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Original Investigation

Effectiveness and safety in the management of chronic inflammatory diseases with etanercept and infliximab biosimilars in Colombian patients

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ABSTRACT

Objective: To determine the effectiveness and safety of infliximab and etanercept biosimilar drugs in patients diagnosed with rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, and psoriasis in a specialized institution in Colombia, between 2015 and 2019.
Methods: A retrospective study in patients treated with infliximab and etanercept biosimilar drugs treated in an institution specializing in the management of rheumatological diseases, to verify the clinimetric indicators of effectiveness and reports of adverse drug reactions. Clinical, sociodemographic, and pharmacological variables were identified over 5 years of follow-up.
Results: 207 patients were identified with a mean age of 48.7 ± 15.1 years, 61.4% were women. Of the patients, 58.0% (n = 120) used infliximab and 42.0% (n = 87) etanercept. It was found that 46 (22.2%) patients had adverse drug reactions. At the end of the observation period, 61.6% (n = 72) of the patients with RA had achieved control of the disease (mild activity or remission), and 57.9% (n = 117) had problems with access to and persistence with therapy.
Conclusion: In a group of patients treated in Colombia, the biosimilars of infliximab and etanercept showed proportions of effectiveness and safety comparable to the reference drugs, but lack of adherence to treatment was quite common.

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Efectividad y seguridad en el manejo de enfermedades inflamatorias crónicas con medicamentos biosimilares de etanercept e infliximab en pacientes colombianos

Palabras clave:
Biosimilares farmacéuticos
Infliximab
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Artritis reumatoide
Colombia

RESUMEN

Objetivo: Determinar la efectividad y la seguridad de medicamentos biosimilares de infliximab y etanercept en pacientes con diagnóstico de artritis reumatoide, espondilitis anquilosante, colitis ulcerativa y psoriasis en una institución especializada de Colombia, entre los años 2015 y 2019.

Métodos: Estudio retrospectivo, en pacientes tratados con infliximab y etanercept biosimilares, atendidos en una institución especializada en el manejo de enfermedades reumatológicas, para verificar los indicadores clinimétricos de efectividad y reportes de reacciones adversas medicamentosas. Se identificaron variables clínicas, sociodemográficas y farmacológicas durante cinco años de seguimiento.

Resultados: Se identificaron 207 pacientes, con una edad media de 48,7 ± 15,1 años, el 61,4% de los cuales eran mujeres. El 58,0% (n = 120) de los pacientes utilizó infliximab y el 42,0% (n = 87) etanercept. Se encontró que 46 (22,2%) pacientes presentaron reacciones adversas al medicamento. Al final del periodo de observación, un 61,6% (n = 72) de los pacientes con AR había alcanzado el control de la enfermedad (actividad leve o remisión), y, en general, el 57,9% (n = 117) tuvo problemas de acceso y persistencia a la terapia.

Conclusión: En un grupo de pacientes tratados en Colombia, los biosimilares de infliximab y etanercept mostraron proporciones de efectividad y seguridad comparables a los medicamentos de referencia, pero fue bastante común la falta de adherencia al tratamiento.

Introduction

Diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriasis, and ulcerative colitis are chronic inflammatory conditions of immunological etiology[1–4]. Some of them are also degenerative and progressive; the vast majority involve functional limitations due to deformities and are associated with both organic and psychological comorbidities[5].

Traditionally, chronic inflammatory diseases have been treated with nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs), to induce remission of symptoms, reduce the frequency of flares or relapses, and allow the gradual reduction of glucocorticoid use, while maintaining disease control[1,6,7].

There is a group of drugs called biological ARDs (bARDs), developed thanks to advances in biotechnology, which have the advantage of being highly effective in the remission of symptoms and preventing disease progression. The indication to start biological therapy depends on patient evolution and the degree of disease activity[1,3,8].

However, these drugs are considerably more expensive compared to conventional therapies, making patient access difficult[9]. However, when the patent for the innovative drug expires, a group of similar biotherapeutic drugs, known as biosimilars, opens, which can be produced and marketed after being approved by drug regulatory agencies, once they have demonstrated similar quality, efficacy, safety, and immunogenicity as the innovator or reference product[10].

