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Effectiveness and Safety of the Switch from Remicade® to CT-P13 in Patients with Inflammatory Bowel Disease

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Abstract

Background and Aims: To evaluate the clinical outcomes in patients with IBD after switching from Remicade® to CT-P13 in comparison with patients who maintain Remicade®.

Methods: Patients under Remicade® who were in clinical remission with standard dosage at study entry were included. The 'switch cohort' [SC] comprised patients who made the switch from Remicade® to CT-P13, and the 'non-switch' cohort [NC] patients remained under Remicade®.

Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; SC, switch cohort; NC, non-switch cohort; PMS, Partial Mayo Score; HBI, Harvey–Bradshaw index; CI, confidence interval; SD, standard deviation; IQR, interquartile range; HR, hazard ratio.

Results: A total of 476 patients were included: 199 [42%] in the SC and 277 [58%] in the NC. The median follow-up was 18 months in the SC and 23 months in the NC [$p < 0.01$]. Twenty-four out of 277 patients relapsed in the NC; the incidence of relapse was 5% per patient-year. The cumulative incidence of relapse was 2% at 6 months and 10% at 24 months in this group. Thirty-eight out of 199 patients relapsed in the SC; the incidence rate of relapse was 14% per patient-year. The cumulative incidence of relapse was 5% at 6 months and 28% at 24 months. In the multivariate analysis, the switch to CT-P13 was associated with a higher risk of relapse (HR = 3.5, 95% confidence interval [CI] = 2–6). Thirteen percent of patients had adverse events in the NC, compared with 6% in the SC [$p < 0.05$].

Conclusions: Switching from Remicade® to CT-P13 might be associated with a higher risk of clinical relapse, although this fact was not supported in our study by an increase in objective markers of inflammation. The nocebo effect might have influenced this result. Switching from Remicade® to CT-P13 was safe.

Key Words: Inflammatory bowel disease; Crohn's disease; ulcerative colitis; switch; Remicade®; sup > CT-P13

1. Introduction

Inflammatory bowel disease [IBD] is a chronic disorder of complex etiology, only partially understood, that involves a pathological response of both the innate and acquired immune system, resulting in chronic inflammation of the gastrointestinal tract. Inflammatory bowel disease is the result of the interaction of different factors, including genetic susceptibility, environmental factors, infectious agents, commensal enteric flora, and immunological alterations.

The era of biologic therapy in the treatment of IBD began in 1998 when the Food and Drug Administration approved infliximab, the first drug directed against tumor necrosis factor-alpha, for the treatment of patients with Crohn's disease [CD]. Anti-TNF drugs have represented a milestone in the treatment of patients with IBD in recent years, decreasing the need for surgery and hospital admissions, and more importantly improving the quality of life. They also have a good safety profile.[1]

Recently, due to the expiration of the original infliximab patent [Remicade®], several biosimilar drugs have been developed with the fundamental objectives of reducing health-care expenditure on costly biologic treatments and improving the access of patients to these drugs. In 2013, the European Medicines Agency approved the infliximab biosimilars Inflectra® and Remsima®, both CT-P13. In the approval process, similarity was demonstrated in preclinical tests, followed by clinical studies in patients with rheumatoid arthritis [PLANETRA] and ankylosing spondylitis [PLANETAS], which showed that CT-P13 was comparable with Remicade® in terms of efficacy, safety, pharmacokinetics, and immunogenicity.[2, 3] Based on these results, the approval was extended to include all the indications approved for the originator, including IBD. After much controversy about the efficacy of CT-P13 in IBD, the major drivers for its use are cost saving for the health system and patient access; thus, the use of CT-P13 in patients starting infliximab treatment has become widely accepted.

