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Prospective Study

Real-world treatment patterns and disease control over one year in patients with inflammatory bowel disease in Brazil

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Abstract

BACKGROUND

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBDs) with a remission-relapsing presentation and symptomatic exacerbations that have detrimental impacts on patient quality of life and are associated with a high cost burden, especially in patients with moderate-to-severe disease. The Real-world Data of Moderate-to-Severe Inflammatory Bowel Disease in Brazil (RISE BR) study was a noninterventional study designed to evaluate disease control, treatment patterns, disease burden and health-related quality of life in patients with moderate-to-severe active IBD. We report findings from the prospective follow-up phase of the RISE BR study in patients with active UC or CD.

AIM

To describe the 12-mo disease evolution and treatment patterns among patients with active moderate-to-severe IBD in Brazil.

METHODS

This was a prospective, noninterventional study of adult patients with active Crohn's disease (CD: Harvey-Bradshaw Index ≥ 8 , CD Activity Index ≥ 220), inadequate CD control (*i.e.*, calprotectin $> 200 \mu\text{g/g}$ or colonoscopy previous results), or active ulcerative colitis (UC: Partial Mayo score ≥ 5). Enrollment occurred in 14 centers from October 2016 to February 2017. The proportion of active IBD patients after 9-12 mo of follow-up, Kaplan-Meier estimates of the time to mild or no activity and a summary of treatment initiation, discontinuation and dose changes were examined.

RESULTS

The study included 118 CD and 36 UC patients, with mean \pm SD ages of 43.3 ± 12.6 and 44.9 ± 16.5 years, respectively. The most frequent drug classes at index were biologics for CD (62.7%) and 5-aminosalicylate derivatives for UC patients

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(91.7%). During follow-up, 65.3% of CD and 86.1% of UC patients initiated a new treatment at least once. Discontinuations/dose changes occurred in 68.1% of CD patients [median 2.0 (IQR: 2-5)] and 94.3% of UC patients [median 4.0 (IQR: 3-7)]. On average, CD and UC patients had 4.4 ± 2.6 and 5.0 ± 3.3 outpatient visits, respectively. The median time to first mild or no activity was 319 (IQR: 239-358) d for CD and 320 (IQR: 288-358) d for UC patients. At 9-12 mo, 22.0% of CD and 20.0% of UC patients had active disease.

CONCLUSION

Although a marked proportion of active IBD patients achieved disease control within one year, the considerable time to achieve this outcome represents an unmet medical need of the current standard of care in a Brazilian real-world setting.

Key Words: Crohn's disease; Ulcerative colitis; Inflammatory bowel diseases; Prospective study

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Core Tip: This was a prospective, noninterventional study of 118 adult patients with active Crohn's disease (CD) and 36 with active ulcerative colitis (UC). The aim was to describe the 12-mo disease evolution and treatment patterns of active moderate-to-severe inflammatory bowel disease (IBD) patients in Brazil. The median time to first mild or no activity was 319 (IQR: 239-358) d for CD and 320 (IQR: 288-358) d for UC patients. A marked proportion of active IBD patients achieved disease control within one year, which is considered a long time to achieve the goal of reducing inflammation.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBDs) with a remission-relapsing presentation and symptomatic exacerbations that have a detrimental impact on patient quality of life and are associated with a high cost burden, especially in the case of moderate to severe disease[1,2]. The pharmacological treatment of IBD aims to achieve and maintain long-term remission and heal the gut mucosa, thus delaying the progression of disease and associated complications as well as the need for surgery[3]. For CD patients with moderate-to-severe disease activity, guidelines usually recommend the use of antitumor necrosis factor- α (anti-TNF α) either as a monotherapy or combined with an immunosuppressant to induce remission for steroid-refractory disease or steroid-intolerant patients[4]. With regard to moderate-to-severe active UC, an immunosuppressant and/or a biologic drug are recommended[5,6]. Systemic 5-aminosalicylate (5-ASA) agents are also indicated for maintenance treatment of UC[1]. Corticosteroids are recommended for short-term use (≤ 3 mo) during relapses of both CD and UC and are not recommended as maintenance therapy[1,4,6].

In clinical practice, physicians often try several options and treatment sequences for IBD management, both in monotherapy or combined regimens[3]. Primary nonresponse, secondary loss of response and development of adverse reactions to anti-TNF α drugs may occur and lead to discontinuation, with the subsequent prescription of a second advanced therapy with a different mechanism of action (*e.g.*, anti-integrins

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or JAK inhibitors)[7-11]. However, some studies have reported that up to half of IBD patients who discontinue their first-line biologic (infliximab or adalimumab) do not restart or switch to another therapy[3,12]. In Brazil, vedolizumab, ustekinumab and tofacitinib are available at private health services, the latter being approved only for UC treatment since 2018. Moreover, the VARSITY study recently demonstrated that the gut-selective anti-integrin vedolizumab was superior to the anti-TNF α adalimumab in achieving clinical remission in patients with moderate-to-severe active UC after one year[13].

Real-world data on IBD management could unveil unmet medical needs and treatment gaps[3]. This is of utmost relevance in developing countries such as Brazil, where the prevalence of IBD is increasing but access to biologic treatment may be restricted, and information on IBD treatment, in general, and associated outcomes is scarce[14,15]. The Real-world Data of Moderate-to-Severe Inflammatory Bowel Disease in Brazil (RISE BR) study was a noninterventional study designed to evaluate disease control, treatment patterns, burden of disease and health-related quality of life in patients with a previous diagnosis of moderate-to-severe active IBD[16,17]. Here, we report findings from the prospective follow-up phase of the RISE BR study in patients with active UC or CD and aim to describe the real-world treatment patterns and outcomes of IBD-related therapies during a 12-mo follow-up period.

MATERIALS AND METHODS

Study design

The RISE BR study (ClinicalTrials.gov Identifier: NCT02822235) was a national, multicenter, noninterventional study designed to evaluate disease control, treatment patterns, burden of disease and health-related quality of life among IBD patients in Brazil. It involved a cross-sectional evaluation of IBD patients (index date) with a retrospective data collection component and a 12-mo prospective follow-up period of IBD patients who had active disease (at the index date). The cross-sectional evaluation was conducted at routine IBD outpatient visits between October 2016 and February 2017, and patients were consecutively recruited from 14 study sites (nine clinics from the public health system and five private clinics) covering Brazil's most populated regions. In this article, we present data from the follow-up period. All participants provided written informed consent prior to the study procedures. The study was approved by the local ethics committees and was conducted according to the principles of the Helsinki Declaration.

