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ORIGINAL ARTICLE - HEALTH SERVICES RESEARCH

Real-world cost-effectiveness of infliximab, etanercept and adalimumab in rheumatoid arthritis patients: results of the CREATE registry

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Abstract Biological drugs have proven efficacy and effectiveness in treatment of rheumatoid arthritis (RA), although none has been shown to be superior. Few studies have evaluated the cost-effectiveness of biological drugs in real-life clinical conditions. The objective of this study was to compare the cost-effectiveness of infliximab, etanercept and adalimumab in achieving clinical remission (DAS28 < 2.6) when used as initial biological therapy. Patients were diagnosed with RA who began treatment with infliximab, etanercept or adalimumab in the Reina Sofia Hospital (Cordoba, Spain) between January 1, 2007, and December 31, 2012. Effectiveness was measured as the percentage of patients who achieved clinical remission after 2 years. The cost analysis considered the use of direct health resources (perspective of the healthcare system). Cost-effectiveness was calculated by dividing the total mean cost of each treatment by the percentage of patients who achieved remission. One hundred and thirty patients were included: 55 with infliximab, 44 with adalimumab and 31 with etanercept. After 2 years, 45.2 % of patients with adalimumab achieved clinical remission, versus 29.1 % with infliximab ($p = 0.133$) and 22.7 % with etanercept ($p = 0.040$), with no differences between etanercept and infliximab ($p = 0.475$). The average total cost at 2 years was €29,858, €25,329 and €23,309 for adalimumab, infliximab and etanercept, respectively, while the mean cost (95 %CI) to achieve remission was €66,057 (48,038–84,076), €87,040 (78,496–95,584) and €102,683 (94,559–110,807), respectively. Adalimumab was more efficient than etanercept ($p < 0.001$) and infliximab ($p = 0.026$), with no differences between etanercept and infliximab ($p = 0.086$). Adalimumab was the most cost-effective treatment in achieving clinical remission in real-life clinical conditions in RA patients during the study period.

Keywords Rheumatoid arthritis · Biological drugs · Cost-effectiveness · Real-life clinical conditions

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by pain, chronic inflammation and joint destruction. In most cases, the course is progressive and leads to irreversible joint damage, resulting in functional impairment, reduced quality of life and premature mortality [1–3]. Recently, however, the development of biological therapy has been an important advance in the treatment of this disease, which is helping to change its prognosis.

The goal of RA treatment is to control pain and inflammation, minimize joint damage and disability, control extra-articular manifestations, improve patients' quality of life and achieve disease remission or at least sustained low clinical activity [4, 5].

Eight biological drugs, with different mechanisms of action, are currently available in Spain: infliximab, etanercept, adalimumab, golimumab and certolizumab pegol,

which are blockers of tumor necrosis factor alpha (anti-TNF); rituximab, an anti-CD20 monoclonal antibody; abatacept, a T cell co-stimulation modulator; and tocilizumab, an interleukin-6 receptor inhibitor. All these drugs have proven efficacy [6–15], as well as an adverse effect profile that requires they be closely monitored, resulting in a major economic impact on the healthcare system.

Although the Andalusian Health Service has a protocol establishing the clinical criteria for initiation of biological therapy [16], and despite recommendations of the Spanish Society of Rheumatology (SER) and the European League Against Rheumatic Diseases (EULAR) [4, 5] establishing the importance of adjusting treatment until remission is achieved, there is no evidence on the preferred drug for initial therapy given the lack of comparative studies to evaluate whether one is more efficacious, safe or efficient than the others [4, 17]. This situation persists despite the major economic impact of these drugs [18, 19] and the fact that it is now considered necessary to incorporate economic aspects when developing clinical practice guidelines [20].

Some studies have described the use of biological drugs as a cost-effective intervention in different scenarios [21], but they do not show which drug is most efficient. Studies are also needed on the cost-effectiveness ratio of biological medications, given that clinical trials [22] represent only part of the general population and do not include cost data adjusted to the actual resources available [23–25].

Given the current economic crisis and the need to adjust healthcare budgets, it is desirable to know which initial therapy is most efficient in clinical practice from the hospital point of view, in order to select the drug that can best fit the available budget while achieving the best possible health outcomes.

The main objective of this study was to compare the cost-effectiveness of three anti-TNF-alpha drugs used as initial biological therapy (infliximab, etanercept or adalimumab) over a 2-year period, from the perspective of the healthcare system. Secondary objectives were to compare drug survival (median time to treatment change), perform a multivariate analysis to identify possible predictive variables of response and, finally, to describe the main adverse effects registered.

