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Alimentary Tract

Patients' perspectives after switching from infliximab to biosimilar CT-P13 in patients with inflammatory bowel disease: A 12-month prospective cohort study

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ABSTRACT

Background: Patients' perspectives after switching from infliximab to a biosimilar have yet to be assessed.
Aim: To assess patients' perspectives in a prospective manner after switching from infliximab to CT-P13.
Methods: 113 consecutive patients with inflammatory bowel disease (IBD) on maintenance therapy with infliximab were switched to CT-P13. Patients' perspectives were assessed by questionnaires, including the Beliefs about Medicines Questionnaire (BMQ) and FACIT-F (questionnaire regarding fatigue), and patient-reported outcomes (IBD disability index) at the inclusion and after the fourth CT-P13 infusion.
Results: After one year, the patients' perspectives did not change after the switch according to BMQ-general, BMQ-specific necessity and BMQ-specific concerns subscales. No difference was observed in the mean IBD-DI score, while a significant improvement in fatigue was observed according to the FACIT-F questionnaire. Patients' concerns were raised about the use of biosimilars and the risks of switching with a significant improvement after switching (65% vs. 42%, respectively, p = 0.01). Fourteen (12.4%) patients experienced loss of response to CT-P13, including 12 with restoration of steroid-free clinical remission after CT-P13 dose optimization.
Conclusion: Although some concerns were reported, no difference was observed in patients' perspectives after switching from infliximab to CT-P13.

1. Introduction

Inflammatory bowel disease (IBD) is a chronic and disabling condition involving the gastrointestinal tract [1,2]. The advent of anti-TNF agents has permitted the achievement of new goals in the management of patients with IBD, including reduced hospitalization and surgery, mucosal healing, and improvements in quality of life and patient's reported outcomes [3–5]. Accordingly, anti-TNF agents are increasingly prescribed and now represent a major component of IBD-related healthcare costs [6,7].

The patent for infliximab has recently expired, leading to the development of biosimilar products. The infliximab biosimilar CT-P13, with the trade names INFLECTRA® and REMSIMA®, was first evaluated in phases 1 and 3 randomized controlled trials in anti-TNF naïve patients with rheumatologic diseases [8,9]. These results led the EMA and FDA to adopt a positive opinion, recommending and granting marketing authorization for treatment in all indications for which infliximab is approved [10]. The effectiveness and safety of switching from infliximab to CT-P13 have been further assessed in prospective observational studies and a subsequent 1-year randomized controlled trial that included 481 patients with various inflammatory disorders (254 patients with IBD) [10–12].

However, some concerns, especially those regarding immunogenicity and multiple switching, have been raised by physicians and patients from the beginning of the development programme of the biosimilar CT-P13 and remain today [13]. Although it has been demonstrated that beliefs and concerns about medicine may affect adherence to the treatment, the patient's perspective regarding the use of infliximab biosimilars has been poorly investigated

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in patients with IBD. An online survey targeting members of the European Federation of Crohn's and Ulcerative Colitis Association (EFCCA) recently highlighted a lack of knowledge and concerns about the effectiveness and safety of infliximab biosimilars [14].

The aim of this study was to assess patients' perspectives concerning infliximab biosimilars after switching from infliximab to CT-P13 during a 1-year period on a prospective basis. In addition, the effectiveness, safety and trough concentrations of CT-P13 were also assessed on a prospective basis.

2. Patients and methods

2.1. Study design

This is a prospective, monocentric, cohort study at Henri Mondor University Hospital. Inclusion criteria included the following: diagnosis of IBD according to ECCO criteria classified as CD, UC or IBD unclassified [5,15]; on-going maintenance therapy with infliximab (REMICADE®) at a stable dose for at least six months; stable steroid-free clinical remission for at least six months according to the Harvey-Bradshaw index (HBI) for patients with CD and partial Mayo Clinic score for patients with UC; switch from infliximab to CT-P13 (INFLECTRA®); age >18 years; and absence of pregnancy. From June to December 2016, all patients fulfilling the inclusion criteria received personalized information on biosimilars using documentation from the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives (GETAID) and the Société Nationale Française de GastroEntérologie (SNFGE). At the next infliximab infusion visit, a switch from infliximab to CT-P13 was offered to all patients. All patients also received written information. Patients accepting the switch were then included in the present study and followed-up until 54 weeks. The protocol was approved by the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé (CCTIRS; no. 16-249) and the Commission Nationale de l'Informatique et des Libertés (CNIL; no. 1955334). All authors had access to the study data and reviewed and approved the final manuscript.

After switching from infliximab to CT-P13, CT-P13 was administered intravenously at the same dose and at the same interval every 6 to 8 weeks. Optimization or de-escalation of CT-P13 after the switch was allowed for insufficient response according to the IBD activity and the investigator's decision. The concomitant use of immunomodulators was allowed but needed to remain stable until the end of the 54-week period of follow-up. Physicians in charge of the patients were free to modify treatment in cases of clinical relapse, elevated CRP and/or evidence of endoscopic activity.

2.2. Data collection

A standardized questionnaire was completed for each patient at the screening visit according to the patient interview and patient case records. The recorded data included the following information: date of birth, gender, detailed account of the IBD diagnosis and history, smoking habits, IBD phenotype according to the Montreal classification, history of treatments and surgery for IBD.

