.001

IFX, infliximab; †† Absolute Mayo subscore for endoscopy of 0 or 1.

Table I-b. ACT 2 study (infliximab vs placebo)

Outcome	ACT 2					
	Placebo (n = 123)	IFX 5 mg/kg (n = 121)	p value	Placebo (n = 123)	IFX 10 mg/kg (n = 120)	p value
Clinical response, n (%)						
Week 8	36 (29.3)	78 (64.5)	< 0.001	36 (29.3)	83 (69.2)	< 0.001
Week 30	32 (26.0)	57 (47.1)	\leq 0.001	32 (26.0)	72 (60.0)	\leq 0.001
Clinical remission, n (%)						
Week 8	7 (5.7)	41 (33.9)	< 0.001	7 (5.7)	33 (27.5)	< 0.001
Week 30	13 (10.6)	31 (25.6)	0.003	13 (10.6)	43 (35.8)	< 0.001
Mucosal healing ^{††} , n (%)						
Week 8	38 (30.9)	73 (60.3)	< 0.001	38 (30.9)	74 (61.7)	< 0.001
Week 30	37 (30.1)	56 (46.3)	0.009	37 (30.1)	68 (46.7)	< 0.001

IFX, infliximab; †† Absolute Mayo subscore for endoscopy of 0 or 1.

Table I-c. Patients refractory to corticosteroid therapy at week 8

Outcome	ACT 1			ACT 2		
	Placebo	IFX 5 mg/kg	IFX 10 mg/kg	Placebo	IFX 5 mg/kg	IFX 10 mg/kg
Clinical response, n (%)						
Week 8	12/34 (35.3)	24/31 (77.4)*	21/31 (67.7) [†]	12/32 (37.5)	19/30 (63.3) [°]	19/29 (65.5) [§]

* p < 0.001 compared to placebo; † p 0.010 compared to placebo; ° p 0.053 compared to placebo; § p 0.011 compared to placebo; IFX, infliximab.

remission with scheduled infusions for up to 3 years. These studies showed also that patients in clinical remission at week 8, who have received IFX infusions, had a sustained clinical remission (namely a clinical response or clinical remission at week 22 and week 46) significantly higher than patients treated with placebo (Table I-a).

The sustained clinical response in steroid-dependent UC patients who achieved clinical remission or response after IFX induction has been confirmed in another recent study by Armuzzi et al. In this study, where 76% of patients achieved clinical benefit after IFX induction, 64% of patients had sustained clinical response and 77% had a colectomy-free survival during a median follow-up, on IFX maintenance therapy, of 41.5 months [8].

Predictor of response. The identification of predictive parameters of response to IFX in UC is useful to minimize the rate of side effects and costs related with useless treatments. Several clinical endoscopic and biochemical prognostic factors of poor or favourable response to IFX therapy have been identified, but most need appropriate validation (Table II) [9].

Table II. Predictor factors of treatment with Infliximab

Positive prognostic factors	Negative prognostic factors
Mucosal healing	Active UC duration ≤ 3 years
High serum level of albumin	High disease severity
Combination therapy IFX+thiopurines (> thiopurine naïve patients)	Mayo endoscopic subscore of 3 at baseline
	Absence of short term clinical response after IFX therapy
	Refractoriness to corticosteroids
	Previous treatment with cyclosporine
	Hospitalization
	High C-reactive protein at baseline or after induction
	Older age
	Hb <9.4 g/dL at induction
	pANCA positive antibodies

UC, ulcerative colitis

Positive prognostic factors include mucosal healing, high serum level of albumin and combination therapy with IFX and thiopurines, mostly for thiopurine naïve patients.

In particular, mucosal healing at week 8 has been found a strong predictor of sustained remission and reduced risk of colectomy in two studies [7, 10].

A high serum level of albumin during IFX therapy has been found to be a significant predictor of favorable response, likely because it maintains higher IFX concentrations, longer half-life and lower clearance than patients with lower serum albumin levels [11].

Several prognostic factors have been found associated with poor response to IFX therapy and increased risk of colectomy, such as active UC with short duration (≤ 3 years), high disease severity or Mayo endoscopic subscore of 3 at baseline, absence of short term clinical response after IFX therapy or corticosteroids or cyclosporine, hospitalization, previous treatment with steroids or cyclosporine, high C-reactive protein at baseline or after induction, older age,

low hemoglobin level at induction, and pANCA positive antibodies [7, 12-14].

