Efficiency of adalimumab, etanercept and infliximab in rheumatoid arthritis patients: dosing patterns and effectiveness in daily clinical practice

E. Ramírez-Herráiz[1], V. Escudero-Vilaplana[2,3], E. Alañón-Plaza[1], N. Trovato-López[2,3], A. Herranz-Alonso[2,3], A. Morell-Baladrón[1], M. Sanjurjo-Sáez[2,3]

[1]Department of Pharmacy, La Princesa University Hospital, Madrid; [2]Department of Pharmacy, Gregorio Marañón University General Hospital, Madrid; [3]Institute for Health Research Gregorio Marañón, Madrid, Spain.

Abstract

Objectives

This retrospective, multicentre, observational study aimed to assess the mean annual doses and associated costs of three anti-tumour necrosis factor agents in daily clinical practice in rheumatoid arthritis patients, correlating these costs with disease activity.

Methods

Adult rheumatoid arthritis patients were treated and followed at the Rheumatology departments of two Spanish hospitals for at least 6 months, with adalimumab, etanercept or infliximab over a 4-year period. ANOVA and multivariate statistical analyses of dosing patterns, disease activity and annualised costs were carried out.

Results

A total of 198 patients, comprising 215 cases, met the inclusion criteria (73 on adalimumab, 81 etanercept and 61 infliximab). Compared to recommended doses, mean doses of adalimumab and etanercept decreased by 7% and 19%, respectively, while the mean dose of infliximab increased by 36%. There were no statistical differences between treatments in terms of clinical effectiveness. The hazard of dose escalation was significantly higher for either adalimumab (4.4-fold) or infliximab (11.8-fold) compared to etanercept ($p<0.05$). Clinical control was achieved and maintained in more than half of the patients treated with reduced doses of etanercept. Associated mean patient-year costs were significantly higher in adalimumab patients (€11.962.58) (etanercept €9.594.73; infliximab €10.094.53; [$p<0.05$]).

Conclusion

In rheumatoid arthritis patients, it is possible to reduce doses and associated costs of biological therapies while controlling disease activity. Mean doses used in our clinical practice were significantly lower with etanercept than with the anti-TNF monoclonal antibodies, adalimumab and infliximab. Dose differences impact directly on associated patient-year costs, and thus on treatment efficiency.

Key words

adalimumab, efficiency, etanercept, infliximab, rheumatoid arthritis

Esther Ramírez-Herráiz, PharmD
Vicente Escudero-Vilaplana, PharmD
Estefanía Alañón-Plaza, PharmD
Nicolás Trovato-López, PharmD
Ana Herranz-Alonso, PharmD, PhD
Alberto Morell-Baladrón, PharmD
María Sanjurjo-Sáez, PharmD

Please address correspondence to:
Esther Ramírez-Herráiz,
La Princesa University Hospital.
Pharmacy Department,
Diego de León 62
28006 Madrid, Spain.
E-mail: eramirez.hlpr@salud.madrid.org

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes pain, swelling and the destruction of joints, as well as systemic disease. Its aetiology is unknown; nevertheless, it is considered an autoimmune disease that can lead to severe disability and premature mortality. The incidence and prevalence of RA varies substantially across studies and time periods, although a decline in incidence over time and a shift toward an older age of onset has been repeatedly reported (1). RA prevalence rates in developed populations seem to be rather uniform: approximately 0.5% to 1% of the adult population, as recently reviewed (2). In Spain, the prevalence of RA is 0.5% (95%CI 0.25–0.85) with an estimated ratio of women to men of 4:1 (3). Data from a nationwide primary care register in Spain showed that the annual incidence of RA was 8.3 cases/100.000 (95%CI 7.5–9.2): 11.3/100.000 in women (95%CI 10.0–12.8), and 5.2/100.000 in men (95%CI 4.3–6.3). However, this incidence increases with age (4).

The therapeutic goals of RA management include controlling pain and inflammation, minimising joint damage and disability, maintaining or improving patient physical function and quality of life, and treating extra-articular manifestations, if they are present (5). The ultimate goal of RA therapy is to achieve remission or low disease activity. RA needs long-term management strategies and it is important that efficacy and safety of therapy remain constant over time.

