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Adherence and persistence to treatment with infliximab: analysis of a patient support program cohort in Brazil

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HIGHLIGHTS

- Monoclonal antibodies have proven efficacy in the management of several conditions and infliximab (IFX) is one of the most important drugs of the class.
- The objective of this study was to describe adherence and persistence rate to IFX treatment and also persistence in the patient support program (PSP).
- We found that many patients leave the program without discontinuing IFX, since the 12-month persistence were very different between program and medication estimates, while high adherence rates were observed among patients enrolled in the PSP. Data highlights the benefits of a PSP.

ABSTRACT – Background – Monoclonal antibodies have proven efficacy in the management of several conditions and infliximab (IFX) is one of the most important drugs of the class. Some recent data have shown low rates of both persistence and adherence to several available biologics. **Objective –** The objective of this study was to describe adherence and persistence rate to IFX treatment and also persistence in the patient support program (PSP), among patients diagnosed with inflammatory bowel diseases (IBD) or rheumatic diseases (RD) enrolled in the program of a large pharmaceutical company in Brazil. **Methods –** Retrospective observational analysis using the PSP database. IBD or RD patients using IFX enrolled on the PSP database between September 2015 and August 2019 were retrospectively evaluated to identify the persistence rate and adherence and followed up until March 1, 2020. Patients were excluded if treatment start date was prior to program entry; first infusion prior to September 1st, 2015 or after August 31st, 2019; the patients did not started treatment; and patients with "OTHERS" in "Indication" field. Persistence was assessed considering both persistence in the program ("PSP persistence") and persistence on IFX in the PSP ("IFX persistence in the PSP"). PSP persistence was defined as the proportion of patients remaining in the program at 6, 12, 24, 36 and 48 months after initiating IFX. To determine IFX persistence in the PSP, censoring was defined at the time the patient left the program, died, or was lost to follow-up. Adherence to treatment was measured by medication possession ratio ((MPR) - All days supply / elapsed days from first prescription to last day of medication possession)). Descriptive statistics were initially used. Kaplan-Meier curve, the median time estimated by the survival function, Cox regression model, and restricted mean survival time (RMST) were used to evaluate the treatment persistence time at 24 months and the logistic regression model was performed aiming to identify variables associated with adherence (MPR ≥80%). **Results –** A total of 10,233 patients were analyzed, 5,826 (56.9%) with the diagnosis of RD and 4,407 (43.1%) of IBD. At the end of the follow-up (median 9.1 months from PSP entry to the last infusion), persistence in the PSP was 65.6%, 48.2%, 31.0%, 20.7% and 13.1% at 6, 12, 24, 36 and 48 months, respectively. Considering persistence on IFX in the PSP, estimates were 93.7%, 87.8%, 77.0%, 62.4% and 53.0% at 6, 12, 24, 36 and 48 months, respectively. Variables associated with the risk of non-persistence were gender, country region and diagnosis of rheumatoid arthritis and ankylosing spondylitis. Median MPR was 94.2%, while the percentage of patients with MPR ≥80% was 91.0%. Variables associated with MPR≥80% were country region and diagnosis of Crohn's disease. **Conclusion –** Many patients leave the program without discontinuing IFX, since the 12-month persistence were very different between program and medication estimates, while high adherence rates were observed among patients enrolled in the PSP. Data highlights the benefits of a PSP.

Keywords – Antibodies; monoclonal; medication adherence; inflammatory bowel diseases; rheumatic diseases.

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INTRODUCTION

Immune-mediated diseases are characterized by immune dysregulation, resulting in chronic inflammation with tissue and organ damage[1]. The role of the immune system in the pathophysiology of diseases like cancer, AIDS, hypersensitivity reactions, inflammatory bowel diseases (IBD) and rheumatologic diseases became evident after the crescent knowledge about basic immunology in the fifties and later, in the seventies, with its applicability on the diagnosis and treatment of these disorders[1].

Monoclonal antibodies were introduced in the early 1970s with the development of hybridoma technology[2]. Its benefits are related to their specificity and the ability to target specific molecules in the inflammatory response/immune system[3]. IBD (Crohn's disease (CD) and ulcerative colitis (UC)), spondyloarthropathies (ankylosing spondylitis, psoriatic arthritis), rheumatoid arthritis and plaque psoriasis are among the immune-mediated diseases with biologic proved efficacy. Infliximab (IFX) is one of the most important monoclonal antibodies indicated in those disorders[4-9].

