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Ustekinumab in Crohn's disease management: a Brazilian observational study

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ABSTRACT – Background – Real-world data on the use of Ustekinumab (UST) in Brazilian and Latin American patients with Crohn's disease (CD) are scarce. **Objective –** The primary endpoint was assessment of clinical remission at weeks 8 and 52, and secondary endpoints were: assessment of clinical response at weeks 8 and 52, endoscopic remission, adverse events, and rates of CD-related abdominal surgery during follow-up. **Methods –** observational and retrospective study, including patients with CD treated at two centers, who received UST at any time during their treatment. Remission and clinical response were defined as a Harvey-Bradshaw index ≤4 and ≥3 points reduction, respectively. **Results –** Seventy-four patients were included, 85.1% previously exposed to anti-TNFs. Clinical remission was observed in 45.8% and 59.4% of patients at weeks 8 and 52, respectively. The clinical response rates were 54.2% and 67.6% at weeks 8 and 52. Endoscopic remission was observed in 21.8% of patients. Seventeen patients had adverse events, mostly mild infections, with 22.9% of patients undergoing abdominal surgery (ileocolectomy being the most common procedure). **Conclusion –** UST therapy resulted in significant rates of remission and clinical response, as described in other real-world studies. Few patients had adverse events during treatment, showing its adequate safety profile.

Keywords – Inflammatory bowel disease; Crohn's disease; Ustekinumab; Interleukin.

INTRODUCTION

Crohn's disease (CD) is a chronic and progressive subtype of inflammatory bowel disease (IBD)[1], with incidence and prevalence rates which have increased in different regions of the world, including Brazil and Latin America[2]. There is a broad drug therapeutic spectrum according to the severity, extent and behavior of the disease, from corticoids to biological therapy[3]. Ustekinumab (UST) is a human IgG1 monoclonal antibody that binds with specificity to the shared p40 protein subunit of interleukins 12 and 23, reducing systemically the inflammatory burden[4,5]. Multicentric studies with UST in CD demonstrated the drug's efficacy and safety profile[6,7]. UST was approved for use in Brazil in 2017, but there is still a scarcity of longer follow-up studies with more solid objective data on the use of the drug in CD in our country. The primary aim of this study was to analyze clinical remission rates in patients with CD treated with UST, at induction (8 weeks) and at maintenance (52 weeks).

METHODS

An observational, retrospective and longitudinal study was carried out in patients with CD who used UST at any time during their treatment, at two tertiary referral centers in the management of IBD, from a large city in the south of Brazil, between August 2019 and February 2021.

Inclusion criteria comprised individuals over 18 years of age, diagnosed with CD, who may have an inflammatory, stenotic or penetrating phenotype of the disease, who received treatment with UST, as monotherapy or combination therapy, with an intravenous induction and maintenance dose of 90 mg every 8 or 12 weeks, for at least 16 weeks. Exclusion criteria: patients diagnosed with severe CD admitted to hospital during flares at treatment initiation and patients with no data available in the analysis of medical records.

Analyzed variables and definitions

The variables analyzed included demographic data such as age, sex, Montreal classification (including age at diagnosis, location of the disease and presentation)[8],as well as disease duration, smoking, previous medications, previous CD-related surgical procedures, concomitant medications (corticosteroids or immunomodulators), need for treatment optimization with UST (90 mg every 4 weeks), need for major abdominal surgeries and adverse events during treatment.

Electronic medical records were retrospectively reviewed, including clinical evaluations at weeks 8, 26, 52 and at the last follow-up, checked according to the Harvey-Bradshaw index (HBI)[9,10]. For definition of clinical response, a reduction in HBI of three or more points was considered, and clinical remission, was defined as HBI≤4[11]. In the analysis of remission and clinical response, patients who had an HBI ≤4 (clinical remission) before induction with UST were excluded. Patients with ileostomy were also excluded from the HBI analysis, as number of bowel movements could not be calculated. The HBI at the last follow-up was

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calculated based on the patient's last clinical assessment before the medication was discontinued or at the end of the study follow-up, regardless of treatment duration. Corticosteroid-free clinical remission was defined as clinical remission in those patients who did not use corticosteroids concomitantly with UST therapy at any time during treatment. Endoscopic evaluation was performed through colonoscopy before and after treatment with UST. Endoscopic remission was defined as complete healing of the intestinal mucosa (absence of ulcerations). The total follow-up time was determined from the first dose of UST until the last date of administration of the medication or interruption. Primary non-responders were defined as those with no clinical improvement after the induction period, according to physicians' discretion. Loss of response was defined as the need for surgery and/or UST optimization during treatment.

