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Alimentary Tract

Switching from infliximab originator to a first biosimilar is safe and effective. Results of a case-control study with drug levels and antibodies evaluation

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ABSTRACT

Background: Inflammatory bowel disease is treated with anti-TNF agents such as infliximab and its biosimilars, but use of biosimilars is limited due to perceived risks of adverse events.
Aim: To explore safety and effectiveness of switching from the infliximab originator to a first biosimilar.
Patients and methods: Clinical and biological outcomes were compared between 53 patients who switched from the infliximab originator to the biosimilar CT-P13 (Switched group) and 13 patients treated with CT-P13 from the beginning (Naïve group). Infliximab trough levels and antidrug antibodies were measured.
Results: At enrolment, patients in the Switched group had a longer median duration of infliximab treatment than Naïve (4.0 vs. 0.6 years, $p < 0.0001$) but similar proportions of patients were in remission (77% and 62%, respectively). Infliximab discontinuation due to adverse events or loss of efficacy was less common in the Switched (26%) than Naïve group (62%, $p = 0.017$). Variables independently associated with time to discontinuation were disease activity ($p < 0.0001$) and immunomodulating treatment ($p = 0.019$) at enrolment. Trough levels and antidrug antibodies were similar between groups during observation.
Conclusion: This study confirms that switching from infliximab originator to a first biosimilar is safe and effective. Patients at highest risk of losing treatment efficacy are those with active disease, irrespective of the therapeutic switch.

1. Introduction

Inflammatory bowel disease (IBD) is a group of chronic disorders characterized by inflammation of the gastrointestinal tract. Crohn's disease (CD) and ulcerative colitis (UC) are the main types of IBD. Treatment goals for IBD patients include relief of symptoms, resolution of inflammation, and prevention of disease progression whenever possible [1]. Inhibitors of tumor necrosis factor alpha (TNFα or simply TNF) have demonstrated efficacy and safety for the treatment of IBD [2]. They are the most used biological treatment for CD and UC, and are recommended by practice guidelines for treating severe active or refractory disease and perianal CD [3–5]. Anti-TNF agents are used as both induction and maintenance treatment for IBD patients. Anti-TNF agents include the monoclonal antibodies infliximab and adalimumab. Due to patent expiration, infliximab biosimilars (and, more recently, also adalimumab biosimilars) became available worldwide and became a standard of treatment [6–9].

In the gastroenterological community, perceptions of the reliability of anti-TNF biosimilars and especially of the safety and efficacy of switching from an originator to a first biosimilar have changed over the past few years. Presently, switching from an originator to a first biosimilar is considered acceptable from both the clinical and economic standpoints [10–13].

Trough levels and antidrug antibody (ADAs) have been extensively studied in IBD patients over the past two decades. Trough levels are good markers of drug activity, while the presence of ADAs signals a loss of activity or the likelihood of adverse drug reactions [14–18].

This study investigated the safety and effectiveness of switching from the infliximab originator (Remicade) to a registered biosimilar (CT-P13, Remsima). In particular, it compared clinical outcomes, biological activity of the drug (trough levels), and safety signals

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(adverse events and ADAs) between patients who switched from the originator to CT-P13 (Switched group) and patients who never switched but were treated from the beginning with CT-P13 (Naïve group).

2. Patients and methods

2.1. Patient enrolment and sampling

Since April 2016, the local government of Piedmont, Italy, has required physicians to systematically switch patients from therapy with the originator infliximab to its biosimilar CT-P13. Since 2015, when CT-P13 (Remsima) became commercially available, patients who required infliximab were started directly with the biosimilar. Two unmatched, unrelated groups of IBD patients were identified and invited to participate in a prospective observational study approved by local Ethical Committee. Altogether, 66 patients agreed to participate in the study, provided written informed consent, and were included:

- Naïve group: 13 IBD patients whose infliximab treatment started, and continued, with CT-P13 (Remsima), according to prescribing indications and practice guidelines.
- Switched group: 53 IBD patients who were initially treated with infliximab originator (Remicade) and who were scheduled to undergo a therapeutic switch to CT-P13 (Remsima) after April 2016.