All patients were asked to complete four questionnaires at the time of inclusion and at the fourth CT-P13 infusion: the BMQ, validated for scoring treatment necessity beliefs and concerns on a 5-point Likert scale (1 = strongly disagree; 5 = strongly agree) comprising 17 questions for patients with IBD. Seven questions measured general concerns about medicines, including the perception of harm and overuse with scores ranging from 5 to 35. Ten questions measured specific beliefs about the prescribed treatment in terms of its perceived necessity and concerns with 5 questions each with scores ranging from 5 to 25 [4]. Higher values denote stronger beliefs. On the basis of the BMQ-specific necessity and concern scores (>15 or ≤15 out of 25), patients were categorized as accepting (high necessity score and low concerns score), ambivalent (high necessity and high concerns scores), sceptical (low necessity and high concerns scores) or indifferent (low necessity and low concerns scores). A differential score was computed by subtracting the specific concerns score from the specific necessity score. A differential score greater than 0 denotes an increased necessity belief towards concerns. The FACIT-F is validated for scoring fatigue on a 4-point Likert scale (1 = strongly disagree; 4 = strongly agree) in patients with IBD comprising 13 questions with scores ranging from 13 to 52 [16]. The IBD-DI is validated for scoring patient-reported outcomes in patients with IBD comprising 14 questions, including 12 questions on a 5-point Likert scale (0 = no limitation; 1 = slight limitation; 2 = moderate limitation; 3 = severe limitation; 4 = extreme limitation), one question with a dichotomous answer for the presence of arthralgia and/or arthritis (no = 0; yes = 4) and one question deriving from the number of daily liquid or very soft stools (none = 0; one = 1; two = 2; three = 3; ≥4 = 4), with scores ranging from 0 to 100 [3]. An 11-question nonvalidated questionnaire was derived from an EFCCA questionnaire about knowledge previously published [14]. All questionnaires were completed before receiving personalized information on biosimilars and before proposing to switch from infliximab to CT-P13.

All patients were submitted to a standardized follow-up protocol with physical examination, concomitant treatment and weight, calculation of body mass index, HBI or partial Mayo clinic score for patients with CD or UC and IBDU and routine laboratory test including C-reactive protein (CRP, mg/L), haemoglobin (g/dL), leukocyte (10^9/L) and platelet (10^9/L) counts and serum albumin (g/L) determination and adverse event collection. Serum samples were collected for CT-P13 trough concentrations and anti-CT-P13 antibody (ACA) using a commercial ELISA (Lisa-Tracker Premium Infliximab; Theradiag, Marne la Vallée, France) before the first CT-P13 infusion at the screening visit and after four CT-P13 infusions [19].

2.3. Outcome measures

The primary outcomes were measured as a change in the BMQ score between the screening visit and the fourth CT-P13 infusion. Secondary outcomes included changes in the IBD-DI score, the FACIT-F score, the 11-item questionnaire about knowledge, beliefs and concerns about biosimilars, and the rates of steroid-free clinical remission and adverse events. A steroid-free clinical remission was defined as an HBI ≤4 for CD patients and a partial Mayo Clinic score <3 with a combined stool frequency and rectal bleeding subscore of ≤1 without steroids [17,18,20]. Relapse was defined as an HBI >4 for patients with CD and partial Mayo score >3 for patients with UC. Steroid-free means the absence of any dose of any oral steroid (prednisone, prednisolone and/or budesonide) and includes the rectal use of betamethasone. Safety was assessed by the physician in charge. Severe adverse events were defined as the occurrence of treatment interruption, hospitalization, disability, persistent damage, colectomy or death.

2.4. Statistical analyses

All of the included patients were evaluated from the inclusion visit through week 52. The data are expressed as a number (%) for qualitative data and mean ± the standard deviation (SD) or median [interquartile range] for quantitative data. Hazard ratios (HRs) were provided with 95% confidence intervals (CIs). The proportions of patients with steroid-free clinical remission were compared at every time point using the chi-squared test. Quantitative data