Despite the initial reluctance, the use of biosimilars is growing; therefore, it is mandatory to fully understand the outcomes in patients treated with biosimilar agents, not only in naïve patients, but also after switching from the originator. However, data about the effectiveness and safety of the switch from Remicade® to CT-P13, particularly in IBD patients, is limited. In this respect, only one randomized clinical trial has evaluated the outcomes after switching from Remicade® to CT-P13 [NOR-SWITCH trial]; this study has several methodological limitations, so its results must be interpreted with caution, especially for IBD.[4]

In clinical practice, few studies have evaluated the switch from Remicade® to CT-P13 in IBD patients, all of them with several limitations: most of them were retrospective, with few patients included, short-term follow-up, and lack of a control group.[5–11] Therefore, the aim of our study was to evaluate in IBD patients the outcomes, both in the short- and long-term, after switching from Remicade® to CT-P13, compared with patients who remain on the original drug. This study will provide post-marketing information useful for understanding IBD patients' outcomes after switching, which will help decision-making in clinical practice, and better management of the arrival in the near future of new biosimilars to the therapeutic armamentarium for IBD.

2. Methods

2.1. Study design

This was a retrospective, cohort, multicentre study in which patients with IBD in stable treatment with infliximab at standard doses were included. The switch cohort [SC] comprised the patients who switched treatment, while the non-switch cohort [NC] comprised the patients who remained on the original drug. The main outcome was the proportion of patients with clinical relapse throughout the follow-up. Demographic data, characteristics of IBD, pharmacological treatments, and surgeries due to IBD were collected from the diagnosis records. Whenever available, results from radiological and endoscopic examination at the end of follow-up were included. The protocol was approved by Ethics Committee of the Clinical Research of Hospital Universitario de La Princesa.

2.2. Study population

The study included patients older than 18 years diagnosed with IBD, in clinical remission at the time of the start of follow-up—defined as a Partial Mayo Score [PMS] of ≤2 in ulcerative colitis [UC],[12] and a score of ≤4 in the Harvey–Bradshaw index [HBI] in CD[13]—and treated with infliximab as the first biologic agent, in the first attempt of treatment with this drug and receiving the drug at standard dosage. The study excluded patients treated with infliximab for an indication other than IBD, those who started the treatment with infliximab while being in remission [e.g. as

prophylaxis of postoperative recurrence] and those who had received treatment with infliximab with a dosage lower or higher than the standard.

Patients of the SC came from centres that made the switch as a generalized practice for all of their patients, to avoid the selection bias that might be caused by choosing to make the switch in those patients who theoretically were more stable and had less risk of relapse. After the approval of the biosimilar infliximab by the Spanish Agency of Medicines and Health Products, CT-P13 was the only infliximab available in the Pharmacy of those hospitals. In addition, patients were informed about the switch but they were not asked about their preferences. Patients from the NC came from centres that did not switch from Remicade® to CT-P13 for any patient.

2.3. Data collection

Study data were collected and managed using an electronic data capture tool [Research Electronic Data Capture[14]], which is hosted at Asociación Española de Gastroenterología [AEG; www.aegastro.es],[14] a non-profit scientific and medical society focusing on gastroenterology. AEG provided this service free of charge, with the sole aim of promoting independent investigator-driven research. REDCap is a secure, web-based application designed to support data capture for research studies that provides the following: [i] an intuitive interface for validated data entry; [ii] audit trails for tracking data manipulation and export procedures; [iii] automated export procedures for seamless data downloads to common statistical packages; and [iv] procedures for importing data from external sources. This system allows remote monitoring, which was carried out by the leading group.

2.4. Study follow-up

In the case of the SC, the follow-up started for each patient on the date of switching and ended on the date of relapse, the date of CT-P13 interruption, or the date of the last visit [whichever occurred first]. In the NC, the follow-up started in March 2015 [the date when the switch was initiated as a generalized practice in the centres that carried out the switch strategy] and ended the date of Remicade® interruption, the date of relapse, or the date of the last visit [whichever occurred first]. All patients who met the inclusion criteria in each participating centre were included in this study to avoid selection bias.

2.5. Definitions

2.5.1. Clinical activity

Clinical relapse was defined as an HBI of >4 points in patients with CD. In UC, clinical recurrence was defined as a PMS of >2 points.