Data were retrospectively collected from clinical records regarding demographic and disease characteristics, disease location and extent [19], disease activity and medical history. For the Switched group, a baseline blood sample was drawn immediately prior to the first infusion of the infliximab biosimilar (so-called therapeutic switch). For all patients, two or three blood samples were drawn during the course of the study for the analysis of trough levels and antidrug antibodies (ADAs). Clinical characteristics and treatment outcomes were collected and aligned at all observation time points.

2.2. Analytical methods

Infliximab trough levels were measured by sandwich ELISA (Immundiagnostik, Bensheim, Germany). Briefly, in a first incubation step, the free infliximab in the sample was bound to a specific anti-infliximab monoclonal antibody coated on the plate. Then, peroxidase-labeled antibody was added, and tetramethylbenzidine was added as a substrate for peroxidase. The intensity of the color reaction is directly proportional to the concentration of free infliximab in the sample. A six-point calibration curve allowed measurement of the drug in each sample diluted 1:200. The level of serum infliximab was considered in the optimal analytical range for concentrations between 3 and 7 μg/ml, detectable if >1 μg/ml, and absent or undetectable when <0.5 μg/ml. In the presence of infliximab ADAs, trough levels are likely to be recorded as absent, due to analytical interaction.

The presence of infliximab ADAs was also determined by sandwich ELISA (Immundiagnostik, Bensheim, Germany). During sample preparation, ADAs were separated from the therapeutic antibody (infliximab) to determine their total amount. Peroxidase conjugate (peroxidase-labeled infliximab) and tracer (biotinylated infliximab) were added, the unmarked therapeutic antibody was replaced, and the marked antibodies formed complexes with the ADAs. These complexes bound via biotin to the streptavidin-coated microtiter plate and were detected via the peroxidase conjugate, with the peroxidase converting the substrate tetramethylbenzidine to a blue product. The enzymatic reaction was stopped by adding an acidic solution, which converted the samples from blue to yellow. The color change was measured in a photometer at 450 nm. The interpretation was made using a cut-off control: samples with a higher average optical density (OD) than the cut-off control were considered positive for ADA (cut-off =10 AU/ml = OD cut-off control).

2.3. Statistical analyses

Statistical analyses were carried out with MedCalc software version 18.11.3 (MedCalc Software, Ostend, Belgium; https://www.medcalc.org; 2019). Differences in categorical variables (e.g. occurrence of adverse events, discontinuation of treatment) were tested for significance using the chi-square test or Fisher's exact test. Continuous variables were compared with the Mann–Whitney test.

Binary time-dependent analyses, to identify covariates significantly associated with different outcomes, were done with Kaplan–Meier survival analysis. When a cut-off value was needed to transform continuous variables into categorical variables, receiver operating characteristics (ROC) analysis was used to identify the best performing value.

Multivariate logistic regression (for categorical outcomes) or Cox proportional hazard regression (for time-dependent multivariate analysis) were used to test independent associations for multivariate analysis.

A p value ≤ 0.05 was considered to indicate significance.

Sample size assumption was based on non-inferiority or superiority, setting as the major clinical outcome the proportion of patients remaining in treatment (75%). With a delta margin of non-inferiority or superiority of 0.10, and with beta power of 0.90 and alpha error of 0.05, the minimal required sample size was calculated to be 26 cases (http://powerandsamplesize.com/Calculators/Test-1-Proportion/1-Sample-Non-Inferiority-or-Superiority).

3. Results

3.1. Characteristics of the study groups

Overall, 66 patients enrolled in the study, including 53 in the Switched group and 13 in the Naïve group (Table 1). The clinical characteristics were matched between the groups, although a smaller percentage of patients in the Switched group had been diagnosed with IBD before age 20 years than in the Naïve group ($p = 0.035$). Moreover, patients in the Switched group had a substantially longer duration of infliximab treatment at enrolment than did patients in the Naïve group ($p < 0.0001$), as well as a longer duration of observation in the study ($p = 0.007$).