Study population

At the index date, patients were included if they were aged 18 years or older and had a confirmed diagnosis of moderate-to-severe CD or UC at least 6 mo prior to index. Patients were excluded if they presented indeterminate/unclassified colitis, mental incapacity, unwillingness, or language barriers precluding adequate understanding or cooperation with the study, were hospitalized, participated in a clinical trial within the last 3 years, or received off-label treatment with vedolizumab. All patients presenting active disease at the index date were invited to participate in the prospective follow-up phase of the study. Active CD was defined as a Harvey-Bradshaw Index (HBI) ≥ 8 points or a Crohn's Disease Activity Index (CDAI) ≥ 220 points or fecal calprotectin levels $> 200 \mu\text{g/g}$ or colonoscopy results in the previous year suggestive of inadequate control (as per investigator criteria)[18]. Active UC was defined as a partial Mayo (pMayo) score ≥ 5 points.

Prospective follow-up period and study variables

The prospective observational period was defined as a 12-mo follow-up since the index date. Data were collected from patients' medical records by staff personnel of the participating site. Sociodemographic characteristics (age, sex, educational level, and professional status), weight and body mass index (BMI), smoking habits, and family history of IBD were collected at the study appointment. Other clinical variables included the time since first IBD diagnosis, extension/severity and location of CD or UC (Montreal classification), corticosteroid dependency/intolerance status, and presence of extraintestinal manifestations. In addition, IBD treatment patterns and changes during the follow-up period (at the index date and the following medical appointments) were collected.

CD activity during follow-up was evaluated with the HBI[18] and/or CDAI[19], depending on local practice. Moderate-to-severe active CD was defined as patients

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with an HBI ≥ 8 or a CDAI ≥ 220 , while CD disease control (*i.e.*, mild or no disease activity) was defined as an HBI < 8 or a CDAI < 220 [18-20]. UC disease activity during follow-up was assessed with the 9-item pMayo score; moderate-to-severe active UC was defined as pMayo ≥ 5 , and UC disease control (*i.e.*, mild or no UC activity) was defined as pMayo < 5 [21]. Given the noninterventional design of the study, there were no predefined time points of IBD activity assessment, and measures were collected in the course of typical disease treatment.

Statistical analysis

Descriptive statistics [mean, median, standard deviation (SD) and minimum-maximum] were used to analyze sociodemographic, clinical, and treatment-related variables. Student's *t*-test for independent samples or the Mann-Whitney test were used to compare CD and UC patients regarding quantitative variables. Fisher's exact test and the chi-square test were used for qualitative variables.

Overall, 407 patients (264 CD and 143 UC) were enrolled in the cross-sectional assessment. All patients with active IBD at the cross-sectional appointment were eligible for the prospective phase of the study, including 118 CD patients and 36 UC patients. These sample sizes allowed the use of a desirable central limit theorem in outcome inference, even accounting for sample losses [11/118 (9.3%) in CD; 2/36 (5.6%) in UC] after 12 mo of follow-up.

The time to disease control was calculated using the Kaplan-Meier approach, defined as the time (in days) from index date until the date of the first documentation of disease control [*i.e.*, achieved disease control, mild or no active disease (defined as event)]. Patients who did not achieve disease control, died (without the event), discontinued the study or were lost to follow-up had their time censored at death or at the date of the last visit.

The proportion of patients with moderate-to-severe active IBD at 12 mo was calculated by IBD type at the last visit between 9 and 12 mo of follow-up.

Treatment changes were defined as drug discontinuations or dose changes (*i.e.*, changes in frequency and/or dosage administered) during follow-up for ongoing medications or initiated at the index date and any new medication initiated after the index date. Patients who did not have any visits during follow-up or patients who had no ongoing treatments were considered missing in the survival analysis.

For each IBD type, bivariate analyses were conducted to evaluate sociodemographic, clinical and treatment-related variables between subjects who achieved disease control during the 12-mo follow-up period *vs* those who did not. Chi-square or Fisher's exact tests were used to compare categorical variables, *t*-tests were used for independent samples, and the nonparametric Mann-Whitney test was used to compare quantitative variables. The incidence rate of treatment changes by person-years was also determined.

All statistical tests were two-tailed, with a significance level of 0.05, using SAS® (version 9.4, SAS Institute Inc., Cary).

RESULTS

Patient disposition and characteristics

Of 407 subjects (75.4%, $n = 307$, from public clinics) evaluated at the index date, 37.8% ($n = 118$ CD and 36 UC) were included in the prospective study phase (Figure 1). The majority of included patients were from public clinics: 74.6% ($n = 88$) CD and 72.2% ($n = 26$) UC patients. During the 12-mo follow-up, 11 (9.3%) CD patients and 2 (5.6%) UC patients discontinued the study, and one CD patient died. Overall, the mean \pm SD follow-up times were 340.4 ± 59.2 d and 339.2 ± 64.8 d for CD and UC patients, respectively. A total of 107 CD patients and 34 UC patients completed the study and had a medical appointment between months 9 and 12, of which 82 CD patients and 25 UC patients had at least one evaluation of disease activity during this time window.

Most patients were female (58.5% and 78.8% of CD and UC patients, respectively), and the mean \pm SD age at baseline was 43.3 ± 12.6 years for CD patients and 44.9 ± 16.5 years for UC patients (Table 1). A total of 45 (38.1%) CD patients and 22 (61.1%) UC patients had their first diagnosis of moderate-to-severe IBD within the past 5 years. The median CD disease duration was similar between patients receiving biologics and those not receiving biologics at the index date [11.0 (IQR: 0.5-11.0) *vs* 11.5 (IQR: 0.5-29.1) years]. UC patients on biologics at index had a shorter disease duration than patients not receiving biologics (6.0 years *vs* 10.0 years).