IFX was the first approved monoclonal antibody and first targeted immune modulator for immune-mediated diseases, in 1998. Two years later, Brazilian regulatory agency (*Agência Nacional de Vigilância Sanitária* – ANVISA) approved it in the country. The first indication was for CD a chronic recidivant disorder with intestinal inflammation, diarrhea and rectal bleeding that, if not treated properly, can lead to several complications from malnutrition and hospitalization to surgical resection and cancer[4]. Historically, in Brazil, it was a disease with low prevalence but recently, the incidence and prevalence are increasing considerably and, because is a chronic disease with low mortality rate, the accumulated prevalence is a matter of concern[10].

Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, and plaque psoriasis are part of a set of immunomediated chronic diseases that must be continuously monitored by the doctor. Moreover, social consequences of those diseases include limitations in performing roles related to working life, as well as family and social life. Early diagnosis and prompt initiation of treatment are critical for controlling disease activity and preventing functional disability. Furthermore, all the work to improve adherence has an impact on disease activity[11-13].

Adherence and persistence are different constructs but related to each other. Medication persistence represents the duration of time from initiation to discontinuation of therapy, while adherence is related to the extent to which a patient acts in accordance with the prescribed interval[14]. Recent studies have shown low rates of both persistence and adherence, in rheumatoid arthritis, inflammatory bowel disease, psoriasis and psoriatic arthritis patients, to several available biologics[15-20]. Persistence to treatment has also an impact on costs. Rheumatoid arthritis patients switching after a 1-year period incurred in higher healthcare costs than the persistent patients[21]. Among patients diagnosed with UC, non-persistence was associated with increased nonmedication-associated resource utilization[22]. Similarly, non-adherence places a significant burden to healthcare systems, with annual cost estimates ranging from $949 to $44190 (in 2015 US$) per person[23].

Different efforts have been made to improve adherence and persistence rates, such as patient support programs (PSP) provided by pharmaceutical industries. Rubin et al. (2017) have assessed the impact of one such program on patient adherence to adalimumab and direct medical costs in CD, UC, rheumatoid arthritis, psoriasis, psoriatic arthritis, and ankylosing spondylitis and an association with greater adherence, improved persistence, and lower medical and total health care costs were reported[24]. However, more information on the impact of programs on these outcomes in patients treated with other biologics is still lacking.

The private sector, especially pharmaceutical industries, develops PSP to improve patient compliance to the treatment. The main objectives of PSP are to stimulate the safety and followed-up health care practice and to involve patients and caregivers in educational processes with guidelines and informative materials. Such programs assist the patients and caregivers in preventing adverse events and supports the physicians in the clinical follow-up of the patient. For this purpose, those programs collect, record, and analyze personal and sensitive data systematically upon patient's consent, but individually. In this context, the objective of this study was to describe adherence and persis-

tence rate to IFX treatment and also persistence in the PSP, among patients diagnosed with IBD or rheumatic diseases (RD) enrolled in the program of a large pharmaceutical company in Brazil.

METHODS

Study design

A retrospective observational analysis using the PSP database was conducted. IBD or RD patients using IFX enrolled on the PSP database between September 2015 and August 2019 were retrospectively evaluated to identify the persistence rate and adherence. Information until March 1, 2020, was collected from database, to answer the proposed objectives. Data collection was held from April 5, 2021 to November 12, 2021.

Setting

Since 2006, the pharmaceutical company has a PSP in Brazil for patients using branded infliximab to offer better care and support, trying to improve the patient experience and medication adherence. Data is captured through telephone, e-mail, and physical documents (if applicable) from patients, physicians, or laboratories. Patients are contacted periodically through phone calls so that the information in the PSP database could be updated. The program has a protocol to call the patients every 15 days during the access period and then every 8 weeks during maintenance or the patient set a time for this call. If the patient does not answer the call, the program starts a protocol of trying to contact the patient. If after 30 attempts on different days and times the patient does not answer, she/he is inactivated and the reason for dropping out is "lack of contact". Since there is no information if that patient is still on medication, such individual is considered as censored.

Participants

Eligible patients were those with the diagnosis of IBD or RD using IFX enrolled on the PSP between September 2015 and August 2019. Exclusion criteria were treatment start date prior to program entry; first infusion prior to September 1st, 2015 or after August 31st, 2019; the patient has not started treatment; and patients with "OTHERS" in "Indication" field.

