Research Article

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Effectiveness and safety of anti-TNF in psoriatic arthritis patients in Brazil: a post-incorporation analysis

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Aim: Psoriatic arthritis is a chronic disease that can result in disability and decreased quality of life. **Materials & methods:** A prospective cohort was conducted in Brazil. Disease activity was measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Clinical Disease Activity Index (CDAI), functionality by the Health Assessment Questionnaire Disability Index (HAQ-DI) and the quality of life by the EuroQol 5D (EQ-5D). **Results:** In total, 122 patients were included. After 6 months, a median reduction of 2.03 in the BASDAI, 7.80 in the CDAI, 0.63 in the HAQ-DI and increase of 0.12 in the EQ-5D was observed. A good clinical response was observed in 45.5% of the patients by BASDAI and 54.5% by CDAI. Higher education and better quality of life were identified as predictors of effectiveness. The most common side effects were the infections. **Conclusion:** Anti-TNF-α drugs were effective and safe. The incorporation of them into the Brazilian Public Health System has provided therapeutic alternatives to the treatment of psoriatic arthritis.

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Keywords: anti-TNF-α • Brazil • cohort study • effectiveness • psoriatic arthritis • safety

Psoriatic arthritis (PsA) is a chronic, inflammatory and low-prevalence disease that can result in significant disability and decreased quality of life [1–3].

PsA treatment comprises of nonpharmacological and pharmacological interventions. Historically, pharmacological treatment options for PsA were limited to nonsteroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease-modifying antirheumatic drugs (csDMARD), such as methotrexate, sulfasalazine and leflunomide [4,5]. NSAIDs are useful for relieving symptoms but do not prevent joint damage [3]. The csDMARD, originally developed to treat rheumatoid arthritis (RA), have shown some benefits in the treatment of inflammation and heterogeneous symptoms of PsA [4,5]. However, there is no evidence that they prevent or significantly retard the progression of structural damage in the joint.

The availability of new medicines over the last decade, known as biological DMARD, which include inhibitors of TNF-α (anti-TNF-α), have revolutionized the treatment, demonstrating efficacy in disease control for patients with loss of effectiveness or toxicity to the use of NSAIDs and csDMARD [4,6,7]. These drugs decrease the signs and symptoms of inflammation, increase functional capacity and quality of life, alongside inhibiting the structural joint damage [1,3]. On the other hand, anti-TNF-α are costly and not easily accessible to all patients, even dependent on the public health system or private health insurance [3].

Despite the high cost of these drugs, a limited number of observational studies have evaluated the effectiveness and safety of anti-TNF-α drugs in the PsA treatment in a real-life scenario [8], mainly in Latin American countries.

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Studies have shown that there are factors that may influence the effectiveness of these drugs, known as predictors, and may be related to socio-demographic and clinical aspects, such as patient's gender, inflammatory markers levels and functional status [9,10]. Another point of interest is the discontinuation of these drugs and its impact or relation to effectiveness. Studies have shown that 20–30% of patients with PsA discontinue the treatment with the anti-TNF-α drug in the first year of treatment, due to therapeutic failure, adverse reactions, nonadherence, among others [8,10].

In Brazil, adalimumab, etanercept and infliximab were the first biological DMARD included for the treatment of PsA in the Public Health System (In Portuguese: *Sistema Único de Saúde* – SUS) in 2009 [11]. However, these drugs have not been evaluated in terms of effectiveness and safety in the Brazilian population.

In this context, this study aims to evaluate the effectiveness, safety and the predictors of effectiveness in both patients diagnosed with PsA and those who were treated with anti-TNF-α drugs by SUS at the Reference Pharmaceutical Center in Belo Horizonte, Brazil.

Materials & methods

We conducted a prospective open cohort of patients with PsA treated by SUS in Belo Horizonte, Brazil, from January 2012 to December 2017. This Reference Center is responsible for the care of patients from 39 municipalities of its administrative region, with a population higher than 5.2 million inhabitants.

Patients at the age of 18 years and over were classified with PsA by the Classification Criteria for Psoriatic Arthritis (CASPAR) [12] and had administrative processes approved by the SUS regarding the use of adalimumab, etanercept or infliximab for the treatment were included. All patients signed an informed consent form to participate in the study.

Follow-up began on the date of the first dispensation of the anti-TNF-α drug. The patients were reassessed approximately 6 months after the first dispensation. Interviews were conducted by a team of pharmacists and pharmacy students trained at a Specialized Rheumatology Center for data collection through a standardized questionnaire.

