Infliximab Originator, Infliximab Biosimilar, and Adalimumab Are More Effective in Crohn's Disease Than Ulcerative Colitis: A Real-Life Cohort Study

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INTRODUCTION: **There are no real-life studies comparing the efficacy and safety of the different antitumor necrosis factor (TNF)-α drugs available in patients with ulcerative colitis (UC) and Crohn's disease (CD). To verify the effectiveness and tolerability of different anti–TNF-α agents (infliximab [IFX] originator, biosimilar CTP13, and adalimumab [ADA]) in patients with moderate-to-severe CD and UC.**

METHODS: **Retrospectively, patients with moderate-to-severe inflammatory bowel disease who completed induction with either ADA, IFX originator, or biosimilar from 2015 to 2017 were included. Patients were evaluated after induction at 30 and 52 weeks. We performed an intention-to-treat analysis to evaluate clinical response and remission, steroid-free clinical remission, and endoscopy response according to different time points. At every time point, the need for dose escalation and occurrence of adverse events have been reported.**

RESULTS: **Eighty-nine patients with UC (31 ADA, 30 IFX originator, and 28 IFX biosimilar) and 90 patients with CD (30 for each drug groups) were enrolled. After induction at week 30 and 52, clinical response was obtained by the following: 84.3%, 86.5%, and 82% of UC and 93.3%, 88.9%, and 80% of CD. Clinical steroid-free remission rates were significantly higher in the CD group compared with the UC group at every time point ($P < 0.05$). At week 52, 31.1% of ADA, 16.7% of IFX originator, and 36.2% of biosimilar patients needed treatment optimization. At week 52, 13 patients had suspended therapy because of severe adverse events, including 3 cases of malignant disease.**

DISCUSSION: **Anti–TNF-α treatment was more effective in patients with CD compared to patients with UC, independently of the drug used.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A286

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INTRODUCTION

Current treatment of inflammatory bowel disease (IBD) is aimed at obtaining deep remission, i.e., clinical regression of symptoms, normalization of inflammation markers, and endoscopic remission. Indeed, it has been shown that the achievement of mucosal healing (MH) and the normalization of inflammatory indices correlate with a lower risk of recurrence and surgery and with minor complications and organ damage (1). For this purpose, different medical options, including conventional (i.e., mesalamine, steroids, and azathioprine) and biologic drugs, are available, with variable efficacy in clinical and endoscopic remissions.

The introduction of biological drugs has radically changed the therapeutic approach and management of patients with IBD. In particular, an increased rate of remission and improved quality of life have been observed compared with the past when only conventional treatments were available (2,3). Therefore, their use in real-world practice is not only limited to the severe and more complicated phases of the disease, in which this therapy has proved effective in inducing and maintaining

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clinical and endoscopic remission, but is also extended to the initial phases in those patients with negative prognostic factors. In fact, increasing evidence emphasizes the improvement in long-term outcomes of individuals with IBD when these drugs are used in the early phase of the diseases (4). Studies have shown their major role in achieving MH—an important prognostic factor anticipating a more favorable course of illness—a better quality of life, and a lower use of surgery and hospitalizations both in ulcerative colitis (UC) and Crohn's disease (CD) (5).

Among biologic treatments, IBD can be actually treated with the antitumor necrosis factor-α (anti–TNF-α) drugs, such as infliximab (IFX) originator and biosimilar, adalimumab (ADA), and golimumab, although the latter is authorized only in patients with UC. All these therapies are indicated for the treatment of moderate-to-severe disease, and the choice of one of them is mainly based on availability, physicians' perspective, and patients' acceptance (2,3). Indeed, the efficacy and safety of each anti–TNF-α drug have been tested in randomized placebo studies, but the evaluation of effectiveness and tolerability of the various compounds in these 2 different diseases (UC end CD) is lacking because it has only been performed indirectly (e.g., through network meta-analysis).

In this perspective, the primary aim of this study was to compare the effectiveness, safety, and tolerability of the various anti–TNF-α agents between patients with CD and UC. Moreover, the percentages of induction of clinical, biochemical, and endoscopic remissions and their maintenance in the long term will be evaluated for each drug in both diseases.

METHODS

This retrospective observational clinical study was conducted at the IBD Unit of Padua University in patients with a diagnosis of moderate-to-severe UC and CD, determined both endoscopically and histologically, who underwent treatment with anti–TNF-α drugs, such as IFX originator (Remicade) or its biosimilar (Remsima) and ADA (Humira). In particular, we included all consecutive patients receiving ADA for a moderate-to-severe IBD from March 2015 to March 2017, who completed at least the induction regimen, and thereafter, we matched them by age and sex with patients receiving IFX originator and its biosimilar in the same time frame. Given the impossibility of treating patients with CD and to compare the effectiveness of the different drugs in both indications (i.e., CD and UC), we excluded patients who underwent treatment with golimumab. To note, patients with endoscopic mild activity or in remission started biologic treatment because of clinical activity and radiological evidence of ileal activity during MRI assessment (11 patients). Similarly, in those cases where a recent endoscopic examination was not available (15.6% of patients with CD), treatment was decided according to the clinical and biochemical activities.

We evaluated the clinical and biochemical features at baseline, after induction (14 weeks for IFX originator and biosimilar and 8 weeks for ADA), and at 30 and 52 weeks of treatment. Moreover, when available, we collected endoscopic data at baseline and after 52 weeks. The following data were collected for each patient at baseline: age, gender, smoking habits, age at diagnosis, disease duration, disease extent, previous biological treatments, presence of extraintestinal manifestations, concomitant immunosuppressive (azathioprine, 6-mercapthopurine, and methotrexate), or steroid treatment.