Variables and data sources/measurements

Both persistence in the program ("PSP persistence") and persistence on infliximab ("IFX persistence") were analyzed for this paper. PSP persistence was defined as the proportion of patients remaining in the program at 6, 12, 24, 36 and 48 months after initiating IFX. To determine IFX persistence in the PSP, censoring was defined at the time the patient left the program, died, or was lost to follow-up. Persistence loss was defined when a treatment interruption of >90 days or a discontinuation event (TABLE 1) was observed. To calculate both persistence times, treatment start and finish dates were compared. The finish date was defined as the date of the last infusion + days of supply of the last infusion. If the loss of follow-up occurred between the last day of supply of the last infusion medication and the gap of 90 days, the date of the last infusion + days of supply of the last infusion + 1 was considered as loss of follow-up day. Days of supply refers to the period comprised by the medical prescription, until the need for a new one.

TABLE 1. Event classifications according to findings described in the PSP database.

Field Content	Event/Censoring
Concurrent disease	Event
Adverse event	Event
Lack of treatment access	Event
Lack of efficacy	Event
Death	Censor
Treatment changed by physician	Event
Follow-up loss	Censor
Patient voluntarily left program	Censor
Treatment never started	Exclusion Criteria

Adherence to treatment was measured by medication possession ratio (MPR). The outcome was calculated considering the ratio between the total days of medication supply (all days supply) and the number of elapsed days from first prescription to last day of medication possession (elapsed days). All days supply was defined by the sum of days of supply between the index date and the last prescription dispensed and the days of supply of the last filled prescription. Elapsed days was defined by the sum of the number of days between the index date and

the last prescription dispensed and days of supply of the last filled prescription during the observation period without substantiated interruption reported by the patient in the PSP database. Treatment adherence was defined as a MPR ≥80%.

Statistical analysis

All data was initially assessed using a descriptive approach. Kaplan-Meier curve, the median time estimated by the survival function, Cox regression model and restricted mean survival time (RMST) were used to evaluate the treatment persistence time at 24 months. The logistic regression model was performed aiming to identify variables associated with adherence (MPR ≥80%). Variables with statistical significance at a 20% significance level in the univariate model were selected for the multivariate model, and only variables with statistical significance at a 5% level were kept in the final model. Other variables were also descriptively analyzed and/or used as independent variables in the Cox's proportional-hazard and linear models: sociodemographic and clinical profile (gender, age group, geographical distribution, and indication), patient flow (naïve to biologics), switch and the number of infusions. Statistical analyses were performed using R software version 4.0.

Ethical aspects

The study protocol was submitted and approved by the Research Ethics Committee of the Ecolyzer Laboratory, under the consubstantiated opinion number 4.619.388 (CAAE: 42120721.0.0000.8227). Considering the retrospective nature of the analysis, informed consent was waived.

RESULTS

Initially, the PSP database contained information for 34,668 patients. After applying eligibility criteria, a total of 10,233 records of patients with the first infusion between September 1st, 2015 and August 31st, 2019 were included in the analysis. FIGURE 1 shows the inclusion flowchart.

TABLE 2 shows demographic and clinical characteristics among the total sample and stratified by IFX indication. The most frequent indication was RD, corresponding to 56.9% of the sample (rheumatoid

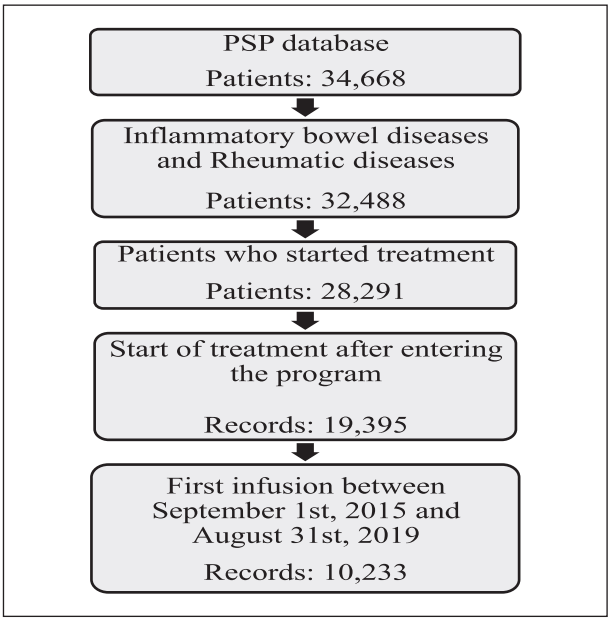

FIGURE 1. Flowchart of the number of patients included in the analysis.
PSP: patient support program.