Through the interviews conducted directly with the patients, sociodemographic characteristics, such as age, gender, municipality of residence, education, marital status and self-declared race, were registered. In addition, patients reported the period of time since the doctor's diagnosis of the disease, current and previous use of PsA drugs and comorbidities. The disease activity was measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) to assess the axial involvement, and the Clinical Disease Activity Index (CDAI) was used to assess peripheral involvement [13]. Effectiveness was defined as the improvement of 50% or the reduction of two units of the BASDAI scale and when patients achieved remission or low disease activity by CDAI. These are considered as a good clinical response. We also evaluated the proportion of patients that reached the status of absence of disease activity, defined as BASDAI < 4.

The functionality was evaluated by the Health Assessment Questionnaire Disability Index (HAQ-DI) and the quality of life by EuroQol 5D (EQ-5D), both versions validated for Brazil. The two EQ-5D components were described as: the utility score and the visual analog scale from 0 to 100, representing the health status of the patient. The utility was calculated based on health conditions estimated by the time trade-off method for the Minas Gerais population [14]. Moreover, the occurrence of side effects to drugs was reported, and other outcome measures included the overall evaluation of the patient's disease activity, enthesitis, fatigue, patient's degree of pain and number of tender and swollen joints.

The continuous variables of interest were evaluated by the Shapiro–Wilk test [15] to verify the normality of the data and define the measures of central tendency and dispersion.

A descriptive analysis was performed with frequency distributions, medians and interquartile ranges (IQR) of the characteristics of the patients at the date of cohort entry and the outcomes measured at 6 months. To verify possible differences, the baseline characteristics of patients who completed follow-up were compared with the baseline characteristics of patients who did not complete the follow-up by the Wilcoxon-1 sample test for continuous variables and by the Pearson's chi-square test for categorical variables at a significance level of 5%.

The differences between the clinical outcomes observed in 6 months in comparison those at the beginning of the study were assessed by the paired Wilcoxon test. To assess the influence of the lost data on follow-up, an intention-to-treat analysis was performed with the multiple imputation of the missing data in clinical measures by Predictive Mean Matching method [16].

Log-binomial regression and relative risk (RR) with a 95% CI were used to identify predictors of good clinical response, by CDAI and BASDAI, in 6 months. Gender, age, education, marital status, race, anti-TNF-α drug in use, use of NSAIDs, csDMARD and corticosteroids at baseline, previous use of anti-TNF-α and csDMARD, duration of the disease, HAQ-DI, EQ-5D (utility), pain and comorbidities were considered as independent variables. Continuous variables were categorized by their median. A significance level of 20% for bivariate analysis and 5% for multivariable analysis was adopted, and statistical analysis was performed using software R, version 3.4.2 [17].

The study was approved by the Ethics Committee Research of the Federal University of Minas Gerais (UFMG), under Nº 0069.0.203.000-1. All procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation and with the Helsinki Declaration in 1964, revised in 2013 [18].

Results

In total, 122 PsA patients were included. The median (IQR) of the age was 51.5 years (42.6–58.2) and median disease duration of 3.0 years (IQR: 1.0–10.0). Most of the patients were white (55.7%), married (57.5%) and had high school education (41.7%; Table 1).

Of the 122 patients, 69 (56.6%) used adalimumab, 36 (29.5%) etanercept and 17 (13.9%) infliximab. In addition, 61 (50.0%) individuals used concomitant csDMARD, being the most used before methotrexate (21 patients, 17.2%). Corticosteroids (29.5%) and NSAIDs (23.0%) were also mentioned to a lesser extent. The most frequent comorbidity was systemic arterial hypertension, followed by depression and dyslipidemia. No differences were observed between patients who completed and those who did not complete the 6-month follow-up (Table 1).

In 6 months, 12 patients on adalimumab (17.4%), six on etanercept (16.7%) and three on infliximab (17.6%) discontinued the treatment – in total, 21 patients (17.2%). The reasons for discontinuation were therapeutic failure (four), side effects (three), inability to contact the patient (three), physician suspended the medication due to remission of the disease (two), withdrawal of consent (two), therapeutic failure and side effects (two), unable to go to the pharmacy (two), unable to go to the doctor to renew the prescription (one) and others (two).

All clinical measures of disease activity, functionality and quality of life presented a statistically significant reduction in 6 months when compared with the beginning of the follow-up. The median reduction was 2.03 on the BASDAI, 7.80 on the CDAI, 0.63 on the HAQ-DI and increase of 0.12 on the utility of the EQ-5D in the per-protocol analysis. In the intention-to-treat analysis, the results were similar to the per-protocol analysis results (Table 2).

