Continuous clinical remission with biologics in ulcerative colitis: the 'AURORA' comparison study

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Objectives Comparative trials among biological drugs for the treatment of ulcerative colitis (UC) provided conflicting results. After patent expire of infliximab originator, adalimumab, infliximab biosimilar, golimumab and vedolizumab have been approved in Italy.
We compared the efficacy of these four biologics in UC according to the concept of continuous clinical remission (CCR).
Methods In a retrospective, multicentre study, all UC patients treated with adalimumab, infliximab biosimilar, golimumab or vedolizumab between 2014 and 2019 were included. All drugs were compared to each other according to the 1-year CCR rate, defined as Mayo partial score ≤2, with bleeding subscore = 0, without any relapse or optimization with dose escalation, topical treatments or steroid use after first clinical remission.
Results Four-hundred sixteen patients (adalimumab = 90, infliximab biosimilar = 105, golimumab = 79, vedolizumab = 142) were included. CCR was achieved in similar percentages among the groups (33%, 37%, 28%, 37%, respectively). All drugs were equivalent in biologic-naive patients, while vedolizumab was better than a second anti-TNFα in prior anti-TNFα agent failures. No differences were found according to type of adverse events or severe adverse events.
Conclusions Based on a strict definition of clinical remission, all biologics appear equally effective at 1 year. Changing to vedolizumab is more effective than switching to another anti-TNFα in TNFα failures. Eur J Gastroenterol Hepatol 34: 1238–1246

Introduction

Ulcerative colitis (UC) is a chronic, idiopathic, inflammatory bowel disease (IBD) that affects the colorectal mucosa. The conventional goals of therapy in UC are to induce and maintain remission, but the definitions of treatment endpoints are still debated and evolving [1].

Infliximab was the first biological drug approved for UC in Italy in 2005 [2]. The patent of Remicade, the infliximab 'originator' (IFX-O), expired in Europe in 2015; recently, other compounds were introduced in the Italian market in sequential order: from the approval of two subcutaneous anti-TNFα-drugs (adalimumab and golimumab) to CT-P13 (the first biosimilar of infliximab) and vedolizumab (the first non-anti-TNFα agent) to adalimumab biosimilars and other infliximab biosimilars, ustekinumab and tofacitinib.

Although the clinical efficacy of each molecule has been demonstrated in placebo-controlled, phase III trials, no randomized, controlled, *head-to-head* comparative trials have clearly described the superiority of a single drug over the others in UC. The only exception is the recent VARSITY trial, which showed the superiority of vedolizumab to adalimumab according to clinical remission at week 52, but not in terms of the more ambitious steroid-free clinical remission (SFCR) [3]. Also, several uncontrolled studies using different end-points reported contradictory results [4–32].

The aim of this study was to compare the efficacy of the first four biological drugs approved for the treatment of moderate to severe UC in Italy, as an alternative to IFX-O, using a novel criterion of efficacy, defined by the induction

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and continuous maintenance of a relapse-free, optimization-free, steroid-free, clinical remission after 1 year of treatment, as primary end-point. Further conventional clinical and endoscopic outcomes were also described as secondary endpoints.

Methods

Study design

The 'AURORA' (Assessing the efficacy of biologics in Ulcerative colitis: a Real-life, Observational Retrospective multicentre study using the propensity score Analysis) study was a multicentre, retrospective, real-life study comparing multiple clinical and endoscopic outcomes among all consecutive patients treated with at least one of the first four biological drugs (infliximab biosimilar, adalimumab originator, golimumab, vedolizumab) approved in Italy as an alternative to IFX-O. Treatment groups were compared to each other using an inverse probability weighting (IPW) analysis. Patients were followed up for 1 year or until early drug withdrawal due to inefficacy or adverse events. The study was approved by local Institutional Review boards.

Patients and drugs

All consecutive patients requiring a biological drug for moderate-severe UC at the participating centers after the patent expire of IFX-O in the years 2014–2019, were included according to the sequential approval of the biological drug as follows:

(1) CTP-13 (Remsima, Celltrion; Inflectra, Pfizer), the first infliximab biosimilar approved in 2014;
(2) adalimumab originator (Humira, Abbvie), approved in 2015;
(3) golimumab (Simponi, MSD), approved in 2015; and
(4) vedolizumab (Entyvio, Takeda), approved in 2016.

More recent infliximab or adalimumab biosimilars, ustekinumab and tofacitinib were not available at the time of study conception. IFX-O was also not included.