Among RA treatments, anti-tumour necrosis factor (anti-TNF) agents take a prominent position as biological response modifiers. Anti-TNFs are effective in RA management. However, since there are no head-to-head studies comparing the efficacy of anti-TNFs in RA patients, the superiority of one anti-TNF cannot be established (6).

Thus, anti-TNF choice is based on a series of factors such as safety, route of administration, dose patterns, patient preferences and, obviously, efficiency.

Nevertheless, anti-TNFs have different molecular structures that result in differences in immunogenicity. Anti-etanercept antibodies have been detected in RA patients at a frequency of 2% to 5.6%, but these antibodies do not seem to be associated with adverse events or a lower clinical response (7, 8). Anti-adalimumab antibodies in RA patients appear at a frequency of 12% to 28% (9, 10), whereas anti-infliximab antibodies are more frequent, ranging from 12% to 44% of patients in clinical studies (7, 11). These antibodies, in contrast, are associated with consequences such as loss of efficacy, dose increases, worse long-term outcome, and raised costs (7, 9, 11).

RA is associated with a substantial economic burden, both in direct and indirect costs (12-14). There is an increasing need for limiting the pharmaceutical costs of chronic diseases. Data on the efficiency of different RA therapies are important for physicians and healthcare systems, as the choice of more efficient treatments may involve substantial savings while maintaining clinical benefits. However, as clinical practice studies have shown, real anti-TNFs costs may vary from the theoretical costs (15-24). Changes in doses, or in frequency of administration, are mirrored by deviations in costs.

The aim of this study was to assess whether, in clinical practice, mean doses of adalimumab, etanercept and infliximab differ from recommended doses in RA patients, to correlate the doses with their effectiveness and, finally, to evaluate the cost implications.

Materials and methods

Patients

All available clinical records of patients on anti-TNF treatment in the two participating hospitals (La Princesa University Hospital and Gregorio Marañón University General Hospital, Madrid, Spain) were retrospectively reviewed. Eligible patients were adults diagnosed with RA (ACR 1987 revised criteria), treated with adalimumab, etanercept or infliximab, and with or without concomitant disease-modifying anti-rheumatic drugs (DMARDs) and followed in the Rheumatology Departments for at least 6 months between 1st October, 2006 and 30th September, 2010. Patients were excluded if they received

any different biological therapy for RA, had a follow-up shorter than 6 months, took part in a clinical trial during the study period or had done so within the previous 3 months.

Enrolled patients could constitute various cases if they received different sequential anti-TNF treatments for at least 6 months, each during the study period.

Study variables

Clinical records were reviewed retrospectively for the following variables:

- Socio-demographic data (age, gender), disease progression and prior and concomitant DMARD therapy;
- Disease activity measured by the 28-joint disease activity score (DAS28) at the onset of each anti-TNF therapy, every time anti-TNF treatment or the dose pattern was changed and at the last recorded visit. According to EULAR criteria, the therapeutic goal was achieved in patients with a DAS28 <3.2;
- Dose patterns prescribed by the rheumatologist for each anti-TNF and any subsequent modifications. These data were used to analyse patient adherence to recommended doses (adalimumab 40 mg every other week; etanercept 25 mg twice a week or 50 mg weekly; infliximab 3 mg/kg every 8 weeks after the third infusion) throughout the study. Initial doses were those indicated in the technical data sheet and approved by the European Medicines Agency.

Annual (52 weeks) costs were calculated using the Spanish ex-factory unitary prices of each agent: €494.61 for 40 mg adalimumab, €227.81 for 50 mg etanercept and €515.90 for 100 mg infliximab, including tax (2011 €). Administered doses were calculated using individual claims data according to Pharmacy Departments' records (number of delivered vials/number of weeks), standardised and adjusted to mean percentage of recommended doses (considered as 100%). Infliximab costs included administration costs in day-care hospitals: €110.93/administration according to the Analytical Accounting Service of the Health Service of Madrid (SERMAS) in 2010. Infliximab vial optimisation was performed, with 0.89% wastage per vial (as estimated by the Pharmacy Department at Gregorio Marañón University General Hospital).