TABLE 2. Demographic and clinical characteristics among RD and IBD patients, treated with infliximab and enrolled in a PSP from September, 2015 to August, 2019 and followed until March, 2020.

	Total sample (n=10,233)		RD (n=5,826)		IBD (n=4,407)	
	n	%	n	%	n	%
Indication						
Rheumatic diseases	5,826	56.9	5,826	100.0	-	-
Rheumatoid arthritis	3,154	30.8	3,154	54.1	-	-
Ankylosing spondylitis	1,740	17.0	1,740	29.9	-	-
Psoriatic arthritis	932	9.1	932	16.0	-	-
Inflammatory bowel diseases	4,407	43.1	-	-	4,407	100.0
Crohn's disease	3,961	38.7	-	-	3,961	89.9
Ulcerative colitis	446	4.4	-	-	446	10.1
Gender						
Male	3,904	38.2	1,760	30.2	2,144	48.6
Female	6,329	61.8	4,066	69.8	2,263	51.4
Age groups (years)						
Mean/SD	46.2	15.5	51.7	13.5	39.0	15.0
0 – 17 years	198	1.9	-	-	198	4.5
18 – 39 years	3,453	33.7	1,153	19.8	2,300	52.2
40 – 59 years	4,372	42.7	2,967	50.9	1,405	31.9
≥60 years	2,210	21.6	1,706	29.3	504	11.4
Region of residence						
Southeast	6,275	61.3	3,215	55.2	3,060	69.4
South	1,826	17.8	1,044	17.9	782	17.7
Northeast	968	9.5	360	6.2	269	6.1
Midwest	629	6.1	708	12.2	260	5.9
North	535	5.2	499	8.6	36	0.8

IBD: inflammatory bowel disease; RD: rheumatic disease; SD: standard deviation.

arthritis: 30.8%; ankylosing spondylitis: 17.0%; psoriatic arthritis: 9.1%). Meanwhile, IBD accounted for 43.1% of the sample (CD: 38.7%; UC: 4.4%). Considering the total sample, most of the patients were female (61.8%), most frequently aged between 40–59 years (42.7%; mean: 46.2, SD: 15.5) and residents in the Brazilian Southeast region (61.3%).

At the end of the follow-up (median 9.1 months from PSP entry to the last infusion), 19.8% of patients voluntarily left the PSP, 7.8% had some IFX discontinuation event (of these, 77.9% were medical treatment switches), 0.6% were lost follow-up and 0.5% died. In addition, 7,297 patients (71.3%) were still active in the PSP without reporting an event. The same pattern was observed among RD and IBD patients (TABLE 3).

TABLE 4 shows the results of both PSP and IFX persistence in the PSP.

TABLE 3. Reasons for leaving the program and follow-up of RD and IBD patients, treated with infliximab and enrolled in a PSP from September, 2015 to August, 2019 and followed until March, 2020.

	Total sample (n=10,233)		RD (n=5,826)		IBD (n=4,407)	
	n	%	n	%	n	%
Reasons for leaving the program						
Voluntary withdrawal from the program	2,025	19.8	1,337	22.9	688	15.6
Discontinuation of Infliximab	797	7.8	529	9.1	268	6.1
Medical treatment switch	621	77.9	415	7.1	206	4.7
Loss of treatment access	128	16.1	85	1.5	43	1.0
Adverse event	36	4.5	24	0.4	12	0.3
Lack of efficacy	11	1.4	5	0.1	6	0.1
Competing disease	1	0.1	-	-	1	0.0
Loss to follow-up	60	0.6	38	0.7	22	0.5
Death	54	0.5	31	0.5	23	0.5
No events reported	7,297	71.3	3,891	66.8	3,406	77.3
Follow-up time (months - median/range)	9.1	3.8–19.0	8.6	3.7-18.1	9.7	3.8-20.5

IBD: inflammatory bowel disease; RD: rheumatic disease.

TABLE 4. Persistence in the program and infliximab persistence in the PSP among RD and IBD patients, treated with infliximab and enrolled in a PSP from September, 2015 to August, 2019 and followed until March, 2020.

