

Disease activity and functional trajectories with biologic DMARDs in Brazil's public health system: the REAL study, 2015--2017

Júlia Andrade Ibiapina Parente

Universidade Católica de Brasília

Victor Eduardo Ramos Camargo

Universidade de Brasília

Diógenes Almeida Zortea

Universidade Católica de Brasília

Andrea Dias Stephanus

Universidade Católica de Brasília

Luiz Sérgio Fernandes de Carvalho

Universidade Católica de Brasília

Alisson Aliel Vigano Pugliesi

alissonvigano@gmail.com

Universidade Estadual de Campinas (UNICAMP)

Cleandro Pires de Albuquerque

Universidade de Brasília

Ana Paula Monteiro Gomides

University Center of Brasília

Ana Beatriz Vargas Santos

Universidade do Estado do Rio de Janeiro

Paulo Louzada-Júnior

Universidade de São Paulo

Rina Dalva Neubarth Giorgi

Instituto de Assistência Médica ao Servidor Público Estadual

Sebastião Cezar Radominski

Universidade Federal do Paraná

Maria Fernanda Brandão Resende Guimarães

Universidade Federal de Minas Gerais

Karina Rossi Bonfiglioli

Universidade de São Paulo

Maria de Fátima Lobato da Cunha Sauma

Universidade Federal do Pará

Ivânio Alves Pereira

Universidade Federal de Santa Catarina

Claiton Viegas Breno

Universidade Federal do Rio Grande do Sul

Licia Maria Henrique da Mota

Universidade de Brasília

Geraldo da Rocha Castelar Pinheiro

Universidade do Estado do Rio de Janeiro

Research Article

Keywords: Rheumatoid Arthritis, Biologic Antirheumatic Agents, Real-World Data, Disease Activity Trajectory, Brazil, Unified Health System, Cohort Study

Posted Date: October 22nd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11133636/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Disease activity and functional trajectories with
biologic DMARDs in Brazil's public health
system: the REAL study, 2015–2017

Júlia Andrade Ibiapina Parente ¹,
Victor Eduardo Ramos Camargo ², Diógenes Almeida Zortea ¹,
Andrea Dias Stephanus ¹, Luiz Sérgio Fernandes de Carvalho
¹, Alisson Aliel Vigano Pugliesi ^{5*},
Cleandro Pires de Albuquerque ², Ana Paula Monteiro Gomides
³, Ana Beatriz Vargas Santos ⁴, Paulo Louzada-Júnior ⁶,
Rina Dalva Neubarth Giorgi ⁷, Sebastião Cezar Radominski ⁸,
Maria Fernanda Brandão Resende Guimarães ⁹,
Karina Rossi Bonfiglioli ¹⁰,
Maria de Fátima Lobato da Cunha Sauma ¹¹,
Ivânio Alves Pereira ¹², Claiton Viegas Brenol ¹³,
Licia Maria Henrique da Mota ²,
Geraldo da Rocha Castelar Pinheiro ⁴

¹Universidade Católica de Brasília, Brasília, DF, Brazil.

²Universidade de Brasília (UnB), Brasília, DF, Brazil.

³Centro Universitário de Brasília (UniCEUB), Brasília, DF, Brazil.

⁴Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro,
RJ, Brazil.

⁵Universidade Estadual de Campinas (UNICAMP), Campinas, SP,
Brazil.

⁶Universidade de São Paulo (USP – Ribeirão Preto), Ribeirão Preto,
SP, Brazil.

⁷Instituto de Assistência Médica ao Servidor Público Estadual
(IAMSPE), São Paulo, SP, Brazil.

⁸Universidade Federal do Paraná (UFPR), Curitiba, PR, Brazil.

⁹Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.

¹⁰Universidade de São Paulo (USP – São Paulo), São Paulo, SP, Brazil.

¹¹Universidade Federal do Pará (UFPA), Belém, PA, Brazil.

¹²Universidade Federal de Santa Catarina (UFSC), Florianópolis, SC, Brazil.

¹³Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.

*Corresponding author(s). E-mail(s): alissonvigano@gmail.com;

Abstract

Background: Real-world evidence on biologic disease-modifying antirheumatic drugs (bDMARDs) in rheumatoid arthritis (RA) is abundant but derived almost entirely from high-income countries; longitudinal Brazilian data are scarce. The trajectories of disease activity and functional capacity were analysed in Brazilian patients with RA receiving bDMARDs within the Unified Health System (SUS).

Methods: This was a retrospective cohort analysis of the REAL, Rheumatoid Arthritis in Real Life, study, a nationwide prospective multicentre cohort of Brazilian patients treated at public referral centres. Sixty-two patients receiving bDMARDs at 8 centres, with complete data across three protocol-driven visits over approximately 12 months (186 observations), were included. Disease activity was assessed by DAS28-CRP, DAS28-ESR, SDAI, CDAI, and RADAI, and functional capacity by the HAQ. Patients received tumour necrosis factor inhibitors (TNFi; n = 31) or non-TNFi agents (n = 31). Linear mixed-effects models with nested random intercepts (patient within centre) were fitted for each outcome.

Results: Rather than improving, disease activity remained stable between the first two visits and then rose significantly at the final visit relative to baseline for DAS28-CRP (p = 0.011), SDAI (p = 0.013), and CDAI (p = 0.019); functional capacity did not improve. Drug class was significantly associated with HAQ (p = 0.007), with the TNFi group showing lower disability, and TNFi patients maintained stable DAS28-CRP remission rates (approximately 55 percent) while non-TNFi patients declined from 35.5 percent to 19.4 percent. However, no visit x drug class interaction was significant (nearest trend: SDAI, p = 0.076), indicating broadly parallel trajectories, and the between-class difference is likely confounded by indication and treatment line. Smoking was associated with worse HAQ (p = 0.004), and corticosteroid use with higher SDAI (p = 0.003), CDAI (p = 0.001), and RADAI (p = 0.009).