Methods

Patients

The data for this study were taken from the registry of the multidisciplinary Team for RA in the Reina Sofia University Hospital, Córdoba, Spain (CREATE Registry). The CREATE registry is a prospective database that systematically includes each patient with inflammatory rheumatoid disease who begins treatment with biological therapy. For each patient diagnosed with RA, information is collected on demographics, disease characteristics, previous treatments used, their duration and reason for suspension, current treatment and its duration, data on disease activity [number of tender joints (NTJ), number of swollen joints (NSJ), erythrocyte sedimentation rate (ESR), C-reactive protein (PCR) and the disease activity score (DAS28)], patient data that could influence treatment, biological drug chosen and concomitant treatment. Each patient is followed up prospectively to monitor the clinical variables collected and any adverse effects that may occur.

From this registry, we selected all patients diagnosed with RA who began biological treatment with infliximab, etanercept or adalimumab in our hospital between January 1, 2007, and December 31, 2012, with 2-year follow-up per patient. The study was limited to this subgroup because these are the three drugs most frequently used as initial therapy in the CREATE registry and are the only ones for which we had 2-year follow-up data after treatment initiation.

RA is diagnosed in accordance with the 1987 ACR criteria, based on the medical history, physical examination, complementary tests (blood count, biochemistry, presence of antibodies), chest and joint radiography and clinical assessment of disease activity using the DAS28.

All patients had to follow the Andalusian Health Service treatment protocol for biological therapies, based on the SER [5] and EULAR [4] recommendations. To begin biological treatment, patients had to have active RA despite treatment for at least 3 months with at least two of the following drugs at the maximum authorized doses: methotrexate, leflunomide or sulfasalazine. The initial biological treatment is selected based on the characteristics of each patient and drug, as well as the cost of each drug to the hospital. In the absence of any limiting constraints (inability to attend the day hospital or to self-administer treatment, or the presence of intestinal inflammatory disease for which biological treatment with infliximab is indicated), the lowest cost drug was used.

Effectiveness

The effectiveness of treatment in actual practice was evaluated by the DAS28 [26]. A value lower than 2.6 was considered clinical remission (CR), and less than 3.2 was considered a low disease activity state (LDAS). The percentage of patients who achieved CR and LDAS was determined.

In addition to the DAS28, we evaluated its components separately: NTJ, NSJ, ESR, CRP and patient global assessment (PGA) on a visual analog scale.

Data were collected on patients' sociodemographic characteristics (age and sex), date of disease diagnosis, and

clinical data including rheumatoid factor (RF±) and previous and concomitant treatments with disease-modifying antirheumatic drugs (DMARDs). The demographic and clinical data on patients were obtained mainly from the CREATE registry and also from the database of the Andalusian Health Service.

Analysis of resources and costs

Two scenarios were considered. *Scenario 1* The cost analysis was made from the perspective of the healthcare system, taking into consideration the use of the following direct health resources: cost of purchasing the drug [ex-factory price (EFP)], consultations with specialists in rheumatology, use of emergency services, complementary tests performed, need for hospitalization and use of the day hospital for intravenous drug administration. The use of resources includes consideration of the health care derived from the RA process as well as any adverse effects that may have occurred. *Scenario 2* In this analysis, the only costs taken into account were the EFP costs.

Data on drug use were obtained from the databases of the Hospital Pharmacy Department. In the case of infliximab, which is dosed by weight, the cost was adjusted to the milligrams actually employed since individual doses are prepared in the Pharmacy Department, avoiding drug wastage. The remaining resources consumed were obtained from the database of the reports manager of the Reina Sofia Hospital and from the Andalusian Health Service database for patients diagnosed with RA and treated with biological agents.

The cost of each drug was obtained using the official EFP, and the costs of the other resources were obtained from the price catalog of the Economics Directorate of the Reina Sofia Hospital (2014, in euros).

Periodically, the Hospital Pharmacy Department negotiates with laboratories discounts on the purchase price of these biologicals. In the absence of any clinical criteria or patient characteristic affecting the choice of anti-TNF (intestinal disease, impossibility of going to the day hospital, etc.), the drug with the lowest cost of acquisition for the hospital was chosen. This situation encouraged competition among laboratories in sales price and discounts to the hospital on the direct market cost of these drugs. An additional cost calculation was performed for scenario 2, using the negotiated purchase price of the drugs in the hospital, to quantify the savings achieved with this negotiation compared to the EFP.

