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Effectiveness and Persistence of Anti-TNFα Treatment in Patients with Rheumatoid Arthritis – A 7 Years Real-World Cohort Study

Pedro Santos-Moreno[1], Gabriel-Santiago Rodríguez-Vargas[2], Pedro Rodríguez-Linares[2], Linda Ibatá[3], Susan Martínez[3], Fernando Rodríguez-Florido[2], Adriana Rojas-Villarraga[1,4]

[1]Rheumatology Department, Biomab IPS, Bogotá, Colombia; [2]Research department, Biomab IPS, Bogotá, Colombia; [3]EpiThink Health Consulting, Bogotá, Colombia; [4]Research Institute, Fundación Universitaria de Ciencias de La Salud – FUCS, Bogotá, Colombia

Correspondence: Pedro Santos-Moreno, Rheumatology, Biomab IPS, 48th Street #13-86, Bogotá, 110221, Colombia, Tel +57 320 8094232, Email pedrosantosmoreno@hotmail.com

Purpose: To describe the effectiveness and persistence of treatment with three anti-TNFα drugs, Infliximab, Etanercept, and Adalimumab, in patients with Rheumatoid Arthritis (RA) in a rheumatology center.

Patients and Methods: A longitudinal, retrospective cohort study was conducted. Data were obtained from the health records of patients with RA who were followed up in a rheumatology center between 2011 and 2019 under a multidisciplinary healthcare model (MCM). The drugs used in this study were indicated according to the treatment guidelines for prescription. In order to follow-up of disease activity, at least three DAS28 reports for every analyzed year were used. The chi-square test and Fisher's exact test were used for statistical analyses of categorical variables. For the analysis of treatment persistence, the Kaplan–Meier method was used based on the recorded follow-up time of disease activity.

Results: One hundred and eighty-three RA patients included (80% women, median age 60 years), who received adalimumab (n = 56) (30.6%), etanercept (n = 64) (34.9%), or infliximab (n = 63) (34.4%) during the 7-year study period. A higher proportion of patients had moderate or high disease activity for all three anti-TNFα. In first-year treatment, 67% to 87% of the cohort achieved disease activity control and disease response to treatment. For the first three years, 95% to 98% of patients continued with the medications. In years 5th and 7th, the proportion of patients on medication was 80% to 90% and 42% to 54%, respectively.

Conclusion: The efficacy and persistence of anti-TNF-α were similar among the three molecules. These findings regarding long-term persistence in treatment may be useful for therapeutic decision-making based on real-life cohort results.

Keywords: rheumatoid arthritis, medication persistence, treatment effectiveness, tumor necrosis factor inhibitors

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that predominantly affects synovial joints, resulting in cartilage damage, bone erosion, and systemic consequences.[1] In addition to disability, there is reduced quality of life, and increased healthcare costs.[2] RA is predominant in women and people over 50 years of age, although it can affect any age group.[1,3] Worldwide, the prevalence of RA has been estimated at 0.3% to 1.2%.[4,5] In Colombia, the prevalence varies from 0.27% to 1.2%.[3]

The gold standard of treatment in RA is "Treat-to-Target" (T2T), with the goal of achieving and maintaining remission, or at least achieving low disease activity, usually measured by DAS28.[6,7] Achieving remission depends on factors such as the therapeutic strategy, type of drug, and patient characteristics.[6] When there is no response to conventional treatments, biological disease-modifying antirheumatic drugs (bDMARDs), especially tumor necrosis factor inhibitors (anti-TNFα), are used to achieve remission or low disease activity.[8] Infliximab, etanercept, and adalimumab account for approximately 90% of anti-TNFα prescriptions for RA.[9] Despite the benefits of treatment with biological

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agents, a significant proportion of patients do not respond to management or experience adverse events; therefore, these patients require more expensive treatments.[10]

Treatment persistence can be used as an indicator of effectiveness, safety, and patient satisfaction with long-term therapy.[11,12] Medication persistence refers to the duration from initiation to discontinuation of therapy, and differs from medication compliance (adherence).[13] Several publications have described medication persistence as an important component of treatment effectiveness in daily clinical practice.[12] In some rheumatic diseases, less persistence with anti-TNF-α has been described due to comorbidities that led to switching to a second anti-TNF-α or another biological.[14–16] Other reasons for discontinuing or changing biological agents were decreased benefits (36 to 67%), perceived harm (30 to 58%),[12] and the availability of drugs with alternative mechanisms of action.[14]