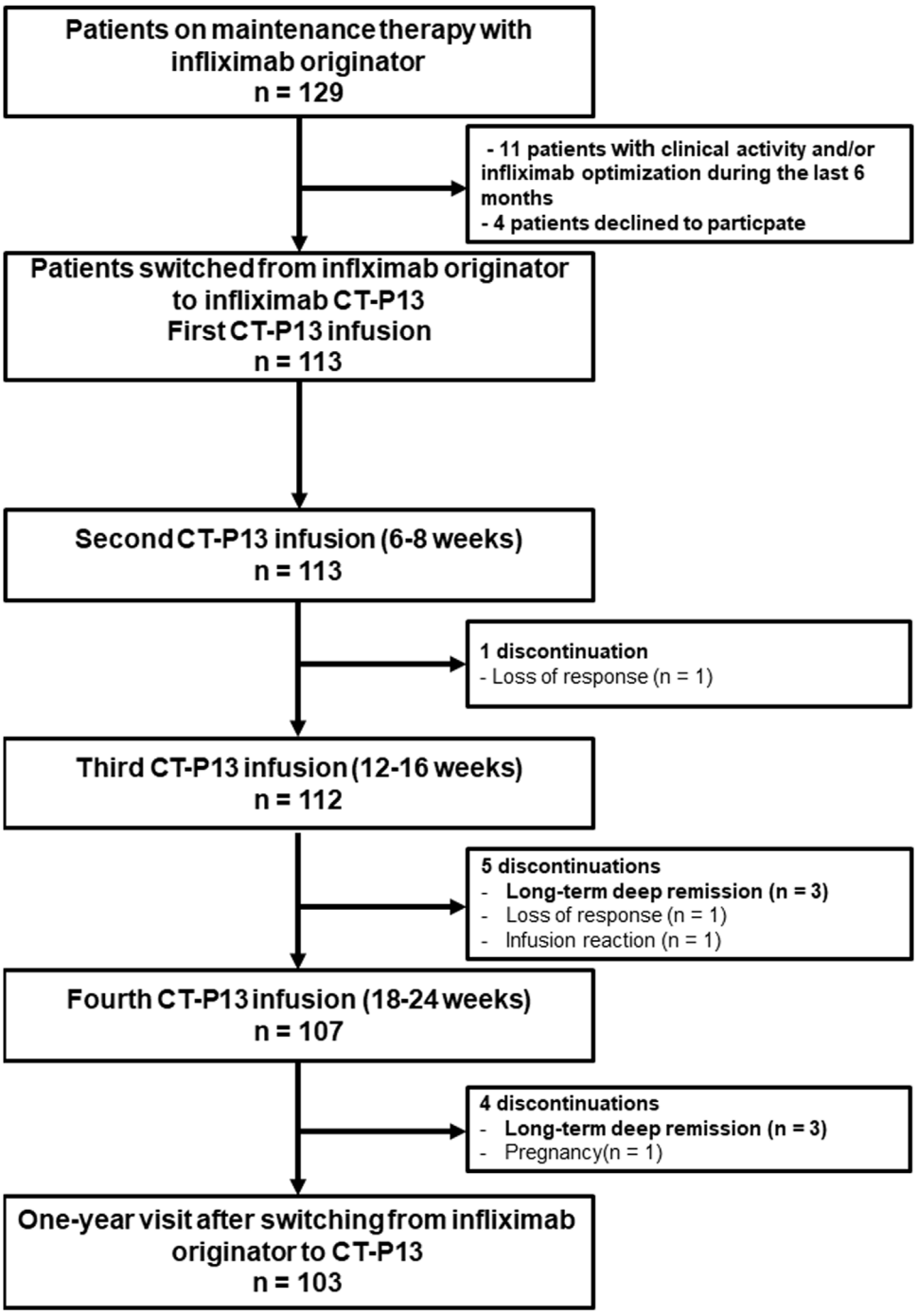

Fig. 1. Flowchart of the study.

were compared at every time point using Wilcoxon's matched-pair signed-rank test. All analyses were computed relative to the whole population included at week 0. Event-free (without loss of clinical remission, infusion reaction and/or need for a new course of steroid) survival was calculated using the Kaplan–Meier method. The survival distributions were compared using the log-rank test. To identify the independent factors, a Cox proportional hazard model was adjusted with an ascending stepwise procedure. Variables with $p < 0.10$ in univariate analysis were considered to be potential adjustment variables for the multivariate analysis. The continuous variables were dichotomised according to the median value. All analyses were two-tailed, and p-values less than 0.05 were considered significant. All statistical evaluations were performed using SPSS (SPSS Inc., v17, Chicago, IL, USA). All authors had access to the study data and reviewed and approved the final manuscript.

3. Results

3.1. Study population

A total of 129 patients were on maintenance therapy with infliximab (Fig. 1). Eleven patients were not eligible for inclusion due to clinical activity and/or infliximab optimization during the last 6 months. Four patients declined to participate. In total, 113 patients fulfilled the inclusion criteria, including 85 patients with

Table 1
Demographic and baseline disease characteristics and medication histories of 113 patients with inflammatory bowel disease before switching from infliximab originator to CT-P13.

Patient's characteristics	Crohn's disease (n = 85)	UC + IBDU (n = 28)	p
Age at inclusion, years	42.7 ± 14.7	43.6 ± 12.6	0.77
Male gender, no (%)	41 (48.2)	15 (53.6)	0.67
BMI, kg/m^2	24.4 ± 5.6	25.2 ± 4.3	0.43
Smoking habits, no (%)			
Past smoker	43 (50.6)	13 (46.4)	0.83
Active smoking	22 (25.9)	3 (10.7)	0.12
Disease duration, (years)	13.6 ± 10.1	9.3 ± 7.2	0.02
History of intestinal resection	21 (24.7)	1 (3.6)	0.01
Extra intestinal manifestations	20 (23.5)	3 (10.7)	0.18
Familial history of IBD	8 (9.4)	3 (10.7)	0.99
Age at diagnosis	29.1 ± 12.5	34.3 ± 9.3	0.02
A1: ≤16 ans	8 (9.4)	1 (3,6)	0.45
A2: 17–40 ans	68 (80.0)	21 (75.0)	0.60
A3: >40 ans	9 (10.6)	6 (21.4)	0.20
Crohn's disease, no (%)			
Disease location, no (%)			
Ileal	25 (25.9)	–	–
Colonic	31 (36.5)	–	–
Ileocolonic	32 (37.6)	–	–
Upper GI tract	9 (10.6)	–	–
Disease phenotype, no (%)			
Non structuring–non penetrating	50 (58.8)	–	–
Structuring	25 (29.4)	–	–
Penetrating	10 (11.8)	–	–
Perianal disease, no (%)	42 (37.2)	–	–
Harvey Brashaw-index	1.6 ± 1.2	–	–
Ulcerative colitis, no (%)			
Proctitis	–	1 (3.6)	–
Left-sided colitis	–	5 (17.9)	–
Pancolitis	–	22 (78.6)	–
Partial Mayo Clinic score	–	0.4 ± 0.6	–
Previous treatment			
Immunosuppressant:	79 (92.9)	25 (89.3)	0.69
Azathioprine	79 (92.9)	25 (89.3)	0.69
Methotrexate	17 (20.5)	2 (7.1)	0.15
anti-TNF:	29 (34.1)	9 (32.1)	0.99
Prior cycle of infliximab	25 (29.4)	7 (25.0)	0.81
Adalinumab	9 (10.6)	2 (7.1)	0.73
Certolizumab pegol	1 (1.2)	–	–
Previous infliximab therapy			
Duration, no (%)	4.9 ± 3.3	3.6 ± 2.3	0.02
Dose, mg/kg	6.8 ± 2.0	6.1 ± 1.9	0.66
Infusion intervals, weeks	7.8 ± 0.8	7.8 ± 0.8	0.72
Concomitant immunomodulator, no (%)	23 (27.1)	8 (28.6)	0.99

BMI: body mass index; IBDU: inflammatory bowel disease unclassified; UC: ulcerative colitis; GI: gastrointestinal; IBD: inflammatory bowel disease.
Variables are presented as n (%). Mean ± standard deviation or median (interquartile range).
P values are based on a two-sided chi-square test for all categorical variables and on Wilcoxon's matched-pair signed-rank test for all quantitative variables.

