The PROSIT Cohort of Infliximab Biosimilar in IBD: A Prolonged Follow-up on the Effectiveness and Safety Across Italy

Alessandro Armuzzi, MD,[*] Gionata Fiorino, MD,[†] Angela Variola, MD,[‡] Natalia Manetti, MD,[§] Walter Fries, MD,[¶] Ambrogio Orlando, MD,[‖] Giovanni Maconi, MD,[**] Fabrizio Bossa, MD,[††] Maria Cappello, MD,[‡‡] Livia Biancone, MD, PhD,[§§] Laura Cantoro, MD,[¶¶] Francesco Costa, MD,[‖‖] Renata D'Incà, MD,[***] Paolo Lionetti, MD,[†††] Mariabeatrice Principi, MD,[‡‡‡] Fabiana Castiglione, MD,[§§§] Maria L. Annunziata, MD,[¶¶¶] Antonio Di Sabatino, MD,[‖‖‖] Maria Di Girolamo, MD,[****] Maria M. Terpin, MD,[††††] Claudio C. Cortelezzi, MD,[‡‡‡‡] Simone Saibeni, MD, PhD,[§§§§] Arnaldo Amato, MD,[¶¶¶¶] Sandro Ardizzone, MD,[‖‖‖‖] Luisa Guidi, MD,[*] Silvio Danese, MD,[†] Arianna Massella, MD,[‡] Agostino Ventra, MD,[¶] Giulia Rizzuto, MD,[‖] Alessandro Massari, MD,[**] Francesco Perri, MD, PhD,[††] and Vito Annese, MD[§]

PROSIT Investigators: Silvia Saettone, MD,[*****] Roberto Tari, MD,[*****] Carlo Petruzzellis, MD,[†††††] Gianmichele Meucci, MD,[‡‡‡‡‡] Gianni Imperiali, MD,[‡‡‡‡‡] Francesco W. Guglielmi, MD,[§§§§§] Silvia Mazzuoli,

Received for publications June 3, 2018; Editorial Decision July 17, 2018.

From the [*]*IBD Unit, Presidio Columbus, Fondazione Policlinico Gemelli Università Cattolica, Rome, Italy*; [†]*Humanitas Research Hospital and University, Gastroenterology and IBD Center, Rozzano, Italy*; [‡]*Centro Malattie retto-intestinali, Sacro Cuore Don Calabria Hospital, Negrar, Italy*; [§]*AOU Careggi, Gastroenterology, Florence, Italy*; [¶]*University of Messina, Clinical Unit for Chronic Bowel Disorders, Messina, Italy*; [‖]*Riuniti Villa Sofia–Cervello Hospital, Internal Medicine 2, IBD Unit Palermo, Italy*; [**]*Luigi Sacco University Hospital, Gastroenterology and IBD Unit, Milan, Italy*; [††]*IRCCS-CSS Hospital, Gastroenterology, San Giovanni Rotondo, Italy*; [‡‡]*Gastroenterology and Hepatology Section, DiBiMis, University of Palermo, Palermo, Italy*; [§§]*University of Rome Tor Vergata, Department of Systems Medicine, Gastroenterology, Roma*; [¶¶]*S. Camillo-Forlanini Hospital, Gastroenterology, Rome, Italy*; [‖‖]*AOUP, Gastroenterology, Pisa, Italy*; [***]*University of Padova, Gastroenterology, Padova, Italy*; [†††]*Meyer Children's Hospital, Gastroenterology and Nutrition, Florence, Italy*; [‡‡‡]*University of Bari, Gastroenterology, Bari, Italy*; [§§§]*Federico II University, Gastroenterology, Naples, Italy*; [¶¶¶]*IRCCS Policlinico, Gastroenterology, San Donato Milanese–Milano, Italy*; [‖‖‖]*First Department of Medicine, S. Matteo Hospital Foundation, University of Pavia, Pavia, Italy*; [****]*University Hospital, Gastroenterology, Modena, Italy*; [††††]*U.O.C. Gastroenterologia ed Endoscopia Digestiva ASST Ovest Milanese, Legnano, Italy*; [‡‡‡‡]*SC Gastroenterology ASST Settelaghi Varese, Italy*; [§§§§]*ASST Rhodense, Rho Hospital, Gastroenterology Unit, Rho, Italy*; [¶¶¶¶]*Ospedale Valduce, Gastroenterology, Como, Italy*; [‖‖‖‖]*Department of Biochemical and Clinical Science "L. Sacco" ASST Fatebenefratelli Sacco–University of Milan, Italy*; [*****]*AOU Maggiore, Gastroenterology, Novara, Italy*; [†††††]*Istituto Fondazione Poliambulanza Hospital, Department of Medicine, Gastroenterology and Digestive Endoscopy, Brescia, Italy*; [‡‡‡‡‡]*S. Giuseppe Hospital, Gastroenterology, Milano, Italy*; [§§§§§]*S. Pellegrino Hospital, Gastroenterology, Trani, Italy*; [¶¶¶¶¶]*IRCCS AOU San Martino IST Gastroenterology Genova, Italy*; [‖‖‖‖‖]*AO Hospital, Internal Medicine, Lecco, Italy*; [******]*Gastroenterology and Endoscopy Unit, IRCCS Ca' Granda Ospedale Maggiore Foundation, Milan, Itay*.

Presentated at Congresses: This study was presented in part as oral communication at plenary session of the 12th ECCO Meeting, February 15–18, 2017, in Barcelona, Spain, and as an oral communication at the DDW May 6–9, 2017, in Chicago, IL, USA.

Author contributions: GF and VA designed the study protocol. FP made the statistical analysis. VA made the first draft of the manuscript. All the authors (except FP) provided the clinical data of the enrolled patients. All authors revised and approved the final manuscript.

Conflicts of interest: AA served as consultant to Abbvie, Allergan, Amgen, Biogen, Celgene, Celltrion, Ferring, Hospira, Janssen, Lilly, MS&D, Mundipharma, Pfizer, Samsung Bioepis, Sofar, Takeda. He received lectures fees from Abbvie, Astra-Zeneca, Chiesi, Ferring, Hospira, Janssen, Medtronic, MS&D, Mitsubishi Tanabe, Mundipharma, Nikkiso, Otsuka, Pfizer, Samsung Bioepis, Takeda, Tigenix, Zambon, and research grant from MS&D. VA served as consultant to Abbvie, Hospira, Mundipharma, MS&D, Takeda, Janssen, Ferring. He received lecture fees from Abbvie, Ferring, Hospira, MS&D, Takeda, Medtronic, Menarini and unrestricted research grants from Giuliani, Ferring, Sofar, Roche, Gillead, MS&D, Abbvie, and Otsuka. MA served as advisory board member for MSD, Takeda, and AbbVie. SA received consulting and advisory board fees and/or research support from AbbVie, MSD, Abbvie, Ferring, MSD, Janssen, Takeda, Mundipahrma, Zambon, and Sofar. BA received speaker fees from Takeda and unrestricted research grant from Sofar. LB received lecture fees from: Takeda, Zambon, Abbvie, MSD, and Wassermann. BS served as consultant to Abbvie, Takeda, and MSD. LC received a speaker fee form MS&D. MC has received lecture fees from MSD, Abbvie, Takeda, and Chiesi and has served as advisory board member for MSD and Abbvie. FC has served as advisory board member for Abbvie, MSD, and Takeda and received speaker fees from Abbvie, MSD, Takeda, Zambon, Otsuka, Phadia, and Diasorin. SD has served as a speaker, consultant, and advisory board member for Schering-Plough, Abbott Laboratories, Merck, UCB-pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Danone, Alpha Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson & Johnson. MDG received speaker fees from Abbvie. GF has served as a consultant and advisory board member for MSD, Takeda, AbbVie, and Janssen. WF received speaker fees form Mundipharma, and Zambon, served on the advisory board for Abbvie, and received an unconditioned grant from MS&D. FWG has served as a speaker and advisory board member for Abbvie, MSD, Takeda, and MultiPharma. LG has served as speaker/consultant for AbbVie, Janssen, Mundipharma, MSD, Shire, Takeda, Vifor Pharma, and Zambon. SM has served as a speaker and advisory board member for Abbvie, MSD, Takeda, and MultiPharma. AK received unconditioned grants from Abbvie and Takeda. MP has served as a speaker and advisory board member for Abbvie, MSD, Takeda, and Chiesi. SR has received lecture fees from Abbvie. MV has received speaker fees, research support, or served as an advisory board member for Abbvie, MSD, Takeda, Mundipharma, Hospira, Otsuka, Pfizer, Amgen, Jannsen, Giuliani, Sofar, Chiesi, and Wasserman. All the other authors have no conflict of interest to declare.