Cost-effectiveness

The cost-effectiveness of each drug was calculated by dividing the average total cost of each treatment by the percentage of patients who achieved CR. This value shows the cost per patient reaching CR with each drug and can identify the most efficient one in actual clinical practice for decision making.

The same analysis was also repeated for the effectiveness outcome "achieving LDAS" and considering as costs only the official purchase price of the drugs dispensed.

Statistical analysis

A descriptive study was conducted, calculating the mean and standard deviation for quantitative variables, and absolute and relative frequencies for qualitative variables. An intention-to-treat analysis was made for each treatment branch.

The bivariate analysis of qualitative variables was made using the Chi-square test or Fisher's test for 2×2 tables with any expected frequency less than 5. Quantitative variables were compared using Student's t test for independent data, simple ANOVA test and one-way ANOVA. Levene's test was used previously to test the homogeneity of variances, and, depending on the results of this test, post hoc comparisons were conducted using the Hochberg or Games–Howell tests. For data that were not normally distributed, we used the Mann–Whitney U test or the Kruskal–Wallis H test.

All comparisons were two-sided and were considered significant for values of $p < 0.05$. The data were processed, tabulated and analyzed using SPSS v17 software.

Using the Kaplan–Meier survival analysis procedure, we examined the distribution of time to effect for the three different medications. The comparison tests showed that there was no statistically significant difference between them.

We built a multiple logistic regression (MLR) model to identify the baseline clinical factors predictive of remission. We previously conducted univariate logistic regressions to establish the association between each of the potentially predictive variables and CR. The degree of association was estimated by the odds ratio (OR) and Cornfield's 95 % confidence interval. The variables that showed an association in the univariate analysis at $p < 0.25$ [age in years, age at diagnosis, RF, NSJ at baseline, baseline DAS28, baseline ESR (mm/1 h) and baseline CRP (mg/dL)] were introduced in the MLR model. Based on the Wald statistic, variables with $p \geq 0.15$ were eliminated one by one from the model (backward selection procedure). The scale of continuous variables was assessed by the Box–Tidwell test. Possible interactions between the variables were studied based on whether there was a significant change in the log-likelihood value after introducing the interaction in the model. Variables with $p > 0.05$ were evaluated as possible confounding factors. Cooks' distance was used as the diagnostic test

Table 1 Patient characteristics at baseline

Baseline characteristics*	Total population ($n = 130$)	Infliximab ($n = 55$)	Etanercept ($n = 44$)	Adalimumab ($n = 31$)	p**
Sex (female)	82.3 %	80 %	81.81 %	87.09 %	NS
RF+	75.4 %	69.1 %	79.5 %	80.6 %	NS
Age (years)	53.0 ± 13.6	51.5 ± 12.7	55.1 ± 14.0	52.9 ± 14.7	NS
Weight (kg)	74.6 ± 15.8	74.8 ± 15.9	72.3 ± 19.6	72.0 ± 18.7	NS
Age at diagnosis (years)	44.0 ± 13.7	43.3 ± 11.4	45.9 ± 16.0	42.7 ± 14.3	NS
Time since diagnosis (years)	9.0 ± 7.1	8.0 ± 6.4	9.4 ± 7.3	10.2 ± 7.9	NS
Initial DAS28	5.7 ± 1.0	5.7 ± 1.1	5.8 +1.1	5.7 ± 0.9	NS
Initial NTJ28	10.4 ± 6.4	9.6 ± 6.3	11.2 ± 6.6	10.5 ± 6.4	NS
Initial NSJ28	7.1 ± 4.9	6.9 ± 5.0	7.7 ± 5.2	6.6 ± 4.2	NS
Initial ESR	33.2 ± 17.7	33.6 ± 18.2	33.9 ± 19.4	31.5 ± 14.4	NS
Initial CRP	19.2 ± 17.7	19.3 ± 17.2	21.3 ± 21.4	16.1 ± 12.0	NS
Initial PGH	69.9 ± 16.8	71.4 ± 49.6	69.6 ± 19.2	67.8 ± 16.4	NS

CRP C-reactive protein, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate *NTJ* number of tender joints, *NSJ* number of swollen joints, *NS* not significant, *PGA* patient global assessment, *RF* rheumatoid factor

* Data expressed as percentage or mean ± standard deviation

** Statistical significance based on Chi-square test (sex and RF) and simple ANOVA test (rest of variables)

for outliers. The Hosmer–Lemeshow statistic was used to assess the goodness of fit.

