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Certolizumab Pegol in Crohn's Disease Management: A Multicentric Brazilian Observational Study

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Abstract

Introduction and Objectives Certolizumab Pegol (CZP) is an anti-TNF agent approved in Brazil for Crohn's disease (CD). There is a lack of data in Brazil and Latin America detailing real-world experiences with CZP. The primary objective was clinical remission in weeks 26 and 54. The secondary endpoints were clinical response in weeks 26 and 54, endoscopic remission, biological switch rates, rates of CD-related surgery, persistence with treatment over time, and adverse events. Remission and clinical response were defined as HBI $\leq$4 and $\geq$3 points reduction of HBI, respectively. Endoscopic remission was defined as the complete healing of the intestinal mucosa.

Methods This observational and retrospective study included patients with CD from 4 Brazilian centers who received CZP during their disease course.

Results Forty-five patients were included. The median age was 42.16 years old, 53.3% had perianal involvement, 37.8% had undergone previous surgery, and 71.1% of patients were anti-TNF naïve. Clinical remission was observed in 73.2% and 62.5% of patients at weeks 26 and 54, respectively. Clinical response was observed in 14.63% and 18.75% in weeks 26 and 54, respectively. Endoscopic remission was observed in 36.4% of patients. A switch to biological therapy was performed in 57.8% of patients. Eleven patients underwent abdominal surgery; 62.25% discontinued treatment with CZP, with a median of 16 months, and 22.2% presented drug-related adverse events.

Conclusions CZP in CD was associated with clinical remission and response rates compatible with international real-world case series. Most patients needed to switch to biological therapy due to inadequate disease control.

Keywords
- inflammatory bowel disease
- Crohn's disease
- monoclonal antibodies
- certolizumab pegol

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Introduction

Crohn's disease (CD) is characterized by periods of activity and remission, with recurrent cycles of inflammation leading to complications such as fistulas and stenosis. Treatment strategies for CD aim to control inflammation and prevent structural damage to the intestine and its complications.[1]

Among the medical therapeutic options for moderate-to-severe CD are biological agents. The most frequently used class comprises TNF-α inhibitors, with certolizumab pegol (CZP) being one of the options, according to previously published studies.[2–5]

Data are scarce on the use of different anti-TNF agents in the handling of CD in Latin America and Brazil. The approval of CZP in Brazil took place in 2011. Its incorporation into therapeutic guidelines from the Ministry of Health took place in 2017, a few years after the experience with infliximab (IFX) and adalimumab (ADA) was consolidated in IBD management in our country. This might be the reason there is a lack of data in Brazil and Latin America detailing experiences with the drug published to date.

The primary aim of this study was to analyze clinical remission rates at maintenance (weeks 26 and 54) and at the last follow-up in CD patients treated with CZP. The secondary objectives were to analyze clinical response rates, determine endoscopic remission, the need for a biologic switch, and the need for surgery during treatment, and analyze possible adverse events of the drug.

Materials and Methods

This was an observational, longitudinal, retrospective, and uncontrolled study of patients with CD who used CZP during any phase of their treatment. The study was conducted in 4 academic IBD tertiary referral centers in Brazil. Convenience sampling was applied. Therefore, all patients who used the drug from January 2018 to January 2021 were eligible for the study. The inclusion criteria comprised patients with CD treated with CZP on an outpatient basis who were more than 18 years of age. We excluded patients with no data in the electronic charts and patients with severe CD admitted to the hospital at CZP treatment initiation.

All patients included in the study received an induction dose of CZP 400 mg subcutaneously at weeks 0, 2, and 4, followed by maintenance of 400 mg every four weeks. The variables analyzed included demographic characteristics such as age at diagnosis, sex, and age at the beginning of treatment with CZP. The Montreal classification was used to identify characteristics of CD, duration of disease from diagnosis to treatment initiation, smoking, concomitant medications (corticosteroids, immunomodulators), previous exposure to other anti-TNF agents, and abdominal surgeries performed. Records of clinical assessments at weeks 26, 54, and the last follow-up were retrospectively checked according to the Harvey-Bradshaw Index (HBI) for clinical activity evaluation for CD. Clinical remission was defined as HBI ≤ 4 points. Clinical response was defined as a reduction in HBI of 3 or more points from the baseline index (at the start of treatment). The patient's last follow-up was considered at the last medical visit in which CZP was maintained (in the case of drug discontinuation, the date of the last dose, and in the case of continuation, the last clinical evaluation in the medical records). The determination of the periods of clinical evaluation (weeks 26 and 54) was mirrored in other clinical studies performed with CZP for indirect comparison between the studies. Mucosal healing was evaluated in the first colonoscopy performed during treatment at different periods and was defined as the complete absence of ulcers. Drug persistence over time (time of drug use) was analyzed, as were treatment interruption and associated reasons. In addition, adverse events of CZP during treatment, infectious or not, were also evaluated.

