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# Adherence to infliximab treatment in patients with immune-mediated inflammatory diseases from a referral center in Brazil: a cohort study

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## Abstract

**Background** Infliximab therapy is effective in controlling symptoms and attaining clinical remission of immune-mediated inflammatory diseases. However, treatment adherence is essential to achieve the therapeutic objective. This study aimed to determine the rate of adherence to infliximab treatment in patients treated at a referral center at a university hospital.

**Method** This ambispective cohort study included patients treated at the Professor Edgard Santos University Hospital (HUPES) referral center of our university hospital between March 2022 and February 2023. Sociodemographic, clinical, and pharmacotherapeutic data were collected from 101 patients through interviews and medical record reviews using a structured form. The adherence rate was defined as the proportion of days covered in a year. Patients who achieved an adherence rate > 80% were considered adherent.

**Results** The treatment adherence rate was 91.04%. Individuals with inflammatory bowel diseases had a 39.1% higher risk of non-adherence to treatment compared with other patients in our sample ($p < 0,05$). Most patients achieved remission or control of the underlying disease activity and had good functional capacities. The main reason for absence on the scheduled date was difficulty traveling to the referral center.

**Conclusions** Despite the reported difficulties, treatment adherence was observed to be high. As the study was conducted in a reference unit with multidisciplinary care and continuous monitoring for treatment effectiveness, safety, and adherence, welcoming and good communication between professionals and patients may have contributed to the high adherence rate.

**Keywords** Adherence, Infliximab, Immune-mediated inflammatory diseases

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## Background

Immune-mediated inflammatory diseases (IMIDs) are a heterogeneous group of conditions characterized by chronic inflammation that affect approximately 3% of the general population. They have notable chronicity, affecting people at a young age and persisting throughout adulthood, with substantial progressions that can lead to the loss of function of the affected organs [1]. TNFα inhibition—a treatment strategy that utilizes drugs that block the interaction of TNFα with its receptors or act as agonists by stimulating reverse signaling, causing apoptosis of cells producing TNFα—is effective against IMIDs [2]. Infliximab, administered intravenously, was the first available TNFα inhibitor, and its benefits in IMID management are well established.

Adequate adherence to infliximab treatment, which is essential to control and prevent IMID progression, is associated with shorter hospital stays and lower hospitalization costs [3]. Low treatment adherence is considered a major challenge for healthcare systems, particularly for chronic conditions [4]. In developing countries, the scarcity of health resources and inequality in access may exacerbate the problem, and diagnostic studies are needed for a complete understanding of the magnitude of the issue and to direct the development of effective supportive policies [5].

National studies performed using administrative databases that document direct expenses for outpatient and drug treatment of autoimmune diseases indicated that medications accounted for 68.72% of the total medical expenditure in patients with rheumatoid arthritis, with the most prescribed biologic medication being infliximab [6]. Considering the high clinical and economic impact of IMIDs and the need for constant monitoring and overcoming barriers to infliximab treatment, investigating treatment adherence in a real-world setting and understanding the particulars of the Brazilian healthcare system and socioeconomic characteristics of patients is essential to support decision-making within the scope of the SUS, both from a clinical point of view and in the formulation of actions and policies aimed at improving the care provided to patients with IMID who are undergoing biologic treatment. This study aimed to determine the rate of adherence to infliximab treatment in patients treated at a referral center at a university hospital.

## Methods

This ambispective cohort study conducted at the Professor Edgard Santos University Hospital (HUPES) referral center between March 2022 and February 2023 aimed to determine the rate of adherence to infliximab treatment in patients.

The HUPES referral center is a healthcare unit with 15 beds for intravenous medication infusion and a multidisciplinary team comprising pharmacists, nurses, doctors, nursing technicians, and administrative staff. Medications are administered daily, and patients undergo pharmaceutical, medical, and nursing consultations, providing opportunities to clarify doubts, encourage adherence, and resolve problems related to medication.

The data used in the study were collected from medical records, medication dispensing records filed at the institution, and the administration of a questionnaire to the patients, available on supplementary file.

The inclusion criteria were as follows: age ≥ 18 years; a confirmed diagnosis of Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, psoriasis, or ankylosing spondylitis; treated using infliximab for at least 1 year at the referral center. Patients transferred from other referral units and those with modified or permanently interrupted treatment during the follow-up period would be excluded from the study, because it would not be possible to evaluate adherence over 1 year.

During pharmaceutical consultation, while attending the unit for treatment with infliximab, patients were interviewed by a trained assistant using a structured form to collect sociodemographic, clinical, and pharmacotherapeutic data. The patients were asked about their knowledge of treatment, beliefs, difficulties encountered in complying with the dosage schedule, occurrence of adverse events, and level of communication with health professionals.

The degree of inflammatory bowel disease (IBD) activity was determined using the Harvey–Bradshaw Index and the partial MAYO index for patients diagnosed with Crohn's disease and ulcerative colitis, respectively, through medical evaluation at the time of inclusion of the patient in the study. Functional capacity and/or disease activity in patients with rheumatological diseases were assessed using the Health Assessment Questionnaire for patients diagnosed with rheumatoid or psoriatic arthritis, and the Health Assessment Questionnaire-Spondylitis and Bath Ankylosing Spondylitis Disease Activity Index for patients with ankylosing spondylitis; the versions of the questionnaires validated in Portuguese were used. These versions were published in official clinical guidelines created by Brazilian Ministry of Health called "*Clinical Protocols* and *Therapeutic Guidelines*" [7].