Considering the response to anti-TNF-α treatment, 55 (54.5%) and 45 (45.5%) patients achieved the expected response to treatment in 6 months by CDAI and BASDAI, respectively. A good clinical response was observed in the subgroup of patients who were in active disease by BASDAI or in moderate-to-high activity disease by CDAI at baseline, which was 47.7% by BASDAI and 45.7% by CDAI. The results were similar in the per-protocol and in the intention-to-treat analyses (Figure 1). In relation to the absence of active disease, 61.6% of the patients achieved BASDAI $\leq$ 4 after 6 months of follow-up.

In the multivariable model, the predictor of effectiveness assessed by CDAI was better quality of life, evaluated by EQ-5D (RR: 1.91; 95% CI: 1.28–2.84; p = 0.001). The predictor of effectiveness assessed by BASDAI was higher education (RR: 1.75; 95% CI; 1.14–2.68; p = 0.001) (Table 3).

The main side effects reported by patients using anti-TNF-α were headache (18.4%), site reaction (15.3%), asthenia (13.3%), influenza (13.3%) and alopecia (13.3%). There were also 28 reported infections: nine urinary infections, nine upper respiratory infections (sinusitis), four fungal infections, three lower respiratory infections (pneumonia), and one herpes zoster infection, as well as dental infection and postsurgical infection. No tuberculosis case was reported (Table 4).

Discussion

This is a new study conducted in Brazil to evaluate PsA patients treated with anti-TNF-α drugs provided by SUS in a real-life clinical setting. The patients followed by the study were living in the metropolitan area of Belo Horizonte and they were attended at the Reference Pharmaceutical Center in Belo Horizonte, Brazil.

From the total number of patients evaluated, 82.8% were followed up for 6 months. The median duration of the disease was 3.0 years. There was a slight predominance of female patients. Most of the patients were white, married and had a high school education, similar to the study by Mease *et al.* [19]. The median age observed was similar to other studies [8,19], as well as the higher prevalence of the disease in the white population [19], which confirms the

Table 1. Sociodemographic and clinical characteristics of patients with psoriatic arthritis at baseline.

Variables	Completed 6 months (101)	Loss of follow-up (21)	Total (122)	p-value
Gender:				0.079
– Female	56 (55.4)	16 (76.2)	72 (59.1)	
– Male	45 (44.6)	5 (23.8)	50 (40.9)	
Age (years)	51.0 (42.6–58.0)	51.8 (42.9–59.2)	51.5 (42.6–58.2)	0.946
Duration of disease (years)	3.00 (1.00–10.00)	4.00 (0.50–8.00)	3.00 (1.00–10.00)	0.530
Race:				0.425
– White	55 (54.5)	13 (61.9)	68 (55.7)	
– Brown	33 (32.7)	4 (19.0)	37 (30.3)	
– Others	13 (12.9)	4 (19.0)	17 (13.9)	
Marital status:				0.328
– Single	25 (25.3)	5 (23.8)	30 (25.0)	
– Married	59 (59.6)	10 (47.6)	59 (57.5)	
– Others	15 (15.2)	6 (28.6)	21 (17.5)	
Education				0.735
– Illiterate	0 (0.0)	0 (0.0)	0 (0.0)	
– Primary	12 (12.1)	1 (4.8)	13 (10.8)	
– Secondary	11 (11.1)	3 (14.3)	14 (11.7)	
– High school	40 (40.4)	10 (47.6)	50 (41.7)	
– University	36 (36.4)	7 (33.3)	43 (35.8)	
Anti-TNF in use				0.994
– Adalimumab	57 (56.4)	12 (57.1)	69 (56.6)	
– Etanercept	30 (29.7)	6 (28.6)	36 (29.5)	
– Infliximab	14 (13.9)	3 (14.3)	17 (13.9)	
csDMARD in use	51 (50.5)	10 (47.6)	61 (50.0)	0.810
NSAIDS in use	25 (24.8)	3 (14.3)	28 (23.0)	0.299
Corticoids in use	28 (27.7)	8 (38.1)	36 (29.5)	0.343
Previous drugs				
– csDMARD	81 (80.2)	15 (78.9)	96 (80.0)	0.900
– Anti-TNF	23 (23.2)	6 (28.6)	29 (24.2)	0.604
CDAI:				0.756
– Inactive disease	31 (30.7)	5 (23.8)	36 (29.5)	
– Moderate activity	30 (29.7)	6 (28.6)	36 (29.5)	
– Active disease	40 (39.6)	10 (47.6)	50 (41.0)	
BASDAI				0.335
– Inactive disease	35 (34.7)	5 (23.8)	40 (32.8)	
– Active disease	66 (65.3)	16 (76.2)	82 (67.2)	
HAQ-DI	1.25 (0.50–1.75)	1.38 (0.75–1.75)	1.25 (0.50–1.75)	0.815
EQ-5D utility	0.672 (0.542–0.817)	0.542 (0.472–0.817)	0.655 (0.522–0.817)	0.309
EQ-5D VAS	70.0 (50.0–80.0)	52.0 (50.0–70.0)	70.0 (50.0–80.0)	0.111
Comorbidities:				
– Hypertension	28 (27.7)	7 (33.3)	35 (28.7)	0.605
– Depression	20 (19.8)	8 (38.1)	28 (23.0)	0.070
– Dyslipidemia	20 (19.8)	5 (23.8)	25 (20.5)	0.679

