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RESEARCH ARTICLE

Efficiency of adalimumab, etanercept and infliximab in ankylosing spondylitis in clinical practice

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Abstract *Background* Information on the use of ankylosing spondylitis (AS) therapies in clinical practice is a key factor in decision making, as more efficient treatments may involve substantial savings while maintaining the clinical benefits for the patient. *Objective* To assess the mean annual doses and associated costs of the three main anti-tumour necrosis factor agents used in Spanish daily clinical practice in ankylosing spondylitis patients and to correlate these costs with disease activity. *Setting* This retrospective, observational study included adult ankylosing spondylitis patients over a 4-year period that had been treated for at least 6 months with adalimumab, etanercept or infliximab at two University Hospitals in Spain. *Methods* Disease activity was estimated with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores at the start of anti-tumour necrosis factor (anti-TNF) therapy and in the last visit or whenever the drug was switched. Mean costs were estimated for a 52-week horizon from the delivered doses registered by pharmacy records. Outcomes were the doses and costs of anti TNFs administered to each patient, and the BASDAI score. *Results* A total of 119 patients (137 cases) were included (28 cases treated with adalimumab, 48 cases with etanercept and 61 with infliximab). Mean doses of adalimumab and etanercept were 92.8 and 88.8 % of the initially prescribed doses, respectively, while the mean dose of infliximab administered was 102 %. There were no statistical differences among treatments in terms of clinical effectiveness. Associated mean patient-year costs were significantly higher in the infliximab group (€14,235), compared to the other treatments [adalimumab €11,934; etanercept €10,516; ($P < 0.05$)]. *Conclusion* In certain ankylosing spondylitis patients, doses and associated costs of biological therapies can be reduced while controlling disease activity. Mean doses used in our clinical practice vary from the recommended doses and are significantly lower for adalimumab and etanercept than for infliximab. These differences impact directly on associated patient-year costs, and, thus, on treatment efficiency.

Keywords Adalimumab · Ankylosing spondylitis · Clinical practice · Cost · Cost-effectiveness · Efficiency · Etanercept · Infliximab · Spain

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Impact of Practice

- In certain ankylosing spondylitis patients it is possible to reduce doses and associated costs of biological therapies while controlling disease activity, achieving a high level of efficiency.
- Adalimumab and etanercept may be the most efficient options in the treatment of ankylosing spondylitis in clinical practice in Spain.

Introduction

Ankylosing spondylitis (AS) is a chronic progressive inflammatory disease which affects mainly the axial skeleton and also large peripheral joints and enthuses [1]. AS may also be associated with extra-articular manifestations, including uveitis, and cardiac, pulmonary and mucous membrane lesions [1, 2]. The aetiology and pathogenesis of AS are not completely understood, but immune disorders are the major mechanism. AS seems to be mainly genetically determined, with a heritability factor presenting in over 90 % of cases [3]. There is a strong correlation between human leukocyte antigen B27 (HLA-B27) and the development of AS, especially in Caucasian men [3, 4]. AS has a worldwide prevalence of 0.1–1.4 %, being nearly three times more frequent in men [4], and the associated disability is comparable to that observed in rheumatoid arthritis [5, 6]. The onset of AS occurs typically in the 20 s, so patients require treatment for several decades [7]. AS has also an important impact to society. One-third of these patients may need sporadic work leave, change their working activities or need a reduction in working hours, and, in the end, early retirement is often unavoidable [7–9].

Ankylosing spondylitis (AS) management includes the control of pain and inflammation, in order to minimize skeletal damage and disability, and the treatment of extra-articular manifestations, if present [2, 10]. The ultimate goal of AS therapy is to achieve and maintain low disease activity, and, thus, maximise long-term health-related quality of life. Recommended treatments include non-steroidal anti-inflammatory drugs (NSAIDs), simple analgesics, local and systemic steroids, physiotherapy, anti-TNF therapy and, ultimately, surgery [10, 11]. Disease activity is mainly assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [12]. In general terms, AS is considered to be active when BASDI $\geq$ 4 [13].