Data from RCTs and of real life also showed that the severity of UC, inflammation burden, refractoriness to intravenous steroids and/or cyclosporine and hospitalization were predictors of non response to IFX [8, 14, 15].

Steroid dependent/refractory UC. Efficacy of IFX in this clinical context has been investigated in several studies showing that high doses of IFX or its combination with azathioprine (AZA) seems to be more effective. In the ACT 1 study, the prevalence of patients who had clinical response was significantly higher in those treated with IFX than in placebo with both 5 mg/Kg ($p < 0.001$) and 10 mg/Kg ($p = 0.010$), whilst in ACT 2, clinical response was significantly greater than placebo only for patients treated with IFX 10 mg/Kg ($p = 0.011$) (Table I-c).

The SUCCESS trial randomised 239 patients with moderate-to-severe UC, biological or AZA naïve or without AZA ≥ 3 months before entry to receive AZA 2.5 mg/kg/day, IFX 5 mg/kg or IFX + AZA for 16 weeks. At 8 weeks, partial Mayo score improvement was greater in patients receiving IFX+AZA or IFX monotherapy than AZA monotherapy. At week 16, the primary endpoint, namely steroid-free remission was achieved at a higher rate in patients in the combined IFX + AZA arm compared to monotherapy with AZA or IFX alone (Table III) [16].

Table III. SUCCESS study

Outcome	UC SUCCESS		
	IFX + AZA (n = 78)	IFX (n = 77)	AZA (n = 76)
Clinical endpoints, week 8			
Partial Mayo score decrease of 1 or more	85.90% [†]	88.31% [†]	66.79%
Partial Mayo score decrease of 2 or more	52.56%	49.35%	36.84%
Clinical endpoints, week 16			
Steroid-free remission	39.74%* [†]	22.08%	23.68%
Mayo score response	76.92% [†]	68.83% [†]	50.00%
Mucosal healing	62.82% [†]	54.55% [†]	36.84%

UC, ulcerative colitis; AZA, azathioprine; IFX, infliximab; * $p < 0.05$ compared to IFX; [†] $p < 0.05$ compared to AZA

In a randomised placebo controlled trial of IFX (5 mg/kg) in the treatment of 43 steroid-resistant UC patients, there was no statistically significant difference between the IFX and placebo groups, so in this trial, the data does not support the use of IFX in the management of moderately active steroid resistant UC [17].

The efficacy of IFX in patients with acute severe steroid-refractory UC has been compared with cyclosporine (CyA) in six retrospective cohort studies (321 patients) and analyzed in a recent meta-analysis that did not show significant differences between IFX and CyA in the colectomy rate, adverse drug reactions and postoperative complications [18].

One of these is a small retrospective cross-over study (19 patients) which evaluated the efficacy of IFX and CyA in patients with severe, corticosteroid-refractory UC, who

failed the first treatment with IFX or CyA or vice versa. Forty percent of patients in the IFX-salvage group and 33% in the CyA-salvage group went into remission, but 16% of the patients treated with IFX experienced severe adverse events including one sepsis and one death [19].

Another study included in the meta-analysis investigated the efficacy of IFX and CyA as a second-line rescue therapy in 86 steroid-refractory UC patients, unsuccessfully treated with CyA (65 patients) or IFX (21 patients). Twenty-six patients of the first group (40%) and 7 patients (33.3%) of the second group failed to respond to the second-line rescue therapy and underwent colectomy within 3 months. Nine patients treated with IFX as rescue therapy and 6 patients treated with CyA underwent colectomy within 1 year, with an overall probability of colectomy-free survival of 61.3% at 3 months and 41.3% at 12 months, without significant differences between the two groups. After the second-line rescue therapy, 19 patients experienced adverse events including 1 case of fatal pulmonary embolism and 9 infectious complications [20].

However, only one randomized trial compared the efficacy of CyA versus IFX in 115 patients with acute severe steroid-refractory UC, 58 treated with intravenous CyA (2 mg/kg/day followed by oral drug administration until day 98) and 57 with IFX (5 mg/kg at week 0-2-6) and with AZA (started at day 7 in patients with a clinical response), in both groups. This trial also showed that CyA is as effective as IFX, with no significant difference regarding clinical response, mucosal healing, colectomy rate and severe adverse events. Therefore, in clinical practice, the treatment choice should be guided by the experience of the physician and the possibility of the centre [21].