Table 1 Sociodemographic and disease characteristics of patients at the index date

	CD patients (n = 118)	UC patients (n = 36)
Age (yr), mean \pm SD	43.3 \pm 12.6	44.9 \pm 16.5
Female, n (%)	69 (58.5)	26 (72.2)
Employed, n (%)	36 (36.7)	5 (16.1)
Attended higher education, n (%)	32 (34.4)	5 (23.8)
Body mass index (kg/m ²), mean \pm SD	24.9 \pm 4.7	24.9 \pm 5.1
Current smokers, n (%) ¹	7 (5.9)	0 (0.0)
Family history of IBD, n (%)	15 (12.7)	2 (5.6)
IBD duration (yr), median (IQR)	11.0 (0.5-11.0)	6.5 (0.5-29.1)
Biologic group	11.0 (5.0-16.0)	6.0 (3.0-13.0)
Nonbiologic group	11.5 (4.5-18.5)	10.0 (4.0-17.0)
5-ASA derivatives group	9.0 (4.0-13.0)	5.5 (4.0-14.0)
Non-5-ASA derivatives group	11.5 (5.0-17.5)	13.0 (4.0-15.0)
Corticosteroid status, n (%) ²		
Steroid-dependent	17 (14.4)	10 (27.8)
Steroid-refractory disease	5 (4.2)	3 (8.3)
Not applicable (no previous use)	33 (28.0)	3 (8.3)
Unknown	37 (31.4)	15 (41.7)
Location of CD, n (%)		
L1 ileal	26 (22.0)	-
L2 colonic	21 (17.8)	-
L3 ileocolonic	71 (60.2)	-
CD Behavior, n (%)		
B1 nonstricturing/penetrating	31 (26.3)	-
B2 stricturing	52 (44.1)	-
B3 penetrating	35 (29.7)	-
Symptomatic perianal disease, n (%)	37 (31.6)	-
HBI result (available for 101 CD patients), median (IQR)	5.0 (1.0-9.0)	-
CDAI result (available for 43 CD patients), median (IQR)	200.0 (114.0-274.0)	-
Fecal calprotectin level > 200 μ g/g during previous year, n (%)	40 (33.9)	-
Colonoscopy with CD activity ³ during previous year, n (%)	69 (58.5)	-
Extent of UC inflammation - Montreal classification, n (%)		
E1 ulcerative proctitis	-	10 (27.8)
E2 left-sided UC	-	8 (22.2)
E3 pancolitis	-	18 (50.0)
Partial Mayo score, median (IQR)	-	6.0 (5.0-6.0)
Total Mayo score (available for 13 UC patients)	-	8.0 (7.0-8.0)
Extra intestinal manifestations ⁴ , n (%)	29 (24.6)	8 (22.2)
Patients with at least one IBD surgery during previous 3 yr, n (%)	32 (27.1)	1 (2.8)
Total colectomy	0 (0.0)	1 (2.8)
Fistulectomy	7 (5.9)	0 (0.0)
Enterostomy	6 (5.1)	0 (0.0)

Partial colectomy	5 (4.2)	0 (0.0)
Closure of enterostomy	5 (4.2)	0 (0.0)
Drainage of anorectal abscess	3 (2.5)	0 (0.0)
Jejunostomy/Ileostomy	1 (0.8)	0 (0.0)
Other	15 (12.7)	1 (2.8)
Patients with at least one IBD-related hospitalizations during previous 3 yr, n (%)	51 (43.1)	11 (30.6)

¹Smoking at Day 1 and has smoked 100 cigarettes in his/her lifetime.

²Steroid-dependent disease - defined as: (1) Being unable to reduce steroids below the equivalent of prednisolone at 10 mg/day within 3 mo of starting steroids, without recurrent disease; or (2) having a relapse within 3 mo of stopping glucocorticoids. Steroid-refractory disease - defined as having active disease despite prednisolone of up to 0.75 mg/kg/d over a period of 4 wk.

³As per investigator criteria.

⁴During the entire study period (3 retrospective years and 1 year of prospective follow-up), extraintestinal manifestations included arthralgia, arthritis, sacroiliitis, ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum, pustular dermatitis, psoriasis, uveitis, sclerosing cholangitis, cholelithiasis, nephrolithiasis, autoimmune disease, hypertension, and dyslipidemia. SD: Standard deviation; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; HBI: Harvey-Bradshaw index; CDAI: Crohn's disease activity index; pMayo: Partial Mayo score; 5-ASA: 5-aminosalicylate; IQR: Interquartile.

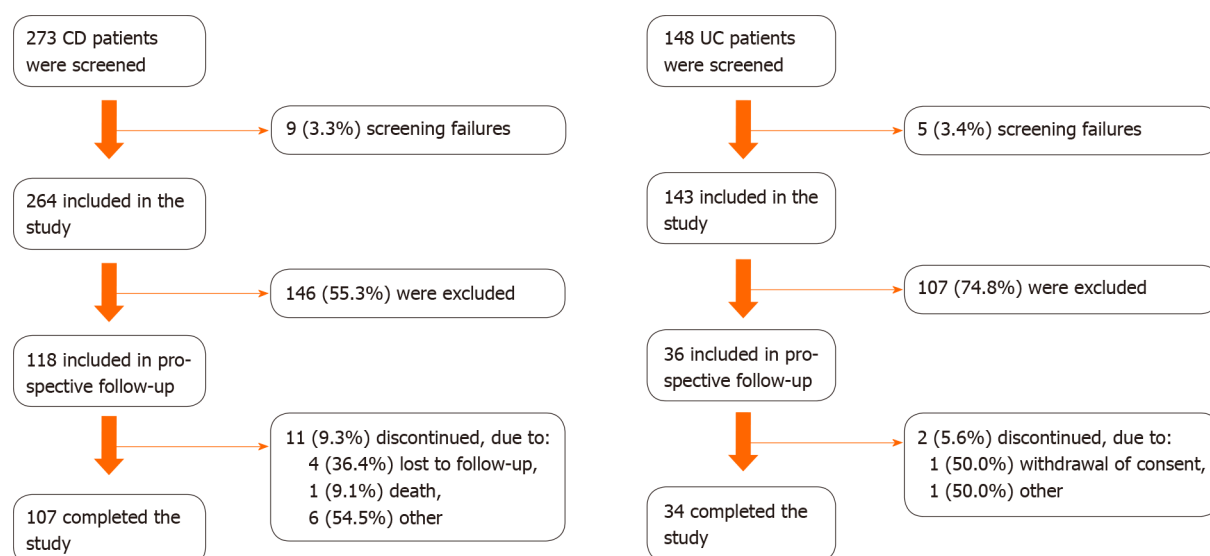


Figure 1 Patient disposition for Crohn's disease patients and ulcerative colitis patients. UC: Ulcerative colitis; CD: Crohn's disease.