Ethical considerations

This study was approved by the Research Ethics Committee of the Pontifical Catholic University of Paraná, via the Ministry of Health's website *Plataforma Brasil,* according to reference number CAAE 10331319.1.0000.0020.

Data analysis

Quantitative variables with normal distribution were presented as mean and standard deviation (SD), and Student's *t* test was used to compare two independent samples. The Mann-Whitney U test were used to compare nonparametric data. Qualitative variables were presented as percentages, and χ^2 or Fisher exact test was used to compare two proportions, and a Kaplan-Meier Meier curve was generated for time-to-event data (time until UST discontinuation in months). We used IBM SPSS Statistics for Windows, version 20 (IBM Corp, Armonk, NY). The significance level adopted for the statistical tests was 5%.

RESULTS

Patient characteristics

Eighty patients who used UST were initially identified for the study. After excluding three patients who had a diagnosis of UC and three patients due to lack of information available in the medical records, data from 74 patients with CD were analyzed (FIGURE 1).

The main clinical and demographic characteristics of the patients are summarized in TABLE 1. The mean follow-up time during UST use for these patients was 20.8±12.9 months. Most patients (59.5%) were female, with a mean age of 40±14.8 years, and only 8.1% were smokers. At the UST induction, patients had approximately 10 years of disease duration from diagnosis. Most patients (66.2%) had a previous history of CD-related surgery, 47.3% with previous bowel resection and 29.7% with previous perianal surgery. Most patients (85.1%) had previously used anti-TNF agents.

Clinical remission and response

Clinical remission was observed in 45.8% of patients at week 8 (22/48) and 59.4% at week 52 (22/37), among patients who reached this period of the study using the drug (FIGURE 2). The clinical response rate at week 8 was 54.2% (26/48) and 67.6% at week 52 (25/37). Corticosteroid-free clinical remission was observed in 25% of the patients at week 8 (12/48) and 32.4% at week 52 (12/37). These data are illustrated in FIGURE 2.