Statistical Analysis

Data were collected and stored in a Microsoft Excel spreadsheet. Quantitative variables with a normal distribution are presented as the mean ± standard deviation (SD). Qualitative variables are presented as percentages. The Kaplan-Meier estimation method was used for drug persistence and the need for surgery during follow-up. The significance level adopted for the statistical tests was 5%. The statistical package used was IBM SPSS (Statistical Package for the Social Sciences) v. 22.0.

Results

Forty-eight patients who met the inclusion criteria were initially identified. However, one case was excluded because the patient used CZP to treat ankylosing spondylitis one year before CD diagnosis. Two other cases were also excluded because of missing data in medical records, resulting in 45 cases being fully analyzed. The follow-up period with the drug ranged from 2 to 27 months, with a median of 16 months (►**Fig. 1**).

Most patients were female (30/45 cases), with a median age of 42.16 (± 13.056) years and a median CD duration prior to CZP use of 6 years (ranging from 2 to 360 months). Overall, 51.1% had ileocolonic disease, 53.3% had perianal disease (active or past), and 48.9% had an inflammatory phenotype (nonstenosing and nonpenetrating). In addition, 20% were smokers, and 37.8% had undergone previous abdominal surgery, the most frequent being ileocaecal resections ($n = 10$), followed by small bowel resections ($n = 5$) and strictureplasties ($n = 2$).

Of the 45 included patients, 32 (71.1%) were naïve to anti-TNF drugs. Of the 13 (28.9%) who had already been treated with TNF inhibitors, 5 had used IFX, 2 had used ADA, and 6 had used both agents. Only one patient had used ustekinumab before CZP, and no cases exposed to vedolizumab before CZP were identified. Moreover, 19 (42.2%) patients received steroids in conjunction with CZP. Azathioprine was used as adjunctive therapy in 22.2% of cases ($n = 10$). No patients received 6-mercaptopurine or methotrexate in association with CZP. The main clinical and demographic baseline characteristics of the patients analyzed are detailed in ►**Table 1**.

Data related to clinical remission were evaluated at weeks 26 and 54 (maintenance) and the patient's last