Some studies have analyzed the persistence of anti-TNF-α for rheumatic diseases, but they are generally 2- or 3-year follow-up studies, and additionally, very few of these studies have been conducted in real settings in Latin America.[11,17] This study aimed to describe the persistence of treatment with three anti-TNFα agents, infliximab, etanercept, and adalimumab, and their effectiveness in patients with RA in a specialized rheumatology center in Bogotá, Colombia. This approach can help decision-makers or payers guide treatment choices with knowledge about medication use and real expectations about outcomes.

Patients and Methods

Study and Population Design

This longitudinal, retrospective cohort study was conducted in a specialized center for the management of RA in Colombia based on a multidisciplinary healthcare model that comprised of a team that included rheumatologists, general physicians, physical and rehabilitation medicine, nutritionists, psychologists, occupational therapists, nurses, pharmaceutical chemists, and physiotherapists by periodical appointments. Consultations are provided monthly or every two/three months, depending on disease activity, as indicated by the treat-to-target (T2T) strategy,[6,18] in which patients must have more frequent rheumatologist appointments depending on disease activity. This strategy and healthcare model are supported by international and national guidelines.[19,20]

Institutional databases from January 2011 to December 2019 were used to select patients undergoing bDMARD treatment with adalimumab, etanercept, and infliximab, regardless of disease activity and duration of bDMARDs use before entering the study. The database was obtained from the review of electronic health records during the study period. Baseline of the study was from January 2011 until December 2019. Patients from 2020 to 2022 were omitted from the analysis because of treatment disruptions resulting from the COVID-19 pandemic, which could introduce reporting biases. It is noteworthy that the patients included in the analysis might or might not have previously received bDMARD treatment, and their treatment initiation may not align with the start of the study in January 2011. All the participants were diagnosed with RA according to the 2010 ACR/EULAR classification criteria.[21] Similarly, all patients at the time of study entry were already receiving anti-TNFα therapy. Treatment was prescribed based on daily clinical practice, physician criteria, and the national recommendations for the treatment of RA.[19]

The drugs used in this study were indicated with standard dosage as follows: adalimumab 40 mg subcutaneously every 15 days, etanercept 25 mg subcutaneous 2 times a week, and infliximab 3 mg/kg body weight intravenously every 8 weeks (according to guidelines).[7] Anti-TNF-α therapies were used as monotherapy or in combination with different csDMARDs (methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, and chloroquine). Patients receive other drugs to control disease activity, such as corticosteroids, deflazacort, methylprednisolone, or prednisolone at minimal doses. Other occasional useful drugs to control the symptoms included nonsteroidal anti-inflammatory drugs, COX2 inhibitors or opioids (Supplemental Table 1). The reasons for drug discontinuation at the end of the persistence period were not captured and/or analyzed during the study.

For data recording and follow-up, the age, sex, disease seropositivity, concomitant medication use, and RA disease activity were recorded for each patient. For follow-up of disease activity, at least three DAS28 reports for every year analyzed were considered. Drug discontinuation was considered when patients exceeded 30 days without the drug, according to institutional protocols.[22] The reasons for discontinuation of therapy were not recorded.

Outcomes Analysis

Treatment effectiveness was assessed using the absolute value of Disease Activity Score-28 joints (DAS28)[23] and in the following disease activity groups: remission (DAS28 <2.6), low disease activity (DAS28≥ 2.6 <3.2), moderate disease activity (DAS28 ≥3.2 and <5.1), and high disease activity (DAS28 ≥5.1). Changes in disease activity in the response and control groups were assessed. Response was defined as a reduction in DAS28 > 1.2 from the baseline level of disease activity according to the EULAR response criteria. Disease control was defined as an achievement of DAS28 <3.2, that is, low disease activity or remission.[24] Persistence was defined as the duration from the initiation to discontinuation of anti-TNFα therapy.

Data Analysis

The frequencies and proportions of baseline characteristics were calculated for each treatment group and the overall population. Differences in disease activity between treatment groups were also estimated. Disease activity for each year of follow-up, as a continuous variable, was evaluated as non-normal according to the Kolmogorov–Smirnov test; therefore, the analyses were performed using the Wilcoxon test for related samples. The chi-square test and Fisher's exact test were used for statistical analyses of categorical variables. For the analysis of treatment persistence, Kaplan–Meier analysis was used based on the recorded follow-up time of disease activity. A subgroup analysis was performed for each anti-TNF-α molecule with respect to the use of methotrexate, other csDMARDs, combination therapy, and steroids.