To assess treatment adherence, patients' medical records were reviewed, which included records of medication infusion schedules, rescheduling requests, and justifications for not attending administration. The adherence rate was defined as the proportion of days covered, presented as percentages ([the total number of days covering medication administration/the total days evaluated] x100) for the last 12 months of treatment. Considering that medication was administered according to the Clinical Protocols and Therapeutic Guidelines every 56

days during the maintenance phase [7], the denominator was adjusted to 336. Temporary suspensions of treatment due to momentary contraindications (infections, surgery, and changes in laboratory parameters), as well as minor advances or postponements of the schedule due to logistical issues and holidays, were not considered failures of treatment adherence in the analyses. Patients were considered adherent when an adherence rate of >80% was achieved. This cut-off point was determined based on previous studies on patients administered immunobiological medications [8]. The number of infusions administered on the scheduled date, late infusions, missed infusions, and infusions suspended for clinical reasons were determined. If an infliximab infusion was not performed on the scheduled date, it was considered lost and an interval of >12 weeks between infusions for patients whose dosage interval was 8 weeks and an interval of >9 weeks for patients whose dosage interval was 6 weeks were generated. Infusions that were rescheduled and performed within this timeframe were considered delayed infusions. Patients were enquired regarding their reasons for missing infusions on the scheduled date. The average interval between infusions and the average number of days not covered over 1 year were calculated.

Data collected from the questionnaires were entered into Microsoft Excel for Windows (Microsoft, WA, USA). The statistical analyses comprised a simple descriptive frequency analysis using central and dispersion measures. The Shapiro–Wilk test was used to test the normality of the data distribution. The mean and standard deviation were assessed for variables with a normal distribution, and median and interquartile range for variables with a non-normal distribution. Categorical variables are presented as frequencies and percentages. The chi-square test or Fisher's exact test was used to assess differences between categorical variables. Student's t-tests were used to compare the means of symmetric quantitative variables, and Mann–Whitney U tests were used to analyze asymmetric quantitative variables. The degrees of association between the variables were assessed using the contingency coefficient and relative risk. Statistical analyses were performed using Jamovi® version 2.3 (2022) and R Core Team® version 4.4 (2021) software. Statistical significance was set at $p<0.05$.

## Results

### Sociodemographic, clinical, and pharmacotherapeutic characteristics of patients

A total of 101 patients were included in this study. No patients were excluded from the study. 61 (60.39%) were men, with a mean age of 42.6±15.1 years. A total of 71 (70.30%) patients lived in a city other than the capital and needed to travel to the capital for each medication administration. The sociodemographic data of the patients are presented in Table 1. Of the evaluated patients, 65 (64.37%) were diagnosed with IBDs. Of them, 58 (57.42%) were diagnosed with Crohn's disease and 7 (6.93%) were diagnosed with ulcerative colitis. The remaining 36 (35.64%) patients had rheumatological and/or dermatological diseases: 15 (14.85%) had ankylosing spondylitis, 11 (10.89%) had psoriatic arthritis, 5 (4.95%) had psoriasis, and 5 (4.95%) had rheumatoid arthritis.

The median distance between the capital and the municipality of residence for the patients lived in a city othen than the capital was 287.29 km (Interquartile range: 333), with the closest municipality located 28 km away and the furthest located 987 km away. Among patients residing in the capital, 48 (67.60%) received the "treatment outside the home" benefit provided by the municipality of their residence to travel to the referral center. The remainder traveled to the referral center using their own resources.

Among the 65 patients diagnosed with IBDs, 56 (86.15%) were classified to be in remission according to the Harvey–Bradshaw Index or the partial MAYO score. Five (7.69%) and four (6.15%) patients had mild and moderate disease activity, respectively; none of the patients who underwent the treatment exhibited severe disease activity. For patients with rheumatological diseases, among the 15 patients with ankylosing spondylitis, 11 (73.33%) had a Bath Ankylosing Spondylitis Disease Activity Index below four, indicating controlled disease activity. Regarding the assessment of the functional capacity of patients with rheumatoid arthritis and psoriatic arthritis, nine (56.25%) obtained an average Health Assessment Questionnaire score lower than one, indicating mild disability; three (18.75%) obtained an average score between 1 and 2, indicating moderate disability; and four (25%) patients had a mean score greater than 2, indicating severe deficiency. The clinical and pharmacotherapeutic characteristics of the patients are described in Table 2.

When comparing clinical and pharmacotherapeutic characteristics of patients with IBD and those with rheumatological and/or dermatological diseases, significant differences were found in the following variables: number of comorbidities, use of synthetic medications, duration of infliximab treatment, need to reduce the dosage interval, and need to increase the standard dose.

### Safety data

Infliximab can elicit infusion reactions, which are generally mild-to-moderate and do not interrupt the treatment. All patients who had experienced a previous infusion reaction used pre-infusion medications, with a combination of hydrocortisone and diphenhydramine being the most common (77%). The infusion reactions experienced by patients are shown in Fig. 1. A total of

**Table 1** Sociodemographic characteristics of the patients

| Variables | Inflammatory Bowel Disease (*n* = 65) | Rheumatological and/or Dermatological Disease (*n* = 36) | All patients (*n* = 101) | *P* |
|---|---|---|---|---|
| Age (in years), mean ± SD | 37.3 ± 13.6 | 52.2 ± 13.1 | 43 ± 15.1 | **< 0.01** |
| Sex, *n* (%) | | | | |
| Female | 29 (44.6) | 11 (30.6) | 40 (39.60) | 0.166 |
| Male | 36 (55.4) | 25 (69.4) | 61 (60.40) | |
| Skin color, *n* (%) | | | | |
| White | 9 (13.8) | 5 (13.9) | 14 (13.86) | 0.104 |
| Black | 19 (29.2) | 4 (11.1) | 23 (22.77) | |
| Brown | 37 (56.9) | 27 (75.0) | 64 (63.37) | |
| Place of residence, *n* (%) | | | | |
| Capital | 21 (32.3) | 9 (25.0) | 30 (29.70) | 0.441 |
| Interior | 44 (67.7) | 27 (75.0) | 71 (70.30) | |
| Marital status, *n* (%) | | | | |
| Single | 37 (56.9) | 11 (30.6) | 48 (47.52) | **0.016** |
| Married | 22 (33.8) | 23 (63.9) | 45 (44.56) | |
| Divorced | 3 (4.6) | 2 (5.6) | 5 (4.95) | |
| Widowed | 3 (4.6) | 0 (0.0) | 3 (2.97) | |
| Occupational status, *n* (%) | | | | |
| Busy | 25 (38.5) | 8 (22.2) | 33 (32.67) | **< 0.01** |
| Unemployed | 13 (20.0) | 6 (16.7) | 19 (18.81) | |
| Retired due to age | 1 (1.5) | 3 (8.3) | 4 (3.96) | |
| Retired due to disability | 12 (18.5) | 19 (52.5) | 31 (30.69) | |
| From home | 5 (13.8) | 0 (0.0) | 9 (8.91) | |
| Student | 9 (13.8) | 0 (0.0) | 5 (4.95) | |
| Family income (in minimum wages), median (IQR) | 2 (1) | 1 (1) | 1 (1) | 0.062 |
| Education, *n* (%) | | | | |
| Incomplete Elementary | 10 (15.4) | 10 (27.8) | 20 (19.80) | 0.554 |
| Complete Fundamentals | 3 (4.6) | 2 (5.6) | 5 (4.95) | |
| Incomplete Medium | 7 (10.8) | 3 (8.3) | 10 (9.90) | |
| Complete Midfielder | 36 (55.4) | 15 (41.7) | 51 (40.50) | |
| Higher | 9 (13.8) | 6 (16.7) | 15 (14.85) | |
| Religion, *n* (%) | | | | |
| Areligious | 17 (26.2) | 10 (27.8) | 27 (26.73) | 0.579 |
| Catholic | 21 (32.3) | 16 (44.4) | 37 (36.63) | |
| Protestant | 23 (35.4) | 10 (27.8) | 33 (32.67) | |
| Umbanda/Candomblé | 1 (1.5) | 0 (0.0) | 1 (0.99) | |
| Spiritist | 3 (4.6) | 0 (0.0) | 3 (2.97) | |