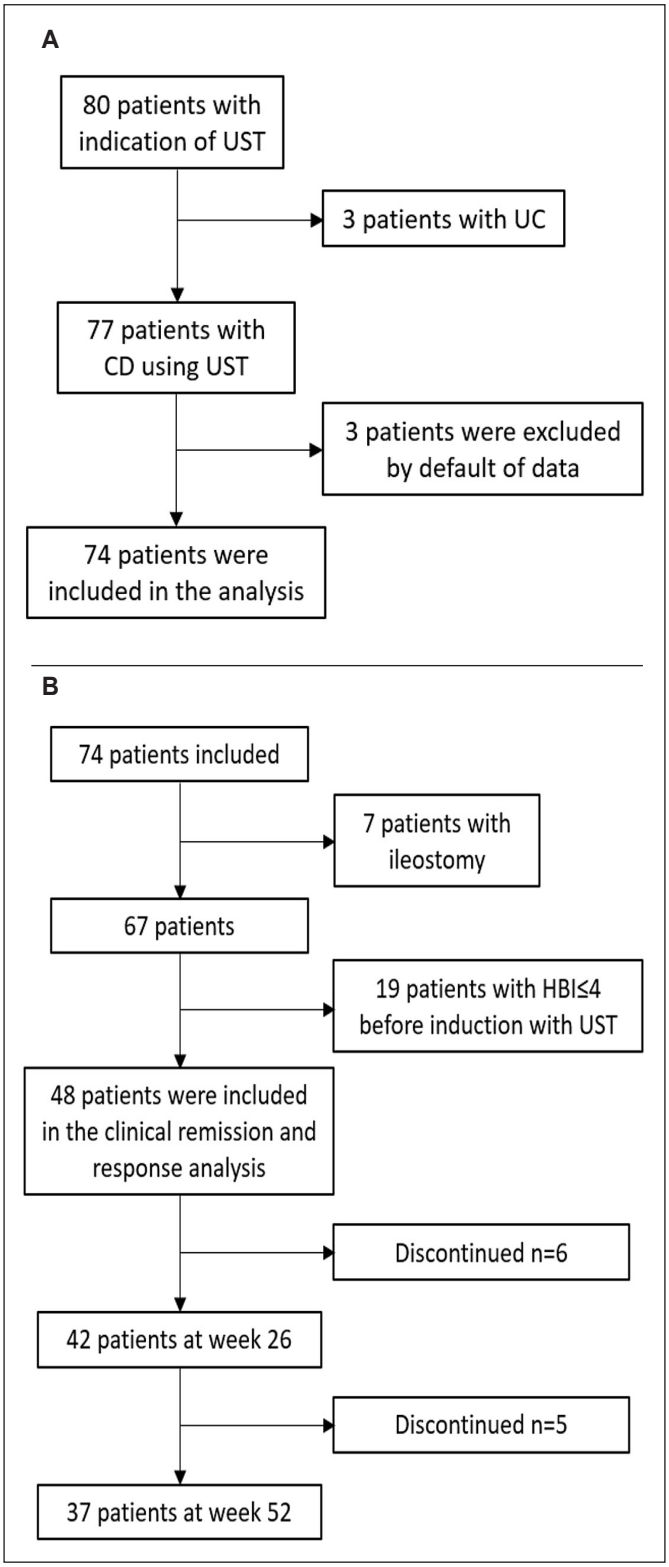

FIGURE 1. Study flow chart. **A)** Disposition of all included patients with CD receiving UST. **B)** Disposition of all included patients in the clinical remission and response analysis.
UST: Ustekinumab, DC: Crohn's disease, HBI: Harvey Bradshaw Index, n: number of patients.

TABLE 1. Baseline patient characteristics.

Characteristic	n=74
Age (median±SD)	40±14.8
Median disease duration before UST (months; median ±SD)	121.62±91.78
Disease duration before UST in years, n (%)	
0–2 years	9 (12.1)
3–10 years	40 (54.0)
>10 years	25 (33.7)
Gender, n (%)	
Female	44 (59.5)
Male	30 (40.5)
Smoking, n (%)	6 (8.1)
Montreal – age at diagnosis, n (%)	
A1 (<17 years)	16 (21.6)
A2 (17–40 years)	49 (66.2)
A3 (>40 years)	9 (12.2)
Montreal – location, n (%)	
L1 (Terminal Ileum)	16 (21.6)
L2 (Colon)	13 (17.6)
L3 (Ileocolonic)	45 (60.8)
Montreal – behaviour, n (%)	
B1 (Inflammatory)	35 (47.3)
B2 (Stricturing)	24 (32.4)
B3 (Penetrating)	15 (20.3)
Perianal disease, n (%)	30 (40.5)
Prior CD-related surgery, n (%)	49 (66.2)
Intestinal resections, n (%)	35 (47.3)
Perianal fistula/ abscess surgery, n (%)	22 (29.7)
Previous anti-TNF therapy, n (%)	63 (85.1)
Infliximab, n (%)	51 (68.9)
Adalimumab, n (%)	47 (63.1)
Certolizumab Pegol, n (%)	7 (9.5)
Previous therapy with Vedolizumab, n (%)	13 (17.6)
Number of previous biologicals, n (%)	
1	21 (28.4)
2	34 (45.9)
3	7 (9.5)
4	2 (2.7)
Concomitant medications, n (%)	
Steroids as co-induction	23 (31.1)
Azathioprine	16 (21.6)
Methotrexate	8 (10.8)
Disease activity in induction, median (IQR)	
Harvey Bradshaw Index	7.4 (4-11)

SD: standard deviation; IQR: interquartile range; UST: Ustekinumab; CD Crohn's disease.