Conclusion: In this Brazilian real-world cohort of long-standing RA treated in the public health system, disease activity was not consistently sustained over 12 months, while functional capacity remained largely unchanged. Effectiveness estimates from other health systems should not be assumed to transfer to the SUS, and closer structured monitoring with timely therapeutic adjustment is warranted.

Keywords: Rheumatoid Arthritis; Biologic Antirheumatic Agents; Real-World Data; Disease Activity Trajectory; Brazil; Unified Health System; Cohort Study

1 Background

Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory disease of the peripheral synovial joints that leads to progressive musculoskeletal damage, functional disability, and reduced quality of life [1, 2]. Because the disease may progress to irreversible joint damage, early diagnosis and tight control of inflammatory activity are central to management [3]. Treatment therefore follows a treat-to-target strategy aimed at achieving remission or low disease activity [4], with routine monitoring relying on composite indices, including the Disease Activity Score in 28 joints (DAS28), the Simplified and Clinical Disease Activity Indices (SDAI and CDAI), and the Rheumatoid Arthritis Disease Activity Index (RADAI), complemented by the Health Assessment Questionnaire (HAQ) for functional capacity [5].

Disease-modifying antirheumatic drugs (DMARDs), synthetic or biologic, are the cornerstone of therapy. First-line treatment is based on conventional synthetic DMARDs, preferably methotrexate [6, 7]. When this strategy fails, treatment may be escalated to biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs), particularly Janus kinase inhibitors (JAKi). bDMARDs comprise tumor necrosis factor inhibitors (TNFi) and non-TNFi agents targeting the interleukin-6 receptor (tocilizumab), T-cell costimulation (abatacept), or B cells (rituximab) [8–10]. Yet achieving an initial therapeutic response is only part of the treatment goal. Long-term management requires sustained control of inflammatory activity and preservation of physical function, making longitudinal trajectories of disease activity and disability a more complete measure of treatment effectiveness over time.

The efficacy of bDMARDs is well established in randomized trials, and observational studies have similarly reported broadly comparable effectiveness across biologic classes in routine care [11–13]. However, most longitudinal real-world evidence derives from North American, European, and Japanese registries, whereas Brazilian and Latin American data remain scarce and are largely cross-sectional or claims-based [14]. How disease activity and physical function evolve over time among patients receiving bDMARDs in Brazilian routine care therefore remains insufficiently characterized. This gap is particularly relevant within the Unified Health System (*Sistema Único de Saúde*, SUS), where delayed diagnosis, long-standing and erosive disease, and persistent moderate-to-high disease activity remain common despite frequent use of glucocorticoids and biologics [15, 16]. These characteristics may influence the ability to achieve and sustain therapeutic targets, and effectiveness estimates from other health systems cannot be assumed to transfer directly to this setting.

The REAL (Rheumatoid Arthritis in Real Life) study was a multicenter prospective cohort of 1,115 Brazilian patients with RA treated at tertiary public referral centers, with protocol-driven visits at baseline, 6, and 12 months [15]. The present retrospective analysis of this prospectively collected cohort characterizes the trajectories of disease activity and functional capacity over approximately 12 months among patients receiving bDMARDs within the Brazilian public health system and, secondarily, explores whether these trajectories differ between TNFi and non-TNFi agents. By focusing on longitudinal trajectories rather than a single endpoint, this study provides a historical real-world benchmark for biologic-treated RA within the Brazilian public health system.

2 Methods

2.1 Study Design

This was a retrospective cohort study based on a secondary analysis of data from the multicenter cohort REAL study. The analysis included previously collected information from patients with rheumatoid arthritis treated at referral centers within the SUS.

The REAL study followed patients for a period of approximately 12 months, allowing a longitudinal analysis of disease progression and therapeutic response, collecting demographic, clinical, laboratory, radiographic, therapeutic, quality-of-life, and treatment adherence data.

2.2 Study Population and Eligibility Criteria

The study population consisted of patients diagnosed with RA who were included in the multicenter REAL study.

Eligibility criteria for patient inclusion in the REAL study were defined in the original study protocol. Briefly, participants were required to have a confirmed diagnosis of RA according to the 1987 American College of Rheumatology (ACR) classification criteria or the 2010 ACR/EULAR classification criteria, be ≥ 18 years of age, and meet the clinical eligibility requirements established in the original study. The Real Life study also excluded patients with conditions that could substantially compromise the evaluation of clinical and functional outcomes, such as severe psychiatric disorders, active malignancy, disabling stroke, or chronic kidney disease requiring renal replacement therapy. Additional details regarding the eligibility criteria and study procedures have been previously described in the original Real Life study protocol.

For the purposes of the present secondary analysis, additional selection criteria were applied to the database. Only patients who received biologic DMARD therapy during follow-up and had available data for disease activity and functional capacity outcomes

across the three study visits (V1, V2, and V3) were included in the analysis. Records with incomplete data for the analyzed outcomes were excluded from the final sample. Additionally, patients classified as “incapable of exercising” in the physical activity variable were excluded from the analysis. The complete sample selection process is depicted in [Figure 1](#).

