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# Drug Survival of Biological Therapy in Patients with Rheumatoid Arthritis

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## Abstract

**Background:** Biological therapy prevents structural damage, improves functional capacity, and has provided an important advance in the treatment of rheumatoid arthritis (RA). In a real-life scenario, drug survival is an indirect measure of the efficacy, safety, and tolerability of a drug. The objective of the study was to analyze the drug survival rate of biological therapy in a national health system (SUS). **Methods:** A retrospective cohort study of the medication process of RA was carried out in public pharmacies of a Brazilian state from January 2010 to April 2017. The Kaplan-Meier survival analysis was applied. The survival rate was defined as the incidence of drug discontinuation. The retention rate was defined as the mean of months using the drug. **Results:** Of the total of 902 individuals, 83.6% were female with a mean age of 56 years. Anti-TNF, mostly adalimumab (ADA), was the main biological agent prescribed. Mean drug retention of the first biological was 59.6 months (95% CI: 56.7 - 62.5), followed by 53.7 (95% CI: 48 - 59.4) and 28.2 (95% CI: 23.1 - 23.3) months for the second and third biologicals, respectively. Among the anti-TNF group, ADA, ETN, IFX had the better retention rate. There was no statistical difference in the general survival analyses ($p = 0.18$) among the groups. However, along the first 2 years, ADA, ETN, and RTX had the three better drug survival. The drug retention seems to increase with age ($p = 0.036$), with the subgroups > 70 years of age having the highest means (70 - 80 years: 67.29; >80: 67.53). Among all, 27.1% of patients switched to a second biologic. **Conclusion:** The anti-TNF group, mostly adalimumab (ADA), is the most prescribed medication as first and second-line therapy, reflecting its accessibility in the SUS and efficiency of the follow-up protocols. Among the anti-TNF group, ADA, ETN, and IFX had the better retention rate. Additionally, ADA and ETN had the better drug survival for the first treatment in the first 2 years. RTX was the non-anti-TNF with the best survival. A quarter of patients who start a biological therapy fail and switch to another drug (27%).

**Keywords**

Rheumatoid Arthritis, Biological Therapy, Survival Rate, Anti-TNF-$\alpha$

## 1. Background

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by involvement of the synovial membrane, which can cause a relevant functional limitation [1]. Biologicals with different mechanisms of action prevent structural damage, improve functional capacity and provide a clear advance in the treatment [1] [2]. In the Brazilian guideline, biological therapy should be used as second-line therapy after six months with at least two different first-line regimens and moderate or high disease activity [3].

The anti-TNF (tumor necrosis factor-alpha inhibitor) agents were introduced in Brazil in 2000, and non-anti-TNF agents were incorporated in 2015 [4]-[7] for the treatment of RA. These therapies are provided by the National Health System ("Sistema Único de Saúde", SUS) [6] [7] and to gain free access, patients need to initiate an administrative process through public pharmacies [8]. The state of Espírito Santo (ES) is considered a model of pharmaceutical assistance in Brazil [9].

Public pharmacies hold a wealth of information within electronic databases, offering advantage of prolonged patient observation compared to randomized clinical trials. These databases provide insights into the indication of biologics by ICD (International Classification of Diseases), patient types, the number of individuals using biologic therapy, biologic switching, and the time between treatment initiation and interruption. This data can be utilized to calculate drug survival, a surrogate measure of efficacy, safety, and tolerability, serving as an indicator of therapeutic success in real-life scenarios. However, limited knowledge exists regarding the actual duration of drug effectiveness and the factors influencing treatment response.

In the medical literature, there are currently no Brazilian studies evaluating drug survival of biological therapy based on data from public pharmacies of the National Health System in patients with rheumatoid arthritis (RA) in a real-life scenario. Therefore, the objective of this study was to analyze the frequency, discontinuation, and drug survival of biological therapy in RA patients in the state of Espírito Santo.

## 2. Methods

### 2.1. Study Design

This retrospective cohort study included 902 rheumatoid arthritis (RA) patients who had active Evaluation and Medication Authorization forms (Specialized Component of Pharmaceutical Care, LME) within the last 6 months. Data were collected from 8 public pharmacies across different geographic regions in the state of Espírito Santo, covering the period from January 2010 to April 2017.

### 2.2. Participants

All patients with active LME, categorized under ICD codes M05.0, M05.8, M06.0, and M06.8, were included in the study. Patients with ICD codes M05.1 (rheumatoid lung disease), M05.2 (rheumatoid vasculitis), and M05.3 (RA with organ and system involvement) were excluded to ensure that no patients with extra-articular manifestations were included. Data were obtained from the electronic health database of the municipal pharmacy. Discontinuation was defined as the initiation of a new immunobiological therapy. Patients were censored if they were still using the biological drug at the end of the study period (seven years).