At the index date, 46 (39.0%) CD patients had active disease according to the CDAI or HBI, of whom 24 were identified based on these indexes only, with six presenting severely active CD (HBI > 16 or CDAI > 450). Regarding disease behavior, 52 (44.1%) and 35 (29.7%) CD patients had B2 stricturing and B3 penetrating disease, respectively. In addition, 40 (33.9%) patients had fecal calprotectin levels > 200 µg/g (22 patients identified only by calprotectin levels), and 69 (58.5%) had a colonoscopy results suggestive of disease activity during the previous year (35 patients identified by this criterion only). UC patients with active disease had a median pMayo of 6.0 (IQR: 5.0-6.0) at baseline, four (11.1%) had severe UC based on pMayo > 7, and 50.0% of patients presented with pancolitis.

IBD treatment patterns and changes during follow-up

Biologics were the most frequent drug class that CD patients were receiving at the index date appointment (62.7%), and 5-ASA derivatives (91.7%) were the most common for UC patients; however, it is important to highlight that biologics were not available as a UC treatment strategy in Brazil at the time of the study (Table 2). Approximately 48% of CD patients and 58.3% of UC patients were receiving corticosteroids at the index date. Half (50.0%) of UC patients had received at least one corticosteroid for a period of 3 mo or longer. At the start of the 12-mo follow-up period, 58.5% of CD patients maintained their current biologic therapy, while 5.1% initiated a new biologic.

Table 2 Treatment patterns and medical appointments during the follow-up period (Crohn's disease and ulcerative colitis patients)

	CD patients (n = 118)	UC patients (n = 36)
IBD treatment at index date appointment, n (%) ¹	111 (94.1)	35 (97.2)
5-ASA derivatives	36 (30.5)	33 (91.7)
Corticosteroids	56 (47.5)	21 (58.3)
Immunosuppressants	65 (55.1)	21 (58.3)
Biologics	74 (62.7)	14 (38.9)
Patients who received at least one corticosteroid for ≥ 3 mo, n (%) ²	31 (26.3)	18 (50.0)
Treatments at the start of 12-mo follow-up (index date), n (%)		
IBD treatment initiated or maintained	112 (94.9)	35 (97.2)
Biologic therapy		
Maintained or initiated at index date	75 (63.6)	14 (38.9)
Maintained	69 (58.5)	11 (30.6)
Initiated new	6 (5.1)	3 (8.3)
Naïve to biologics ³	1 (0.8)	1 (2.8)
Discontinued at index date	0 (0.0)	0 (0.0)
Immunosuppressants		
Maintained or initiated at index date	73 (61.9)	19 (52.8)
Maintained	71 (60.2)	14 (38.9)
Initiated new	2 (1.7)	5 (13.9)
Discontinued at index date	1 (0.8)	0 (0.0)
5-ASA compounds		
Maintained or initiated at index date	19 (16.1)	27 (75.0)
Maintained	17 (14.4)	20 (55.6)
Initiated new	2 (1.7)	5 (13.9)
Naïve to 5-ASA compounds	2 (1.7)	5 (13.9)
Discontinued at index date	1 (0.8)	0 (0.0)
Corticosteroids		
Maintained or initiated at index date	16 (13.6)	15 (41.7)
Maintained	9 (7.6)	6 (16.7)
Initiated new	6 (5.1)	8 (22.2)
Naïve to corticosteroids ³	2 (1.7)	1 (2.8)
Discontinued at index date	2 (1.7)	4 (11.1)
Any antibiotic initiated at index date	12 (10.2)	5 (13.9)
Treatment changes during 12-mo follow-up period		
New treatment initiated during follow-up	77 (65.3)	31 (86.1)
Discontinuation or dose change during follow-up ²	77 (68.1)	33 (94.3)
Median (IQR) number of treatment changes by patient	2 (2-5)	4 (3-7)
Biologic therapy		
Initiated	45 (38.1)	6 (16.7)
Naïve to biologics ⁴	13 (11.0)	1 (2.8)
Discontinued	23 (19.5)	5 (13.9)
Dose change	14 (11.9)	4 (11.1)

Immunosuppressants		
Initiated	24 (20.3)	14 (38.9)
Naïve to immunosuppressants ⁴	4 (3.4)	2 (5.6)
Discontinued	20 (16.9)	11 (9.3)
Dose change	7 (5.9)	7 (19.4)
5-ASA derivatives		
Initiated	10 (8.5)	21 (58.3)
Naïve to 5-ASA compounds ⁴	1 (0.8)	2 (5.6)
Discontinued	7 (5.9)	8 (22.2)
Dose change	4 (3.4)	14 (38.8)
Corticosteroids		
Initiated	24 (20.3)	16 (44.4)
Naïve to corticosteroids ⁴	5 (4.2)	2 (5.6)
Discontinued	23 (19.5)	17 (47.2)
Any antibiotic initiated after index date	23 (19.5)	5 (13.9)

¹Inflammatory bowel disease (IBD) treatment patients were receiving at the time of enrollment, irrespective of the physician's decision to continue or discontinue it at the end of the medical appointment.

²Percentages calculated from 113 Crohn's disease and 35 ulcerative colitis patients, since two patients had no IBD medication and four had no medical appointments during follow-up.

³Assuming the information from the previous 3 year.

⁴Assuming the information from the previous 3 years and index date. Values are *n* (%), and percentages calculated within the total of the study population in each group, except if otherwise mentioned. SD: standard deviation; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; 5-ASA: 5-aminosalicylate.

Regarding UC patients, 30.6% maintained their biologic therapy, while 8.3% initiated a new biologic treatment. Current 5-ASA agents were maintained by 14.4% of CD patients, while 55.6% of UC patients maintained the same therapy.

During follow-up, 65.3% of CD and 86.1% of UC patients switched to a new treatment at least once. Discontinuation or dose changes (excluding antibiotics) of IBD-related treatments occurred in 68.1% of CD and 94.3% of UC patients.