Address correspondence to: Vito Annese MD, Gastroenterology Department, Valiant Clinic, 13th Street City Walk, Dubai, UAE. E-mail: vito.annese@valiant.ae.

doi: 10.1093/ibd/izy264
Published online 18 August 2018

*MD,[§§§§§] Luigi Caserta, MD,[¶¶¶¶] Maria Caterina Parodi, MD,[¶¶¶¶] Agostino Colli, MD,[‖‖‖‖‖] Anna Ronchetti, MD,[‖‖‖‖‖] Daniela Pugliese, MD,[*] Andrea Geccherle, MD,[‡] Francesca Rogai, MD,[§] Stefano Milani, MD,[§] Sara Renna, MD,[‖] Andrea Cassinotti, MD,[**] Angelo Andriulli, MD,[††] Giuseppina Martino, MSN,[††] Barbara Scrivo, MD,[‡‡] Edoardo Troncone, MD,[§§] Anna Kohn, MD,[¶¶] Lorenzo Bertani, MD,[‖‖] Greta Lorenzon, MSN,[***] Silvia Ghione, MD,[†††] Olga Nardone, MD,[§§§] Maurizio Vecchi, MD,[¶¶¶,******] Angela Bertani, MD,[****] Matteo A. Bosani, MD,[††††] Cristina Bezzio, MD, PhD,[§§§§] and Raffaele Salerno, MD[‖‖‖‖‖]*

Background: We report a prospective, nationwide cohort evaluating the safety and effectiveness of CT-P13.

Methods: A structured database was used to record serious adverse events (SAEs), clinical remission/response, inflammatory biomarkers (CRP and calprotectin), and endoscopic findings.

Results: Eight hundred ten patients with inflammatory bowel disease (IBD) (452 Crohn's disease [CD]) were enrolled. Four hundred fifty-nine patients were naïve to anti-TNFα (group A), 196 had a previous exposure (group B), and the remaining 155 were switched to CT-P13 (group C). All patients were included in the safety evaluation with a mean follow-up of 345 ± 215 days and a total number of 6501 infusions. One hundred fifty-four SAEs were reported (19%), leading to cessation of the biosimilar in 103 subjects (12.7%). Infusion reactions were 71, leading to cessation of the biosimilar in 53 subjects (6.5%), being significantly more frequent in patients pre-exposed to anti-TNFα ($P = 0.017$). The efficacy of therapy was calculated in 754 IBD patients, with a mean follow-up of 329 ± 202 days. Forty-eight patients had a primary failure (6.4%), and 188 (25.6%) lost response during follow-up. Six hundred twenty-eight (364 CD) and 360 IBD patients (222 CD) completed the follow-up at 6 and 12 months, respectively. At 12 months, patients without loss of response were 71%, 64%. and 82% in groups A, B, and C, respectively (log rank $P = 0.01$). Clinical/endoscopic scores and inflammatory biomarkers dropped significantly in CD and UC patients ($P = 0.01$ and $P < 0.0001$) compared with baseline.

Conclusions: In this large prospective cohort, no further signals of difference in safety and effectiveness of CT-P13 in IBD has been observed.

Key Words: Crohn's disease, ulcerative colitis, inflammatory bowel disease, Infliximab, Remsima, Inflectra, biosimilar, CT-P13

INTRODUCTION

The introduction of biologic therapies for inflammatory bowel disease (IBD) proved to be a breakthrough for patients with Crohn's disease (CD) and ulcerative colitis (UC).[1] Since infliximab (Remicade, Janssen) was approved in 1998, antitumor necrosis factor alpha (anti-TNFα) monoclonal antibodies (mAb) have been demonstrated to be a very potent class of therapeutic agents inducing mucosal healing and prolonged remission, with reduction of hospitalizations and surgical procedures.[2] However, anti-TNFα agents are also expensive and have become a burden on pharmacy budgets in most countries, possibly restricting access for many patients.[3,4] As the patent of infliximab and other biologic products used for inflammatory diseases is expired or close to expire in the European Union (EU) and the United States (US), the emergence of biosimilar therapies is an inevitable outcome.[5]

CT-P13 (Celltrion, Inc., Incheon, Republic of Korea) has been the first mAb biosimilar of infliximab evaluated and approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA). The program to demonstrate its biosimilarity consisted of a phase 1 pharmacokinetic study in patients with ankylosing spondylitis (AS)[6] and a phase 3 study evaluating efficacy in patients with rheumatoid arthritis (RA).[7] Both were randomized, double-blinded, multinational trials and provided data up to 30 weeks of treatment.[6,7] Subsequently, data up to 54 weeks[8–10] with a following open-label 48-week extension, in which patients initially receiving reference infliximab were switched to CT-P13, have been published.[11,12] These studies have demonstrated pharmacokinetic equivalence and clinical efficacy in both AS and RA[6,7] up to 102 weeks and in patients switched from infliximab to CT-P13[11,12]. The development of antidrug antibodies (ADA) was similar in CT-P13 and infliximab in both trials.[7,12]

Based on extensive in vitro product characterization, comparability exercise,[13] and these clinical data, CT-P13 became the first mAb in 2013 approved by the EMA[14] not only in RA and AS but also in adult and pediatric CD and UC, psoriatic arthritis, and psoriasis. Similarly, it has been licensed for all these indications in South Korea,[15] Japan,[16] the United States,[17] and Canada.[18]

The introduction of biosimilars has certainly reduced the financial burden and generated competition in the pharmaceutical market, allowing more patients to access the treatment.[19] However, there was an initial lack of experience and confidence in using biosimilar infliximab in IBD,[20] both because of the lack of clinical studies in IBD and potential different downstream effects in the mechanism of action[21] and different immunogenicity[22] of infliximab in IBD compared with rheumatologic diseases. Of note, infliximab in RA is thought to act predominantly through the neutralization of soluble and transmembrane TNFa, whereas in CD, signalling through membrane-associated forms of TNFa and Fcg receptor seems to play a more important role.[23,24]

Most information about the efficacy and safety of CT-P13 in IBD patients naïve to anti-TNFα or after switching from infliximab were confined to studies with small sample size

and short follow-up, as recently reviewed by Komaki Y et al in 2017.[25]

A single randomized controlled noninferiority, double-blinded, phase 4 trial with 52 weeks of follow-up has been recently published (NCT02148640).[26] Adult patients on stable treatment with infliximab originator with different immune-mediated diseases treated in a hospital setting for at least 6 months were eligible for participation. Four hundred eighty-two patients were enrolled and randomized (241 to infliximab originator, 241 to CT-P13 group), including 155 and 93 patients with CD and UC, respectively. After switching to biosimilar, the frequency of serious adverse events (10% vs 9%) and disease worsening (26% vs 30%) was similar in patients using infliximab or CT-P13.

Since February 2015, the patent for infliximab is expired in Italy, and two CT-P13 formulations became available on market, REMSIMA (Celltrion Healthcare Hungary Kft. 1023 Budapest) and INFLECTRA (Hospira, UK Limited, Maidenhead UK). We planned a prospective, nationwide, observational study to evaluate the effectiveness, safety, and immunogenicity of CT-P13 in patients with IBD, in induction and maintenance of remission, either in patients naïve to anti-TNFα, previously exposed to anti-TNFα, or switched from infliximab. The preliminary data of 547 patients with a mean follow-up of 4.3 months have been published elsewhere.[27]

We report here an expansion of the original cohort (n = 810), with a mean follow-up of 1 year and—more importantly—including data on modification of endoscopic activity and inflammatory biomarkers.