### 2.3. Survival Analyses

The survival was defined as the time between the exposure (onset of biological drug use) until the event (drug discontinuation). The survival rate was defined as the incidence of drug discontinuation. The retention rate was defined as the mean of months using the drug.

### 2.4. Statistical Analysis

Categorical variables were presented as the number of individuals and corresponding percentages. Continuous variables were described using mean, media, and standard deviation. Normality was assessed using the Shapiro-Wilk test. For parametric data, a t-test was used (or Fisher's exact test when subgroup counts were < 5), and analysis of variance (ANOVA) was applied for comparisons involving more than two groups, followed by appropriate pairwise comparisons. Non-parametric data were analyzed using the Mann-Whitney and Kruskal-Wallis tests, followed by respective post-hoc comparisons. Survival analyses were performed using the Kaplan-Meier method, with drug discontinuation as the event of interest, stratified by gender, sex, and the specific biological drug used. A p-value of <0.05 was considered statistically significant for all analyses. Statistical analyses were conducted using SPSS (version 26) and Jamovi (version 2.3.26)

## 3. Results

The study analyzed 902 rheumatoid arthritis (RA) patients, showing a predominant female population (83.6%) with a mean age of 56 years (Table 1).

The initial treatment for most patients (92.5%) involved anti-TNF drugs with adalimumab (ADA) being the most prescribed (40%), followed by infliximab (IFX) (20%), and etanercept (ETN) (18.6%). The remaining 7.5% were started on non-anti-TNF drugs, primarily rituximab (RTX) and abatacept (ABAT) (3% each).

A total of 244 patients (27.1%) switched to a second biological treatment. Of these, 65% were switched to another anti-TNF drug, with ADA (24.6%) and ETN (23.4%) being the most common. The remaining 35% were switched to non-anti-TNF drugs, notably ABAT (18.9%) and tocilizumab (TOCI) (12.7%).

**Table 1.** Demographic characteristics of the study population.

| Variables | First biological (n = 902) | Second biological (n = 244) | Third biological (n = 55) |
|---|---|---|---|
| **Age (years) - mean (±SD)** | 56 (±13.3) | 54 (±13) | 53.1 (±14) |
| **Gender - n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Female | 754 (83.6) | 209 (85.7) | 55 (100) |
| **Medication** | **n (%)** | **n (%)** | **n (%)** |
| Infliximab | 180 (20) | 6 (2.5) | 0 (0) |
| Adalimumab | 361 (40) | 60 (24.6) | 5 (9.1) |
| Etanercept | 168 (18.6) | 57 (23.4) | 9 (16.4) |
| Golimumab | 96 (10.6) | 27 (11.1) | 3 (5.5) |
| Certolizumab | 29 (3.2) | 8 (3.3) | 3 (5.5) |
| Abatacept | 27 (3) | 46 (18.9) | 16 (29.1) |
| Tocilizumab | 14 (1.6) | 31 (12.7) | 14 (25.5) |
| Rituximab | 27 (3) | 9 (3.7) | 5 (9.1) |
| **Class of medication** | **n (%)** | **n (%)** | **n (%)** |
| anti-TNF | 834 (92) | 158 (65) | 20 (36.4) |
| non-anti-TNF | 68 (8) | 86 (35) | 35 (63.6) |

SD: standard deviation.

In the first biological treatment, IFX had the highest discontinuation rate at 44.4%, followed by ADA at 24.4%, ETN at 20.8%, certolizumab pegol (CERT) at 20.7%, and golimumab (GOL) at 16.7%. Among non-anti-TNF therapies, ABAT had a discontinuation rate of 37%, while RTX followed with 29.6%. Tocilizumab (TOCI) demonstrated the lowest discontinuation rate at 7.1% (Table 2).

In the second biological treatment, IFX again had the highest discontinuation rate, reaching 50%, followed by ETN at 24.6%, CERT at 25%, ADA at 23.3%, and GOL at 18.5%. For the non-anti-TNF group in this stage, ABAT had the highest discontinuation rate at 32.6%, followed by RTX at 22.2%, with TOCI having a lower discontinuation rate of 16.1% (Table 2).

Overall, only 60 patients (24.5%) switched from the second to the third biological treatment. Notably, the non-anti-TNF agents were preferred in this transition, with 39 patients (65%) opting for these treatments compared to 21 patients (35%) who chose anti-TNF therapies. ABAT was the most frequently prescribed medication in this group, accounting for 30% of prescriptions, followed by TOCI at 26.7%.