Regarding the infliximab regimen at the first (baseline) observation, all patients were on a 5 mg/kg dose (Switched vs. Naïve groups, $p = 1.000$). Their dosing intervals were variable but did not differ significantly between groups: 35 patients (66%) in the Switched group and 9 (69%) in the Naïve group were receiving infliximab every 7–weeks ($p = 0.828$). Baseline median C-reactive protein (CRP) levels were 2.0 mg/l (95% CI, 1.3–2.9 mg/l) in the Switched group and 2.6 mg/l (95% CI, 1.3–8.3 mg/l) in the Naïve group ($p = 0.256$), and the percentages of cases with abnormal CRP levels (i.e. > 5 mg/l) were similar between groups ($p = 0.299$).

3.2. Clinical outcomes

Before the end of the study, infliximab treatment was stopped in 22 patients (33% of the entire study population) due to adverse outcomes (e.g. intolerance, adverse events or loss of efficacy). They stopped treatment after a median overall period of 10.2 months (95% CI, 5.6–12.8. The percentage of patients stopping treatment was significantly less in the Switched group (26%; 14 of 53) than in

Table 1
Clinical characteristics of inflammatory bowel disease patients enrolled in the study.

	Switched group (n = 53)	Naïve group (n = 13)	All patients (n = 66)	p[d]
Diagnosis, n (%)				
- CD	29 (55)	3 (23)	32 (49)	0.069
- UC	24 (46)	10 (77)	43 (52)	
Gender, female, n (%)	20 (38)	4 (31)	24 (36)	0.642
Age at diagnosis <20 years, n (%)	7 (13)	5 (39)	12 (18)	**0.035**
Disease duration, years, median (95% CI)	16 (12.6-18.0)	11 (4.5–12.7)	14.3 (11.9–17.3)	0.178
CD location, n (%)[a,b]				
- L1 Terminal ileum	3 (10)	1 (33)	4 (13)	0.462
- L2 Colon	3 (10)	0 (0)	3 (9)	
- L3 Ileocolonic	19 (66)	1 (33)	20 (63)	
- L4 Upper GI tract	4 (14)	1 (33)	5 (16)	
CD behavior, n (%)[a,b]				
- B1 Non-stricturing–nonpenetrating	9 (31)	0 (0)	9 (28)	0.251
- B2 Stricturing	7 (24)	2 (67)	9 (28)	
- B3 Penetrating	13 (45)	1 (33)	14 (44)	
Perianal CD, n (%)[a]	15 (52)	1 (33)	16 (50)	0.551
UC extent, n (%)[b,c]				
- E1 Proctitis	1 (4)	0 (0)	1 (3)	0.759
- E2 Left side	13 (54)	5 (50)	18 (53)	
- E3 Subtotal, pancolitis	10 (42)	5 (50)	15 (44)	
Familial history, n (%)	4 (8)	1 (8)	5 (8)	0.986
Active smoking, n (%)	12 (23)	2 (15)	14 (21)	0.569
Extraintestinal manifestations, n (%)	24 (45)	4 (31)	28 (42)	0.346
BMI, kg/m^2, median (95% CI)	23.1 (22.4–25.3)	22.9 (19.8–26.8)	23.1 (22.3–24.5)	0.578
Concomitant immunosuppressants, n (%)	7 (13)	4 (31)	11 (17)	0.131
Indication for anti-TNF, n (%)				
- Refractory luminal disease	37 (70)	9 (69)	46 (70)	0.640
- Fistulizing disease	3 (6)	0 (0)	3 (5)	
- Steroid dependency	13 (25)	4 (31)	17 (26)	
Infliximab treatment duration prior to enrolment, years, median (95% CI)	4.0 (2.4–6.5)	0.6 (0.4–1.0)	2.4 (1.4–4.4)	**<0.0001**
Duration of observation after enrolment, months, median (95% CI)	20.6 (17.0–22.1)	12.4 (4.9–19.4)	20.1 (15.1–20.7)	**0.007**
Remission at baseline observation, n (%)	41 (77)	8 (62)	49 (74)	0.246