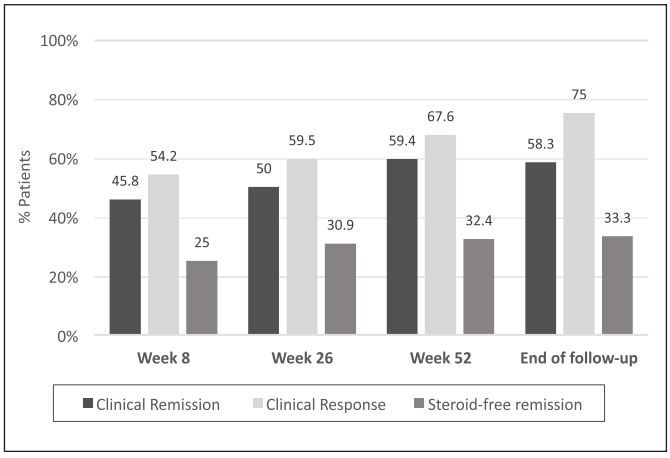

FIGURE 2. Clinical remission, response and steroid-free remission rates at weeks 8, 26 and 52, and at the last follow-up.

Regarding clinical remission rates among patients naive to anti-TNF therapy (n=8), these were observed in 75% at week 8 and 83.3% of the patients at week 52 (FIGURE 3). There was a significant difference in the comparison of clinical remission rates between the groups of patients naive to anti-TNF and those previously exposed to these agents (n=40) at weeks 8, 52 and end of follow-up (P<0.05), as demonstrated in FIGURE 3.

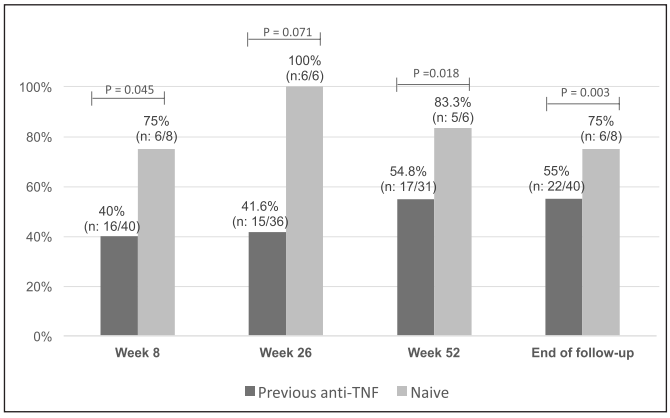

FIGURE 3. Clinical remission rates at weeks 8, 26 and 52, and in the last follow-up according to the status of previous exposure to anti-TNF agents. Numbers of patients are indicated below the percentages.

Mucosal healing

The mean time for follow-up colonoscopy after induction was 10.9±4.9 months. Endoscopic remission was observed in 21.8% (12/55) of patients who underwent an endoscopic examination for monitoring treatment response.

Loss of response, discontinuation and optimization

Thirteen patients were considered primary non-responders to UST (17.6%) and 31 patients had secondary loss of response (41.9%). Among patients who failed to respond, 19.3% required surgery, 41.9% medication optimization, and 38.7% both. The median time to loss of response was 32 months (95%CI 26.914–37.701) of treatment. No worsening of the disease status was observed in non-responders, according to HBI values in follow-up.

The mean time to discontinuation of treatment with UST was 58 months (95%CI 48.850–67.212). It was observed that 89.7% of patients continued treatment with UST after 12 months of follow-up (FIGURE 4). The need for UST dose optimization (90 mg every 4 weeks) was observed in 39/74 (52.7%) patients. This proportion comprises 25 patients with secondary loss of response, ten who were considered primary non-responders who had dose optimization according to physicians' discretion, and four patients who had dose optimization to improve partial response, to target mucosal healing. The mean time to UST optimization was 30 months (95%CI 24.928–35.971). After optimization, 20/39 patients were lost to follow-up, 19/39 had efficacy data, with 11 in clinical remission (57.8%). Only 15/39 had an endoscopic evaluation, with 2/15 (13.3%) presenting mucosal healing.