For all tests, statistical significance was set at $p < 0.05$. R software was used for all statistical calculations.

Ethics Approval and Informed Consent

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Research Ethics Committee on Human Beings, Hospital de San José, Bogota, Colombia (Record 0317–2021, June 1st 2021). In Colombia, this type of retrospective observational study without patient contact is considered of minimal risk. Therefore, it does not require informed consent. Nevertheless, an authorization for the use and analysis of the data was taken from each patient. The confidentiality of the patients' data was guaranteed, as the names were not included in the forms or database.

Results

There were 183 RA patients included, who received adalimumab (n = 56) (30.6%), etanercept (n = 64) (34.9%), or infliximab (n = 63) (34.4%) during the 7-year study period. Most patients were women (8 of 10 subjects), and the median age of all subjects included in the study was 60 years (range, 25–87 years), with no statistically significant differences between the groups analyzed. Seropositive RA was predominant in all treatment groups, and the proportion of seronegative RA in infliximab users was higher than in the other groups (23.8% vs 12.5% with adalimumab and 7.8% with etanercept; the difference was not significant) (Table 1). Some of the patients did not complete their follow-up period due to administrative issues such as transfers of affiliation to another insurer, death of the patient, lost in follow-up, etc.

The baseline state of disease activity, assessed using DAS28, differed between the treatment groups (p = 0. 032), with a higher proportion of patients in moderate or high disease activity among those receiving infliximab (73%) and a lower proportion in the adalimumab group (57.2%) and etanercept group (42.2%) (Table 1).

The drug-free permitted interval was less than 20–25 days in the entire cohort (according to a previous definition, when patients exceeded 30 days without the drug, it was considered a disruption in persistence). The analysis of drug persistence showed a similar trend for the three anti-TNFα drugs evaluated (Figure 1). For the first three years, 95% to 96% of adalimumab patients continued with the medication, 97% to 98% of infliximab patients continued with the medication, and 94% to 97% of the etanercept group persisted with the anti-TNF-α medication (p = 0.124 at year 3). At year 5 the proportion of patients continuing medication was 80% to 90% (numerically lower for adalimumab and higher for infliximab, p-value 0.29 for the difference between groups). Higher rates of medication discontinuation were evident in subsequent years; half of patients with anti-TNFα drugs were persisting with medication by year 7 (42% for

Table 1 Baseline Characteristics in Patients with RA and Anti-TNFα Therapy

	Overall n=183	Adalimumab n=56	Etanercept n=64	Infliximab n=63	p value*
Age, years. Median (Range)	60 (25 to 87)	58, 5 (30 to 77)	64 (32 to 87)	57 (25 to 76)	0.623
Sex, Female. n (%)	147 (80, 3)	44 (78, 6)	52 (81, 3)	51 (81)	0.923
Diagnosis					0.127
Seropositive RA. n (%)	156 (85, 2)	49 (87, 5)	59 (92, 2)	48 (76, 2)	
Seronegative RA. n (%)	27 (14, 8)	7 (12, 5)	5 (7, 8)	15 (23, 8)	
Disease activity, DAS28					0.032
Remission. n (%)	49 (26, 8)	17 (30, 4)	22 (34, 4)	10 (15, 9)	
LDA. n (%)	29 (15, 8)	7 (12, 5)	15 (23, 4)	7 (11, 1)	
MDA. n (%)	72 (39, 3)	23 (41, 1)	19 (29, 7)	30 (47, 6)	
HDA. n (%)	33 (18, 0)	9 (16, 1)	8 (12, 5)	16 (25, 4)	

Notes: *Chi-square test was performed. DAS28, Disease activity score – 28 joints count.
Abbreviations: HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity.

etanercept, 48% for adalimumab and 54% for infliximab, p value 0.41 for difference between groups). Median treatment persistence for the groups was 88 months (95% CI 87.3 to 88.7), 87 months (95% CI 86.2 to 87.8) and 89 months (95% CI 88.4 to 89.6) for adalimumab, etanercept, and infliximab, respectively.