METHODS

Study Population and Data Collection

Consecutive IBD patients treated with CT-P13 were enrolled in 30 academic (n = 12), and tertiary (n = 18) referral centers in Italy from April 2015 to August 2017. Eligible patients were previously diagnosed either as UC or CD based on clinical, radiological, endoscopic, and histological criteria.[28–30] Clinical data were anonymized and organized in a structured database during the entire follow-up. The study protocol was approved by each participating center and registered as EUDRACT 2015-005254-35.

For each patient, the following clinical features were collected: gender, age at diagnosis, type of disease, age at start of therapy with CT-P13, commercial name and batch of CT-P13, use of combo therapy, indication for CT-P13 therapy, previous therapy with anti-TNFα (name of drug, duration, and results), duration of follow-up with CT-P13, number of infusions of CT-P13, evaluation of efficacy with reason for withdrawal, other immune-mediated associated diseases, number and details of serious adverse events, date of last follow-up, and any occurrence of surgery along the follow-up. The clinical and endoscopic evaluation was performed in UC by using the Mayo score, while the Harvey-Bradshaw index (HBI), Simple Endoscopic Score (SES-CD), and Rutgeerts score were used for CD. In addition, rate of primary failure, loss of response, and need for dose escalation were also recorded (see further for definitions). According to site routine clinical practice, blood samples were taken at different time points for evaluation of C reactive protein (CRP), fecal calprotectin (FC), detection of drug trough levels (TL), and antidrug antibodies (ADA).

Outcome Measures

The primary endpoint was the evaluation of safety in terms of rate of serious adverse events (SAEs) along the follow-up. Secondary endpoints were a) the effectiveness, evaluated both in terms of clinical remission/response and treatment persistency; b) the change of HBI, Mayo Score, SES-CD, Rutgeert's score, CRP, and FC; c) the immunogenicity evaluated as the occurrence of infusion reactions and loss of response; and d) predictive factors of safety and efficacy.

Serious adverse events (SAEs) were defined as the occurrence of death, a life-threatening adverse event, impatient hospitalization, prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, and any condition that on appropriate medical judgement might jeopardize the patient and might require medical or surgical intervention, including withdrawal of the ingoing therapy with CT-P13.

Clinical remission for UC was considered as a partial Mayo score (pMS) <2 with no partial score >1 and no rectal bleeding, whereas response was a 30% and 3 points reduction of pMS.[31] Clinical remission for CD was considered a Harvey-Bradshaw Index (HBI) ≤4, whereas response was taken as a 3-point reduction of HBI.[32] Endoscopic remission was defined as endoscopic Mayo score of 0, SES-CD <4, and Rutgeerts score ≤ir2, respectively.

Primary failure of CT-P13 was defined as no or minor clinical response at 8 weeks after the induction regimen or deterioration of clinical condition leading to surgery, early therapy change, or withdrawal.[33] Loss of response was defined as a clinical situation arising in patient with an initial response to the CT-P13, followed by a diminished or less durable response over time leading to drug discontinuation or dose escalation, according to investigator's evaluation.[34, 35] Dose escalation was performed as either increasing dosage (10 mg/Kg) or reducing the infusion intervals (every 4–6 weeks), according to investigator's preference.

Statistical Analysis

Descriptive statistics of the baseline data are presented as means ± standard deviation (SD), medians and interquartile ranges (IQR), or as percentages, when appropriate. Most variables were non-normally distributed; thus, nonparametric tests (the χ^2 test and the Kruskal-Wallis [equality-of-populations] rank test) were used.

Primary failure to CT-P13 was assessed among patients who had completed a minimum treatment and follow-up time of 8 weeks. Then, loss-of-response was studied among responders at week 8 using time-to-event methods for censored observations (i.e., patients withdrawn from the study due to AEs and patients who had not lost response on the final data collection date were considered "censored"). On the other hand, patients for whom treatment dose was optimized were considered to have lost response. Time to event was defined as the time from week 8 until the date of event or censoring. Kaplan-Meier estimates were used to draw cumulative incidence curves, compared by the log-rank test and Hazard Ratios (HR) derived from Cox proportional hazards analysis. In an alternative approach, we analyzed treatment persistency, taking into account those patients for whom treatment dose was optimized while remaining on CT-P13 treatment.

P values less than 0.05 were considered statistically significant. All statistical tests are 2-sided. Stata software was used for all statistical analyses (Stata Corp., College Station, TX, USA).

RESULTS

The main clinical characteristics of the study cohort are summarized in Table 1.

The study population included 810 patients (452 CD, 358 UC): 459 were naïve to anti-TNFα (group A); 196 were pre-exposed to 1 or more anti-TNFα agents (group B) (36 infliximab, 124 adalimumab, 27 golimumab, and 9 had two different anti-TNFα). The anti-TNFα agents were stopped in these patients for any reasons except intolerance 4 to 24 months before starting CT-P13. The remaining 155 patients were switched from infliximab to CT-P13 after a mean of 17 ± 13 infusions (range 2–72) (group C). The 3 groups differed regarding type of disease (CD or UC), age at diagnosis, frequency of combo therapy (usually with thiopurines), use of steroids at baseline, and average time of follow-up, but not for disease duration, gender, and smoking status.

Of note, 51 pediatric patients were also included in the cohort (31 CD); 27 of them naïve to anti-TNFα, and the remaining switched from infliximab.

Safety

Two hundred ninety patients received Inflectra and the remaining 520 Remsima, for a cumulative number of 6,501 infusions and a mean follow-up of 344.7 ± 215.6 days (median 327, IQR: 161–530 days) and 764 patient-years. Main data are given in Tables 2 and 3.

Any serious adverse events

Serious adverse events (including infusion reactions) occurred in 79 of 459 patients (17%) in group A; 57 of 196 (29%) in group B; and 18 of 155 (11.6%) in group C. The detailed list of SAEs is depicted in Table 2. More specifically, most common infections were pneumonitis (4 cases) and herpes zoster (3 cases). The corresponding rates (with person-years in the denominator) were 74, 48.5, and 18.5 per 100 person-years (p-y) for groups A, B, and C, respectively.

When the incidence rates were calculated as relative risk (Table 3), SAEs in patients who had been previously exposed to anti-TNFα were twice as frequent as in naïve patients and 2.5 times as frequent as in patients who switched (both comparison were statistically significant).

TABLE 1: Characteristics of Naïve Patients (group A, n = 459); Patients Previously Exposed to Anti-TNFs (group B, n = 196); and Patients Who Switched from Infliximab (group C, n = 155)

	Total Cohort	group A	group B	group C	*P*
Gender (males, %)	450/360 (55%)	246/213 (53%)	106/90 (54%)	98/57 (63%)	0.20
Diagnosis (CD/UC)	452/358	238/221	127/69	87/68	**0.025**
Age at diagnosis (yrs)	31.8 ± 13.7 29 (22–41)	32.6 ± 13.6 30 (22–41)	31.3 ± 14 28 (21–44)	29.3 ± 13.6 27 (18–38)	0.069
Duration of disease (yrs)	8.1 ± 7.9 5.5 (2–12)	7.1 ± 8 4 (1–11)	9.7 ± 7.8 7 (3–15)	8.8 ± 7.4 7 (3–13)	0.1
Smoking status (Yes/No/Ex)	133/573/104	81/319/59	34/132/30	18/122/15	0.35
Active smokers	133/677 (16.4%)	81/378 (17.6%)	34/162 (17.3%)	18/137 (11.6%)	0.35
Combo therapy (y/n)	175/635 (21.6%)	76/383 (16.5%)	51/145 (26%)	48/107 (31%)	**0.0006**
Steroids (y/n)	279/531 (34.4%)	190/269 (41.4%)	68/128 (34.7%)	21/134 (13.5%)	**<0.00001**
Follow-up (days)	344.7 ± 215.6 327 (161–530)	342.4 ± 206.4 335 (165–511)	312.2 ± 216.3 285 (126–497)	392.8 ± 232 356 (184–629)	**0.009**

Data are presented as means ± SD; medians and interquartile ranges in bracket, or percentages when appropriate. The ^{2} test and the Kruskal-Wallis (equality-of-populations) rank test were used for the statistical evaluations.