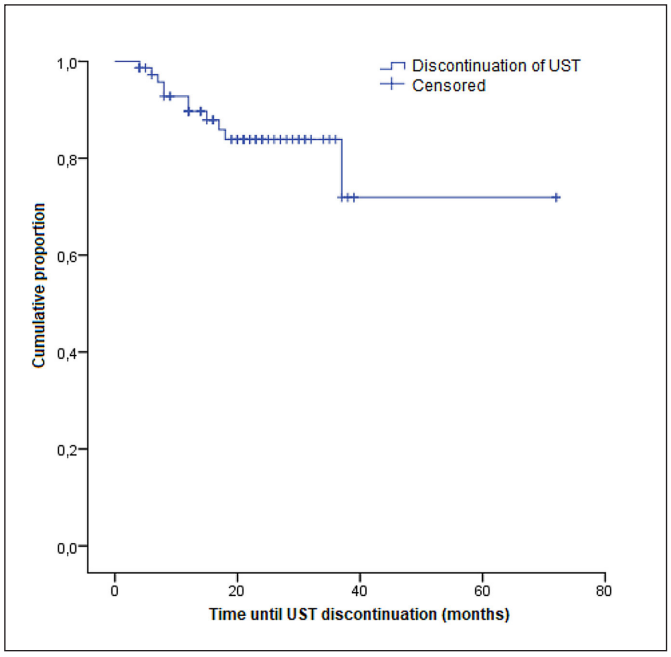

FIGURE 4. Kaplan Meier curve showing time-to-event analysis of UST discontinuation during follow-up.

Adverse events

Seventeen (23%) patients had an adverse event during UST treatment, the most common being infectious events (TABLE 2). No patient discontinued the medication due to adverse effects. There were no deaths of patients using UST in the present study.

Surgery during treatment

Twenty-six patients (35.1%) underwent some type of surgery during treatment with UST, and 22.9% underwent abdominal major surgical procedures. The most common procedure performed was ileocolectomy in 10.8%, small bowel resection in 5.4%, total colectomy in 2.7%, followed by bypass colostomy, sigmoid resection and surgery for adhesion lysis. We observed one anastomotic leak in a young male patient submitted to an ileocecal resection and a small bowel obstruction in a female patient submitted to a total colectomy, both submitted to reoperations. We observed no perioperative mortality. Eight patients underwent perianal interventions while using UST (10.9%). One patient underwent neurosurgery for meningioma resection.

TABLE 2. Adverse events during treatment with Ustekinumab.

Adverse events	Total (n=17)
Perianal abscess n (%)	6 (8.1%)
Upper respiratory infection n (%)	3 (4.1%)
Clostridioides difficile colitis n (%)	2 (2.7%)
COVID n (%)	2 (2.7%)
Herpes Zoster n (%)	1 (1.4%)
Cytomegalovirus colitis n (%)	1 (1.4%)
Nephrolithiasis n (%)	1 (1.4%)
Bowel obstruction n (%)	1 (1.4%)
Cutaneous reaction n (%)	1 (1.4%)
Infusion reaction n (%)	2 (2.7%)
Asthenia	1 (1.4%)
Headache	1 (1.4%)

DISCUSSION

UST has been available for use in clinical practice in Brazil for 4 years, and this is one of the first real world studies in Latin America to assess the effectiveness of this agent in the short and long term. UST was shown to be effective and safe in patients with CD refractory to other biological agents (85.1% to anti-TNF and 17.6% to VDZ), and with severe phenotypes (disease duration >10 years, 40.5% with perianal disease and 47.3% previous intestinal resection). Clinical remission was achieved at weeks 8 and 52 in 45.8% and 59.4% of patients, respectively.

Our clinical remission results were similar to those found in studies which also used the HBI ≤4 score to define remission and analyzed the same period of treatment. The ENEIDA group study, which evaluated 305 patients from 42 centers in Spain, 96% who had previously failed anti-TNF therapy, described clinical remission rates of 47% and 64.4%[12,13]. Another Spanish study showed remission rates of 40.8% and 60.5% of the 98 patients analyzed[14].