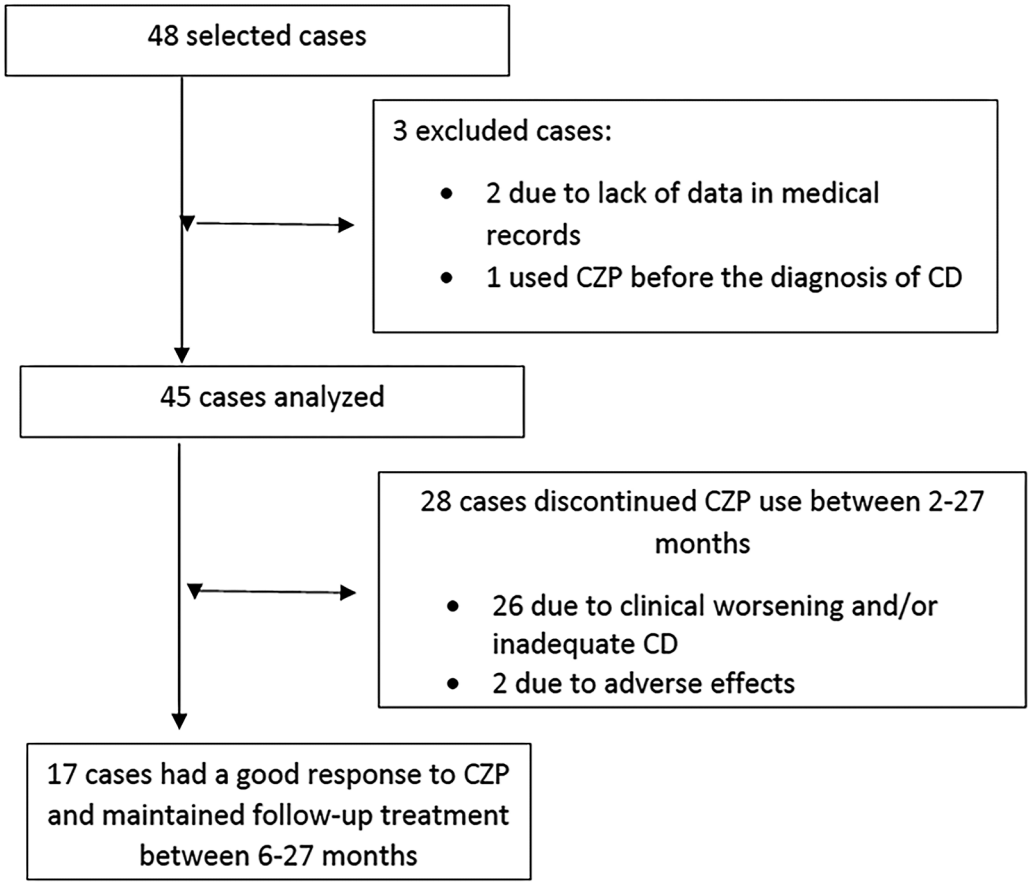

Fig. 1 Study flowchart.

Table 1 Demographic characteristics

Characteristic	Total ($n = 45$)
Gender	
Female	30 (66.7%)
Male	15 (33.3%)
Age in years	42.16 ± 13.056
Diagnosis time before the onset of the average CZP in years	6 years (2–360 months)
Montreal A	
A1 A2 A3	5 (11.1%) 26 (57.8%) 14 (31.1%)
Montreal L	
L1 (ileal) L2 (colonic) L3 (ileocolonic) L4 (upper GI)	8 (1.,8%) 12 (26.7%) 23 (51.1%) 1 (22%)
Montreal B	
B1 (inflammatory) B2 (stenosing) B3 (penetrating)	22 (48.9%) 11 (24.4%) 12 (26.7%)
Perianal disease	24 (53.3%)
Smoking	9 (20%)

(*Continued*)

Table 1 (*Continued*)

Characteristic	Total ($n = 45$)
Previous abdominal surgery	17 (37.8%)
• Ileocolectomy • Enterectomy • Strictureplasty • Ileocolectomy+ enterectomy • Ileocolectomy+ enterectomy + strictureplasty • Abdominal abscess drainage • Colostomy • Gastroplasty • Fistulotomy • Rectosigmoidectomy + Appendectomy due to entero-cutaneous fistula	6 (35.3%) 1 (5.9%) 1 (5.9%) 2 (11.8%) 1 (5.9%) 1 (5.9%) 1 (5.9%) 1 (5.9%) 1 (5.9%) 1 (5.9%) 1 (5.9%)
Prior use of ANTI-TNF	13 (28.9%)
Anti-TNF used before CZP	
Infliximab Adalimumab Infliximab + Adalimumab	5 (3847%) 2 (15.38%) 6 (46,15%)
Use of corticosteroids as coinduction with CZP	19 (42.2%)
Concomitant use of Azathioprine	10 (22.2%)
Follow-up time with the drug	2–27 Months (median 16 Months)

follow-up. It is noteworthy that 33.3% ($n = 15$) of the sample had an HBI ≤ 4 at CZP induction (entered the study already in remission). At week 26, the denominator dropped to 41 patients because 3 had already discontinued CZP, and in 1 case, there were no records of clinical data in the charts. At week 54, 13 patients were no longer using CZP, leaving a denominator of 32 patients. The clinical remission rates identified at weeks 26 and 54 were 73.20% and 62.50%, respectively. At the last clinical follow-up, 57.8% of the patients were in remission. Clinical response rates in weeks 26 and 54 were 14.63% and 18.75%, respectively. Clinical response at the last follow-up was observed in 11.1% of cases. Remission and clinical response rates at the various analysis time points are illustrated in ►**Fig. 2**. ►**Fig. 3** demonstrates the median HBI indices in the analyzed periods. The outcomes were not considered at the end of induction due to the scarcity of data at this specific time point.