Continuous variables: median and interquartile range. Tests: Wilcoxon one sample for continuous variables and chi-squared for categorical variables.
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CDAI: Clinical Disease Activity Index; csDMARD: Conventional synthetic disease-modifying antirheumatic drug; EQ-5D: EuroQol 5D; HAQ-DI: Health Assessment Questionnaire Disability Index; NSAIDS: Nonsteroidal anti-inflammatory drugs; VAS: Visual analogic scale.
p-value: 0.05.

Table 2. Disease activity, functionality and quality of life of patients with psoriatic arthritis at the baseline (beginning) and 6 months after the use of anti-TNF-α.

Variables	Beginning (n = 122)	6 months – per-protocol (n = 101)	p-value	6 months – intention to treat (n = 122)	p-value
CDAI:	16.70 (8.78–32.80)	8.90 (2.30–17.60)	<0.001	8.80 (2.70–16.32)	<0.001
– Counting tender joints	4.00 (1.00–11.00)	1.00 (0.00–6.00)	<0.001	1.50 (0.00–6.00)	<0.001
– Counting swollen joints	1.00 (0.00–6.00)	0.00 (0.00–2.25)	0.002	0.00 (0.00–2.00)	<0.001
– Disease activity by the physician	4.30 (1.60–6.20)	2.00 (0.50–4.80)	<0.001	1.95 (0.70–4.60)	<0.001
– Disease activity by the patient	5.95 (3.00–7.50)	2.60 (0.60–5.90)	<0.001	2.20 (0.52–5.90)	<0.001
Pain	5.15 (2.38–7.68)	2.90 (0.30–6.00)	<0.001	2.60 (0.20–5.90)	<0.001
BASDAI:	5.24 (3.05–6.85)	3.21 (1.03–4.96)	<0.001	3.23 (1.63–4.68)	<0.001
– Fatigue	5.70 (2.62–8.18)	3.70 (0.85–6.65)	<0.001	3.80 (1.35–6.70)	<0.001
– Axial pain	4.85 (1.72–7.98)	1.80 (0.40–6.25)	<0.001	1.75 (0.50–6.32)	<0.001
– Peripheral edema and pain	5.15 (1.60–7.48)	2.70 (0.70–5.60)	<0.001	2.40 (0.70–5.58)	<0.001
– Enthesitis	4.75 (2.02–7.55)	2.20 (0.25–6.60)	<0.001	2.20 (0.60–6.70)	<0.001
– Morning Stiffness†	5.62 (2.52–7.30)	2.65 (0.62–5.72)	<0.001	2.85 (1.10–5.36)	<0.001
HAQ	1.25 (0.50–1.75)	0.62 (0.00–1.38)	<0.001	0.75 (0.12–1.38)	<0.001
EQ-5D:	0.66 (0.52–0.82)	0.78 (0.59–0.88)	<0.001	0.78 (0.59–0.88)	<0.001
– EQ-5D VAS	70.00 (50.00–80.00)	80.00 (60.00–90.00)	<0.001	80.00 (60.00–90.00)	<0.001

Median and interquartile range. Statistic test = Wilcoxon paired.
†Defined as the mean of the morning stiffness time and the morning stiffness intensity.
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CDAI: Clinical Disease Activity Index; HAQ-DI: Health Assessment Questionnaire Disability Index; EQ-5D: EuroQol 5D; VAS: Visual analogic scale.

findings of the present study. The pain scale values, diagnostic period of the disease and patients in concomitant use of corticosteroids were similar to those observed in the cohort of Aaltonen *et al.* [8].

The patients' profiles at the baseline indicate that two-thirds of the patients were with the active disease, as measured by BASDAI. In addition, the patients had previously used or were using csDMARD and NSAIDs when requesting anti-TNF-α. This is in accordance with both the Clinical Protocol and Therapeutic Guideline of the PsA in Brazil and the recommendations of the European League Against Rheumatism that indicate the use of anti-TNF-α after failure with those drugs [7,20].