An indirect comparison between our study and the main previously published real-life studies regarding clinical remission is shown in TABLE 3. It is important to take into account that there is significant heterogeneity in methodology and patient populations in these real-life studies, which limits extensive comparisons with our results. Real-life studies often describe higher remission and response rates as compared to prospective randomized clinical trials. The explanation for this discrepancy is not exclusive to the present analysis or specific to UST, and probably results from the definitions of remission and response in real-life studies, in addition to the possibility of associating treatments (steroids or immunosuppressants) which are often not allowed in randomized trials.

Clinical remission rates at weeks 8 and 52 in naive patients (75% and 83.3%) to previous treatment with anti-TNF were higher than in exposed patients (40% and 54.8%). Comparatively, in the study by Biemans et al., short and long-term clinical remission rates of 25.3% and 42.9% were described in patients who failed anti-TNF therapy, which represented 98.6% of the sample[15]. Previous exposure to anti-TNF agents seems to be a factor which influences the response to other biologics used in the treatment of CD, with a greater response always observed in naive patients. A possible explanation for this effect could be the greater severity of CD or changes in inflammatory pathways after exposure to anti-TNF agents[13].

TABLE 3. Indirect comparison of clinical remission rates with UST among major real-life studies.

Author	Year	Patients with UST (n)	Country	Clinical short term	
				Remission (%)	Long term
Ma et al.	2017	167	Canada	15%-week 12	27.9%-week 48
Parra et al.	2019	44	Brazil	38.6%-week 8	75%-week 44
Kubesch et al.	2019	106	Germany	24.7%-week 8	26.9%-week 48
Hoffman et al.	2019	57	Germany	–	35.1%-week 24
Miyazaki et al.	2019	47	Japan	44.4%-week 8	50%-week 48
Liefferinckx et al.	2019	152	Belgian	28.2%-week 8	25.7%-week 48
Biemans et al.	2019	221	Netherlands	30.7%-week 12	39.4%-week 52
Iborra et al.	2019	305	Spain	47%-week 8	–
Eberl et al.	2019	48	Finland	63%-week 16	52% end of follow-up
Bar-Gil Shitrit et al.	2020	106	Israel	–	31%-week 24
Iborra et al.	2020	407	Spain		64.4%-week 52
Lorenzo González et al.	2020	98	Spain	40.8%-week 8	60.5%-week 52
Present study	2021	74	Brazil	45.8%-eek 8	59.4%-week 52

UST: Ustekinumab.

The clinical response rate at week 8 in our study was 54.2%, similar to those described in the studies by Liefferinckx et al. (59.2%) and by Kubesch et al. (54.8%). However, when comparing the long-term clinical response rate (67.6%), our numbers were higher than those described in the two aforementioned studies (42.1% and 51.6% respectively)[16,17]. Until the end of the follow-up, 55 patients (74.3%) had an objective assessment of CD through endoscopic examinations, with 21.8% achieving remission. These data are similar to those found in other real-life studies, such as those by Ma et al., with 167 patients with CD from two Canadian centers, showing rates of endoscopic remission of 27.2%[6]. A similar rate was also described in the American study by Bennett et al. with 96 patients, where 25% achieved endoscopic remission[18].

In a systematic review published in 2019, which included eight real-life studies with UST in CD, six percent of patients underwent some type of surgery during treatment[19]. In the present study, 22.9% of patients underwent a major abdominal CD-related surgical procedure. One could question if UST had been used earlier in these patients, as a first line of treatment, surgical procedures could have been avoided, since the mean disease duration at the beginning of UST therapy was approximately 10 years and most patients failed other biological drugs.

The safety profile of UST in international studies has been favorable, with few serious adverse events reported. The most common complications included myalgia, arthralgia, infections and headache. Serious adverse events are rare, need for medication discontinuation was infrequent and there does not appear to be an increased risk for malignancies[5]. The overall rate of adverse events described in the systematic review by Engel et al., as a combined proportion of real-life studies, was 21%[19]. In the present study, seventeen patients had some adverse effects while using UST (23%). Iborra et al. evaluated 407 patients with CD using UST, and during the 52 weeks of follow-up 14.2% of the patients had an adverse event, mostly bacterial infections (34%)[12]. In the Belgian study that evaluated 152 patients, during the 12-month follow-up, 11 adverse events were observed and one patient discontinued the medication due to myalgia and severe pain[16]. In a Japanese study, 47 patients with CD using UST were included, and only one patient discontinued the drug due to skin rash and two patients (4.3%) had a diagnosis of cancer after UST treatment[20].