Mucosal healing. Mucosal healing represented the secondary end-point of several trials, including ACT and SUCCESS trials [7, 16, 22], and has been reported with a prevalence ranging from 30 to 45% at one year, with higher rates with combo therapy (IFX+AZA, but it was evaluated in the SUCCESS trial just up to 16 weeks), where one-year healing rate reached 63%.

However, the prognostic significance of mucosal healing after IFX therapy in UC is still a matter of debate.

A recent study evaluated the proportion of mucosal healing after one-year of IFX in 22 UC patients, achieving clinical remission in 12 (55%) and mucosal healing in 7 (32%). However, clinical remission was achieved in 71% of UC patients with mucosal healing, and deep remission, namely mucosal healing plus clinical remission, in only 5 (22.7%) UC patients. After stopping therapy, in 13 UC patients (59%), 5 in deep remission, IFX needed to be restarted after a median of 7.5 months and the response rate for retreatment was 54%. In univariate analysis, no demographic or clinical parameter was associated with the need of restarting therapy and no association was found between mucosal healing and combined immunomodulator therapy [23].

These data were not confirmed in another French study, which comprised 63 patients with refractory UC who received maintenance treatment with IFX. Thirty patients (48%) achieved mucosal healing and had better long-term outcomes, with significantly reduced colectomy rates (cumulative 1, 2 and 3 years survival rates of 100, 96 and 96% vs 80, 65 and

65%, respectively; $p=0.004$) compared with patients without mucosa healing, which was the only factor associated with colectomy free survival by multivariate analysis (OR=18.01; CI95% 1.58-204.92) [24].

Recently, mucosal healing was considered as a treatment target for UC because it is associated with improved clinical outcomes. Bouguen et al. evaluated the feasibility of "treating to target" according to endoscopic findings, to reach mucosal healing and histological healing. A total of 60 patients underwent at least two consecutive endoscopic assessments with an adjustment of medical therapy in cases of persistent endoscopic activity. They demonstrated that treatment towards the target of mucosal healing is feasible in clinical practice in UC patients and seems to be of benefit [25].

ADALIMUMAB

Adalimumab (ADA) is a human monoclonal antibody against TNF- α , that is subcutaneously administered at a standard induction dose of 160 mg followed by 80 mg after 2 weeks and then 40 mg every 2 weeks. The efficacy and safety of ADA in UC has been investigated in two large randomized controlled double blind trials (ULTRA 1 and ULTRA 2). Both these trials included patients with moderately to severely active UC, non-responders or intolerant to conventional therapies, despite concurrent and stable treatment with oral corticosteroids and/or immunomodulators [26].

Acute UC. ULTRA 1 included 576 anti-TNF naïve UC patients, randomised into 3 treatment arms: ADA 160 mg (at week 0), 80 mg (at week 2), 40 mg (at week 4, 6); ADA 80 mg (at week 0), 40 mg (at week 2, 4, 6) and placebo. At 8 weeks, the clinical remission was achieved in 18.5% of patients in high ADA dose ($p=0.031$ vs. placebo) whilst lower ADA doses were not significantly different from placebo. Clinical response and mucosal healing were obtained in 55% and 47% of patients treated with ADA 160/80 and in 51% and 38% with ADA 80/40, respectively. These rates were not statistically significantly different from those obtained in the placebo group (45% and 41%, respectively) [26].

ULTRA 2 included 494 patients, 40% of whom had been already treated with anti-TNF α agents (but discontinued in the last 8 weeks) and 50% had pancolitis. The patients were randomised in two treatment arms: ADA 160 mg (at week 0)/ 80 mg (at week 2)/ 40 mg (every other week) and placebo. Clinical remission at week 8 (primary end point) was achieved in 16.5% of patients with ADA vs. 9.3% in the placebo arm ($p=0.019$), and clinical response was achieved in 50.4% of patients with ADA vs. 34.6% in the placebo arm ($p<0.001$). Mucosal healing was achieved in 41.1% of patients with ADA and in 31.7% of patients treated with placebo ($p<0.032$) (Table IV-a,b). Serious infections occurred in 1.6% of patients given ADA and 1.9% given placebo [27].

