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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Observational Study

Real-world data on the infliximab biosimilar CT-P13 (Remsima®) in inflammatory bowel disease

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Abstract

BACKGROUND

In recent years, biological therapies have revolutionized the management of inflammatory bowel disease (IBD); however, they are expensive. The development of biosimilar products has allowed us to reduce healthcare costs and improve patients' access to these treatments. Although various studies support the similarity between infliximab and its biosimilar CT-P13 in terms of efficacy and safety, there are unmet needs regarding research on these agents in the context of IBD.

AIM

To analyze clinical response rates to CT-P13 and adverse events in IBD patients

Sandoz, Kern Pharma, and Takeda. Marta Maia Bosca-Watts declares educational activities, research projects, scientific meetings, and advisory boards sponsored by MSD, Ferring, AbbVie, Janssen, Biogen and Takeda. Marian Aguas has received speaker's honoraria from MSD and Pfizer. Nuria Maroto declares educational activities, research projects, scientific meetings, and advisory boards sponsored by MSD, AbbVie, Takeda, and Ferring. Jose María Paredes declares educational activities, research projects, scientific meetings, and advisory boards sponsored by Takeda, AbbVie, MSD, and Janssen. Xavier Cortés, Lidia Martí, and Cirilo Amorós declare that they have no conflicts of interest.

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treated in real-life practice.

METHODS

An observational, prospective, multicenter study of IBD patients treated with CT-P13 in clinical practice who were naïve to biological treatments or failed to respond to other anti-tumor necrosis factor drugs or had switched from infliximab originator was carried out. No diagnostic or follow-up interventions were conducted on patients outside usual clinical practice. The primary endpoints were clinical response rates and number of adverse events. The primary efficacy variable was the proportion of patients who were in clinical remission and/or had a clinical response at 3, 6, 9, and 12 mo.

RESULTS

A total of 220 IBD patients treated with CT-P13 (Remsima®) were included in the study: 87 (40%) with ulcerative colitis and 133 (60%) with Crohn's disease. Mean age of the patients was 41.47 (SD 15.74) years, and 58% were female. Nineteen (9%) patients started treatment with CT-P13 after switching from infliximab. Of the remaining 201 patients, 142 (65%) were naïve to biologic agents. At baseline, 68.6% ($n = 138/201$) of patients presented with active disease. After 12 mo of treatment, 14.8% ($n = 12/81$) presented with active disease, and 64.2% ($n = 52/81$) were in clinical remission without corticosteroids. After 3 mo, 75.5% ($n = 115/152$) had a clinical response or achieved clinical remission, which was sustained for 12 mo (85.2%; $n = 69/81$). There was a decrease in specific IBD indices at 3, 6, 9, and 12 mo ($P < 0.001$). A total of 34 adverse events were reported by 27 (12.3%) patients, 9 (26.5%) of which were serious.

CONCLUSION

CT-P13 is an effective and safe infliximab biosimilar for the treatment of IBD in real-life practice and may be a valid and attractive alternative for the treatment of IBD.

Key Words: Crohn's disease; Ulcerative colitis; Inflammatory bowel disease; Infliximab; Biosimilar; CT-P13

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Core Tip: In this study, the effectiveness and safety of the infliximab biosimilar CT-P13 in the treatment of inflammatory bowel disease (IBD) in real-life practice were analyzed. Our results show that CT-P13 is an effective and safe biosimilar of infliximab, and is a valid and attractive alternative for the treatment of IBD as it allows for a reduction of healthcare costs and facilitates access to biological treatments for more patients.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are the two main conditions of inflammatory bowel disease (IBD). CD is characterized by chronic inflammation of any part of the gastrointestinal tract, has a progressive and destructive course, and is increasing in incidence worldwide. UC is a chronic IBD of unknown etiology affecting the colon and rectum. Multiple factors, such as genetic background, environmental and luminal factors, and mucosal immune dysregulation, have been suggested to contribute to its pathogenesis[1,2]. Both chronic diseases are associated with high morbidity and strongly affect quality of life[3-8]. In the last two decades, biological therapies have

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revolutionized the management of these diseases. Seven biologic agents are currently approved by the United States Food and Drug Administration (FDA) for IBD treatment, although only five are approved by the European Medicines Agency (EMA): three anti-tumor necrosis factor (TNF) agents (infliximab, adalimumab, and golimumab), one anti-IL12/23 (ustekinumab), and one anti-integrin agent (vedolizumab)[9]. These biological treatments induce mucosal healing, prolong periods of remission, and improve patients' quality of life, leading to a reduction in hospitalizations and surgical procedures[5,9-15]. However, they are expensive; consequently, their high costs have become a burden for healthcare systems worldwide and access is restricted for many patients[9,10,16-18].