In the analysis of effectiveness, a reduction in disease activity, measured by DAS28, was observed in all three groups evaluated, particularly in the first 2 years of therapy and was maintained over time for up to 7 years (Figure 2). In the first year of treatment, 67% to 87% of the cohort patients achieved disease activity control and disease response to treatment (Table 2). Subjects receiving etanercept therapy showed higher rates of treatment response (up to 94%) and disease control (up to 95%) in the second and third years of biological use. Response rates and disease control in each cohort were maintained after 5 and 7 years of treatment, respectively (Tables 2 and 3).

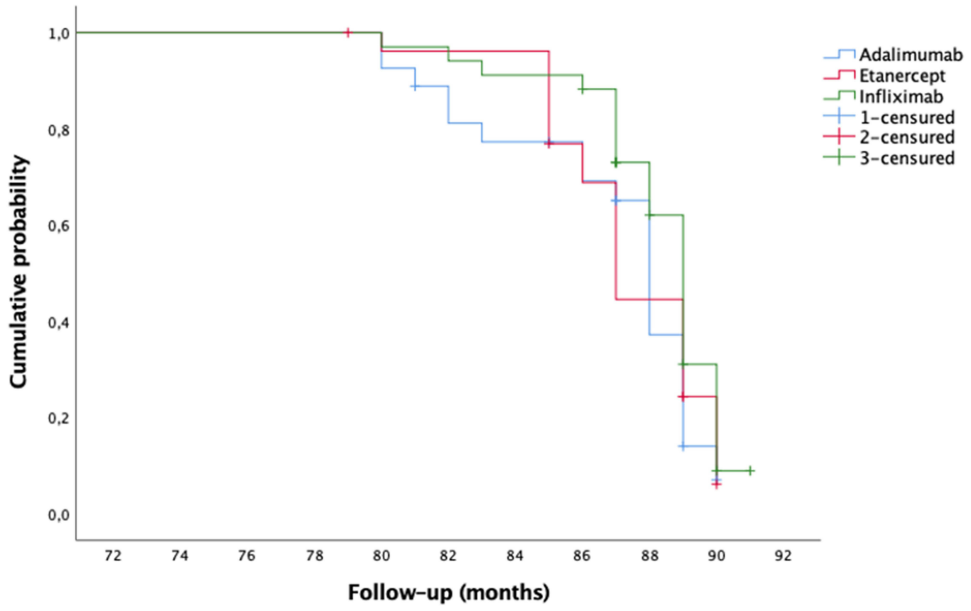

Figure 1 Persistence in anti-TNFα therapy in patients with rheumatoid arthritis until year 7.

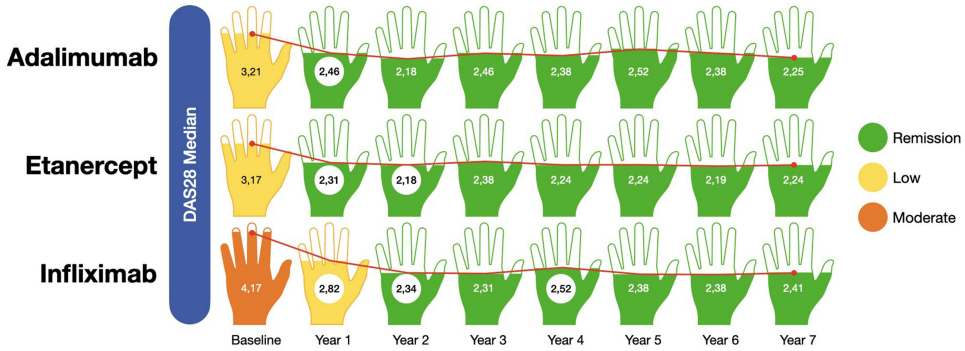

Figure 2 Disease activity evolution with three different anti-TNFα therapies along 7 years.

In the subgroup analysis, there were no significant differences in disease response in the three anti-TNFα cohorts regarding the use of csDMARDs (methotrexate, chloroquine, hydroxychloroquine, leflunomide, and sulfasalazine) or csDMARD combination therapy (Supplemental Table 1). Steroid use was associated with lower response rates until year 5 in the adalimumab group and up to year 7 in the etanercept group. (Supplemental Table 1).