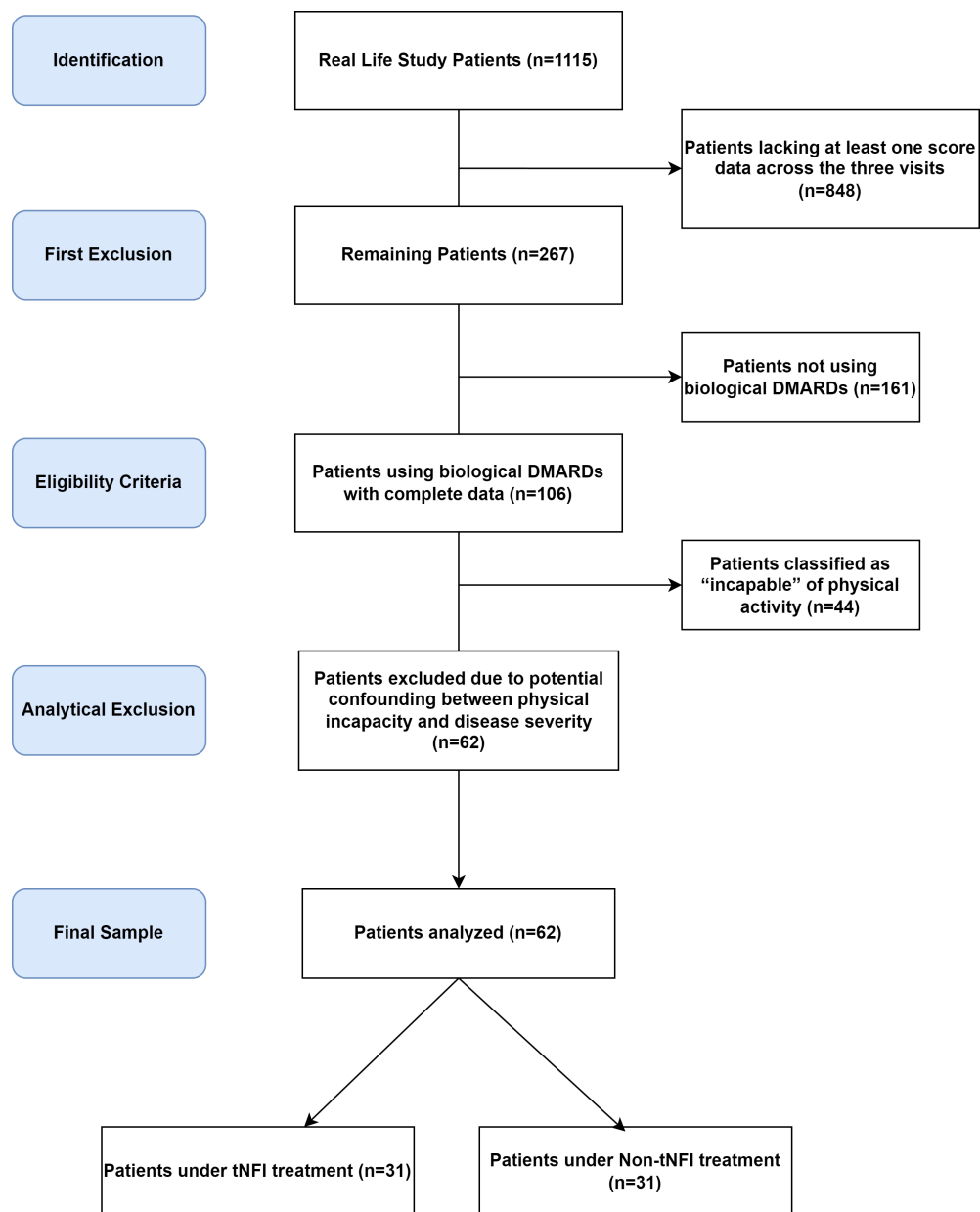


Fig. 1 STROBE flowchart

2.3 Data Collection and Extraction

The REAL study included 1,115 patients, with an approximate 4:1 distribution between synthetic and biologic DMARD users. Data were obtained from the digital platform Meconsulte and from clinical records of participating centers. For the present study, data were extracted and processed using R software in the RStudio environment. From the original 1,115 patients, those receiving biologic DMARD therapy with complete data across three study visits were selected, resulting in 106 patients. After excluding 44 patients classified as “incapable of exercising” in the physical activity variable, the final analytical sample comprised 62 patients (186 observations across three visits).

The REAL database collected a broad range of demographic, socioeconomic, clinical, laboratory, therapeutic, and patient-reported variables. For the purposes of the present analysis, only variables relevant to the study objectives were selected. These included age, sex, physical activity level, smoking status, rheumatoid factor (RF) status, symptoms time, corticosteroid use, concomitant synthetic DMARD use, visit index, and pharmacological treatment group (TNFi vs. non-TNFi).

2.4 Outcomes

The primary outcomes analyzed were rheumatoid arthritis disease activity and functional capacity, assessed using the following validated indices:

Primary outcomes:

- DAS28-CRP and DAS28-ESR (Disease Activity Score in 28 joints)
- HAQ-DI (Health Assessment Questionnaire – Disability Index)

Secondary outcomes:

- CDAI (Clinical Disease Activity Index)
- SDAI (Simplified Disease Activity Index)

- RADAI (Rheumatoid Arthritis Disease Activity Index)

Physical activity was categorized into two groups according to the frequency of exercise reported by patients in the Real Life database: “active” (exercise performed ≥ 3 times per week) and “inactive” (exercise performed < 3 times per week). Patients classified in the database as “incapable of exercising” were excluded from the analysis, as this category may reflect underlying disease severity or functional limitation rather than solely the absence of physical activity.

