

Infliximab biosimilar CT-P13 is effective and safe in treating inflammatory bowel diseases: a real-life multicenter, observational study in Italian primary inflammatory bowel disease centers

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Abstract

Background The purpose of this study was to assess the efficacy and safety of biosimilar infliximab (IFX) CT-P13 in treating outpatients with inflammatory bowel disease (IBD) in Italian primary gastroenterology centers.

Methods Consecutive IBD outpatients who completed the induction treatment were evaluated retrospectively. Clinical activity was scored according to the Mayo score for ulcerative colitis (UC) and to the Harvey-Bradshaw Index (HBI) for Crohn's disease (CD). The primary endpoint was the achievement of clinical remission (Mayo score ≤ 2 in UC and HBI ≤ 5 in CD). Secondary endpoints were clinical response to treatment, achievement of mucosal healing, and safety.

Results One hundred forty-one patients (96 UC and 45 CD) were enrolled. Previous treatment with anti-tumor necrosis factor (TNF) α had been provided to 26% of UC patients and 28.9% of CD patients. Remission was achieved in 57.3% UC patients and in 75.6% CD patients during a median (interquartile range) follow up of 24 (6-24) months. Clinical response and mucosal healing were achieved in 87.5% and 75.0% of UC patients and in 84.4% and 84.2% of CD patients, respectively. By both univariate and multivariate analysis, age >40 years, presence of comorbidities, and naivety to anti-TNF α were significantly related to remission. Only one (0.7%) adverse event was reported in the CD group. Surgery was performed in 2.1% of UC patients and 6.7% of CD patients. Switching from IFX originator to biosimilar did not influence the maintenance of the clinical remission.

Conclusion This study confirmed the long-term efficacy and safety of CT-P13 therapy in IBD, in both naïve patients and those switching from IFX originator.

Keywords Biosimilar, CT-P13, Crohn's disease, infliximab, ulcerative colitis

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Introduction

Inflammatory bowel diseases (IBD) are mainly represented by ulcerative colitis (UC) and Crohn's disease (CD). Both diseases arise from an interaction between genetic and environmental factors, and they are predominantly observed in developed countries [1]. Both UC and CD are characterized by a relapsing and remitting course, sometimes requiring an aggressive therapeutic approach to prevent complications [2]. The discovery that tumor necrosis factor (TNF) α plays an important role in the pathogenesis of IBD [1] and the introduction of the monoclonal anti-TNF α antibody infliximab (IFX) have greatly improved treatment options in IBD patients refractory to or intolerant of standard therapies [2,3], for either CD or UC [1].

Obviously, this treatment entails a much higher financial burden than do traditional therapies [4-6]. In response to the often high costs of originator biologics, interest has grown in biosimilar alternatives, which are cost-effective, "follow-on" biologic drugs with highly similar quality, efficacy, and safety compared to an already licensed biologic [6,7]. Biosimilar IFX CT-P13 (RemsimaTM, InflectraTM) is a biosimilar alternative to the IFX "reference medicinal product" (RMP) (RemicadeTM) and is the first monoclonal antibody biosimilar to be approved by the European Medicines Agency. Biosimilar IFX CT-P13 and the IFX RMP are chimeric monoclonal IgG1 antibodies, produced in independently developed cell lines, derived from the same murine hybridoma cell type [8].

After the first positive experiences in rheumatic diseases [9,10], biosimilar IFX CT-P13 was approved for all of the same indications as the RMP, including CD and UC, in Europe, Japan and South Korea [8,11,12]. Subsequently, several recent studies found biosimilar IFX CT-P13 to be effective and safe in patients with CD or UC [13-23], and a recent position paper from the European Crohn's and Colitis Organization states that biosimilar IFX can be expected to have the same efficacy and safety as the originator [24]. However, the vast majority of the studies were performed in secondary or tertiary centers [11-23].