Maintenance of remission. ULTRA 1 and ULTRA 2 studies also assessed the efficacy and safety of ADA for maintenance of remission. In ULTRA 1, 390 patients who responded in the acute phase, after week 8, entered an open-label extension study and were maintained on ADA 40 mg every 2 weeks for 52 weeks. In ULTRA 2, patients were randomized to placebo vs ADA 40 mg every 2 weeks for 52 weeks. At 52 weeks, the rates of

Table IV-a. ULTRA 1 study after amendment 3

Outcome	ULTRA 1		
	Placebo (n = 130)	ADA 80/40 (n = 130)	ADA 160/80 (n = 130)
Clinical response (%)			
Week 8	44.6	51.5	54.6
Clinical remission (%)			
Week 8	9.2	10.0	18.5*
Mucosal healing (%)			
Week 8	41.5	37.7	46.9
Rectal bleeding subscore ≤1			
Week 8	62.2	70.0	77.7†
PGA subscore ≤ 1			
Week 8	46.9	53.8	60.0*
Stool frequency subscore ≤ 1			
Week 8	37.7	36.2	48.5

ADA, adalimumab; PGA, physician's global assessment; * p=0.031; † p=0.035 versus placebo; ‡ p=0.038

Table IV-b. ULTRA 2 study

Outcome	ULTRA 2		p value
	Placebo (n = 246)	ADA 160/80 (n = 248)	
Clinical response (%)			
Week 8	34.6	50.4	< 0.005
Week 52	18.3	30.2	<0.05
Clinical remission (%)			
Week 8	9.3	16.5	<0.05
Week 52	8.5	17.3	< 0.005
Mucosal healing (%)			
Week 8	31.7	41.1	<0.05
Week 52	15.4	25.0	<0.05
Rectal bleeding subscore ≤1			
Week 8	58.1	70.2	0.06
PGA subscore ≤ 1			
Week 8	37.4	46.0	ns
Stool frequency subscore ≤ 1			
Week 8	28.5	37.9	0.028

ADA, adalimumab. PGA, physician's global assessment

clinical remission, clinical response and mucosal healing were significantly higher than in the placebo group (Table IV) [28].

In particular, the remission rate at week 52 was 17.3% in the ADA group vs. 8.5% in the placebo group (p=0.004), and the clinical response was achieved in 30.2% of patients with ADA vs. 18.3% in the placebo arm (p=0.002). Mucosal healing rate was 25% in the ADA group vs 15.4% in the placebo group (p=0.009) [27].

Patients who completed the ULTRA study (588 patients) entered an extension, open-label study (ULTRA 3), receiving ADA 40 mg every 2 weeks. Results of ULTRA trials after 4 years of treatment report the data of 199 patients from ULTRA 1, 2 and the open-label extension ULTRA 3. At week 208, the rate of remission per partial Mayo score (clinical remission)

was 24.7%, remission per IBDQ (IBD Questionnaire) score was 26.3%, mucosal healing was 27.7%, rate of corticosteroid discontinuation was 59.2%. Of the patients who were followed up in ULTRA 3 (588/1,094), a total of 360 patients remained on ADA 3 years later. After ULTRA 1 or 2 to year 3 of ULTRA 3, remission per partial Mayo score and mucosal healing were maintained by 63.6% and 59.9% of patients, respectively. Adverse event rates were stable over time; no new safety signals were reported [29].

Besides ULTRA studies, other open-label retrospective studies have been published so far. All these studies confirm that ADA is effective in active UC and that it can prevent colectomy in most patients (colectomy rate 20-25% after a mean time of 4-6 months) [30-34].

Oussalah et al. investigated the efficacy of ADA in 13 UC patients previously treated with IFX (100%) and thiopurines (90.31%). After a median follow-up of 41 weeks, 32.5% of patients remained in ADA because of lack of response and 46% of patients underwent colectomy [35, 36].

The long-term outcome of patients treated with ADA was investigated in a study by McDermott et al. This study, which included 23 patients previously treated with IFX and immunosuppressants, showed that only 7 patients maintained a clinical remission at 2 years, while 70% of them discontinued the treatment with ADA due to failure or loss of response [31].

Predictor of response. As already shown for IFX treatment, the early response in the acute phase seems to be the best predictive factor of favourable long-term outcome [27, 37].

The ULTRA studies showed that ADA is less effective in patients with more severe disease, with high body mass index or high body weight (>82 Kg) and elevated C-reactive protein [28].

The role of previous treatment with anti-TNF is still controversial [34, 38].