**Table 2.** Discontinuation rate of biological treatment.

| Medication | First biological n (%) | Second biological n (%) | Third biological n (%) |
|---|---|---|---|
| Infliximab | 80 (44.4) | 3 (50) | 0 (0) |
| Adalimumab | 88 (24.4) | 14 (23.3) | 1 (33.3) |
| Etanercept | 35 (20.8) | 14 (24.6) | 1 (11.1) |
| Golimumab | 16 (16.7) | 5 (18.5) | 0 (0) |
| Certolizumab | 6 (20.7) | 2 (25) | 1 (33.3) |
| Abatacept | 10 (37) | 15 (32.6) | 6 (33.3) |
| Tocilizumab | 1 (7.1) | 5 (16.1) | 2 (12.5) |
| Rituximab | 8 (29.6) | 2 (22.2) | 2 (28.6) |

Mean drug retention of the first biological was 59.6 months (95% CI; 56.7 - 62.5), followed by 53.7 (95% CI; 48 - 59.4) and 28.2 (95% CI; 23.1 - 23.3) months for the second and third biological, respectively. Among the anti-TNF group, ADA, ETN, IFX had the better retention rate, and GOL and CERT the worst. Detailed pairwise comparisons of drug retention for the first treatment can be found in Table 3.

Table 3. Comparison of drug retention between the biologicals in the first medication.

| | Sum of Squares | Mean Square | df | F | $\eta^2$ | p |
|---|---|---|---|---|---|---|
| Medication | 16984 | 2426 | 7 | 8.95 | 0.075 | **<0.001** |
| Residuals | 210420 | 271 | 776 | | | |
| **Pairwise comparison** | | **Mean Difference** | **SE** | **df** | **t** | $p_{tukey}$ |
| Abatacept | Adalimumab | −1895 | 3.36 | 776 | −0.565 | 0.999 |
| | Certolizumab | 13720 | 4.48 | 776 | 3059 | 0.047 |
| | Etanercept | 1026 | 3.49 | 776 | 0.294 | 1000 |
| | Golimumab | 9150 | 3.64 | 776 | 2513 | 0.191 |
| | Infliximab | −3484 | 3.58 | 776 | −0.974 | 0.978 |
| | Rituximab | 4850 | 4.77 | 776 | 1017 | 0.972 |
| | Tocilizumab | 8220 | 5.46 | 776 | 1506 | 0.804 |
| Adalimumab | Certolizumab | 15615 | 3.24 | 776 | 4815 | **<0.001** |
| | Etanercept | 2922 | 1.60 | 776 | 1830 | 0.599 |
| | Golimumab | 11045 | 1.91 | 776 | 5776 | **<0.001** |
| | Infliximab | −1589 | 1.79 | 776 | −0.887 | 0.987 |
| | Rituximab | 6745 | 3.63 | 776 | 1860 | 0.579 |
| | Tocilizumab | 10115 | 4.49 | 776 | 2251 | 0.323 |
| Certolizumab | Etanercept | −12693 | 3.38 | 776 | −3759 | **0.005** |
| | Golimumab | −4570 | 3.54 | 776 | −1292 | 0.902 |
| | Infliximab | −17204 | 3.47 | 776 | −4953 | **<0.001** |
| | Rituximab | −8870 | 4.69 | 776 | −1891 | 0.558 |
| | Tocilizumab | −5500 | 5.39 | 776 | −1020 | 0.971 |
| Etanercept | Golimumab | 8124 | 2.13 | 776 | 3812 | **0.004** |
| | Infliximab | −4511 | 2.02 | 776 | −2229 | 0.335 |
| | Rituximab | 3823 | 3.75 | 776 | 1020 | 0.971 |
| | Tocilizumab | 7193 | 4.59 | 776 | 1567 | 0.770 |
| Golimumab | Infliximab | −12634 | 2.28 | 776 | −5539 | **<0.001** |
| | Rituximab | −4300 | 3.89 | 776 | −1105 | 0.956 |
| | Tocilizumab | −0.930 | 4.71 | 776 | −0.197 | 1000 |
| Infliximab | Rituximab | 8334 | 3.83 | 776 | 2173 | 0.369 |
| | Tocilizumab | 11704 | 4.66 | 776 | 2510 | 0.193 |
| Rituximab | Tocilizumab | 3370 | 5.63 | 776 | 0.599 | 0.999 |

There was no statistical difference in survival analyses overall (p = 0.18) nor in the post-hoc pairwise comparisons during the first treatment among the different groups, as shown in graphic 1 - 2 and Table 4. Similarly, there were no significant differences in discontinuation rates during the second and third treatments among the groups, with p-values of 0.39 and 0.09, respectively.