The following demographic and clinical data were collected at baseline: sex, age, disease duration, disease extent, smoking status, BMI, steroid-dependency or refractoriness defined according to European Crohn's and Colitis Organisation guidelines, clinical and endoscopic activity according to the Mayo scores, extra-intestinal manifestations, previous and concomitant medications. Optimization of biologics, through increased dose (for infliximab biosimilar and golimumab) or frequency (for infliximab biosimilar, adalimumab and vedolizumab) was recorded when prescribed according to the physician's judgment, which was based on clinical data and supported by biochemical data such as C-reactive protein (CRP) and/or fecal calprotectin, if available. Any other rescue therapies with oral/topical mesalamine or topical/systemic steroids were also recorded during the induction and/or maintenance phases of treatment. Clinical activity was monitored at 2, 6 and 14 weeks, then every 8 weeks until 1 year or early withdrawal for drug failure or intolerance. At each medical examination, any change in the patient's clinical status was recorded in the clinical charts by the physician, with particular regard to blood and stool frequency, two well-recognized patient-reported outcomes (PROs) included in the partial Mayo score. Endoscopic activity was assessed at baseline and after 1 year or in case of early drug withdrawal.

Primary endpoint

The primary endpoint was the achievement and maintenance of a steroid-free, continuous clinical remission (CCR) during the first year (54 weeks). CCR was defined as a Mayo partial score ≤2 (with no bleeding), without any clinical relapse or treatment optimization after the first remission was achieved, and without drug withdrawal due to adverse events. Treatment optimization was defined as the addition of systemic/topical steroids, oral/topical mesalazine or any dose escalation of biologics, according to the physician's clinical judgment, supported by biochemical data (including CRP and/or fecal calprotectin).

Secondary endpoints

The following secondary endpoints were also analyzed at 1 year:

- SFCR was defined as a Mayo partial score ≤2 (with no bleeding) at 1 year, irrespective of previous optimizations and/or rescue therapies, but with no concomitant steroids at the end of follow-up; SFCR was analyzed in the overall population as well as in the subgroup of patients with concomitant steroid therapy at baseline;
- *first clinical remission*, defined as patients achieving clinical remission at least one time during their 1-year follow-up, irrespective of concomitant treatments and later relapse; the number of patients achieving their first clinical remissions, subtracted from the total number of patients, provides the rate of primary non-responders;
- *relapse rate*, defined as secondary loss of response (LOR) with patients having a clinical relapse (according to a Mayo partial score >2) before 54 weeks, after the achievement of their first clinical remission;
- *persistence on treatment*, defined as patients on continuous treatment through 54 weeks, irrespective of their disease activity status at 1 year and irrespective of intercurrent rescue therapies;
- *endoscopic remission*, defined as Mayo endoscopic subscore = 0 at the end of their follow-up; a more permissive definition based on Mayo endoscopic subscore 0-1 was also analyzed;
- *colectomy*, defined as patients requiring surgical treatment for refractory or complicated disease at 1 year;
- *treatment failures for safety*, defined as patients with adverse events requiring drug withdrawal;
- *adverse events*, defined as the occurrence of any adverse event, irrespective of drug withdrawal.

Concerning early outcomes, the two PROs (blood and stool scores = 0) included in the partial Mayo score were also separately analyzed at 2, 6 and 14 weeks.

Treatment outcomes were analyzed in the overall population and stratified according to previous exposure to biologics.

Sample size calculation

At the time of study conception, no studies were available reporting the rate of 1-year CCR or SFCR for each

biological used in our cohort. In a smaller pilot exploratory analysis with the same study design, no statistically significant differences emerged among biologics, despite some numerical differences, in terms of 1-year CCR (infliximab biosimilar 32%, adalimumab 36%, golimumab 12%, vedolizumab 26%) [33]. Assuming a treatment efficacy around 35%, 30%, 25% and 15%, respectively, and with a different reduction by 25% based on the IPW adjustment, a sample size of 75 patients for each treatment group resulted in 80% power in detecting significant differences between the comparison groups. The Cochrane–Armitage test was used in the sample calculation.