Persistence time	Total sample (N)	PSP Persistent patients (N)	Persistence in the PSP (%) *	Uncensored patients (N)	IFX persistence in the PSP (%) **
Total sample					
6 months	10,233	6,713	65.6	7,167	93.7
12 months	8,842	4,258	48.2	4,849	87.8
24 months	6,000	1,859	31.0	2,414	77.0
36 months	3,195	660	20.7	1,058	62.4
48 months	953	125	13.1	236	53.0
Rheumatic diseases					
6 months	5,826	3,790	65.1	4,089	92.7
12 months	5,041	2,313	45.9	2,711	85.3
24 months	3,459	965	27.9	1,340	72.0
36 months	1,833	315	17.2	581	54.2
48 months	508	58	11.4	133	43.6
Inflammatory bowel diseases					
6 months	4,407	2,923	66.3	3,078	95.0
12 months	3,801	1,945	51.2	2,138	91.0
24 months	2,541	894	35.2	1,074	83.2
36 months	1,362	345	25.3	477	72.3
48 months	445	67	15.1	103	65.0

IFX: infliximab; PSP: patient support program; IBD: inflammatory bowel disease; RD: rheumatic disease. *persistent patients / total sample; **persistent patients / uncensored patients.

FIGURE 2 shows adherence to treatment results. Median MPR was 94.2%, 93.9% and 94.8%, while the percentages of patients with MPR ≥80% were 91.0%, 90.8% and 91.2% for the total sample, RD and IBD, respectively.

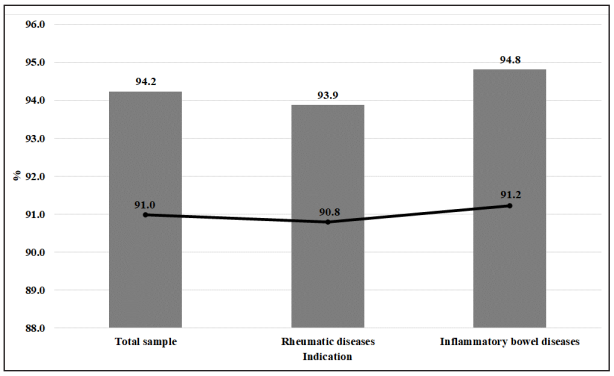

FIGURE 2. Adherence to treatment with infliximab among RD and IBD patients enrolled in a PSP from September, 2015 to August, 2019 and followed until March, 2020.
MPR: medication possession rate; IBD: inflammatory bowel disease; RD: rheumatic disease; PSP: patient support program.

Cox's multivariate model was built to identify variables associated with 24-month persistence and these data (risk of non-persistence) are shown in TABLE 5. Men had 30.0% lower risk of non-persistence (*P*-value: <0.001), patients residing in Midwest (HR: 1.429; *P*-value: 0.016), Northeast (HR: 1.697; *P*-value: 0.002), North Region (HR: 1.549; *P*-value: 0.011) and Southeast Region (HR: 1.245; *P*-value: 0.034) had a higher risk of non-persistence compared to patients residing in South Region, patients with psoriatic arthritis (HR: 1.749; *P*-value: <0.001), rheumatoid arthritis (HR: 1.452; *P*-value: <0.001) and ankylosing spondylitis (HR: 1.470; *P*-value: 0.001) had a higher risk of non-persistence compared to patients with CD and naïve patients had 70.6% lower risk of non-persistence (*P*-value: <0.001). Except for the comparison between the South and Southeast regions, the analysis of the area under the survival curve using the RMST showed greater 24-month persistence for the same groups.

The logistic regression model was performed to identify variables associated with MPR ≥80% (TABLE 6). Patients residing in the South and Southeast regions (compared to those residing in the Midwest Region) had 67.2% (*P*-value: <0.001) and 2.2 times (*P*-value: <0.001) higher chance of having MPR ≥80%, patients with CD had 37.2% (*P*-value: <0.001) and 38.1% (*P*-value: 0.009) higher chance of having MPR ≥80% compared to patients with rheumatoid arthritis and UC, respectively.

TABLE 5. Cox's proportional hazards model to assess variables associated with 24-month persistence in the PSP among RD and IBD patients, treated with infliximab and enrolled in a PSP from September, 2015 to August, 2019 and followed until March, 2020.