2.5 Study Period and Visit Intervals

Data collection in the REAL study spanned from August 2015 to May 2017. V1 (baseline) visits occurred between August 2015 and April 2016, V2 (intermediate) visits between January 2016 and November 2016, and V3 (final) visits between July 2016 and May 2017.

In the REAL study, V1 corresponded to the baseline visit of study follow-up, which could occur either at the initiation of biologic therapy or during ongoing treatment, depending on the patients clinical status at the time of enrollment. Patients were subsequently followed for approximately 12 months, with V2 representing an intermediate assessment and V3 corresponding to the final evaluation. The mean intervals between V1–V2 and V2–V3 were approximately 6 months each, with an overall follow-up from V1 to V3 of about 12 months.

2.6 Ethical Considerations

The primary REAL study was approved by the Brazilian National Research Ethics Commission (CONEP) of the Ministry of Health under approval number 45781015.8.1001.5259. All participants provided written informed consent prior to inclusion in the original study.

The present study consisted of a secondary analysis of anonymized data from this previously approved database. All analyses were conducted in aggregated form, without individual identification of participants, ensuring confidentiality and data protection in accordance with the ethical principles established by Resolution 466/12 of the Brazilian National Health Council (CNS) and the Brazilian General Data Protection Law (LGPD, Law 13.709/2018).

2.7 Statistical Analysis

A linear mixed-effects model (LMM) was employed for each outcome, appropriate for longitudinal data in which multiple correlated observations are collected from the same individual over time. The visit variable was converted from an ordered factor to an unordered categorical factor (treatment contrasts), allowing direct pairwise comparison of each follow-up visit (V2 and V3) against baseline (V1).

An initial full model was fitted for each of the six outcomes (DAS28-CRP, DAS28-ESR, SDAI, CDAI, RDAI, HAQ), including the following fixed effects: visit (V1 as reference, V2, V3), drug class (TNFi vs. non-TNFi), the visit $\times$ drug class interaction, age (continuous), sex (male vs. female), smoking status (never, former, current; three levels), physical activity (active vs. inactive), rheumatoid factor status (negative, low positive, high positive; three levels), symptoms time (continuous, in months), corticosteroid use (yes vs. no), and concomitant synthetic DMARD use (yes vs. no). Only the visit $\times$ drug class interaction was included; no other covariate $\times$ visit interactions were specified.

In this full model, age, sex, physical activity, rheumatoid factor, symptoms time, and concomitant synthetic DMARD use were not statistically significant in any of the six outcome models (all $p > 0.05$ in Type II ANOVA). These variables were therefore removed, yielding a parsimonious model with the following fixed effects:

- Visit (V2 and V3 vs. V1 reference; 2 parameters)

- Drug class (TNFi vs. non-TNFi; 1 parameter)
- Visit $\times$ Drug class interaction (2 parameters)
- Smoking status (former and current vs. never; 2 parameters)
- Corticosteroid use (yes vs. no; 1 parameter)

This resulted in 9 fixed-effect parameters (including the intercept) for 62 patients (186 observations).

Random effects were specified as nested random intercepts: a random intercept for hospital center and a random intercept for patient nested within hospital center. This accounts for (i) inter-center variability across the 8 referral sites and (ii) intra-individual correlation from repeated measurements on 62 patients. No random slopes for visit were included; the model assumed that the temporal trajectory was adequately captured by the fixed-effect structure, and the limited number of time points (three) and sample size (62 patients across 8 centers) would not reliably support random slope estimation.

The specification of random intercepts only implies a compound symmetry (CS) covariance structure for the within-patient residuals, that is, constant correlation between any two study visits for the same patient and homogeneous residual variance across time points. This assumption was considered appropriate given the three equally spaced visits and the relatively small sample size.

Final model parameters were estimated using restricted maximum likelihood (REML). For model comparison between the full and parsimonious specifications, both models were refitted using maximum likelihood (ML) to allow valid likelihood ratio tests (LRT). Model selection was additionally evaluated using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). In all six outcomes, the LRT was non-significant (p -values ranging from 0.21 to 0.51), and both AIC and BIC favored the parsimonious model, confirming that the removed covariates did not contribute meaningful explanatory power.

The significance of fixed effects was assessed using Type II Analysis of Variance with Satterthwaite’s approximation for denominator degrees of freedom. Marginal R^2 (variance explained by fixed effects only) and conditional R^2 (variance explained by both fixed and random effects) were computed following the Nakagawa & Schielzeth method.

Residual diagnostics for the parsimonious models included: (i) the Shapiro–Wilk test for normality of scaled residuals, (ii) assessment of skewness and excess kurtosis, (iii) identification of potential outliers (observations with standardized residuals exceeding $|3|$ in absolute value), and (iv) evaluation of heteroscedasticity through the Pearson correlation between absolute residuals and fitted values (values > 0.3 suggesting potential heteroscedasticity).

The adopted significance level was $\alpha < 0.05$, and all statistical analyses were performed using R software through the RStudio environment, with the `lme4` package for model fitting and the `lmerTest` package for Satterthwaite-based inference.

3 Results

3.1 Sample Characteristics

The final analytical sample comprised 62 Brazilian patients with rheumatoid arthritis receiving biologic DMARD therapy within the SUS, equally distributed between the TNFi group ($n = 31$; adalimumab, infliximab, etanercept) and the non-TNFi group ($n = 31$; tocilizumab, abatacept). A total of 186 observations were analyzed across three study visits (62 patients $\times$ 3 visits). The sample was drawn from 8 public referral centers participating in the REAL cohort. The demographic and baseline characteristics of the patients of the present study are presented in Table 1.