IQR, interquartile range

**Table 2** Clinical and pharmacotherapeutic characteristics of the patients

| Variables | Inflammatory Bowel Disease (*n* = 65) | Rheumatological and/or Dermatological Disease (*n* = 36) | All patients (*n* = 101) | *P* |
|---|---|---|---|---|
| Presence of comorbidity, *n* (%) | 35 (53.85) | 23 (63.89) | 58 (57.43) | 0.328 |
| Number of comorbidities, median (IQR) | 1 (1) | 1.5 (3) | | **0.018** |
| Need for hospitalization in the last year, *n* (%) | 5 (7.7) | 1 (2.8) | 6 (5.94) | 0.417 |
| Association with synthetic medicines, *n* (%) | 51 (78.5) | 17 (47.2) | 68 (67.33) | **< 0.01** |
| Previous use of another biologic *n* (%) | 6 (9.2) | 2 (5.6) | 8 (7.92) | 0.708 |
| Duration of infliximab treatment in months, median (IQR) | 46 (40) | 120 (60) | 64 (80) | **< 0.01** |
| Need to reduce dosage, *n* (%) | 4 (6.2) | 8 (22.2) | 12 (1.88) | **0.017** |
| Need to increase the standard dose, *n* (%) | 21 (32.3) | 5 (13.9) | 26 (25.74) | **0.043** |

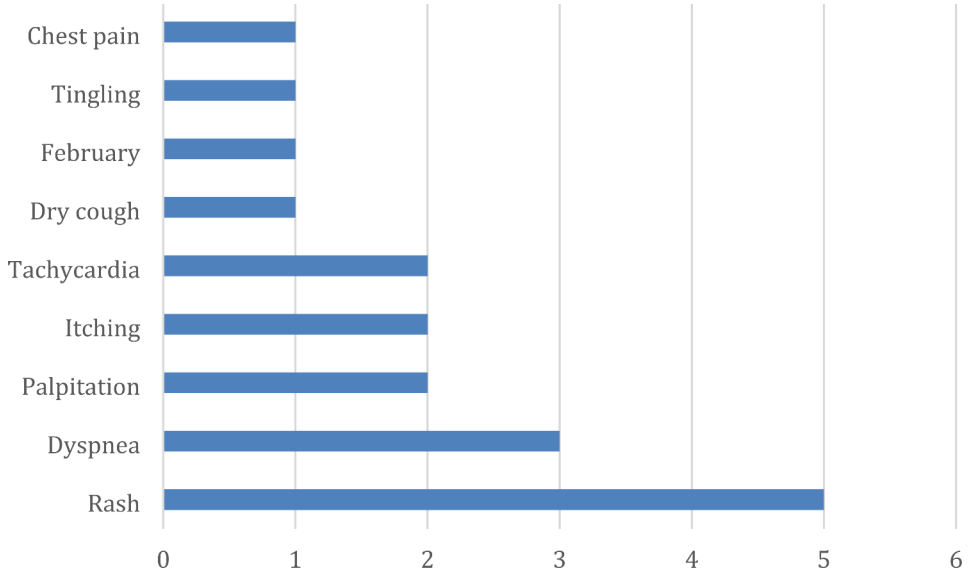


**Fig. 1** Absolute frequency of infusion reactions experienced by patients

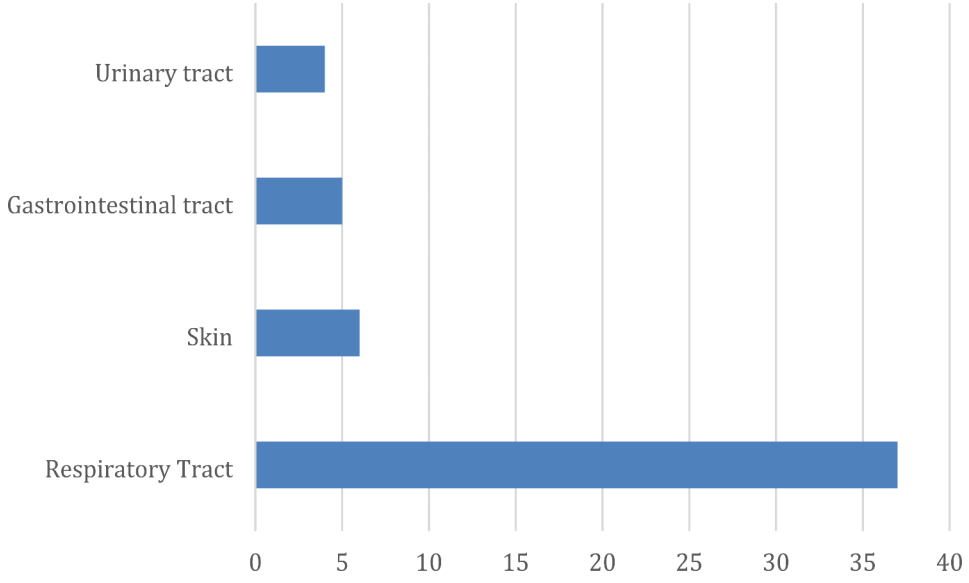


**Fig. 2** Absolute frequency of infectious diseases by site of infection reported by patients

48 (47.52%) patients reported at least one episode of an infectious disease during the previous year of treatment. The data are shown in Fig. 2.