Statistical analysis

The categorical variables were described by counts and percentages, the quantitative variables by mean and standard or median deviation and interquartile range. All estimates were presented with their 95% confidence intervals. Comparisons between two groups for quantitative variables were made using the Student's *t*-test for independent data (or a non-parametric analog in the case of asymmetric data distribution), while for qualitative variables the chi-square test or Fisher's exact test were used, as appropriate. The association between the percentage of patients who have achieved and maintained CCR after 54 weeks and the drug category are investigated using an IPW multinomial logit model in which the main dependent variable is remission (or the secondary outcomes), independent variables are disease duration, age, sex and smoking. IPW estimators use weighted regression coefficients to compute averages of treatment-level predicted outcomes, where the weights are the estimated inverse probabilities of treatment. IPTW uses the propensity score to balance baseline patient characteristics in the exposed and unexposed groups by weighting each individual in the analysis by the inverse probability of receiving his/her actual exposure. To 'adjust' the estimate for the factors that determine treatment group, weights were calculated taking into account not only demographic factors but also the main factors that may influence the response (clinical and endoscopic disease activity, concomitant and previous therapies including being naive or not to biological drugs, resistance to steroids versus corticosteroid dependency). Models are also fitted in patients naive to biologics, as subgroup analysis. The overlap assumption that requires that each individual have a positive probability of receiving each treatment was assessed graphically (Fig. 1). Balancing was assessed through standardized mean difference and variance ratio at baseline and after adjustment and tested with Imai and Ratkovic covariate balancing propensity score test for 2 × 2 comparisons (each drug against the others) that can be executed after IPW [34]. If the treatment model is well specified, IPW functions of the covariates from the model are balanced. Overlap assumptions were met and balancing was achieved for all comparisons (we cannot reject the null hypothesis that the IPW model balanced all covariates).

Results

Patients and drugs

In the study period (May 2014–April 2019), 438 patients with moderate-severe UC were treated with the biologics included in our comparisons. Twenty-two patients (5%) were excluded due to incomplete follow-up. Therefore, 416 patients were included in the final analysis and treated with infliximab biosimilar ($n = 105$), adalimumab ($n = 90$), golimumab ($n = 79$) and vedolizumab ($n = 142$). Endoscopic data were available from 374 patients (90% of the total). The baseline characteristics of the included patients are summarized in Table 1. The IPW analysis was applied to adjust significant differences among the groups (Fig. 1).

Efficacy

Table 2 reports the efficacy in the overall population. Tables 3 and 4 show the outcomes in patients naive to biologics and failures to anti-TNFα, respectively.

Primary outcome

Overall, CCR was achieved in 34% of patients at 1 year. Despite some minor differences that emerged among biologic drugs (infliximab biosimilar 37%, adalimumab 33%, golimumab 28%, vedolizumab 37%), none were statistically significant. These findings were also confirmed in the subgroup of patients naive to biologics ($n = 223$), in which CCR was achieved in 38% of patients, without significant differences among the drugs. By contrast, in patients who failed a previous anti-TNFα drug ($n = 159/193$ previously exposed patients), vedolizumab was more effective compared to a second-line anti-TNFα agent (CCR: 36% vs. 18%, $P = 0.004$).

Secondary outcomes

Overall, clinical remission and SFCR were achieved in 63% and 44% of patients, respectively, without significant differences among the drugs. A slightly higher SFCR rate was observed in patients naive to biologics (51%). In this subgroup, adalimumab performed better than golimumab (SFCR 62% vs. 28% $P \leq 0.05$).

The overall relapse rate, due to LOR after the first clinical remission, was 36%, with vedolizumab showing significantly lower rates (32%) than adalimumab (41%) and golimumab (43%).

More than half of the patients (55%) were still on therapy at one year, with higher persistence rate for vedolizumab compared to adalimumab and golimumab.

Endoscopic remission was similar among all groups according to the Mayo 0-1 criteria, while a higher endoscopic remission rate was evident for infliximab biosimilar and adalimumab compared to golimumab when a Mayo endoscopic subscore = 0 was considered.

The overall colectomy rate was 8%, without differences between each drug.

Early outcomes

Table 5 shows the secondary outcomes in the overall population at 2, 6 and 14 weeks. The only drug that performed differently from *all* other single compounds was vedolizumab, just for lower rates of stool remission at week 2. Other significant differences were variably found only for a few comparisons between single drugs, but they were lost along the follow-up.

Drugs optimizations

Before entering their first clinical remission within 1 year, 92 patients received at least one form of optimization (Table 6). Systemic steroids and topical therapies were added in 4% and 9% of patients, respectively, without significant differences among the four groups. On the contrary, biological drug dose escalation was used in 11% of patients and less frequently with golimumab than infliximab biosimilar ($P = 0.004$), adalimumab ($P = 0.0183$) and vedolizumab ($P = 0.0118$).