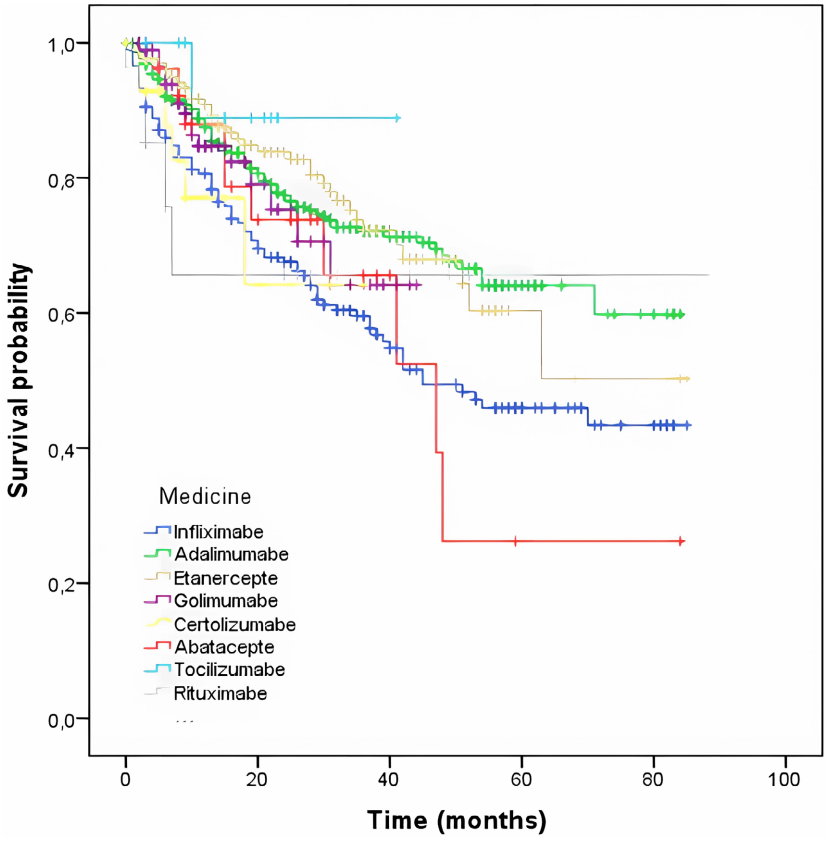


**Figure 1.** Drug survival of the first treatment.

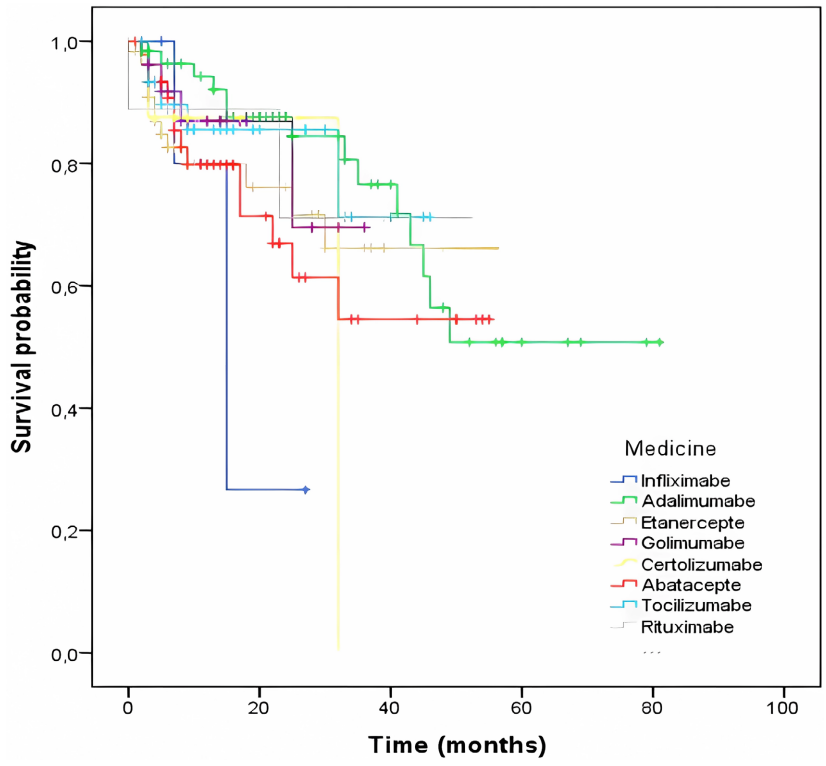


**Figure 2.** Drug survival of the second treatment.

**Table 4.** Pairwise comparisons—Hazard Ratio evaluation (post-hoc log-rank analysis) in the first treatment.

| | | HR | *p* |
|---|---|---|---|
| Abatacept | Adalimumab | HR = 0.55 (95% CI: 0.29 - 1.07) | 0.080 |
| Abatacept | Certolizumab | HR = 1.18 (95% CI: 0.43 - 3.26) | 0.752 |
| Abatacept | Etanercept | HR = 0.53 (95% CI: 0.26 - 1.08) | 0.079 |
| Abatacept | Golimumab | HR = 0.65 (95% CI: 0.30 - 1.44) | 0.291 |
| Abatacept | Infliximab | HR = 0.78 (95% CI: 0.39 - 1.57) | 0.491 |
| Abatacept | Rituximab | HR = 0.88 (95% CI: 0.32 - 2.43) | 0.811 |
| Abatacept | Tocilizumab | HR = 0.26 (95% CI: 0.03 - 2.04) | 0.200 |
| Adalimumab | Certolizumab | HR = 2.13 (95% CI: 0.92 - 4.93) | 0.078 |
| Adalimumab | Etanercept | HR = 0.95 (95% CI: 0.63 - 1.45) | 0.824 |
| Adalimumab | Golimumab | HR = 1.18 (95% CI: 0.68 - 2.03) | 0.555 |
| Adalimumab | Infliximab | HR = 1.41 (95% CI: 0.96 - 2.09) | 0.083 |
| Adalimumab | Rituximab | HR = 1.60 (95% CI: 0.69 - 3.67) | 0.271 |
| Adalimumab | Tocilizumab | HR = 0.47 (95% CI: 0.07 - 3.39) | 0.455 |
| Certolizumab | Etanercept | HR = 0.45 (95% CI: 0.19 - 1.08) | 0.074 |
| Certolizumab | Golimumab | HR = 0.55 (95% CI: 0.22 - 1.42) | 0.218 |
| Certolizumab | Infliximab | HR = 0.66 (95% CI: 0.28 - 1.58) | 0.356 |
| Certolizumab | Rituximab | HR = 0.75 (95% CI: 0.24 - 2.34) | 0.620 |
| Certolizumab | Tocilizumab | HR = 0.22 (95% CI: 0.03 - 1.84) | 0.163 |
| Etanercept | Golimumab | HR = 1.24 (95% CI: 0.67 - 2.27) | 0.493 |
| Etanercept | Infliximab | HR = 1.48 (95% CI: 0.92 - 2.38) | 0.104 |
| Etanercept | Rituximab | HR = 1.67 (95% CI: 0.70 - 4.02) | 0.249 |
| Etanercept | Tocilizumab | HR = 0.49 (95% CI: 0.07 - 3.62) | 0.488 |