Reduced dosages could result from either down-titration of the dose or an increase in the dosing interval. Dose escalation could result from either up-titration of the dose or a decrease in the dosing interval. These changes in dosages were established according to the rheumatologist's criteria after patient agreement. Due to potential biases in the study design, dosing patterns were considered modified when there was a change of more than 15% from the recommended dose (corresponding to ±2 days for adalimumab, ±1 day for etanercept and ±1.2 weeks for infliximab intervals). Potential biases included adherence irregularities, dispensing or delivery mistakes and patient misuse. Cost-effectiveness ratios were calculated from mean annualised costs observed in daily clinical practice and the percentage of patients who achieved low disease activity.

The study was approved by the Ethics Committee of La Princesa University Hospital and was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Statistical analyses

Results were expressed as mean and standard deviation. Unless otherwise stated, all statistical tests were 2-sided tests at a significance level of 0.05 and were performed using IBM SPSS® Statistics software version 19.0. Differences in subject characteristics between the three cohorts were examined using chi-square test for categorical variables and an ANOVA model for continuous variables. Adherence to recommended doses over time was evaluated with the Kaplan-Meier method and pair-wise comparison was performed with the Mantel-Cox log rank test. A p-value <0.05 was considered statistically significant.

In order to determine whether there were any confounding factors associated with the annual mean cost of anti-TNF therapy (other than therapy itself), an analysis of covariance (ANCOVA) and a multivariate regression analysis were carried out.

Results

A total of 198 patients, comprising 215 cases, met the inclusion criteria: 73 on adalimumab (66 first line, 7 second line), 81 on etanercept (71 first line, 9 second line, 1 third line), and 61 on infliximab (all first line). At baseline, the mean age of the patients was 60.7 (SD: 13.1) years and 158 (80.2%) were women. The three cohorts were well balanced in terms of demographic and clinical characteristics (Table I). Early RA, defined as RA with an interval of less than 4 years between the onset of symptoms and RA diagnosis, was found in 76.6% of patients. At baseline, mean DAS28 was 4.38 (SD: 1.52), corresponding to moderate RA activity according to EULAR criteria. Significantly more patients in the infliximab group had received prior methotrexate (MTX) therapy and prior DMARD therapy (p<0.05 *vs*. adalimumab and etanercept for both comparisons). MTX and DMARD use was significantly lower at the end of the study (p<0.05 for both therapies). On the other hand, significantly more patients in the etanercept group had received a different anti-TNF therapy prior to the study period (p<0.05 *vs*. adalimumab and infliximab) (Table I).

Adherence to label or reduced doses for the treatment groups over the 4 years of the study period was estimated using Kaplan-Meier survival analysis (Fig. 1). There were significant differences between all treatment groups (Mantel-Cox log rank p<0.05). The hazard of dose escalation was 4.4 times higher for adalimumab-treated patients and 11.8 times higher for infliximab-treated patients compared with etanercept-treated patients.

Effectiveness, assessed as the percentage of patients achieving a final DAS28 <3.2, was observed in 67.12%, 65.43% and 62.30% of patients treated with adalimumab, etanercept and infliximab, respectively. Differences between treatment groups, as well as in RA improvement according to EULAR criteria, were not statistically significant (p=0.841 and p=0.179, respectively).

Table I. Study baseline socio-demographic and clinical data.