Endoscopic/radiologic activity: Information about endoscopic or radiologic activity was provided only in cases in which those explorations were performed. In CD, endoscopic activity was rated based on the endoscopist's criteria [mild, moderate, or severe activity]. Rutgeerts score was used to rate endoscopic activity in CD patients in postoperative setting. In UC, endoscopic severity was rated based on the endoscopic subscore of the Mayo index. Only complete colonoscopies with ileoscopy were considered in CD patients with ileal involvement. Radiologic activity assessment was based on radiologists' criteria focused on the increase in bowel wall thickness and enhancement with intravenous gadolinium, with or without accompanying perienteric changes.

2.6. Statistical analysis

For categorical variables, percentages were calculated (with their 95% confidence intervals [CIs]). The descriptive analysis of quantitative variables calculated the mean and standard deviation [SD], or the median and interquartile range [IQR], depending on whether they were normally distributed or not. In the univariate analysis, categorical variables were compared using the Chi-square [χ^2] test, and quantitative variables using the appropriate test. Bonferroni correction was applied in case of multiple comparisons; for example, when comparing C-reactive protein [CRP] concentration between cohorts and in patients with and without relapse within each cohort; statistical significance was considered present when p was <0.008 [six comparisons].

The Kaplan–Meier method, when patients who relapsed were censored, was used to evaluate the cumulative incidence of relapse, and any differences between survival curves were evaluated with the log-rank test. Stepwise multivariate analysis using the Cox model was used to investigate factors potentially associated with patient relapse. In the log-rank test and in the multivariate analysis, statistical significance was considered present when p was <0.05.

3. Results

A total of 476 patients were included: 42% in the SC and 58% in the NC. The median follow-up was 18 months (Interquartile range [IQR] = 10–22 months) in the SC and 23 months [IQR = 19–25 months] in the NC [$p < 0.01$]. The median time of treatment with Remicade® before starting the follow-up was similar in both cohorts [45 months in the SC and 37 in the NC]. The characteristics of both cohorts are summarized in Table 1. Female gender and the proportion of patients with perianal CD were significantly higher in the SC, while the proportion of patients with previous surgery due to IBD was higher in the NC. With respect to the indication of infliximab treatment, the proportion of patients that received infliximab due to top-down strategy was significantly higher in the NC, whereas the proportion of patients that received infliximab due to steroid dependency was significantly higher in the SC. The distribution of other characteristics did not differ between both cohorts.

3.1. Effectiveness

Of the 199 patients in the SC, 38 relapsed after a median follow-up of 18 months [IQR = 10–22 months]. In the NC, 24 out of 277 patients relapsed after a median follow-up of 23 months [IQR = 19–25]. The incidence rate of relapse was significantly higher in patients in the SC [14% per patient-year, 95% CI = 10–18.9%] than in patients in the NC [5% per patient-year, 95% CI = 2.9–7.1%] [$p < 0.05$]. The cumulative incidence of relapse was 5% at 6 months, 14% at 12 months, and 28% at 24 months in the SC, and 2% at 6 months, 4% at 12 months, and 10% at 24 months in the NC [$p < 0.05$] [Figure 1].

In the univariate analysis, infliximab treatment due to steroid dependency and switch from Remicade® to CT-P13 [vs maintained on Remicade® treatment] were significantly associated with higher risk of relapse. In the multivariate analysis, switch from Remicade® to CT-P13 [vs maintained on Remicade® treatment], adjusted by the time on infliximab treatment before starting the follow-up, was the only factor significantly associated with higher risk of relapse [hazard ratio = 3.5, 95% CI = 2–6]. Other factors such as type of IBD, concomitant treatment with immunosuppressant,

Table 1. Characteristics of the study population.