In recent years, anti-TNF agents have played a central role as biological response modifiers [13], and they have been recommended for patients with persistently high disease activity despite conventional treatments [10]. The choice of anti-TNF is based on safety, efficiency, route of administration and patient preferences. Although most of the clinical trials with regard to anti-TNF agents were performed in biologic-naïve patients, switching these drugs is a usual practice with good results [14]. Effectiveness of anti-TNF may depend not only on whether the therapy is the first anti-TNF or it is a second or third line, but also whether the switch is due to lack of effectiveness or due to adverse events [15].

Ankylosing spondylitis (AS) entails a considerable economic burden, both in direct and indirect costs to society and healthcare systems [7]. The current economic situation has increased the awareness and the need for effective management of the pharmaceutical costs of chronic diseases. Thus, information on the use of AS therapies in clinical practice is a key factor in decision making, as more efficient treatments may involve substantial savings while maintaining the clinical benefits for the patient. The real cost of anti-TNF therapies may vary from the costs associated with the initially prescribed treatment [16–19], since any change in the dosage pattern produces deviations in the theoretical calculations.

Aim of the study

To assess the real efficiency of adalimumab, etanercept and infliximab for the treatment of AS in clinical practice.

Ethical approval

This study was carried out in two Spanish university hospitals. The study protocol was approved by the Ethics Committees of the hospitals and was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Methods

Patients

An observational, retrospective, economic evaluation was performed. Clinical data were extracted from the medical records of patients treated with anti-TNF therapy in the two hospitals participating in the study. The study included adults who had been diagnosed with AS [20], treated with adalimumab, etanercept or infliximab and had available medical history for a minimum period of 6 months in the Rheumatology Departments. The inclusion period was from 1st October 2006 until 30th September 2010. Exclusion criteria were the following: patients treated with a different biological agent from the ones included in the study, patients monitored for less than 6 months and those who had collaborated in a clinical trial at any time between 3 months before starting the study.

A case was defined as one treatment of at least 6 months with an anti-TNF agent, so a single patient could constitute several cases during the four-year follow-up period.

Study variables

Sociodemographic characteristics (age, gender), disease progression, prior or concomitant therapy with disease-modifying antirheumatic drugs (DMARDs), HLA-B27 and axial/peripheral involvement were recorded. Disease activity was measured using the Spanish version of the BASDAI [12, 21] at the start of each anti-TNF therapy and at the last recorded visit. Clinical control was defined when a patient achieved a BASDAI < 4 [10].

In order to analyse patients' adherence to the initial doses, any prescribed dose pattern modifications were recorded throughout the study. Initial doses were those established in the product data sheet: adalimumab 40 mg every other week; etanercept 25 mg twice a week or 50 mg/week; infliximab 5 mg/kg on week 0, 2 and 6, followed by a maintenance dose of 5 mg/kg every 8 weeks.

Mean costs for each agent were estimated for a period of 1 year (52 weeks) using the 2011 Spanish ex-factory unitary prices of each drug: €494.60 for 40 mg adalimumab, €227.80 for 50 mg etanercept and €515.90 for 100 mg infliximab and individual anti-TNF administered doses. Theoretical costs were considered as the costs of 52 weeks of anti-TNF treatment at the labelled dose.

These doses were standardised and adjusted in order to calculate the mean percentage of the initial recommended doses (considered as 100 %). The cost of the intravenous administration of infliximab in the hospital setting (€110.90) was included in the total cost of this drug, according to the costs of the Healthcare Services of the Madrid Region (SERMAS; 2010).

Modifications in dosing regimens were established according to the rheumatologist's criteria after agreement with the patient. An increase in dose could result from up-titrating the dose or from reducing the dosing interval. Dose reduction could result from down-titrating the dose or from increasing the dosing interval. In order to avoid potential biases caused by the study design, dosing regimens were considered modified when the variation of dose was more than 15 %, either from increase or decrease in the dose or from variations in the administration schedule (corresponding to intervals of ± 2 days for adalimumab, ± 1 day for etanercept and ± 1.2 weeks for infliximab).