Clinical activity was measured by using the partial Mayo (p-Mayo) Score and Harvey-Bradshaw Index (HBI) for UC and CD, respectively. Both indexes were collected at baseline, after induction, and at week 30 and 52 of treatment, whereas the Mayo Endoscopic Score and Simple Endoscopic Score for Crohn's Disease (SES-CD) or the Rutgeerts scores were applied only at baseline and at week 52. Patients with a p-Mayo ≥ 5, and/or Mayo Endoscopic score ≥ 2 and HBI > 7, and/or SES-CD ≥ 7, and/or Rutgeerts ≥ 2 at baseline were considered affected by moderate-to-severe disease. C-reactive protein (CRP) levels (positive if $>$ of 0.5 mg/dL) and fecal calprotectin (FC) values > 250 μg/g (6) were also evaluated at the same time points.

Initially, drugs were administered at standard dosage to all patients (i.e., IFX 5 mg/kg at week 0, 2, 6, and then every 8 weeks, whereas ADA 160 mg, 80 mg, and 40 mg every 2 weeks), but during outpatient follow-up visits (after induction, 6 months, 12 months, or in case of disease recurrence), each physician (E.V.S., R.D.) decided whether to optimize the drug based on clinical and biochemical responses. The methods of therapeutic optimization were the following: 5 mg every 6 weeks, 5 mg every 4 weeks, or 10 mg every 8 weeks for IFX originator and biosimilar and 40 mg every week or 80 mg every 2 weeks for ADA.

According to the medical literature, we defined, respectively, for UC and CD, *clinical remission* as p-Mayo score < 2 and HBI < 5, *steroid-free clinical remission* as p-Mayo score < 2 and HBI < 5 without steroids use, and *clinical response* in case of more than 2 points reduction of the baseline p-Mayo score and in case of more than 3 points reduction of baseline HBI score, with a concomitant decrease of steroid dosage until its discontinuation within 8 weeks. The *endoscopic response* was defined as a $\geq$ 1-point reduction of the endoscopic Mayo score and as a reduction of 50% of baseline SES-CD and Rutgeerts score at the endoscopic reevaluation. Finally, treatment failure was defined as the discontinuation of biological therapy because of adverse events (AEs), lack of clinical response, and need of hospitalization/surgery. All AEs, not only those that lead to discontinuation of therapy, were recorded.

Statistical analysis

Data were analyzed using STATA11 software. Continuous variables were reported as medians with ranges, and categorical variables were reported as frequency and percentage. Comparison among more than 2 groups was performed using Kruskal–Wallis tests, whereas comparison between 2 groups using Mann–Whitney tests. The χ^2 test was used to compare categorical variables. A multivariate logistic regression was performed to evaluate the risk of clinical response, clinical remission, and steroid-free clinical remission in CD compared with UC adjusted for all variables statistically significant different at baseline between 2 groups. We performed an intention-to-treat analysis. A P value ≤ 0.05 was considered statistically significant.

RESULTS

Study population and disease characteristics at baseline

A total of 184 patients with a moderate-to-severe IBD were selected; however, 5 were not included in the final analysis because they did not complete the induction phase because of the need for surgery. The final study population was composed by 179 patients with IBD, 89 patients with UC (58/31 M/F, median age 44 years, range 18–80), and 90 patients with CD (54/36 M/F, median age 47 years, range 19–76). In particular, a total of 61 patients treated

with ADA (31 UC and 30 CD) were included, and, for comparison, 60 sex- and age-matched patients treated with IFX originator (30 UC and 30 CD) and with IFX biosimilar (28 UC and 30 CD) were enrolled. The main characteristics of our population are reported in Table 1.

In particular, when considering the endoscopic activity, we observed a great variability between patients with UC and CD ($P < 0.001$): 52.8% and 47.2% of patients with UC presented a moderate and severe endoscopic activity, respectively, compared with 32.2% of patients with CD presenting severe activity and 45.6% moderate activity. Of note, endoscopic disease activity was more severe in patients treated with IFX originator than in patients treated with ADA. Disease duration in different treatment groups was longer in patients with IBD treated with ADA compared with the other treatment groups, with statistically significant difference between patients with UC and CD (15 [1–37] for UC and 10 [1–42] for CD, $P = 0.023$). In addition, the percentage of naive patients was lower in ADA compared with IFX originator and biosimilar treatment in both UC and CD (ADA: 41.9% and 53.3%; IFX originator 93.3% and 86.7%; and IFX biosimilar 85.7% and 56.7% for UC and CD, respectively). Moreover, at baseline 19.1% of UC and 48.9% of patients with CD presented active extraintestinal manifestations ($P < 0.001$). Finally, regarding the biochemical activity of the disease, the median values of FC were similar in the 2 groups (800 μg/g with range 250–3,000 in UC and 785 μg/g with range 152–2,100 in CD, $P = 0.44$), whereas CRP was positive in 45.4% of patients with CD (median 15.6, range 1.2–87) and in 26.2% of patients with UC (median 8.6, range 0.5–75), with statistically significative difference ($P = 0.009$).

Clinical and biochemical data after induction

After induction (Table 2, Figure 1), clinical response was achieved by 93.3% of patients with CD and by 84.3% of patients with UC ($P = 0.05$). A statistically significative difference ($P = 0.03$) has been observed between the number of patients with CD in steroid-free remission and those with UC (58.8% and 42.7%, respectively). On the other hand, clinical remission was reached by 60% of patients with CD and 48.3% of patients with UC ($P = 0.11$).

After induction, 4 patients discontinued anti–TNF-α treatment, 2 patients with CD, 1 treated with ADA and 1 with IFX originator, because of AEs (see Supplementary Table I, Supplementary Digital Content 1, http://links.lww.com/CTG/A286) and 2 patients with UC, 1 treated with ADA and 1 with IFX biosimilar, because of the lack of efficacy and need for surgery, respectively.

Clinical and biochemical data after 30 weeks of treatment

After 30 weeks of treatment (Table 2, Figure 1), clinical response was obtained by 86.5% of patients with UC and by 88.9% of patients with CD ($P = 0.87$). Steroid-free clinical remission was statistically significant lower in patients with UC than patients with CD (50.6% vs 72.2%, respectively, $P = 0.01$). On the other hand, clinical remission was achieved by 53.9% of patients with UC and by 73.3% of patients with CD ($P = 0.02$). Regarding steroid-free clinical remission and clinical remission, we observed a statistically significant difference between the 2 diseases in patients treated with IFX originator only ($P = 0.05$ in both cases).