The mean age was 56.1 years, with a predominance of females ($n = 58$; 93.5%). The mean disease duration at baseline was 196.5 ± 107.9 months (median: 175.0 months; range: 45–590 months), that is, a median of more than 14 years of symptoms.

Regarding rheumatoid factor status, 45.2% of patients presented high-titer positivity, 25.8% low-titer positivity, and 29.0% were negative. Concerning physical activity, after excluding patients classified as “incapable of exercising”, 21.0% of patients were classified as active (≥ 3 times per week) and 79.0% as inactive (< 3 times per week). Smoking status distribution was: never smoker (64.5%), former smoker (25.8%), and current smoker (9.7%). Ethnicity distribution was: White (56.5%), Mixed race (30.6%), Black (9.7%), and Asian (3.2%).

Table 1 Demographic and baseline characteristics of patients treated with TNFi and non-TNFi agents ($N = 62$).

Characteristic	TNFi ($N = 31$)	Non-TNFi ($N = 31$)
Age, mean $\pm$ SD (years)	56.6 $\pm$ 10.3	55.5 $\pm$ 10.9
Symptoms time, mean $\pm$ SD (months)	173.6 $\pm$ 86.8	219.4 $\pm$ 122.8
Sex — no. (%)		
Female	29 (93.5)	29 (93.5)
Male	2 (6.5)	2 (6.5)
Ethnicity — no. (%)		
White	20 (64.5)	15 (48.4)
Mixed race	7 (22.6)	12 (38.7)
Black	3 (9.7)	3 (9.7)
Asian	1 (3.2)	1 (3.2)
Rheumatoid Factor — no. (%)		
Negative	9 (29.0)	9 (29.0)
Positive (low)	11 (35.5)	5 (16.1)
Positive (high)	11 (35.5)	17 (54.8)
Physical Activity — no. (%)		
Inactive ($< 3\times/\text{week}$)	23 (74.2)	26 (83.9)
Active ($\geq 3\times/\text{week}$)	8 (25.8)	5 (16.1)
Smoking Status — no. (%)		
Never	19 (61.3)	21 (67.7)
Former	10 (32.3)	6 (19.4)
Current	2 (6.4)	4 (12.9)
Disease activity at baseline, mean $\pm$ SD		
CDAI	7.8 $\pm$ 6.2	9.6 $\pm$ 7.6
SDAI	8.5 $\pm$ 6.0	10.4 $\pm$ 7.9
DAS28-CRP	2.5 $\pm$ 0.7	2.9 $\pm$ 1.1
DAS28-ESR	3.0 $\pm$ 1.2	3.4 $\pm$ 1.2
HAQ	0.7 $\pm$ 0.6	1.0 $\pm$ 0.6
RADAI	2.7 $\pm$ 1.9	3.2 $\pm$ 1.7
Concomitant treatment — no. (%)		
Corticosteroid use	7 (22.6)	14 (45.2)
No csDMARD	4 (12.9)	13 (41.9)
csDMARD use	27 (87.1)	18 (58.1)
Methotrexate	21 (67.7)	14 (45.2)
Leflunomide	6 (19.4)	4 (12.9)
csDMARD combination	1 (3.2)	1 (3.2)
Biologic agent — no. (%)		
Adalimumab	7 (22.6)	0 (0.0)
Infliximab	12 (38.7)	0 (0.0)
Etanercept	12 (38.7)	0 (0.0)
Tocilizumab	0 (0.0)	10 (32.3)
Abatacept	0 (0.0)	21 (67.7)

3.2 Observed Trajectories of Disease Activity and Functional Capacity

Disease activity and functional capacity were assessed at three consecutive visits over approximately 12 months of follow-up. The observed trajectory of each outcome is summarized in Table 2.

Table 2 Trajectory of disease activity scores and functional capacity across the three study visits ($N = 62$ patients, 186 observations). Values for each visit are means.

Score	Visit 1	Visit 2	Visit 3	Overall Mean (SD)	Min	Max
DAS28-CRP	2.66	2.66	2.95	2.76 (1.03)	0.99	5.97
DAS28-ESR	3.20	3.12	3.43	3.25 (1.29)	0.00	6.71
SDAI	9.48	9.35	11.58	10.14 (8.34)	0.10	40.04
CDAI	8.69	8.55	10.76	9.33 (8.15)	0.00	37.00
RDAI	2.95	3.05	3.24	3.08 (1.91)	0.00	7.42
HAQ	0.83	0.78	0.86	0.82 (0.60)	0.00	2.62

The trajectory was not one of progressive improvement. Across all six outcomes, scores were essentially flat between V1 and V2 and then rose at V3: DAS28-CRP moved from 2.66 to 2.66 to 2.95, DAS28-ESR from 3.20 to 3.12 to 3.43, SDAI from 9.48 to 9.35 to 11.58, CDAI from 8.69 to 8.55 to 10.76, and RDAI from 2.95 to 3.05 to 3.24. HAQ remained substantively unchanged (0.83, 0.78, 0.86). A similar V1–V2 plateau followed by higher V3 scores was observed across disease activity indices, while HAQ remained largely stable.

3.3 Adjusted longitudinal analyses

DAS28-CRP remission rates remained stable at approximately 55% across visits in the TNFi group, whereas they decreased from 35.5% at V1 to 19.4% at V3 in the non-TNFi group.