| Golimumab | Infliximab | HR = 1.20 (95% CI: 0.66 - 2.16) | 0.546 |
| Golimumab | Rituximab | HR = 1.35 (95% CI: 0.53 - 3.48) | 0.529 |
| Golimumab | Tocilizumab | HR = 0.40 (95% CI: 0.05 - 3.01) | 0.373 |
| Infliximab | Rituximab | HR = 1.13 (95% CI: 0.48 - 2.67) | 0.782 |
| Infliximab | Tocilizumab | HR = 0.33 (95% CI: 0.05 - 2.43) | 0.278 |
| Rituximab | Tocilizumab | HR = 0.30 (95% CI: 0.04 - 2.46) | 0.259 |

However, when comparing the drugs during the first two years, it was observed that adalimumab (ADA), etanercept (ETN), and rituximab (RTX) had the highest drug survival rates for the first treatment (Table 5)

**Table 5.** Pairwise comparisons between medications: discontinuation of first treatment.

| | | Discontinuation in 1 year | | Discontinuation in 2 years | |
|---|---|---|---|---|---|
| | | RR | *p* | RR | *p* |
| Abatacept | Adalimumab | RR = 0.99 (95% CI: 0.33 - 2.94) | 0.982 | RR = 0.82 (95% CI: 0.41 - 1.64) | 0.550 |
| Abatacept | Certolizumab | RR = 0.35 (95% CI: 0.10 - 1.25) | 0.091 | RR = 0.45 (95% CI: 0.20 - 1.01) | 0.064 |
| Abatacept | Etanercept | RR = 1.29 (95% CI: 0.40 - 4.16) | 0.672 | RR = 1.39 (95% CI: 0.64 - 2.99) | 0.420 |
| Abatacept | Golimumab | RR = 0.67 (95% CI: 0.21 - 2.17) | 0.492 | RR = 0.66 (95% CI: 0.31 - 1.44) | 0.279 |
| Abatacept | Infliximab | RR = 0.68 (95% CI: 0.23 - 2.02) | 0.469 | RR = 0.86 (95% CI: 0.42 - 1.73) | 0.656 |
| Abatacept | Rituximab | RR = 0.34 (95% CI: 0.10 - 1.11) | 0.052 | RR = 0.71 (95% CI: 0.30 - 1.67) | 0.431 |
| Abatacept | Tocilizumab | RR = 1.23 (95% CI: 0.15 - 10.29) | 0.849 | RR = 0.60 (95% CI: 0.13 - 2.80) | 0.563 |
| Adalimumab | Certolizumab | RR = 0.36 (95% CI: 0.17 - 0.76) | **0.014** | RR = 0.42 (95% CI: 0.25 - 0.69) | **0.012** |
| Adalimumab | Etanercept | RR = 1.31 (95% CI: 0.73 - 2.35) | 0.367 | RR = 1.28 (95% CI: 0.83 - 1.97) | 0.246 |