Cox's proportional hazards model	Univariate model		Multivariate model	
	HR	*P*-value	HR	*P*-value
Gender				
Female	1.000	-	1.000	-
Male	0.620	<0.001	0.700	<0.001
Age	1.002	0.313	-	-
Region				
South	1.000	-	1.000	-
Midwest	1.354	0.041	1.429	0.016
Northeast	1.426	0.039	1.697	0.002
North	1.589	0.006	1.549	0.011
Southeast	1.157	0.155	1.245	0.034
Disease				
Crohn's disease	1.000	-	1.000	-
Psoriatic arthritis	1.860	<0.001	1.749	<0.001
Rheumatoid arthritis	1.730	<0.001	1.452	<0.001
Ulcerative colitis	1.577	0.013	1.427	0.055
Ankylosing spondylitis	1.455	0.001	1.470	0.001
Naive patient				
No	1.000	-	1.000	-
Yes	0.293	<0.001	0.294	<0.001

HR: Hazard ratio; PSP: patient support program; IBD: inflammatory bowel disease; RD: rheumatic disease.

DISCUSSION

Patients with immune-mediated diseases have experienced an improvement in health-related quality of life, relief of symptoms, and decreased disease progression since monoclonal antibodies were included in the therapeutic arsenal for such conditions. Monoclonal antibodies, a new form of biologic therapy, enabled targeting specific molecules in the inflammatory response, starting a revolution with targeted immune modulators. IFX was the first agent and first monoclonal antibody approved as a targeted immune modulator in the treatment of chronic immune mediated inflammatory diseases. However, proper treatment maintenance, in terms of both adheren-

TABLE 6. Logistic regression model to assess variables associated with MPR ≥80% among RD and IBD patients, treated with infliximab and enrolled in a PSP from September, 2015 to August, 2019 and followed until March, 2020.

Logistic regression model	Univariate model		Multivariate model	
	OR	*P*-value	OR	*P*-value
Gender				
Female	1.000	-	-	-
Male	0.985	0.972	-	-
Age				
	1.002	0.876	-	-
Region				
Midwest	1.000	-	1.000	-
Northeast	>100	0.988	1.285	0.067
North	>100	0.990	1.054	0.729
Southeast	5.223	<0.001	1.672	<0.001
South	25.063	0.003	2.166	<0.001
Disease				
Crohn's disease	1.000	-	1.000	-
Psoriatic arthritis	1.057	0.944	0.878	0.132
Rheumathoid arthritis	1.966	0.306	0.729	<0.001
Ulcerative colitis	>100	0.986	0.724	0.009
Ankylosing spondylitis	0.528	0.199	0.887	0.083
Naive patient				
No	1.000	-	-	-
Yes	0.673	0.390	-	-

HR: Hazard ratio; PSP: patient support program; IBD: inflammatory bowel disease; RD: rheumatic disease.

ce and persistence, is the key to these positive outcomes because a lack of consistency to any such treatment regimen puts patients at a higher risk for disease flare and treatment failure[25]. Greater adherence, improved persistence, and reduced medical and total health care costs could be achieved for patients with immune-mediated diseases by enrollment in a PSP[26]. The analysis presented here enables a better understanding of the association between PSP participation, long-term medication-taking behavior, and patients' characteristics.

Initially, the persistence in the program was assessed through the calculation of the proportion of patients remaining in the PSP at different timepoints after initiating IFX. A decline in this measure could be observed, ranging from 48.2% for 12 months to 13.1% for 48 months. It is expected that patients leave the program. However, the enrollment in a PSP was previously associated with higher persistence rates on monoclonal antibodies treatment[27]. The major reasons for PSP exiting or treatment discontinuation were voluntarily leaving the program (19.8%) and treatment switching (6.1%). In the program, an attempt of contact with participants is initially performed every 15 days and every 8 weeks thereafter and the last information is provided in the database. The request to leave the program is a possibility and may be attributed to a treatment discontinuation, since there were few options to IFX access in Brazil during the study period. However, a conservative approach for the persistence analysis was adopted and such patients were defined as censored.