During the evaluation period, 709 infliximab infusions were administered. In total, 52 infusions (6.83%) were suspended and rescheduled for clinical reasons to preserve patient safety. The causes of the suspension are shown in Fig. 3.

In total, 30 patients (29.70%) reported experiencing at least one infliximab-related adverse event in the previous year. The frequency of adverse events reported by patients is shown in Fig. 4.

No statistically significant differences were found in the frequency of infusion reactions, occurrence of infectious diseases, infusion suspensions for clinical reasons, or perception of adverse events between the IBD and rheumatological and/or dermatological disease groups (Table 3).

### Treatment adherence

A total of 92 patients (91.1%) achieved a treatment adherence rate of >80% using the proportion of days covered method and were considered adherent. The average adherence rate of survey participants was 94%. In total, 51 patients (50.49%) achieved 100% adherence to infliximab treatment in the previous year; the lowest

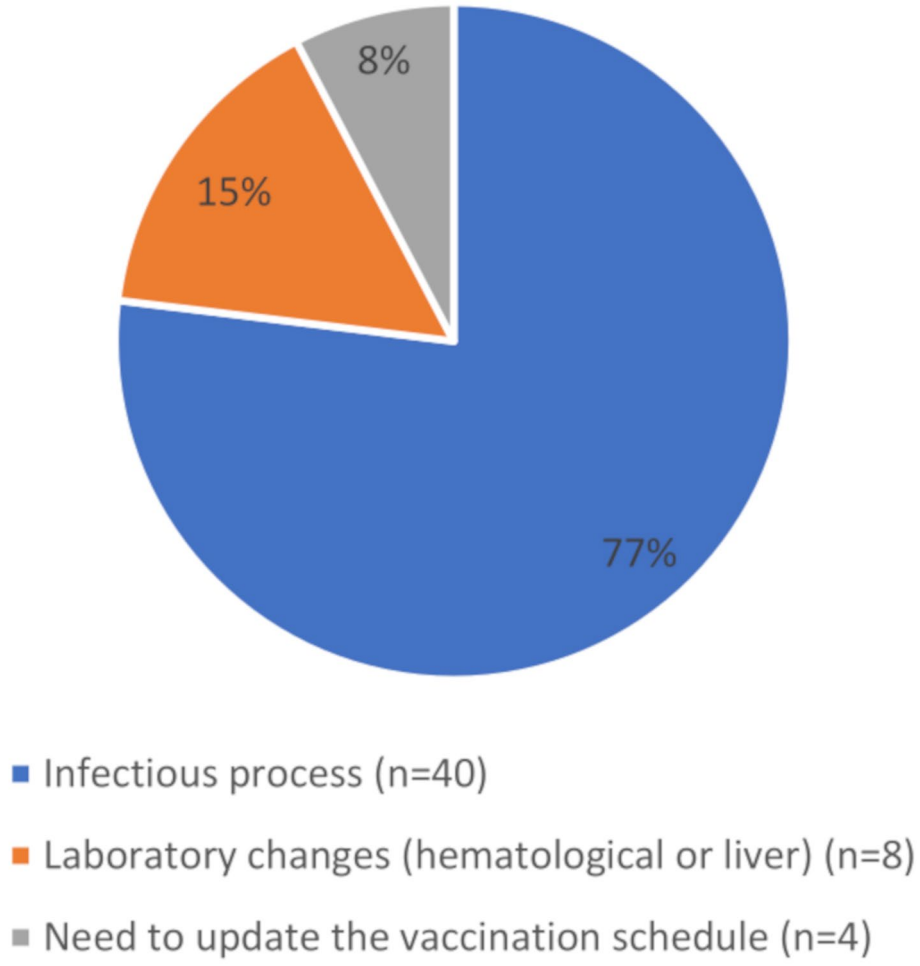


**Fig. 3** Relative frequency of causes of infusion suspension in patients

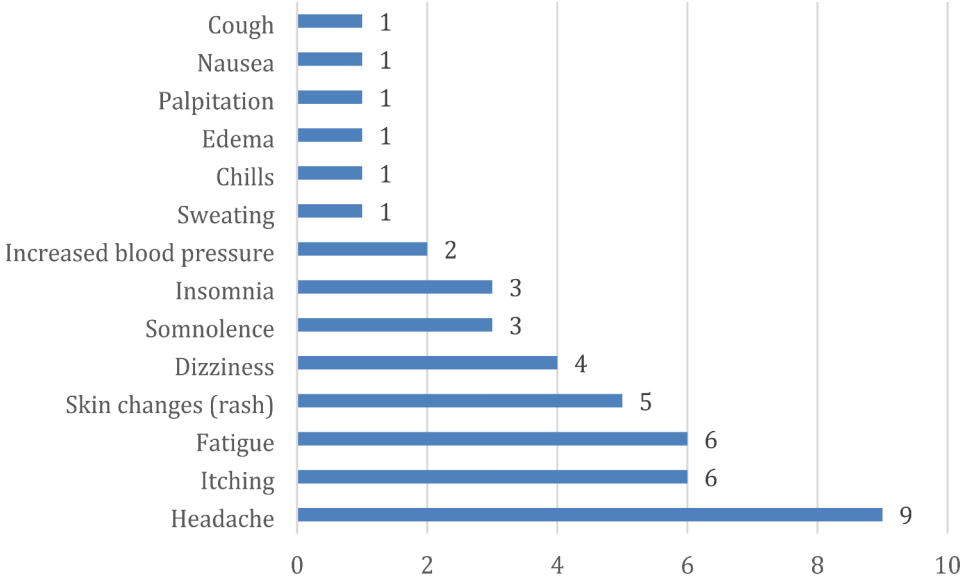


**Fig. 4** Frequency of adverse events reported by patients

**Table 3** Frequency of infusion reactions, infections, suspension of infusions, and occurrence of adverse events

| Variables | Inflammatory Bowel Disease (*n* = 65) | Rheumatological and/or Dermatological Disease (*n* = 36) | All patients (*n* = 101) | *P* |
|---|---|---|---|---|
| Infusion Reactions, *n* (%) | 9 (13.8) | 2 (5.6) | 11 (10.9) | 0.319 |
| Infections in the last year, *n* (%) | 30 (46.2) | 18 (50.0) | 48 (47.5) | 0.711 |
| Number of infusions suspended for clinical reasons in the last year, median (IQR) | 0 (1) | 0 (1) | 0 (1) | 0.776 |
| Occurrence of adverse events in the last year, *n* (%) | 16 (24.6) | 14 (38.9) | 30 (29.7) | 0.173 |

IQR, interquartile range

adherence rate was 21%. The average number of days of the year was 22.3 days per patient.

A significant difference was found in adherence between patients with rheumatological and/or dermatological diseases and those with IBDs. In total, 36 (100%) patients with rheumatological and/or dermatological diseases achieved an adherence rate of >80% and were considered adherent. Among patients with IBDs, 56 (86.2%) were classified as adherent ($p$=0.025; RR=0.609). In this study, individuals with inflammatory bowel diseases had a 39.1% higher risk of non-adherence to treatment compared with other patients in our sample.

No significant associations were observed between treatment adherence and independent variables (Table 4). However, a lower median age was observed in the non-adherent group ($p$=0.054).

Weak associations were identified between adherence and marital status (C=0.208), education level (C=0.154), religion (C=0.143), occupational status (C=0.283), occurrence of adverse events (C=0.126), and infusion reactions (C=0.109). There was a higher proportion of married patients who retired due to disability, individuals with higher education, and Catholics in the group of patients classified as adherent to treatment. A higher proportion of individuals who experienced infusion reactions and infliximab-related adverse events was observed in the group of adherent patients who had greater exposure to the drug throughout the year.