The study was approved by the Ethical Committee of the Reina Sofia University Hospital.

Results

Between January 1, 2007, and December 31, 2012, a total of 130 patients in the CREATE registry who began treatment with biological therapy for the first time were included in the study: 55 with infliximab, 44 with etanercept and 31 with adalimumab. Baseline patient characteristics are shown in Table 1. No statistically significant differences were found between persons in the groups taking infliximab, etanercept or adalimumab.

Effectiveness

Adalimumab was more effective than etanercept in attaining CR after 2 years, but was not significantly different from infliximab. There were no differences between infliximab and etanercept.

The percentage of patients who achieved LDAS at 2 years was higher with adalimumab than with infliximab, with no differences for the rest of the possible comparisons. No differences were found for any of the secondary variables of effectiveness (Table 2).

Analysis of resources and costs

No significant differences were found in the volume of non-drug resources used, except for a significantly higher use of magnetic resonance imaging (MRI) with adalimumab than with infliximab, and greater use of the day hospital for infliximab compared with etanercept and adalimumab, due to its route of administration (Table 3).

The same as with resources, no significant differences were found in the total cost or in any cost components, except for a higher cost of MRI in the adalimumab arm and of the day hospital for infliximab (Table 4). The main cost component comes from the cost of purchasing the drugs, which averaged about 83 % of the total cost.

Cost-effectiveness

Scenario 1: Direct health costs

The average cost per patient of reaching CR at 2 years of treatment, taking into account direct health costs, was €83,522.99 (95 % CI 76,209.84–90,836.43). The most efficient drug in achieving CR was adalimumab, which was significantly superior to both infliximab and etanercept. No differences were found between infliximab and etanercept.

When LDAS was considered as the effectiveness outcome, the most efficient drugs were adalimumab and etanercept, both of which were superior to infliximab, but not significantly different from each other (Table 5).

Table 2 Comparative effectiveness at 2 years

	Total population	Infliximab (I)	Etanercept (E)	Adalimumab (A)	*p***
Primary variables					
% Patients with DAS28 < 2.6 (CR)	30.8 %	29.1 %	22.7 %	45.2 %	A versus E = 0.040 A versus I = NS E versus I = NS
% Patients with DAS28 < 3.2 (LDAS)	56.2 %	47.3 %	54.5 %	74.2 %	A versus E = NS A versus I = 0.015 E versus I = NS
Secondary variables*					
DAS28	3.3 ± 1.1	3.4 ± 1.2	3.3 ± 1.0	2.9 ± 1.1	NS
NTJ28	1.9 ± 2.7	2.1 ± 3.2	1.7 ± 2.3	1.6 ± 2.3	NS
NSJ28	1.1 ± 2.0	1.2 ± 2.2	1.0 ± 1.8	0.8 ± 1.7	NS
ESR	22.5 ± 14.8	22.4 ± 14.4	25.4 ± 16.1	18.7 ± 13.0	NS
CRP	8.2 ± 11.3	8.9 ± 12.2	8.7 ± 11.8	5.9 ± 8.9	NS
PGA	42.6 ± 23.3	44. 5 ± 22.8	45.7 ± 22.8	34.7 ± 24.1	NS

CR clinical remission, *CRP* C-reactive protein, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *LDAS* low disease activity state, *NPJ* number of tender joints, *NSJ* number of swollen joints, *NS* not significant, *PGA* patient global assessment

* Mean ± standard deviation

** Statistical significance based on Chi-square test (primary variables) and simple ANOVA test (secondary variables)

Table 3 Comparison of resources used (mean number of units used per patient at 2 years ± standard deviation)