The incidence rates of drug discontinuations and dose changes were 9.2 and 6.8 changes/person-years for CD and UC patients, respectively (data not shown). During follow-up, the median number of treatment changes among CD patients was 2.0 (IQR 2-5), with 26 (33.8%) patients having more than four changes. Regarding drug classes, 19.5% of CD patients discontinued biologic therapy, 16.9% discontinued immunosuppressants, and 5.9% discontinued 5-ASA derivatives.

In UC patients, the median number of treatment changes was 4.0 (IQR 3-7), with 18 (54.5%) patients having more than four treatment changes. Regarding drug classes, 22.2% of UC patients discontinued 5-ASA derivatives, 13.9% discontinued biologics, and 9.3% discontinued immunosuppressants.

Azathioprine was the most frequently maintained or newly initiated agent in CD patients (61.9%), while mesalazine was the agent most maintained or newly initiated treatment by UC patients (72.2%), whether as monotherapy or combination therapy (Figure 2).

Treatment patterns at the medical appointments during follow-up

The vast majority (96.6%) of CD patients had at least one outpatient visit during the follow-up period, with a mean \pm SD number of 4.4 ± 2.6 visits per patient and a total of 518 visits. Treatment changes were observed in 25.3% (*n* = 131) of CD outpatient visits, and disease activity was assessed by the HBI and/or CDAI scores in 12.6% (*n* = 51) and 6.4% (*n* = 26) of visits, respectively.

Biologics were the most frequent treatments used during follow-up (76.8% in the first quarter of the follow-up), followed by immunosuppressants (65.2%) and 5-ASA compounds (16.1%). The use of corticosteroids started to decrease from the third quarter of follow-up (Figure 3).

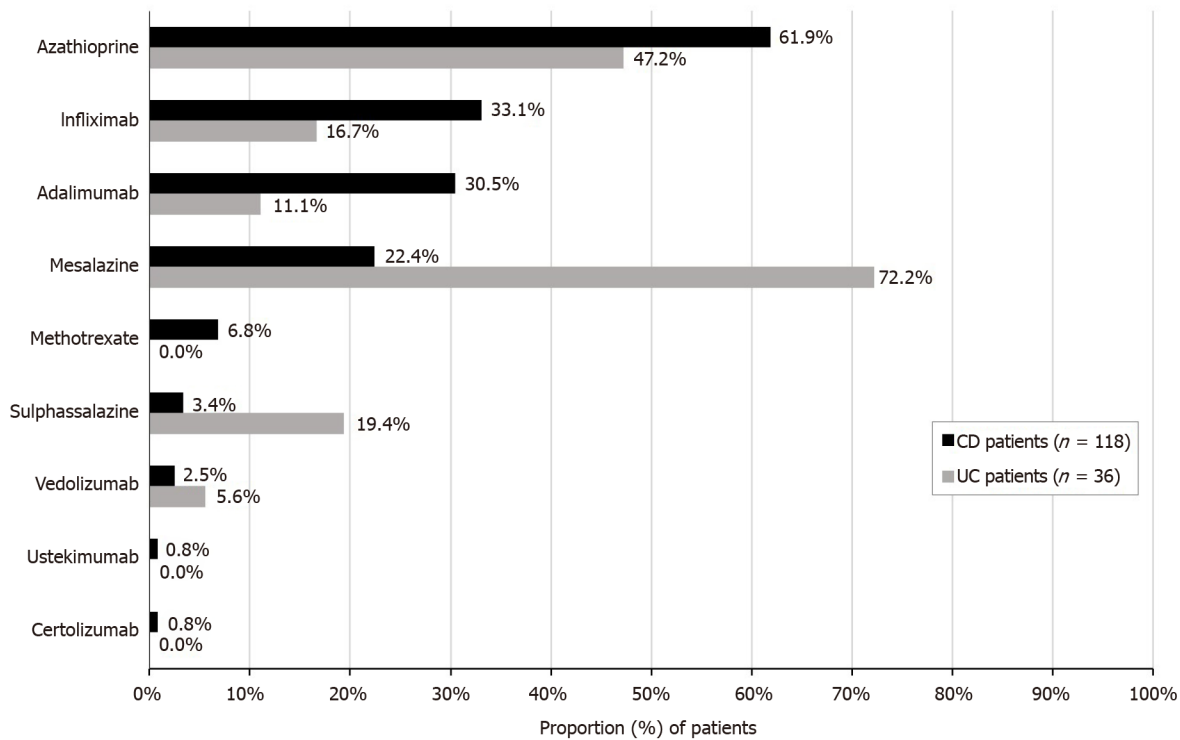


Figure 2 Proportion (%) of Crohn's disease and ulcerative colitis patients who maintained or initiated new inflammatory bowel disease drugs at the index date. UC: Ulcerative colitis; CD: Crohn's disease.

All UC patients had at least one visit during the follow-up period, with a mean \pm SD number of 5.0 ± 3.3 visits per patient and a total of 179 visits. Treatment changes were observed among 40.2% ($n = 72$) of UC outpatient visits, and the assessment of UC activity with the Mayo score was performed in 11.2% ($n = 16$) of visits. The most prescribed agent during the first quarter of follow-up was 5-ASAs (83.3%), followed by immunosuppressants (58.3%) and biologics (38.9%). Corticosteroid use decreased from 50.0% in the first trimester to 26.5% in the last trimester of follow-up (Figure 3).

Time to IBD disease control during follow-up

During the 12-mo follow-up period, 86 (72.9%) CD patients achieved disease control. The median time to first disease control for CD from the index date was 319 d (IQR 239-358) [95%CI: 295-330], *i.e.*, approximately 10.6 mo (Figure 4A). There were five switches from "mild or no disease activity" to "moderate or severe disease" among the patients who had the event (control disease, $n = 86$).

Overall, 25 (69.4%) UC patients achieved disease control at least once, with 30.6% ($n = 11$) of patients remaining with "moderate or severe" disease at the end of the 12-mo period (censored observations). The median time for achieving the first episode of disease control from the index date was 320 d (IQR: 288-358) [95%CI: 302-358], *i.e.*, approximately 10.7 mo (Figure 4B), and there were two changes from "mild or no disease activity" to "moderate or severe disease".