TABLE 2: Type of SAEs in the Whole Cohort and in the Three Different Subgroups

	Total Cohort (n = 810)	Naïve to anti-TNFα (n = 459) A	Pre-exposed to anti-TNFα (n = 196) B	Switch from infliximab (n = 155) C
Total SAEs, n (%)	154 (19%)	79 (17%)	57 (29%)	18 (11.6%)
Infusion reactions, n (%)	71 (8.7%)	34 (7.4%)	26 (13.2%)	11 (7.1%)
Skin reactions, n (%)	34 (4.2%)	20 (4.3%)	11 (5.6%)	3 (1.9%)
Infections, n (%)	14 (1.7%)	7 (1.5%)	6 (3.1%)	1 (0.6%)
Others, n (%)	16 (2%)	11 (2.4%)	5 (2.5%)	0
Arthralgia, n (%)	8 (1%)	5 (1.1%)	3 (1.5%)	0
Neurological, n (%)	3 (0.4%)	1 (0.2%)	1 (0.5%)	1 (0.6%)
Immunological, n (%)	8 (1%)	1 (0.2%)	5 (2.5%)	2 (1.3%)
Neoplasia, n (%)	0	—	—	—
Death, n (%)	0	—	—	—
Drug withdrawal, n (%)	103 (12.7%)	58 (12.6%)	35 (17.8%)	10 (6.4%)
Stop for infusion reactions, n (%)	53 (6.5%)	28 (6.1%)	21 (10.7%)	4 (2.6%)
Stop for SAEs, n (%)	50 (6.2%)	30 (6.5%)	14 (7.1%)	6 (3.9%)

Any serious adverse events (excluding infusion reactions)

Aside from infusion reactions, other serious adverse events occurred in 45 of 459 patients (9.8%) in group A; 31 of 196 (15.8%) in group B; and 18 of 155 (11.6%) in group C. The corresponding rates were 42, 26.4, and 19 per 100 p-y for groups A, B, and C, respectively. The relative risk was significantly more frequent in group B compared with group A ($P = 0.03$) and C ($P = 0.0019$). The most frequent events were skin reactions. No death, neoplasia, or unexpected SAEs were reported.

Infusion reactions

Infusion reactions occurred in 34 of 459 patients (7.4%) in group A, 26 of 196 (13.2%) in group B, and 11 of 155 (7.1%) in group C. The corresponding rates were 31.8, 22.5, and 11.8 per 100 p-y for groups A, B, and C, respectively. Infusion reactions in patients previously exposed to anti-TNFα were twice as frequent as for naïve patients and twice as frequent as in patients who switched. Only the first comparison was statistically significant ($P = 0.017$). By evaluating patients of group B, it was discovered that 45 were previously exposed to infliximab and 151 were not. Among the 45 previously exposed to infliximab, 11 infusion reactions (24.4%) were reported. Among the 151 previously exposed to other anti-TNFα, 15 infusion reactions (9.9%) were reported. This gives a relative risk of =2.24 (1.21–4.97), $P = 0.012$.

Serious adverse events leading to discontinuation (excluding infusion reactions)

Serious adverse events leading to discontinuation occurred in 30 of 459 patients (6.5%) in group A; 14 of 196 (7.1%) in group B; and 6 of 195 (3.9%) in group C. By considering these SAEs, no significant difference was found among the 3 groups. More specifically, they were skin lesions (16), serious

TABLE 3: Evaluation of the Relative Risk of the SAEs and Infusion Reactions in the Three Subgroups of Patients. Values Given With 95% Confidence Interval and *P*.

	All SAEs	Infusion reactions	Other SAEs	Stop for SAEs (no infusion)	Stop for infusion reactions
Group A vs Group B	**0.59** (0.43–079) **0.0005**	**0.55** (0.34–0.90) **0.017**	**0.62** (0.4–0.95) **0.03**	0.91 (0.49–1.68) 0.7	**0.56** (0.33–0.97) **0.04**
Group A vs Group C	1.48 (0.91–2.39) 0.10	1.04 (0.54–2) 0.89	2.17 (0.99–4.7) 0.05	1.68 (0.71–3.97) 0.2	2,36 (0.84–6.63) 0.10
Group B vs Group C	**2.5** (1.5–4.1) **0.0002**	1.86 (095-3.66) 0.06	**3.5** (1.58–7.73) **0.0019**	1.84 (0.72–4.69) 0.19	**4.15** (1.45–11.8) **0.0078**

infections (11), immunologic problem (7), severe arthralgia (6), surgery for perianal fistula (4), transient ischemic attack (2), headache (1), alteration of liver functions tests (2), and lack of adequate venous access (1).

Infusion reactions leading to discontinuation

Infusion reactions leading to discontinuation occurred in 28 of 459 patients (6.1%) in group A; 21 of 196 patients (10.7%) in group B; and 4 of 155 patients (2.6%) in group C. The relative risks ratios were significantly higher in patients previously exposed to anti-TNFα but did not differ among groups A and C. Infusion reactions were twice as frequent as in naïve patients and four times as frequent as in patients who switched. Both comparisons were significant (P = 0.04; P = 0.0078, respectively). Within the group, the discontinuation due to infusion reaction was significantly more frequent in patients previously exposed to infliximab compared with other anti-TNFα (20% vs 8%; relative risk 2.5; 95% CI, 1.13–5.58; P = 0.023).

Of note, at the end of follow-up (August 2017), in 78 patients a colectomy (34 UC) or intestinal resection (44 CD) was performed or planned. Forty-nine patients were naïve to anti-TNF, 18 were pre-exposed, and the remaining 11 patients (10 CD) were switched after a mean of 36 months of infliximab therapy (range 8–66 months) and 13.8 months of biosimilar (range 5–24 months). The rate of surgery was 10.6%, 9.3%, and 7.1% with no significant difference among groups A, B and C, respectively.

Effectiveness

Overall, 754 patients had completed the minimum treatment and follow-up time of 8 weeks or had failed earlier. There were 433 in group A, 170 in group B, and the remaining 151 in group C. Among them, 48 patients had a primary failure (6.4%, 95% CI, 5.7–11.0); more specifically, the failure rate was 7.4% in group A (95% CI: 5.2%–10.2%), 7.6% in group B (95% CI: 4.5%–12.6%), and 2% in group C (95% CI: 0.7%–5.7%) (P = 0.047).

Next, we explored the loss of response among week 8 responders (n = 722) using time-to-event methods. One hundred eighty-eight patients (25.6%) lost response during the follow-up (from week 8 onwards: total time at risk was approximately 609 patient-years or 315 days per patient on average).

In Figure 1, the Kaplan-Meier estimates for the probability to respond are shown up to the end of follow-up. A significant difference between the 3 groups was found (log rank test, P = 0.01) (Fig. 1). More specifically, patients of group C did significantly better than those of groups A and B (P = 0.006 and P = 0.004, respectively). However, this finding should be tempered by considering that most patients in group C were already responders at the time of switching and more frequently under combo therapy compared with naïve (31% vs 21%; P 0.001). The Kaplan-Meier estimates (with 95% CIs) for probability of response at predetermined time-points are depicted in Table 4.

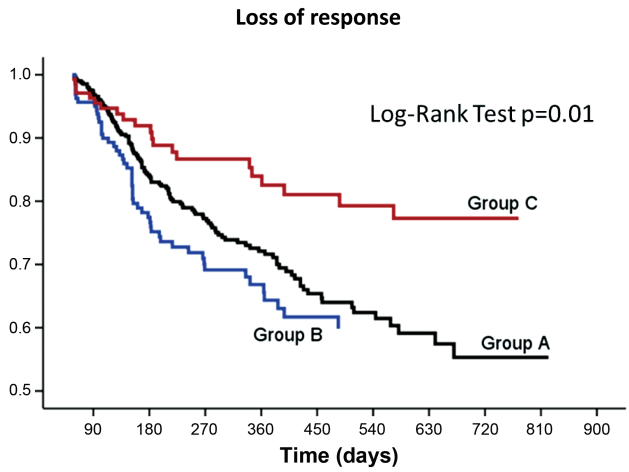

FIGURE 1. Kaplan-Meier estimation for probability of response in groups A (black), B (blue), and C (red). Total Log-rank test: P = 0.01; A vs B P = 0.46, B vs C P = 0.004; A vs C P = 0.006

In an alternative approach, we evaluated treatment persistency among responders at week 8 (n = 722). In 78 patients (10.5%), treatment was withdrawn during follow-up, and dose intensified in 203 (27.5%) more patients. Kaplan-Meier estimates for probability of treatment persistency are depicted in Fig. 2. In this evaluation, difference among subgroups was not statistically significant (log rank test, P = 0.25). The Kaplan-Meier estimates (with 95% CIs) for probability of treatment persistency at predetermined time-points are depicted in Table 4.