Non-drug resources*	Total population	Infliximab (I)	Etanercept (E)	Adalimumab (A)	*p***
Consultations	13.5 ± 3.6	14.1 ± 3.5	12.8 ± 3.4	13.6 ± 4.1	NS
Rheumatology	13.2 ± 3.3	13.8 ± 3.1	12.5 ± 3.3	13.2 ± 3.7	NS
Emergency services	0.3 ± 0.6	0.3 ± 0.7	0.3 ± 0.6	0.4 ± 0.6	NS
Complementary tests	23.1 ± 10.4	23.8 ± 11.2	20.5 ± 5.5	25.3 ± 13.5	NS
Laboratory	13.6 ± 4.8	14.2 ± 4.9	12.6 ± 3.3	14.0 ± 6.1	NS
Total CT	0.3 ± 0.9	0.3 ± 0.9	0.02 ± 0.15	0.5 ± 1.3	NS
MRI	0.2 ± 0.5	0.07 ± 0.32	0.1 ± 0.3	0.6 ± 0.7	ANOVA = 0.021 A versus I = 0.019 Rest NS
Radiological tests	8.8 ± 6.6	9.0 ± 6.8	7.5 ± 5.5	10.2 ± 7.3	NS
Ultrasound scans	0.3 ± 0.5	0.3 ± 0.6	0.2 ± 0.5	0.2 ± 0.4	NS
Days of hospitalization	2.6 ± 19.1	1.6 ± 6.8	0.1 ± 0.9	8.0 ± 38.0	NS
Day hospital	6.4 ± 7.2	13.0 ± 4.3	1.5 ± 4.7	1.6 ± 4.40	ANOVA < 0.001 I versus A < 0.001 I versus E < 0.001 A versus E = NS

ANOVA analysis of variance, *CT* computed tomography, *MRI* magnetic resonance imaging, *NS* not significant

* Mean ± standard deviation

** Statistical significance based on simple ANOVA test; if ANOVA < 0.05, then the Hochberg test for multiple comparisons was calculated

Scenario 2: Only drug costs

When cost-effectiveness was analyzed considering only the cost of purchasing the drugs as direct health costs, adalimumab was again statistically more efficient in achieving CR than either etanercept or infliximab, while infliximab was in turn more cost-effective than etanercept.

Considering LDAS as the effectiveness outcome, adalimumab was the most efficient of the three agents, with no differences between infliximab and etanercept (Table 5).

Savings to the public health system

The price negotiations between the Hospital Pharmacy Department and the drug manufacturers resulted in a

Table 4 Comparative costs (€) at 2 years

Source of costs	Total population		Infliximab (I)		Etanercept (E)		Adalimumab (A)		*p**
	Mean (95 % CI)	% Cost (%cum.)	Mean (95 % CI)	% Cost (%cum.)	Mean (95 % CI)	% Cost (%cum.)	Mean (95 % CI)	% Cost (%cum.)	
Cost of consultations	819.5 (780.4–858.7)	3.2 % (3.2 %)	847.6 (787.2–908.1)	3.3 % (3.3 %)	778.0 (716.9–839.1)	3.3 % (3.3 %)	828.7 (734.0–923.4)	2. 8 % (2.8 %)	NS
Rheumatology	779.6 (748.0–811.2)		810.8 (765.0–856.5)		740.6 (686.4–794.8)		779.6 (705.0–854.3)		NS
Emergency services	40.0 (25.4–54.2)		36.9 (13.4–60.3)		37.4 (13.1–61.8)		49.1 (20.5–77.6)		NS
Complementary tests	949.2 (883.5–1015)	3.7 % (6.9 %)	983.4 (879.0–1088)	3.9 % (7.2 %)	862.0 (802.3–921.6)	3.7 % (7.0)	1012.6 (820.1–1205)	3.4 % (6.2 %)	NS
Laboratory	850.9 (798.8–903.0)		884.5 (801.5–967.6)		790.2 (726.8–853.6)		877.4 (736.5–1018)		NS
CT	16.7 (5.7–27.7)		22.0 (2.2–41.8)		1.9 (–1.9–5.7)		28.3 (−2.5–59.0)		NS
MRI	13.5 (6.8–20.2)		6.1 (−1.3–13.4)		11.4 (2.6–20.2)		29.4 (7.9–51.4)		ANOVA = 0.021 A versus I = 0.019 Rest = NS
Simple X-ray	61.1 (53.2–69.1)		62.6 (49.9–75.4)		52.2 (40.5–63.9)		71.0 (52.2–89.7)		NS
Ultrasound	7.1 (4.6–9.6)		8.1 (3.8–12.4)		6.3 (1.9–10.8)		6.3 (2.0–10.6)		NS
Cost of hospitalization	1668.5 (421.6–3759)	6.5 % (13.4 %)	1020.3 (144.4–2185)	4.0 % (11.2 %)	86.0 (87.4–259.4)	0.4 % (7.4 %)	5064.7 (3720–13,850)	17.0 % (23.2 %)	NS
Day hospital	801.2 (647.6–954.7)	3.1 % (16.5 %)	1593.8 (1429–1.759)	6.3 % (17.5 %)	249.8 (68.4–431.2)	1.1 % (8.5 %)	177.3 (17.9–336.8)	0.5 % (23.7 %)	ANOVA < 0.001 A versus I < 0.001 E versus I < 0.001 Rest = NS
Total non-drug costs	4238 (2105–6372)	16.5 %	4445 (3228–5662)	17.5 %	1976 (1650–2302)	8.5 %	7083 (1871–16,037)	23.7 %	NS
Drug cost at EFP	21,487 (20,232–22,742)	83.5 %	20,884 (18,535–23,232)	82.5 %	21,333 (19,532–23,135)	91.5 %	22,774 (20,564–24,98)	76.3 %	NS
Total	25,725 (23,473–27,978)	100 %	25,329 (22,842–27,815)	100 %	23,309 (21,465–25,153)	100 %	29,858 (21,713–38,002)	100 %	NS