Since 2007, the World Health Organization (WHO) has recognized and approved the use of biosimilars to increase availability and reduce access barriers and treatment costs per person[8]. In Colombia, there are 37 biosimilars authorized by the National Institute for Food and Drug Surveillance (INVIMA), including infliximab and etanercept biosimilars, useful in the treatment of some inflammatory diseases[4,10,11].

One of the disadvantages of biologics compared to synthetics is their greater immunogenicity, with the potential to develop antibodies against the drug that affect its effectiveness and safety. In certain circumstances, they can even cause adverse events such as host hypersensitivity, which affects their safety profile[12,13]. Therefore, we sought to determine the effectiveness and safety of infliximab and etanercept biosimilars in subjects treated for rheumatoid arthritis (RA), ankylosing spondylitis, ulcerative colitis, and psoriasis, in a specialized institution in different cities in Colombia, from 2015 to 2019.

Methods

A retrospective cohort study of patients treated at the Audifarma SA Specialized Service Provider Institution (S-SPI) –a care and treatment center for patients with certain rheumatic diseases in 13 different cities in Colombia– who had a diagnosis of rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, or psoriasis, according to the International Classification of Diseases version 10 (ICD-10), and who were also receiving drug treatment between January 1, 2015, and May 31,

2019, with infliximab (Remsima®) and etanercept (Etanar®) biosimilars.

A database was built from the clinical and dispensing records of each patient. The following groups of variables were considered:

1 Sociodemographic: age, sex, city of residence.
2 Anthropometric measures: weight, height, body mass index (BMI).
3 Clinical: diagnosis according to ICD-10 code for rheumatoid arthritis (M068, M069, M052, M053, M058, M059, M060), ankylosing spondylitis (M45X, M468, M469), ulcerative colitis (K51), and psoriasis (L40, L400, L401, L405, L408, L409), recorded by the attending physician in the medical chart and on the prescription.
4 Paraclinical: Complete blood count (hemoglobin and hemoleukogram), C-reactive protein, erythrocyte sedimentation rate, transaminases (ALT and AST), creatinine, rheumatoid factor (RF), and anti-citrulline antibodies.
5 Drug therapy: a) Conventional DMARDs (methotrexate, leflunomide, chloroquine, hydroxychloroquine, sulfasalazine, etc.); b) biosimilar ARDs (infliximab and etanercept); and c) glucocorticoids (prednisone, deflazacort, etc.). The duration of therapy, dose, and dosing interval were identified.
6 Therapy effectiveness: Measurement of the Disease Activity Score (DAS28) for rheumatoid arthritis, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for ankylosing spondylitis, the Psoriasis Area Severity Index (PASI) for psoriasis, and the American College of Gastroenterology Ulcerative Colitis Activity Index for ulcerative colitis, at the beginning and the end of the follow-up. The therapy was considered effective (low activity) with DAS28 < 3.2, and as remission criteria DAS28 ≤ 2.6 in patients with rheumatoid arthritis, a BASDAI < 4 in those with ankylosing spondylitis, a PASI < 5 in cases of psoriasis, and a mild Ulcerative Colitis Activity Index or in remission for those with ulcerative colitis. For monitoring, the level of activity at the beginning and end of the study period (remission or low, moderate, or high activity) was considered for each patient, during the time they were using infliximab or etanercept biosimilars. Clinimetry records were collected by the treating specialist physician at follow-up visits.
7 Security: Identification of reports of adverse events recorded by the treating physician in the clinical history, associated with infliximab and etanercept biosimilars, as well as reports from the pharmacovigilance system of S-SPI and Audifarma SA. The type of adverse drug reaction was included (ADR), according to the Rawlins and Thompson classification (A: increased pharmacological effect, B: bizarre effects or effects not related to the pharmacological effect, C: related to the time of use and dose, D: delayed, E: due to withdrawal, F: therapeutic failure), in addition to the WHO ADR probability classification (definitive, probable, possible, unlikely, conditional, not evaluable). This classification of the registered adverse events is carried out by the pharmaceutical chemist of the pharmaceutical care/pharmacovigilance program of the S-SPI and Audifarma SA, who analyzes each case of suspected ADR, classifies it, and reports it to the regulatory agencies and the treating physician.
8 Therapeutic failure: it was considered for those patients who did not achieve remission or low activity (previous failures), three months after beginning the biosimilar; no difference was established between primary or secondary therapeutic failure[14].
9 Changes: any occasion in which a drug was replaced by another; the frequencies of change and the reason for doing so were recorded.
10 Non-adherence: postponement of the drug application for more than seven days after the stipulated date, according to the dosing interval of the infliximab and etanercept biosimilar. This definition was taken mainly to evaluate the persistence of continuous use and possible administrative problems for access to therapy.
11 Comorbidities were identified, according to ICD-10 diagnostic codes: arterial hypertension, heart failure, dyslipidemia, chronic obstructive pulmonary disease, diabetes mellitus, osteoporosis, other autoimmune diseases, tuberculosis, fibromyalgia, hypothyroidism, and chronic gastritis.