Before treatment with CZP, 43 patients (95.6%) had endoscopically active disease. After starting treatment with the drug, 33 patients underwent colonoscopies in a time interval ranging from 2 to 18 months, and 21 (63.6%) patients still had active disease. Only 12 patients (36.4%) achieved full mucosal healing, 10 of whom were not previously exposed to biological therapy, and only 2 had perianal disease. ►**Supplementary Fig. S1** illustrates HBI evolution throughout CZP treatment in patients who achieved endoscopic remission, and ►**Supplementary Fig. S2** shows the evolution of HBI in patients who did not have endoscopic remission.

Of the 45 patients, 26 (57.8%) needed to switch medications to another biological drug due to treatment failure: infliximab ($n = 12$), adalimumab ($n = 7$), ustekinumab ($n = 5$), and vedolizumab ($n = 2$).

During treatment with CZP, 11 patients underwent surgery from 0 to 23 months after drug initiation, with a median of 7 months (95% CI: 3.873–10.127). In 5 patients, surgery was performed to treat active perianal disease, 4 had abdominal procedures (ileocolectomy, segmental colectomy, enterectomy, gastroenteroanastomosis), 1 had a colostomy closure, and 1 had a cesarean section. ►**Fig. 4** demonstrates the timeline of the need for surgery over time.

A change to CZP 200 mg subcutaneously every 2 weeks was observed in 14 cases (31.1%), aiming to recover clinical response after the secondary loss of response. In 28 patients (62.2%), CZP therapy was discontinued due to failure or adverse effects. The drug's persistence ranged from 2 to 27 months, with a median of 16.0 months (95% CI 10.634–21.366). This is illustrated in ►**Fig. 5**.

Overall, 10 patients had adverse events with CZP. One patient was in clinical and endoscopic remission with CZP but presented with pharmacodermia requiring a biologic switch. Another patient presented dyspnea after the CZP injection, again requiring a switch to another agent. Some patients had more than one adverse effect, such as upper respiratory and *Clostridioides difficile* infection, bacterial pneumonia and pharmacodermia, oral candidiasis, and arthralgia. There were no deaths during follow-up. No cases of active tuberculosis or neoplasia were identified. Adverse events with CZP treatment are shown in ►**Table 2**.

Discussion

CZP is a therapeutic option for CD treatment, but its role as a first-line drug is still uncertain. This is a study of patients with CD treated with CZP from four Brazilian centers, monitored for