The cost-effectiveness ratio was defined as cost-per-responder ratio, calculated using the mean yearly costs observed in clinical practice and the percentage of patients who achieved clinical control.

Statistical analyses

Results were expressed as mean and standard deviation. Unless otherwise stated, all statistical tests were 2-tailed and the significance level was set at 0.05. All tests were performed using IBM SPSS® Statistics software version 19.0.

Differences in subject characteristics among the three cohorts were examined using the Chi-square test for categorical variables and an analysis of variance (ANOVA) model for continuous variables. Adherence to the 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 the therapy itself), an analysis of covariance (ANCOVA) and a multivariate regression analysis were carried out including all socio-demographic and clinical data performed using a stepwise method.

Results

A total of 119 patients were included in the study, constituting 137 cases (28 patients were on adalimumab, 48 on etanercept and 61 on infliximab). The mean age at the start of the study was 42.9 (SD = 13) years-old and 112 (82.0 %) were men. Socio-demographic and clinical characteristics were similar within the three groups (Table 1). A Kaplan–Meier survival analysis (Fig. 1) was carried out to estimate maintenance at the labelled dose or dose reduction for the treatment groups over the 4 years of the study period. Significant differences were observed between the three groups (Mantel–Cox log-rank $P < 0.05$).

There were not found statistically significant differences in the percentage of patients who achieved a final BASDAI < 4 (Fig. 2).

In those patients who achieved clinical control, mean dose was decreased by 5.9 and 13.8 % in adalimumab and etanercept groups, respectively. Table 2 shows the dose analysis by effectiveness for each drug. The mean cost of drug therapy for clinically controlled patients was lower in the adalimumab (€12,097.30) and etanercept (€10,212.90) groups than in the infliximab group (€14,173.90).

The mean yearly cost per patient was significantly lower ($P < 0.05$) for adalimumab (€11,933.70) and etanercept (€10,516.40) when compared to infliximab (€14,235.30) (Fig. 3). Cost-per-responder ratio, calculated as the ratio between yearly patient costs and clinical efficacy (BASDAI < 4) was €19,889.50 for adalimumab, €17,392.50 for etanercept and €24,403.30 for infliximab.

Both ANCOVA and multivariate analysis showed that anti-TNF treatment was the only variable that interfered with patient-year cost. None of the other variables studied (socio-demographic data, use of DMARD, disease activity, evolution or prior anti-TNF therapy) influenced the mean doses and costs of anti-TNF therapy.

Table 1 Socio-demographic and clinical characteristics at baseline

	ADA	ETN	IFX
Patients (n)	22	41	56
Cases (n)	28	48	61
Age (years)	43.3 (11.5) (38.8–47.7)	42.6 (10.7) (39.5–45.7)	42.9 (12.8) (39.7–46.2)
Gender (men)	23 (82.1 %)	41 (85.4 %)	48 (78.7 %)
Positive HLA B27	24 (83.3 %)	40 (83.3 %)	52 (84.7 %)
Mainly axial AS manifestation	15 (54.2 %)	31 (64.4 %)	38 (62.7 %)
Time of disease evolution (years)	7.51 (7.02) (4.70–10.3)	7.32 (6.74) (5.27–9.37)	8.60 (9.39) (6.16–11.1)
Baseline BASDAI	5.16 (1.91) (4.40–5.91)	4.98 (2.73) (4.13–5.83)	4.31 (2.40) (3.70–4.93)
Final BASDAI	3.33 (2.06) (2.48–4.18)	3.49 (2.32) (2.78–4.21)	3.33 (2.38) (2.71–3.94)
Baseline BASFI	5.12 (2.19) (4.06–6.17)	5.29 (2.43) (4.41–6.16)	3.74 (2.69)† (2.97–4.51)
Final BASFI	3.73 (2.23) (2.58–4.87)	3.68 (2.76) (2.56–4.79)	3.97 (2.65) (2.85–5.86)
Baseline CRP	2.00 (2.24) (1.08–2.93)	1.46 (1.61) (0.97–1.95)	0.83 (0.94)* (0.58–1.09)
Final CRP	0.40 (0.34) (0.26–0.5)	0.57 (0.62) (0.38–0.77)	0.92 (1.56) (0.46–1.37)
Prior DMARD (%)	21 (75.0 %)	35 (72.9 %)	38 (62.3 %)
Concomitant use of DMARD (%)	13 (46.4 %)	26 (54.2 %)	26 (42.6 %)
Prior anti-TNF therapy (%)	12 (25.0 %)	8 (28.6 %)	5 (8.2 %)
ADA	3 (25 %)		1 (20 %)
ETN		6 (75 %)	4 (80 %)
IFX	9 (75 %)	2 (25 %)	