Clinical scores

The clinical scores at baseline, 6 months, and 12 months are summarized on Table 5. For UC, 358 patients were evaluated at baseline, 264 after 6 months, and 138 at 12 months. Of note, 70 and 8 patients were still available up to 18 and

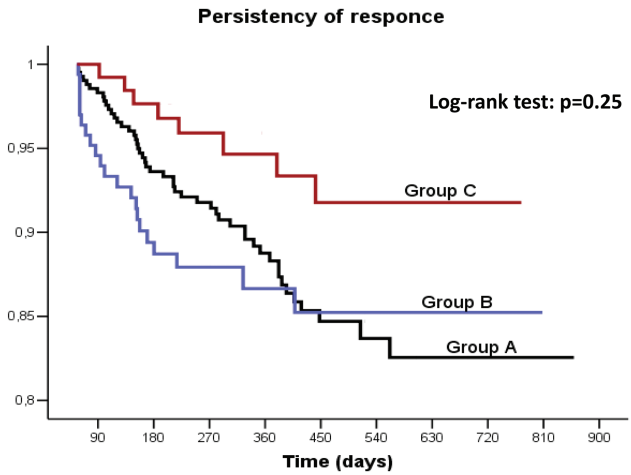

FIGURE 2. Kaplan-Meier estimation for probability of treatment persistency in groups A (black), B (blue), and C (red). Total Log-rank Test: P = 0.25; A vs B P = 0.70; A vs C P = 0.28; A vs C P = 0.09

TABLE 4: Kaplan-Meier Estimates (With 95% CIs) for Probability of Response and Persistency at Predetermined Time-points After the Initial 8 Weeks of Therapy

RESPONSE	Overall	Group A	Group B	Group C
6 months	83% (80–86)	83% (80–87)	75% (69–82)	90% (84–95)
12 months	72% (68–76)	71% (66–76)	64% (56–73)	82% (75–90)
18 months	64% (60–69)	61% (55–68)	60% (50–72)	77% (68–86)
24 months	58% (55–66)	52% (47–63)	58% (50–72)	75% (67–84)
6 months	93% (91–95)	93% (91–98)	89% (84–94)	96% (94–99)
12 months	90% (87–92)	89% (85–91)	87% (81–92)	95% (90–99)
18 months	86% (82–89)	84% (79–88)	84% (78–91)	91% (86–97)
24 months	84% (80–87)	81% (75–85)	82% (76–89)	90% (85–91)

24 months, respectively. For CD, 452 patients were evaluated at baseline, 364 at 6 months, and 222 at 12 months. In addition, 124 and 18 patients reached a follow-up of 18 and 24 months, respectively.

Both Mayo score and HBI in the full cohort decreased significantly at month 6 ($P < 0.0001$) and remained stable at month 12. This reduction was significant not only in groups A and B ($P < 0.0001$) but also in group C ($P = 0.01$, $P < 0.001$), despite lower baseline values being most of the patients already in remission at the start of biosimilar infusion.

Endoscopic scores

An endoscopic evaluation was available at baseline and after 12 months in 333 of 358 (93%) and 131 of 138 (95%) of UC and 343 of 452 (76%) and 135 of 222 (61%) of CD patients, respectively. More specifically, in 43 CD patients, the biosimilar therapy was undertaken for postsurgical recurrence and endoscopic activity evaluated with the Rutgeerts score. The Mayo score and SES-CD were both significantly improved ($P < 0.0001$) at the evaluation at 12 months. After stratifying patients in groups, besides the significant improvement for groups A and B ($P = 0.002$, $P < 0.0001$), a further improvement in group C was calculated (Mayo: $P = 0.01$; SES-CD: $P = 0.06$). The Rutgeerts score was significantly improved in the whole cohort ($P = 0.01$), with a trend toward improvement in all subgroups.

Inflammatory biomarkers

C reactive protein evaluation was available in 805, 620, and 355 of patients at baseline, 6 moths, and 12 months, respectively; fecal calprotectin was available only in approximatively 25% of cases. In the overall cohort, CRP and calprotectin were significantly reduced from the baseline to 6 and 12 months ($P < 0.01$ to <0.0001).

After stratifying by groups in UC patients, a significant reduction of CRP was found in groups A and B, while there was no significant change compared with baseline in group C. In Crohn's disease, a significant reduction for CRP in groups A and B was found, but not in group C.

The calprotectin was significantly reduced in UC and CD patients in groups A and B and only numerically reduced in group C.

Deep remission

At the end of follow-up, a deep remission including clinical remission, mucosa healing and normalization of inflammatory biomarkers was achieved in 48 of 117 (41%) and 35 of 141 (25%) of CD and UC patients in whom all information were available, respectively.

Steroids free remission

At the beginning of biosimilar therapy, 167 of 358 UC patients (46.6%) and 112 of 452 CD patients (24.8%) were on steroid therapy, mainly in groups A (n = 190) and B (n = 68). At the last follow-up, 61 (17%) UC and 45 (10%) CD patients were still on steroids. However, only 5 of 231 (2.2%) CD and 6 of 150 (4%) UC patients in clinical remission, respectively, were still on steroid therapy.

Multivariate analysis

The Cox proportional hazards analyses identified some prognostic factor for loss of response and SAEs (Supplementary Tables 1 and 2). More specifically, patients of groups A and B and UC patients had a significantly greater hazard ratio (HR) to lose response ($P = 0.033$; $P = 0.024$; $P = 0.028$, respectively), while the opposite was true for patients with no steroids at last follow-up (<0.0001). By evaluating risk factors for SAEs, patients of subgroup B had a significantly higher HR ($P = 0.003$), and a similar trend was also seen in group A ($P = 0.057$); conversely, the HR was significantly lower in male compared with female patients ($P = 0.001$) and patients off steroids at last follow-up ($P = 0.010$).

Cost savings

Estimated cost saving was over 3.8 million Euros per year of treatment in our cohort, by considering approximately

TABLE 5: Clinical and Endoscopic Scores and Biomarkers in the Whole Cohort and Different Subgroups at the Beginning of the Biosimilar Treatment, at 6 Months, 12 Months, and Final Follow-Up. *P* Values Obtained by Student T test. Baseline Values Compared With 6 ([a]) and 12 ([b]) Months