In the parsimonious linear mixed-effects models, the V3-versus-V1 coefficient was significant for DAS28-CRP ($p = 0.011$), SDAI ($p = 0.013$), and CDAI ($p = 0.019$),

whereas the corresponding coefficients were not significant for DAS28-ESR ($p = 0.074$), RADAI ($p = 0.580$), or HAQ ($p = 0.517$). Because the models included a visit $\times$ drug class interaction, these visit coefficients refer to the non-TNFi reference group. Importantly, however, no visit $\times$ drug class interaction was statistically significant for any of the six outcomes, providing no evidence of differential trajectories between TNFi and non-TNFi groups (Table 3).

Drug class showed a significant overall association with DAS28-CRP ($p = 0.005$), DAS28-ESR ($p = 0.021$), SDAI ($p = 0.009$), CDAI ($p = 0.005$), and HAQ ($p = 0.007$), but not RADAI ($p = 0.156$). For HAQ, TNFi treatment was associated with lower disability (estimate = -0.443 , $p = 0.003$). Smoking status was also associated with HAQ (overall $p = 0.004$), with former smokers showing greater disability than never smokers (estimate = 0.491 , $p = 0.001$). Corticosteroid use was associated with higher SDAI ($p = 0.003$), CDAI ($p < 0.001$), and RADAI ($p = 0.009$). Full model coefficients and diagnostic results are provided in the Supplementary Material.

Table 3 Summary of adjusted longitudinal associations for disease activity and functional outcomes.

Outcome	V3 vs V1 p^*	Drug class p	Visit $\times$ drug class p
DAS28-CRP	0.011	0.005	0.167
DAS28-ESR	0.074	0.021	0.470
SDAI	0.013	0.009	0.151
CDAI	0.019	0.005	0.201
RADAI	0.580	0.156	0.793
HAQ	0.517	0.007	0.358

Note: V3-versus-V1 p values refer to the non-TNFi reference group because the models included a visit $\times$ drug class interaction. Drug class and interaction p values correspond to Type II ANOVA tests.

An additional tables file shows Type II ANOVA results, fixed-effects coefficients, variance components, residual diagnostics and full vs. parsimonious model comparisons for the primary (DAS28-CRP, DAS28-ESR, HAQ) and secondary (SDAI, CDAI, RADAI) outcomes in more details[see Additional file 1].

4 Discussion

This study provides a period-specific longitudinal view of disease activity and functional capacity among Brazilian patients with RA receiving biologic DMARDs within the SUS between 2015 and 2017, showing that the observed course did not follow a simple pattern of progressive or sustained improvement. By providing structured longitudinal data from a universal public health system in a middle-income country, it also adds an underrepresented health-system perspective to the international real-world evidence on biologic-treated RA. Descriptively, disease activity remained relatively stable between the first two visits and was higher at the final assessment, whereas functional capacity remained largely unchanged. In adjusted analyses, V3-versus-V1 increases in DAS28-CRP, SDAI, and CDAI were statistically significant in the non-TNFi reference group; however, no visit $\times$ drug class interaction reached statistical significance, providing no evidence that longitudinal trajectories differed between biologic classes. These findings should therefore be interpreted primarily as a description of disease-control trajectories within this specific historical and health-system context, rather than as evidence of treatment failure or comparative superiority between biologic classes.

Several factors may account for the observed pattern. The higher disease activity at the final visit may reflect fluctuations inherent to RA, changes in concomitant therapy or adherence, or variation in treatment response over time, none of which can be distinguished within the present design. Importantly, the baseline visit did not necessarily correspond to bDMARD initiation, precluding interpretation of the trajectory as an initial treatment response followed by loss of efficacy. The findings are nevertheless consistent with previous reports from the broader REAL cohort, in which moderate-to-high disease activity and failure to achieve treat-to-target goals remained frequent despite substantial use of glucocorticoids and biologic therapy [15, 16]. The clinical context may also be relevant: patients had a median symptom duration of

more than 14 years and were treated at tertiary public referral centers. These characteristics differ from those of many clinical-trial populations [17, 18] and reinforce the importance of generating longitudinal effectiveness data within the health systems in which treatment is delivered.

Drug class was associated with several disease activity measures and with functional capacity, with lower scores observed among TNFi-treated patients, particularly for HAQ. Remission rates were also numerically more stable in the TNFi group. These findings should not, however, be interpreted as evidence of TNFi superiority. Treatment allocation was not randomized, baseline characteristics differed between groups, and non-TNFi agents may have been used later in the treatment sequence; confounding by indication and treatment line is therefore highly plausible. Consistent with this interpretation, no visit $\times$ drug class interaction was significant in any outcome. Smoking status was associated with HAQ, driven by greater disability among former smokers, while corticosteroid use was associated with higher SDAI, CDAI, and RADAI. Given the observational design, these associations are better regarded as markers of patient and disease characteristics than as causal effects.

This study has several strengths, including multicenter data collection, protocol-driven longitudinal assessments, multiple validated measures of disease activity and function, and an analytical approach accounting for repeated measurements and center-level variability. Important limitations should also be acknowledged. The analytical sample was small and restricted to patients with complete data across all three visits, limiting statistical power and generalizability. Exclusion of patients classified as unable to exercise may have preferentially removed individuals with greater disease severity or disability. The observational, non-randomized design leaves the analyses vulnerable to residual confounding and confounding by indication, and the three

assessments at approximately six-month intervals cannot capture short-term fluctuations in disease activity. Baseline did not uniformly represent treatment initiation, and multiple outcomes were evaluated without formal adjustment for multiplicity.

Although these data represent the 2015–2017 treatment landscape, they provide a historical benchmark from an underrepresented health-system context and underscore the value of expanding longitudinal RA registries beyond high-income settings.