The expiry of patents for some biologics has led to the development of biosimilar products with two main goals: reducing healthcare costs and improving patients' access to these treatments[10,16,19]. According to the World Health Organization (WHO), a biosimilar is a biotherapeutic product similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product[10,20]. Although a biosimilar and its reference drug are mostly the same product, there may be differences between them due to the use of living organisms in their manufacture. Therefore, it is necessary to prove the clinical effectiveness and safety of the biosimilar [10,19,21,22]. The first infliximab biosimilar, CT-P13, was approved by the EMA in 2013 and came onto the market in 2016[10,21].

Although various studies support the similarity between CT-P13 and infliximab in terms of efficacy and safety, there are unmet needs regarding research on these agents in the context of IBD. Due to this fact and limited evidence in real-life practice, many physicians are still reluctant to prescribe biosimilars[10]. Most observational trials that have evaluated CT-P13 in patients who were naïve to biological treatment or had switched from infliximab had a retrospective design and limited sample size[23,24], with few exceptions[25,26]. Furthermore, prospective trials had follow-up periods of less than one year and/or study samples of less than 100 patients[27-32], with the exception of the studies by Kolar *et al*[33], Jung *et al*[26], and Bergqvist *et al*[34]. Up to now, only one randomized controlled trial has compared infliximab with CT-P13 in IBD patients[35]. Furthermore, most studies included patients who were either naïve to biologic agents or had switched from infliximab to CT-P13, although little is known regarding patients switching from other biologic agents, such as adalimumab[10,36].

In this study, we aimed to analyze clinical response rates to CT-P13, marketed under the trade name of Remsima®, and adverse events in patients with IBD treated in real-life practice.

MATERIALS AND METHODS

Study design

This observational, prospective, multicenter study was conducted at eight Spanish hospitals: Hospital General Universitario de Valencia, Hospital de Sagunto, Hospital Universitario Dr. Peset, Hospital Arnau de Vilanova de Valencia, Hospital Universitari i Politécnic la Fe, Hospital Clínico Universitario de Valencia, Hospital Francisc de Borja de Gandia, and Hospital de Manises, Valencia.

Patients' assignment to a specific therapeutic strategy was determined as in daily clinical practice. Thus, the decision to prescribe a drug was clearly dissociated from the decision to include a patient in the study. No diagnostic or follow-up interventions were conducted on patients outside usual clinical practice, and all data were collected in a case report form (CRF) for the epidemiological analysis by the attending physician.

The duration of the study was at least one year. Study variables were recorded in patients' clinical histories and in an electronic database (Excel).

The study was conducted following the principles outlined in the current revised version of the Declaration of Helsinki and in compliance with Good Clinical Practice (GCP) and all applicable laws and regulatory requirements in Spain. The study was approved by the Hospital General Universitario de Valencia Ethics Committee, and all patients signed an informed consent.

Usual clinical practice

Based on the ECCO guidelines, patients start biological treatment for CD or UC with moderate to severe activity when they have presented an inadequate response to conventional treatment, which includes corticosteroids and immunomodulators (IMM), such as 6-mercaptopurine (6-MP) or azathioprine (AZA), or when they are

intolerant or have medical contraindications to such treatments. Biological treatment is also started in active, fistulizing CD that has not responded despite a complete and adequate course of conventional treatment (including antibiotics, drainage, and immunosuppressive therapy)[37,38].

Subjects

The study included IBD patients treated with Remsima® (infliximab biosimilar, CT-P13, Kern Pharma, Spain) in clinical practice who were naïve to biological treatments, or had failed to respond to other anti-TNF drugs, or had switched from infliximab originator (Remicade®). Patients who were unresponsive to infliximab or allergic or intolerant to infliximab or its excipients or had a contraindication to infliximab were excluded. CT-P13 (Remsima®) was administered at a standard dose of 5 mg/kg *via* a 2-h intravenous infusion. Patients were invited to take part and were included in the study if they agreed to participate and their eligibility was confirmed.

Variables and endpoints

The primary endpoints were clinical response rate and number of adverse events in IBD patients treated with CT-P13 (Remsima®) in real-life practice. Variables were collected at baseline and every three months during the 12 mo follow-up period (Table 1). CT-P13 (Remsima®) trough levels and anti-drug antibodies were determined according to clinical practice before each infusion. The primary efficacy variable was the proportion of patients who were in clinical remission and/or had a clinical response at each visit.

Clinical disease was considered active when the HBI (Harvey-Bradshaw Index) was > 4 (CD) or PMS (Partial Mayo Score) was > 2 (UC) or the patient had an active perianal fistula in CD. A fistula was considered active if it presented suppuration spontaneously or with digital pressure, and inactive if there was no suppuration. Clinical remission was defined as $\text{HBI} \leq 4$ (CD) or $\text{PMS} \leq 2$ (UC), without corticosteroids, or an inactive perianal fistula. A clinical response was defined as a decrease of at least 2 points in the HBI or PMS or improvement of the perianal fistula. The disease was considered stable when $\text{HBI} \leq 4$ (CD) or $\text{PMS} \leq 2$ (UC) and C-reactive protein (CRP) was < 5 mg/L for at least 6 mo. Relapse or exacerbation was defined as the need to scale the dosage of CT-P13 (Remsima®) (shorten interval and/or increase doses), the addition of corticosteroids, or switching to another biologic agent based on the physician's decision. Loss of response was defined as active disease after a primary response following at least the first four infusions of the biologic drug.