Parameters	Baseline	6 months	12 months	*P*
UC Total	**(n = 358)**	**(n = 264)**	**(n = 138)**	
Mayo Score	6 ± 3	2.2 ± 2.3	1.6 ± 2.1	**<0.0001[a,b]**
Mayo Endo	2.38 ± 0.85	—	1.2 ± 1.2	**<0.0001[b]**
CRP (mg/L)	14.2 ± 25.4	4.9 ± 12.3	4.5 ± 8.8	**<0.0001[a,b]**
Calpro (mcg/g)	686.2 ± 700.5	395 ± 611.1	164.3 ± 391.5	**0.01[a], <0.001[b]**
UC group A	(n = 221)	(n = 147)	(n = 95)	—
Mayo Score	6.6 ± 2.4	4.1 ± 2.3	1.8 ± 2.3	**<0.0001 [a,b]**
Mayo Endo	2.5 ± 0.6	—	1.4 ± 1.3	**<0.0001 [b]**
CRP (mcg/g)	15.5 ± 26.9	5.6 ± 14.9	3.9 ± 6.7	**<0.0001 [a,b]**
Calpro (mcg/g)	745 ± 745	338 ± 573	298 ± 513	**0.01[a], 0.007[b]**
UC group B	(n = 69)	(n = 62)	(n = 15)	—
Mayo Score	6.9 ± 2.3	2.1 ± 2.4	1.5 ± 1.7	**<0.0001[a,b]**
Mayo Endo	2.5 ± 0.5	—	0.8 ± 0.7	**0.002[b]**
CRP (mcg/g)	12.8 ± 18.2	4.3 ± 4.4	5.9 ± 8.1	**0.002[a], 0.09[b]**
Calpro (mcg/g)	719 ± 658	220 ± 131	50 ± 53	**0.009[a,b]**
UC group C	(n = 68)	(n = 55)	(n = 28)	—
Mayo Score	3 ± 3.5	1.3 ± 1.9	1.1 ± 1.7	**<0.001[a,b]**
Mayo Endo	1.4 ± 1.2	—	0.9 ± 0.7	**0.01[b]**
CRP (mcg/g)	4 ± 7.8	2.78 ± 10.5	7.4 ± 17.3	**NS**
Calpro (mcg/g)	412.6 ± 461	592 ± 922	13.9 ± 9.5	**NS**
CD Total	(n = 452)	(n = 364)	(n = 222)	—
Harvey-Bradshaw	6.9 ± 4.4	3.1 ± 2.9	2.6 ± 2.7	**<0.0001[a,b]**
SES-CD	9.4 ± 6.4	—	3.9 ± 4.5	**<0.0001[a,b]**
Rutgeerts score	3.3 ± 1.1	—	2.4 ± 1.3	**0.01[b]**,
CRP (mcg/g)	11.2 ± 18.5	5.7 ± 11	5.1 ± 7.5	**0.04[a], <0.01[b]**
Calpro (mcg/g)	477.9 ± 563.9	279.6 ± 409.5	173.7 ± 343.9	**0.006[a], 0.001[b]**
CD group A	(n = 238)	(n = 190)	(n = 116)	—
Harvey-Bradshaw	7.5 ± 4	2.8 ± 2.9	2.6 ± 2.7	**<0.0001[a,b]**
SES-CD	10.8 ± 5.5	—	4.6 ± 5.1	**<0.0001[b]**
Rutgeerts score	3.8 ± 0.5	—	2.9 ± 1.2	**0.07[b]**
CRP (mcg/g)	13.4 ± 20.7	6.6 ± 10.8	5.2 ± 7.8	**0.0001[a,b]**
Calpro (mcg/g)	548 ± 647	275 ± 455	201 ± 402	**0.01[a], 0.007[b]**
CD group B	(n = 127)	(n = 96)	(n = 58)	—
Harvey-Bradshaw	8.6 ± 4.3	3.9 ± 3.5	3.7 ± 3.3	**<0.0001[a,b]**
SES-CD	11.1 ± 6.9	—	4.8 ± 4	**<0.0001[b]**
Rutgeerts score	3.2 ± 1.2	—	2.7 ± 1.3	**0.3**
CRP (mcg/g)	11.4 ± 18.3	6 ± 13.3	5.2 ± 8	**0.02[a], 0.004[b]**
Calpro (mcg/g)	444 ± 389	131 ± 93	123 ± 89	**0.001[a], 0.009[b]**
CD group C	(n = 87)	(n = 78)	(n = 48)	—
Harvey-Bradshaw	3 ± 3.2	2.1 ± 2.4	1.8 ± 2.3	**0.01[a,b]**
SES-CD	3.7 ± 4.5	—	1.5 ± 2	**0.06[b]**
Rutgeerts score	2.8 ± 1.2	—	1 ± 0.7	**0.01[b]**
CRP (mcg/g)	2.9 ± 2.8	2.2 ± 2.7	3.2 ± 3.1	**NS**
Calpro (mcg/g)	289.2 ± 356	165.3 ± 330	110 ± 188	**NS**

350 mg of CT-P13 for each infusion, with a mean 35% price reduction compared with Remicade's cost.

DISCUSSION

In this study, we prospectively followed a large cohort of patients using CT-P13, the first mAb approved in IBD, in real-life condition. The main findings are that a) the rate (19%) and characteristics of SAEs are in line with previous experience with infliximab; b) the occurrence of infusion reactions and drug withdrawal for SAEs was 8.7% and 12.7%, respectively; c) drug withdrawal due to infusion reactions was significantly more frequent in patients pre-exposed to anti-TNFα, especially infliximab; d) the whole effectiveness in terms of induction or maintainance of remission/response was high with an estimated effectiveness at 12 months of about 71% in naïve and 82% after the switch; e) the rate of primary failure (6.4%) and loss of response (25.6%) is in line with previous experience with infliximab; and f) after the switch, patients had less or comparable incidence of SAEs and significantly lower rate of loss of response as compared with patients naïve or pre-exposed to anti-TNFα.

The availability of the mAB biosimilar on the market has been a major breakthrough because of the pharmaco-economic implications. In the United States, because of the raising prescription, biologics as a whole account for 28% of all drug spending, and it is expected that biologic sales will reach $180 billion USD during 2017.[36] Approximatively half of these sales will likely be attributed to 11 biologics that will lose exclusivity within the next 5 years.[36] Biosimilars are less costly primarily because they do not have to undergo the intensive clinical development process of approval and have a reduced cost of marketing. IMS Health in 2016 estimated that the use of biosimilars would save over $56 billion USD and potentially up to $112 billion for the health care system in Europe and the United States, respectively, over the following 5 years.[37] The anti-TNFα biosimilar has already a 72% share in Europe with an increase in volume of prescription (infliximab + biosimilar) of about 20%. The use of biosimilars by reducing the cost of IBD treatment can potentially improve access to medication. This has already proven to be the case in several European countries.[38]

An important issue, however, is the extrapolation to the same indications of the originator in the absence of clinical data and the dilemma that clinicians face utilizing new biotech agents with scarce clinical information in their own disease of interest. This is the case now for CT-P13 and Flixabi in Italy for IBD, but it will be the same in the near future for other infliximab and adalimumab biosimilars.[39, 40]

Although introduced in 2013 in Korea, data on safety and efficacy of CT-P13 in IBD are still scanty. A recent systematic review and meta-analysis reported data of only 829 patients from 11 observation series. Adverse events in naïve patients were 0.08 (95% CI, 0.02–0.26) and 0.08 (95% CI, 0.03–0.17) in CD and UC, respectively, with as slight numerical increase after switching (CD = 0.10 [95% CI, 0.02–0.31]; UC 0.22 [95% CI, 0.04–0.63]). The pooled rate of clinical response at 24–30 weeks were 0.77 (95% CI 0.62–0.86) and 0.77 (95% CI 0.67–0.85) in CD and UC, respectively. After switching the sustained clinical response at 48–63 weeks were 0.75 (95% CI, 0.44–0.92) and 0.83 (95% CI, 0.19–0.99). Of note, the largest cohort had 210 patients followed for 54 weeks.[41] After this review, a few other large series have been published, including our own.[42–51]

The occurrence of SAEs in our study (19%) is in line with previous experience with infliximab and CT-P13, and no unexpected safety signals have been reported in the evaluated timeframe, although the median duration of treatment for a single patient was still 11 months. Of note, skin reactions were the most frequent SAEs (34 of 810, 4.2%), excluding infusion reactions, and lead to drug withdrawal in 16 patients. More importantly, infusion reactions were significantly more frequent in patients pre-exposed (13.2%) with a double relative risk compared with naïve patients (P = 0.017) or those who switched from infliximab (P = 0.06). In group B, infusion reactions were more than twice as frequent in patients previously exposed to infliximab compared with patients exposed to other anti-TNFα agents. Similarly, infusion reactions leading to discontinuation were twice as frequent as in naïve patients, and 4 times as frequent as in patients who switched, being significantly more frequent in patients previously exposed to infliximab (RR = 2.5, P = 0.023), thus suggesting specific caution in these patients (Tables 2 and 3).