Data were analyzed using the statistical package SPSS Statistics version 25.0 for Windows (IBM Corp., Armonk, NY, USA). Univariate descriptive analyzes were performed with frequencies and proportions for the categorical variables and measures of central tendency and dispersion for quantitative.

The protocol was approved by the Bioethics Committee of the Universidad Tecnologica de Pereira, under the category of "risk-free research"; the principles established by the Declaration of Helsinki were respected. In addition, informed consent was obtained from the patients.

Results

A total of 207 patients were identified on treatment with infliximab and etanercept biosimilars, whose mean age was 48.7 ± 15.1 years (range = 10–85), of whom 127 (61.4%) were women. The city with the largest number of patients was Bogota (n = 106, 51.2%). Mean weight was 65.4 ± 13.5 kg, height 161 ± 12 cm, and BMI 25.4 ± 3.9 kg/m2.

Most patients had rheumatoid arthritis (n = 110, 53.1%), followed by ankylosing spondylitis (n = 70, 33.8%), ulcerative colitis (n = 12, 5.8%), and psoriasis (n = 3, 1.4%); the remaining 12 subjects presented a combination of some of the above diseases. The supplementary table shows the sociodemographic and paraclinical variables distributed by diagnosis.

The main comorbidities identified were osteoporosis (n = 58; 28%), arterial hypertension (n = 55; 26.5%), osteoarthritis (n = 50; 24.1%), dyslipidemia (n = 44, 21.2%), latent tuberculosis (n = 41, 19.8%), fibromyalgia (n = 21, 10.1%), and diabetes mellitus (n = 19, 9.1%). Some complications were documented such as fatty liver (n = 4; 1.9%), uveitis (n = 3; 1.4%), and hearing loss (n = 2; 0.9%).

Regarding drugs administered, 57.9% (n = 120) of the individuals used the infliximab biosimilar and 42.1% (n = 87) the etanercept biosimilar. Table 1 depicts the patterns of use of biosimilars, as well as the frequency of use of other conven-

Table 1 – Medications used in 207 patients with rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, and psoriasis in a specialized institution in Colombia between 2015–2019.

Medication	Number of		Dose (mg)			Dose frequency		Duration (months)	
	patients	%	Mean	SD	DDD		%[a]	Mean	SD
Infliximab*	120	57.1	284.5	±76.8	NA	8 weeks	54.2	79.85	±46.64
Rheumatoid arthritis	42	35.8	283.8	±76.3	NA	8 weeks	48.8	82.07	±46.79
Ankylosing spondylitis	67	56.6	284.9	±77.1	NA	8 weeks	58.8	78.89	±46.84
Ulcerative colitis	15	11.6	284.6	±76.8	NA	8 weeks	57.1	79.85	±46.64
Psoriasis	7	5.8	281.8	±76.7	NA	8 weeks	28.5	84.64	±46.59
Etanercept	87	42.9	44.7	±10.2	NA	Weekly	83.3	55.3	±32.29
Rheumatoid arthritis	72	82.2	44.7	±10.3	NA	Weekly	85.1	55.2	±32.45
Ankylosing spondylitis	13	13.3	44.8	±10.2	NA	Weekly	83.3	54.1	±32.00
Ulcerative colitis	1	1.1	50	NA	NA	Weekly	100.0	67	NA
Psoriasis	2	2.2	50	±10.5	NA	Weekly	100.0	59.7	±23.94
DMARD									
Methotrexate	108	51.4	13.3	±5.8	0.76	Weekly	100.0		
Prednisone	73	34.8	7.5	±7.03	0.75	QD	100.0		
Leflunomide	63	30	20	±0	1	QD	100.0		
Sulfasalazine	54	25.7	1,120.3	±399.7	0.56	BID	68.5		
Deflazacort	20	9.5	8.4	±3.01	0.56	QD	100.0		
Chloroquine	18	8.6	188.8	±50.1	0.37	QD	100.0		
Azathioprine	13	6.2	108.3	±66.8	0.72	BID	50.0		
Mesalazine	10	4.8	1,940	±625.7	1.29	TID	40.0		
Hydroxychloroquine	5	2.4	200	±0	0.38	QD	100.0		