IFX CT-P13 reimbursement for CD and UC was approved in Italy in 2014 [24,25]. Two Italian studies have investigated the efficacy and safety of this IFX biosimilar. However, the short follow up [15,23] and the small sample enrolled [26] limited the impact of these studies. The aim of the present study was to assess the efficacy and safety of biosimilar IFX CT-P13 in treating a large IBD outpatient population in some

Italian primary IBD centers, following approval of biosimilar IFX CT-P13 reimbursement for IBD by the Italian Regulatory Authorities.

Patients and methods

This was a retrospective, observational, multicenter study that included outpatients with UC or CD unresponsive to standard treatments and were treated with biosimilar IFX CT-P13 (RemsimaTM) in 14 Italian primary IBD centers (namely, centers identified by the Italian National and Regional Health Systems as able to manage uncomplicated IBD patients). We assessed patients enrolled from 1st May 2015 to 31st December 2017, who completed at least the induction treatment. Eligible patients included men and women, at least 18 years of age, with an established diagnosis of UC or CD according to standard endoscopic and/or radiology and/or histological criteria [1].

A shared common database was used to collect demographic and clinical data. Data collected at baseline were sex, age at diagnosis, smoking status, disease extension, disease duration, previous immunosuppressive and anti-TNF α therapies, concomitant medications at baseline, C-reactive protein and fecal calprotectin levels, Mayo score and Mayo subscore for endoscopy for UC patients, and Harvey-Bradshaw Index (HBI) for CD patients. Patients were clinically assessed at entry, after 2, 3, 6, and then every 6 months.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients gave written informed consent before undergoing endoscopy and IFX CT-P13 treatment. Formal consent is not required for this type of study.

Study treatment

All patients were eligible for infusion of biosimilar IFX after exclusion of active hepatitis B virus infection, active cytomegalovirus infection, and tuberculosis infection. After pre-treatment with methylprednisolone 20 mg intravenously (or chlorphenamine 10 mg intramuscular in patients intolerant of steroids) at every infusion, biosimilar IFX CT-P13 (RemsimaTM) was administered at a dose of 5 mg/kg via 2-h intravenous infusion at weeks 0, 2, and 6 in order to obtain remission, and thereafter every 8 weeks in order to maintain remission. Dose escalation to maintain remission, namely an infusion regimen increasing to 10 mg/kg and/or every 4 instead of 8 weeks, was applied when necessary. If dose escalation was applied, it was recorded and reported.

The need for treatment discontinuation was left to the investigators' judgement, as were concomitant medications including oral and topical aminosalicylates, steroids and immunosuppressants.

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Clinical assessment

Disease extension was assessed according to the Montreal classification [27]. Severity was assessed according to the Mayo score [25] in UC patients and according to HBI [28] score in CD patients. All patients had active disease despite concomitant treatment, defined as a Mayo score ≥ 3 points [29] for UC patients and an HBI score >5 points [11] for CD patients. As stated, patients were clinically assessed at entry, after 2, 3, 6, and then every 6 months.

Endoscopy

As standard protocol for patients under treatment with biologics in the participating centers, ileocolonoscopy was performed in all enrolled patients at entry, after 6, 12, and every 12 months thereafter during treatment. CD patients with an upper gastrointestinal location underwent both esophagogastroduodenoscopy and ileocolonoscopy, both at diagnosis and during the follow up.

Endoscopic severity in UC patients was assessed according to the Mayo subscore for endoscopy [29]. Endoscopic severity in CD patients was assessed by the simple endoscopic score for CD (SES-CD) [30,31].

Endpoints

Primary endpoints were: a. induction of remission, defined as Mayo score ≤ 2 in UC patients and HBI ≤ 5 in CD patients; and b. safety of biosimilar IFX CT-P13, defined as absence of adverse events (AE) during treatment. The AE were subdivided into early (occurring during infusion) and late (occurring at least one week after the infusion) events, and were graded as mild (not requiring cessation of treatment) and severe (requiring cessation of treatment). The occurrence of opportunistic infections was also considered as an AE. An opportunistic infection was defined as any infection caused by microorganisms that have limited pathogenic capacity under normal circumstances, but that have been able to cause disease because of the predisposing effect of another disease or its treatment [32].