Forty-two patients (46%) achieved their first remission after these optimizations; the corresponding rates of clinical remission for each form of optimization were 75% (topical therapies), 47% (steroids) and 23% (dose escalation), respectively, with significant differences only between infliximab biosimilar and vedolizumab in terms of clinical remission after biological drug dose optimization (44% vs. 6%; $P = 0.009$) and between adalimumab and vedolizumab in terms of clinical remission after any form of optimization (62% vs. 25%; $P = 0.006$).

Among 94 patients who experienced a secondary LOR, 27 had to stop the treatment, while 55 patients had at least one rescue therapy added while continuing their biologic, with similar rates among the four groups (Table 7). Topical therapies were added in 31% of patients, without differences among the four groups. Systemic steroids were added in 18% of patients, with higher rates for golimumab (37%) than adalimumab (8%; $P = 0.016$) and vedolizumab (11%; $P = 0.032$). Biologics were optimized in 27% of patients, less frequently with golimumab (11%) than adalimumab (38%; $P = 0.012$) and infliximab biosimilar (38%; $P = 0.044$). Overall, 40% of patients receiving any rescue therapy after secondary LOR, regained and maintained clinical remission at one year, without differences among the treatment groups and the type of rescue strategy.

Safety

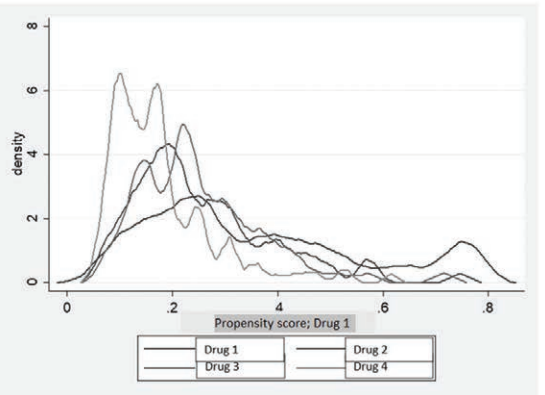
Overall, adverse events during biological treatment were reported in 17% of patients, but only 5% had to stop the drug for intolerance. The main side effects are listed in Table 8. Infliximab biosimilar had a significantly higher rate of total adverse events compared to adalimumab and vedolizumab in the overall population (28% vs. 10% vs. 11%), but not in naive patients. However, withdrawal rates due to drug intolerance did not differ between different biologics. Moreover, no differences were found according to the type of adverse events (including infusion reactions and infections) or severe adverse events.

Discussion

In this multicentre real-life study, none of the first four biological drugs sequentially approved in Italy for the treatment of moderate-severe UC as an alternative to IFX-O, showed significant superiority in terms of CCR, defined as SFCR, with no rescue therapies after the achievement of their first remission. Our study is the first to use this clinical endpoint in the effort to provide, in our opinion, a more transparent definition of response to biologics, which is crucial in the specific setting of comparative trials. In fact, despite several previous studies did not show a significant advantage of a single drug according to a variety of endpoints [4–8,10,12,13,15,16,18–20,25], other studies periodically reported the superiority of single drugs [9,11,17,23,24,27,30,32], thus feeding a continuous and inconclusive debate on this argument. Only two retrospective studies have been previously published comparing infliximab, adalimumab, golimumab and vedolizumab in UC, providing opposite results. In the first one, Long *et al*. described the superiority of infliximab over adalimumab in terms of patients remaining steroid-free through 12 months of follow-up, but no data were reported on disease activity and, therefore, clinical remission rates [22]. Chen *et al*., on the contrary, showed the superiority of adalimumab over all other drugs in terms of persistence in treatment after 1 year [14]. Even less informative are four, more recent, retrospective studies, which compared vedolizumab to all three anti-TNFα agents considered as a whole [28–31], thus lacking specific comparisons between single drugs.

The confusion is further fuelled by the lack of an agreement on the definition of remission in UC [35,36]; as a consequence, even the only prospective, controlled, comparative trial between vedolizumab and adalimumab may be misinterpreted since vedolizumab had higher rates of clinical remission than adalimumab, but achieved similar rates of SFCR [3].