Of the 107 patients who had a final evaluation during the remaining 90 d of the follow-up period, 23 (21.5%) showed moderate or severe disease activity. The proportions of CD and UC patients with active disease at the last follow-up visit were 22.0% ($n = 15/82$, 95%CI: 13.6%-32.5%) and 20.0% ($n = 5/25$, 95%CI: 6.8%-40.7%), respectively.

CD patients with active disease at the end of follow-up had a higher mean BMI at index than patients with 'mild or no activity' (27.5 ± 3.7 vs 24.2 ± 4.4 ; $P = 0.007$) (Table 3). Higher education was also more frequent among CD patients with mild or no disease activity at the end of follow-up than among patients with moderate-to-severe activity (42.6% vs 12.5%; $P = 0.029$).

Despite a higher proportion of CD patients with symptomatic perianal disease among patients with moderate to severe disease activity, the results were not statistically significant (55.6% vs 30.2% among patients with mild or no disease activity; $P = 0.066$).

Table 3 Sociodemographic, clinical and treatment characteristics of ulcerative colitis and Crohn's disease patients at the index date according to the final disease activity assessment

Characteristics at index date	CD patients (n = 82)			UC patients (n = 25)		
	Moderate-to-severe activity (n = 18)	No or mild activity (n = 64)	P value	Moderate-to-severe activity (n = 5)	No or mild activity (n = 20)	P value
Age (yr), mean \pm SD	42.0 \pm 13.0	43.1 \pm 12.7	0.732 ³	38.0 \pm 14.4	46.9 \pm 17.5	0.310 ⁴
Female, n (%)	12 (66.7)	39 (60.9)	0.786 ⁵	4 (80.0)	15 (75.0)	> 0.999 ⁵
Employed, n (%)	4 (23.5)	22 (45.8)	0.328 ⁶	1 (20.0)	2 (10.5)	0.977 ⁵
Attended higher education, n (%)	2 (12.5)	20 (42.6)	0.029 ⁶	1 (20.0)	2 (18.2)	0.462 ⁵
Body Mass Index (kg/m ²), mean \pm SD	27.5 \pm 3.7	24.2 \pm 4.4	0.007 ⁴	25.4 \pm 7.5	24.8 \pm 5.5	0.838 ³
Current smokers, n (%) ¹	2 (12.5)	4 (7.0)	0.607 ⁵	0 (0.0)	0 (0.0)	NA
IBD duration (yr), median (IQR)	6.0 (1-27)	13.0 (0-45)	0.0433 ³	5 (1-23)	6.5 (1-23)	0.7032 ⁴
Time since moderate to severe IBD (yr), median (IQR)	5.5 (1-25)	7.0 (0-26)	0.8839 ³	2 (0-18)	3.5 (1-16)	0.8101 ³
Extra intestinal manifestation, n (%)	3 (50.0)	17 (51.5)	0.946 ⁶	1 (33.3)	4 (40.0)	NA
HBI result, median (IQR)	9.0 (7-13)	4.0 (1-8)	NA	-	-	-
CDAI result, median (IQR)	200.0 (114-311)	224.0 (113-281)	NA	-	-	-
Previous calprotectin level > 200 μ g/g, n (%)	3 (16.7)	24 (37.5)	0.097 ⁶	-	-	-
Previous colonoscopy with CD activity, n (%)	12 (66.7)	33 (51.6)	0.256 ⁶	-	-	-
Ileocolonic disease, n (%)	13 (72.2)	36 (56.3)	0.282 ⁵	-	-	-
Stricture or penetrating CD behavior, n (%)	11 (61.1)	48 (75.0)	0.247 ⁶	-	-	-
Symptomatic perianal disease, n (%)	10 (55.6)	19 (30.2)	0.066 ⁶	-	-	-
Partial Mayo score, median (IQR)	-	-	-	7.0 (5-8)	6.0 (5-6)	NA
Left-sided or pancolitis UC, n (%)	-	-	-	3 (60.0)	15 (75.0)	-
Current IBD treatment at baseline ² , n (%)	15 (83.3)	61 (95.3)	0.233 ⁵	5 (100.0)	19 (95.0)	0.871 ⁵
Treatment ongoing or initiated at index, n (%)	16 (88.9)	62 (96.9)	0.416 ⁵	5 (100.0)	20 (100.0)	NA
5-ASA compounds	2 (12.5)	10 (16.1)	3 (60.0)	-	16 (80.0)	-
Biologic therapy	13 (81.3)	41 (66.1)	3 (60.0)	-	4 (20.0)	-
Corticosteroids	3 (18.8)	9 (14.5)	3 (60.0)	-	9 (45.0)	-
Immunosuppressants	5 (31.3)	44 (71.0)	3 (60.0)	-	10 (50.0)	-

¹Smoking at Day 1 and has smoked 100 cigarettes in his/her lifetime.²Ongoing or discontinued at baseline.³P values from the Mann-Whitney test.⁴t-test.⁵Fisher's exact test.⁶Chi-square test. SD: Standard deviation; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; HBI: Harvey-Bradshaw index; CDAI: Crohn's disease activity index; pMayo: Partial Mayo score; 5-ASA: 5-aminosalicylate; NA: Not applicable.

No statistically significant differences were observed when comparing sociodemographic, clinical and treatment characteristics between UC patients with *vs* without disease activity at the end of follow-up.