5 Conclusion

In this multicenter Brazilian cohort, disease activity and functional trajectories among patients with RA receiving biologic DMARDs within the SUS between 2015 and 2017 did not follow a simple pattern of progressive or sustained improvement over 12 months. Disease activity was relatively stable initially and higher at the final assessment, whereas functional capacity remained largely unchanged. Although outcome levels differed between TNFi and non-TNFi groups, no significant differences in longitudinal trajectories were demonstrated between biologic classes. These findings provide a period-specific real-world benchmark from an underrepresented universal public health system and highlight the value of longitudinal evidence from settings beyond the predominantly high-income registries that inform current RA effectiveness literature. Given the small, selected sample and observational design, the findings should be considered exploratory and require confirmation in larger contemporary cohorts.

List of Abbreviations

- ACPA: Anti-citrullinated protein antibodies;
- ACR: American College of Rheumatology;
- AIC: Akaike Information Criterion;
- Anti-CCP: Anti-cyclic citrullinated peptide antibodies;
- BIC: Bayesian Information Criterion;

- CCEB: Brazilian Economic Classification Criterion;
- CD28: Cluster of Differentiation 28;
- CDAI: Clinical Disease Activity Index;
- CNS: National Health Council;
- CONEP: Brazilian National Research Ethics Commission;
- CRP: C-reactive protein;
- CS: Compound symmetry;
- DAS28: Disease Activity Score in 28 Joints;
- DAS28-CRP: Disease Activity Score in 28 Joints using C-reactive protein;
- DAS28-ESR: Disease Activity Score in 28 Joints using erythrocyte sedimentation rate;
- DMARDs: Disease-modifying antirheumatic drugs;
- DNA: Deoxyribonucleic acid;
- ESR: Erythrocyte sedimentation rate;
- EULAR: European Alliance of Associations for Rheumatology;
- HAQ: Health Assessment Questionnaire;
- HAQ-DI: Health Assessment Questionnaire – Disability Index;
- HLA: Human leukocyte antigen;
- IL-6: Interleukin 6;
- LGPD: Brazilian General Data Protection Law;
- LMM: Linear mixed-effects model;
- LRT: Likelihood ratio test;
- ML: Maximum likelihood;
- MMAM: Morisky Medication Adherence Measure;
- mRNA: Messenger ribonucleic acid;
- NSAIDs: Nonsteroidal anti-inflammatory drugs;
- R^2 : Coefficient of determination;

- RA: Rheumatoid arthritis;
- RADAI: Rheumatoid Arthritis Disease Activity Index;
- RANKL: Receptor Activator of Nuclear Factor Kappa-B Ligand;
- REML: Restricted maximum likelihood;
- RF: Rheumatoid factor;
- SDAI: Simplified Disease Activity Index;
- SUS: Brazilian Unified Health System;
- TNF: Tumor necrosis factor;
- TNFi: Tumor necrosis factor inhibitors;
- V1: Visit 1;
- V2: Visit 2;
- V3: Visit 3;

Declarations

- **Ethics approval and consent to participate:** The primary Real Life database study was approved by the Brazilian National Research Ethics Commission (CONEP) of the Ministry of Health under approval number 45781015.8.1001.5259. All included patients signed an informed consent form and were informed about the objectives of the research.
- **Consent for publication:** Not applicable.
- **Availability of data and materials:** The datasets used and analysed during the current study are available from the corresponding author on reasonable request.
- **Competing interests:** The authors declare that they have no competing interests.
- **Funding:** The REAL, Rheumatoid Arthritis in Real Life, study, which provided the data analysed here, was supported by the Brazilian Society of Rheumatology (*Sociedade Brasileira de Reumatologia*, SBR) through its Research Support Fund (*Fundo de Apoio da Sociedade Brasileira de Reumatologia*). The present secondary

analysis received no additional or dedicated funding. The funder had no role in the design of the present analysis, in the interpretation of data, or in the decision to publish.

- **Authors contributions:** JAIP was responsible for the study conception and design, data curation, statistical analysis using the linear mixed-effects model, interpretation of findings, and drafting and critical revision of the manuscript for important intellectual content.

VERC was responsible for writing the data cleaning and model fitting code, and contributed to the statistical analysis.

DAZ contributed to writing the Discussion and Results sections, and to the interpretation of the linear mixed-effects model.

ADS contributed to the conceptualization of the statistical analysis, provided methodological guidance, critically revised the manuscript for important intellectual content, and reviewed the results obtained.

LSFC contributed to the conceptualization of the statistical analysis, provided methodological guidance, critically revised the manuscript for important intellectual content, clarified methodological questions, and assisted in the submission process.

AAVP was responsible for patient recruitment, clinical assessment and data acquisition at their respective centers, contributed to the interpretation of the findings, critically revised the manuscript for important intellectual content, refined and improved specific sections of the text, provided guidance on the structure and organization of the manuscript and on aspects related to its publication

CPA, APMG, ABVS, PLJ, RDNG, SCR, MFBRG, KRB, MFLCS, IAP, CVB, LMHM and GRCP were responsible for patient recruitment, clinical assessment and data acquisition at their respective centers, contributed to the interpretation of the findings, and critically revised the manuscript for important intellectual content.

The authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

- **Acknowledgements:** The authors gratefully acknowledge the Brazilian Society of Rheumatology (*Sociedade Brasileira de Reumatologia*, SBR) for establishing and supporting the REAL, Rheumatoid Arthritis in Real Life, study, and for making this nationally representative Brazilian cohort available to the research community. The authors also thank the investigators and staff of the participating public referral centres, and the patients of the Unified Health System who consented to take part in the original cohort.