CD and 28 patients with UC or IBDU. Patient demographic data, baseline disease characteristics and medication history are listed in Table 1. None of the patients had concomitant steroids, and 31 (27.4%) had concomitant immunosuppressants. The mean dose of infliximab was 6.7 ± 1.9 mg/kg, and the mean interval of infusion was 7.8 ± 0.8 weeks.

During the one-year study period, ten patients discontinued CT-P13 maintenance therapy (Fig. 1). Seven patients discontinued CT-P13 maintenance therapy while in steroid-free clinical remission by mutual agreement with their doctor in 6 cases and due to pregnancy in one. Two patients discontinued CT-P13 due to a loss of response to CT-P13, and one experienced an infusion reaction after 2 infusions of CT-P13. At the end of follow-up, 103 patients were still treated with CT-P13 maintenance therapy (Table 2).

3.2. Patient perspective on medicines before and after switching from infliximab to CT-P13

3.2.1. Beliefs about medication in general

According to BMQ-general subscale results, we found a significant proportion of patients with negative beliefs about medication in general (18.2 ± 5.9 for a maximum score of 35) (Table 3). Indeed, 13%–22% of patients selected agree or strongly agree, respectively, with any items quantifying perception of harm or overuse, and 47.5% agreed or strongly agreed to at least one item. There was no difference in BMQ-general subscale scores according to age, gender, duration of maintenance infliximab therapy and type of IBD. There was no difference in BMQ-general subscale scores after switching from infliximab to CT-P13 (18.2 ± 5.9 vs. 18.3 ± 5.9, p = 0.87), confirming that the latter score was not specific to the prescribed treatment.

3.3. Specific beliefs about infliximab and CT-P13

The BMQ-specific necessity subscale score indicated a relatively high perceived need for infliximab maintenance therapy (19.8 ± 4.7 for a maximum of 25) although the BMQ-specific concerns subscale score was also elevated (14.9 ± 4.98) (Table 3). Based on BMQ-specific necessity and concerns scores, patients were categorized as follows: 46 patients were accepting (44.7%), 42 patients were ambivalent (40.8%), 9 patients were indifferent (8.7%) and 6 patients were sceptical (5.8%). However, the differential BMQ-specific score indicated a higher perceived need for infliximab maintenance therapy towards concerns (+4.9 ± 6.7). There was no difference in BMQ-specific scores, BMQ-specific differential score and categorization of patients according to BMQ-specific scores after switching from infliximab to CT-P13 (Fig. 3).

3.4. Patient knowledge about biosimilars

Patient knowledge about biosimilars was assessed using the 11-item EFCCA questionnaire (Table 4). Before switching from infliximab to biosimilar CT-P13, most of the patients (80.4%) had never heard about biosimilars. Additionally, concerns were raised about numerous issues, including the risk of a different molecular basis, lower effectiveness and safety, worrying about switching from infliximab to an infliximab biosimilar and its consequences, and increased worrying that pharmacists may make the switch without physicians' consent due to generic similarities. However, most of the patients trust their physician to inform them, explain the rationale of the biosimilarity to them and ensure similar effectiveness and safety in case of a switch.

After switching from infliximab to CT-P13, 86.4% of patients reported to be informed about biosimilars and disclosed better knowledge and confidence about biosimilars and generics. There was an increase in the rates of patients trusting their physician about the switch and the evidence of maintaining good effectiveness and safety and accepting to continue maintenance therapy with CT-P13. Importantly, patients remained opposed to the possibility of being switched by pharmacists without their physician's consent. Patients also remained worried about the fact that the cost of a treatment could come before its effectiveness and safety and remained pessimistic about the impact of biosimilars on the management of IBD.

Table 2
Changes of clinical and biological parameters evaluating disease activity and patient perspective scale scores between inclusion and the different visits.

	First infusion (inclusion visit)	Second infusion	Third infusion	Fourth infusion	1-year visit
Number of patients	113	113	112	107	103
Harvey-Bradshaw index (n = 85)	1.6 ± 1.2	1.4 ± 1.2 (p = 0.14)	1.4 ± 1.5 (p = 0.43)	±1.2 (p = 0.63)	±1.2 (p = 0.002)
Partial Mayo Clinic score (n = 28)	0.4 ± 0.6	0.4 ± 0.7 (p = 0.71)	0.8 ± 1.1 (p = 0.05)	0.5 ± 1.0 (p = 0.38)	0.4 ± 1.2 (p = 0.78)
Steroid-free clinical remission without relapse (%)	113 (100%)	112 (99.1%)	106 (94.6%)	101 (94.4%)	89 (86.4%)
Leukocytes (/mm^3)	7016 ± 1877	7199 ± 2255 (p = 0.12)	7338 ± 2378 (p = 0.15)	7427 ± 1908 (p = 0.06)	7098 ± 1919 (p = 0.82)
Hemoglobin (g/dL)	14.0 ± 1.3	14.1 ± 1.3 (p = 0.62)	13.9 ± 1.9 (p = 0.70)	14.0 ± 1.4 (p = 0.91)	14.0 ± 1.4 (p = 0.89)
Platelets (/mm^3)	268 ± 89	278 ± 87 (p = 0.003)	278 ± 90 (p = 0.70)	286 ± 98 (p = 0.001)	269 ± 74 (p = 0.93)
C-reactive protein (mg/L)	3.7 ± 4.4	5.2 ± 9.7 (p = 0.05)	5.3 ± 10.3 (p = 0.03)	5.2 ± 7.6 (p = 0.01)	3.7 ± 6.2 (p = 0.94)
Serum albumin (g/L)	41.1 ± 3.8	41.3 ± 5.3 (p = 0.53)	41.2 ± 3.9 (p = 0.81)	40.7 ± 4.3 (p = 0.23)	40.7 ± 4.3 (p = 0.18)
Infliximab trough level (μg/mL)	3.8 ± 3.0	–	–	–	4.9 ± 4.2 (p = 0.04)
Presence of antibody to infliximab (%)	3 (2.7%)	–	–	–	1 (0.9%)
IBD-DI score (n = 103)	22.4 ± 16.0	–	–	21.9 ± 16.4 (p = 0.74)	–
FACIT-F score (n = 103)	25.5 ± 5.9	–	–	23.2 ± 4.3 (p < 0.001)	–