BMI, body mass index; CD, Crohn's disease; CI, confidence interval; GI, gastrointestinal; UC, ulcerative colitis.
In bold highlighted significant p values.
[a] Percent of patients with CD.
[b] Graded according to the Montreal classification [19].
[c] Percent of patients with UC.
[d] Switched group vs. Naïve group.

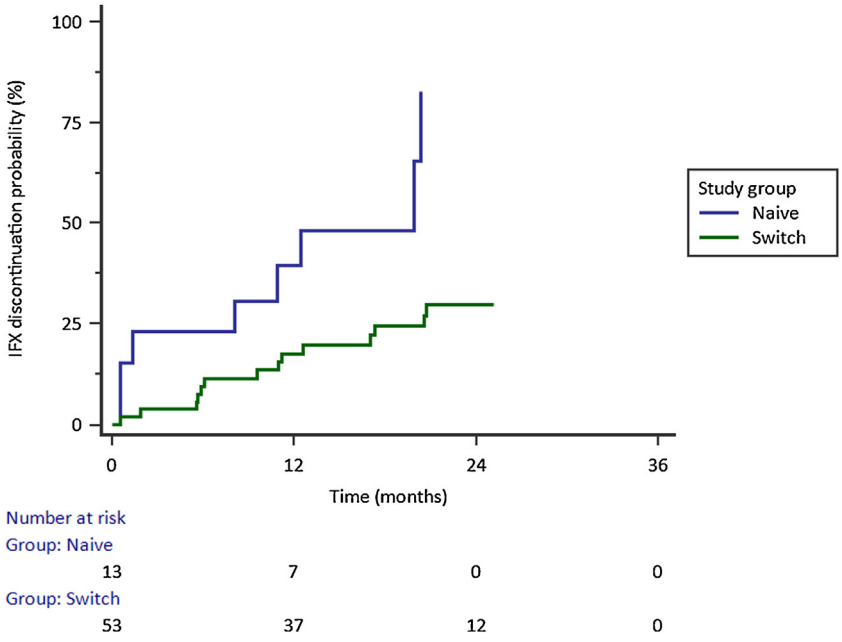

Fig. 1. Kaplan–Meier analysis of survival free from the need to discontinue infliximab due to adverse events or loss of clinical effectiveness, for patients in the Naïve and Switched groups. The difference between groups is highly significant (p = 0.002).

the Naïve group (62%; 8 of 13) (p = 0.017). A cumulative probability chart (Fig. 1) shows that patients in the Naïve group discontinued infliximab treatment faster than did those in the Switched group.

Univariate analysis identified several clinical variables that associated with the dichotomous outcome of infliximab treatment discontinuation. When these variables were entered into a multivariate analysis, which was statistically significant overall (p = 0.003), only gender (p = 0.019) and study group (Switched vs. Naïve, p = 0.012) were significantly and independently associated with the outcome. In time-dependent analyses, several other clinical variables associated with infliximab discontinuation (Table 2). According to the time-dependent multivariate analysis, which was highly significant overall (p < 0.0001), only the presence of active disease and the absence of immunomodulatory co-treatment at the baseline evaluation were independently and significantly associated with the time to drug discontinuation.

The occurrence of any adverse event was non-significantly lower in the Switched group (4 of 53, 8%) than in the Naïve group (3 of 13, 23%; p = 0.106). During the course of the observation period, 43 patients of the Switched group (81%) and 8 in the Naïve group (62%) experienced a remission or decrease in disease activity (p = 0.134), while the remaining patients had progression of disease activity or a remitting/relapsing pattern over time. In 8 patients of the Switched group (15%) and 1 patient of the Naïve group (8%), infliximab treatment was discontinued due to deep remission (p = 0.489), after a median time after study entry of 10.5 months (95% CI, 6.0–11.5 months). The decision to discontinue treatment was initiated either by the physician or the patient.