At week 30, 16 patients stopped treatment (10 CD and 6 UC) because of either the lack of efficacy or AEs. Overall, the highest number of global dropouts (3 UC and 5 CD) and of AE-induced dropouts (1 UC and 3 CD) were registered in the IFX biosimilar group, whereas ADA group registered the highest of number of withdrawn because of the lack of efficacy (3 UC and 2 CD) (see Supplementary Table I, Supplementary Digital Content 1, http://links.lww.com/CTG/A286).

Clinical and biochemical data after 52 weeks of treatment

After 52 weeks of treatment (Table 2, Figure 1), clinical response was obtained by 82% of patients with UC and by 80% of patients with CD ($P = 0.6$). Steroid-free clinical remission was higher in patients with CD (72.2%) compared with patients with UC (60.7%), with statistically significant difference ($P = 0.03$). On the other hand, regarding the clinical remission, we detected a statistically significant difference between the 2 groups ($P = 0.02$), being the percentage lower in UC (63%) than in CD (73.3%).

At the end of the follow-up, 21 patients stopped the treatment, with the lack of efficacy being the main reason. At this time point, the endoscopic data were available for 100% of patients with UC and for 47.4% of patients with CD (81 and 37 of subjects reaching week 52, respectively) (Figure 2). Patients treated with ADA obtained the best endoscopic response (ADA 51% vs 43.4% IFX originator vs 41.7% IFX biosimilar).

Figure 3 showed the trend of FC from baseline to 52 weeks of treatment in patients with UC and CD.

Tolerability profile of drugs

The whole number of AEs has been documented at the different study time points (see Supplementary Table I, Supplementary Digital Content 1, http://links.lww.com/CTG/A286). In total, 14 AEs were registered after induction (6 UC and 8 CD, $P = 0.6$), 23 at week 30 (6 UC and 17 CD, $P = 0.01$) and 20 at week 52 (9 UC and 11 CD, $P = 0.4$). In total, 13 patients stopped treatment for adverse reaction, with allergic reactions, dermatologic manifestations (paradox psoriasis, rash, and dermatitis), and infections (respiratory tract, urinary tract, conjunctivitis, and blepharitis) the most frequent. During treatment, we observed 3 cases of incident neoplasia (lungs, melanoma *in situ*, and a biliary tract neoplasia).

Therapeutic optimization

Data regarding therapeutic optimization in those patients whose response was unsatisfactory at the study time points or in case of recurrence were reported in Supplementary Table II (see Supplementary Digital Content 2, http://links.lww.com/CTG/A286). The only significant difference ($P = 0.03$) was found in the IFX originator group at week 30, when 20% of patients with UC needed therapeutic optimization compared with none of the patients with CD.

Finally, as Table 3 shows, we used a multivariate analysis to compare our main outcomes between CD and UC, adjusting for those variables resulted statistically significant different at baseline: concomitant use of steroid, CRP value, presence of extraintestinal manifestations, disease clinical activity, and endoscopy activity. Patients with CD had a possibility to reach a clinical remission more than 3 times higher than patients with UC at 30 and 52 weeks and a steroid-free clinical remission higher compared with UC at each time.

DISCUSSION

Anti–TNF-α are widely used in the treatment of IBD, but only few studies directly compared the effectiveness of the various agents

Table 1. Study population characteristics at the baseline (median and range)

	All population			ADA		P value	IFX originator		P value	IFX biosimilar		P value
	UC	CD	P value	UC	CD		UC	CD		UC	CD	
Number	89	90		31	30		30	30		28	30	
Males, N (%)	58 (65.2)	54 (60)	0.475	22 (71)	18 (60)	0.37	21 (70)	16 (56.3)	0.18	15 (53.6)	20 (66.7)	0.31
Age at diagnosis, yr	30 (11–76)	28 (10–74)	0.93	28 (16–55)	31.5 (10–58)	0.57	29.5 (14–65)	27 (13–56)	0.54	31 (11–76)	29.5 (14–74)	0.79
Disease duration, yr	11 (1–37)	8.5 (1–42)	0.06	15 (1–37)	10 (1–42)	0.02	10 (1–29)	8.5 (1–34)	0.74	8 (1–27)	6 (1–29)	0.77
Median age, yr	44 (18–80)	47 (19–76)	0.79	48 (23–78)	48 (19–76)	0.55	43.5 (19–65)	40 (21–68)	0.98	40.5 (18–80)	48 (20–76)	0.94
Montreal classification, N (%)			—			—			—			—
L1	—	8 (8.9)		—	2 (6.6)		—	4 (13.3)		—	2 (6.7)	
L2	—	24 (26.7)		—	6 (20)		—	10 (33.3)		—	8 (26.7)	
L3	—	50 (55.5)		—	20 (66.7)		—	14 (46.7)		—	16 (53.3)	
L4	—	8 (8.9)		—	2 (6.7)		—	2 (6.7)		—	4 (13.3)	
B1	—	50 (55.5)		—	19 (63.3)		—	14 (46.7)		—	17 (56.7)	
B2	—	24 (26.7)		—	8 (26.7)		—	10 (33.3)		—	6 (20)	
B3	—	7 (7.8)		—	1 (3.4)		—	1 (3.3)		—	5 (16.67)	
B2 + B3	—	9 (10)		—	2 (6.6)		—	5 (16.7)		—	2 (6.7)	
E1	8 (9)	—		0	—		4 (13.4)	—		4 (14.3)	—	
E2	31(34.8)	—		10 (32.3)	—		13 (43.3)	—		8 (28.6)	—	
E3	50 (56.2)	—		21 (67.7)	—		13 (43.3)	—		16 (57.1)	—	
Disease activity (p-mayo-HBI), N (%)			<0.001			0.14			0.001			0.27
Remission	—	—		—	—		—	—		—	—	
Mild	—	—		—	—		—	—		—	—	
Moderate	70 (78.6)	87 (96.7)		25 (80.6)	28 (93.3)		20 (66.7)	30 (100)		25 (89.3)	29 (96.7)	
Severe	19 (21.3)	3 (3.3)		6 (19.3)	2 (6.7)		10 (33.3)	—		3 (10.7)	1 (3.3)	
Disease activity (Mayo endo—SES-CD—Rutgeers), N (%)			<0.001			0.04			0.05			0.10
Remission	—	1 (1.1)		—	—		—	1 (3.3)		—	—	
Mild	—	5 (5.6)		—	1 (3.3)		—	3 (10)		—	1 (3.3)	
Moderate	47 (52.8)	41 (45.6)		23 (74.2)	17 (56.7)		10 (33.3)	8 (26.7)		14 (50)	16 (53.3)	
Severe	42 (47.2)	29 (32.2)		8 (25.8)	6 (20)		20 (66.7)	14 (46.7)		14 (50)	9 (30)	
Missing	—	14 (15.6)		—	6 (20)		—	4 (13.3)		—	4 (13.3)	