	Switch cohort [*N* = 199]	Non-switch cohort [*N* = 277]	*p*
Age [years] [median, IQR]	42 [31–53]	43 [31–52]	N.S.
Time of IBD evolution before starting infliximab [months] [median, IQR]	45 [13–187]	48 [12–139]	N.S
Time under infliximab treatment at the beginning of follow-up [months] [median, IQR]	45 [17–81]	37 [17–58]	N.S.
Time of follow-up [months] [median, IQR]	18 [10–22]	23 [19–25]	<0.01
Female gender, *n* [%]	107 [54]	111 [40]	<0.01
Crohn's disease, *n* [%]	142 [71]	211 [76]	N.S.
Ileal, *n* [%]	44 [31]	84 [40]	N.S.
Colonic, *n* [%]	44 [31]	42 [20]	
Ileocolonic, *n* [%]	54 [38]	85 [40]	
Upper GI tract, *n* [%]	11 [5.5]	15 [5.4]	
Inflammatory phenotype, *n* [%]	84 [59]	115 [54]	N.S.
Stricturing phenotype, *n* [%]	22 [16]	31 [15]	
Fistulizing phenotype, *n* [%]	36 [25]	65 [31]	
Perianal, *n* [%]	76 [38]	81 [29]	<0.05
Ulcerative colitis, *n* [%]	57 [29]	66 [24]	N.S.
Pancolitis, *n* [%]	32 [56]	38 [58]	N.S.
Left-sided colitis, *n* [%]	19 [33]	25 [38]	
Extraintestinal manifestations, *n* [%]	51 [25.6]	64 [23]	N.S.
Surgery, *n* [%]	51 [25.6]	96 [34.7]	<0.05
Indication for infliximab treatment			
Refractoriness to immunomodulators, *n* [%]	101 [51]	130 [47]	N.S.
Intolerance to immunomodulators, *n* [%]	30 [15]	32 [11.6]	N.S.
Top-down strategy, *n* [%]	2 [1]	17 [6]	<0.01
Steroid-dependency, *n* [%]	57 [28.6]	44 [16]	<0.01
Steroid-refractoriness, *n* [%]	18 [9]	27 [10]	N.S.
Fistulizing disease, *n* [%]	33 [16.6]	45 [16]	N.S.
Perianal disease, *n* [%]	31 [15.6]	33 [12]	N.S.
Concommitant treatments			
Mesalazine, *n* [%]	46 [23]	55 [20]	N.S.
Azathioprine, *n* [%]	90 [45]	112 [40.4]	N.S.
Mercaptopurine, *n* [%]	3 [1.5]	7 [2.5]	N.S.
Methotrexate, *n* [%]	13 [6.5]	12 [4.3]	N.S.

Non-statistically significant, N.S.; interquartile range, IQR.

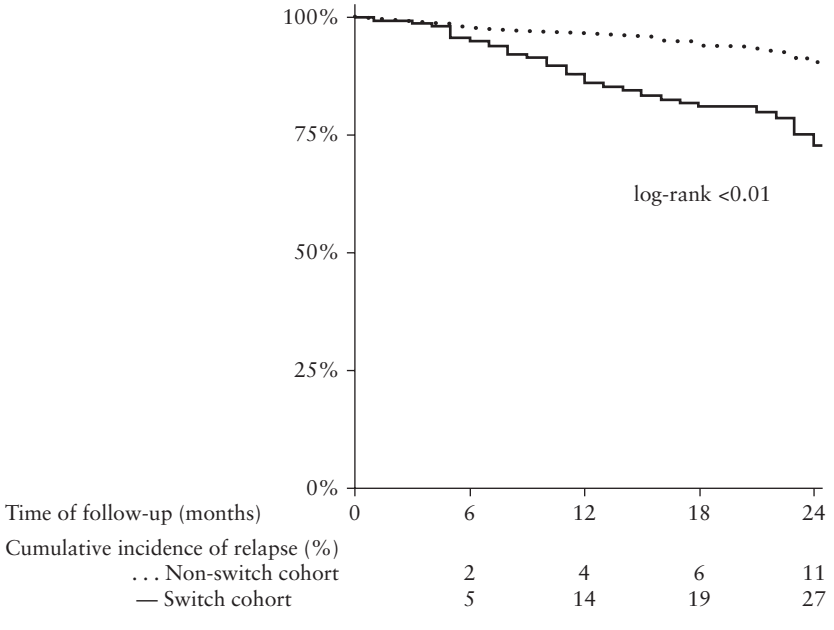

Figure 1. Cumulative incidence of relapse in patients maintained on Remicade® and in patients switched to CT-PT13.

extraintestinal manifestations, and previous surgery were not associated with risk of relapse [Table 2].