The CD activity index (CDAI) was determined in patients with Crohn's disease at baseline and at each of the evaluations. The Truelove-Witts index was used in patients with UC.

Safety measures

The safety variable was the number of adverse effects described in the follow-up.

Adverse events: Type, severity (low, mild, severe), whether they were related to CT-P13 (Remsima®) or not, duration (days), hospitalization (yes or no), and need for surgery (if yes, the reasons for surgery). Variables were collected in a CRF every three months.

Statistical analysis

The statistical analyses in this study were performed by Joaquin Peña Siles and Jose Antonio Parejo Maestre from the University of Seville. Sample size was not defined. The choice of treatment was based on usual clinical practice. A descriptive analysis of all the variables of interest was made. The results of continuous variables are presented as mean \pm SD. The results for categorical variables are presented as frequencies and percentages. The statistical analysis included appropriate measures for statistical significance (Student's paired two-sample *t*-test) using the standard cutoff for significance of $P < 0.05$ *via* Microsoft Excel.

RESULTS

Patient characteristics

A total of 220 IBD patients treated with CT-P13 (Remsima®) were included in the study: 87 (40%) with UC and 133 (60%) with CD. At the time of starting CT-P13 (Remsima®) treatment, the mean age was 41.47 (SD 15.74) years. Patients were evenly

Table 1 Variables collected at baseline and during follow-up visits

| Variable | Baseline | Follow-up |
|---|----------|-----------|
| Demographic data | | |
| Date of birth | X | - |
| Gender | X | - |
| Smoking habit | X | - |
| Disease data | | |
| Date of diagnosis | X | - |
| IBD type (Crohn's disease, ulcerative colitis) | X | - |
| Montreal classification | X | - |
| Type of fistula (perianal, entero-enteral, enterovesical, enterovaginal, enterocutaneous, other) | X | - |
| Intra-intestinal complications (yes or no) | X | - |
| Extraintestinal complications (dermatological, osseous, optical, hepatic) | X | - |
| Harvey-Bradshaw index | X | X |
| Crohn's disease activity index | X | X |
| Partial Mayo Score | X | X |
| Truelove-Witts severity index | X | X |
| Laboratory analysis | | |
| C-reactive protein | X | X |
| Erythrocyte sedimentation rate | X | X |
| Hemoglobin | X | X |
| Calprotectin | X | X |
| CT-P13 trough levels and antibodies ^x | - | X |
| Imaging tests | | |
| Disease severity and lesion location according to endoscopy result (mild, moderate, severe) | X | X |
| Disease severity and lesion location according to magnetic resonance enterography result (mild, moderate, severe, fibrotic stenosis) | X | X |
| Treatment data | | |
| Current treatments (mesalazine, cortisone, AZA/6-MP, MTX) | X | X |
| Previous treatments (mesalazine, corticosteroids, AZA/6-MP, MTX, infliximab, adalimumab) | X | - |
| Reasons to start treatment with CT-P13 (corticosteroid dependence, corticosteroid resistance, failure of AZA/6-MP, perianal disease/fistula, start of severe illness) | X | - |
| Clinical situation | | |
| Active clinical disease | X | X |
| Clinical remission | X | X |
| Clinical response | - | X |

IBD: Inflammatory bowel disease; AZA: Azathioprine; 6-MP: 6-Mercaptopurine; MTX: Methotrexate.

distributed by sex: 42% were male and 58% were female. Most patients (140, 63.6%) were non-smokers, 37 (16.8%) were smokers, and 28 (12.8%) were former smokers.

Table 2 shows the clinical characteristics of the study patients at baseline, including previous and current treatments. Before their inclusion in the study, some of the patients had previously been treated with biologic agents: 35 patients (21 with CD and 14 with UC) had received treatment with infliximab, and 22 (15 with CD and seven with UC) with adalimumab. At the time of the study, 74 (35%) patients were concomitantly treated with corticosteroids. The disease phenotypes of CD and UC according