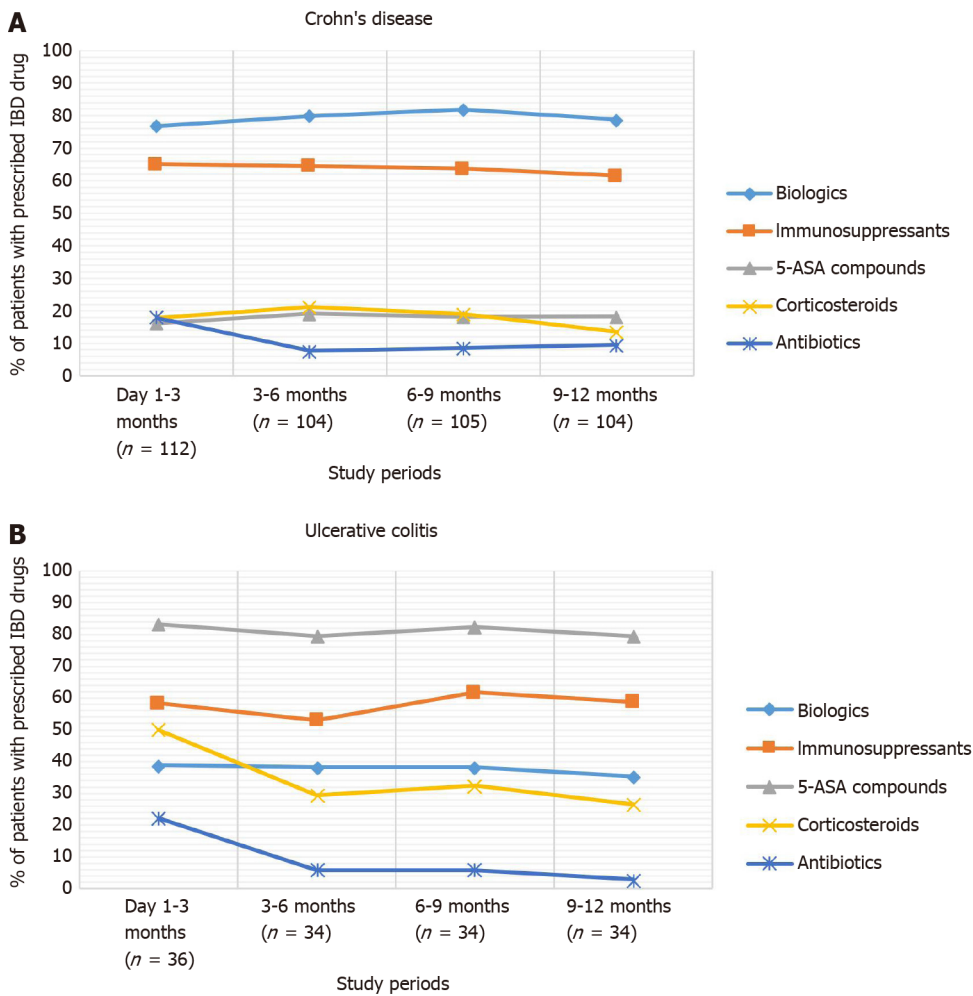


Figure 3 Proportion of patients by prescribed inflammatory bowel disease treatment classes during the prospective phase and grouped by trimester for Crohn's disease (A) and ulcerative colitis patients (B) with at least one treatment. 5-ASA: 5-aminosalicylate.

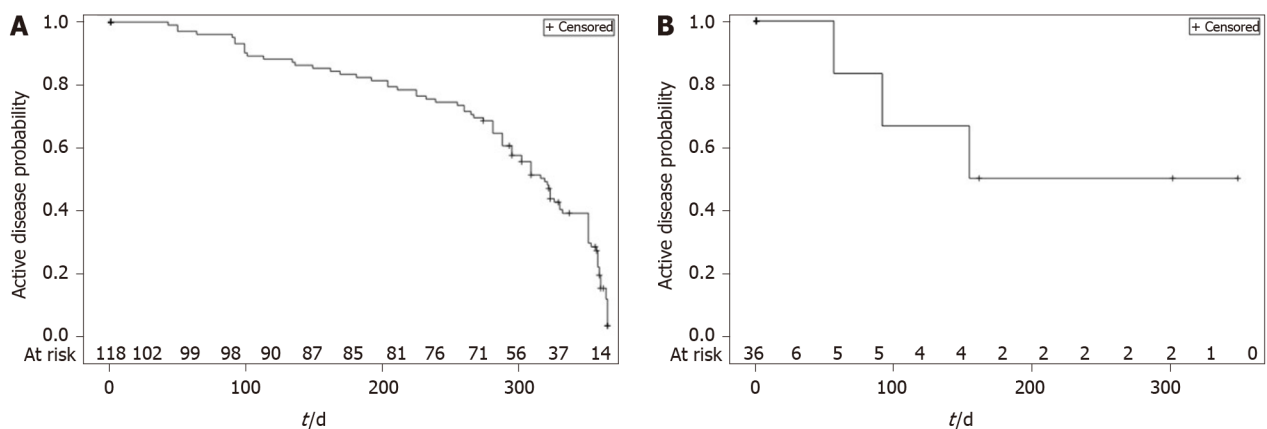


Figure 4 Probability of staying in active disease over 12 mo in Crohn's disease (A) and ulcerative colitis (B) patients.

DISCUSSION

This study aimed to provide a real-world perspective on the management of moderate-to-severe active IBD patients in Brazil, with a focus on treatment patterns and outcomes.

We found that more than two-thirds of IBD patients (73% and 69% for CD and UC patients) with active disease at the index date achieved disease control at least once during the 12-mo period. In addition, at the end of follow-up, approximately 20% of

IBD patients had moderate-to-severe activity.

On average, almost 11 mo were required for half of UC and CD patients to achieve disease control. Considering that this is an observational study with no predefined visits, some patients did not undergo the 12-mo visit. Ideally, the control of disease activity should be achieved within 4-6 mo[22,23]. One possible explanation for this long period could be attributed to the difficulty in the public setting in Brazil to access fecal biomarkers (such as calprotectin) or routinely perform colonoscopy, which are essential assessments to evaluate the response to treatment[2,6,24]. These barriers can delay the assessment of treatment response and thus the optimization of or change in medications.

The lack of public access to serum and anti-drug antibody level testing (unless solicited and justified) could also contribute to this delay. Evidence shows the usefulness of these tests in the decision to proactively or reactively change or optimize biologic therapies[25,26]. During the follow-up period, a mean of 4.4 medical appointments were required for CD patients and 5.0 for UC patients. We observed that clinical scores to assess disease activity were not collected at the majority of appointments (the HBI was assessed only in 12.6%, the CDAI in 6.4% and the Mayo score in 11.2% of outpatient visits).

Since the assessment of symptoms is part of several disease activity scores and relevant for both patients and physicians[27-30], these data suggest that assessment of IBD activity can be improved.

For the purpose of this study, we grouped “no activity” and “mildly active” disease in the same category. The ultimate treatment goal in IBD consists of achieving mucosal healing; however, the definition for this outcome can vary. Some studies in UC consider an endoscopic response as a Mayo endoscopic score ≤ 1 [6].