SD: Standard deviation; DDD: Defined daily dose; NA: Not applicable; DMARD: Disease-modifying antirheumatic drug; QD: Daily; BID: Twice a day; TID: Three times a day.

[a] Proportion of patients receiving the medication in the recommended dosing interval.

* n value may be higher, because the patients are categorized by disease, in such a way that a patient with a double diagnosis was counted in the frequency of each disease.

Table 2 – First medication switch in a group of patients with antirheumatic therapy modification with etanercept and infliximab biosimilars during the effectiveness and safety follow-up in S-SPI from Colombia 2015–2019.

Biosimilar	*Infliximab*						
Disease	n (%)	Switch	n (%)			n	%
Rheumatoid arthritis	12 (41,4)	Adalimumab	3 (25,0)	Reason for switch	Therapeutic failure	20	9,52
		Certolizumab	2 (16,6)		ADR	4	1,9
		Golimumab	2 (16,6)		Increased activity	2	0,95
		Other DMARD	9 (75,0)		Patient request	1	0,48
		Total	12 (100,0)		Total	**27**	12,86
Ankylosing spondylitis	9 (31,0)	Certolizumab	2 (22,2)				
		Secukinumab	2 (22,2)				
		Otros ARME	5 (55,5)				
		Total	9 (100,0)				
Biosimilar	Etanercept						
Disease	n (%)	Switch	n (%)			n	%
Rheumatoid arthritis	11 (64,7)	Certolizumab	4 (36,3)	Reason for switch	Therapeutic failure	9	4,29
		Abatacept	2 (18,2)		ADR	4	1,9
		Other DMARD	5 (45,4)		Increased activity	2	0,95
		Total	11 (100,0)		Medical order	3	1,43
Ankylosing spondylitis	2 (11,7)	Secukinumab	1 (50,0)		Non-specified	1	0,48
		Golimumab	1 (50,0)		Total	19	9,05
		Total	2 (100,0)				

S-SPI: Specialized Service Provider Institution; DMARD: Disease-modifying antirheumatic drug; ADR: adverse drug reaction.

tional DMARDs and immunomodulators in general, according to each diagnosis. In addition, therapy changes could be identified during follow-up; in rheumatoid arthritis and ankylosing spondylitis, there were changes from infliximab and etanercept to another bARD; Table 2 also shows the main reasons for this change.

In general, it was possible to identify that 61.6% of the patients with rheumatoid arthritis were in low activ-

Table 3 – Follow-up and disease control scales in patients treated with infliximab biosimilar 2015–2019. Initiation and end of follow-up.

Patients treated with biosimilar infliximab/disease	Number of patients	Low activity/ remission-beginning of follow-up		High/moderate activity		Low activity/ remission-end of follow-up		High/moderate activity-end of follow-up	
		Start of follow-up							
	n = 120*	N	%	n	%	n	%	n	%
Rheumatoid arthritis	42	18	42.8	24	57.2	22	52.3	20	47.6
Ankylosing spondylitis	67	42	62.6	25	37.4	45	67.2	22	32.8
Ulcerative colitis	15	3	20.0	12	80.0	15	100	0	0
Psoriasis	7	4	57.1	3	42.8	4	57.1	3	42.8

Disease index	Initial mean	SD	Final mean	SD
DAS 28	3.35	±1.56	3.55	±1.42
BASDAI	3.65	±2.51	2.54	±2.13
PASI	24.75	±22.20	15.32	±16.78

* Patients with available data on initial and final disease activity. The n value may be higher because patients are categorized by disease in such a way that a patient with a double diagnosis was counted in the frequency of each disease.