Table 2 Clinical characteristics of study patients at baseline, *n* (%)

| | Overall (<i>n</i> = 220) | CD (<i>n</i> = 133) | UC (<i>n</i> = 87) |
|---|---------------------------|----------------------|---------------------|
| Endoscopic findings (presence and size of ulcers) | | | |
| Unaffected | 9 (4) | 7 (5) | 2 (2) |
| Mild (1-5 mm) | 7 (3) | 1 (1) | 6 (7) |
| Moderate (5-20 mm) | 54 (25) | 21 (16) | 33 (38) |
| Severe (> 20 mm) | 41 (19) | 25 (19) | 16 (18) |
| Fibrotic stenosis | 7 (3) | 7 (5) | 0 (0) |
| Not performed | 102 (46) | 72 (54) | 30 (34) |
| Ultrasound findings (hyperemia of the bowel wall assessed by color Doppler ultrasound) | | | |
| Unaffected | 5 (2) | 5 (4) | - |
| Mild (2 signal dots/cm ²) | 7 (3) | 7 (5) | - |
| Moderate (3-5 signal dots/cm ²) | 34 (15) | 34 (26) | - |
| Severe (> 5 signal dots/cm ²) | 22 (10) | 22 (17) | - |
| Not performed | 152 (69) | 65 (49) | 87 (100) |
| Previous treatments | | | |
| Mesalazine | 97 (44) | 37 (28) | 60 (69) |
| Corticosteroids | 131 (60) | 73 (55) | 58 (67) |
| AZA/6-MP | 135 (61) | 82 (62) | 53 (61) |
| MTX | 12 (5) | 10 (8) | 2 (2) |
| Remicade® | 35 (16) | 21 (16) | 14 (16) |
| Humira® | 22 (10) | 15 (11) | 7 (8) |
| Concomitant treatments | | | |
| Mesalazine | 77 (35) | 28 (21) | 49 (56) |
| Corticosteroids | 74 (35) | 37 (28) | 37 (43) |
| AZA/6-MP | 115 (52) | 67 (50) | 48 (55) |
| MTX | 15 (7) | 15 (11) | 0 (0) |

CD: Crohn's disease; UC: Ulcerative colitis; AZA: Azathioprine; 6-MP: 6-Mercaptopurine; MTX: Methotrexate.

to the Montreal classification[39] are shown in Table 3.

Only 19 (9%) patients started treatment with CT-P13 (Remsima®) after switching from infliximab. Of the remaining 201 patients, 142 (65%) were naïve to biologic agents; 25 (11%) started treatment with CT-P13 due to failure to respond to previous biological treatments [21 (84%) to adalimumab, 1 (4%) to certolizumab, 1 (4%) to vedolizumab, and 2 (8%) unspecified]; 20 (9%) had been treated with Inflectra®, another commercial name for CT-P13; and in 14 (6%) cases, treatment was not specified. These patients had pharmacological and clinical reasons for starting CT-P13 (Remsima®). Among the pharmacological reasons, we found dependence on or resistance to corticosteroids, intolerance or resistance to IMM, and combinations of these reasons. The most frequent reasons were resistance to IMM (15%), dependence on corticosteroids (12%), and intolerance to IMM (10%). The main clinical reason for starting CT-P13 (Remsima®) was moderate exacerbation (42%). Other clinical reasons included severe exacerbation (12%), mild exacerbation (5%), perianal disease (5%), extraintestinal manifestations (1%), and combinations of some of these reasons.

Clinical course

Of the 19 patients who switched from infliximab original (Remicade®), 12 had already completed 12 mo of follow-up at the time of the study. Of these, 10 patients (83.3%)

Table 3 Montreal classification of Crohn's disease and ulcerative colitis at baseline, *n* (%)

| Montreal classification of CD | CD (<i>n</i> = 133) |
|--|---------------------------|
| Age of diagnosis | |
| A1 (below 16 yr) | 15 (11) |
| A2 (between 17 and 40 yr) | 90 (68) |
| A3 (above 40 yr) | 18 (14) |
| - | 10 (8) |
| Location | |
| L1 (ileal) | 62 (47) |
| L2 (colonic) | 16 (12) |
| L3 (ileocolonic) | 47 (35) |
| - | 8 (6) |
| Location L4 ¹ (concomitant UGI disease) | |
| Yes | 4 (3) |
| No | 87 (65) |
| - | 42 (32) |
| Behavior | |
| B1 (non-stricturing, non-penetrating) | 60 (45) |
| B2 (stricturing) | 24 (18) |
| B3 (penetrating) | 38 (29) |
| - | 11 (8) |
| P ² (concomitant perianal disease) | |
| Yes | 38 (29) |
| No | 84 (63) |
| - | 11 (8) |
| Montreal classification of UC | UC (<i>n</i> = 87) |
| Extent | |
| E1 (Ulcerative proctitis) | 10 (11) |
| E2 (Left-sided UC - distal UC) | 18 (21) |
| E3 (Extensive UC - pancolitis) | 48 (55) |
| - | 11 (13) |
| Severity | |
| S1 (Mild UC) | 8 (9) |
| S2 (Moderate UC) | 54 (62) |
| S3 (Severe UC) | 15 (17) |
| - | 10 (11) |

¹May coexist with L1-L3.²May coexist with B1-B3.

CD: Crohn's disease; UC: Ulcerative colitis; UGI: Upper gastrointestinal.

remained in remission.