To improve the descriptors of treatment outcomes, we decided to use CCR as our primary endpoint. The concept of CCR was introduced as a primary endpoint in the PURSUIT maintenance trial with golimumab in UC [37]. In this trial, any use of concomitant medications, as well as surgery, were considered treatment failures and defined as loss of the CCR status within the 54 weeks of treatment. The concept of CCR, therefore, encompasses the idea of continuous control of disease severity as an optimal indicator of favorable outcomes [38]. In fact, CCR without treatment failure was associated with major clinical, endoscopic, quality of life and long-term benefits in patients with moderate to severe UC treated with golimumab [39]. Certainly, it may be argued that treatment optimization should not be considered a failure if most patients can achieve clinical remission at the end of follow-up. However, we believe that such consideration should not be done in the context of comparative studies, especially in uncontrolled and/or retrospective series in which the treatment strategies might not be standardized and well distributed across the groups of patients. Another distinguishing aspect of our study is the definition of remission according to the best outcomes for current clinical and endoscopic indices of activity: our primary end-point includes the absence of blood in stools (Mayo bleeding score = 0), which is one of the PRO now recommended by regulatory agencies for industry trials, and strongly associated with endoscopic improvement [40]. Furthermore, a Mayo endoscopic subscore = 0 was chosen, in contrast to other trials in which mild endoscopic activity was tolerated, as well as residual bleeding [3]. In this regard, interestingly, only one-third of patients achieved complete mucosal healing, a lower rate than that reported in previous trials of biologics in UC which used the Mayo 0-1 criteria [41].



Overidentification test for covariate balance

H0: Covariates are balanced

Drug 1 vs other
chi2(12) = 11.1 Prob > chi2 = 0.52
Drug 2 vs other
chi2(12) = 5.41 Prob > chi2 = 0.94
Drug 3 vs other
chi2(12) = 7.27 Prob > chi2 = 0.84
Drug 4 vs other
chi2(12) = 4.77 Prob > chi2 = 0.97

Fig. 1. Test for covariate balancing according to the Imai and Ratkovic covariate balancing propensity score test for 2 × 2 comparisons.

Table 1. Baseline characteristics of the entire cohort of patients included in the study

	Infliximab biosimilar (*n* = 105)	Adalimumab (*n* = 90)	Golimumab (*n* = 79)	Vedolizumab (*n* = 142)	*P*
Male gender, *n* (%)	59 (56.2)	53 (58.9)	48 (60.8)	95 (66.9)	NS
Age, years (mean ± SD)	39.1 (±14.4)	42.6 (±14.8)	42.2 (±13.2)	47 (±16.9)	<0.05
Never or past smokers, *n* (%)	101 (96.2)	82 (91.1)	74 (93.7)	136 (95.8)	NS
Previous appendectomy, *n* (%)	4 (3.8)	3 (3.3)	3 (3.8)	9 (6.3%)	NS
BMI, *n* (%)					
Normal	82 (78.1)	73 (81.1)	60 (75.9)	107 (75.4)	NS
>25	21 (20)	16 (17.8)	17 (21.5)	30 (21.1)	NS
<18.5	2 (1.9)	1 (1.1)	2 (2.5)	5 (3.5)	NS
Disease duration, years–mean (IQR)	6.6 (2–9)	10.1 (3–14.8)	10.4 (2–15)	10 (4–14)	<0.05
Disease extension, *n* (%)					
Proctitis	10 (9.5)	10 (11.1)	13 (16.5)	19 (13.4)	NS
Left colitis	33 (31.4)	30 (33.3)	33 (41.8)	53 (37.3)	NS
Pancolitis	62 (59)	50 (55.6)	33 (41.8)	70 (49.3)	NS
Extraintestinal manifestations, *n* (%)					
None	92 (87.6)	72 (80)	65 (82.3)	124 (87.3)	NS
Articular	13 (12.4)	18 (20)	14 (17.7)	18 (12.7)	NS
Dermatological	0	0	0	0	NS
Steroid dependency, *n* (%)	62 (59)	68 (75.6)	56 (70.9)	100 (70.4)	NS
Steroid refractoriness, *n* (%)	38 (36.2)	16 (17.8)	15 (19.0)	29 (20.4)	<0.05
Naive to immunosuppressors, *n* (%)	53 (50.5)	45 (50.9)	40 (50.6)	52 (36.6)	NS
Naive to biologics, *n* (%)	73 (69.5)	56 (62.2)	60 (75.9)	34 (23.9)	<0.05
Failures to previous biologics, *n* (%)	21 (20)	25 (28)	16 (20)	97 (68)	<0.05
Disease activity, *n* (%)					
Moderate (full Mayo Score 6-10)	74 (70.5)	77 (85.6)	71 (89.9)	136 (95.8)	<0.05
Severe (full Mayo Score > 10)	31 (29.5)	13 (14.4)	8 (10.1)	6 (4.2)	<0.05
Endoscopic activity, *n* (%)					
Mayo 1	3 (2.9)	3 (3.3)	10 (12.7)	4 (2.8)	<0.05
Mayo 2	35 (33.3)	45 (50.0)	39 (49.4)	76 (53.5)	<0.05
Mayo 3	67 (63.8)	42 (46.7)	30 (38.0)	62 (43.7)	<0.05
Concomitant treatments at baseline, *n* (%)					
Systemic steroids	61 (58.1)	45 (50.0)	27 (34.2)	60 (42.3)	<0.05
Immunesuppressors	19 (18.1)	12 (13.3)	15 (19.0)	19 (13.4)	NS
Oral mesalazine	64 (61)	50 (55.6)	52 (65.8)	83 (58.5)	NS
Topical steroids or mesalazine	54 (51.4)	43 (47.8)	44 (55.7)	61 (43.0)	<0.05