**Continued**

| | | | | | |
|---|---|---|---|---|---|
| Adalimumab | Golimumab | RR = 0.68 (95% CI: 0.37 - 1.23) | 0.212 | RR = 0.61 (95% CI: 0.40 - 0.95) | **0.046** |
| Adalimumab | Infliximab | RR = 0.69 (95% CI: 0.45 - 1.04) | 0.075 | RR = 0.79 (95% CI: 0.59 - 1.06) | 0.122 |
| Adalimumab | Rituximab | RR = 0.35 (95% CI: 0.19 - 0.63) | **0.002** | RR = 0.66 (95% CI: 0.37 - 1.16) | 0.183 |
| Adalimumab | Tocilizumab | RR = 1.24 (95% CI: 0.19 - 8.06) | 0.817 | RR = 0.56 (95% CI: 0.14 - 2.25) | 0.485 |
| Certolizumab | Etanercept | RR = 3.64 (95% CI: 1.54 - 8.59) | **0.005** | RR = 3.08 (95% CI: 1.69 - 5.60) | **0.003** |
| Certolizumab | Golimumab | RR = 1.89 (95% CI: 0.79 - 4.49) | 0.170 | RR = 1.48 (95% CI: 0.81 - 2.70) | 0.256 |
| Certolizumab | Infliximab | RR = 1.91 (95% CI: 0.90 - 4.05) | 0.120 | RR = 1.90 (95% CI: 1.14 - 3.17) | 0.056 |
| Certolizumab | Rituximab | RR = 0.96 (95% CI: 0.40 - 2.30) | 0.930 | RR = 1.58 (95% CI: 0.79 - 3.19) | 0.225 |
| Certolizumab | Tocilizumab | RR = 3.46 (95% CI: 0.48 - 24.86) | 0.157 | RR = 1.33 (95% CI: 0.31 - 5.75) | 0.658 |
| Etanercept | Golimumab | RR = 0.52 (95% CI: 0.25 - 1.08) | 0.079 | RR = 0.48 (95% CI: 0.28 - 0.82) | **0.011** |
| Etanercept | Infliximab | RR = 0.53 (95% CI: 0.29 - 0.95) | **0.028** | RR = 0.62 (95% CI: 0.40 - 0.95) | **0.024** |
| Etanercept | Rituximab | RR = 0.26 (95% CI: 0.13 - 0.56) | **0.001** | RR = 0.51 (95% CI: 0.27 - 0.98) | 0.060 |
| Etanercept | Tocilizumab | RR = 0.95 (95% CI: 0.14 - 6.48) | 0.959 | RR = 0.43 (95% CI: 0.10 - 1.82) | 0.340 |
| Golimumab | Infliximab | RR = 1.01 (95% CI: 0.55 - 1.86) | 0.968 | RR = 1.29 (95% CI: 0.83 - 2.01) | 0.285 |
| Golimumab | Rituximab | RR = 0.51 (95% CI: 0.24 - 1.08) | 0.086 | RR = 1.07 (95% CI: 0.56 - 2.06) | 0.833 |
| Golimumab | Tocilizumab | RR = 1.83 (95% CI: 0.27 - 12.53) | 0.513 | RR = 0.90 (95% CI: 0.21 - 3.81) | 0.894 |
| Infliximab | Rituximab | RR = 0.50 (95% CI: 0.27 - 0.93) | **0.043** | RR = 0.83 (95% CI: 0.47 - 1.47) | 0.544 |
| Infliximab | Tocilizumab | RR = 1.81 (95% CI: 0.28 - 11.77) | 0.508 | RR = 0.70 (95% CI: 0.17 - 2.85) | 0.660 |
| Rituximab | Tocilizumab | RR = 3.60 (95% CI: 0.53 - 24.66) | 0.120 | RR = 0.84 (95% CI: 0.19 - 3.71) | 0.830 |

Furthermore, with respect to age, significant differences were found in drug retention during the first treatment ($p = 0.036$). The highest drug retention means were observed in the age group over 70 years (70 - 80 years: 67.29 months; >80 years: 67.53 months). Detailed pairwise comparisons indicated significant differences between the 70 - 80 years and 40 - 50 years groups ($p = 0.034$), as well as between >80 years and both the 40 - 50 years ($p = 0.038$) and 20 - 30 years groups ($p = 0.042$). In contrast, while individuals over 80 years seemed to have slightly lower mean drug retention in the second biological treatment, this difference was not statistically significant. Regarding sex, there were no statistically significant differences in discontinuation rates for both the first ($p = 0.81$) and second medications ($p = 0.31$).