Of the remaining 201 patients, 81 had already completed 12 mo of follow-up at the time of the study. At baseline, 68.6% (*n* = 138/201) of patients presented with active disease; the remainder were in remission after having started treatment with corticosteroids (see Table 2, concomitant treatments). After one year of treatment with CT-P13

(Remsima®), the proportion of patients with active disease was 14.8% ($n = 12/81$), and the proportion of patients who achieved clinical remission (without corticosteroids) was 64.2% ($n = 52/81$) (Table 4). At the time of the study, 152 patients had completed 3 mo of follow-up. As early as 3 mo, 75.5% ($n = 115/152$) of patients treated with CT-P13 (Remsima®) had a clinical response or achieved clinical remission, which was sustained during one year of treatment (85.2%; $n = 69/81$) (Table 4). A statistically significant decrease was observed in specific CD and UC indices [HBI and CDAI for CD and PMS for UC] after 3, 6, 9, and 12 mo of treatment with CT-P13 (Remsima®) ($P < 0.001$) (Figure 1). As shown in Figure 1B, according to the Truelove-Witts index, the number of patients with moderate UC decreased after three months of treatment, which was sustained for 12 mo; the number of patients with mild disease increased consistently.

General inflammatory blood biomarkers decreased after 12 mo of CT-P13 (Remsima®) treatment in CD and UC patients. In CD patients, blood CRP levels decreased from 14.51 mg/L (SD 20.78; $n = 108$) at baseline to 4.17 mg/L (SD 5.80; $n = 50$) ($P < 0.001$); fecal calprotectin levels decreased from 638.99 µg/g (SD 584.32; $n = 57$) to 268.58 µg/g (SD 354.65; $n = 31$) ($P = 0.0018$); and the erythrocyte sedimentation rate (ESR) decreased from 20.65 mm/h (SD 16.91; $n = 49$) to 11.97 mm/h (SD 8.16; $n = 30$) ($P = 0.010$) (Figure 2A). In UC patients, CRP decreased from 14.20 mg/L (SD 22.56; $n = 62$) at baseline to 2.64 mg/L (SD 4.31; $n = 33$) ($P = 0.0045$); fecal calprotectin levels decreased from 990.112 µg/g (SD 755.46; $n = 43$) to 121.67 µg/g (SD 157.58; $n = 18$) ($P < 0.001$); and ESR decreased from 23.00 mm/h (SD 24.50; $n = 17$) to 6.83 mm/h (SD 5.95; $n = 12$) ($P = 0.0344$) (Figure 2B).

At the beginning of the study, 11 patients had active perianal disease (5.4%) and had started treatment for this reason. Perianal disease remained active after one year of follow-up in 3 patients (3.7%, 3/81). The low number of patients with active perianal disease did not allow us to draw conclusions from the analysis.

Immunogenicity

Considering patients who switched and those who did not, antibodies to CT-P13 were measured in 22.2% (38/171), 17.9% (25/139), 15.3% (15/98), and 24.7% (23/93) of patients at 3, 6, 9, and 12 mo, respectively. At three months, four (10.5%) patients had detectable antibodies, one (4%) at six months, one (6.7%) at nine months, and six (26.1%) at 12 mo.

Mean CT-P13 trough levels were 5.74 µg/mL (SD 3.64), 5.26 µg/mL (SD 3.74), 3.83 µg/mL (SD 3.46), and 3.45 µg/mL (SD 3.63) at 3, 6, 9, and 12 mo, respectively. At 3, 6, and 9 mo, the CT-P13 level was 0 µg/mL in those patients with detectable antibodies. At 12 mo, five (83.3%) patients with detectable antibodies had CT-P13 levels of 0 µg/mL, and one (26.7%) had a CT-P13 level of 2 µg/mL.

Safety

A total of 34 (15.45%) adverse events (AEs) were reported by 27 patients; of these, nine (26.5%) were serious. Of all the AEs reported, 19 (55.9%) were probably associated with treatment, five (14.7%) were possibly associated with treatment, one (2.9%) was probably not associated with treatment, and one (2.9%) was not related to treatment. Ten (29.4%) of the 34 adverse events reported required hospitalization (they were all flares of the disease). The most frequent AEs were due to infections (23.5%) (mainly urinary and upper respiratory tract) and mild acute infusion-related reactions (26.5%) (Table 5). No patient discontinued treatment due to an AE. No patient required surgery during the study.

DISCUSSION

In this real-life practice study, we analyzed the efficacy and safety of infliximab biosimilar, CT-P13 (Remsima®) for the treatment of patients with IBD. At 12 mo of treatment, the proportion of patients with active disease was only 14.8%. Similarly, the proportion of patients in clinical remission or with a clinical response was 85.2% after one year of treatment. Moreover, the decrease in the number of patients with active disease and the increase in clinical remission rates were already observed as early as after three months of treatment with CT-P13 (Remsima®). Thus, this biosimilar can be considered to have an acceptable safety profile, as no serious AEs proved to be treatment-related.