Beyond the heterogeneous definitions of clinical and endoscopic endpoints, different behaviors on the use of biologics can also influence the data on their performance in comparative trials. This is even more evident in the current era in which many biologics are available and steroid therapy is no longer the only rescue strategy applied in clinical practice [42]. For example, optimization of biological drugs through their dose escalation is an option now available in real life, which has been reported to restore clinical response in uncontrolled studies in UC [43–45]. On the other hand, it may lead to misinterpretation of the comparative outcomes when optimization schedules are not standardized. In our study, one-third of patients received at least one form of rescue therapy to 'help' maintain clinical remission in the short term; half of these patients had a clinical benefit, thus permitting the clinician to avoid or postpone the failure of the biological drug. Therefore, the rate of patients on persistent treatment exceeds the rate of patients experiencing more important clinical endpoints, such as CCR or relapse rate. These data support two critical considerations: firstly, even SFCR may not correctly describe the continuous control of the disease in the current scenario of biological therapies in UC; secondly, they suggest that the use of persistence in treatment as clinical endpoint can be misleading, despite its use in numerous comparative studies [4,14,25,29,31,32].

Switching and swapping to an alternative biologic is another option in case of primary and secondary non-response. However, it can similarly influence the persistence of treatment and the interpretation of long-term efficacy in comparative trials of biologics. From this point of view, we observed an unbalanced use of the

Table 2. Primary and secondary outcomes in the overall population at 1 year

Clinical endpoints	Total ($n=416$)	Infliximab biosimilar ($n=105$)	Adalimumab ($n=90$)	Golimumab ($n=79$)	Vedolizumab ($n=142$)
Continuous clinical remission	34%	37%	33%	28%	37%
Steroid-free clinical remission					
All patients	44%	50%	50%	34%	41%
Only patients with steroids at baseline	40%	44%	51%	33%	32%
First clinical remission	63%	66%	71%	59%	62%
Relapse rate	36%	33%	41%	43%	32%^{*ADA,GOL}
Persistence on treatment	55%	55%	54%	42%	63%^{*ADA,GOL}
Endoscopic endpoints	Total ($n=374$)	Infliximab biosimilar ($n=88$)	Adalimumab ($n=85$)	Golimumab ($n=78$)	Vedolizumab ($n=123$)
Endoscopic remission (Mayo 0)	14%	23%	22%	13%^{*CTP,ADA}	13%
Endoscopic remission (Mayo 0-1)	24%	33%	34%	28%	25%

*$P \leq 0.05$ compared to the single drug indicated in superscript form in the head-to-head comparisons.

Table 3. Primary and secondary outcomes in patients naive to biologics

Clinical endpoints	Total ($n=223$)	Infliximab biosimilar ($n=73$)	Adalimumab ($n=56$)	Golimumab ($n=60$)	Vedolizumab ($n=34$)
Continuous clinical remission	**38%**	**41%**	**39%**	**32%**	**41%**
Steroid-free clinical remission					
All patients	51%	53%	62%^{*GOL}	38%	47%
Only patients with steroids at baseline	49%	51%	58%	37%	38%
First clinical remission	69%	67%	80%^{*GOL,VDZ}	60%	68%
Relapse rate	22%	29%^{*GOL}	33%	39%	22%^{*ADA,GOL}
Persistence on treatment	58%	58%	66%	42%^{*ADA,VDZ}	74%
Endoscopic endpoints	Total ($n=198$)	Infliximab biosimilar ($n=58$)	Adalimumab ($n=53$)	Golimumab ($n=59$)	Vedolizumab ($n=28$)
Endoscopic remission (Mayo 0)	20%	19%	26%	17%	14%
Endoscopic remission (Mayo 0-1)	29%	24%	32%	32%	20%

*$P \leq 0.05$ compared to the single drug indicated in superscript form in the head-to-head comparisons.