Table 4 – Follow-up and disease control scales in patients treated with etanercept biosimilar 2015–2019. Initiation and end of follow-up.

Patients treated with etanercept biosimilar /disease	Number of patients n = 87*	Low activity/ remission-beginning of follow-up		High/moderate activity		Low activity/remission		High/moderate activity	
		Start of follow-up				End of follow-up		End of follow-up	
		no	%	no	%	no	%	no	%
Rheumatoid arthritis	72	45	62.5	27	37.5	51	70.8	21	29.2
Ankylosing spondylitis	13	8	61.5	5	38.5	7	53.8	6	46.2
Ulcerative colitis	1	1	100	0	0	1	100	0	0
Psoriasis	2	0	0	2	100	0	0	2	100

Disease index	Initial mean	SD	Final mean	SD
DAS 28	3.13	±1.61	2.92	±1.27
BASDAI	3.99	±2.29	3.34	±2.23

* Patients with available data on initial and final disease activity. The n value may be higher because patients are categorized by disease in such a way that a patient with a double diagnosis was counted in the frequency of each disease.

ity/remission at the end of the observation period, as well as 72.5% of the patients with ankylosing spondylitis, and 100% of the subjects with ulcerative colitis. Table 3 presents the results of effectiveness and clinimetry for the infliximab biosimilar and Table 4 illustrates the data for the etanercept biosimilar.

In those cases treated with infliximab (n = 120), it was possible to establish that 20 of them (16.6%) were on monotherapy, while the remaining 100 (83.4%) received combined therapy, more commonly with methotrexate (n = 35; 29.2%), sulfasalazine (n = 16; 13.3%), and methotrexate plus sulfasalazine (n = 7; 5.8%). In those on monotherapy with the infliximab biosimilar with rheumatoid arthritis (n = 4), therapy effectiveness was identified, going from a mean DAS28 of 4.93 to 2.71 points; In addition, it was found that two patients with high activity moved down to mild activity and remission. In patients managed with the etanercept biosimilar (n = 87), it was established that 11 (12.6%) received monotherapy, while the remaining 76 (87.4%) were treated with combinations of DMARDs, more frequently with methotrexate (n = 23; 25.6%) and leflunomide (n = 16; 17.8%). In those individuals with RA on monotherapy with the etanercept biosimilar (n = 3), therapy effectiveness was identified, going from a mean DAS28 of 2.94 to 2.47 points; all patients ended in mild activity and remission.

In the clinical records or the S-SPI pharmacovigilance program, a total of 74 reports of ADRs were identified in 58 patients (28.0%), the most frequent being respiratory and constitutional symptoms in patients receiving infliximab, and skin hypersensitivity reactions in those receiving etanercept. Table 5 shows the frequency, the type of ADR, and the causality classification; in addition, it is interesting to note that 12 infections associated with the use of these drugs occurred: pneumonia, latent tuberculosis, and sepsis. Regarding latent tuberculosis, this was only identified in a patient with rheuma-

Table 5 – Reports of adverse reactions related to infliximab and etanercept biosimilars, their classification according to causality, and the type of reaction in a group of patients treated at a specialized institution in Colombia 2015–2019.

	Medications		
	Infliximab	Etanercept	n (%)
Adverse reactions			
Constitutional	14	0	14 (18.9)
Cardiorespiratory	15	2	17 (23.0)
Headache and nausea	6	0	6 (8.1)
Musculoskeletal pain	5	3	8 (10.8)
Gastrointestinal	3	1	4 (5.4)
Infection	9	3	12 (16.2)
Rash/skin reactions	8	5	13 (17.6)
Total	60	14	74 (100.0)
Causality			
Definitive	1	0	1 (1.4)
Possible	30	7	37 (50.0)
Likely	29	7	36 (48.6)
Total	60	14	74 (100.0)
ADR type			
A (increased)	52	11	63 (85.1)
B (bizarre or unrelated with the pharmacological effect)	7	3	10 (13.5)
C (use time)	1	0	1 (1.4)
Total	60	14	74 (100.0)

ADR: Adverse drug reaction.

toid arthritis who was in remission and receiving etanercept, which was identified and switched to certolizumab.