References

- [1] Singh JA. Treatment guidelines in rheumatoid arthritis. *Rheum Dis Clin North Am.* 2022;48(3):679–689. <https://doi.org/10.1016/j.rdc.2022.03.005>.
- [2] Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet.* 2016;388(10055):2023–2038. [https://doi.org/10.1016/S0140-6736\(16\)30173-8](https://doi.org/10.1016/S0140-6736(16)30173-8).
- [3] O’Neil LJ, Alpízar-Rodríguez D, Deane KD. Rheumatoid arthritis: the continuum of disease and strategies for prediction, early intervention, and prevention. *J Rheumatol.* 2024;51(4):337–349. <https://doi.org/10.3899/jrheum.2023-0334>.
- [4] Conley B, et al. What are the core recommendations for rheumatoid arthritis care? Systematic review of clinical practice guidelines. *Clin Rheumatol.* 2023;42(9):2267–2278. <https://doi.org/10.1007/s10067-023-06654-0>.
- [5] Frazzei G, et al. Prevention of rheumatoid arthritis: a systematic literature review of preventive strategies in at-risk individuals. *Autoimmun Rev.* 2023;22(1):103217. <https://doi.org/10.1016/j.autrev.2022.103217>.
- [6] Conran C, et al. A review of difficult-to-treat rheumatoid arthritis: definition, clinical presentation, and management. *Curr Rheumatol Rep.* 2023;25(12):285–294. <https://doi.org/10.1007/s11926-023-01117-6>.
- [7] da Mota LMH, Kakehasi AM, Gomides APM, et al. 2017 recommendations of the Brazilian Society of Rheumatology for the pharmacological treatment of rheumatoid arthritis. *Adv Rheumatol.* 2018;58(1):2. <https://doi.org/10.1186/s42358-018-0005-0>.
- [8] Lin YJ, Anzaghe M, Schülke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. *Cells.* 2020;9(4):880. <https://doi.org/>

[10.3390/cells9040880](https://doi.org/10.3390/cells9040880).

- [9] Braverman G, Bridges SL, Moreland LW. Tapering biologic DMARDs in rheumatoid arthritis. *Curr Opin Pharmacol*. 2022;67:102308. <https://doi.org/10.1016/j.coph.2022.102308>.
- [10] Wang Z, et al. Comparison of the efficacy and safety indicators of DMARDs for rheumatoid arthritis: a network meta-analysis. *Medicine (Baltimore)*. 2021;100(29):e26524. <https://doi.org/10.1097/MD.00000000000026524>.
- [11] Hochberg MC, et al. Mixed treatment comparison of efficacy and tolerability of biologic agents in patients with rheumatoid arthritis. *Curr Med Res Opin*. 2013;29(10):1213–1222. <https://doi.org/10.1185/03007995.2013.813839>.
- [12] Harrold LR, et al. The comparative effectiveness of abatacept versus anti-tumour necrosis factor switching for rheumatoid arthritis patients previously treated with an anti-tumour necrosis factor. *Ann Rheum Dis*. 2015;74(2):430–436. <https://doi.org/10.1136/annrheumdis-2013-203936>.
- [13] Castro CT, et al. Real-world effectiveness of biological therapy in patients with rheumatoid arthritis: systematic review and meta-analysis. *Front Pharmacol*. 2022;13:927179. <https://doi.org/10.3389/fphar.2022.927179>.
- [14] Alves C, et al. Real-world treatment patterns of rheumatoid arthritis in Brazil: analysis of DATASUS national administrative claims data for pharmacoepidemiology studies (2010–2020). *Sci Rep*. 2023;13(1):17601. <https://doi.org/10.1038/s41598-023-44389-9>.
- [15] da Rocha Castelar-Pinheiro G, Vargas-Santos AB, de Albuquerque CP, et al. The REAL study: a nationwide prospective study of rheumatoid arthritis in Brazil. *Adv Rheumatol*. 2018;58(1):9. <https://doi.org/10.1186/s42358-018-0017-9>.

- [16] Gomides APM, de Albuquerque CP, Santos ABV, et al. Rheumatoid arthritis treatment in Brazil: data from a large real-life multicenter study. *Adv Rheumatol.* 2020;60(1):16. <https://doi.org/10.1186/s42358-020-0119-z>.
- [17] Kerschbaumer A, et al. Efficacy of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis.* 2023;82(1):95–106. <https://doi.org/10.1136/ard-2022-223365>.
- [18] Su QY, et al. Efficacy and safety of current therapies for difficult-to-treat rheumatoid arthritis: a systematic review and network meta-analysis. *J Transl Med.* 2024;22(1):795. <https://doi.org/10.1186/s12967-024-05569-x>.
- [19] Prasad P, et al. Rheumatoid arthritis: advances in treatment strategies. *Mol Cell Biochem.* 2023;478(1):69–88. <https://doi.org/10.1007/s11010-022-04492-3>.
- [20] Hua C, Buttgereit F, Combe B. Glucocorticoids in rheumatoid arthritis: current status and future studies. *RMD Open.* 2020;6(1):e000536. <https://doi.org/10.1136/rmdopen-2017-000536>.
- [21] Sacilotto NdC, Giorgi RDN, Vargas-Santos AB, et al. REAL — rheumatoid arthritis in real life — study cohort: a sociodemographic profile of rheumatoid arthritis in Brazil. *Adv Rheumatol.* 2020;60(1):20. <https://doi.org/10.1186/s42358-020-0121-5>.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [additionalfiles1.pdf](#)