Table 4. Primary and secondary outcomes in patients failures to a first anti-TNFα agents and treated with a rescue therapy based on vedolizumab or second-line anti-TNFα agents

Clinical endpoints	Vedolizumab ($n=97$)	Anti-TNFα ($n=62$)	*P*
Continuous clinical remission	**36%***	**18%**	**0.004**
Steroid-free clinical remission			
All patients	38%	24%	NS
Only patients with steroids at baseline	30%	24%	NS
First clinical remission	59%	52%	NS
Relapse rate	35%*	53%	**0.021**
Persistence on treatment	58%*	35%	**0.002**
Endoscopic remission (Mayo 0)	13%	7%	NS
Endoscopic remission (Mayo 0-1)	26%	16%	NS

*$P \leq 0.05$.

various drugs during the study period, favoring vedolizumab over golimumab or adalimumab. In fact, despite vedolizumab being the latest drug approved in UC during the study period, its use was very frequent, perhaps due to a greater interest linked to its different mechanism of action. On the other hand, the use of golimumab seems to have suffered a sort of negative bias, demonstrated by the inferior number of patients treated and the lower severity of disease at baseline (in terms of endoscopic activity and refractoriness to other biologics), perhaps partly due to the lack of dose optimization during the study period, which was not approved in Italy until later. By considering drug optimization as a treatment failure, our definition of CCR enables the comparison of golimumab with the other drugs. On the other hand, previous real-life studies showed that a quarter of patients needed golimumab dose escalation, and 71% of these regained responses after optimization [46]. Moreover, dose intensification predicted late clinical response and higher persistence with golimumab [44,47].

Patients naive to biologics are an interesting clinical setting in which no evidence-based choice can be made about the best first-line biological drug. Few previous studies on purely naive patients limited the comparison to infliximab and adalimumab, without showing substantial clinical differences [5,9,10,15,19]. Also, a recent study by Bressler *et al*., including 604 UC patients naive to biologics, did not describe a superiority of any drug, except for higher persistence rates (but not clinical effectiveness) with vedolizumab compared to three anti-TNFα agents as a whole [31]. Our results confirm that no single drug was superior to any other according to the continuous disease control primary endpoint. Considering the current availability of biosimilars, their lower cost will probably make infliximab and adalimumab yet very attractive as a first choice in naive patients. On the contrary, in patients refractory to anti-TNFα agent, vedolizumab appears to have a better outcome compared to switching to another anti-TNFα. In our study this is supported by the superiority of vedolizumab according to both primary and secondary endpoints.

Our study has several limitations. Obviously, it is limited by its retrospective, not randomized, design. The use of a statistical analyses based on the propensity score was a precise choice to overcome distortions in the comparison. Another limitation is the lack of data regarding inflammatory markers like CRP and fecal calprotectin, and their correlation with clinical and endoscopic outcomes, as well as the influence of drug levels and anti-drug antibodies. This reflects different strategies in disease monitoring across the recruiting centers. On the other hand, neither fecal calprotectin nor drug through levels or antibodies is currently reimbursed by the public Italian healthcare system, thus limiting their extensive use. More important, despite a plausible sample size calculation for a real-life, unsponsored study, this is still a small study with

Table 5. Early outcomes in the overall population at 2, 6 and 14 weeks

Endpoint	Infliximab biosimilar ($n=105$)	Adalimumab ($n=90$)	Golimumab ($n=79$)	Vedolizumab ($n=142$)
T2 stool remission	23%	29%	27%	**11%*** IFX-B, ADA, GOL
T2 blood remission	37%	41%	43%	40%
T2 clinical remission	22%	34%	35%	**19%*** ADA, GOL
T2 steroid-free clinical remission	11%	21%	27%	**13%*** GOL
T6 stool remission	31%	33%	24%	20%
T6 blood remission	48%	49%	39%	59%
T6 clinical remission	31%	37%	29%	40%
T6 steroid-free clinical remission	**20%*** VDZ	27%	24%	35%
T14 stool remission	37%	44%	**32%*** ADA	29%
T14 blood remission	60%	61%	47%	61%
T14 clinical remission	45%	53%	41%	47%
T14 steroid-free clinical remission	41%	46%	41%	46%

*$P \leq 0.05$.