In terms of mechanisms of action, no significant differences in drug survival were noted between the anti-TNF and non-anti-TNF groups for either the first or second biological treatment ($p = 0.517$). However, in the first treatment, pairwise comparisons showed that ADA, ETN, and IFX had lower discontinuation rates than other anti-TNF agents during the first year ($p < 0.01$).

## 4. Discussion

This study provides valuable insights into the epidemiological characteristics of rheumatoid arthritis (RA) patients undergoing biological therapy within the public health system of Espírito Santo state. Anti-TNF drugs represented the most common initial therapy, as seen in several cohorts [10]-[13]. The preference for ADA is supported by its favorable performance as an initial treatment option and its availability within the healthcare system. Key factors influencing this preference included its availability, safety profile, low incidence of side effects, lower direct

cost and better dosage convenience [10] [14]. ADA is a humanized monoclonal antibody, with lower production of anti-drug antibodies compared to IFX [15], another commonly used anti-TNF therapy.

The high prevalence of anti-TNF agents as a first and second biological therapies for rheumatoid arthritis (RA) in Brazil aligns with historical treatment patterns. For many years, anti-TNF therapies were the only biologic options available in Brazil [5] [7] [16]. Both brazilian and international treatment guidelines recommended initiating biological therapy with these agents, largely due to the existing knowledge and experience with their use in clinical practice [3] [17]. It wasn't until the end of 2015, following the publication of the Clinical Protocol and Therapeutic Guidelines (PCDT) for RA, that non-anti-TNF biologics were incorporated into the National Health System (SUS) in Brazil, including the state of Espírito Santo [18]. However, prescriptions for these newer agents were restricted to cases where the first anti-TNF treatment had failed (third line). This delay in access to non-anti-TNF medications reflects broader trends seen in the Brazilian cohort BIOBADABRASIL, which highlighted the necessity of adhering to PCDT guidelines for acquiring biological therapies [10].

The use of TNF inhibitors for treating rheumatoid arthritis (RA) has shown favorable results in your study; however, the discontinuation rate remains a concern. The observed 27.05% discontinuation rate for biological treatment aligns with findings from other studies. This discontinuation can often be attributed to various factors, including ineffectiveness (primary failure) or loss of ineffectiveness (secondary failure), adverse events, other factors such as drug shortage, pregnancy or interest of the patient [19]. The literature suggests that the discontinuation rate for the first anti-TNF therapy tends to be higher within the initial 3 - 5 years, stabilizing and becoming for those who remain on the medication for five years [20]. Additionally, evidence indicates that an increase in the number of treatment switches correlates with a heightened risk of discontinuation for any biological therapy [21].

It is plausible that while short-term efficacy among TNF inhibitors is comparable, their long-term safety and efficacy may vary significantly [22]. Although current guidelines do not rank these medications hierarchically, differences in clinical practices among them have been noted. Additionally, studies that feature larger patient populations or head-to-head comparisons are essential. These studies should also examine the duration from diagnosis to the decision to switch treatments, as this timeframe could influence overall.

Infliximab has demonstrated the lowest survival rates among the three most prescribed anti-TNF agents, as noted in several registry studies. This finding aligns with reports indicating that IFX has lower retention rates compared to ADA and ETN [10] [13] [22] [23]. The lower survival of IFX can partly be attributed to infusion reactions, which are more common due to its chimeric structure containing a murine component, resulting in increased immunogenicity [23].

Tocilizumab, though less commonly prescribed, has demonstrated the lowest discontinuation rate across all treatment lines, potentially attributed to its superior efficacy in some studies and the ability to be used in monotherapy. This

advantage may enhance patient adherence and treatment outcomes [10] [24].

Survival rates between anti-TNF and non-anti-TNF agents were found to be similar when used as first or second biological treatments. Among the anti TNF-group, ADA, ETN, IFX exhibited better retention rates, while GOL and CERT the worst. Literature comparing these two classes of biologics is limited, primarily because non-anti-TNF agents were introduced to the market later and only gained widespread acceptance as first-line treatments in RA in 2013. Recent studies, including Brazilian and Hungarian cohorts, suggest that non-anti-TNF agents may perform better than their anti-TNF counterparts [10] [21].