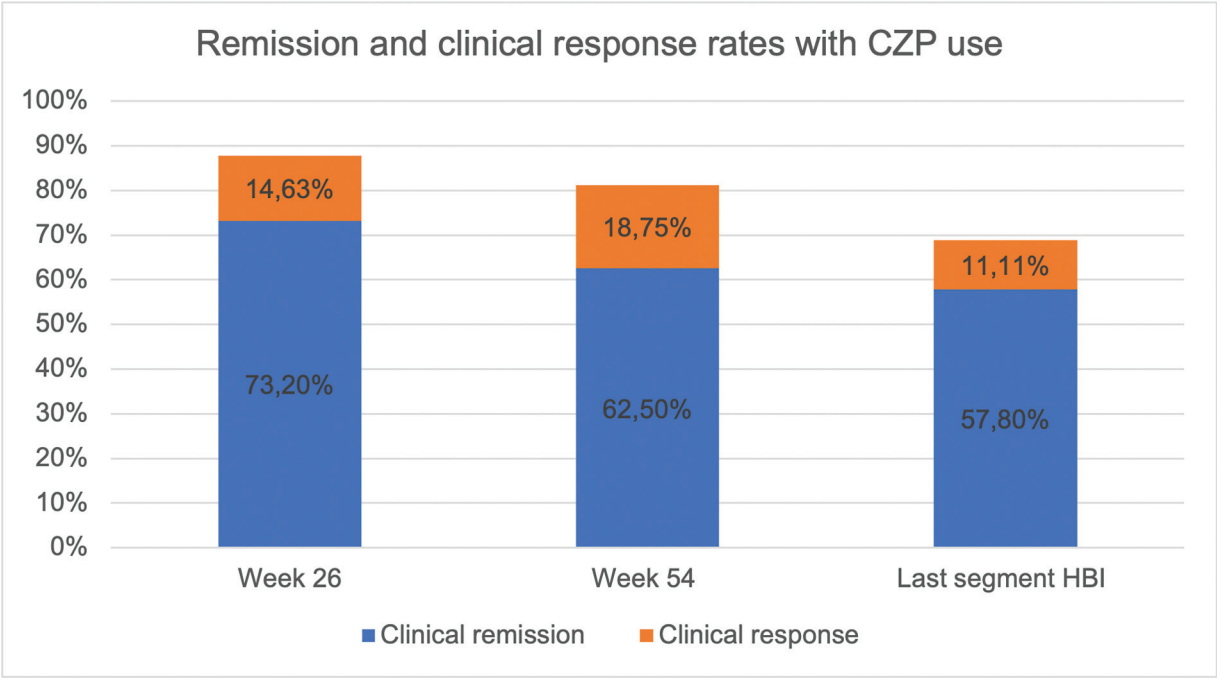

Fig. 2 Clinical remission and response rates in weeks 26 ($n = 41$), 54 ($n = 32$), and at the last follow-up ($n = 45$).

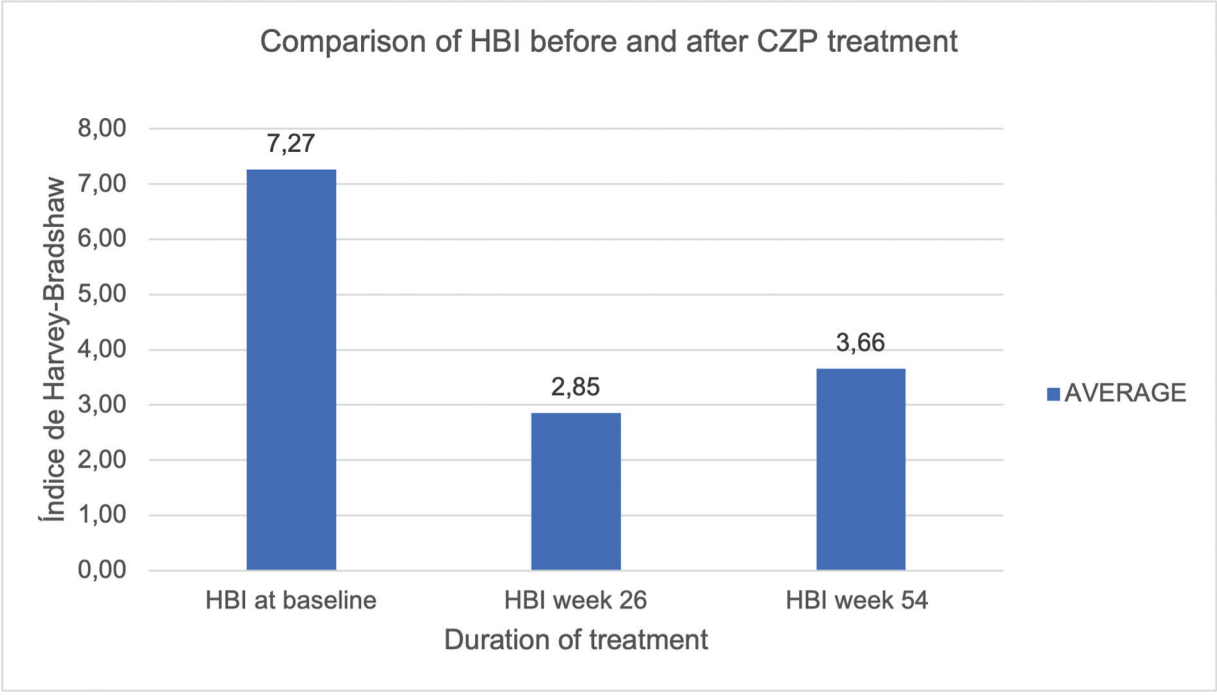

Fig. 3 Comparison of the median HBI after treatment with CZP in the study periods.

up to 27 months of drug treatment. Most patients were female, with an average age of 42 years, and diagnosed with CD ~6 years before starting treatment with CZP. They had disease predominantly in the ileocolonic location (51.1%) and an inflammatory phenotype - Montreal B1 (48.9%). There was active or past perianal involvement in 53.3% of cases ($n = 24$), 18 with CZP discontinuation during follow-up. Regarding previous exposure to other biologics, 71.1% had never had previous biologic therapy. These characteristics make this population an interesting target for drug efficacy analysis. If, on the one hand, the patients had severity criteria (such as high rates of perianal CD and previous surgeries), more than 70% of the patients were naïve to biologics, which would demonstrate the real potential efficacy of the drug in clinical practice.