Discussion

The results of this study show that treatment with traditional anti-TNF-α therapy maintains effectiveness and disease activity control until the fifth year of life. The persistence in treatment was sustained throughout the sixth year and was preserved in half of the patients at year seven without differences between the three molecules in patients with RA under a multidisciplinary health care model. These findings may be useful for therapeutic decision-making based on real-life results regarding disease activity outcomes and persistence.

Table 2 Disease Activity Control in Patients with RA in Three Different Anti-TNF, at 7 Years

	Follow Up by Year						
	1	2	3	4	5	6	7
Adalimumab	45 (83%)	44 (81%)	46 (87%)	46 (87%)	39 (87%)	29 (88%)	25 (93%)
Etanercept	49 (82%)	59 (95%)	58 (91%)	58 (92%)	49 (91%)	35 (92%)	23 (85%)
Infliximab	41 (67%)	51 (82%)	54 (87%)	50 (82%)	45 (79%)	40 (93%)	28 (82%)

Notes: Control of disease activity was defined as a measurement of DAS 28 <3.2.

Table 3 Response to Treatment in Patients with RA in Three Different Anti-TNFα, at 7 Years

	Follow Up by Year						
	1	2	3	4	5	6	7
Adalimumab	45 (81%)	44 (78%)	46 (70%)	46 (86%)	39 (80%)	29 (82%)	25 (78%)
Etanercept	49 (80%)	59 (94%)	58 (91%)	58 (82%)	49 (81%)	35 (79%)	23 (81%)
Infliximab	41 (74%)	51 (74%)	54 (77%)	50 (65%)	45 (74%)	40 (84%)	28 (74%)

Notes: Response to treatment was defined as a decreasing in disease activity ≥1, 2 from baseline according to EULAR response criteria.[24]

The use of anti-TNF-α agents has increased in Colombia in recent years. A descriptive observational study described the use of anti-TNFα in a cohort of 316 patients, with a mean age of 44.6 (SD ±13.9 years). The most commonly used drugs were adalimumab (37.3%), infliximab (37.3%) and etanercept (25.4%). Of the patients, 10.4% had a record of adverse drug reactions.[25] According to the 2019 National Rheumatoid Arthritis Registry,[3] the country treated 81,386 patients with RA and 13,588 patients were using biologics. About 22.5% used etanercept, 10.24% adalimumab, and 1.43% infliximab. However, this registry does not indicate the persistence time of specific treatments.

Different studies have reported similar persistence with different anti-TNF-α agents,[11] comparable to the present study, without significant differences in persistence between non-naïve infliximab, adalimumab, and etanercept prescribed in RA patients. This could reflect similarities in the benefits and harms of the three drugs despite their different pharmacological properties. Dos Santos et al, shown in a prospective cohort study of bDMARD-naïve patients with anti-TNFα, there is an 80% of persistence at 6th month and more than 60% of these patients persisted with treatment at 12th month. The benefits of anti-TNF-α therapy were shown in the HAQ, EQ-5D, and CDAI, which improved with respect to its previous use.[26] According to our results, the persistence of biologic treatment during the first year could be due to the fact that the patients evaluated in our study were non-naïve to biologics, while the study by Dos Santos evaluated only naïve patients. Other study written by Fisher et al[12] concluded that persistence with infliximab, adalimumab, and etanercept is similar in patients with RA, considering that the benefits and harms of the drugs could be considered equivalent, and the decision for their use could include the convenience and cost of RA treatment.[12] For example, infliximab is administered intravenously, whereas adalimumab and etanercept are administered subcutaneously (SC) and can be self-administered; therefore, their indication is influenced by physician and patient preference for this route of administration.[11]

Previous results have shown that persistence may not be a relevant factor when selecting an anti-TNFα agent in patients with RA because of the different factors involved in treatment adherence.[12] Some studies, such as those by Machado et al,[27] showed a general trend of higher rates of therapy persistence with anti-TNFα as compared to csDMARDs in a study period that comprised 5 years and analyzed 11,642 Latin American (ie, Brazilians) RA patients. However, some studies in Latin America showed poor persistence of medication at 2 years of follow-up, perhaps due to variation in management protocols in some specific populations, factors that influence drug administration, and may be related to the study methodology.[28]

The study by Svedbom et al[11] showed that patients treated with their first subcutaneous anti-TNFα had greater persistence than patients treated with a second subcutaneous anti-TNFα in psoriatic arthritis (PsA) ($p = 0.036$), RA ($p = 0.048$), and all combined diagnoses ($p < 0.001$). Patients treated with a second subcutaneous anti-TNFα therapy had higher costs than those treated with their first anti-TNFα therapy, so it may be beneficial to prescribe anti-TNFα therapy with the best long-term persistence. Similar results were found by Prior-Español et al,[29] who showed that survival for first-line treatment was greater in all three groups evaluated, including RA, PsA, and ankylosing spondylitis patients analyzed from the BIOBADASER registry, which recruited patients from 28 large public hospitals throughout Spain.