Secondary endpoints were: a. clinical response, defined as reduction of at least 2 points in the Mayo score in UC patients and at least 3 points in the HBI score in CD; b. achievement of mucosal healing, defined as Mayo subscore for endoscopy ≤ 1 in UC and SES-CD score ≤ 2 in CD; c. reduction in steroid use during the study; d. prevention of colectomy in UC and any surgical procedure related to the disease in CD; and e. assessment of any difference between patients naïve to IFX and patients switching from Remicade™ to Remsima™.

Statistical analysis

Data were analyzed using MedCalc® Release 14.8.1. The characteristics of the study group were analyzed as median

(interquartile range [IQR]) for continuous non-parametric variables and as number (percentage) for categorical variables. Fisher's exact test was used to compare categorical variables. Clinical remission was considered as the primary endpoint. The prognostic value of clinical parameters was evaluated using time-to-event methods for censored observations, because of the varying length of follow up. Follow-up times were calculated from the date of diagnosis to the date of event or censorship. Time-to-event analysis was carried out using Kaplan-Meier estimates to draw the cumulative incidence curves, compared by log-rank tests, as well as by univariate and multivariate Cox's proportional hazards models of prognostic variables. The hazard ratios are presented with 95% confidence intervals and P-values. A ratio higher than unity implies that an event has a higher probability compared to the reference group. P-values <0.05 were considered to be statistically significant.

Results

One hundred forty-one patients were enrolled according to the inclusion criteria. The characteristics of the study group according to UC and CD are reported in Table 1. Both groups were similar with respect to demographic and clinical characteristics. The majority of patients enrolled in both groups were naïve to anti-TNF α (26% of UC patients and 28.9% of CD patients were previously treated with anti-TNF α). Patients previously treated with anti-TNF α were enrolled because of a secondary loss of response to the treatment in the majority of subjects in both groups.

Primary endpoints

Overall, remission was achieved in 55 of 96 (57.3%) UC patients and in 34 of 45 (75.6%) CD patients during a median (IQR) follow up of 24 (6-24) months, with no significant difference (Fig. 1). In patients previously exposed to anti-TNF α , remission was achieved in 12 of 25 (48.0%) UC patients and in 8 of 13 (61.5%) CD patients. By both univariate and multivariate analysis, age over 40 years, the presence of comorbidities and naivety to anti-TNF α were significantly related to remission (Table 2).

With respect to safety, only one (0.7%) AE was reported in the CD group. It was a mild skin atopic reaction that occurred in a 21-year-old male at the first biosimilar IFX CT-P13 infusion and led to prompt interruption of the treatment.

Secondary endpoints

Secondary end-points are shown in Table 3. All parameters assessed showed significant efficacy of biosimilar IFX CT-P13. In particular, achievement of mucosal healing and steroid withdrawal during the follow up showed very high percentages, confirming the efficacy of this biosimilar drug. Finally, all the

Table 1 Demographics, disease characteristics and concomitant medications

Characteristics	UC (n=96)	CD (n=45)
Male sex	46 (47.9)	21 (46.7)
Mean (95%CI) age, years	46.5 (43.7-49.3)	39.1 (34.6-43.7)
Median (IQR) disease duration, years	5 (3-13)	4 (3-9)
Presence of comorbidities	31 (32.3)	16 (35.6)
Previous appendectomy	6 (6.2)	8 (17.8)
Concomitant therapy		
Mesalazine	93 (96.9)	42 (93.3)
Steroids	94 (98.9)	43 (95.6)
Thiopurine	3 (3.2)	2 (4.4)
Previous anti-TNF α		
Adalimumab	7 (28.0)	8 (61.5)
Golimumab	18 (72.0)	5 (38.5)
Primary non-responders	7 (28.0)	1 (7.7)
Secondary loss of response	18 (72.0)	12 (92.3)
Montreal classification of extent of UC		
Left-sided colitis	28 (29.1)	-
Extensive colitis	67 (69.9)	-
Montreal classification of CD		
Isolated ileal disease	-	19 (42.21)
Isolated colonic disease	-	11 (24.4)
Ileocolonic disease	-	15 (33.3)
Concomitant UGI disease	-	-
Concomitant perianal disease	-	9 (20.0)
Non stricturing, non-penetrating	-	20 (44.4)
Stricturing	-	17 (37.8)
Penetrating	-	8 (17.8)
Median (IQR) CRP, (mg/L)	16.0 (8.7-28.5)	15.0 (7.0-30.0)
Median (IQR) fecal calprotectin (μ g/g)	340 (240-645)	485.0 (203.2-856.5)
Median (IQR) partial Mayo score	7 (6-8)	-
Median (IQR) Mayo subscore for endoscopy	3 (2-3)	-
Median (IRQ) HBI	-	10 (6-15)
Median (IRQ) SES-CD	-	10 (7-14)