Table 4 Clinical course of all patients (Crohn's disease + ulcerative colitis) (those who switched from infliximab originator are excluded), *n* (%)

| | Active disease | Clinical remission | Clinical response |
|----------------------------|----------------|--------------------|-------------------|
| Baseline (<i>n</i> = 201) | 138 (68.6) | - | - |
| 3 mo (<i>n</i> = 152) | 37 (24.4) | 81 (53.2) | 34 (22.3) |
| 6 mo (<i>n</i> = 122) | 21 (17.2) | 74 (60.7) | 27 (22.1) |
| 9 mo (<i>n</i> = 84) | 8 (9.5) | 61 (72.6) | 15 (17.9) |
| 12 mo (<i>n</i> = 81) | 12 (14.8) | 52 (64.2) | 17 (21) |

Table 5 Type of adverse events reported, *n* (%)

| Number of AEs ¹ | 34 (15.45) |
|----------------------------|------------|
| Hypersensitivity | 9 (26.5) |
| Malignant neoplasm | 1 (2.9) |
| Infections (any type) | 8 (23.5) |
| Respiratory infections | 2 (5.9) |
| Other infections | 6 (17.6) |
| Other AEs | 8 (23.5) |
| Non-specified | 8 (23.5) |

¹Any type. AEs: Adverse events.

As this was a real-life practice study, not all patients had active disease when CT-P13 (Remsima®) was started. This is due to the fact that a percentage of patients had started other treatments (for example corticosteroids) to induce remission immediately before initiation of Remsima® (sometimes initiation is delayed due to lack of a Mantoux result for example). Another example of this situation would be a corticosteroid-dependent patient with no response to immunosuppressants starting infliximab who is probably in remission due to concomitant treatment with corticosteroids. It is for this reason that at baseline, only 68.6% of the patients had active disease and not 100%.

Remission rates in our study varied from 64.2% (observed at 12 mo) to 53% (at three months), which are similar to those reported in other studies (remission rates ranging from 32% to 56%)[26,36,40-46]. Some studies found much higher remission rates, such as the randomized NOR-SWITCH study, in which a 52-wk remission rate of 65% and 93% for CD and UC, respectively, was observed[35].

This study has the advantages of a real-life-practice study in that the patients were similar to those clinicians find in medical settings; thus, they are more heterogeneous and present with more comorbidities than the patients usually studied in clinical trials [47]. In real life, some hospitals change the brand name of CT-P13 (Remsima® for Inflectra® and *vice versa*), and this situation is reflected in our study. Similarly, this work shows the limitations of a real-life study: As the patients were not assigned beforehand to any therapeutic strategy, it makes the interpretation of results difficult. A reflection of this is the change in the CT-P13 brand that the patients take when they leave some hospitals. In this sense, it would have been interesting to compare results from patients who started treatment with CT-P13 (Remsima®) after switching from Remicade® with those who were naïve to biological treatment. However, the number of patients in each group was unequal – only 19 (9%) patients included in the study had switched from adalimumab, and 142 (65%) were naïve to biological treatment – thus making the comparison between groups difficult.

In 2018, Bergqvist *et al*[34] published a large series on switched IBD patients and demonstrated that Remicade® can be switched to CT-P13 with preserved therapeutic efficacy and safety in both CD and UC.

Another limitation was that available data were heterogeneous across visits; moreover, some parameters could not be included because they had not been measured in routine practice (for example endoscopy or ultrasound). CT-P13 has been