The discontinuation of treatment was observed in 17.2% of the participants, mainly related to therapeutic failure and side effects, without differences between anti-TNF drugs. Aaltonen *et al.* demonstrated a 20% discontinuation rate in the first year of follow-up of patients who used anti-TNF-α drugs for PsA treatment [8]. Glintborg *et al.*, in a retrospective data analysis, observed a discontinuation rate of 30% in the first year of follow-up, associated to the use of infliximab, to the female gender, to the absence of concomitant use of synthetic DMARD and to the greater number of tender joints [10].

After 6 months of follow-up, a significant improvement in clinical measures of effectiveness, functionality, and quality of life was observed. A good clinical response was observed in 45.5% of the patients by BASDAI and 54.5% by CDAI. When the patients with moderate-to-high disease activity by the CDAI at the baseline were evaluated, the effectiveness was lower, 45.7%, which demonstrates the importance of evaluating this subgroup of patients. The treatment effectiveness measured by BASDAI was the half found by Soubrier *et al.* [21] in 3 months of follow-up for anti-TNF-α drugs and lower than the effectiveness found after 12 months of follow-up by Lubrano *et al.*, 77%, in patients taking etanercept [22]. Soubrier *et al.* demonstrated an absolute reduction in the activity of the axial and peripheral disease in 3 months measured by BASDAI and tender and swollen joints count, which was also observed in this study [21].

A systematic review that evaluated functionality reported that anti-TNF-α drugs, such as adalimumab, etanercept and infliximab were better than placebo for the HAQ outcome in PsA patients [23]. Observational studies demonstrated a reduction in HAQ after 6 months compared with the baseline for the anti-TNF-α adalimumab [24], etanercept [24,25] and infliximab [24].

Observational studies also reported, in PsA patients in use of anti-TNF-α, reduction in tender and swollen joints counts, besides the improvement in the assessment of the disease activity by the patient [21,24,25], reduction of pain