Data are given as number (percentage) of patients unless otherwise indicated

IQR, interquartile range; CRP, C-reactive protein; HBI, Harvey-Bradshaw index; SES-CD, simple endoscopic score for Crohn's disease; TNF, tumor necrosis factor; UGI, upper gastrointestinal

parameters assessed were reported with similar percentages in both UC and CD patients.

With respect to surgery, colectomy was performed in 2 (2.1%) UC patients at 1 and 6-month follow up, and ileocolic resection in 3 (6.7%), at 2, 3 and 18-month follow up.

Finally, a switch from IFX originator to IFX biosimilar occurred in 22 patients (15.6% of the overall population): 15 (15.6%) UC patients and 7 (15.5%) CD patients. All these patients were under stable remission at the time of switching, performed with a view to significant cost saving.

As reported in Table 2, switching from IFX originator to biosimilar did not influence the maintenance of the remission.

Discussion

Biosimilars have been developed because they entail a much lower financial cost than that for traditional treatment options.

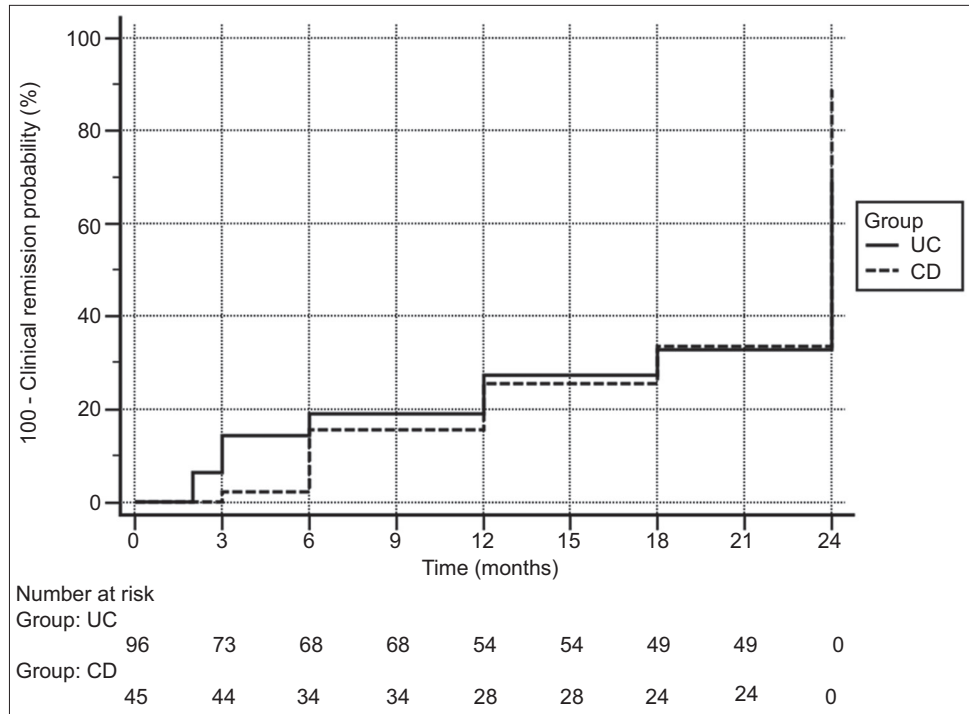


Figure 1 Estimated cumulative clinical remission probability during follow up in patients with ulcerative colitis (UC) or Crohn’s disease (CD). Log-rank test