Table 6. Drugs optimizations before entering the first clinical remission

	Any rescue therapy added before first remission	First clinical remission after any rescue therapy	Systemic steroids added	Firs clinical remission after steroids	Topical therapy added	First clinical remission after topical therapy	Biological drug escalation	First clinical remission after biological drug escalation
Infliximab biosimilar	27 (26%)	13 (48%)	4 (4%)	2 (50%)	9 (9%)	5 (56%)	16 (15%)	7 (44%)
Adalimumab	24 (27%)	15 (62%)	6 (7%)	4 (67%)	10 (11%)	9 (90%)	11 (12%)	3 (27%)
Golimumab	13 (16%)	7 (54%)	4 (5%)	1 (25%)	8 (10%)	7 (87%)	2 (3%)*	0 (0%)
Vedolizumab	28 (20%)	7 (25%)***	3 (2%)	1 (33%)	9 (6%)	6 (67%)	18 (13%)	1 (6%)**
Total	92 (22%)	42 (46%)	17 (4%)	84 (47%)	36 (9%)	27 (75%)	47 (11%)	11 (23%)

*$P \leq 0.05$ GOL vs. IFX-B, ADA, VDZ. **$P \leq 0.05$ VDZ vs. IFX-B. *** $P \leq 0.05$ VDZ vs. ADA.
ADA, adalimumab; VDZ, vedolizumab; IFX-B, infliximab biosimilar.

Table 7. Management of secondary loss of response

	No. of patients with clinical relapse	Treatment stopped	Any rescue therapy added	Rescue systemic steroids	Rescue topical therapy	Rescue biological drug escalation	Clinical remission after any rescue therapy
Infliximab biosimilar	21	5 (24%)	14 (67%)	5 (24%)	4 (19%)	8 (38%)	7 (50%)
Adalimumab	26	9 (35%)	13 (50%)	2 (8%)	6 (23%)	10 (38%)	7 (54%)
Golimumab	19	6 (32%)	13 (68%)	7 (37%)*	8 (42%)	2 (11%)**	5 (36%)
Vedolizumab	28	7 (25%)	14 (50%)	3 (11%)	11 (39%)	5 (14%)	3 (21%)
Total	94	27 (29%)	55 (59%)	17 (18%)	29 (31%)	25 (27%)	22 (40%)

*$P \leq 0.05$ vs. ADA, VDZ. **$P \leq 0.05$ vs. ADA, IFX-B.
ADA, adalimumab; VDZ, vedolizumab; IFX-B, infliximab biosimilar.

Table 8. Adverse events in the treatment groups (overall population)

	Infliximab biosimilar	Adalimumab	Golimumab	Vedolizumab
Adverse events - any (%)	28% *ADA,VDZ	10%*CTP,GOL	19%	11%
Infusion reactions, *n* (%)	11 (10.5%)	0	0	0
Skin reactions, *n* (%)	2 (1.9%)	2 (2.2%)	7 (8.9%)	1 (0.7%)
Infections, *n* (%)	6 (5.7%)	3 (3.3%)	3 (3.8%)	8 (5.6%)
Arthralgia/myalgia, *n* (%)	3 (2.9%)	0	0	3 (2.1%)
Miscellaneous, *n* (%)	7 (6.7%)	4 (4.4%)	5 (6.3%)	4 (2.8%)
Drug withdrawal for intolerance (%)	13	2	4	1

*$P \leq 0.05$ compared to the single drug indicated in superscript form in the head-to-head comparisons.

the risk of underpowering, especially in subgroup analysis of small groups of patients. Finally, another limitation is the potential influence of different therapeutic approaches among the participating centers, with different thresholds for some critical behaviors like treatment optimization or withdrawal. In the effort to decrease the impact of this factor, the participating centers were chosen according to a well-established collaboration in education and clinical research with the Postgraduate School of Gastroenterology of Milan University; notably, quite all authors collecting the data were past fellows at that School and shared similar clinical formation in their management of IBD.

In conclusion, recent biologics approved for moderate-severe UC provide similar clinical outcomes when rigorous definitions of continuous disease control are used. A significant rate of patients still fails to reach disease control in the short and long term. Swapping to vedolizumab could be a more effective strategy rather than intra-class

switching after the failure of a first anti-TNFα agent. On the contrary, the choice of the first-line drug in patients naive to biologics seems not to be supported by clinical outcomes and, therefore, should consider other factors such as costs and patient preferences. Our study provides a picture of our current performance in UC requiring biologic use and suggests the need to reconsider our treatment endpoints when comparative studies are designed to better support our therapeutic choices. Further comparative data about more recent biologics, such as ustekinumab and tofacitinib, are also awaited.

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Conflicts of interest

There are no conflicts of interest.

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