No significant differences were found between adherent and non-adherent patients with IBD in disease activity (Table 5).

Adherence was assessed using 749 medication administration schedules. A total of 639 (85.31%) doses were administered according to the dosage schedules and intervals, with no failures in patient compliance. A total of 70 (9.35%) administrations were performed late due to patient noncompliance. In total, 40 scheduled administrations (5.34%) were not performed and were considered missed because of a lack of adherence. Figure 5 summarizes the frequencies of missed and delayed administrations due to failure to adhere and suspension for clinical reasons. Most patients (66.34%) received at least one infusion that was not performed on the scheduled date owing to poor adherence or clinical reasons.

The most common reason for absence on the scheduled date was difficulty traveling to the referral center (28.18% of infusions were delayed or missed). The reasons the patients were absent for medication administration are shown in Fig. 6.

When enquired about the challenges encountered in complying with the dosage interval and adapting the administration of the medication to their routine, most patients (69 [68.32%]) reported receiving support from third parties for treatment. However, 29 (28.71%) patients believed that the administration of the medication greatly interfered with work or other life activities, and 47 (46.53%) reported missing important appointments because of the administration of the medication. A total of 35 (34.65%) patients reported having stopped taking the medication at some point because of difficulty in traveling to the healthcare unit.

When patients were enquired about their relationship with the healthcare team, 99 (98.02%) patients reported that the team spoke easy-to-understand language and 100 (99.01%) felt comfortable asking questions about treatment. A total of 4.95% of patients reported feeling uncomfortable when in contact with doctors, pharmacists, and other healthcare professionals or inside a hospital. The responses to the questionnaire are presented in Table 6.

## Discussion

This study made it possible to obtain a comprehensive understanding of aspects related to adherence to infliximab treatment in a real-world cohort by determining the contribution of sociodemographic, clinical, and pharmacotherapeutic factors. No other studies were found in the literature about adherence to infliximab, broadly involving patients with IMIDs, nor studies that compare adherence in different pathologies. Non-adherence to treatment is an important public health problem that is quite common among patients with chronic diseases, with an average adherence rate of 50% in developed countries and worse rates in developing countries [9]. In patients with IBDs, non-adherence to infliximab treatment is associated with greater morbidity and mortality, relapse, loss of response, and higher hospitalization costs [3]. In Brazil, free access to infliximab is regulated