INFLIXIMAB VS ADALIMUMAB

A recent meta-analysis compared the efficacy of ADA and IFX in the treatment of moderate to severe UC assessing clinical remission, clinical response, mucosal healing, quality of life, serious adverse events and discontinuation due to adverse events at week 8 and at week 52. However, the comparison of these studies is difficult because, although the study setting and clinical context are similar, the study protocols and primary outcomes are different. In the ACT 2 trial patients were randomized at baseline and no modification was allowed to the assigned investigational product (IFX or placebo) during the 52 weeks; in the ULTRA 2 trial patients with inadequate response at week 12, or later could switch to ADA or escalate their dose, and patients who switched were analyzed as non-responders.

However, this meta-analysis suggests that both IFX and ADA are superior to placebo, and IFX is more effective than ADA in the induction of remission, response and mucosal healing at 8 weeks, while the efficacy of IFX and ADA is comparable at 52 weeks. Certainly, controlled studies are required to better investigate and confirm these data [39].

As far as the costs are concerned, a recent cost-per-remission analysis for patients with moderate to severe UC suggested a lower cost for IFX compared with ADA, but additional evaluations are also needed [40].

VEDOLIZUMAB

Vedolizumab is a humanized monoclonal antibody that specifically recognizes the $\alpha 4\beta 7$ integrin heterodimer, and selectively blocks gut lymphocyte trafficking without interfering with trafficking to the central nervous system. A predecessor molecule, natalizumab, another monoclonal antibody, inhibits both $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins and has been associated with progressive multifocal leukoencephalopathy (PML), a serious brain infection; the reason for this is that natalizumab blocks lymphocyte trafficking to multiple organs, including the brain and gut, while vedolizumab blocks only gut trafficking.

Two integrated randomized, double-blind, placebo-controlled trials of vedolizumab in patients with active moderate-severe ulcerative colitis (GEMINI) showed its efficacy to induce and to maintain remission in patients who have failed previous treatment with corticosteroids, thiopurines or anti-TNF agents.

In the GEMINI induction trial, 374 patients (cohort 1) received vedolizumab (at a dose of 300 mg) or placebo intravenously at weeks 0 and 2, and 521 patients (cohort 2) received open-label vedolizumab at weeks 0 and 2, with disease evaluation at week 6. At week 6, the primary outcome for induction therapy was a clinical response and secondary outcomes were clinical remission and mucosal healing. Rates of clinical response, clinical remission and mucosal healing were significantly greater in the vedolizumab groups vs the placebo group (Table V-a).

In the GEMINI maintenance study, patients who responded to the induction therapy with vedolizumab at week 6 in the GEMINI induction trial, were randomized to vedolizumab every 8 or 4 weeks or switched to placebo for up to 52 weeks.

The primary outcome for maintenance therapy was clinical remission at week 52. At week 52, patients randomized to continue receiving vedolizumab were more likely to be in clinical remission than those randomized to receive placebo.

At week 52, rates of durable clinical response and durable clinical remission (at both weeks 6 and 52), mucosal healing, and glucocorticoid-free remission were significantly higher in patients assigned to the vedolizumab regimens than in those assigned to placebo. No clear differences in efficacy were observed between the two vedolizumab regimes (Table V-b,c).

Concurrent treatment with glucocorticoids or immunosuppressants or previous treatment with anti-TNF did not substantially affect the efficacy of vedolizumab. The frequency of adverse events was similar in the vedolizumab and placebo groups [41-43].

GOLIMUMAB

This is a transgenic fully human monoclonal immunoglobulin G1 antibody, subcutaneously injected.

The PURSUIT (Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment) trial demonstrated the efficacy of golimumab in UC patients naïve to anti-TNF alpha. It included a double-blind phase 2 dose-finding and a phase 3 dose-confirmation trial in a study

Table V-a. GEMINI study (induction).

GEMINI INDUCTION			
Outcome	Placebo (n = 149)	Vedolizumab (n=225)	p value
Clinical response n (%)			
Week 6	38 (25.5)	106 (47.1)	< 0.001
Clinical remission n (%)			
Week 6	8 (5.4)	38 (16.9)	0.001
Mucosal healing n (%)			
Week 6	37 (24.8)	92 (40.9)	0.001

Table V-b. GEMINI study (maintenance – vedolizumab every 8 weeks)

GEMINI MAINTENANCE (every 8 weeks)			
Outcome	Placebo (n = 126)	Vedolizumab (n=122)	p value
Durable clinical response n (%)			
Weeks 6 and 52	30 (23.8)	69 (56.6)	< 0.001
Clinical remission n (%)			
Weeks 52	20 (15.9)	51 (41.8)	< 0.001
Mucosal healing (%)			
Weeks 52	25 (19.8)	63 (51.6)	< 0.001