The clinical remission rates were 73.2% in week 26 and 62.5% in week 54. It is noteworthy that 33.3% of the cases started treatment with CZP in clinical remission, with the use of the drug indicated due to endoscopic or radiological

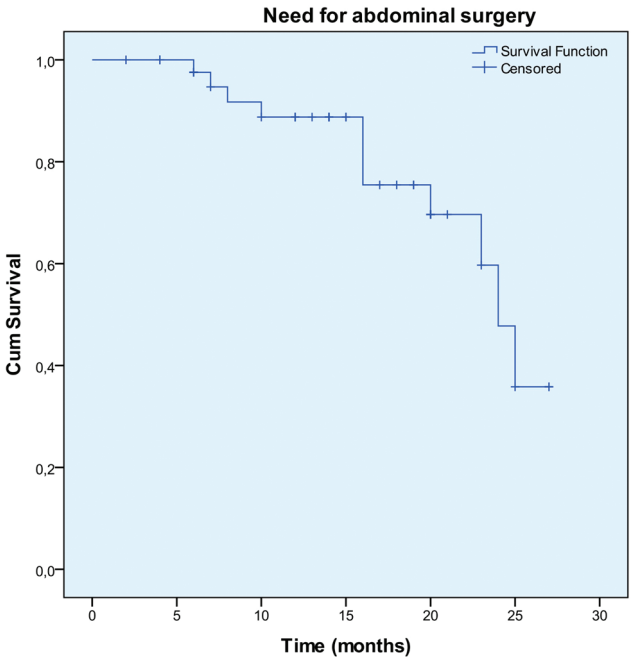

Fig. 4 Need for surgery during treatment (Kaplan-Meier).

activity of CD or a switch of treatment due to adverse events of previous medications. In addition, 42.2% of patients received conduction with corticosteroids, which could contribute to the observed clinical remission rates. In studies where patients are symptomatic and awaiting medication approval from the health care system, conduction with corticosteroids is common and may have influenced the results.[6] Combination therapy with azathioprine was used in only 22.2% of patients.

In 2008, Danese et al. evaluated the efficacy of CZP in 21 refractory patients who had lost response or were IFX intolerant. After induction with 400 mg of CZP in weeks 0 and 2, 43% of patients achieved clinical remission, and 52%

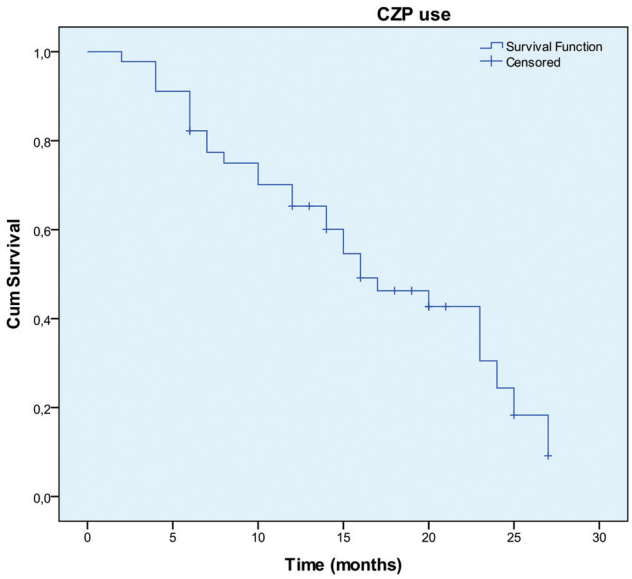

Fig. 5 CZP Time-of-Use Curve (Kaplan-Meier).

Table 2 Adverse events with CZP treatment

Adverse event	Total ($n = 10/45$)
Infections	11
• Upper respiratory tract infection	4
• *Clostridioides difficile* infection	1
• Perianal Abscess	1
• Bacterial pneumonia	1
• Urinary tract infection	1
• Gastroenteritis	1
• Oral Candidiasis	1
• Vaginal candidiasis	1
• Parotiditis	1
Arthralgia	1
Colonic perforation	1
Pruritus	1
Dyspnea after injection	1
Pharmacodermia	1

achieved clinical response. These numbers are compatible with those observed in our study.[2]

The clinical response rates observed in weeks 26 and 54 were 14.63% and 18.75%, respectively. As previously mentioned, these rates are considered low, as many patients entered the study already in clinical remission. In addition, HBI at baseline ranged from 0 to 24, with a 7-point average, a low value compared with other studies, such as PRECISE 3, in which the average HBI at baseline was 9.[3] These factors probably account for the lower response rates compared with remission rates. Other observational studies are summarized below in ►**Table 3**, indirectly comparing remission and clinical response rates with our data. As observed, real-life studies tend to have higher remission and response rates due to less rigorous patient selection and follow-up. Furthermore, unlike pivotal studies, observational studies allow the addition of new drugs and variations in dosage. Therefore, the numbers in this analysis are higher in terms of clinical remission and lower concerning clinical response than in the other studies. The characteristics of the included population and methodological issues are possibly linked to these differences.