3.3. Markers of drug activity

Drug trough levels were assessed at baseline (study entry) and at three time points over one year (Table 3). No significant difference was observed between the study groups at any time point, regarding both the drug concentration and the percentage of patients with detectable levels. At the same time points, the concentration of ADAs was also measured. Similarly, no significant difference was observed between groups, for both the concentration and the percentage of cases positive for the presence of antibodies.

4. Discussion

Infliximab is used as monotherapy or in combination with immunomodulating drugs. Therapeutic monitoring of drug activity, by measuring trough levels and ADAs, has been shown to help reduce treatment costs when integrated into the treatment algorithm [14–18]. However, at the individual level, these markers of drug activity can provide conflicting results, and therefore have little use in clinical decision making [20].

When biosimilar drugs were marketed for infliximab, and more recently for adalimumab, the medical community was initially reluctant to consider them as effective as the originators [12,13]. Yet the more these drugs were used in clinical practice, the more gastroenterologists learned about them and gained confidence in their reliability and effectiveness [11]. The main advantage of using biosimilar drugs is a reduction of direct pharmaceutical costs, due to the lower costs of marketing. Still, some physicians are skeptical about switching patients from an anti-TNF originator to a biosimilar. This study confirms that switching from the infliximab originator to a first biosimilar is safe and effective.

This study compared two groups of patients: those who switched from infliximab originator to the biosimilar CT-P13 (Switched group) and those who were firstly and only treated with the biosimilar agent CT-P13 (Naïve group). Unexpectedly, a trend to more adverse outcomes and greater need to discontinue infliximab treatment were observed in the Naïve group than in the Switched group. This finding should not be interpreted as a protective effect of switching against adverse outcomes. First, the population studied is overall small, and the group of naïve cases was even smaller. Therefore, a few cases with unusual outcomes may have had an impact on group comparisons. Furthermore, there was a large and significant difference in the median duration of infliximab treatment before study initiation, which was roughly 4 years for the Switched group but only 0.6 years for the Naïve group. This latter group, therefore, was more likely to experience loss of efficacy and adverse reactions (which are more likely in the first year after starting infliximab treatment). Moreover, the longer duration on infliximab treatment in the Switched group may have selected patients who were more drug tolerant and less likely to react to a slightly different drug. Finally, patients in the Naïve group were more at risk of losing disease control due to a shorter remission time, and to higher baseline disease activity.

Time-dependent multivariate analysis revealed that two covariates were significantly associated with the time to infliximab discontinuation, namely disease activity and co-treatment with immunomodulators at enrolment. Some remaining disease activity at study start might have affected the outcomes of subsequent treatments, as compared to patients in clinical remission. However, disease activity may be a circular argument, because patients failing to maintain stable clinical remission are probably more likely to lose their clinical response sooner than patients maintaining stable and deep clinical remission, irrespective of the treatment given or changed. Co-treatment with immunomodulatory drugs could be protective because of a pharmacodynamic effect facilitating higher infliximab availability and lower drug immunogenicity. However, since immunomodulatory drugs were taken by only 11 cases of the entire study population (17%), with similar proportions in the two study groups, a note of caution on this protective effect is needed.

We measured drug trough levels and ADAs to be able to detect subclinical signals in individual patients before adverse outcomes became clinically apparent. Our working hypothesis was that if an immunogenic effect of switching from infliximab originator to a first biosimilar should emerge, trough levels should decrease and ADAs should increase even before adverse events manifested. Besides single cases with an evident increase of ADAs preceding infusion reactions (which might also be observed outside the setting of switching from an originator to its biosimilar), there was no clear signal of relevant immunogenicity. There was an overall low level of circulating drug, possibly explained by test performance or by the particular clinical setting, but no significant differences were observed between the two groups of patients or over time within each group. These findings support the safety of switching from an infliximab originator to a first infliximab biosimilar, and confirm the limited usefulness, in routine clinical practice, of serial therapeutic drug monitoring tests.