Median CRP concentration was similar at baseline and at the end of follow-up both in the SC and the NC [0.14 mg/dL vs 0.2 mg/dL, $p > 0.05$, and 0.19 mg/dL vs 0.2 mg/dL, $p > 0.05$, respectively]. The median CRP concentration was also similar at baseline and at the end of follow-up within the SC [0.14 mg/dL vs 0.19 mg/dL, $p > 0.05$] and within the NC [0.2 mg/dL vs 0.2 mg/dL, $p > 0.05$]. Moreover, this parameter did not change between baseline and the end of follow-up in patients who maintained remission within the SC [0.2 mg/dL vs 0.19 mg/dL, $p > 0.05$].] or within the NC [0.2 mg/dL vs 0.17 mg/dL, $p > 0.05$]. However, the median CRP concentration was significantly higher at the end of follow-up than it was at baseline in patients who relapsed, both in the SC [0.6 mg/dL vs 0.12 mg/dL, $p < 0.001$] and in the NC [0.8 mg/dL vs 0.2 mg/dL, $p < 0.001$].

A total of 152 patients [32%] had endoscopic/radiologic assessment at the end of follow-up. In the SC, 67 [33%] had endoscopic/radiologic assessment: 9 of them had clinical relapse, and 7 of these 9 patients had active inflammation in the endoscopic/radiologic examination. In the NC, 85 patients [30%] had endoscopic/radiologic assessment: 11 of them had clinical relapse; endoscopic/radiologic activity was present in 7 out of these 11 patients with clinical relapse.

3.2. Safety

A total of 48 patients developed 61 adverse events during follow-up. The proportion of patients that developed adverse events was 13% in the NS and 6% in the SC [$p < 0.05$]. Main adverse events are summarized in Table 3.

3.3. Reasons for treatment cessation

From 277 patients in the non-switch cohort, 24 [8.7%] relapsed and 209 [75.5] were receiving Remicade® at the last visit. In addition, 24 patients [8.7%] stopped the treatment with Remicade® before the last visit, 18 [6.5%] changed the biologic treatment for a reason different from IBD, and 2 [0.7%] were switched to CT-P13.

On the other hand, from 199 patients in the SC, 38 patients [19%] relapsed after switching to CT-P13, and 115 [57.8%] maintained the treatment with CT-P13 at the last visit. In addition, 43 [21.6%] stopped the treatment with CT-P13 before last visit, and 3 [1.5%] had to change the biologic treatment for a reason different from IBD.

4. Discussion

To the best of our knowledge, this is the largest study with the longest follow-up that has evaluated the outcomes of IBD patients in remission switched from Remicade® to CT-P13 in clinical practice, comparing them with a control group of patients who were maintained on Remicade®. We observed that the cumulative incidence of clinical relapse was significantly higher in patients switched to CT-P13 than in those who maintained Remicade® [14% per patient-year vs 5% per patient-year, respectively].

As a secondary end point, we analysed the changes in the CRP concentration, as an objective marker of disease activity. The median CRP concentration at baseline was similar in the SC and the NC, and, overall, it did not change between baseline and the end of follow-up in any of these groups. Therefore, differences in clinical relapse were not supported by differences in biomarkers of inflammation.

Up till now, few studies have evaluated the evolution of IBD patients switched from Remicade® to CT-P13. In a recent review published by our group, disease control [absence of disease worsening after switching] was confirmed in 88% of patients after the switch.[15] Another systematic review evaluated the efficacy of biosimilars after switching from Remicade® to CT-P13, finding that pooled rates of sustained clinical remission among CD and UC patients at 16 and 51 weeks after switching were 74% and 92% in CD, and 62% and 83% in UC.[16] All these figures are similar to the cumulative incidences of relapse reported in our study, in which 14% of patients per year relapsed after switching. In addition, this incidence rate is similar to that observed in IBD patients under Remicade® [~13% per patient-year].[17, 18]

The NOR-SWITCH trial is the only randomized controlled trial that has examined non-medical switching of CT-P13 across indications.[4] Across all diagnoses, the proportion of patients with disease worsening after 52 weeks was 26.2% for the Remicade® arm and 29.6% for the CT-P13 arm. In UC, disease worsening was reported in 9.1% of patients with Remicade® and in 11.9% with CT-P13. However, there was a trend towards higher risk of disease worsening in CD patients switched to CT-P13: 21.2% of patients treated with Remicade® and 36.5% of patients treated with CT-P13 [difference –14.3%, with a non-inferiority margin set to 15%]. Although authors concluded that it is effective and safe to switch biologic therapy, the NOR-SWITCH trial has some limitations that might impact the interpretation of the results.