Variables are presented as mean ± standard deviation.
P values are based on a Wilcoxon's matched-pair signed-rank test for all quantitative variables. Comparison were performed between the follow-up visits and the inclusion visit (first switch CT-P13 infusion).
Steroid-free clinical remission was defined as an Harvey-Bradshaw index ≤4 for patients with Crohn's diseaseand a partial Mayo Clinic score <3 with a combined stool frequency and rectal bleeding subscore of ≤1 for patients with ulcerative colitis without steroids.

Table 3
Changes of patient knowledge according to a 11-item European Federation of Crohn's and ulcerative Colitis Association questionnaire.

	Before the switch (n = 103)	After the switch (n = 103)	P
BMQ general concerns			
BMQ general concerns subscale score	18.2 ± 5.9	18.3 ± 5.9	0.87
BMQ general overuse subscale score	10.5 ± 3.5	10.6 ± 3.4	0.74
- Doctors use too many medicines	2.5 ± 1.1	2.5 ± 1.1	0.89
- Doctors place too much trust on medicines	2.8 ± 1.2	2.7 ± 1.2	0.38
- If doctors had more time with patients they would prescribe fewer medicines	2.6 ± 1.1	2.7 ± 1.2	0.23
- Natural remedies are safer than medicines	2.6 ± 1.1	2.6 ± 1.1	0.74
BMQ general harm subscale score	7.7 ± 3.0	7.7 ± 2.9	0.95
- People who take medicines should stop their treatment for a while every now and then	2.7 ± 1.3	2.6 ± 1.2	0.66
- Most medicines are addictive	2.8 ± 1.2	2.8 ± 1.2	0.72
- All medicines are poison	2.2 ± 1.1	2.3 ± 1.2	0.52
BMQ specific beliefs			
Specific necessity subscale score	16.0 ± 3.7	16.3 ± 3.2	0.42
- My health, at present, depends on my medicine	4.1 ± 1.1	4.2 ± 0.9	0.32
- My life would be impossible without my medicine	3.8 ± 1.2	4.0 ± 1.1	0.23
- Without medicine I would be very ill	3.8 ± 1.2	4.0 ± 1.1	0.23
- My health in the future will depend on my medicine	3.9 ± 1.1	3.9 ± 1.2	0.56
- My medicine protects from becoming worse	4.1 ± 1.2	4.2 ± 1.0	0.42
Specific concerns subscale score	14.9 ± 4.8	15.7 ± 4.8	0.11
- Having to take my medicine worries me	2.8 ± 1.5	3.0 ± 1.4	0.25
- I sometimes worry about long term effects of my medicine	3.5 ± 1.3	3.6 ± 1.3	0.13
- My medicine is a mystery to me	2.9 ± 1.3	3.0 ± 1.3	0.55
- My medicine disrupts my life	2.6 ± 1.3	2.7 ± 1.3	0.47
- I sometimes worry about becoming too dependent on my medicine	3.1 ± 1.3	3.3 ± 1.3	0.19
Specific differential score	4.9 ± 6.7	4.6 ± 6.0	0.39

Variables are presented as mean ± standard deviation.
P values are based on a Wilcoxon's matched-pair signed-rank test for all quantitative variables. Comparison were performed between the fourth-infusion visit and the inclusion visit (first switch CT-P13 infusion).
For the Beliefs about Medicines Questionnaire, the higher values denote the stronger beliefs. BMQ specific beliefs subscales measure beliefs about the prescribed treatment i.e. infliximab. BMQ general concerns subscale score measure general concerns about medicines including perception of harm and overuse.

3.5. Clinical activity after switching from infliximab to CT-P13

Overall, fourteen patients experienced loss of response during the one-year period following CT-P13 maintenance therapy, including twelve patients who were successfully managed by dose and/or infusion interval escalation and two patients who were switched to ustekinumab. Conversely, 89 patients remained in stable steroid-free clinical remission, including 19 patients whose CT-P13 maintenance therapy dose and/or infusion interval was de-escalated without any clinical consequences.

No changes were observed for the FACIT-F evaluating fatigue and the IBD-DI evaluating IBD-related disability between the inclusion and the one-year visits. No changes were observed for clinical activity scores with the exception of a decrease in the HBI after one year in patients with CD and a transient increase in the partial Mayo Clinic score at the third CT-P13 infusion for patients with UC (Table 2). No changes were observed for biological parameters during follow-up with the exception of an increase in CRP levels at the second, third and fourth infusion that was reduced after one year of CT-P13 maintenance therapy. Mean infliximab trough lev-

Table 4
Changes of patient knowledge according to a 11-item European Federation of Crohn's and ulcerative Colitis Association questionnaire.