Table 1. (*continued*)

	All population			ADA			IFX originator			IFX biosimilar		
	UC	CD	*P* value	UC	CD	*P* value	UC	CD	*P* value	UC	CD	*P* value
FC value, μg/g			0.44			0.13			0.08			0.19
Median (range)	800 (250–3,000)	785 (152–2,100)		650 (250–3,000)	950 (305–2,100)		1,000 (441–2,100)	785 (152–2,100)		762.5 (344–2,100)	542.5 (157–2,100)	
CRP (mg/L) (n.v. < 6) value positive			0.009			0.03			0.8			0.03
N (%)	22 (26.2)	40 (45.4)		6 (20.7)	14 (46.7)		8 (29.6)	9 (32.1)		8 (28.6)	17 (56.7)	
Median (range)	8.6 (0.5–75)	15.6 (1.2–87)		6.6 (0.5–56)	10.8 (1.2–45)		11.8 (2.4–75)	9.1 (3.3–87)		7.1 (1.4–53)	12.3 (2.5–44)	
Extraintestinal manifestation, N (%)			<0.001			0.05			0.03			0.001
Total	17 (19.1)	44 (48.9)		9 (29)	16 (53.3)		3 (10)	10 (33.3)		5 (17.9)	18 (60)	
Articular	14	39		8	14		2	9		4	16	
Dermatological	2	4		1	2		—	1		1	1	
Ocular	1	1		—	—		1	—		—	1	
Naive biologic, N (%)	65 (75.03)	59 (65.6)	0.278	13 (41.9)	16 (53.3)	0.37	28 (93.3)	26 (86.7)	0.39	24 (85.7)	17 (56.7)	0.015
Concomitant immunosuppressants, N (%)	16 (18)	16 (17.8)	0.972	7 (22.6)	3 (10)	0.2	6 (20)	7 (23.3)	0.75	3 (10.7)	6 (20)	0.33
Concomitant steroids, N (%)	15 (16.8)	26 (29.2)	0.05	3 (9.7)	9 (30)	0.05	5 (16.7)	6 (20)	0.74	7 (25)	11 (37.9)	0.3
Smoking, N (%)	9 (10.1)	17 (18.9)	0.09	2 (6.4)	8 (26.7)	0.03	3 (10)	4 (13.3)	0.7	4 (14.3)	5 (16.7)	0.8

ADA, adalimumab; CD, Crohn's disease; CRP, C-reactive protein; FC, fecal calprotectin; HBI, Harvey-Bradshaw Index; IFX, infliximab; p-Mayo, partial Mayo; SES-CD, Simple Endoscopic Score for Crohn's Disease; UC, ulcerative colitis.

Table 2. Steroid-free clinical remission, clinical response, treatment failure, and endoscopic response among patients with UC and CD treated with IFX originator, IFX biosimilar, and ADA after induction and at 30 and 52 weeks

				Clinical response		Clinical remission		Steroid-free clinical remission		Treatment failure				
	N	N (PP)	Type of anti–TNF-α	N (%)	*P* value	N (%)	*P* value	N (%)	*P* value	N (%)	Inefficacy N	AEs N	Surgery N	*P* value
After induction	89	—	All UC	75 (84.3)	0.05	43 (48.3)	0.11	38 (42.7)	0.03	2 (2.3)	1	—	1	0.63
	90	—	All CD	84 (93.3)		54 (60)		50 (58.8)		2 (2.2)	—	2	—	
	31	—	ADA UC	25 (80.6)	0.14	11 (35.5)	0.38	10 (32.2)	0.26	1 (3.2)	1	—	—	0.57
	30	—	ADA CD	28 (93.3)		14 (46.7)		13 (46.4)		1 (3.3)	—	1	—	
	30	—	IFX originator UC	25 (83.3)	0.08	15 (50)	0.3	13 (43.3)	0.15	0	—	—	—	0.31
	30	—	IFX originator CD	29 (96.7)		19 (63.3)		18 (62.1)		1 (3.3)	—	1	—	
	28	—	IFX biosimilar UC	25 (89.3)	0.93	17 (60.7)	0.46	15 (53.6)	0.27	1 (3.7)	—	—	1	0.28
	30	—	IFX biosimilar CD	27 (90)		21 (70)		19 (67.9)		0	—	—	—	
30 wk	89	—	All UC	77 (86.5)	0.87	48 (53.9)	0.02	45 (50.6)	0.01	6 (6.7)	4	1	1	0.6
	90	—	All CD	80 (88.9)		66 (73.3)		65 (72.2)		10 (11.1)	5	5	—	
	31	—	ADA UC	25 (80.6)	0.79	12 (38.7)	0.25	11 (35.5)	0.11	3 (9.7)	3	—	—	0.9
	30	—	ADA CD	26 (86.7)		18 (60)		18 (60)		4 (13.3)	2	2	—	
	30	—	IFX originator UC	28 (93.3)	0.6	17 (56.7)	0.05	17 (56.7)	0.05	—	—	—	—	0.35
	30	—	IFX originator CD	27 (90)		24 (80)		24 (80)		1 (3.3)	1	—	—	
	28	—	IFX biosimilar UC	24 (85.7)	0.57	19 (68)	0.4	17 (60.7)	0.33	3 (10.7)	1	1	1	0.48
	30	—	IFX biosimilar CD	27 (90)		24 (80)		23 (76.7)		5 (16.7)	2	3	—	
52 wk	89	81	All UC	73 (82)	0.6	56 (63)	0.02	54 (60.7)	0.03	8 (9)	7	1	—	0.35
	90	78	All CD	72 (80)		66 (73.3)		65 (72.2)		13 (14.4)	8	5	—	
	31	27	ADA UC	22 (71)	0.7	20 (64.5)	0.9	18 (58.1)	0.9	4 (12.9)	4	—	—	0.74
	30	25	ADA CD	23 (76.7)		19 (63.3)		18 (60)		4 (13.3)	4	—	—	
	30	30	IFX originator UC	28 (93.3)	0.35	20 (66.7)	0.08	20 (66.7)	0.08	2 (6.7)	1	1	—	0.27
	30	28	IFX originator CD	26 (86.7)		24 (80)		24 (80)		4 (13.3)	1	3	—	
	28	24	IFX biosimilar UC	22 (78.6)	0.97	16 (57.1)	0.08	16 (57.1)	0.08	2 (7.1)	2	—	—	0.31
	30	25	IFX biosimilar CD	23 (76.7)		23 (76.7)		23 (76.7)		5 (16.7)	3	2	—	