Although our results suggest that switching from Remicade® to CT-P13 in IBD patients might have a negative impact on patients' clinical outcomes, the difference between the cohorts [SC and NC] is not necessarily attributable to CT-P13 itself, but could also represent a 'nocebo effect'. The nocebo effect is also called the 'evil brother of the placebo effect' and has become a subject of growing interest. Nocebo response usually refers to new and worsening symptoms that are caused only by negative expectations of the patient or negative verbal and non-verbal communications from the treating person. Thus, nocebo effects can modulate the outcome of a given therapy in a negative way, much as placebo effects do in a positive way.

Boone et al. have described infliximab biosimilar implementation in IBD and rheumatology practice, particularly focusing on the nocebo response by quantifying patients' acceptance.[19] In this study, an overall nocebo response of 13% was found among the patients

Table 2 Multivariate analysis of factors associated with the risk of relapse during follow-up.

	Hazard ratio	95% confidence interval
Switch cohort [vs non-switch cohort]	3.5	2–6
Time under infliximab treatment at the beginning of follow-up [months]	0.99	0.98–1.01

Table 3. Adverse events during follow-up.

	Switch cohort	Non-switch cohort	*p*
Infections, *n* [%]	1 [0.5]	18 [6.5]	<0.05
Infusional reactions, *n* [%]	0	6 [2.2]	<0.05
Lupus, *n* [%]	0	2 [0.7]	>0.05
Skin lesions, *n* [%]	3 [1.5]	11 [4]	>0.05
Others, *n* [%]	8 [0.4]	2 [0.7]	<0.05

during a minimal observation period of 6 months after the switch to CT-P13, which is higher than the difference in the incidence rate of relapse that we found between the SC and the NC [11%]. Authors observed that patient empowerment and registration of treatment outcomes could reduce nocebo response rates.

Two recent surveys investigating patients' and physicians' perspectives on biosimilar drugs showed that the majority of respondents had concerns about the safety and efficacy of biosimilar agents.[23] Given the uncertainties regarding the efficacy and safety of CT-P13 in IBD patients, and the beliefs of both clinicians and patients, the introduction of CT-P13 must be done in a carefully controlled environment. In this respect, Razanskaite et al. published the outcomes of a service evaluation of switching IBD patients under Remicade® to CT-P13, using a managed switching program funded via a gain share agreement in the UK.[7] The early results of the program did not reveal significant differences in patients' outcomes after switching. The authors highlighted that, by ensuring the incentivization of all the stakeholders, including patients, the agreement is important for the success of a switching program.

With respect to the safety of the switch, in our study the proportion of patients with adverse events was significantly higher in the NC than in the SC. The proportion of patients with adverse events was within the expected limits in both groups. However, due to the retrospective design of the study, the registration of adverse events largely depends on the awareness of the clinician, and therefore mild adverse events might be underreported. Based on our results, we can conclude that switching from the originator to CT-P13 is a safe strategy; the higher proportion of patients with adverse events in the NC might be irrelevant from the clinical point of view.

Limitations of our study include the fact that the switch was unblinded. The double-blind set-up of the NOR-SWITCH trial excludes possible bias caused by the nocebo effect; however, blinded transition to a biosimilar drug is not allowed in daily practice. In fact, the effects of open-label transitioning to CT-P13 are of great interest because they reflect what happens in real life. In this respect, although patients of the SC came from centres that made the switch as a generalized practice for all their patients, and patients from the NC came from centres that did not switch from Remicade® to CT-P13 in any patient, differences in practices in different centres could not be ruled out as a potential cause of bias.