When considering IFX persistence in the PSP, it also declined over time, ranging from 87.8% at 12 months to 53.0% at 48 months. Decreasing pattern over time is consistent with previous data. However, in our analysis, persistence in the first year is higher than that reported by Chen et al. (2019), 47.6% among patients with CD and 44.91% among those with UC[18]. Santos et al. (2019) reported IFX persistence rates of 52% after 12 months of follow-up in a historical cohort composed of rheumatoid arthritis users of the Brazilian National Health System[28]. These data may highlight the role of PSP in treatment persistence, however, further analysis designed to test such hypotheses among Brazilian patients are still needed. In a recent study, the PSP cohort consistently demonstrated higher adalimumab persistence than the non-PSP cohort at 12 (49% vs 34%; $P<0.0001$; 42% greater), 24 (36% vs 26%; $P< 0.0001$; 37% greater), and 36 (27% vs 19%; $P< 0.0001$; 44% greater) months. Improved medication-taking behavior for the PSP cohort, including higher adherence, lower risk of discontinuation, and longer duration of persistence, was found across all therapeutic areas[29]. Additionally, Srulovici et al. (2018) compared the enrollment in a PSP using a random sample and found no confounding factors, which highlights the benefit of such programs[27].

Although 20.6% of the sample has been lost to follow-up or left the program, the use of the measures obtained from PSP analysis may be considered as a good proxy to understand the persistence to treatment with IFX among patients with the diagnosis of IBD or RD in a real-world context, during the study period (2015–2019). According to records provided in the Brazilian national agency (*Agência Nacional*

de Vigilância Sanitária – ANVISA) website, IFX was initially registered in the country as a branded drug in 2007[30]. In Brazil, the Ministry of Health has a program called "Partnership for Productive Development" that aims to expand the access to drugs in the public healthcare system through technology transfer agreements between government and pharmaceutical companies. Until the end of the transfer, most of the products sold in the country are bought from the owner of the registry[31]. The first IFX biosimilar was launched in Brazil in 2022 and, until then, most of the patients were treated with the branded product and consequently enrolled in the PSP[32]. In addition, the program offers the beginning of the treatment, which reinforces the theory of an extensive inclusion of patients. Many patients left the program without reporting treatment discontinuation in the follow-up period, so the persistence observed in the PSP and IFX in the PSP were very different, 48.2% and 87.8% at 12-months, respectively. However, it is not possible to assume that it is representative of the whole country and such limitation must be considered during data generalization.

Many factors were associated with nonadherence or non-persistence to treatment. Although some are demographic or socioeconomic, others are related to patients' choices or understanding of treatment pathways. For example, a systematic literature review of US-based studies showed nonadherence among patients with rheumatoid arthritis and psoriatic arthritis and non-persistence among patients with rheumatoid arthritis were associated with younger age, female gender, non-white race, and refilling prescriptions at retail pharmacies[15]. In Brazil, access to treatment may differ across country regions, which may explain the associations found.

The present study results suggest that non-naïve patients, female gender, living outside the Brazilian South region, with rheumatoid arthritis and ankylosing spondylitis diagnosis were associated with lower IFX persistence rates. These results are generally consistent with those of a Brazilian study that showed that younger individuals, living in regions with higher social inequality, had a higher risk of non-persistence to treatment with biological drugs such as IFX[28]. Furthermore, highest prevalence of low adherence to pharmacological treatment of chronic diseases was associated with living in the Northeast and Midwest regions of the country and with worse self-perception of health[33]. Andrade et al. (2020) assessed adherence to treatment among patients with the diagnosis of IBD in Bahia, Brazil, and most of them were classified as non-adherent (72.7%). Significant differences in adherence pattern were only found for gender among patients with UC[34].

US-based systematic literature on medication adherence and persistence to biologics and associated factors also showed low biologic adherence and persistence rates in rheumatoid arthritis, psoriasis, and psoriatic arthritis, with significant improvement opportunities. Various factors – including a decrease in disease severity, reduction of comorbidities, lower out-of-pocket costs, refilling at specialty pharmacies, and awareness of drug effectiveness, safety, and tolerability – can inform targeted approaches to improve these rates[15]. Other factors that may influence prescription abandonment include fear of side effects associated with starting a new medication and a lack of understanding of the long-term benefits of therapy[35].

The major strength of this study is the analysis of a large sample of patients treated with IFX, however, some limitations need to be addressed. Most of the limitations are related to the data source, that uses self-reported information collected through a phone call. The program's rule states that patients are contacted every 15 days, however, such attempts are not always successful, allowing some loss to follow-up. The sample is also composed by different diseases, which may have an impact on the reported outcomes. As stated above, the persistence described in this analysis reflects the outcome within the program. In addition, despite the program has begun in 2006, only data from August, 2015, was considered due to the quality of information available.