ADA, adalimumab; AE, adverse event; CD, Crohn's disease; IFX, infliximab; PP, per protocol study population—intention-to-treat study population analysis reported; TNF, tumor necrosis factor; UC, ulcerative colitis.

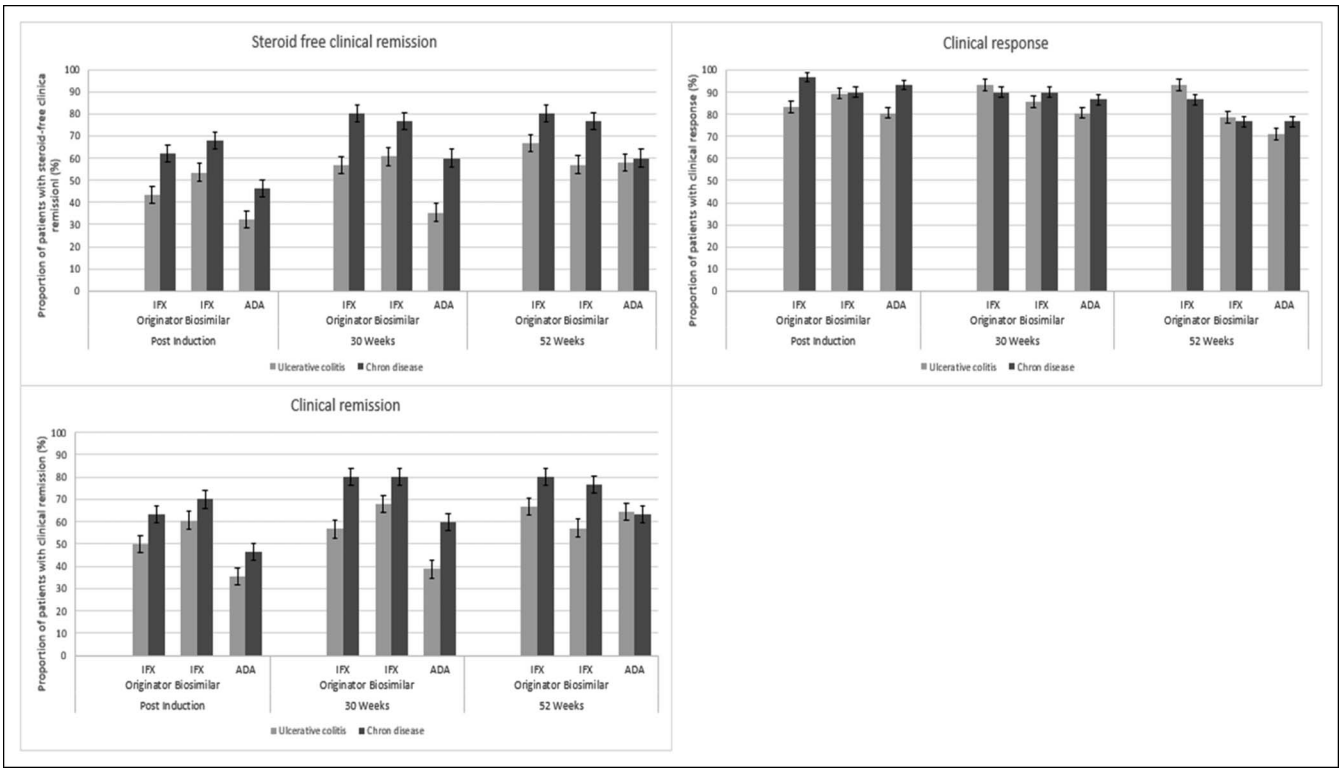

Figure 1. Clinical response, clinical remission, and steroid-free clinical remission among patients with ulcerative colitis and Crohn's disease treated with IFX originator, IFX biosimilar, ADA after induction at 30 and 52 weeks with SE. ADA, adalimumab; IFX, infliximab.

and their biosimilars between UC and CD. A deeper understanding of the peculiarities of each drug and their different effectiveness in CD and UC could provide the physician a better tool to choose the most suitable therapy for every single patient (tailored therapy). Therefore, the aim of this study was to compare the effectiveness and tolerability of IFX originator, ADA, and biosimilar infliximab (IFX biosimilar) between UC and moderate-to-severe CD. Overall, in our study, we observed a better clinical response to anti–TNF-α treatment in patients with CD: IFX originator treatment showed more outstanding results, whereas ADA proved more effective in achieving a 1-year endoscopic response in patients with UC. Treatment optimization occurred in 40% of patients with CD and 44% of patients with UC. The highest number of AEs was recorded with IFX biosimilar, which was also the treatment that leaded to a higher number of discontinuations because of them. On the other hand,