%cum. % cumulated, *ANOVA* analysis of variance, *CT* computed tomography, *EFP* ex-factory price, *MRI* magnetic resonance imaging, *NS* not significant

* Statistical significance based on simple ANOVA test; if ANOVA < 0.05, then the Hochberg test for multiple comparisons was calculated

savings to the public health system (in relation to the EFP) of €343,346, which represented 10.27 % of the EFP.

Drug survival

Over 50 % of the patients in each treatment branch maintained their initial treatment at the end of 2-year follow-up (median exposure time for the three groups was 23.98 months). The discontinuation rates were very similar: 21.8 % (for infliximab), 20.5 % (for etanercept) and 22.6 % (for adalimumab), with no significant differences between them (Chi-square test, $p = 0.974$).

Multivariate analysis

The multivariate analysis of patient clinical and demographic variables identified sex and ESR value as factors predictive of remission. The rest of the potential variables considered were eliminated one by one from the analysis. For the same ESR, the probability of achieving remission

Table 5 Comparative cost-effectiveness at 2 years

Variable (95 % CI) Value expressed in €	Total population Mean (95 % CI)	Infliximab (I) Mean (95 % CI)	Etanercept (E) Mean (95 % CI)	Adalimumab (A) Mean (95 % CI)	*p**
Scenario 1 (all direct health costs)					
Cost per patient in remission (DAS28 < 2.6)	83,523 (76,210–90,836)	87,040 (78,496–95,584)	102,683 (94,559–110,807)	66,057 (48,038–84,076)	ANOVA < 0.001 A versus E < 0.001 A versus I = 0.026 I versus E = NS
Cost per patient in LDAS (DAS28 < 3.2)	45,774 (41,766–49,782)	53,549 (48,292–58,805)	42,769 (39,385–46,153)	40,240 (29,263–51,216)	ANOVA = 0.005 A versus E = NS A versus I = 0.013 I versus E = 0.029
Scenario 2 (considering as direct costs only the EFP of acquiring the drug)					
Cost per patient in remission (DAS28 < 2.6)	69,762 (65,688–73,836)	71,765 (63,694–79,835)	93,979 (86,044–101,915)	50,386 (45,497–55,275)	ANOVA < 0.001 A versus E ≤ 0.001 A versus I ≤ 0.001 I versus E ≤ 0.001
Cost per patient in LDAS (DAS28 < 3.2)	38,233 (35,999–40,465)	44,151 (39,186–49,116)	39,144 (35,839–42,449)	30,693 (27,715–33,672)	ANOVA < 0.001 A versus E < 0.001 A versus I < 0.001 I versus E = NS

ANOVA analysis of variance, *DAS* disease activity score, *LDAS* low disease activity state, *EFP* ex-factory price, *NS* not significant

* Statistical significance based on simple ANOVA test and for post hoc tests: Hochberg test in scenario 1 and Games–Howell in scenario 2

was 3.6 times lower in women than in men [OR 0.28 (95 % CI 0.08–0.98)]. For the same sex, the probability of achieving remission decreased 5 % for each unit increase in the ESR value [OR 0.95 (95 % CI 0.92–0.99) (Hosmer–Lemeshow test, $p = 0.477$)].