Table V-c. GEMINI study (maintenance – vedolizumab every 4 weeks)

GEMINI MAINTENANCE (every 4 weeks)			
Outcome	Placebo (n = 126)	vedolizumab (n=125)	p value
Durable clinical response n (%)			
Weeks 6 and 52	30 (23.8)	65 (52.0)	< 0.001
Clinical remission n (%)			
Weeks 52	20 (15.9)	56 (44.8)	< 0.001
Mucosal healing n (%)			
Weeks 52	25 (19.8)	70 (56.0)	< 0.001

of 1,064 adults with UC. In the PURSUIT induction study, patients were randomized into 3 groups given golimumab at different doses at week 0 and at week 2 (400/200 mg, 200/100 mg), or placebo. The end points were clinical response, clinical remission, mucosal healing and IBDQ score change, at week 6. Rates of clinical remission and mucosal healing and mean changes in IBDQ scores were significantly greater in both golimumab groups vs. the placebo group. Serious adverse events occurred in 6.1% in the golimumab groups and 3.0% in the placebo group. Rates of serious infection were 1.8% and 0.5% in the placebo and golimumab groups, respectively. Results are shown in Table VI-a [44].

In the PURSUIT maintenance study, patients who responded to the induction therapy with golimumab (n=464) in the PURSUIT induction trial were randomized to groups given placebo or injections of 50 or 100 mg golimumab every 4 weeks through week 52. Patients who responded to the placebo in the induction study continued to receive the placebo. Non-responders in the induction study received 100 mg golimumab. The end points were clinical response maintained through to week 54, clinical remission and mucosal

Table VI-a. PURSUIT study (induction)

PURSUIT INDUCTION			
Outcome	Placebo (n = 256)	Golimumab 200/100 mg (n=257)	Golimumab 400/200 mg (n=258)
Clinical response %			
Week 6	30.3	51.0	54.9
p vs placebo		≤ 0.0001	≤ 0.0001
Clinical remission %			
Week 6	6.3	18.7	17.8
p vs placebo		< 0.0001	< 0.0001
Mucosal healing %			
Week 6	28.5	43.2	45.3
p vs placebo		0.0005	< 0.0001

Table VI-b. PURSUIT study (maintenance)

PURSUIT MAINTENANCE			
Outcome	Placebo	Golimumab 50 mg	Golimumab 100 mg
Clinical response %			
Week 54	31.2	47.0	49.7
p vs placebo		0.010	<0.001
Clinical remission %			
Weeks 30 and 54	15.6	23.2	27.8
p vs placebo		0.122	0.004
Mucosal healing %			
Weeks 30 and 54	26.6	41.7	42.2
p vs placebo		< 0.05	0.002

healing at weeks 30 and 54. Results are shown in Table VI-b. Serious adverse events occurred in 7.7%, 8.4%, and 14.3% of the patients given placebo, 50 mg or 100 mg golimumab, respectively; serious infections occurred in 1.9%, 3.2%, and 3.2% of patients, respectively. Among patients treated with golimumab, 3 died for systemic infections and 4 developed active tuberculosis [44].

Actually, golimumab is approved for UC treatment by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA). The induction treatment consists

of 200 mg at week 0 and 100 mg at week 2; for maintenance therapy FDA advises using 100 mg every 4 weeks, whereas EMA advice is to use 50 mg every 4 weeks in patients with a body weight < 80 Kg and 100 mg every 4 weeks in patients with a body weight > 80 Kg [45].

BIOSIMILAR MEDICINES

Further new drugs with new mechanisms of actions to treat UC, and biosimilar drugs using current knowledge to develop biotherapeutic products, that are similar to conventional drugs in terms of quality, efficacy and safety, are able to enter the market once the original's product patent expires. There are three categories of biosimilar medicines: a product very similar to natural body substances, monoclonal antibodies and engineered proteins. Their properties depend upon the manufacturing process used; for this they are similar to conventional drugs, but not identical and certainly they are priced below their reference product.

For IBD, two biosimilar infliximabs have already been authorized by the EMA [46, 47].

OTHER DRUGS [48-54]

Many studies are continuing to identify potential therapeutic targets for moderate to severe UC.