**Table 4** Sociodemographic, clinical, and pharmacotherapeutic characteristics of adherent and non-adherent patients

| Variables | Adherents (*n* = 92) | Non-Adherents (*n* = 9) | *P* | W | RR |
|---|---|---|---|---|---|
| Age, median (IQR) | 44 (25.5) | 35 (21) | 0.054 | | |
| Sex, *n* (%) | | | | | |
| Male | 56 (60.9) | 5 (55.6) | 0.756 | 0.0309 | 1.02 |
| Female | 36 (39.1) | 4 (44.4) | | | |
| Place of residence, *n* (%) | | | | | |
| Capital | 28 (30.4) | 2 (22.2) | 0.722 | 0.0511 | 1.04 |
| Interior | 64 (69.6) | 7 (77.8) | | | |
| Marital status, *n* (%) | | | | | |
| Single | 42 (45.7) | 6 (66.7) | 0.179 | 0.208 | |
| Married | 43 (46.7) | 2 (22.2) | | | |
| Divorced | 5 (5.4) | 0 (0.0) | | | |
| Widowed | 2 (2,2) | 1 (11.1) | | | |
| Occupational status, *n* (%) | | | | | |
| Employed | 30 (32.6) | 3 (33.3) | 0.184 | 0.283 | |
| Unemployed | 17 (18.5) | 2 (22.2) | | | |
| Retired due to age | 4 (4.4) | 0 (0.0) | | | |
| Retired due to disability | 30 (32.6) | 1 (11.1) | | | |
| From home | 5 (5.4) | 0 (0.0) | | | |
| Student | 6 (6.5) | 3 (33.3) | | | |
| Family income (in minimum wages), median (IQR) | 1 (1) | 2 (1) | 0.286 | | |
| Education, *n* (%) | | | | | |
| Incomplete Elementary | 18 (19.6) | 2 (22.2) | 0.544 | 0.154 | |
| Complete Fundamentals | 4 (4.3) | 1 (11.1) | | | |
| Incomplete Medium | 9 (9.8) | 1 (11.1) | | | |
| Complete Midfielder | 46 (50.0) | 5 (55.5) | | | |
| Higher | 15 (16.30) | 0 (0.0) | | | |
| Religion | | | | | |
| Areligious | 23 (25.0) | 4 (44.5) | 0.601 | 0.143 | |
| Catholic | 35 (38.0) | 2 (22.2) | | | |
| Protestant | 30 (32.6) | 3 (33.3) | | | |
| Spiritist | 3 (3,3) | 0 (0.0) | | | |
| Umbanda/Candomblé | 1 (1,1) | 0 (0.0) | | | |
| Distance from the Infusion Center (in km) | 137 | 102 | 0.538 | | |
| Treatment time (in months), median (IQR) | 62(88) | 72(39) | 0.99 | | |
| Number of comorbidities, median (IQR) | 1 | 1 | 0.407 | | |
| Dose increase, *n* (%) | | | | | |
| Yes | 23 (25.0) | 2 (22.2) | 1 | 0.0183 | 1.01 |
| Infusion Reactions, *n* (%) | | | | | |
| Yes | 11 (12.0) | 0 (0.0) | 0.592 | 0.109 | 1.11 |
| Infections in the last year, n(%) | | | | | |
| Yes | 43 (46.7) | 5 (55.6) | 0.733 | 0.0502 | 0.969 |
| Occurrence of adverse events, *n* (%) | | | | | |
| Yes | 29 (31.5) | 1 (11.1) | 0.274 | 0.126 | 1.09 |

C, contingency coefficient; RR, relative risk; IQR, interquartile range

**Table 5** Disease activity of adherent and non-adherent patients with IBD

| Variables | Adherents (*n* = 56) | Non-Adherents (*n* = 9) | *P* |
|---|---|---|---|
| Disease activity | | | 0.541 |
| Remission, *n* (%) | 48 (85.7) | 8 (88.9) | |
| Light, *n* (%) | 5 (8.9) | 0 (0) | |
| Moderate, *n* (%) | 3 (5.4) | 1 (11.1) | |
| Severe, *n* (%) | - | - | |

IBD, inflammatory bowel disease; IQR, interquartile range

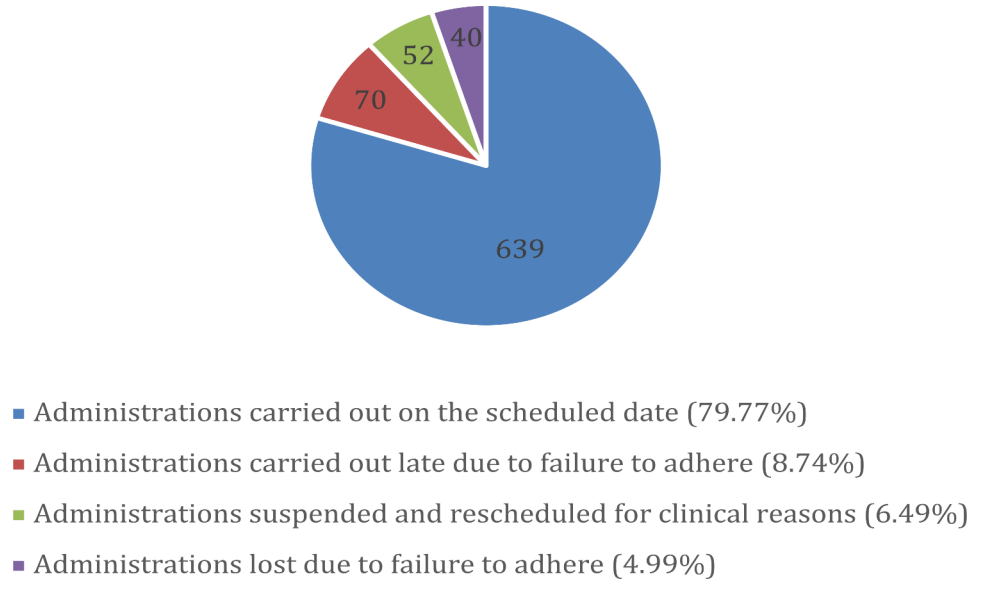


**Fig. 5** Frequency of delayed and missed administrations due to failure to adhere and suspension for clinical reasons

**Table 6** Frequency of affirmative responses to questions in the treatment adherence questionnaire

| Question | Frequency of affirmative response, *n* (%) |
|---|---|
| Do you think that taking your medication interferes too much with your work or other activities in your life? | 29 (28.71) |
| Have you ever had to miss an important appointment because of taking medication? | 47 (46.53) |
| Do you have someone who can help you with your treatment, a family member, friend, or partner? | 69 (68.32) |
| Have you ever stopped using your medication due to any physical disability? | 24 (23.76) |
| Have you ever stopped using your medication for financial reasons? | 19 (18.81) |
| Have you ever stopped using your medication due to difficulty traveling to the health unit? | 35 (34.65) |
| Have you ever stopped taking your medication because you were feeling well or were asymptomatic? | 8 (7.92) |
| Have you ever stopped taking your medication because you forgot the scheduled date? | 14 (13.86) |
| Have you ever stopped using your medication because you feared side effects? | 2 (1.98) |
| Are you opposed to using your medicine for philosophical, religious, or spiritual reasons? | 0 (0) |
| Do you find that your emotional state changes when you think about your medication? | 35 (34.65) |
| Has the consumption of alcohol or drugs ever interfered with the use of your medication? | 1 (0.99) |
| Have you ever stopped using your medicine to use herbal medicine? | 0 (0) |
| Do you feel uncomfortable when in contact with doctors, pharmacists, or other healthcare professionals or when inside a hospital? | 5 (4.95) |
| Do you think that the healthcare team treats you ineffectively because they do not understand your cultural habits? | 0 (0) |
| Do you feel bad if other people watch you while you take your medication? | 2 (1.98) |
| Do you think the healthcare team speaks a language that is easy to understand? | 99 (98.02) |
| Do you feel comfortable asking questions about your treatment? | 100 (99.01) |

through the Specialized Component of Pharmaceutical Assistance, a strategy to allow access to medicines within the scope of the Unified Health System that seeks to guarantee the completeness of treatments at the outpatient level through lines of care defined in the Clinical Protocols and Therapeutic Guidelines published by the Ministry of Health [7].

