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Use and cost of biological disease-modifying anti-rheumatic drugs in Spain (PRAXIS study)

C. Rubio-Terrés, J. P. Ordovás Baines[1], R. Pla Poblador[2], C. Martínez Nieto[3], M. J. Sánchez Garre[4], M. A. Rosado Souvirón[5], on behalf of the Research Group for the PRAXIS study*

Health Value. Health Economics and Research of Outcomes Consulting. Madrid, Spain. Pharmacy Department.
[1]General Hospital of Alicante. Spain. [2]Mútua de Terrassa Hospital. Terrassa. Barcelona, Spain.
[3]La Princesa Hospital. Madrid, Spain. [4]Virgen de la Arrixaca University Hospital. Murcia, Spain.
[5]Complejo Hospitalario Carlos Haya. Málaga, Spain

Resumen

Objetivo: Analizar la utilización de recursos sanitarios en la artritis reumatoide (AR) y los costes asociados en los pacientes tratados con tres medicamentos modificadores biológicos de la enfermedad (MBE): etanercept, infliximab y adalimumab.

Método: *Diseño:* observacional, reprospectivo, multicéntrico. Horizonte temporal: 6 meses. *Población:* pacientes con AR; al menos 1 año de tratamiento. *Perspectiva:* hospitales del Sistema Nacional de Salud. *Utilización de recursos:* revisión, por los servicios de farmacia hospitalaria, de las historias clínicas de todos los pacientes incluidos. *Costes sanitarios:* los unitarios obtenidos de bases de datos españolas; los de la enfermedad por paciente con cada MBE, estimados de los resultados de utilización de recursos (€ de julio de 2006). *Análisis de sensibilidad:* simples unifactoriales del caso básico. *Análisis del impacto presupuestario:* de la sustitución de infliximab o adalimumab por etanercept sobre el presupuesto de tres poblaciones hospitalarias.

Resultados: 1.111 historias clínicas revisadas, de 41 hospitales, 432 pacientes tratados con etanercept, 396 con infliximab y 283 con adalimumab. *Dosis promedio:* de etanercept 48,90 mg semanales; de infliximab 4,14 mg/kg cada 8 semanas; de adalimumab de 41,58 mg cada dos semanas (97,8, 138 y 104% de las dosis recomendadas, respectivamente). El tratamiento con etanercept generó menos costes. Frente a infliximab, con etanercept se redujeron los costes semestrales por paciente del tratamiento con el MBE (232,23 €), por fracasos terapéuticos (163,42 €), por consultas (54,88 €), por pruebas (22,52 €) y por la administración del MBE (474,42 €). El ahorro por paciente con etanercept durante seis meses fue de 577,94 €, en comparación con infliximab. En comparación con adalimumab, los ahorros con etanercept se produjeron principalmente en los costes del MBE (1.111,74 €) y en las pruebas (10,16 €) con un ahorro total semestral por paciente tratado con etanercept de 906,68 €. Los análisis de sensibilidad confirmaron la estabilidad del caso básico en la mayoría de los supuestos considerados, con ahorros semestrales por paciente que oscilaron entre 395,79 y 644,32 € en comparación con infliximab y entre 672,09 y 1.159,46 € en comparación con adalimumab. El tratamiento con infliximab fue más barato que con etanercept y adalimumab cuando se consideró el mínimo número posible de dosis del primero (3 dosis al semestre). La reducción en los costes de los pacientes tratados con etanercept, podría generar ahorros en el presupuesto hospitalario que oscilarían, aproximadamente y según la población considerada (50 a 200 pacientes), entre 14.500 y 231.100 € si etanercept sustituyera infliximab y entre 22.600 y 362.600 €, si etanercept sustituyera adalimumab.

Conclusiones: De acuerdo con los resultados obtenidos, en la mayoría de los escenarios el tratamiento de la artritis reumatoide con etanercept reduce los costes sanitarios hospitalarios, en comparación con infliximab y adalimumab.

Palabras clave: Artritis. Etanercept. Infliximab. Adalimumab. Costes.

Summary

Objective: To analyse the use of health care resources and the associated costs in patients with rheumatoid arthritis (RA) treated with three biological disease-modifying anti-rheumatic drugs (bDMARDs): etanercept, infliximab and adalimumab.