	Before the switch (n = 103)	After the switch (n = 103)	P
1- Have you ever heard of biosimilars?			
a] Yes	19.6%	86.4%	<0.001
b] No	80.4%	12.6%	
2- Concerning biosimilars. you worry [choose the option]:			
a] That the molecular basis of the biosimilar is different from that of the reference drug.	36.3%	8.8%	
b] About safety profile [mainly infections and cancers].	10.8%	22.5%	
c] About tolerability.	5.9%	7.8%	<0.001
d] That the biosimilar could be less effective than the reference drug.	30.4%	30.4%	
e] You have no specific concerns about biosimilars.	16.7%	30.4%	
3- The biosimilar will be less expensive than the reference drug. You think that:			
a] This is good news because more patients will be treated with biologics	30.4%	33.3%	
b] The cost of a treatment should not come before its effectiveness or safety/tolerance.	50.0%	49.0%	0.61
c] This will help cost savings.	4.9%	7.8%	
d] You do not think that a lower cost will change anything.	14.7%	9.8%	
4- The biosimilar of REMICADE [infliximab] has been successfully developed and used for the treatment of rheumatologic diseases. On June 27. 2013 the biosimilar of REMICADE [infliximab] received positive opinion from the European Medicines Agency [EMA] for the treatment of inflammatory bowel disease by extrapolating data from rheumatoid arthritis.			
a] You think that it makes sense. Because its efficacy and safety profile has been established for chronic conditions other than IBD.	4.9%	5.9%	
b] You would prefer if it could be tested for inflammatory bowel diseases before extrapolating data from rheumatologic disorders.	25.5%	20.6%	0.002
c] You trust the decisions made by regulatory agencies and you are not waiting for data in IBD.	8.8%	3.9%	
d] You trust your treating physician. Who would make the decision to use biosimilars in your treatment.	42.2%	65.7%	
e] You trust your pharmacist to make the decision to use biosimilars in your treatment.	1.0%	1.0%	
f] You are waiting for more data in IBD before accepting a biosimilar for either Crohn's disease or ulcerative colitis.	17.6%	2.9%	
5- Now that biosimilars are coming onto the market. You think:			
a] That patient associations should be informed and should be able to give their opinion.	17.6%	18.8%	0.20
b] That patients should systematically be given information.	52.9%	65.3%	
c] That we should wait for many patients to receive biosimilars in a real-life setting before recommending its use in a large population of IBD patients.	20.6%	11.9%	
d] We should know in which country the drug has been tested/created before using it in our own country.	7.8%	4.0%	
6- In the future. Biosimilars could be interchangeable with the reference drug.			
a] You are opposed to this idea if the patient is not aware of the decision.]	11.8%	10.9%	
b] You think that this is acceptable. Provided patients are systematically informed.	34.3%	31.7%	
c] You might accept this exchange if the drug is delivered by your usual pharmacist.	2.9%	1.0%	0.67
d] You accept this exchange if your treating physician gives his approval	31.4%	43.6%	
e] You accept this exchange if EBM [evidence-based medicine] data are available.	19.6%	12.9%	
7- The biosimilar will have the same pharmacological name as the reference drug; thus when prescribed. There will be no way to distinguish it from the reference drug.			
a] You wish to know whether you receive the biosimilar or the reference drug.	42.2%	42.6%	
b] You do not mind as long as the biosimilar has the same efficacy and safety profile as the reference drug.			0.10
c] You would like to be informed about it. But you trust the pharmacist or your treating physician if he prescribes/delivers it.	31.4%	43.6%	
d] You wish to have all the necessary information before the drug is administered and obtain written information [e.g. card] to be used for future care.	3.9%	3.0%	
8- Do you think that the arrival of biosimilars will have an impact on the management of IBD?	22.5%	10.9%	
a] Yes. Completely.	9.8%	6.9%	0.24
b] Probably.	16.7%	28.7%	
c] Maybe a little.	15.7%	15.8%	
D] Not at all	6.9%	8.9%	
e] Do not know.	51.0%	39.6%	
9- If a biosimilar is prescribed and explained to you by your treating physician:			
a] You will be fully confident	35.3%	54.5%	
b] You will be worried, but you will accept the treatment	48.0%	36.6%	
c] You will probably not accept it and express yourself on this matter.	10.8%	5.9%	0.01
d] You will ask another physician.	4.9%	0%	
e] You do not know.	1.0%	3.0%	
10- If the pharmacist hands out the biosimilar, changing the initial prescription without the consent of the prescribing physician:			
a] You will accept it because of the lower cost of the biosimilar.	12.7%	13.7%	
b] You will accept it because of available scientific evidence.	23.5%	34.3%	0.35
c] You disagree, but you acknowledge that you will have to accept it	18.6%	14.7%	
d] You will try to obtain the reference drug.	45.1%	37.3%	
11- After starting a treatment with biosimilar:			
a] You will carefully follow the treatment.	52.9%	69.6%	
b] You will be worried and will probably stop the treatment at the first doubt or alternative event.	33.3%	13.7%	0.004

Table 4 (*Continued*)

	Before the switch (n = 103)	After the switch (n = 103)	P
c] You will be worried, but the fact that the treatment has been approved by the European Medicines Agency is reassuring.	13.7%	16.7%	
12- You believe that biosimilars:			
a] Are like generic drugs.	49.0%	53.9%	
b] Are close to generic drugs.	8.8%	17.6%	0.05
c] Are not at all like generics.	42.2%	28.4%	
d] You do not know.	0%	0%	
13- Regarding generic treatments:			
a] You take them without worries.	34.3%	52.9%	
b] You accept to take them, but you have some doubts.	34.3%	32.4%	
c] You refuse them when you can.	23.5%	8.8%	0.007
d] You have never thought about this.	4.9%	1.0%	
e] You do not know.	2.9%	4.9%	

Variables are presented as mean ± standard deviation.
P values are based on a Chi^2 test for all quantitative variables. Comparison were performed between the fourth-infusion visit and the inclusion visit (first switch CT-P13 infusion).