Data are expressed as mean (SD) and 95 % confidence interval (95 % CI) for continuous variables and frequencies (percentage) for categorical variables

ADA adalimumab, *ETN* etanercept, *IFX* infliximab, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *DMARD* disease-modifying anti-rheumatic drug, *CRP* C-reactive protein

* Differences with the group of patients with ADA ($P < 0.05$)

† Differences with the group of patients with ETN ($P < 0.05$)

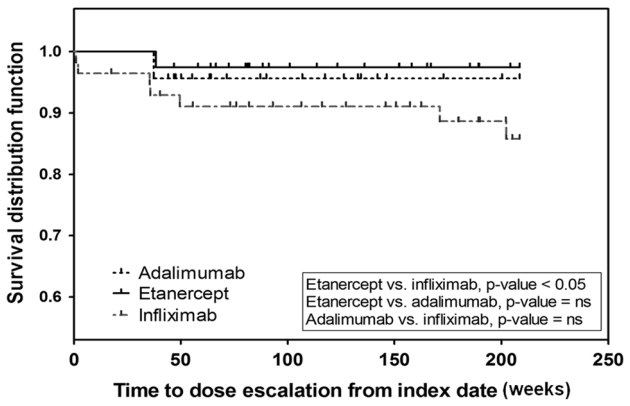

Fig. 1 Survival analysis. Time to dose escalation between groups throughout the study period, estimated using Kaplan–Meier analysis

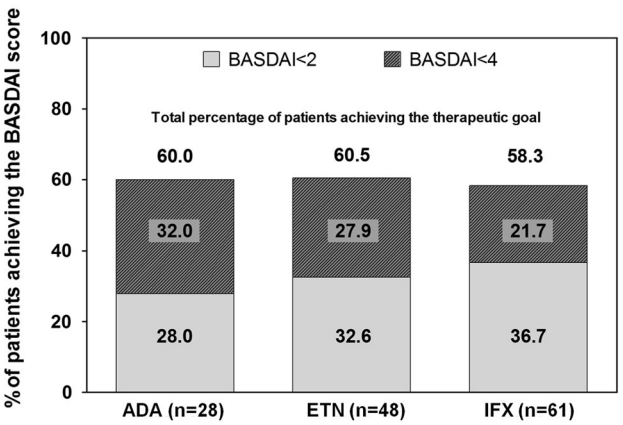

Fig. 2 Achievement of the therapeutic goal in each group as measured by BASDAI score. Clinical control of the disease was considered achieved when BASDAI < 4. ADA, adalimumab; ETN, etanercept; IFX, infliximab

Discussion

Our study showed differences between clinical practice and accepted recommendations regarding anti-TNF doses for the treatment of AS in Spain. Despite dose modifications, anti-TNF agents studied showed high effectiveness since most of the patients achieved their therapeutic goal. Around 60 % of patients achieved BASDAI scores <4,