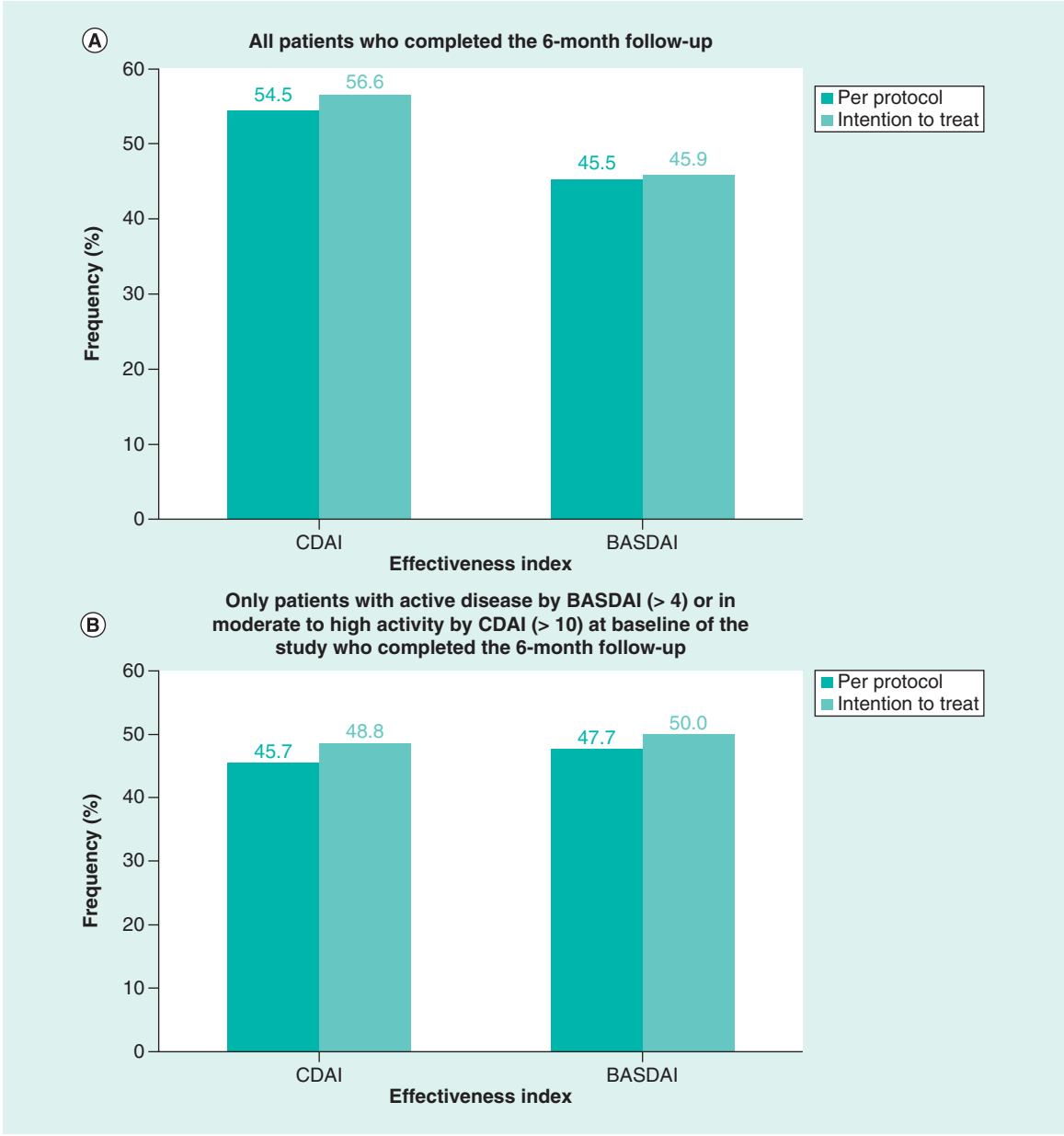

Figure 1. Patients who achieved good clinical response at 6 months of follow-up. (A) Proportion of psoriatic arthritis patients who achieved treatment response in 6 months by BASDAI and CDAI. **(B)** Proportion of psoriatic arthritis patients in disease activity (BASDAI > 4) or in moderate to high disease activity (CDAI > 10) at baseline who achieved good response to treatment at 6 months follow-up.
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CDAI: Clinical Disease Activity Index.

by the visual analog scale with the use of adalimumab [26] and the improvement in the assessment of the disease activity by the physician for the etanercept [25]. These results were also verified by this study.

Another systematic review demonstrated the benefit of anti-TNF-α drugs in the outcomes of fatigue, functionality, enthesitis, effectiveness measured by PsARC (response criteria for PsA), PASI (index of severity and area of psoriasis), ACR20, ACR50 and ACR70 (at least 20, 50 or 70% improvement in the American College of Rheumatology response criteria) [27].

Saad *et al.* demonstrated in a retrospective observational study that patients receiving infliximab achieved a lower remission of the disease evaluated by DAS28 in 6, 12 and 18 months (19.7, 28.9 and 26.9%), compared with etanercept (30.9, 37.3 and 36.5%) and adalimumab (30.1, 45.1 and 41.5%) [28]. However, no differences

Table 3. Predictors of 6-month effectiveness by Clinical Disease Activity Index and Bath Ankylosing Spondylitis Disease Activity Index.

CDAI	Bivariate		Multivariable		BASDAI	Bivariate		Multivariable	
Basal characteristics	Crude RR (CI 95%)	p-value	Adjusted RR (CI 95%)	p-value	Basal characteristics	Crude RR (CI 95%)	p-value	Adjusted RR (CI 95%)	p-value
Gender:					**Education:**				
– Male	1.00	0.028	–	–	– Until high school	1.00	0.030	1.00	0.001
– Female	0.67 (0.47–0.96)		–	–	– Undergraduate	1.61 (1.05–2.48)		1.75 (1.14–2.68)	
Depression:					**Previous biological DMARD:**				
– No	1.00	0.199	–	–	– No	1.00	0.164	–	–
– Yes	0.69 (0.39–1.22)		–	–	– Yes	0.63 (0.32–1.21)		–	–
Corticoid:					**EQ-5D:**				
– No	1.00	0.043	–	–	– ≤ 0.65	1.00	0.131	–	–
– Yes	0.58 (0.34–0.98)		–	–	– >0.65	1.41 (0.90–2.21)		–	–
HAQ:					**Corticoid:**				
– ≤ 1.25	1.00	0.003	–	–	– No	1.00	0.172	–	–
– >1.25	0.54 (0.35–0.81)		–	–	– Yes	0.67 (0.38–1.19)		–	–
EQ-5D:					–	–	–	–	–
– ≤ 0.65	1.00	0.001	1.00	0.001	–	–	–	–	–
– >0.65	1.94 (1.29–2.91)		1.91 (1.28–2.84)		–	–	–	–	–
Biological DMARD in use:	–	–	–	–	–				
– Adalimumab	1.00		–	–	–	–	–	–	–
– Etanercept	0.95 (0.65–1.39)	0.791	–	–	–	–	–	–	–
– Infliximab	0.48 (0.20–1.13)	0.092	–	–	–	–	–	–	–
PAIN:					–	–	–	–	–
– ≤ 5.15	1.00	0.025	–	–	–	–	–	–	–
– >5.15	0.65 (0.45–0.95)		–	–	–	–	–	–	–
Marital status:					–	–	–	–	–
– Married	1.00	0.178	–	–	–	–	–	–	–
– Not married	0.76 (0.51–1.14)		–	–	–	–	–	–	–