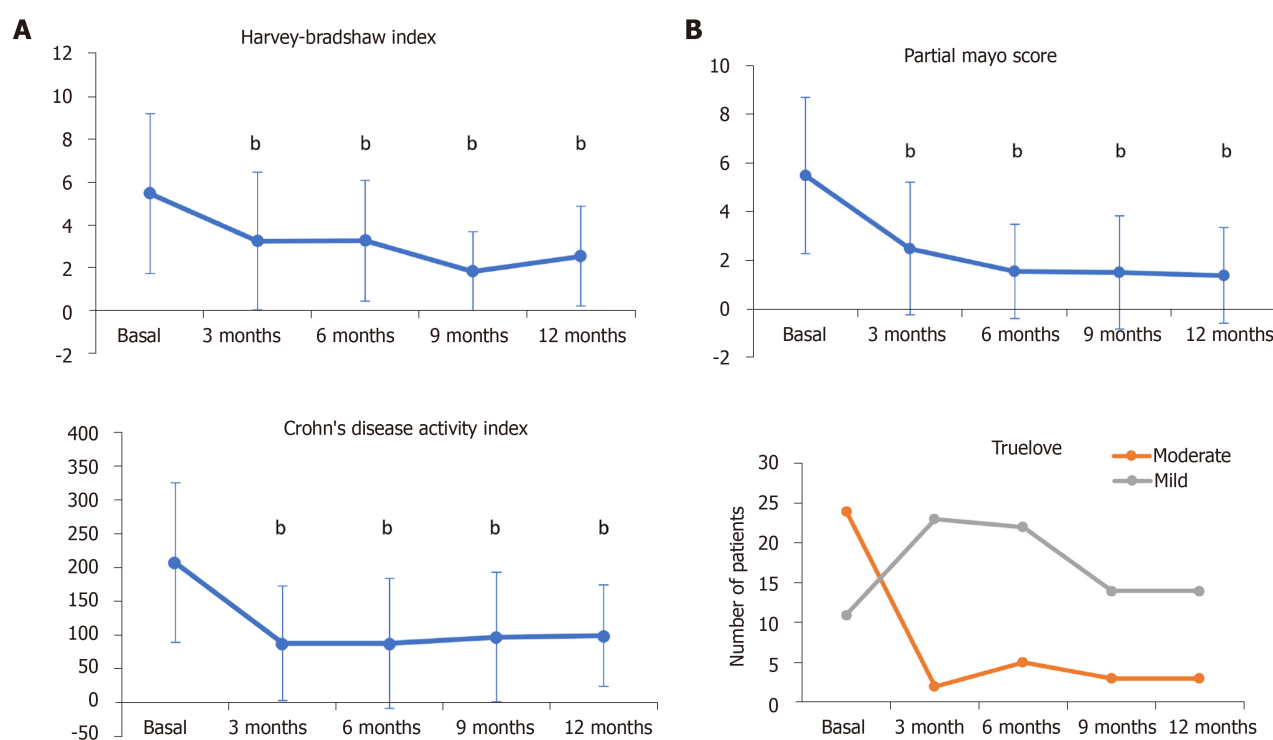


Figure 1 Crohn's disease (A) and ulcerative colitis (B) indices after 3, 6, 9, and 12 mo of CT-P13 treatment. Error bars indicate SD. ^b*P* < 0.001 vs baseline conditions.

shown to achieve mucosal healing both in patients with UC and in those with CD[48, 49]. However, in our real-world study, not all patients were evaluated by endoscopy if mucosal healing was observed.

In a systematic review published in 2018, Gisbert and Chaparro pointed out, as a limitation of most of studies, that the effectiveness of CT-P13 had been evaluated through clinical assessments, or sometimes using additional biological parameters, although most authors did not perform endoscopic evaluations[10]. In our study, we used disease-specific indices (HBI and CDAI for CD, and PMS and Truelove for UC) and measured biological parameters indicative of inflammation, such as CRP, fecal calprotectin, and ESR.

Safety data with original and biosimilar infliximab have been variable, sometimes due to different definitions. Our finding of 15.45% for AEs is similar to that reported in other clinical practice series[50].

Finally, immunogenicity is also a main concern when switching patients from a reference product to its biosimilar. The development of antibodies against the drug is one of the main factors that can cause loss of response to a biological agent. We observed a correlation between the presence of anti-drug antibodies and low CT-P13 trough levels. In those patients with detectable anti-drug antibodies, drug levels were 0 µg/mL, with the exception of one patient. However, the CT-P13 trough level in this patient at 12 mo was lower than the mean level at that time point (2 µg/mL *vs* 3.63 µg/mL).

It is important to note that the physicians had no incentive to switch from original to biosimilar or to start a biosimilar in naive patients. In our area, physicians had total freedom of prescription in relation to reference biological drugs and biosimilars, although there was a guideline to start infliximab-naïve patients with biosimilars.

CONCLUSION

In summary, CT-P13 (Remsima®) is an effective and safe biosimilar of infliximab for the treatment of CD and UC in real-life practice. It is a valid and attractive alternative for the treatment of IBD, as it reduces healthcare costs and facilitates access to biological treatments for more patients.