Tofacitinib is an oral inhibitor of Janus kinases 1, 2, and 3 with *in vitro* functional specificity for kinases 1 and 3 over kinase 2, which is expected to block signals involving gamma chains containing cytokines including interleukins 2, 4, 7, 9, 15, and 21. These cytokines are integral to lymphocyte activation, function, and proliferation.

In a double-blind, placebo-controlled, phase 2 trial, the efficacy of tofacitinib was evaluated in 194 adults with moderate to severe active UC. Patients were randomly assigned to receive tofacitinib at a dose of 0.5 mg, 3 mg, 10 mg, or 15 mg or placebo twice daily for 8 weeks. The primary outcome was a clinical response at 8 weeks and secondary outcomes were clinical remission, endoscopic response and remission at 8 weeks. Results are reported in Table VII. In conclusion, tofacitinib at the highest dose seems to be more effective than placebo.

Table VII. Efficacy of tofacitinib in ulcerative colitis at week 8

Outcome	Placebo (n=48)	Tofacitinib 0.5 mg (n=31)	Tofacitinib 3 mg (n=33)	Tofacitinib 10 mg (n=33)	Tofacitinib 15 mg (n=49)
Clinical response (%)	42	32	48	61	78
p value compared with placebo		0.39	0.55	0.10	<0.001
Clinical remission (%)	10	13	33	48	41
p value compared with placebo		0.76	0.01	<0.001	<0.001
Endoscopic response (%)	46	52	58	67	78
p value compared with placebo		0.64	0.30	0.07	0.001
Endoscopic remission (%)	2	10	18	30	27
p value compared with placebo		0.14	0.01	<0.001	<0.001

There was a dose-dependent increase in both low-density and high-density lipoprotein cholesterol. Three patients treated with tofacitinib had an absolute neutrophil count of less than 1,500 [55].

Abatacept. This is a selective co-stimulation modulator that prevents the delivery of co-stimulatory signals to T cells. A study showed negative results in UC [56].

Natalizumab, a humanized monoclonal antibody to the $\alpha 4\beta 7$ integrin molecule is licensed for use in the USA for Crohn's disease, but has been assessed in UC in just one small pilot study and could have serious complications, such as progressive multifocal leucoencephalopathy, so its use cannot be advised [57].

Etrolizumab is a humanised monoclonal antibody that selectively binds the $\beta 7$ subunit of the heterodimeric integrins $\alpha 4\beta 7$ and $\alpha E\beta 7$. In a double-blind, placebo-controlled, randomised, phase 2 study, 124 UC patients with moderately-to-severe active disease who had not responded to conventional

therapy (58% non anti-TNF naïve) were randomized in 3 arms: one received placebo, one received subcutaneously etrolizumab 100 mg at weeks 0, 4, 8 (and placebo at week 2) and one received etrolizumab 420 mg at week 0 followed by 300 mg at week 2, 4, 8 (loading dose group).

The primary endpoint was clinical remission at week 10. The secondary endpoints were clinical remission at week 6, clinical response and achievement of endoscopic subscore and rectal bleeding subscore of 0. Results reported in Table VIII demonstrated that etrolizumab is more likely to lead to clinical remission at week 10 than placebo [58].

Additional emerging therapies are listed in Table IX.

CONCLUSIONS

A significant amount of data shows that agents are effective for inducing and maintaining remission in UC. In particular IFX and ADA are effective in the treatment of moderate to severe UC to achieve clinical remission, clinical response, mucosal healing, improvement of quality of life for patients with steroid refractory diseases, with acceptable adverse events.

However, in most patients treated with these biologics, responses are not achieved in a variable percentage varying from 30 to 50%, sometimes anti-TNF therapy loses its efficacy and even after optimization of therapy [59], patients ultimately require colectomy. Therefore, additional agents are necessary. However, the data about the efficacy of these drugs are hardly comparable, as shown in Table X [60]:

- for different randomization schemes (for example PURSUIT and GEMINI studies have two randomizations, at the start of the study and after induction, for patients who respond to therapy; in these patients it is more probable that they respond to therapy);
- for previous exposition to anti-TNF (only ULTRA 2 and GEMINI evaluated anti-TNF failure patients);
- for different timing of primary endpoints;
- for the presence of forced corticosteroids tapering.