Endoscopic remission is one of the targets of CD treatment and is related to reduced intestinal damage.[7] In this study, endoscopic remission with CZP was observed in 36.4% of patients, similar to other real-life studies. Ramos et al. demonstrated rates of 39.2% and Moon et al. of 43.2% in colonoscopies performed at a median of 9 months after CZP initiation.[6,8] These findings are higher than those found in the MUSIC study, which demonstrated endoscopic improvement of lesions as early as week 10 but with low mucosal healing rates (4% at week 10 and 8% at week 54).[9]

Approximately one-third of patients with CD may not respond to induction therapy with anti-TNF agents. Among those who respond, up to 45% will progressively lose response over time, with a relapse of clinical symptoms and an alteration in inflammatory markers.[10] Therefore, treatment optimization strategies such as reducing the drug application

Table 3 Indirect comparative analysis of the main studies with CZP

Author	Year	Country	Clinical remission (%)	Clinical response (%)	Sample (n)	Population characteristics
Schreiber et al (Precise 2)[5]	2007	Multinational	43% (week 6) 48% (week 26)	64% (week 6) 63% (week 26)	428	76% without prior anti-TNF exposure
Danese et al[2]	2008	Italy	43% (week 4)	52% (week 4)	21	100% refractory or INF-intolerant
Lichtenstein et al (Precise 3)[3]	2010	Multinational	47.9% (week 26) 40.9% (week 52) 36.3% (week 80)	56.3% (week 26) 45.1% (week 52) 40% (week 80)	241	81% without prior anti-TNF exposure
Stein et al[13]	2014	USA	14.9%	31%	87	75.9% with previous exposure to anti-TNF
Moon et al[6]	2015	USA		19.9% (week26) Corticosteroid-free response	358	86.9% with prior exposure to biological therapy
Present study	2021	Brazil	73.2% (week 26) 62.5% (week 54)	14,63% (week 26) 18,75% (week 54)	45	71.1% no previous exposure to biological drugs

interval or dose adjustment may be necessary throughout treatment. In 14 (31.1%) patients, treatment optimization was attempted with dose adaptation (200 mg of CZP every 2 weeks, according to the label), with a recovered clinical response in only four patients. CZP was the first biological agent used by these patients who benefited from optimization, and their duration of treatment ranged from 12 to 27 months. This strategy is supported by a real-life study that evaluated recovered clinical responses with dose fractionation.[11] The PRECISE 4 study showed that using an additional dose of CZP 400 mg was effective as a recovery strategy in patients who had a clinical relapse while on the drug.[12] Stein et al. evaluated optimization strategies by applying an additional dose of CZP 400 mg and dose escalation (more than 400 mg in a 4-week interval). However, most patients who received the reinduction dosage did not have a sustained clinical response or remission, and maintenance dose escalation failed in all cases.[13] In our study, no additional CZP dose or doses higher than 400 mg every 4 weeks were used because most patients received treatment through the public health system, which does not provide dose variations.

Vande Casteele et al. using a pharmacokinetic model that accounts for the time-varying nature of covariates to simulate CZP concentrations to evaluate the exposure-response relationship for CZP in Crohn's disease, analyzed nine clinical trials (2157 patients) and found that patients who achieved clinical response and clinical remission at week 6 had significantly higher CZP concentrations at week 2, week 4, and week 6 relative to those who did not. Furthermore, the concentrations were significantly higher in patients who achieved C-reative protein ≤ 5 mg/L and faecal calprotectin ≤ 250 µg/g at week 6, demonstrating the role of the drug concentration during induction and maintenance therapy in achieving a better biological and clinical response, which could be an independent factor influencing the drug efficiency.[14]