Biological agents were the most frequent treatment among CD patients, while 5-ASA compounds were largely the most common therapy among UC patients. Despite 5-ASA derivatives not being recommended for routine use in CD patients for induction or maintenance therapy, 14.4% of CD patients received this treatment strategy. This highlights the need for continuing education of gastroenterologists in Brazil. In addition, the lack of other therapies in some regions of the country may have led to the prescription of salicylic derivatives as the only CD treatment option. In a systematic literature review conducted in 2019, the lack of evidence for conventional treatment effectiveness, especially for remission maintenance, mucosal healing and fecal calprotectin, was highlighted[31].

We observed that the majority (65.5%) of CD patients started a new therapy after the study appointment, and the most common new treatment was biologics. New treatments were found for 86.1% of UC patients, with 5-ASA compounds being the most frequent. The more recent treatment guidelines, which are also followed in Brazil, recommend 5-ASA compounds in UC treatment irrespective of disease activity, while CD patients with moderate-to-severe disease activity would benefit more from the early use of biologics and immunosuppressants[2,6]. However, we cannot exclude differences in accessibility to new and more effective drugs, as clinics from the public health system in Brazil have no reimbursement when prescribing biologics to UC patients. Furthermore, the use of immunosuppressants and biologics increased among UC patients during follow-up, suggesting that 5-ASA compounds may not be enough for achieving disease control in many patients.

A relevant proportion of CD and UC patients were receiving biologic therapy, not only at the time of the study appointment but also during the follow-up period. This finding suggests that despite difficulties in accessing biologic therapies in hospitals in Brazil, especially in UC, physicians prescribe these agents for patients with moderate-to-severe disease activity. At the time of data collection, biologic therapy was available for use but not reimbursed by public or private healthcare systems in Brazil (which would mean medication without cost for patient); however, patients with UC had access to biologics *via* other strategies such as judicial petition and out-of-pocket. Only from March 2020, was infliximab available for patients diagnosed with UC in the public healthcare system; infliximab, vedolizumab and golimumab were only available in the private setting in 2021. We observed a decrease in the use of corticosteroids during follow-up for both CD and UC, suggesting an adequate control of disease overtime. Nevertheless, approximately one-quarter of CD patients and half of UC patients required corticosteroids for a period longer than three months.

One of the strengths of this study was the inclusion of treated IBD patients from both public and private settings, allowing a broad characterization of this population.

Some study limitations should be recognized. The inclusion of prevalent IBD cases, with baseline variability in terms of time since diagnosis and previous treatments, was a barrier to the assessment of the association between treatment options and disease

activity. Even though we found no statistically significant association between clinical and treatment variables and presenting disease activity at the end of follow-up, we cannot exclude that treatment at the index date and during follow-up may have contributed to this outcome, as we did not adjust for combined therapy, dosing information or duration of treatment (due to missing information). Moreover, the disease activity outcome was assessed at one time point only during the prospective phase (end of follow-up or month 12), making it difficult to determine whether it was a sustained control.

The inclusion of patients who had a previous event of moderate-to-severe IBD (irrespective of disease activity at index date) may affect the generalization of results for the whole IBD population in Brazil, even though these patients were selected for their higher burden of disease and thus needed closer medical follow-up. Disease activity was not assessed with the proposed scores in all outpatient medical appointments. Nevertheless, concerning disease activity, one limitation was the subjective assessment of colonoscopy, which was based on investigator criteria, which also impacted the selection of UC patients. The prospective design aimed to reduce missing data, but due to the observational character of the study, we did not proactively interfere with the usual practices for IBD activity evaluation. Finally, the sample size affected the group comparison regarding the main baseline and follow-up variables, especially for the UC patients. Furthermore, due to the small sample, one should be cautious when extrapolating the findings to a nationwide population. Additional studies are required to further understand the management of IBD in Brazil and understand the gaps and barriers in this setting.

CONCLUSION

In conclusion, to our knowledge, this was the first study aiming to characterize IBD evolution in a real-world setting in Brazil. Although a marked proportion of patients with active IBD achieved disease control within one year, the prolonged time to achieve this outcome suggests an area of unmet need with the current standard of care.

ARTICLE HIGHLIGHTS

Research background

The Real-world Data of Moderate-to-Severe Inflammatory Bowel Disease in Brazil (RISE BR) study was a noninterventional study designed to evaluate disease control, treatment patterns, disease burden and health-related quality of life in patients with moderate-to-severe active inflammatory bowel diseases (IBD).

Research motivation

Real-world data on IBD management could unveil unmet medical needs and treatment gaps. This is of utmost relevance in developing countries such as Brazil, where the prevalence of IBD is increasing, but access to biologic treatment may be restricted, and information on IBD treatment, in general, and associated outcomes is scarce.

Research objectives

The aim was to describe the 12-mo disease evolution and treatment patterns among patients with active moderate-to-severe IBD in Brazil.

Research methods

We report findings from the prospective follow-up phase of the RISE BR study in patients with active ulcerative colitis (UC) or Crohn's disease (CD). This was a prospective, noninterventional study of adult patients with active CD, inadequate CD control or active UC. The proportion of active IBD patients after 9-12 mo of follow-up, the time to mild or no activity and a summary of treatment initiation, discontinuation and dose changes were evaluated.

Research results

The study included 118 CD and 36 UC patients. The most frequent drug classes at

index were biologics for CD (62.7%) and 5-aminosalicylate derivatives for UC patients (91.7%). During follow-up, 65.3% of CD and 86.1% of UC patients initiated a new treatment at least once. Considering the prospective follow-up period, discontinuations/dose changes occurred in 68.1% of CD patients [median 2.0 (IQR: 2-5)] and 94.3% of UC patients [median 4.0 (IQR: 3-7)]. On average, CD and UC patients had 4.4 ± 2.6 and 5.0 ± 3.3 outpatient visits, respectively. The median time to first mild or no activity was 319 (IQR: 239-358) d for CD and 320 (IQR: 288-358) d for UC patients. At 9-12 mo, 22.0% of CD and 20.0% of UC patients had active disease.

Research conclusions

Although a marked proportion of active IBD patients achieved disease control within one year, the considerable time to achieve this outcome represents an unmet medical need of the current standard of care in a Brazilian real-world setting.

Research perspectives

This was the first study aiming to characterize IBD evolution in a real-world setting in Brazil. Additional studies are required to further understand the management of IBD in Brazil and understand the gaps and barriers in this setting.

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