In addition, the main outcome of our study was clinical relapse, which was based on HBI and PMS. These scores include subjective symptoms, which can be easily modulated by patients' and clinicians' beliefs and expectations. However, CRP concentration, which is an objective marker of inflammation, showed no differences between the SC and NC; therefore, differences in clinical relapse rate were not associated with differences in objective biomarkers of inflammation, suggesting that the nocebo effect phenomena might be causing the onset of clinical symptoms within the SC.

One-third of the patients had endoscopic/radiologic assessment at the end of follow-up. Most of the patients with endoscopic/radiologic evaluation and clinical relapse had active inflammation; however, a selection bias towards performing complementary examinations in the most severe patients cannot be ruled out. In addition, due to the characteristics of the Mayo endoscopic score, it is possible to calculate it retrospectively, with the information that is commonly included in the endoscopic report; in fact, the Mayo endoscopic score is routinely used in many endoscopic units to rate the activity in UC patients. On the contrary, it is not possible to calculate the SES-CD score retrospectively based on the description of the findings in the endoscopic report. Finally, data of trough levels of Remicade® or CT-P13 and antibodies against infliximab were not available in our study, and therefore we could not assess whether differences in the pharmacokinetics of the drugs existed. Nevertheless, no infusional reactions were reported in the SC [vs 6 in the NC], and previous studies have proven that there is no increased risk of immunogenicity in patients switched to CT-P13.[4, 10, 2]

Our study is the largest so far including patients switched from Remicade® to CT-P13 in clinical practice. More importantly, we were able to directly compare the outcomes for patients switched to CT-P13 with those of patients maintained on Remicade®. As this is an observational study, to avoid selection bias, only centres where the switch was performed for all their patients were included. Finally, our cohorts were very homogeneous. In this regard, infliximab was the first line of biologic treatment in those patients, all of them were in clinical remission with infliximab at the standard dose, and none of them had received an escalated dose.

In conclusion, switching from Remicade® to CT-P13 might be associated with a higher risk of clinical relapse in IBD patients [in comparison with those maintained on Remicade®], although this fact was not supported in our study by an increase in objective markers of inflammation. However, due to the study design, a nocebo effect cannot be ruled out as a factor influencing this difference. The introduction of biosimilar agents as a treatment option for IBD patients could achieve substantial cost saving for health-care systems. However, given the significant impact that nocebo effects can have on patients' quality of life and health services, it is important to develop interventions to minimize the appearance of these effects. With new biosimilar agents entering the market in the near future, specific programs based on gain share agreements should be developed to ensure that all stakeholders are convinced and motivated to accept the switch, with the consequent benefits to the patients and the health-care system.

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Conflict of Interest

MC has served as a speaker, or has received research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr. Falk Pharma, and Tillotts Pharma. JPG has served as a speaker, a consultant and advisory member for or has received research funding from MSD, Abbvie, Hospira, Pfizer, Kern Pharma, Biogen, Takeda, Janssen, Roche, Celgene, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, and Vifor Pharma. MBdA has served as a speaker, a consultant and advisory member for or has received research funding from MSD, Abbvie, Hospira, Pfizer, Kern Pharma, Biogen, Takeda, Janssen, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, and Vifor Pharma. MR has served as a speaker, a consultant and advisory member for Merck Sharp and Dohme, and Abbvie and Janssen. AM has served as a speaker, a consultant, advisory member or has received research funding from Abbvie, Allergan, Astra Zeneca, Lilly, Pfizer, Kern, Novartis, Biogen, Janssen, Roche, Merck, MSD, Menarini, Servier, Ipsen, and Shire y Sandoz. MI has served as a speaker and consultant for MSD and Takeda. EL has served as a speaker, or has received research or education funding from MSD, Abbvie, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr. Falk's, and Tillotts Pharma. FB has served as a speaker, a consultant and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Takeda, and Janssen. MM has served as a speaker, or has received

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Author Contributions

MC and JPG: study design, data collection, data analysis, data interpretation, and writing the manuscript. AG: Data collection and database monitoring. Remaining authors: study design, patient inclusion, and data collection. All authors approved the final version of the manuscript.

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