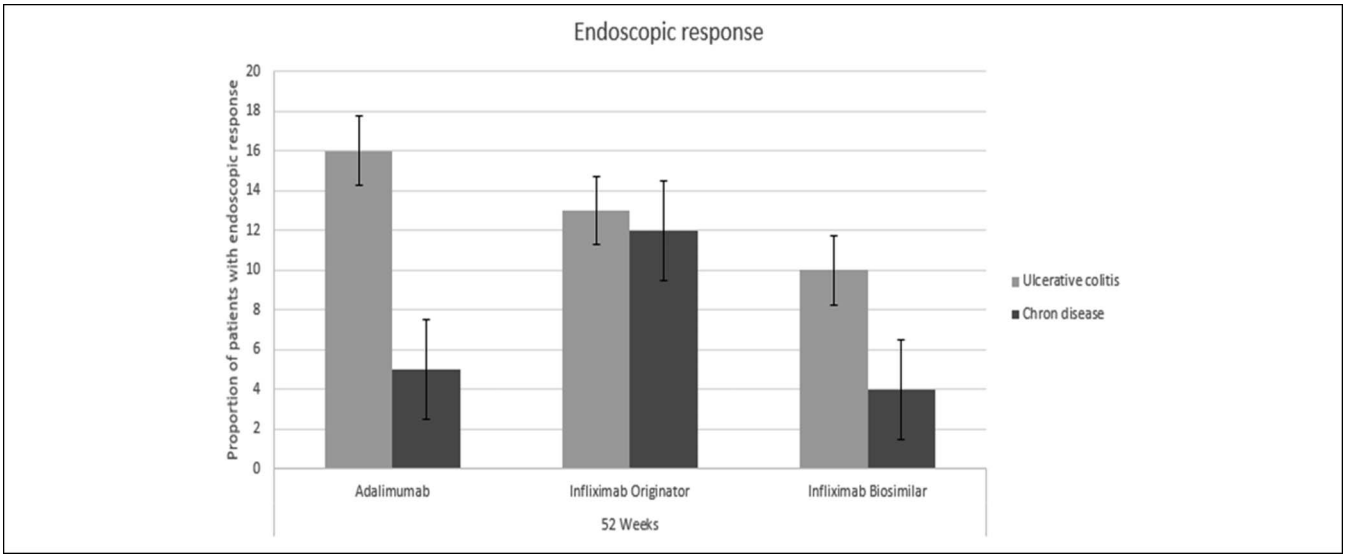

Figure 2. Endoscopic response among patients with ulcerative colitis and Crohn's disease treated with infliximab originator, infliximab biosimilar, and adalimumab at 52 weeks with SE.

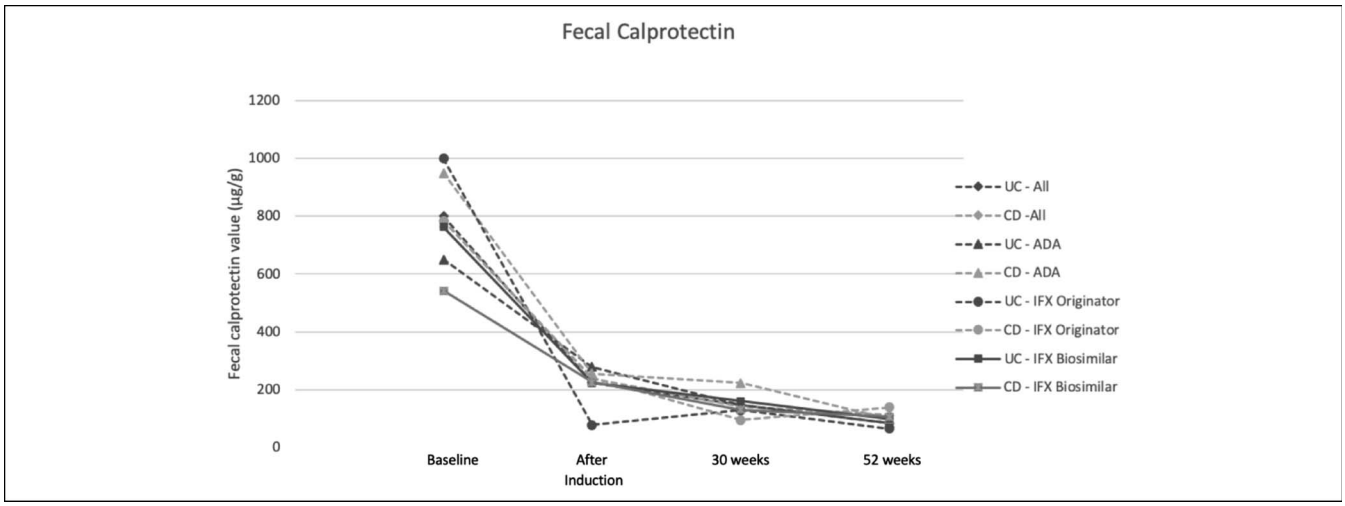

Figure 3. Trend of fecal calprotectin levels among patients with UC and CD treated with IFX originator, IFX biosimilar, and ADA from baseline to 52 weeks. ADA, adalimumab; CD, Crohn's disease; IFX, infliximab; UC, ulcerative colitis.

no significant differences in the safety and tolerability of ADA and IFX originator were detected. It is worth to mention that 3 of the suspensions were due to malignant diseases (melanoma *in situ*, biliary tract neoplasia, and lung neoplasia).