Table 2 Dose analysis by effectiveness for each study group

	ADA	ETN	IFX
% administered dose versus theoretical dose	92.8 (17.8)	88.8 (24.4)	102.0 (30.6)
% administered dose versus initial dose in clinical control patients	94.1	86.2	101.0
% administered dose versus initial dose in non-clinical control patients	91.7	92.0	103.3
% of patients with incremented dose	10.7	12.5	21.3
% of clinical control patients with incremented dose	13.3	11.5	20.0
% of non-clinical control patients with incremented dose	10.0	11.8	24.0
% of patients with unmodified doses	60.7	45.8	47.5
% of clinical control patients with unmodified dose	60.0	42.3	45.7
% of non-clinical control patients with unmodified dose	60.0	52.9	48.0
Patients with reduced dose (%)	28.6	41.7	31.2
% of clinical control patients with reduced dose	26.7	46.2	34.3
% of non-clinical control patients with reduced dose	30.0	35.3	28.0

Data are expressed as mean (SD) for continuous variables and percentage for categorical variables

No significant differences were observed; *ADA* adalimumab, *ETN* etanercept, *IFX* infliximab

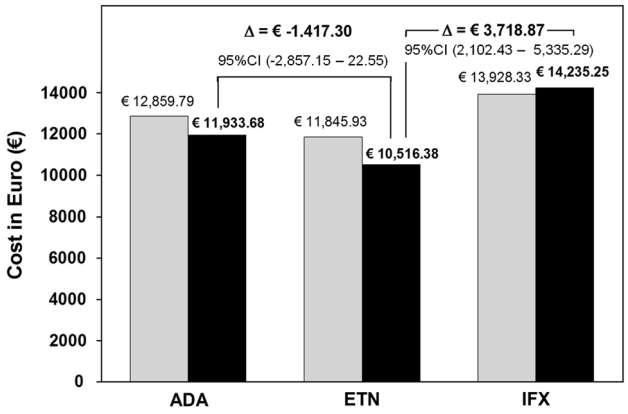

Fig. 3 Annualized cost of each anti-TNF group. *Light columns* represent patient-year cost, based on recommended doses and *dark columns* account for patient-year cost, based on mean doses in study patients. Costs were calculated based on ex-factory prices including taxes (2011€). Infliximab data included indirect costs (€110.93/infusion). Differences were significant ($P < 0.05$) between ADA versus IFX [€-2301.56 (95 %CI: −3947.61 to −655.52)] and between ETN versus IFX [€-3718.86 (95 %CI: −5335.29 to −2102.43)], according to costs based on study dosing. ADA, adalimumab; ETN, etanercept; IFX, infliximab

regardless of the type of anti-TNF agent received. These outcomes coincide with those obtained in randomized, double-blind, placebo-controlled studies, which show clinical responses in more than 50 % of patients treated with anti-TNF drugs [22–26], with a BASDAI improvement in nearly 50 % of patients at week 24. The main differences observed in our population compared to clinical trials are related to previous anti-TNF therapy and baseline disease status, with an initial BASDAI > 6 in the trial setting. In our study, mean initial BASDAI was 4.8, lower than in clinical trials, probably because 21.0 % of our patients had been treated with another anti-TNF agent previously. For this reason, studies that analyse daily clinical practice have gained in relevance, since they complement the information obtained in clinical trials and provide useful data about the management of different treatment strategies often used but considered off-label [27].

With regard to used doses in clinical practice, mean reduced doses were found in 28.6 % of adalimumab, 41.7 % of etanercept and 31.2 % of infliximab-treated patients respectively. Besides, 21.3 % of patients from the infliximab group required an increase in dose compared to 10.7 and 12.5 % of patients in the adalimumab and etanercept groups respectively. This affected the overall mean dose computed during the study period, so that the mean infliximab dose was 102.0 % of the initial prescribed dose, whereas mean adalimumab and etanercept doses were 92.8 and 88.8 % respectively. Variations in anti-TNF doses were not related to clinical control, but had an important impact on associated costs. Studies in clinical practice show that, in certain controlled patients, downward dosage adjustment of anti-TNF drugs in AS is effective in maintaining remission and is associated with lower costs [17–19, 28–30]. Significant differences were found between mean patient costs and mean yearly initial costs for the adalimumab and etanercept groups. Paccou et al. [30] estimated a cumulative probability of 79 % for continuing anti-TNF after dosage adjustment at 12 months with a slight drop to 71 % at 24 months. This data is consistent with our results, in which therapeutic goals are obtained despite dose reductions. Besides, mean costs do not depend on socio-demographic or clinical variables but only on the