	ADA	ETN	IFX	*p*-value
Cases (n)	73	81	61	
Patients (n)	66	71	61	
Age (years)	61.3 (13.7)	58.1 (13.7)	62.6 (11.8)	NS
Sex (female)	75.8%	76.1%	90.2%	NS
Baseline DAS28	4.51 (1.44)	4.41 (1.49)	4.17 (1.66)	NS
Time from onset of symptoms to diagnosis (years)	2.86 (1.02)	3.53 (1.41)	2.93 (1.46)	NS
Early RA (<4 years between onset of symptoms and diagnosis) (%)	86.0	72.6	69.4	NS
Time from diagnosis to first biological therapy (years)	7.8 (7.0)	8.4 (8.1)	9.1 (7.9)	NS
Prior to MTX (%)	83.6%	80.3%	98.4%	*
Prior to MTX dose (mg)	14.9 (4.3)	14.4 (4.2)	13.9 (4.6)	NS
Prior to DMARD	89.0%	85.2%	100.0%	*
Prior to anti-TNF therapy (%)	6.9%	22.2%	3.3%	**
ADA	–	22.2%	50.0%	
ETN	40.0%	–	50.0%	
IFX	60.0%	77.8%	–	

Unless otherwise indicated, data are expressed as mean (SD).
ADA: adalimumab; ETN: etanercept; IFX: infliximab; MTX: methotrexate; DMARD: disease-modifying anti-rheumatic drug; NS: not significant.
*p<0.05 infliximab *vs*. adalimumab, infliximab *vs*. etanercept; **p<0.05 etanercept *vs*. adalimumab, etanercept *vs*. infliximab.

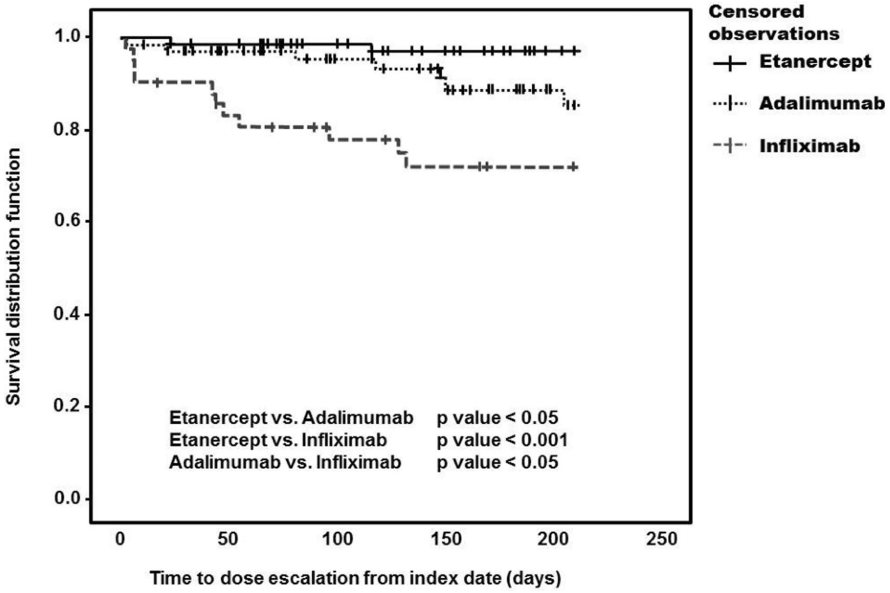

Fig. 1. Survival analysis. Time to dose escalation between groups throughout the study period, estimated using Kaplan-Meier analysis. Eighteen patients of the infliximab group were excluded because their doses were increased at the study baseline.

Mean doses and associated costs are shown in Table II. These costs differed significantly (p<0.05) from patient-year costs based on label dosing for the studied anti-TNFs. Adalimumab and etanercept costs diminished, while infliximab cost increased (Fig. 2). Up to 9.59% of adalimumab-treated patients had their mean doses increased, compared to 3.7% and 75.4% of etanercept and infliximab-treated patients, respectively.

To analyse the relationship between dose and effectiveness, dose patterns were considered modified when mean dose changed by >15% of recommended dose. Cases were categorised as clinically controlled (DAS28 <3.2) and not clinically controlled (DAS28 ≥3.2) (Table III). Compared to recommended dose, the mean dose in the clinical control group was 8.30% lower (reduced dose) for adalimumab and 22.60% lower for etanercept, but 34.50% higher (increased dose) for infliximab. Interestingly, among patients clinically controlled, 36.73% of adalimumab cases and 52.83% of those treated with etanercept remained in reduced doses. By contrast, infliximab required an increased dose to achieve clinical control in 76.32% of cases. The cost per responder was significantly lower (p<0.05) for etanercept (€14.663.65) when compared with adalimumab (€17.821.80) and infliximab (€16.204.38).