Real-world effectiveness data of ADA in CD and UC are sparse and not unique. In the Dutch study of Peters et al. (7), CD patients treated with ADA showed a good clinical response (after induction: 92.5%, week 52: 83.3%), similar to our case history (93.3% and 76.7%, respectively). Our results differed, however, in steroid-free remission and therapeutic failure: In the Dutch study, only 20.3% reached steroid-free remission at week 52, compared with 58.8% in our study. This discrepancy can be partly explained by the differences in the baseline population: The Dutch study included patients who started biological therapy for extra-intestinal manifestations or fistulizing disease, whereas our patients were selected based on luminal clinical activity. Orlando et al. (8) reported results analogous to ours because they observed clinical benefit in 91% of the CD population after the induction visit. Clinical steroid-free remission was achieved in 45.5% of cases after induction and in 64.5% of patients at month 14, similarly to our outcomes (46.4% and 60%, respectively). Instead, the real-life study conducted by Renna et al. (9) reported that at the end of week 8, 78.8% of patients with UC showed a clinical response and 40.7% were in clinical steroid-free remission, and at the end of the follow-up, figures were 66.9% and 42.4%, respectively. Our results after induction showed a clinical response in 80.6% and 32.2% steroid-free clinical remission. At week 52, the respective percentages were of 71% and 58.1%, indicating that response to ADA was slightly higher in our cases.

Regarding IFX biosimilar, after 14 weeks of treatment, a Norwegian study (10) reported clinical remission in 56% of patients with UC and 79% of patients with CD. Similarly, at the

Table 3. Multivariate analysis: unadjusted and adjusted risk of clinical response, clinical remission, and steroid clinical remission in CD compared with UC

	Clinical response		Clinical remission		Steroid-free clinical remission	
	Unadjusted OR(95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
After induction						
UC	1	1	1	1	1	1
CD	2.6 (0.9–7.1)	10.2 (2.07–52.9)	1.6 (0.88–2.9)	2.07 (0.98–4.36)	1.91 (1.04–3.5)	2.7 (1.24–5.7)
30 wk						
UC	1	1	1	1	1	1
CD	1.29 (0.5–3.4)	2.6 (0.7–9.6)	2.43 (1.3–4.6)	3.5 (1.5–7.8)	2.6 (1.4–4.9)	3.9 (1.7–9.0)
52 wk						
UC	1	1	1	1	1	1
CD	1.31 (0.4–3.9)	2.1 (0.6–7.6)	2.4 (1.1–5.3)	4.2 (1.5–11.6)	2.5 (1.2–5.3)	4.1 (1.5–10.9)

CD, Crohn's disease; CI, confidence interval; OR, odds ratio; UC, ulcerative colitis.
Note: Adjusted for those variables statistically significant different at baseline between CD and UC: concomitant use of steroid, C-reactive protein value, presence of extraintestinal manifestations disease clinical activity and endoscopy activity.

same time point, we observed clinical remission in 60.7% of patients with UC and in 70% of patients with CD and clinical response in 89.3% and 90%, respectively. A Hungarian real-life study (11), on the other hand, reported almost equal responses between the 2 diseases at week 14. Indeed, clinical response was achieved by 81.4% and clinical remission by 53.6% of patients with UC, whereas the results for patients with CD were 77.6% and 58.6%, respectively. In addition, a Romanian study (12) conducted on a cohort of patients with moderate-to-severe IBD reported similar responses between the 2 diseases: At week 30, clinical remission was obtained by 47.4% of patients with UC and by 48.9% of patients with CD. In comparison, at the same time point, we observed clinical remission in 68% of patients with UC and 80% of patients with CD, indicating a considerably higher response in the latter, but without statistical significance ($P = 0.4$). In a subanalysis of the SONIC (13) study, treatment of moderate-to-severe CD with IFX originator–induced steroid-free remission in 44.4% of patients at week 26 and in 60.8% at week 50. In our CD cases, percentage of remission were remarkably higher, being 80% both at 30 and at 52 weeks. The pivotal clinical trial ACT1 (14) with IFX originator in patients with UC revealed that clinical response and clinical remission were, respectively, achieved in 69.4% and in 38.8% of the population after induction, in 52.1% and in 33.9% at week 30 and in 45.5%, and in 34.7% after 52 weeks of treatment. In our study, clinical response and clinical remission were observed, respectively, in 83.3% and 50% of patients at week 14, in 93.3% and 56.7% at week 30, and in 93.3% and 66.7% of patients at week 52.

Regarding therapeutic optimization, the only statistically significant difference observed analyzing the 2 diseases was in the IFX originator group: At week 30, all CD patients received the standard dose, whereas 20% of patients with UC had to adjust the therapy by shortening the interval between the infusions ($P = 0.03$). If we consider the 2 diseases individually, we can observe that in patients with CD treated with IFX originator showed a lower tendency to therapy optimization (no patients after induction and week 30 and 6.7% at week 52), compared with patients with UC (3.3% after induction, 20% at week 30, and 26.7% at week 52). In the ADA group, the trend is similar between the 2 diseases: 6.6% CD and 6.4% UC after induction, 20% CD and 16.1% UC at week 30, and 26.7% CD and 35% UC at week 52. Finally, in the IFX biosimilar group, we noted a higher optimization rate at week 52 in patients with CD as compared to patients with UC (46% vs 26%). In a subanalysis of the CHARM (15) study, which assessed the efficacy of ADA in maintaining remission in 778 patients with CD, the increased frequency of injections in open-label patients was evaluated. At the end of the study (1-year average follow-up), 27% of patients who had started therapy with 1 injection every 2 weeks had switched to a weekly interval because of the lack of response (52%) or exacerbation (48%). The median value of duration using standard dose, before the changeover, was 173 days (range: 106–338). In our study, at the end of week 52, 31.1% of patients with ADA needed to optimize treatment, similar to what was reported in the literature. Regarding IFX originator, Regueiro et al. (16) analyzed a cohort of 293 patients with CD both naive and previously exposed to biological therapy, who started therapy with this anti–TNF-α drug. Overall, after 30 months, 54.3% of patients had changed the dosage or interval of administration, and no predictive factors were identified. In our study, only the 16.7% of patient treated with IFX originator needed optimization, although it has to be considered the shorter follow-up period compared with the work of Regueiro's group. For IFX biosimilar, the only study currently available in the literature assesses the loss of response in patients who switched from IFX originator to biosimilar. In this Norwegian study (17), 6 months after the switch, 23% had increased the frequency or dosage, and of these, a third had already optimized the therapy at the time of switch. In our study, 36.1% of patients receiving IFX biosimilar had optimized at week 52, compared with 16.7% of patients with IFX originator. There are no other studies that compare the need for optimization between IFX originator and IFX biosimilar. Very few studies evaluate the need to optimize therapy and surprisingly, there are no comparative studies in this regard between patients receiving IFX biosimilar and those receiving IFX originator. In our opinion, it is crucial, from a clinical and economic point of view, to evaluate and compare therapeutic optimization in a larger cohort of patients.