Herein, a high proportion of patients adhered to treatment with infliximab (91.04%), especially in the group with rheumatological and/or dermatological diseases, in which 100% of patients were classified as adherent. The definitions of adherence and the methods for calculating adherence rates vary considerably in the literature, making comparisons with other studies difficult. A systematic review that evaluated adherence to biologic treatment for rheumatoid arthritis found that 81% of patients adhered to treatment with infliximab. Of the 52 studies included in this review, 73% were based in Europe, and 21% were based in the United States [10]. A retrospective cohort study reported 70% adherence to infliximab therapy in patients with IBDs [11]. The lower adherence rate compared with that in our study can be justified by

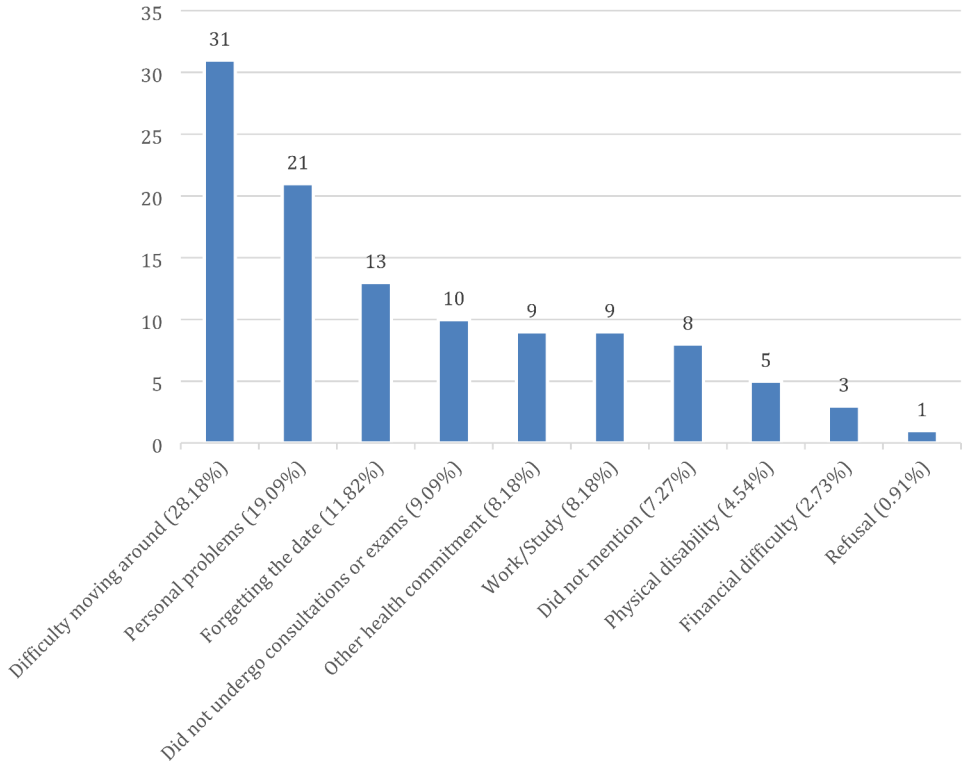


**Fig. 6** Frequency of reasons for non-attendance reported by patients

methodological differences, since in the aforementioned study, any infusion missed within 2 years was categorized as non-adherence. In a systematic review that evaluated adherence to infliximab treatment in patients with IBDs, the adherence rate was 82.6% in general and 70.7% in patients treated with infliximab [8].

The sociodemographic and clinical characteristics of patients with rheumatological and/or dermatological diseases may have contributed to the classification of all patients in this group as adherents. Considering that this group comprised patients with a higher average age and had a higher proportion of retired individuals due to disabilities, greater convenience in accessing treatment may have contributed to greater adherence. An observational study conducted in France identified the main cause of non-adherence to infliximab treatment to be professional restrictions [12]. The literature also suggests that younger individuals, including Brazilians, tend to have lower adherence to the treatment of chronic diseases [13]. Herein, in the comparison of the adherent and non-adherent groups, regardless of the underlying disease, only weak associations were found between the study variables and adherence. There was a higher proportion of patients who were married, older, retired due to disability, had higher education, and were Catholic in the adherent group.

Most evaluated patients were in remission or had controlled disease activity and had good functional capacity. A total of 94.06% of the patients did not require hospitalization in the previous year. An association between adherence to infliximab treatment and better clinical outcomes and quality of life has been observed in several studies [3, 12, 14, 15]. Taking these into account, the following may be considered: a high adherence to treatment contributes to the control of the disease and its complications, and adequate control of the disease and improvement in the quality of life provided by treatment encourage greater treatment adherence. A population-based study conducted in Brazil on patients with chronic diseases showed that poor self-perception of health was strongly associated with low treatment adherence [13]. In the present study, no significant differences were found in disease activity between adherent and non-adherent patients. It is worth noting that these outcomes were evaluated in a cross-sectional manner when the patients were included in the study (after 1 year of treatment), and it was not possible to evaluate the response to treatment or associate adherence failures with relapses within the study period. Additionally, endoscopic evaluation was not performed to assess remission. These limitations make it difficult to establish an association between high adherence and clinical response.