Colombel et. al also reported that higher CZP serum concentrations at week 8 were significantly associated with endoscopic response and clinical remission at week 10. At week 54, the rates of endoscopic remission also correlated with CZP plasma concentrations.[15] Antidrug antibodies (ADAbs) seem to play an important role in serum drug concentration.[8,14,16]

Currently, therapeutic drug monitoring (TDM) offers the potential to optimize therapy in individual patients, being reactive TDM supported by guidelines and widely adopted in clinical practice. We are the opinion that TDM, by allowing precise dose adjustments, can improve the response to immunobiological agents in Crohn's disease.[8,14,16]

In this series, 11 patients underwent surgical treatment during CZP treatment, with a median of 7 months (95% CI: 3.873–10.127). Among the surgical procedures, 5 were for complementary treatment of perianal disease, and 4 patients had abdominal surgeries. Moon et al[6] found a cumulative probability of 29.4% experiencing intestinal or perianal complications while using CZP in the first year and 39.2% in the second year of treatment. These findings question the effectiveness of the medication in controlling disease progression, despite being compatible with other agents from the same class.

A Swiss observational study conducted by Vavricka et al[17] mostly with patients already exposed to anti-TNF therapy, with a follow-up of up to 5 years of CZP use, showed that at the end of follow-up, only 34.6% maintained their CZP treatment. According to the medical evaluations, the number of patients who continued using CZP in weeks 26 and 56 was 62.5% and 46.7%, respectively. However, patients who maintained the medication for longer than 12–18 months experienced a sustained benefit. The PRECISE 3 study found lower rates of drug discontinuation, 29.2% in the first year.[18] In our study, 37.8% maintained treatment at a median of 16 months (95% CI 10.634–21.366), and 62.2% (28/45) of patients discontinued CZP. Most of the adverse events reported were mild infections, similar to other studies.[19] A multicenter retrospective study evaluating IFX and ADA in monotherapy found a cumulative odds ratio of staying on anti-TNF from

initiation in monotherapy of 90.6% in the first year and 57.9% in 5 years.[20] These findings demonstrate the difficulties with CZP treatment durability in our daily practice, which may limit its choice as first-line therapy in favor of agents that present more dosing flexibility (possibility of optimization with higher doses) and longer-lasting efficacy, such as infliximab and adalimumab.

Our study is associated with some limitations that need to be discussed. First, this is a retrospective study based on medical record analysis. Furthermore, this is a convenience cohort with limited patients and varying CD phenotypes treated in varying academic referral centers. The definition of remission and response assessed by HBI may underestimate the real inflammatory activity of the disease. Endoscopic remission assessment did not use endoscopic scores, which are not routinely applied in endoscopic examinations at most centers. The use of biomarkers such as fecal calprotectin was also limited because it was unavailable in most centers. Despite these limitations, the study had some strengths including clear and defined objectives, representing the first detailed data of CZP in CD in Latin America. This may help to define the role of medication in treatment algorithms on our continent.

In summary, CZP for CD management was related to clinical benefit and good tolerability in this cohort of patients. In addition, remission and clinical response rates were compatible with international real-life studies. However, because most patients need to switch to different biologic agents for inadequate disease control and more than 60% of cases discontinued the drug, its long-term efficacy is questionable. Thus, CZP's use as a first-line agent in CD management remains debatable.

Ethical considerations

This study was approved by the Research Ethics Committee from the Catholic University of Paraná and all additional centers under reference number CAAE: 30359020.8.0000.0020, from the Ministry of Health National Ethics Board. Clinical research protocols and data confidentiality demands were followed, keeping the anonymity of each patient's data.

Authors' Contributions

Study concept and design (Thaisa Kowalski Furlan, Paulo Gustavo Kotze), acquisition of data (Thaisa Kowalski Furlan, Marcello Imbrizi, Paula Cenira Senger de Castro, Rodrigo Bremmer Nones, Eron Fábio Miranda) analysis and interpretation of data (Thaisa Kowalski Furlan, Daniela Magro, Paulo Gustavo Kotze), drafting of the manuscript (Thaisa Kowalski Furlan), critical revision of the manuscript for important intellectual content (Thaisa Kowalski Furlan, Paulo Gustavo Kotze), administrative, technical, and material support (Thaisa Kowalski Furlan, Paulo Gustavo Kotze), and study supervision (Paulo Gustavo Kotze, Daniela Magro). All authors have made a significant contribution to this study and have approved the final manuscript

Conflict of Interest

None.

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