Safety

The safety analysis took account of both the 130 patients included in the study and the fact that 17 of the 28 patients who changed treatment changed to one of the three anti-TNFs in the study: 4 changed to infliximab, 10 to etanercept and 3 to adalimumab. This led us to modify the sample size for the descriptive analysis of safety, incorporating those patients who received another study of anti-TNF as rescue therapy during the first 2 years.

About half of the patients reported some adverse effect of treatment, a proportion that was higher in the group that received etanercept, in which two-thirds of patients reported these effects. Of these, some 15 % in the infliximab arm, 24 % in the etanercept arm and nearly 12 % in the adalimumab arm had to suspended treatment. The main reasons for suspension were infusion reactions and infections (7 and 2 patients, respectively) in the case of infliximab, and cutaneous reactions and infections (8 and 2 patients, respectively) for etanercept. Four patients suspended adalimumab treatment, notably one of them due to development of multiple sclerosis.

Overall, the most frequently reported adverse effect was infection, especially respiratory infections. Also commonly reported were infusion reactions with infliximab and cutaneous reactions, primarily with etanercept (Table 6).

Discussion

Our study suggests that adalimumab is the most cost-effective anti-TNF drug at 2 years of treatment for achieving CR and LDAS in patients with active RA despite combined treatment at the maximum possible doses with methotrexate, sulfasalazine, leflunomide and corticosteroids. This result is the same both when considering direct health costs and when considering only the official direct purchase price of the drug. The analysis of the components of cost-effectiveness in actual clinical practice shows differences that are favorable in effectiveness for adalimumab, with no overall differences in cost.

This study sought to deepen our knowledge of the effectiveness and efficiency of infliximab, etanercept and adalimumab in real-life clinical practice when used in RA patients who are naive to biological therapy. Its design has both limitations and advantages. One limitation is that since it was observational, it was an open and non-randomized study. Despite the lack of randomization, however, it is important to note that each patient always received the most appropriate treatment for his or her situation, which

Table 6 Description of adverse effects

Adverse effect (AE)	Total *N*	Infliximab *N*	Etanercept *N*	Adalimumab *N*
Patients with any AE	86 (66.2 %)	34 (57.6 %)	35 (64.8 %)	17 (50 %)
AE leading to suspension	26 (17.68 %)	9 (15.2 %)	13 (24.07 %)	4 (11.7 %)
Infections	53	28	18	7
Cutaneous reactions	17	3	10	4
Infusion reactions	10	10		
Cardiovascular events	7	3	3	1
Influenza-like illness	5	2	3	–
Abdominal pain	4	2	1	1
Dyspnea	1	–	–	1
Tiredness	1	–	1	–
Anemia	1	–	–	1
Lymphadenopathy	1	–	–	1
Depressive syndrome	1	–	1	–
Nausea	1	–	–	1
Neuropathy	1	1	–	–
Pulmonary nodules	1	1	–	–
Deep vein thrombosis	1	–	1	–
Hypertriglyceridemia	1	1	–	–
Kidney failure	1	1	–	–
Multiple sclerosis	1	–	–	1

was decided in a joint session of the Rheumatology and Pharmacy Departments. If there was no patient characteristic that conditioned or advised against a specific biological, the one with the lowest cost to the hospital at the time was chosen. Another limitation is the small sample size, given that it was conducted in a single center, although proportionally and compared with other similar studies, the number of patients included per center is not low.

One of the study strengths derives from the database, the CREATE registry, which systematically includes all patients treated with biological therapy, with a prospective follow-up of all patients, in accordance with the recommendations of the SER and EULAR and with standardized data collection. Patients are evaluated monthly by a multidisciplinary team of health professionals comprising rheumatologists, a pharmacist, a nurse and a statistician. Decisions on the initiation, maintenance or change of biological therapy are shared by the whole team. All of these make the study more rigorous and exhaustive.

In this case, an observational design is recommended to advance our knowledge of actual cost-effectiveness [27], in contrast to other health economics studies that use models with numerous assumptions or data from clinical trials of highly selected patients. The cost data for the different health resources used were provided by the Pharmacy Department, and the statistical analysis was performed by an independent investigator, ensuring high-quality data collection and processing.