On the other hand, a study by Acar et al[30] described a variation in actual persistence to anti-TNFα in patients with immune-mediated rheumatic disease, with a median treatment persistence of 18 months (95% CI 13 to 22) for adalimumab and 15 months (95% CI 12 to 20) for etanercept. Persistence was shorter when anti-TNF-α was given second-line, with a median of 12 months for adalimumab (95% CI, 10 to 16) and 9 months for etanercept (95% CI, 6 to 15). In this study, the median persistence rates with anti-TNFα were higher, probably in relation to the close follow-up in a multidisciplinary program in a specialized center.

Regarding the causes of nonpersistence, one study described lack of efficacy (64%), the presence of adverse events (28%), and poor adherence (8%). The adverse events reported in this study were injection site reactions, upper respiratory tract infections, hepatotoxicity, adverse skin reactions, and flu-like syndrome.[31] In the BIOBADASER registry,[29] it were shown that RA patients had a greater risk of bDMARDs discontinuation if they were younger, if they were receiving anti-TNFα therapy (as compared with the group receiving other bDMARDs), and if they had more comorbid conditions. Similar results were shown in a systematic literature review by Murage et al,[22] where younger age, female sex, higher out-of-pocket costs, greater disease severity, and more comorbidities were associated with lower bDMARDs adherence and persistence rates. The Aaltonen network meta-analysis[32] concluded that the addition of anti-TNF-α agents (adalimumab, etanercept,

infliximab, golimumab, and certolizumab) increased the risk of discontinuation of therapy for any adverse event. However, they also found that etanercept was the safest treatment option. A previous study by our group showed similar results and reported other adverse events, including dermatitis, blood pressure elevation, and herpes zoster.[33] Adverse event rates have been reported, in order, with infliximab (24 events per 100 persons per year; 95% CI, 19 to 29), adalimumab (22 per 100 persons per year; 95% CI, 18 to 27), and etanercept (12 events per 100 persons per year; 95% CI, 8 to 16) meaning etanercept is likely the safest.[33] Evidence has shown that non-persistence in first-line anti-TNFα therapy in RA is associated with higher costs. Persistent patients significantly reduced their costs related to medical care and disability due to illness over the same period. Therefore, future studies should analyze the cost-effectiveness of non-persistence in the use of biologics.[34]

The limitations of the present study are related to the observational design in which data were obtained from institutional medical records, and treatment effectiveness may be influenced by various factors in actual practice. In addition, we did not analyze the association between treatment effectiveness, medical persistence, and comorbidities, as has been pointed out in other studies. Another limitation of this study is that we did not consider the health literacy and socioeconomic status of patients, which could influence the levels of adherence and persistence of medications. On the other hand, we did not analyze the association between the persistence level of anti-TNFα and the concomitant use of methotrexate, which, in another study, methotrexate addition was associated with bDMARDs persistence. In addition, since patients were not naïve, we did not analyze the repercussions of the use of previous biologics in the study. This may have repercussions in other treatments. An additional weakness of the study is that the reasons for drug discontinuation (neither patients who had therapeutic failure nor adverse events related to the drug) were collected, and it is important to analyze the adverse effects of the drugs, as shown in the article by Dos Santos et al,[26] in order to demonstrate changes in persistence secondary to these adverse effects. Second, we did not measure the impact of the multidisciplinary healthcare model on the results, but showed that when a model was carried out, it could improve the effectiveness and persistence of treatment.

Conclusion

The analysis of the effectiveness and persistence of anti-TNF-α drugs showed a similar trend for the three agents evaluated, consistent with previous studies. These findings may be useful for evaluating the best therapeutic option in terms of treatment persistence and disease control for more than 5 years.

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