Both ANCOVA and multivariate analysis determined that none of the variables studied influenced patient-year costs, except anti-TNF treatment. No statistically significant differences in mean annualised cost of anti-TNF therapy were observed, whether combined with MTX or not (p=0.770), in disease activity (p=0.618), in therapeutic goal achievement (p=0.125) or in disease improvement (p=0.822).

Discussion

Our study shows significant differences between clinical practice and recommended doses that impact directly on mean patient-year costs in Spain. Our data provide further evidence that all the studied therapies are highly effective, achieving clinical control of RA in over 60% of patients, but the mean doses required imply disparities in efficiency. The main strength of our study is that, to our knowledge, this is the first study to analyse the doses of the three anti-TNFs most commonly used in clinical practice and to correlate these doses with their effectiveness in a 4-year scenario.

Efficiency

The proportion of patients achieving therapeutic goals was similar among the treatments (67.1% with adalimumab, 65.4% with etanercept and 62.3% with infliximab). However, mean doses required for achieving this effectiveness were 91.7% of the recommended dose for adalimumab and 77.4% for etanercept, but 134.5% for infliximab. These values implied an overall dose decrease of 7% for adalimumab and 19% for etanercept, but an increase of 36% for infliximab.

Table II. Doses and costs.

	ADA	ETN	IFX*
Cases	73	81	61
Recommended dose	40 mg biw	50 mg weekly	3 mg/kg/8 weeks
Patient-year cost (recommended dose)	€12.859.79	€11.845.93	€7.566.27
Average dose (study dose)†	37.21 (9.61) mg/biw	40.5 (13.46) mg weekly	4.07 (1.13) mg/kg/8 weeks
Study dose (% of recommended dose)	93.02%	81.00%	135.73%
Patient-year cost (study dose) ‡	€11.962.58	€9.594.73	€10.094.53
Patient-year costs differences (recommended *vs*. study dose) †	€-897.22	€-2.251.20	€+2.528.26

ADA: adalimumab; biw: twice weekly; ETN: etanercept; IFX: infliximab; DAS28: 28-item Disease Activity Scale; RA: rheumatoid arthritis. Costs are calculated based on ex-factory prices including taxes (2011 €).
*includes indirect costs (€110.93 per infusion) and 0.89% vial wastage; † $p<0.05$ between all groups; ‡ $p<0.05$ ADA *vs*. ETN, ADA *vs*. IFX.