dose of the anti-TNF. Therefore, our results indicate that clinical control can be maintained in certain patients with reduced doses. However, some patients with reduced dosing regimens have a high BASDAI. Most of these patients likely have well-established AS with irreversible lesions and, therefore, BASDAI remains high despite the activity disease is controlled. The strategy in these patients is to use the minimal dose effective to relief symptoms and to try to reduce exposure to the drug.

According to the literature, anti-TNF therapy for AS can be considered, in most cases, to be cost-effective for long-term horizons, without exceeding incremental €30,000/quality-adjusted life years (QALY) compared to non-biologic therapies [31–33]. Because of its retrospective design, our study did not estimate QALYs, as these data were not available in all cases. However, the fact that the estimated cost-per-responder ratio was lower than €30,000 per patient achieving BASDAI < 4 in all cases could be considered as an interesting approach to the decision threshold. The disease model structure assumed stable BASDAI scores, independent of disease duration [31]. Therefore, the maintained cost-effectiveness ratio could be extrapolated over time.

The main limitations of our study are the different follow-up periods for each enrolled patient and the heterogeneous population, extracted from the clinical practice of two hospitals, which determines different time courses from diagnosis and anti-TNF onset. Therefore, clinical outcomes and final BASDAI evaluation could not be entirely comparable. Most of the commonly studied variables were analysed, and none of them influenced the main findings of our analysis. The representativeness of our sample may also be limited by the small sample size.

The burden of AS must be considered taking into account both direct and indirect costs, as well as work capacity, early retirement, sick leave or reduced income [34]. Our study only includes—drug costs fixed in 2011 on the basis of manufacturers' ex-factory prices, which could differ from certain hospital prices, and infliximab administration costs, excluding preparation of the intravenous solution. However, cost differences persist if the cost of infliximab infusion is excluded. We did not compute other direct costs, such as inpatient stays, tests or community care. We have shown that practical use of anti-TNF increases its efficiency by maintaining clinical control in certain patients with mean reduced doses. Likewise, cost estimations are based on Spanish prices and their international applicability is limited. However, dose changes in any clinical settings may involve cost and efficiency changes similar to those reported here, independently of the figures.

Our patient sample represents a real population of patients with AS in the daily clinical setting, as opposed to clinical trials, which use strict inclusion and exclusion criteria. Thus, our results may be applicable to the normal clinical practice of most hospitals. The results are satisfactory (over 60 % of patients reached their clinical goal) in the conditions under which this observational study was carried out, and coincide with other studies.

Our results have some implications for clinical management. On the one hand, it can be stated that some patients may maintain clinical effectiveness on a reduced dose, leading to a decrease in associated costs, allowing a higher number of patients to be treated with a fixed budget. This implication is especially important in the current economic situation. On the other hand, a decision-making algorithm for prescription and usage could be developed with the results of a hypothetical study, in order to provide clinicians with a tool for maintaining effectiveness while reducing the medication usage, thus, increasing the efficiency of these drugs.

Conclusion

Our study shows that, in our clinical practice, mean administered doses of anti-TNF vary from standard doses in the treatment of ankylosing spondylitis patients, achieving a high level of efficiency. According to our results, adalimumab and etanercept are related to the lowest costs, and may be the most efficient options in the treatment of adults with AS in our clinical setting. Prospective studies are warranted to confirm the present findings.

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