Likewise, 57.9% (n = 120) of the individuals were not adherent to therapy during treatment, the main causes being personal situations that prevented attendance to controls or the application of the medication (n = 53; 25, 6%), administrative problems in insurance companies (n = 50; 24.1%), and the occurrence of ADR (n = 6; 2.8%).

Discussion

This analysis was able to determine infliximab and etanercept biosimilars effectiveness and safety in real-life conditions, in patients with specific autoimmune and autoinflammatory diseases. This information is useful for the healthcare decision-making of these subjects (insurers, service providers, and physicians), as it provides useful data of high-cost medications and clinical results in routine practice in subjects with rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, and psoriasis.

Rheumatoid arthritis and ankylosing spondylitis patients' distribution by age and sex is consistent with that reported in Colombia[15] and a meta-analysis by Graudal et al., based on 36 randomized studies of biosimilars in patients with rheumatoid arthritis[16].

Several patients were found with a diagnosis of simultaneous autoimmune diseases and one (0.5%) with the triple association of rheumatoid arthritis, psoriasis, and Crohn's disease, complying with polyautoimmunity criteria (two or more diseases)[17]. It has been reported in patients with rheumatoid arthritis that up to 13.6% of them during follow-up met criteria for another autoimmune diagnosis such as Sjögren's syndrome and systemic lupus erythematosus[18]. The use of etanercept and infliximab biosimilars in groups of patients with polyautoimmunity is an interesting finding in this analysis, since these patients are infrequently enrolled in clinical trials, and it is relevant for new studies to be able to establish whether there are differences in effectiveness or safety in patients with prescriptions for any of the drugs included in these subpopulations.

The effectiveness of etanercept and infliximab biosimilars is expected to be comparable to that of reference drugs in the management of rheumatoid arthritis, as reported by Choe et al. in 2017, who showed that they were effective in approximately 60% of the cases, like current study, being especially high (up to 70.8% of remission/low activity) in subjects treated with etanercept (Table 4) [19–22]. However, when analyzing the average DAS28 follow-up scale for patients with rheumatoid arthritis, the data at the beginning and end of the follow-up were very similar, as presented in Table 4, but an increase of 20% was evident in the proportion of cases with low activity/remission between the beginning and the end of follow-up.

An increase of up to 67.2% in the number of patients with ankylosing spondylitis in remission could be observed, as well as an average reduction of more than one point in the BASDAI activity score during follow-up in patients treated with the infliximab biosimilar, like other cohorts of patients with biosimilars, such as Ji et al.[23], who found an average decrease of 0.6 in activity scores in those individuals with biosimilars, compared to the group without therapy, difference statistically significant[23], and comparable to patients treated with reference infliximab[24].

The results in patients with ulcerative colitis, despite the low number of cases, showed that 20% of patients with remission at the beginning of the observation period, moved at the end of the follow-up period with low activity or remission, which is an indicator of adequate response to therapy. The

study by Rutgeerts et al. established the efficacy of innovative infliximab in ulcerative colitis and showed low activity or remission between 61 and 64% of patients, depending on the dose used, a condition that was met in all subjects in this cohort with the infliximab biosimilar[25], data consistent with the reported literature, which shows a positive experience like the innovative drug in inflammatory bowel disease[26].

The most used dose of etanercept was 50 mg/week, and 300 mg every eight weeks for infliximab, which is consistent with the usual recommended doses for these medications[27–29]. It was also possible to establish that these biosimilars were frequently combined with different DMARDs, being the most common methotrexate, leflunomide, and sulfasalazine, a situation that can be explained by the importance of combined therapy to achieve control[27,29], as well as superior effectiveness than monotherapy in different rheumatic disorders[28].