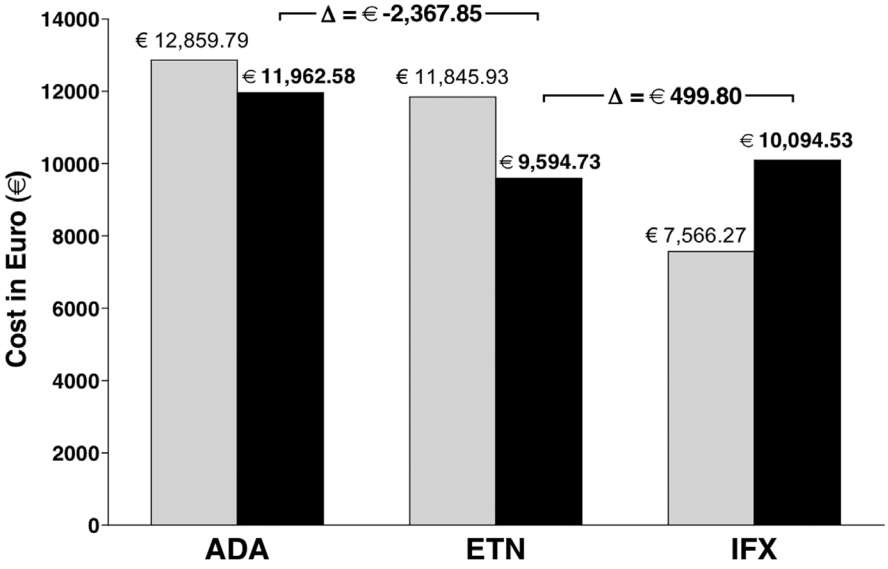

Fig. 2. Annualised cost of each anti-TNF group. Light columns represent patient-year cost based on recommended doses and dark columns account for patient-year cost based on mean doses in study patients. *p*-value was less than 0.05 for all therapies *vs*. theoretical cost. Costs are calculated based on ex-factory prices including taxes (2011 €).
$p<0.05$ adalimumab *vs*. etanercept, and adalimumab *vs*. infliximab according to costs based on study dosing. Infliximab data include indirect costs (€110.93/infusion) and 0.89% vial wastage.
ADA: adalimumab; ETN: etanercept; IFX: infliximab.

There were also a percentage of patients with reduced dosing regimens and high DAS28 values. Most of these patients are expected to have well-established RA and/or chronic radiological damage that may increase their DAS28 but no current clinical activity. However, this hypothesis has not been confirmed.

On the other hand, patients on escalated doses were similarly distributed between clinically-controlled and non-controlled groups. This might show that dose increase may be neither effective nor efficient. Further studies should be performed in order to confirm these hypotheses, although evidence from several studies suggests that increasing the dose of adalimumab and infliximab may not be useful. In our study, dose escalation was less frequent among patients treated with etanercept (3.70%) compared to adalimumab (9.59%) and particularly compared to infliximab (75.41%). With some exceptions (16, 22), infliximab dose escalation has been reported at percentages higher than 50% (17-23, 25, 26). It has been suggested that dose increases of infliximab can improve clinical outcomes (27). Nevertheless, the results of a study performed in clinical practice indicated that dose increases of infliximab may have less clinical benefit than expected or perceived, and that the supposed benefit is a regression effect (28). The percentage of infliximab-treated patients with dose escalation in our study could be inflated, since infliximab was the first anti-TNF available for RA treatment, and most of the patients were receiving infliximab long before the start of the study. The results of a retrospective analysis of the Arthritis, Rheumatism and Aging Medical Information System (ARAMIS) (29) suggest the possible relevance of length of treatment in increased dose escalation in infliximab-treated patients. However, other studies have not found significant differences (30). The definition of dose escalation varied between the cited studies, but a comparison of five methods for evaluating dose escalation in RA patients treated with anti-TNFs showed that the overall comparative result remains the same (31). It has also been reported that adalimumab dose escalation seems to be ineffective (24). In RA patients treated with adalimumab who had not achieved minimal disease activity, 80% did not achieve it even after increasing their doses (10). It is clear that the etanercept dose is less likely to be escalated than the infliximab dose or even the adalimumab dose, as our findings also point out. In our study, the hazard of dose escalation was higher between adalimumab and infliximab-treated patients when compared to etanercept-treated patients. This finding has been found in previous studies in the clinical practice setting (32). Nevertheless, as shown in Table III, dose escalation was not associated with better clinical control.

Figure 1 shows data from clinical records that corresponded to the physician-prescribed doses. However, these data differ from percentages of patients with increased doses, which were determined according to the doses delivered to each patient by the pharmacy departments. These differences could be due to the fact that patients acquired their medication according to their

Table III. Dose analysis by effectiveness for each study group.