The most common AEs recorded in our study were dermatological, particularly erythema at the injection site and limbs, and paradoxical psoriasis, being the latter a reason of therapy discontinuation if not manageable with topical medication. We reported 6 cases of paradoxical psoriasis in patients with CD treated with ADA (n = 1) and IFX originator (n = 5), which in 2 cases led to suspension of the drug (1 in ADA and 1 in IFX originator). All 6 cases occurred in patients with CD, in line with the literature, which reported a higher incidence of paradoxical psoriasis during therapy with anti–TNF-α drugs in Crohn's disease compared with UC (18). In our cases, a large number of infections have been reported, especially for IFX originator and biosimilar groups (7 cases of UTIs, 1 of folliculitis, and 5 of upper respiratory tract infections). Regarding IFX originator, the ACCENT I (19) and ACT I (14) pivotal studies reported a similar rate of AEs among patients taking placebo and those taking IFX therapy, being the rate of infection higher in the latter. Furthermore, in ACCENT I, 6% of patients had infusion reactions (with dyspnea, flushing nausea, and headache) that were not observed in our population. In our patients on ADA therapy, several cases of wheals or erythema were reported at the injection site, consistent with what was reported in the literature (20). In the study by Orlando et al. (8), at the end of the follow-up, 17.2% of the cohort presented a moderate AE, which allowed continuation of therapy, whereas 6.3% withdrew because of a serious AE. In our study, 4 patients (13.3%) reported a moderate AE and 3 patients (10%) discontinued therapy for AEs. Moreover, in our study, 13 patients discontinued treatment for a severe AE: 3 on ADA, 8 on IFX biosimilar, and 2 on IFX originator. Thus, 3 patients discontinued therapy because of malignant diseases: An *in situ* melanoma in a patient with screening dermatological test without atypical finds; a pulmonary neoplasia in a nonsmoking patient, without family history for neoplasm and with negative screening chest radiograph; a biliary tract malignancy in a patient without previous diagnosis of primary sclerosing cholangitis. All of them were identified during the first 3 months of treatment and so far unlikely related to the use of biologics. Although there are no evidence of biliary tract malignancy described so far in patients under anti–TNFα, other cases of pulmonary cancers have been observed in patients taking anti–TNFα (21–23). Nevertheless, from the ENCORE registry (24), in which more than 1,500 patients on IFX therapy were followed prospectively, it seemed that these drugs were correlated with a higher risk of infections and hematological disorders, rather than malignant diseases. However, this confirms the need not only for a scrupulous

screening but also for a careful and comprehensive follow-up of the patient in biological therapy, also taking into account the individual risk factors (e.g., smoking habits).

So far, the comparison between the effectiveness and safety of anti–TNF-α in CD and UC has been performed only indirectly through meta-analysis studies. Indeed, there is a lack of head-to-head studies that compared the derivable outcomes with the various drugs between the 2 diseases. Our study wanted to fill this gap and fit into this research horizon. From our analysis, it seems that therapy with anti–TNF-α drugs is more effective in inducing and maintaining clinical remission and steroid-free clinical remission in CD. This applies to postinduction week 30 and week 52 treatment evaluation. In the different drug subgroups, an overall greater response was observed in CD, however, without reaching statistical significance. It is worth of note, however, that the clinical score in CD takes also into account the intestinal manifestations of illness, present in 48.9% of our patients, and the subjective component of perception of the patients' health status.

Despite the remarkable results obtained, our study has some limitations. First, the sample size is limited. However, this drawback is balanced by the fact that every patient was strictly followed-up by at maximum 2 physicians with the same standardized management approach. Second, follow-up is not long enough to gather reliable data about the long-term response and correlation of serious AEs with biological therapy. Furthermore, the retrospective design of the study has caused it to be lacking in some data, such as the endoscopic and histological evaluation at 52 weeks. This prevented a comparison of MH achievable among the various treatments in the 2 diseases; therefore, further studies are needed to evaluate this parameter, given its relevance as therapeutic goal in IBD care (25). Finally, the study population showed a remarkable heterogeneity, including both patients already exposed to biological, as well as naive, patients treated with biological monotherapy or patients receiving immunosuppressant concomitant therapy. On the other hand, this can be considered a representation of the clinical reality: heterogeneous groups rather than the selected cohorts of registration trials.

In conclusion, we found that a greater percentage of clinical efficacy was achieved in patients with CD as compared to UC. Moreover, similar efficacy and safety was observed among the different treatments in both conditions. However, the occurrence of malignant disease underlines the need of a strict follow-up during time. We believe that this study could be the starting point for future prospective studies, based on large case studies and randomized, to compare the efficacy and safety in real life of biological drugs currently in use in the 2 diseases.

CONFLICTS OF INTEREST

Guarantor of the article: Fabiana Zingone, MD, PhD.

Specific author contributions: B.B., F.Z., and E.V.S.: study concept and design, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. B.B., R.D., L.R., L.B., G.B., M.G., A.G., D.M., and G.L.: acquisition of data and critical revision of the manuscript. B.B. and F.Z.: statistical analysis.

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Study Highlights

WHAT IS KNOWN

✓ There are no real-life studies comparing the efficacy and safety of the different anti–TNF-α drugs available in patients with UC and CD.

WHAT IS NEW HERE

✓ Anti–TNF-α treatment was more effective in patients with CD compared with UC, and it was independent from the drug used which showed similar effectiveness.

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