Table 2 Predictors of clinical remission

Factors	Univariate Cox PH model				Multivariate analysis Cox PH model		
	χ^2	P	HR	95% CI	HR	95% CI	P
UC vs. CD	1.253	0.263	1.214	0.782 to 1.883	-	-	-
Sex, male	0.134	0.714	1.064	0.700 to 1.616	-	-	-
Age >40 years	11.355	0.001	1.773	1.119 to 2.807	0.590	0.386-0.904	0.015
Disease duration >5 years	0.858	0.354	0.856	0.565 to 1.295	-	-	-
No appendectomy	0.936	0.333	1.322	0.690 to 2.533	-	-	-
Presence of comorbidities	6.566	0.010	1.561	0.984 to 2.474	1.556	1.011-2.396	0.044
Naïve to anti-TNF α	13.475	0.000	1.959	1.286 to 2.986	1.815	1.145-2.878	0.011
Anti-TNF α switch from originator	2.289	0.084	0.658	0.389 to 1.119	-	-	-

UC, ulcerative colitis; CD, Crohn disease; PH, proportional hazards; HR, hazard ratio; CI, confidence interval; TNF, tumor necrosis factor

Table 3 Outcomes of secondary end-points during follow up

Outcomes	UC (n=96)	CD (n=45)
Clinical response	84 (87.5)	38 (84.4)
Previous anti-TNF α	19/25 (76.0)	11/13 (84.6)
Mucosal healing	42/56 (75.0)	16/19 (84.2)
Reduction in steroids	93 (96.9)	44 (97.8)
Surgery	2 (2.1)	3 (6.7)

Data are given as number (percentage) of patients unless otherwise indicated
UC, ulcerative colitis; CD Crohn’s disease

Biosimilar IFX CT-P13 has shown its efficacy and safety in the treatment of rheumatic disease [9,10], and has been approved for all of the same indications as RMP, including CD and UC, in Europe, Japan and South Korea [8,11,12].

Since the “extrapolation” of clinical data from rheumatic to gastrointestinal indications triggered a large debate, several observational “real world” studies are becoming available. To date, most of these studies found that biosimilar IFX CT-P13 was also effective and well-tolerated in IBD patients [13-23]. However, all of these studies were conducted in academic or tertiary IBD centers. Our previous pilot study found biosimilar

IFX CT-P13 to be effective and well-tolerated in active UC outpatients [26]. This larger study confirms these results and raises several clinical considerations.

This is the first large study with a long-term follow up (24 months) conducted in Italy in primary IBD centers to assess the efficacy and safety of biosimilar IFX CT-P13. Looking at the primary endpoints, the first consideration is that biosimilar IFX CT-P13 is really effective and safe in real life, even when managed in primary IBD centers. A significant remission rate and a very high clinical response rate were obtained in our population, in both UC and CD subjects. Literature data showed that biosimilar IFX CT-P13 achieved remission in 50-80% of UC and CD patients, while a clinical response was recorded in 54-100% of patients [13-23]. Our results are in line with these experiences, and better to the one recently reported by Fiorino *et al*, who described the real-life experience from using biosimilar IFX CT-P13 in Italian academic or tertiary IBD referral IBD centers [13]. It is likely that our results may be influenced by the less complex patients managed in primary IBD centers, which generally manage patients who do not require complex clinical and therapeutic approaches.

With respect to safety, we found biosimilar IFX CT-P13 to have an excellent safety profile, since we recorded an AE rate <1%. This result deserves an adequate analysis. From October 2015 to October 2017, a rapid increase in the utilization of biosimilar IFX CT-P13 was recorded across Italy [33]. However, this increase was also associated with an increase in the reports of AE induced by IFX biosimilars [33]. This seems to contrast with a recent study by Gonçalves *et al*, who found a similar antigenic profile for IFX originator and IFX biosimilar CT-P13 [34]. Finally, the recent PROSIT Italian cohort study found a 19% rate of AE [23]. As hypothesized for our efficacy results, the less complex patients managed in primary IBD centers may explain our excellent results concerning safety. The characteristics of our study group may also explain why comorbidity is not a risk factor for loss of response: probably comorbidities were not severe, and therefore were not able to negatively influence the course of the disease.