	ADA		ETN		IFX	
	Clinical control (n=49)	Non-clinical control (n=24)	Clinical control (n=53)	Non-clinical control (n=28)	Clinical control (n=38)	Non-clinical control (n=23)
Increased dose	8.16%	12.50%	1.89%	7.14%	76.32%	73.91%
Recommended dose ±15%	55.10%	62.50%	45.28%	57.14%	15.79%	17.39%
Reduced dose	36.73%	25.00%	52.83%	35.71%	7.89%1	8.70%
% of recommended dose received	91.71%	95.69%	77.40%	87.80%	134.50%	137.75%
Mean patient-year cost (€)	11.794.32	12.306.10	9.168.73	10.401.09	10.064.95	10.290.71

Dosing schedule was considered modified when the mean dose changed >15% with respect to the recommended dose. Cases with clinical control were those who achieved the therapeutic goal (DAS28 <3.2).
ADA: adalimumab; ETN: etanercept; IFX; infliximab; DAS28: 28-item Disease Activity Scale.

health status and regardless of the prescribed dose.

Dose escalation and associated costs

Studies in clinical practice settings have found statistically significant differences in the costs of adalimumab, etanercept and infliximab in RA patients, suggesting that costs were increased because of dose escalation (15, 17, 30, 32). The relationship between dose escalation and cost of anti-TNF therapy was previously assessed in prior studies, the findings of which also suggested that dose escalation was associated with significant cost increases (30, 32). Adalimumab and infliximab dose escalation were associated with statistically significant increases in total cost of care, but etanercept dose escalation did not involve a significant cost increase (32). As shown in Figure 1, we found statistically significant differences between patient-year costs based on recommended doses and mean study doses. Adalimumab and etanercept mean study costs were lower than the theoretical costs, while the cost of infliximab was higher.

Analysis of other factors

Our study also analysed any factor that could contribute to observed differences in mean annualised costs between anti-TNF therapies. In the ANCOVA test, prior MTX or DMARD therapy did not account for differences, anti-TNF treatment itself being the only variable that interfered with mean annualised cost. Use of concomitant MTX, disease activity, achieving the therapeutic goal and disease improvement did not influence mean annual doses and costs of anti-TNF therapy. A multivariate logistic regression model showed that none of the analysed variables were associated with observed mean patient-year cost. These analyses support the findings in our population and increase the robustness of the study. Further studies in different populations should be performed to validate these findings.

Study limitations

As a retrospective study, the study is limited by available data and potential bias may have been introduced through unobserved variables. However, most of the commonly studied variables were analysed, and none influenced the main findings. There could also be a potential selection bias because study data were obtained only from two hospitals and, therefore, their representativeness may be limited.

As usual in clinical studies, cost data were based on manufacturers' ex-factory prices. However, these prices could differ from certain hospital prices, and thus, mean patient-year cost may vary. Likewise, cost estimations are based on Spanish prices and their international applicability is limited. In this respect, it has been reported that in the United States these biologics start at relatively the same price, but as the dose increase observed is similar, infliximab ends up costing more than adalimumab and etanercept for the same efficacy (33), although more recent data could shed some light on the present situation. Despite these considerations, dose changes in clinical setting may involve cost and efficiency changes, independently of what price is used for cost calculation.

Other treatments that are approved nowadays such as certolizumab pegol, golimumab, tocilizumab and abatacept, were not available during the entire study period, and thus were not included. An assessment including adalimumab, certolizumab, etanercept, golimumab, tocilizumab, abatacept and infliximab management should be performed for a complete overview.

Although a cost-effectiveness ratio only gives partial information, it allows for the identification of inefficiencies, which is a key factor for decision-makers. This study analyses the efficiency of adalimumab, etanercept and infliximab in the real world, not in a clinical trial setting. This approach is more useful for understanding dosing administered in clinical practice and the effectiveness of therapies.

Finally, effectiveness has only been assessed through the DAS28 activity index. However, more information could be obtained with the use of instruments such as the Health Assessment Questionnaire (HAQ), the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) and the analysis of parameters such as rheumatoid factor (RF) or anticyclic citrullinated peptide antibodies (anti-CCP). This data were not fully available in our clinical records.

Conclusion

Our study shows that in our clinical practice, mean doses of etanercept are significantly lower compared to adalimumab and infliximab, related with higher rates of dose escalation. It also shows that, in certain scenarios, it is possible to reduce anti-TNF doses while maintaining low disease activity. These differences involve significant variations in costs that should be taken into account when choosing the most efficient therapy.

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