Table VIII. Efficacy of a etrolizumab in ulcerative colitis in induction therapy

Outcome	ETROLIZUMAB		
	Placebo (n = 41)	Etrolizumab 100 mg (n = 39)	Etrolizumab 300 mg + LD group (n = 39)
Clinical remission n (%)			
Week 6	2 (5)*	4 (10)*	3 (8)*
Week 10	0	8 (21)†	4 (10)°
Clinical response n (%)			
Week 6	14 (34)	19 (49)*	15 (38)*
Week 10	12 (29)	13 (33)*	12 (31)*
Endoscopic and rectal bleeding subscore of 0 n (%)			
Week 6	1 (2)	3 (8)*	1 (3)*
Week 10	0	4 (10)*	3 (8)*

* p= ns; † p=0,0040 versus placebo; °p=0,048 versus placebo

Table IX. Emerging new therapies

COMPOUND	MECHANISM OF ACTION
AVX-470	Ab of pregnant dairy cows immunized with recombinant human TNF
AMG-181	Selective anti-migration agents
PF-547659	Selective anti-migration agents
GSK-1607586	Selective anti-migration agents
BMS-936557	Selective anti-migration agents
rhuMAb Beta7	Selective anti-migration agents
Bertilimumab	Selective anti-migration agents
ASP-2002	Selective anti-migration agents
Sotrastaurin	Anti T-cell activation
HE-3286	Anti-cytokines
Vidofludimus	Anti-cytokines
MDX-1100 (CXCL 10 chemokine)	Anti-chemokine receptors
Tralokinumab	Anti-cytokines
PUR-0110	Anti-cytokines

Table X. Differences in trial design

Study	Design	Anti-TNF naive patients	Primary endpoint	Forced corticosteroid taper	Required for steroid and /or ISS failure
ULTRA 1	Parallel group	X	Remission at week 8	No	X
ULTRA 2	Parallel group	No	Remission at week 8 and at week 52	No	X
ACT 1	Parallel group	X	Response at week 8	X	X
ACT 2	Parallel group	X	Response at week 8	X	No
PURSUIT	Re-randomized responders	X	Response at week 6 and week 54	X	No
GEMINI	Re-randomized responders	No	Response at week 6 Remission at week 52	X	X

ISS: immunosuppressants.

EXPERT OPINION

All agents currently available in the therapeutic armamentarium of UC have shown a good tolerability profile and a comparable efficacy in inducing remission, and in achieving a clinical response and maintaining clinical remission.

Nevertheless, in clinical practice we have to consider that the efficacy of drugs observed in clinical trials does not exactly reflect real life and that, anyway, a wide range of patients do not achieve and maintain clinical remission. Moreover, despite the fact that biologics have been widely investigated and used for a decade, head-to-head comparative studies are still very limited to IFX and ADA, and new biological agents are still investigated by comparing their efficacy with that of placebo.

All these considerations may justify some of the difficulties in choosing the correct biological agent and in optimizing the biological treatment in IBD. In addition, recent paradigms have led the treatment for UC in looking beyond the symptom control, such as in obtaining mucosal healing and fecal biomarkers' normalization, in view of the fact that this could change the natural history of the disease.

Therefore, the choice of an agent rather than a steroid treatment or surgery is driven by specific features of the patients, the local expertise, facilities and costs, and not merely by therapeutic guidelines. This is valid for the choice between CyA and IFX in acute UC, and for IFX and ADA, golimumab and vedolizumab in active steroid-refractory UC.

However, taking into account all limitations, when comparing the studies that used biologics in UC, some considerations originating from data of the literature could be undertaken when choosing a specific treatment.

Infliximab seems to provide a quick response and should be preferred as the biological treatment of choice in patients with acute UC refractory to steroid treatment, including those with concomitant *Cytomegalovirus* infection and should be a valid alternative to cyclosporine.

All biological agents currently available on the market have a similar long-term therapeutic response. Anti-integrin therapy with vedolizumab shows some adjunct benefit compared to chimeric and fully humanized monoclonal antibodies against TNF-alfa. However, at best, long-term clinical remission is maintained in 30-40% of patients and mucosal healing in no more than 50% of patients, thus making mandatory the optimization of the treatment.

Therefore, the proper assessment of risk factors of response and therapeutic failure, the optimization of the doses of anti-TNF-alpha and concomitant use of immunomodulators, and the therapeutic drug monitoring with the use of anti-TNF-alpha antibodies may be essential to maximize therapeutic benefits and minimize treatment failures.

Conflicts of interest. The authors declare that there is no conflict of interest.

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