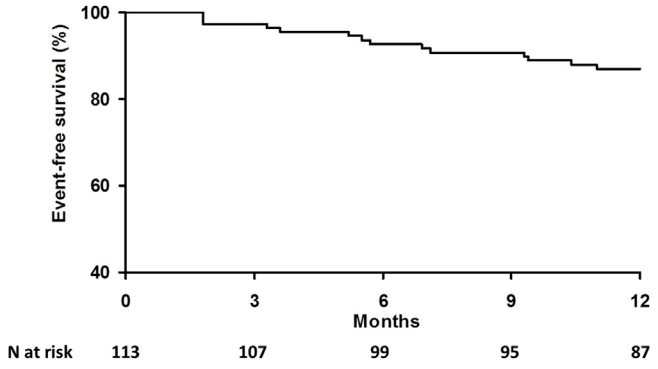

Fig. 2. Kaplan–Meier curves of 113 patients with inflammatory bowel disease after switching from infliximab maintenance therapy to CT-P13 assessing event (clinical relapse and/or infusion reaction)-free survival.

els increased after switching from infliximab to CT-P13 (3.8 ± 3.0 vs. 4.9 ± 4.2 μg/mL, p = 0.04).

The probability of event-free survival (without loss of clinical remission, infusion reaction and/or need for a new course of steroids) after switching from infliximab to CT-P13 was 97.3%, 92.7%, 90.8% and 86.9% at the second, third and fourth CT-P13 infusion and one year, respectively (Fig. 2). In the multivariate analysis, the occurrence of the event of loss of response after switching from infliximab to CT-P13 was significantly decreased in patients with a prior infliximab maintenance therapy duration >4 years (HR = 0.15 IC 95% [0.04–0.57], p = 0.006) and significantly increased in patients previously treated with adalimumab (HR = 6.31 IC 95% [1.79–22.28], p = 0.004) and with CRP level >2 mg/L at the time of inclusion (HR = 6.32 IC 95% [1.61–24.82], p = 0.008).

3.6. Safety

The analysis of adverse events was performed for all patients who received at least one dose of CT-P13. Adverse events occurred in 20 (18.0%) out of 113 patients. Serious adverse events occurred in two (1.8%) patients. One patient developed cutaneous basal cell carcinoma that was fully resected. This patient was treated with infliximab monotherapy and had a prior history of 5 cutaneous basal cell carcinomas. Adverse events of infection were the most commonly reported, including pharyngitis in 4 patients, flu- or flu-like infection in 3 patients, upper respiratory tract infection in 2 patients, *Clostridium difficile* infection in one patient, undocumented gastrointestinal infection in one patient, sinusitis in one patient, and conjunctivitis and folliculitis in one. One patient experienced a dermatological paradoxical skin reaction treated with topical steroids. One pregnancy was reported. One infusion reaction was reported.

4. Discussion

Since the patent for infliximab has expired, many biosimilar products have been reported either in randomized controlled trials or real-world settings, confirming the biosimilarity in terms of effectiveness and safety. Herein, we report a prospective experience of switching from infliximab to the biosimilar CT-P13 in patients with IBD in stable steroid-free clinical remission with a specific focus on patient perspectives after the switch.

The persistence of CT-P13 was 91% at 52 weeks, including 7 patients who discontinued CT-P13 by mutual agreement with the physician while in stable steroid-free clinical remission independent of the switch. Loss of response was observed in 14 patients (12.4%) and was successfully managed by dose and/or infusion interval optimization in 11 patients. These results are consistent with the 10–20% loss of response per year in patients treated with maintenance infliximab therapy and with recent reports on the safety and effectiveness of the switch in a real world setting [21–24]. Moreover, 19 patients were de-escalated during the same period.

No major changes were observed in the clinical and biological parameters evaluating IBD activity after switching from infliximab to CT-P13. Infliximab trough concentrations significantly increased after the switch after excluding patients who were optimized or de-escalated. No changes were noticed in fatigue according to the FACIT-F score or in IBD-related disability according to the IBD-DI score.

Beliefs about medicines are highly relevant in patients with chronic diseases and have been linked with adherence to treatment [4]. The BMQ is a valuable and validated tool for assessing general beliefs about medication and specific beliefs of necessity and concerns about a prescribed treatment [25]. In the present study, we showed that approximately one-half of patients had negative beliefs about medication in general. Although it is difficult to correlate general beliefs and beliefs about a prescribed treatment, improvement in the quality of information given by the physician to patients and developing shared decision processes may be helpful to improve confidence and adherence in IBD management [26–28]. In this study, there was no predictor of negative beliefs on medications in general, suggesting that this effort should not be restricted to a category of patients according to age, gender, type and duration of IBD but to the entire population of patients with IBD.