The clinical effectiveness was evaluated during a median of 11 months, although the follow-up was significantly longer in patients who switched from infliximab (11.9 months). Given these differences, the estimated efficacy was calculated using time-to-event methods for censored observations up to 24 months from the beginning of therapy. Seven hundred fifty-four patients had at least 8 weeks of follow-up or had failed earlier; 38 were primary failures (6.4%). In the remaining subject responders at 8 weeks, 72% and 58% did not lose efficacy at 12 and 24 months, respectively (Table 5). When considering patients still under treatment after dose optimization, they were 90% and 84% at 12 and 24 months, respectively (Table 4). Next, we evaluated possible differences among groups; no significant difference in term of loss of response and persistency was found among patients naïve to or pre-exposed to anti-TNFα therapy (Figs. 1 and 2).

The great strength of this study is that besides the clinical evaluation, we have information at baseline, 6 months, and 12 months regarding inflammatory biomarkers and endoscopic activity. In Table 4, these data are depicted as total cohort of CD and UC and split in subgroups. In the overall cohort and all subgroups, there was a significant improvement both in CD and UC patients in the clinical score at 6 and 12 months (HBI and Mayo, $P < 0.0001$) and the endoscopic score at 12 months (Mayo, SES-CD, $P < 0.0001$) (Rutgeerts, $P = 0.01$). In addition, CRP was significantly improved at 6 and 12 months in both

UC patients ($P < 0.0001$) and CD patients (6 months $P = 0.04$, 12 months $P < 0.01$). Similarly, calprotectin was significantly improved at 6 and 12 months in UC ($P = 0.01$, $P < 0.0001$) and CD patients ($P = 0.006$, $P = 0.001$), respectively.

It is still debated whether switching between biosimilar and originator biologic is still appropriate in a patient who is doing well not because of medical reason but to save money. The NOR-SWITCH study is the only controlled trial available to look at this issue, but several methodological issues have been raised.[52] The study did not include information such as mucosal healing, had a duration of 52 weeks, and looked at different endpoints with different disease states with an arbitrary cutoff of a clinical insignificance difference of 15%. Because of the noninferiority design, a very large sample size would have been needed to discern meaningful differences, while only fewer than 250 IBD patients were enrolled, and only a single switch from the originator to the biosimilar was evaluated. Another study, sponsored by Celltrion, has been designed to assess noninferiority in efficacy and to assess overall safety of CT-P13 compared with infliximab in patients with active Crohn's disease up to week 54 [ClinicalTrials.gov Identifier: NCT02096861]. This study will also provide information about switching from infliximab to CT-P13 and from CT-P13 back to infliximab; the enrollment is closed with 220 patients included, but no data are available yet.

In our study, which reports thus far the largest number of IBD patients (n = 155) switched from infliximab to biosimilar, including the NOR-SWITCH trial, data are reassuring. Not only was the rate of SAEs numerical lower than naïve and pre-exposed patients despite a significantly longer follow-up but loss of response was also significantly lower ($P = 0.004$) with a trend toward and higher persistency of treatment ($P = 0.09$). This is probably explained also by selection bias, since patients were already responders and "tolerant" to infliximab therapy, with a significant higher use of combo therapy compared with naive. Interestingly, we demonstrated in this subgroup of patients that at 12 months, there was a significant further improvement of total Mayo score and endoscopic Mayo score in UC patients and HBI, SED CD and Rutgeert's scores in CD patients, respectively, despite the fact that patients were mostly under remission at the time of switching. C reactive protein and calprotectin, although declining, did not reach a statistical difference. Similar data have been reported in other noncontrolled cohorts.[42, 44, 46, 49, 51]

Using the multivariate analysis, some predictive factors of loss of efficacy and SAEs were identified. Hazard ratios (HR) for loss of response were significantly increased in UC vs CD in patients of subgroups A and B vs C, while significantly decreased in patients without steroids at last follow-up. The HR for SAEs was significantly higher in group B vs C and lower in male (vs female) and patients without steroids at last follow-up. These findings once again underline the caution in patients previously exposed to anti-TNF and who are under steroids therapy.

Our study, which is the largest available so far to our knowledge, has some limitations: no data of trough levels of CT-P13 or antidrug antibodies are available due to economic constraints, except in a subgroup of patients published elsewhere,[53] the mean duration of follow-up is still limited at 1 year, and the estimation of remission and response is evaluated by different clinicians but corroborated by endoscopic and inflammatory biomarkers evaluation. More importantly, no direct comparison with infliximab was made. On the other hand, the strength of the study is that it reflects the daily practice in the large majority of Italian centers prescribing biologic therapy in IBD; it also collects a considerable number of patients with endoscopic and inflammatory biomarkers, even in pediatric age patients who switched from infliximab to CT-P13, and cumulatively reports a significant length of time to investigate SAEs. Finally, this study is investigator-driven, without any support from pharmaceutical companies.

CONCLUSIONS

In summary, this study demonstrated in the evaluated timeframe that the safety profile and effectiveness of CT-P13 biosimilar is in line with the existing literature of infliximab. No alarming signals of immunization have been detected in patients switched from infliximab. However, infusion reactions and drug discontinuation for infusion reactions were 2- and 3-fold more frequent in patients pre-exposed to infliximab, respectively. Importantly, this study is reassuring regarding patients after the switch; they had a comparable rate of SAEs and significantly less loss of response compared with naïve patients and previously exposed patients. Not less important is the estimated saving of about 4 million Euros for the National Health Service in about 1 year of biosimilar utilization.

The biosimilar infliximab CT-P13 is available almost all over the world. Given this growth in the use of biosimilar, it is important to fully understand the efficacy and safety in clinical use in the long term. More importantly, because multiple biosimilars of the same originator are already available and more are to come,[54–57] it is possible that patients will undertake multiple switches and still not know the consequences of such an environment for patient safety. Clinical trials, registries, and long-term pharmacovigilance studies will provide more evidence to inform clinical decision-making and close the gaps in knowledge.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

ACKNOWLEDGMENT

The authors thank Dr. Andrew Jamieson MB, ChB(Hons), BSc(Hons), PhD MRCP(UK), FRCPGlasg, AFHEA, for the careful language review.

REFERENCES

1. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. *Nat Rev Gastroenterol Hepatol*. 2015;12:537–545.