n = 101.
Reference comparator: 1,00
Only the variables with p < 0.20 values in the bivariate analysis were presented. Pain, EQ-5D, HAQ and diagnostic time were stratified by the median. Education was stratified into high school complete (including incomplete upper) and complete upper (undergraduate).
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CDAI: Clinical Disease Activity Index; DMARD: Disease-modifying antirheumatic drug; EQ-5D: EuroQol 5D; HAQ-DI: Health Assessment Questionnaire Disability Index; VAS: Visual analog scale; RR: Relative risk.

were observed in the effectiveness of infliximab compared with adalimumab and etanercept for the outcomes of peripheral arthritis [8,29] in the other observational studies. The Brazilian Society of Rheumatology also indicates that infliximab, etanercept, adalimumab and golimumab have similar efficacy based on data from published studies [30].

To the best of our knowledge, there are no published studies in Brazil that have evaluated the effectiveness of anti-TNF-α for PsA treatment. In light of studies of patients with other rheumatic diseases in Brazil, our results suggest that PsA patients treated with anti-TNF-α presented higher effectiveness measured by CDAI than patients with RA [31]. However, the effectiveness is lower when compared with that observed in patients with ankylosing spondylitis by BASDAI [32].

A better quality of life of the patients at the baseline was a predictor of effectiveness by CDAI. A recent study has shown that patients with better quality of life at baseline reached a significantly higher minimal disease activity in the PsA treatment with adalimumab. However, the authors did not investigate the causality of that result [33]. One possible explanation would be the fact that PsA patients with a better quality of life generally have less pain, structural damage and better work productivity, which may indicate less progression of the disease and better control of disease at baseline [34,35], and contribute towards achieving or maintaining a good clinical response by CDAI. In addition, PsA is a disease associated with decreased quality of life and causes psychosocial morbidity,

Table 4. Main side effects reported by patients with psoriatic arthritis using anti-TNF-α.

Adverse reactions	n (%)
Headache	18 (18.4)
On-site reaction	15 (15.3)
Asthenia (fatigue)	13 (13.3)
Flu	13 (13.3)
Alopecia	13 (13.3)
Urinary infection	9 (9.2)
Sinusitis	9 (9.2)
Nausea	9 (9.2)
Itching	6 (6.1)
Diarrhea	6 (6.1)
Fungal infection	4 (4.1)
Pneumonia	3 (3.1)
Skin rash	3 (3.1)
Hypertension	3 (3.1)
Urticaria	3 (3.1)
Rhinitis	3 (3.1)
Abdominal pain	3 (3.1)
Osteoporosis	2 (2.0)
Fever	2 (2.0)
Coryza	2 (2.0)
Backache	2 (2.0)
Herpes zoster	1 (1.0)
Other infections	2 (2.0)

due to emotional problems, such as stress, anxiety or depression, stigma and physical discomfort [36]. The control of these problems can lead to a greater control of the disease and facilitate the achievement of the effectiveness of treatment, as observed in patients with RA [23,37].

Higher education was a predictor of effectiveness by BASDAI. None of the studies in PsA patients had observed an association between effectiveness and education. For other outcomes, such as inability to work and unemployment, higher education was associated with better results in PsA patients [38]. A study in patients with RA showed that higher education was a predictor of effectiveness in anti-TNF-α drugs use [31].

In total, 28 infections were reported, the most common being related to the respiratory and urinary tract. Minozzi *et al.* demonstrated in a systematic review that the use of anti-TNF-α drugs increases the risk of infections by 20%, severe infections by 40% and *Mycobacterium tuberculosis* infections by 250% [39]. In our study, infections were the most frequently observed adverse events, including severe infections such as herpes zoster. However, no tuberculosis case was identified. Headache, reaction at the site of application, asthenia, flu and alopecia were also common adverse reactions. The reaction at the site of application was mainly related to etanercept and infliximab. In general, anti-TNF-α drugs were well tolerated. According to Lemos *et al.*, their use can be considered safe and side effects are manageable [27].

These results are very useful because the real-world utility profile of these new drugs cannot be adequately assessed in clinical trials, as trials are restricted by their inclusion criteria, being used for primary efficacy outcomes, resulting in a low external validity for the real world [40]. According to Warren *et al.*, the clinical factors that influence the effectiveness and safety of these new agents are largely unknown [41]. In our study, we observed that better quality of life and higher education were predictors of effectiveness. Furthermore, other relevant information was obtained, such as the discontinuation of treatment due to inability to go to the pharmacy to get the drugs or to go to the doctor to renew the prescription. In addition, some patients had difficulty in finding a place for the administration of injections, difficulty in self-administration of the drugs or fear of the administration of drugs. Therefore, social characteristics of the patients and difficulty to access health services can also influence the results of the treatment.