With regard to specific beliefs on infliximab maintenance therapy, we showed that beliefs on the necessity of treatment were

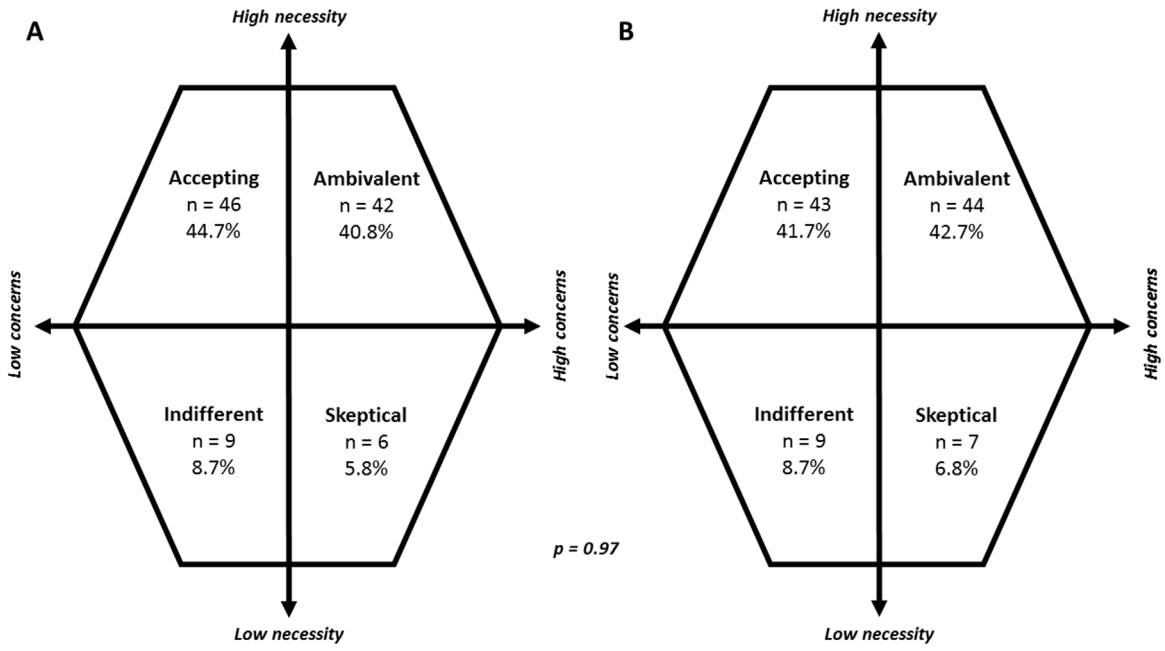

Fig. 3. Categorization of patients in four belief subgroups on the basis of their beliefs about Medicines Questionnaire necessity and concerns subscores before switching from infliximab to CT-P13 (A) and after the fourth infusion of CT-P13. On the basis of the BMQ-specific necessity and concern scores (>15 or ≤15 out of 25), patients were categorized as accepting (high necessity score and low concerns score), ambivalent (high necessity and high concerns scores), sceptical (low necessity and high concerns scores) or indifferent (low necessity and low concerns scores).

high and significantly more important than specific concerns. It is conceivable that these results may be biased by the long duration of infliximab maintenance therapy prior to the inclusion, which was almost 5 years in the present study. Interestingly, there were no changes in specific beliefs on necessity and concerns 52 weeks after switching from infliximab to CT-P13, demonstrating good adhesion of patients to their treatment. We thought that these positive results might not be easy to achieve. Indeed, greater than 80% of patients had never heard about biosimilars at the time of inclusion, and we spent approximately half an hour explaining the rationale of their use in IBD at the first CT-P13 infusion. In the absence of a control group, it is difficult to extrapolate those results, but we believe that informed and shared decisions before switching are highly relevant and even mandatory in the setting of chronic disease.

We also evaluated patient knowledge about biosimilars using an 11-item questionnaire developed by the EFCCA in an online survey of 1181 patients with IBD [14]. Most patients were unfamiliar with biosimilars at baseline and reported to be sceptical about various aspects of biosimilars. A majority have trust in their physician for addressing those issues rather than regulatory agencies and pharmacists. Providing information on biosimilars at the baseline permitted improved knowledge about biosimilars and reinforced the patient-doctor relationship and confidence towards biosimilars. Interestingly, patients remained sceptical about the potential impact of the biosimilars on the management of IBD and remained concerned about the potential handling of the switch by pharmacists and regulatory agencies without the consent of their physician.

Our study has several limitations. First, the absence of a control group and the limited size of the study population may underestimate the impact of switching from infliximab to a biosimilar. However, all data collection was performed prospectively and included all routinely collected data evaluating active IBD and infliximab trough concentrations. In addition, patients were all correctly controlled with the infliximab originator before the switch. Second, the benefits of information about biosimilars on patient perspective and knowledge are purely hypothetical since we did not perform a controlled study with or without individual information at baseline. However, we thought that shared decision processes should be fostered through education and the provision of prospective up-to-date information as recommended by regulatory agencies and IBD and affiliate ECCO societies [29,30]. Third, patients' perspectives on the acceptability of the switch were not evaluated in this study. In fact, only 4 out of 117 patients denied switching. All had an ambivalent pattern with high concerns as evaluated with the BMQ-specific questionnaire. Finally, we did not assess outcomes of the switch in patients with active disease which could be altered by the course of the disease rather than the switch. To date, Bronswijk et al. recently reported a large cohort of 361 patients switching from infliximab to CT-P13 of whom 55.6% were in clinical remission, without increased risk of treatment discontinuation, loss of clinical remission, adverse events and similar infliximab trough levels [24].

In conclusion, our results confirm the effectiveness and safety of CT-P13 after switching from infliximab to CT-P13 for maintenance therapy in a real-world setting. Switching from infliximab to CT-P13 had no impact on fatigue and IBD-related disability and did not alter the doctor-patient relationship or patient beliefs on medication and possibly adherence.

Conflict of interest

Charlotte Gagnière received travel accommodations from Takeda.

Iradj Sobhani received travel accommodations from Biocodex, Pfizer, IPSEN, Novartis.

Aurelien Amiot received consulting fees from Abbvie, Hospira, Takeda, Gilead and Biocodex as well as lecture fees and travel accommodations from Abbvie, Grifols, Janssen, Biocodex, Ferring, Takeda and MSD. This author has also received advisory board fees from Gilead, Takeda and Abbvie.

No conflicts of interest are claimed by the remaining authors.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.08.020.

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