In the present study, 41.9% of patients experienced loss of response to UST, compared to approximately 20 to 35% in previous studies[21]. Common reasons for non-response to biological drugs include subtherapeutic drug concentrations and immunogenicity. In these patients, increasing the dose or shortening the interval may be considered in order to recapture the response and avoid drug discontinuation[22]. In the present study, half of the patients (52.7%) required UST dose optimization for injections every 4 weeks. This is probably related to the severity of the disease in this mostly refractory population. In the study by Kopylov et al. dose optimization was observed in 47.7% of cases, while in the study by Obando et al. occurred in only 17.9% of the 214 patients evaluated[23,24].

The present study is associated with some limitations, which need to be discussed in the analysis of the results. As UST was approved for use in Brazil in 2017, the sample size was limited, as the analysis had an inclusion period that started in 2019. The high proportion of patients treated with UST previously exposed to other biological treatments is not surprising, given the recent approval of the medication. The performance of the endoscopic examination was not centralized, and no objective score was used as an to determine endoscopic remission or response. On the other hand, the present study has some strengths. With a substantial sample size for a real-life study, a representative cohort that reflects daily clinical practice was analyzed by evaluating efficacy and safety in patients who would probably be excluded from clinical trials (exposure to multiple biological agents, previous bowel resections, immunosuppressive treatment or concomitant corticosteroids for co-induction). The exclusion of patients who started the medication in clinical remission, limiting the denominator of the analyses, reduces the bias of our findings. The results of the present study represent one of the first solid and detailed data on Brazilian and Latin American CD patients using UST and may be useful in choosing the most appropriate treatment for patients in our continent.

In summary, UST therapy resulted in significant rates of clini-

cal remission and response, which are comparable to other real-life studies from different countries. Few patients had an adverse event while using the medication, showing its adequate safety profile. The need for dose optimization and drug discontinuation were also compatible to other studies from the globe. Future studies are needed to assess predictors of UST response in Latin American patients with CD.

Authors' contribution

Castro PCS performed the project design, collected the data and wrote the manuscript. Magro DO performed the statistical analysis of the data. Nones RB, Furlan TK and Miranda EF supported data curation and production of manuscript. Kotze PG supported supervision of all stages, reviewed and edited the manuscript.

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RESUMO – Contexto – Dados de vida real sobre o uso de Ustequinumabe (UST) em pacientes brasileiros e latino-americanos com doença de Crohn (DC) são escassos. **Objetivo –** O desfecho primário foi a avaliação da remissão clínica nas semanas 8 e 52, e os desfechos secundários foram: avaliação da resposta clínica nas semanas 8 e 52, remissão endoscópica, eventos adversos e taxas de cirurgia abdominal relacionada à DC durante o seguimento. **Métodos –** Estudo observacional e retrospectivo, incluindo pacientes com DC tratados em dois centros, que receberam UST em qualquer momento do tratamento. A remissão e a resposta clínica foram definidas como índice de Harvey-Bradshaw ≤4 e ≥3 pontos de redução, respectivamente. **Resultados –** Foram incluídos 74 pacientes, 85,1% previamente expostos a anti-TNFs. A remissão clínica foi observada em 45,8% e 59,4% dos pacientes nas semanas 8 e 52, respectivamente. As taxas de resposta clínica foram de 54,2% e 67,6% nas semanas 8 e 52. A remissão endoscópica foi observada em 21,8% dos pacientes. Dezessete pacientes apresentaram eventos adversos, principalmente infecções leves, sendo 22,9% dos pacientes submetidos à cirurgia abdominal (sendo a ileocolectomia o procedimento mais comum). **Conclusão –** A terapia com UST resultou em taxas significativas de remissão e resposta clínica, conforme descrito em outros estudos do mundo real. Poucos pacientes apresentaram eventos adversos durante o tratamento, mostrando seu adequado perfil de segurança.

Palavras-chave – Doença inflamatória intestinal; doença de Crohn; Ustequinumabe; Interleucina.

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