Our results contrast with those of other studies in Spain. The PRAXIS study, conducted in 2007 in 41 hospitals in Spain, was also a retrospective observational study of cost-effectiveness [28]. Its objective was to analyze the use of healthcare resources and their associated costs, from the hospital perspective, in RA patients treated with etanercept, infliximab and adalimumab. The study concluded that in most of the scenarios analyzed, treatment of RA at 6 months with etanercept reduced the hospital costs as compared to infliximab and adalimumab. The 6-month time frame is an important limitation of the study. Other observational studies [29, 30] conducted in Spain more recently in patients treated with adalimumab, etanercept or infliximab found similar effectiveness of the three drugs at 6 months, but with differences in the mean cost (including only the direct cost of purchase), due primarily to the different doses used as compared to conventional doses.

Our study differs from the aforementioned ones in several important aspects that could explain the different results. First, the time frame was 2 years, which is more appropriate for treatment of a chronic disease, as opposed to 6 or 12 months. Second, for patients in the CREATE registry, there was no provision to escalate the drug dose in cases of incomplete response (DAS28 > 3.2) [31]. Finally, the main objective of treatment effectiveness was measured based on CR (DAS28 < 2.6) and not on LDAS (DAS28 < 3.2).

The current strategy in RA management is to "treat to target" (T2T), exerting all possible efforts to achieve CR [32–35]. On this basis, stringent treatment to achieve CR, or failing that, LDAS, allows better disease control over time, less joint damage and dose optimization, making this the most efficient strategy to achieve a good health outcome.

In this regard, the results of the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry recently showed that the strategy of treating to the target of CR, as opposed to conventional care, became cost-effective after 3 years [36]. The percentage of patients who achieved the target effectiveness in the T2T arm of the DREAM registry was higher than in our study. In the CREATE registry, only patients treated with adalimumab had results close to those reported in the Dutch study. However, patients in the CREATE registry had slightly higher disease activity (baseline DAS28 5.71 ± 1.02 vs. 5.0 ± 1.1) and, since they had established RA, had received intensive treatment with combinations of classical DMARDs at the maximum tolerated doses, similar to patients in the Finnish cohort reported by Sokka et al. [37]. The results of the latter study support the efficacy of treatment with combinations of DMARDs to reach and maintain remission before using biological therapy.

Our cost analysis was made from the perspective of the healthcare system, which includes the costs of all healthcare resources involved in treating this disease. Nevertheless, some studies [38–44] have suggested the societal perspective as more appropriate for a study of RA costs. We decided to remain with the hospital perspective, however, for various reasons:

- First, the current economic crisis has made it necessary to assign a target budget to be met by each medical department. Accordingly, the proposed study objective was to analyze which drug was most efficient from the point of view of the payer—the hospital—which meant that indirect healthcare costs were not taken into account.
- Second, although an analysis from the societal perspective may be more complete, it is a more complex study that requires certain assumptions, since indirect and intangible costs are difficult to define and quantify [27, 45–47]. The results of such a study would be somewhat theoretical, involving a level of uncertainty that would make them less valid and applicable; this is the exact opposite of the aim of our study: to find the most efficient drug in actual clinical practice. In any case, pharmacoeconomic analyses should always specify the study perspective and state the reasons why it was chosen in order to determine whether the results can be extrapolated [27].

Finally, it is important to note that the cost-effectiveness results were calculated considering the EFP. The discounts on the EFP obtained by each country and hospital may change this result, since the main cost component is the purchase price of the drug. The arrival of biosimilars is key in this respect. The entry into the market of biosimilar infliximab may reduce the direct cost of the drug, making it more cost-effective. This could also indirectly affect the price of etanercept, adalimumab and other biological agents, which may be lowered to remain competitive.

Conclusions

Adalimumab was the most cost-effective drug in regular clinical practice for achieving both CR and LDAS in patients included in the CREATE registry. The actual negotiated price of acquiring these drugs is a key factor in the final analysis of cost-effectiveness.

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Compliance with ethical standards

The study meets the standards of Good Clinical Practice, the principles of the Declaration of Helsinki and Order SAS 347/2009 of December 16, which develops guidelines on observational post-authorization studies for drugs used in humans in Spain. Patient data are coded to maintain anonymity in the study and to prevent their identification by third parties. The study was approved by the Ethical Committee of the Reina Sofia University Hospital of Cordoba.

Conflict of interest Cárdenas M, Font P, Castro-Villegas and Collantes-Estévez E report grants, consulting fees, or lecture fees from MSD, Pfizer or AbbVie, none of which were related to the present work. De la Fuente S, Romero-Alonso M, Calvo-Gutiérrez J, Escudero-Contreras A, Casado MA and Del Prado JR have no conflict of interest.

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