Among the patients evaluated, 10.89% experienced infusion reactions. This result is similar to previous studies, wherein infusion reactions were reported in 5–23% of patients with IBD who participated in a large

randomized clinical trial involving infliximab [16]. In a study conducted in Canada on patients with rheumatic diseases, 12.3% reported at least one infusion reaction [17]. The reactions were mild-to-moderate, allowing the patient to be re-exposed to the medication using specific protocols to prevent and treat these reactions; there was no impact on adherence in the evaluated context. No statistically significant differences were found in the safety profile between compliant and non-compliant patients. Similarly, in a study conducted in China, the occurrence of adverse events was not significantly associated with adherence to infliximab [18].

The main reason for absence on the scheduled date was difficulty in traveling to the infusion center located in the state capital, which led to 28.18% of infusions being delayed or missed. Most patients participating in the study (70.30%) lived outside the city where the medication was administered, requiring a median travel distance of 287.29 km, which may explain the high frequency of this motivation. A study conducted in China found that a longer time spent at the referral center and greater costs incurred by the patient led to a lower adherence to infliximab treatment [18]. Considering the territorial extension of the state of Bahia, the strategic decentralization of medication administration to units in other cities could contribute to greater convenience and patient adherence to treatment, making it accessible to patients who are indicated for use. However, they do not do so because of the primary barrier to access.

In a study from the UK that found an infliximab adherence rate of 76.83%, most patients (94.12%) who missed scheduled infusions cited "inconveniences" that made attendance difficult as the reason [19]. An observational study conducted in France identified professional restrictions as the main cause (44.9%) of non-adherence to treatment with infliximab [12]. The sociodemographic characteristics of the population, as well as the conditions of access to health resources at the research site, are different and can greatly influence the results. However, in agreement with the literature, it was observed that unintentional failures to adhere, such as limitations in availability and resources, were more frequent than intentional causes of nonadherence (refusal due to preferences or beliefs).

In addition to the cost, the complexity of the therapeutic regimen, access to healthcare services, and other treatment-related factors, such as relationships with the healthcare team, can influence adherence [13]. In this study, good communication was observed between health professionals and patients; patients reported that the healthcare professionals used easy-to-understand language and that they felt comfortable asking questions. As the study site is a reference unit with multidisciplinary care and continuous monitoring of effectiveness, safety, and treatment adherence, the welcoming and good degree of communication between professionals and patients may have contributed to the high adherence rates. The observance of higher rates of adherence to intravenous medications when compared to oral medications for other chronic diseases (approximately 50%) may be justified by the positive influence of the nursing team, pharmacy, and doctors who facilitated adherence, provided scheduled infusion dates, and monitored and addressed attendance issues [14]. Only 4.95% of the patients reported feeling uncomfortable in the hospital environment or in contact with healthcare professionals. Continuous monitoring through the assessment of clinical symptoms and signs, assessments of laboratory tests preceding medication administration, and monitoring the occurrence of infusion reactions during administration can contribute positively to patient adherence by promoting environmental safety.

However, two issues should be considered. First, in our study, 32.10% of infusions were not performed on the scheduled date and were rescheduled for clinical reasons and changes in laboratory parameters, such as infections, to guarantee patient safety. Second, the cut-off point of 80% adopted allows the patient, within a year, to have up to 73 days of treatment covered days due to adherence failure and still be considered adherent, which explains the high proportion of adherent patients despite a relevant proportion of patients having at least one delayed infusion. It is important to note that the cut-off point was adopted to facilitate comparison with previous studies and to consider a real-life scenario. Nevertheless, the overall average treatment adherence rate was 94%, and 51% of patients achieved 100% adherence during the 1-year treatment duration. The average number of uncovered days of treatment during the year due to adherence failure was only 22.3 days per patient, demonstrating that although most patients delayed at least one infusion, the adopted cut-off point did not overestimate patient adherence in this study.

This study had some limitations. Regarding external validity, it may not be possible to generalize the results to patients under different scenarios. As this study included retrospective analysis of data and some variables were collected through a questionnaire that relied on patients recalling events from the previous year, it is subject to memory bias. Another limitation is selection bias. Patients whose treatment was suspended or replaced owing to the occurrence of a serious adverse reaction or failed treatment response before the study were not included. Therefore, the positive results in controlling the underlying disease and safety of infliximab exclusively reflect the reality of patients who continue to use the medication. Further studies are needed to determine the positive impact of treatment adherence on clinical

outcomes, such as disease remission and improved quality of life, as well as its economic impact.

## Conclusions

A high proportion of patients were observed to be adherent to infliximab treatment (91.04%), especially in the group with rheumatological and/or dermatological diseases, in which 100% of patients were classified as adherent. Individuals with IBDs had a 39.1% higher risk of non-adherence to treatment compared with other patients. Most evaluated patients were in remission or had controlled disease activity and had good functional capacity. The main reason for the absence on the scheduled date was difficulty traveling to the referral center (28.18% of infusions were delayed or missed). Reception and a good level of communication between professionals and patients can contribute to higher adherence rates.

### Abbreviations

| | |
|---|---|
| IMID | Immune-mediated inflammatory diseases |
| TNFα | Tumor necrosis factor α |
| IBD | Inflammatory bowel disease |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-024-03455-w.

Supplementary Material 1

### Author contributions

PML wrote the main manuscript text. PMS, FSP, AMNWB have made substancial contributions to the conception and design of the work. FSP had the responsibility for ensuring the accuracy of the data entered into the Excel sheet. LBO and PMS have made substantial contribuitions to analysis and interpretation of data. LACBN, GOS and PMS have drafted the work and substantively revised it. All authors reviewed the manuscript.

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### Data availability

Sequence data that support the findings of this study is available on this link: https://docs.google.com/spreadsheets/d/1jQxnWz7EMXJ0ZSGnGtXnSbj5OwlBfg43/edit?usp=sharing&ouid=107792188550663295743&rtpof=true&sd=true.

## Declarations

### Ethical approval and consent to participate

This study was approved by the Research Ethics Committee of Professor Edgard Santos University Hospital (No. 2.702.265). All patients signed an informed consent form, and their identification data were kept confidential.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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## Publisher's note