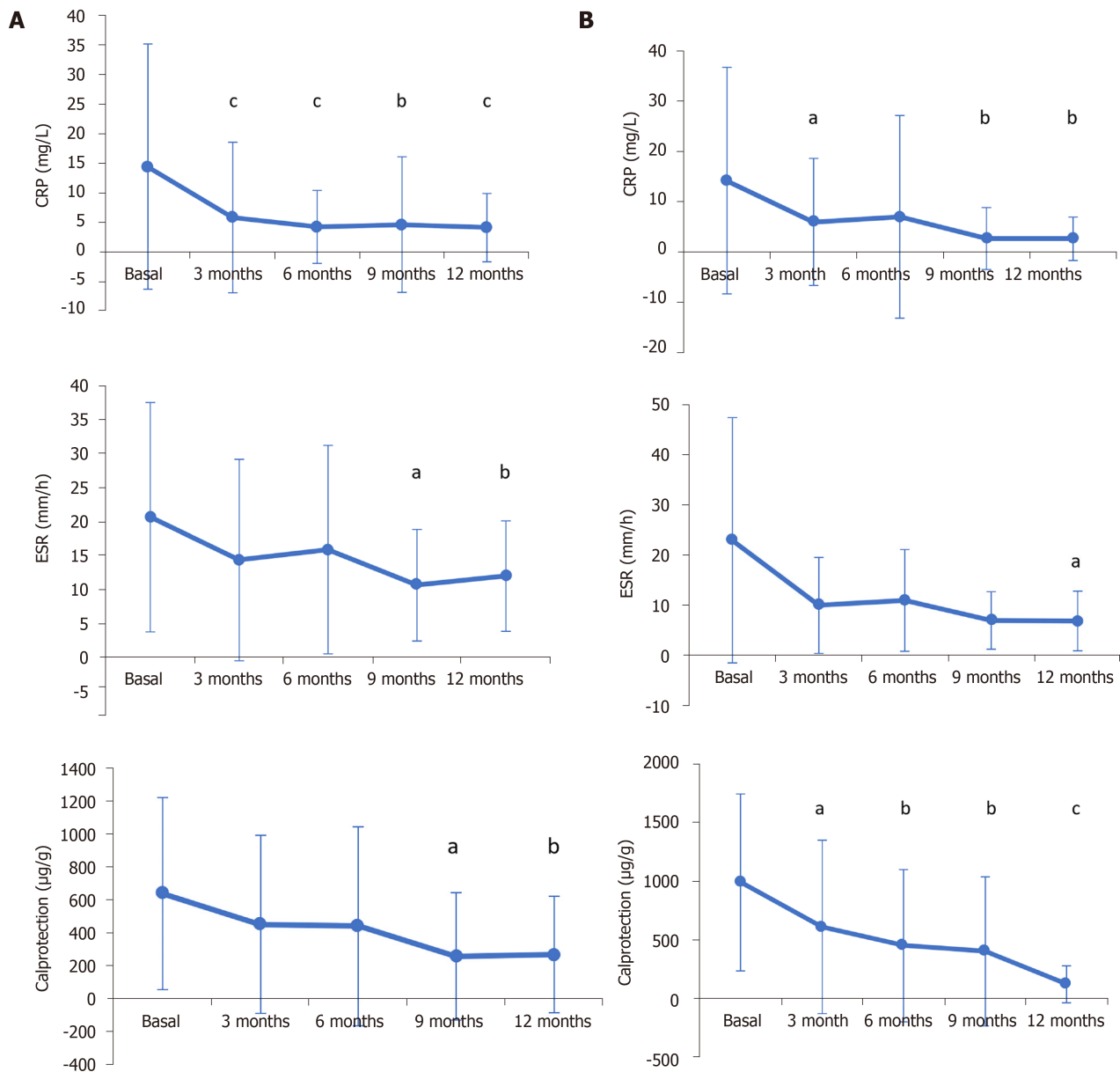


Figure 2 General inflammatory blood biomarkers. C-reactive protein levels, erythrocyte sedimentation rate, and fecal calprotectin levels were measured at baseline and after 3, 6, 9, and 12 mo of CT-P13 treatment in patients with Crohn's disease (A) and ulcerative colitis (B). Error bars indicate SD. ^a $P < 0.05$ vs baseline conditions; ^b $P < 0.01$ vs baseline conditions; ^c $P < 0.001$ vs baseline conditions.

ARTICLE HIGHLIGHTS

Research background

Authorization of infliximab biosimilars has revolutionized the treatment of inflammatory bowel disease (IBD), in terms of both clinical practice and cost reduction. Although several studies have evaluated the safety and efficacy of infliximab biosimilar, some have retrospective designs and small study populations.

Research motivation

There is a need to evaluate the effectiveness and safety of these drugs in daily clinical practice in patients with IBD.

Research objectives

The objective of the present study was to evaluate the efficacy and safety of infliximab biosimilar in real-world practice.

Research methods

The authors performed a multicenter, observational, prospective study in Spanish hospitals based on the real-world clinical practice of the participating physicians.

Research results

After 12 mo of treatment, 64.2% ($n = 52/81$) of patients were in clinical remission without corticosteroids. After 3 mo, 75.5% ($n = 115/152$) had achieved a clinical response or clinical remission, which was sustained for 12 mo (85.2%; $n = 69/81$). There was a decrease in specific IBD indices at 3, 6, 9, and 12 mo ($P < 0.001$). A total of 34 adverse events were reported by 27 (12.3%) patients; of these, nine (26.5%) were serious.

Research conclusions

CT-P13 (Remsima®) is an effective and safe infliximab biosimilar for the treatment of Crohn's disease and ulcerative colitis in real-life practice. It is a valid and attractive alternative for the treatment of IBD, as it reduces healthcare costs and facilitates access to biological treatments for more patients.

Research perspectives

New studies will be necessary to provide more in-depth information on the management of IBD with infliximab biosimilar in clinical practice.

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