Among the different rheumatic diseases evaluated, therapeutic failures of infliximab and etanercept biosimilars were reported, overall, in 13.8% of the patients[30,31], below the reported from other studies, in which, for example, in ankylosing spondylitis, at 12 months, 30.3% of the cases had discontinued the bARD for different reasons[23]. The effectiveness, in general, has remained similar in patients treated with the reference etanercept and the biosimilar; changes in therapy, including therapeutic failures, have been explained by patient-related factors, rather than to the drug[32], added to other factors that may limit effectiveness, such as barriers to access to therapies or lack of patient adherence[33].

During follow-up, medical records reports of ADRs were searched, and it was found that 27.6% of the individuals reported some, mainly associated with infliximab. This prevalence is similar to the reported by Santos-Moreno et al.[34] in a Colombian cohort of patients with rheumatoid arthritis, who found an incidence of 20.3% each year, more commonly in patients receiving innovative infliximab, compared with those treated with innovative and biosimilar etanercept and, in addition with other therapies, like adalimumab or golimumab[34]; however, the most frequently reported ADRs in the literature were rash and dermatitis, associated with general hypersensitivity to anti-TNF-alpha[35,36]. This finding differs from the current study. in which cardiorespiratory events such as tachycardia, dyspnea, chest pain, palpitations, and hypertension were the most common for infliximab, a situation that can be explained by the recording and identification of the ADRs during its application in infusion rooms, in which the health team can identify the appearance of any ADR, contrary to etanercept, which is self-administered subcutaneously, and the patient may not always report or identify ADRs. It is also possible that some patients do not report mild ADRs because they underestimate their importance, which leads to underreporting. No other types of severe ADRs were found to be associated with the use of bARD, such as neutropenia, application site infections, heart failure, or malignancies, possibly explained by its low frequency of appearance in the population treated with anti-TNF-alpha, as well as by the limited number of patients included in the study, which made its identification during the observation period unlikely[37,38].

Poor adherence to pharmacological treatment of autoimmune inflammatory diseases is associated with less effectiveness in their control[39]. In this study, it was evidenced that 57.1% of the patients did not receive the medication promptly during follow-up, mainly due to personal difficulties that avoid timely application, as well as administrative problems of the insurer, which can make access difficult to these high-cost therapies. These findings are consistent with those published by Rincón et al.[39], who identified that the main reasons for poor adherence and lack of persistence to drug treatment in patients with rheumatoid arthritis were difficulties in access and availability of the drug, the use of medication for long periods, and the appearance of related ARDs[39].

It is important to identify some limitations of this study, typical of observational analyses, including the fact that medical records could be found with incomplete records, without data on effectiveness, follow-up, or reporting of possible adverse reactions, so underreporting could not be ruled out in some of these data that avoid an adequate estimation of the activity during visit follow-up. Treatment failures were not differentiated into primary or secondary. Only patient adherence was considered, without contemplating the duration of non-adherence or the number of times with application delays. The small sample size, especially in ulcerative colitis and psoriasis, made it difficult to draw conclusions or make more in-depth analyzes in these cases. The conclusions, according to the findings can be extrapolated only in populations with similar insurance features. However, the study has important strengths, such as the close follow-up carried out by the service-providing institution to the patients using infliximab and etanercept biosimilars, as well as the follow-up data collected in most cases, providing useful information for decision-making and management optimization of this type of subjects.

Finally, it can be concluded that therapy with anti-TNF-alpha with infliximab and etanercept biosimilars in individuals with rheumatoid arthritis and ankylosing spondylitis, showed comparable effectiveness and safety results with different published studies, and in those patients with ulcerative colitis, psoriasis, or polyautoimmunity, with small sample sizes, it was possible to identify the response to therapy, adding knowledge in the use of these therapies in real life. This pharmacoepidemiological approach to these bARD in Colombia offers a starting point for new studies and the expansion of knowledge on the subject so that the necessary tools can be provided to make decisions that improve access to this type of therapy.

Ethical considerations

In addition, informed consent of the patients was obtained.

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Conflict of interests

The authors declare that they have an absence of any conflict of interest for the preparation of this manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.rcreue.2021.05.002.

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