With respect to the secondary endpoints, biosimilar IFX CT-P13 shows an excellent high rate of achieving mucosal healing, clinical response and steroid sparing. Therefore, in our experience, biosimilar IFX CT-P13 seems to work as well as the originator [35] and better than other anti-TNF α medications such as adalimumab [36] and golimumab [37]. Of course, these comparisons must be made with appropriate reservations, since the populations enrolled are not the same, with different follow-up periods and different percentages of patients previously exposed to anti-TNF α .

Another finding that deserves some comment is that multivariate analysis found IFX CT-P13 to be more effective in patients older than 40 years and with comorbidities. This may seem counterintuitive, since we know that older age is a risk factor for lower treatment efficacy [38] and older people show a higher AE rate [39]. It is not easy to explain our results. The mean disease duration of the enrolled population was quite short (no more than 5 years): this could have played a positive role in their response to the treatment and in reducing the risk of AE despite the older age and the presence of comorbidities.

However, this does not fully explain the better response in older patients; thus, larger and longer studies are needed in this specific setting.

These excellent results of biosimilar IFX CT-P13 in achieving both primary and secondary endpoints lead to the last clinical consideration: namely, whether and when we can switch from Remicade' to Remsima' appropriately. This is a key point for clinical practice, because it may lead to significant cost-sparing. Switching from originator to biosimilar is generally advised in patients under stable remission with an IFX originator. Current literature data found switching from Remicade' to Remsima' safe and feasible in both pediatric and adult IBD patients [13,28,40-43], though a recent systematic review recommends caution in switching from originator to biosimilar [44]. In our study group there were only few patients switched from IFX originator to biosimilar IFX CT-P13, and we did not find any significant difference between patients naïve to IFX and patients switching from IFX originator to IFX biosimilar with respect to achievement of remission. It is noteworthy to underscore that all our patients were under stable remission when they were switched to IFX biosimilar. This may explain the good results we observed in this subgroup of patients. However, the small number of patients does not allow us to draw definite conclusions.

The present study suffers from some limitations. The first is the retrospective design, which did not allow us to enroll patients with the same timing through the follow up, either clinical or endoscopic. The second is that only outpatients with mild-to-moderate disease were enrolled. Since this study

Summary Box

What is already known:

- Infliximab biosimilar CT-P13 is the first available biosimilar for the treatment of inflammatory bowel diseases (IBD)
- Short-term follow-up studies found infliximab biosimilar CT-P13 effective both in naïve patients and in those previously exposed to other anti-tumor necrosis factor (TNF) α agents
- Some real-life studies have investigated its efficacy and safety, but were performed in secondary/tertiary centers

What the new findings are:

- This is the first study conducted in primary IBD centers in Italy
- In this setting, over a long-term follow up, infliximab biosimilar CT-P13 seems to be effective both in naïve patients and in those with prior exposure to other anti-TNF α agents
- Infliximab biosimilar CT-P13 also seems to be safe over a long-term follow up

was conducted by primary IBD centers, the patients managed were generally less complex and the majority of anti-TNF α prescriptions were subcutaneous anti-TNF α antibodies, since these are easier to use for outpatients. This amounts to a selection bias, which may have influenced the final results. It may also explain why Italian academic and referral IBD centers enrolled a large population on biosimilar IFX CT-P13 [23].

In conclusion, this large real-life cohort study from primary Italian IBD centers shows that biosimilar IFX CT-P13 is as effective and safe as the originator IFX in managing IBD outpatients. Longer real-life studies are needed to confirm the possibility of switching from IFX originator to IFX biosimilar without any loss of efficacy and safety.

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