CONCLUSION

The analysis of this cohort of patients enrolled in a PSP showed that many patients leave the program without discontinuing IFX, since the 12-month persistence were very different between program and medication estimates. On the other hand, pa-

tients who remained on the PSP had a high treatment adherence rate, with the median MPR being 94.2%. These data highlight the benefits of a PSP; however, more research is needed to understand why patients voluntarily chose to leave such initiative.

Authors' contribution

Branco ABXC: data collection, project management, protocol writing, project execution, statistical analysis, manuscript editing, review and approval. Argolo W, Santos N, Hernandez G, Kakehasi A and Sobrado CW: project execution, statistical analysis, manuscript editing, review and approval. Melsheimer R: statistical analysis, manuscript editing, review and approval.

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RESUMO – Contexto – Os anticorpos monoclonais têm eficácia comprovada no manejo de diversas condições e o infliximabe (IFX) é um dos medicamentos mais importantes da classe. Alguns dados recentes demonstram baixas taxas de persistência e adesão a vários dos biológicos disponíveis. **Objetivo –** O objetivo deste estudo foi descrever a adesão e persistência ao tratamento com IFX e a persistência no programa de suporte ao paciente (PSP), entre pacientes diagnosticados com doenças inflamatórias intestinais (DII) ou doenças reumáticas (DR) inscritos no PSP de uma grande indústria farmacêutica no Brasil. **Métodos –** Análise observacional retrospectiva utilizando o banco de dados do PSP. Pacientes com DII ou DR usando IFX inscritos no banco de dados do PSP entre setembro de 2015 e agosto de 2019 foram avaliados retrospectivamente para identificar a taxa de persistência e adesão e acompanhados até 1º de março de 2020. Os pacientes foram excluídos se a data de início do tratamento fosse anterior à entrada no programa; primeira infusão antes de 1º de setembro de 2015 ou após 31 de agosto de 2019; o paciente não iniciou o tratamento; e pacientes com "OUTROS" no campo "indicação". A persistência foi avaliada considerando tanto a persistência no programa ("persistência PSP") quanto a persistência em uso de infliximabe no PSP ("persistência IFX no PSP"). A persistência no PSP foi definida como a proporção de pacientes que permaneceram no programa aos 6, 12, 24, 36 e 48 meses após o início do IFX. Para determinar a persistência do IFX no PSP, a censura foi definida quando o paciente deixou o programa, morreu ou perdeu o acompanhamento. A adesão ao tratamento foi medida pela razão de posse do medicamento (MPR)) – todos os dias de fornecimento / decorridos da primeira prescrição ao último dia de posse do medicamento). A estatística descritiva foi inicialmente utilizada. A curva de Kaplan-Meier, o tempo mediano estimado pela função de sobrevida, o modelo de regressão de Cox e o tempo de sobrevida médio restrito (RMST) foram utilizados para avaliar o tempo de persistência do tratamento em 24 meses e o modelo de regressão logística foi realizado para identificar variáveis associadas à adesão (MPR ≥80%). **Resultados –** Foram analisados 10.233 pacientes, 5.826 (56,9%) com diagnóstico de DR e 4.407 (43,1%) de DII. Ao final do seguimento (mediana de 9,1 meses desde a entrada no PSP até a última infusão), a persistência no PSP foi de 65,6%, 48,2%, 31,0%, 20,7% e 13,1% aos 6, 12, 24, 36 e 48 meses, respectivamente. Considerando a persistência no IFX no PSP, as estimativas foram de 93,7%, 87,8%, 77,0%, 62,4% e 53,0% aos 6, 12, 24, 36 e 48 meses, respectivamente. As variáveis associadas ao risco de não persistência foram sexo, região do país e diagnóstico de artrite reumatoide e espondilite anquilosante. A mediana do MPR foi de 94,2%, enquanto o percentual de pacientes com MPR ≥80% foram de 91,0%. As variáveis associadas a MPR ≥80% foram região do país e diagnóstico de doença de Crohn. **Conclusão –** Muitos pacientes abandonam o programa sem interromper o IFX, pois a persistência em 12 meses foi muito diferente entre as estimativas do programa e da medicação, enquanto altas taxas de adesão foram observadas entre os pacientes inscritos no PSP. Os dados destacam os benefícios de um PSP.

Palavras-chave – Anticorpos monoclonais; adesão à medicação; doenças inflamatórias intestinais; doenças reumáticas.

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