In terms of drug survival specifically for the anti-TNF group, ADA and ETN demonstrated similar effectiveness across multiple studies, with systematic reviews indicating modest differences in survival rates between them [22] [25] [26]. However, due to the infrequent prescription of CERT and GOL, assessing their survival curves remains challenging.

Rituximab (RTX) showed superior survival rates compared to other non-anti-TNF. According to a 2017study by Hungarian researchers, patients receiving RTX as a second-line treatment had a mean survival time of 1302 days, indicating that it outperformed both anti-TNF and non-TNF agents in this context [21]. Further supporting these findings, a 2018 study reported that more than half of the cohort treated with RTX continued their therapy after four years, highlighting its efficacy and tolerability [27].

Retention rates are similar to those reported in other studies, as is the case of the American CORRONA cohort, 85% after one year [28]; from the German RABBIT, 70% after three years [29]; and from Belgium, 50% after 4 years [30].

The preference for rituximab (RTX) in treating rheumatoid arthritis (RA) is supported by its established efficacy and safety profile in both RA and other immune-mediated diseases, such as Hodgkin's Lymphoma. As the first commercially approved non-anti-TNF biologic, RTX has been well-studied, leading to greater familiarity among clinicians. This drug is particularly beneficial in cases where anti-TNF therapies are not suitable, such as in patients with complications from visceral vasculitis or pneumonitis. Additionally, RTX has shown better outcomes in patients with more severe disease, particularly those with positive rheumatoid factor (RF). Studies suggest that it can be a viable alternative for patients who have not responded adequately to other treatments, including biologic DMARDs. Furthermore, its use in specific clinical situations underscores its versatility as a treatment option in RA management [21].

The finding that elderly individuals have longer survival times with the first anti-TNF therapy is intriguing and adds a new dimension to the understanding of treatment outcomes in rheumatoid arthritis (RA). This observation suggests that older patients may respond more favorably to anti-TNF therapy compared to younger cohorts.

Several studies have noted that younger patients often present with more severe disease and worse prognoses, which could account for the poorer performance observed in this demographic.

Moreover, the differences in treatment responses among age groups may also be influenced by various factors, including comorbidities, immune system differences, and the potential for different pharmacodynamics and pharmacokinetics in older versus younger patients.

This unique finding in your study highlights the importance of considering age as a significant factor when evaluating treatment options and outcomes in RA patients. Future research should further explore the reasons behind this disparity in treatment effectiveness to optimize therapeutic strategies for different age groups.

## 5. Conclusions

In this study on patients with rheumatoid arthritis receiving biological therapies, anti-TNF drugs were the most commonly used treatments, especially as first and second-line options, with an ADA being the most prescribed. Over a seven-year period, there were no significant statistical differences in the overall retention and survival rates of the biological therapies. Within the anti-TNF group, ADA, ETN, and IFX demonstrated better retention, while GOL and CERT had the lowest retention rates. Notably, drug retention increased among elderly patients, regardless of sex.

In terms of drug survival, ADA and ETN had better results in the first two years of treatment, while IFX and GOL exhibited worse survival rates, especially in the second year. Rituximab (RTX) was the best-performing non-anti-TNF agent in terms of drug survival. Approximately 27% of patients switched therapies due to treatment failure.

This is the first Brazilian study to examine the use of biological therapies for RA and assess drug survival in a state cohort from the public health system. The findings provide valuable insights into the selection of biological therapies and suggest areas for future research, including pharmacoeconomics and public policy on biosimilars. Future studies should focus on comparing newer biological drugs, exploring long-term outcomes, and examining the impact of different clinical scenarios on drug survival. This will help optimize treatment strategies and healthcare resource allocation for RA patients.

## Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee of the University Hospital of the Federal University of Espírito Santo (HUCAM/UFES), on March 26, 2017 (approval number 1.983.289). The terms of consent, responsibility and confidentiality for research within the scope of SESA-ES were presented and signed by the authors.

## Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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## List of Abbreviations

| | |
|---|---|
| ABAT | Abatacept |
| ADA | Adalimumab |
| Anti | TNF-Anti-Tumor Necrosis Factor |
| AR | Rheumatoid Arthritis |
| CERT | Certolizumab |
| ETN | Etanercept |
| ICD | International Classification of Diseases |
| GOL | Golimumab |
| HUCAM | Cassiano Antônio de Moraes University Hospital |
| ICD | International Classification of Diseases |
| IFX | Infliximab |
| SUS | National Health System |
| PCDT | Clinical Protocol and Therapeutic Guidelines |
| RTX | Rituximab |
| SBR | Brazilian Society of Rheumatology |
| SCPA | Specialized Component of Pharmaceutical Assistance |
| TNF | Tumor Necrosis Factor |
| TOCI | Tocilizumab |
| UFES | Federal University of Espírito Santo |