2. Annese V, Duricova D, Gower-Rousseau C, et al. Impact of new treatments on hospitalisation, surgery, infection, and mortality in IBD: a focus paper by the epidemiology committee of ECCO. *J Crohns Colitis*. 2016;10:216–225.
3. van der Valk ME, Mangen MJ, Leenders M, et al.; COIN study group and the Dutch Initiative on Crohn and Colitis. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-tnfα therapy: results from the COIN study. *Gut*. 2014;63:72–79.
4. Cohen RD, Thomas T. Economics of the use of biologics in the treatment of inflammatory bowel disease. *Gastroenterol Clin North Am*. 2006;35:867–882.
5. Zheng MK, Shih DQ, Chen GC. Insights on the use of biosimilars in the treatment of inflammatory bowel disease. *World J Gastroenterol*. 2017;23:1932–1943.
6. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicenter, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis*. 2013;72:1605–1612.
7. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis*. 2013;72:1613–1620.
8. Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. *Ann Rheum Dis*. 2017;76:346–354. pii: annrheumdis-2015-208783.
9. Yoo DH, Racewicz A, Brzezicki J, et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. *Arthritis Res Ther*. 2016;18:82.
10. Yoo D, Yagensky A, Toncheva A, et al. Impact of CT-P13 and originator infliximab treatment on quality of life derived from the Health Assessment Questionnaire (AQ) and Short-Form 36 (SF- 36) from a randomized, double-blind trial in patients with active RA [abstract no. 2392]. In: ACR/ARHP Annual Meeting, San Diego; October 26–30 2013.
11. Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. *Ann Rheum Dis*. 2017;76:346–354.
12. Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. *Ann Rheum Dis*. 2017;76:355–363.
13. McKeage K. A review of CT-P13: an infliximab biosimilar. *Biodrugs*. 2014;28:313–321.
14. European Medicines Agency. Committee for medicinal products for human use (CHMP). Assessment report: Remsima (infliximab). 2013. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/WC500151486.pdf (June 1, 2018, date last accessed).
15. Generics and biosimilars initiative online. Biosimilars approved in South Korea. 2015. http://gabionline.net/Biosimilars/General/Biosimilars-approved-in-South-Korea (June 1, 2018, date last accessed).
16. Generics and biosimilars initiative online. Biosimilars approved in Japan. 2015. http://gabionline.net/Biosimilars/General/Biosimilars-approved-in-Japan
17. www.fda.gov/downloads/.../UCM484859.pdf (June 1, 2018, date last accessed).
18. Health Canada. Summary basis of decision – Inflectra. 2016. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/rds-sdr/drug-med/rds-sdr-infectra-184564-eng.php (June 1, 2018, date last accessed).
19. Jha A, Upton A, Dunlop WC, et al. The budget impact of biosimilar infliximab (remsima®) for the treatment of autoimmune diseases in five European countries. *Adv Ther*. 2015;32:742–756.
20. Danese S, Fiorino G, Michetti P. Viewpoint: Knowledge and viewpoints on biosimilar monoclonal antibodies among members of the European Crohn's and colitis organization. *J Crohns Colitis*. 2014;8:1548–1550.
21. Feagan BG, Choquette D, Ghosh S, et al. The challenge of indication extrapolation for infliximab biosimilars. *Biologicals*. 2014;42:177–183.
22. Ben-Horin S, Heap GA, Ahmad T, et al. The immunogenicity of biosimilar infliximab: can we extrapolate the data across indications? *Expert Rev Gastroenterol Hepatol*. 2015;9(Suppl 1):27–34.
23. Van den Brande JM, Koehler TC, Zelinkova Z, et al. Prediction of antitumour necrosis factor clinical efficacy by real-time visualisation of apoptosis in patients with Crohn's disease. *Gut*. 2007;56:509–517.
24. Tilg H, Moschen A, Kaser A. Mode of function of biological anti-TNF agents in the treatment of inflammatory bowel diseases. *Expert Opin Biol Ther*. 2007;7:1051–1059.
25. Komaki Y, Yamada A, Komaki F, et al. Systematic review with meta-analysis: the efficacy and safety of CT-P13, a biosimilar of anti-tumour necrosis factor-α agent (infliximab), in inflammatory bowel diseases. *Aliment Pharmacol Ther*. 2017;45:1043–1057.
26. Jørgensen KK, Olsen IC, Goll GL, et al.; NOR-SWITCH study group. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet*. 2017;389:2304–2316.
27. Fiorino G, Manetti N, Armuzzi A, et al.; PROSIT-BIO Cohort. The PROSIT-BIO cohort: a prospective observational study of patients with inflammatory bowel disease treated with infliximab biosimilar. *Inflamm Bowel Dis*. 2017;23:233–243.
28. Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl*. 1989;170:2–6; discussion 16.
29. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *J Crohns Colitis*. 2012;6:965–990.
30. Van Assche G, Dignass A, Panes J, et al.; European Crohn's and Colitis Organisation (ECCO). The second European evidence-based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *J Crohns Colitis*. 2010;4:7–27.
31. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353:2462–2476.
32. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet*. 1980;1:514.
33. D'Haens GR, Panaccione R, Higgins PD, et al. The London position statement of the world congress of gastroenterology on biological therapy for IBD with the European Crohn's and colitis organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol*. 2011;106:199–212; quiz 213.
34. Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther*. 2011;33:987–995.
35. Ding NS, Hart A, De Cruz P. Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease - algorithm for practical management. *Aliment Pharmacol Ther*. 2016;43:30–51.
36. Lichtenstein GR. Introduction to biosimilar use in patients with inflammatory bowel disease. *Gastroenterol Hepatol (N Y)*. 2017;13:612–614.
37. 2017 IMS Biosimilar report - The Impact of Biosimilar Competition in Europe. http://ec.europa.eu/growth/content/impact-biosimilar-competition-price-volume-and-market-share-update-2017-0_en (February 27, 2007, date last accessed).
38. 2017 IMS Biosimilar report - The Impact of Biosimilar Competition in Europe. (June 1, 2018, date last accessed).
39. Choe JY, Prodanovic N, Niebrzydowski J, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis*. 2017;76:58–64.
40. Jani RH, Gupta R, Bhatia G, et al. A prospective, randomized, double-blind, multicenter, parallel-group, active controlled study to compare efficacy and safety of biosimilar adalimumab (exemptia; ZRC-3197) and adalimumab (humira) in patients with rheumatoid arthritis. *Int J Rheum Dis*. 2016;19:1157–1168.
41. Gecse KB, Lovász BD, Farkas K, et al. Efficacy and safety of the biosimilar infliximab CT-P13 treatment in inflammatory bowel diseases: a prospective, multicenter, nationwide cohort. *J Crohns Colitis*. 2016;10:133–140.
42. Schmitz EMH, Boekema PJ, Straathof JWA, et al. Switching from infliximab innovator to biosimilar in patients with inflammatory bowel disease: a 12-month multicenter observational prospective cohort study. *Aliment Pharmacol Ther*. 2018;47:356–363.
43. Richmond L, Curtis L, Garrick V, et al. Biosimilar infliximab use in pediatric IBD. *Arch Dis Child*. 2018;103:89–91.
44. Eberl A, Huoponen S, Pahikkala T, et al. Switching maintenance infliximab therapy to biosimilar infliximab in inflammatory bowel disease patients. *Scand J Gastroenterol*. 2017;52:1348–1353.
45. Farkas K, Rutka M, Ferenci T, et al. Infliximab biosimilar CT-P13 therapy is effective and safe in maintaining remission in Crohn's disease and ulcerative colitis - experiences from a single center. *Expert Opin Biol Ther*. 2017;17:1325–1332.
46. Smits LJT, Grelack A, Derikx LAAP, et al. Long-term clinical outcomes after switching from remicade® to biosimilar CT-P13 in inflammatory bowel disease. *Dig Dis Sci*. 2017;62:3117–3122.
47. Bálint A, Rutka M, Végh Z, et al. Frequency and characteristics of infusion reactions during biosimilar infliximab treatment in inflammatory bowel diseases: results from central European nationwide cohort. *Expert Opin Drug Saf*. 2017;16:885–890.
48. Argüelles-Arias F, Guerra Veloz MF, Perea Amarillo R, et al. Effectiveness and safety of CT-P13 (biosimilar infliximab) in patients with inflammatory bowel disease in real life at 6 months. *Dig Dis Sci*. 2017;62:1305–1312.
49. Razanskaite V, Bettey M, Downey L, et al. Biosimilar infliximab in inflammatory bowel disease: outcomes of a managed switching programme. *J Crohns Colitis*. 2017;11:690–696.
50. Kolar M, Duricova D, Bortlik M, et al. Infliximab biosimilar (remsima™) in therapy of inflammatory bowel diseases patients: experience from one tertiary inflammatory bowel diseases center. *Dig Dis*. 2017;35:91–100.
51. Buer LC, Moum BA, Cvancarova M, et al. Switching from remicade® to remsima® is well tolerated and feasible: a prospective, open-label study. *J Crohns Colitis*. 2017;11:297–304.
52. Feagan B. Benefits, concerns, and future directions of biosimilars in inflammatory bowel disease. *Gastroenterol Hepatol*. 2017;13:745–747.

53. Fiorino G, Correale C, Radice S, et al. Letter: immunogenicity of infliximab originator vs. CT-P13 in IBD patients. *Aliment Pharmacol Ther*. 2017;46:903–905.
54. BIOGEN. FLIXABI®, Biogen's Infliximab Biosimilar Referencing Remicade®, approved in the European Union 2016. URL:http//media.biogen.com/press-release/biosimilars/flixabi-biogens-infliximab-biosimilar-referencing-remicade-approved-europe (June 1, 2018, date last accessed).
55. Choe JY, Prodanovic N, Niebrzydowski J, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis*. 2017;76:58–64.
56. A study of PF-06438179 (Infliximab-Pfizer) and Infliximab in combination with methotrexate in subjects with active Rheumatoid Arthritis (REFLECTIONS B537-02). ClinicalTrials.gov2016. https://clinicaltrials.gov/ct2/show/NCT02222493
57. Rajan C. Epirus' Biosimilar Arthritis Drug wins approval in India. Bioprocess Online 2014. hhtp://www.bioprocessonline.com/doc/epirus-s-biosimilar-arthritis-drug-wins-approval-in-india-0001 (June 1, 2018, date last accessed).