Despite all the already achieved advances, the outcomes of the treatment with anti-TNF-α drugs can be improved with complementary actions. New therapeutic approaches are needed, including supportive measures, such as

multidisciplinary team monitoring, already seen for other rheumatic diseases, such as gout and osteoarthritis [42,43]. Another important approach is a more rigorous evaluation of the treatment, enabling a better effectiveness results and an optimized control of the PsA [4,44]. The follow-up for a multidisciplinary team, including social assistance to some patients, is very important for improving the quality of information and care provided to patients.

The study has some limitations. PsA-related skin lesions were not evaluated. However, the PsA's Clinical Protocol and Therapeutic Guideline of Brazil only considers measures of disease activity and treatment effectiveness for peripheral and axial arthritis, which supports only the evaluation of these measures in this study [20]. The patients were not divided into clinical subgroups according to axial or peripheral joint involvement due to the lack of this information for some patients followed-up. Radiographical changes, such as bone erosions, were not considered in the follow-up process. Another limitation is the sample size and the method applied to select the patients, since only the individuals who attended the Reference Pharmaceutical Center in Belo Horizonte were eligible to participate in the cohort, whereas the dispensing of the drug can be performed for a family member in situations where patients are unable to go to the service, and therefore more severe cases of PsA may not have been included and or may have been lost during follow-up as well as the fact that serious side effects may not have been reported. We tried to minimize this limitation through home visits to patients who were unable to go to the pharmacy for health reasons or work. However, this strategy brought few results, due to patient noncompliance and operational difficulties. Finally, some data were from the patients' self-report, which may be conditioned by memory bias and/or the individual's perception.

Conclusion

This study demonstrates the effectiveness of anti-TNF-α drugs for peripheral and axial disease activity, pain, functionality and quality of life in Brazilians patients with PsA. The drugs were well tolerated and showed already established side effects, such as infections, headache and reaction at the application site. These results are useful because they were obtained in a real-life scenario in patients from Latin America with sociocultural particularities. Anti-TNF-α drugs are important in the management and control of PsA and their incorporation in SUS has been an important step, providing therapeutic alternatives to treatment with csDMARD and NSAIDs.

Future perspective

Anti-TNF-α drugs have not been previously evaluated for their efficacy, safety and cost–effectiveness for PsA in Brazil. Due to this, it becomes necessary to continuously evaluate the drugs incorporated into SUS, especially in a scenario where there is a wide availability of health technologies, as well as successive increases in health costs in recent years. It contrasts with the current economic situation of Brazil, that faces severe limitations in public spending, including health system. Therefore, it is of utmost importance to perform epidemiological and economic analyses of the drugs available for the treatment of PsA and other diseases. These are fundamental to support the rational use of drugs and the efficient use of public funds, with the purpose to contribute to the pharmaceutical assistance and, consequently, to SUS.

Executive Summary

- A total of 122 psoriatic arthritis patients began the treatment with anti-TNF drugs, of whom 102 completed 6 months of follow-up.
- An intention-to-treat analysis was performed as a sensitivity analysis to evaluate the influence of loss of follow-up in the results.
- A significant improvement in clinical measures of effectiveness, functionality and quality of life was observed.
- The percentage of patients achieving good clinical response was 45.5% by Bath Ankylosing Spondylitis Disease Activity Index and 54.5% by Clinical Disease Activity Index.
- No differences were observed in per-protocol and intention-to-treat analyses.
- Better quality of life was a predictor of effectiveness assessed by Clinical Disease Activity Index and higher education by Bath Ankylosing Spondylitis Disease Activity Index.
- Anti-TNF-α drugs were well tolerated, and the most common side effects were infections and headache.
- Anti-TNF-α drugs are important in the management and control of psoriatic arthritis and their incorporation in *Sistema Único de Saúde* has been an important step, providing therapeutic alternatives to treatment with conventional synthetic disease-modifying antirheumatic drug and nonsteroidal anti-inflammatory drugs.

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Authors' contributions

MRR da Silva and JBR dos Santos collected and analyzed the data and wrote the manuscript; HA Oliveira Junior collected data, contributed with the discussion and reviewed the manuscript; J Alvares contributed with the discussion and reviewed the manuscript; AM Almeida, AM Kakehasi and FA Acurcio designed the study, contributed with the discussion and reviewed the manuscript. All authors approved the final version of the manuscript.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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