Our study focused on the typical population of patients eligible to undergo a therapeutic switch, i.e. patients mostly in remission, with a long prior exposure to the active compound. Still, the few patients with active disease at enrolment were those at highest risk of losing treatment effectiveness over time, irrespective of the therapeutic switch. This fact is easily supported by the observation that patients with disease activity, irrespective of any treatment, are at high risk of losing drug effectiveness, even if optimization is used. Therefore, in the clinical setting, whenever a patient with active disease is evaluated for a therapeutic switch, the physician should inform the patient about the likelihood of losing treatment effectiveness in the short-term, irrespective of the therapeutic choice to switch or not to a biosimilar drug. Informing patients is needed to prevent the risk of a false perception that the change in treatment might be a causative factor of subsequent loss of effectiveness.

Table 2
Univariate time-dependent analysis according to Kaplan–Meier statistics and multivariate time-dependent analysis according to Cox proportional backward hazard regression.

Covariate	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	p
Study group (Switched vs. Naïve)	0.287	0.044–0.508	**0.002**	–	–	–
Gender (female vs. male)	2.67	1.22–7.5	**0.016**	–	–	–
Baseline steroid co-treatment (yes vs. no)	2.47	0.67–22.72	0.131	–	–	–
Disease activity at entry (moderate-severe vs. remission-mild)	12.60	8.33–255	**<0.0001**	17.84	5.11–62.40	**<0.0001**
Immunomodulator use at entry (yes vs. no)	0.298	0.043–0.567	**0.005**	0.292	0.122–0.827	**0.019**
Infliximab frequency at entry (q7–8 w vs. q4–6 w)	0.480	0.183–1.093	0.078	–	–	–
Disease duration at entry (<5 years vs. ≥ 5 years)	3.64	1.88–45.68	**0.006**	–	–	–
Previous surgery (yes vs. no)	0.526	0.229–1.44	0.235	–	–	–

CI, confidence interval; HR, log-rank hazard ratio; q4–6 w, every 4–6 weeks; q7–8 w, every 7–8 weeks.
In bold highlighted significant p values.

Table 3
Infliximab trough levels and antidrug antibodies (ADAs) to infliximab, by study group over time.

Time point	Infliximab trough levels		Antidrug antibodies	
	Median (95% CI), μg/ml	Detectable, %[a]	Median (95% CI), AU	Positive, %[b]
Baseline (entry)				
Switched	1.41 (0.80–1.99)	62	14.6 (10.7–35.3)	69
Naïve	ND	ND	ND	ND
3 months				
Switched	1.27 (0.78–1.65)	61	13.3 (9.6–37.2)	63
Naïve	0.86 (0.31–2.97)	50	17 (7.1–198)	63
P	0.552	0.587	0.988	0.972
6 months				
Switched	0.98 (0.68–1.46)	50	23.6 (14.1–55.8)	72
Naïve	1.15 (0.16–3.87)	57	13.6 (8–411)	71
P	0.818	0.732	0.974	0.966
12 months				
Switched	1.07 (0.58–1.76)	51	17.4 (9.5–39.6)	63
Naïve	1.38 (0.18–4.30)	57	13.5 (8.6–337)	57
p	0.736	0.785	0.686	0.779

AU, arbitrary unit; ND, not determined.
[a] Above the 1 μg/ml detection threshold.
[b] Above 10 AU threshold.

The results of this study confirm the findings of published studies on the topic. We therefore conclude that switching from infliximab originator to a first biosimilar is safe and effective, and thus ethically acceptable for the purpose of reducing costs of health care. In patients with active disease, probably the safest and most effective option is to change the active compound to a different anti-TNF agent or to a drug with a different mechanism of action, while switching to a biosimilar and optimizing the dose is an alternative to be carefully proposed to patients.

Conflict of interest
None declared.

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