Method: *Design:* observational, retrospective, multicentre study. *Length of study:* 6 months. *Target population:* patients with RA, who have been undergoing treatment for at least one year. *Scope:* Spanish National Health System hospitals. *Use of resources:* review of the patient records of all patients included in the study by the Hospital Pharmacy Departments. Health care

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** The complete list of researchers is attached in the appendix at the end.

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Correspondence: Carlos Rubio Terrés. Health Value. Health Economics and Research of Outcomes Consulting. C/ Virgen de Aránzazu, 21. 28034 Madrid. e-mail: crubioterres@healthvalue.org.

costs: the unit costs were obtained from Spanish databases; disease costs per patient were estimated from the use of resources results (€ in July 2006). *Sensitivity analysis:* univariate of base case. *Budget impact analysis:* replacement of infliximab and adalimumab by etanercept for three hospital populations.

Results: 1,111 patient records from 41 Spanish hospitals were reviewed, 432 patients were treated with etanercept, 396 were treated with infliximab and 283 with adalimumab. Mean doses: etanercept: 48.90 mg per week; infliximab: 4.14 mg/kg every 8 weeks; adalimumab: 41.58 mg every two weeks (97.8, 138 and 104% respectively, of recommended doses). Treatment with etanercept led to fewer costs. Compared to infliximab, six-monthly costs per patient were reduced with etanercept as follows: bDMARD treatment (€ 232.23), treatment failure (€ 163.42), consultations (€ 54.88), tests (€ 22.52) and costs associated to bDMARD administration (€ 474.42). The saving per patient treated with etanercept compared to infliximab for six months was € 577.94. With respect to adalimumab, the savings with etanercept were mainly related to bDMARDs (€ 1,111.74) and test costs (€ 10.16), obtaining a six-monthly saving of € 906.68 per patient treated with etanercept. Sensitivity analysis confirmed the robustness of the base case in the majority of cases, with six-monthly savings of € 395.79-644.32 per patient compared to infliximab and of € 672.09-1.159.46 compared to adalimumab. Infliximab treatment was less expensive than etanercept and adalimumab treatment when taking into consideration the minimum possible number of doses of infliximab (3 doses for six months). Hospital budget savings could be obtained as a consequence of a reduction in costs due to use of etanercept, ranging from € 14,500-231,100 when replacing infliximab with etanercept and from € 22,600-362,600 when replacing adalimumab with etanercept, according to the hospital population included (50 to 200 patients).

Conclusions: Our results showed that in most cases, the treatment of rheumatoid arthritis with etanercept compared to infliximab and adalimumab reduced hospital costs.

Key words: Arthritis. Etanercept. Infliximab. Adalimumab. Costs.

INTRODUCCIÓN

There is a 0.5% prevalence of rheumatoid arthritis (RA) in the Spanish population (95% CI: 0.2-0.8) and this disease has a significant impact on the quality of life and functional capacity of the patients affected[1]. The estimated annual cost of rheumatoid arthritis in Spain is between 590 and 1,262 million euros (€)[2,3]. A study carried out by the Spanish Society of Rheumatology showed that the drug cost corresponds to 56% of the total cost of the disease[3] with the highest costs corresponding to second-line treatments, in particular biological drugs, which have an annual average cost per patient of € 5,111 (between 1,616 and 15,345)[3].

There are currently three biological disease-modifying anti-rheumatic drugs (bDMARDs) which neutralise the tumour necrosis factor alpha (hence their name anti-TNF drugs): etanercept, infliximab and adalimumab[4-6].

Various long-term observational studies comparing bDMARDs in the treatment of RA[7-9], which have recently been published, show that rates for ceasing treatment are very similar for etanercept, infliximab and adalimumab (between 15 and 20%). When the reason for ceasing treatment is lack of treatment response, the results are equally similar for the three drugs. It should be borne in mind that decisions relating to failed treatment in these observational studies are based on the clinical opinion of the prescribing doctors and not on pre-defined levels of disease activity.

Although the data obtained in one of the studies[7] suggests that the pharmacological resistance to the three drugs observed could be higher with infliximab (due to the increases in doses for this drug in the population), this factor should be interpreted with care, since it is not clear if this is a case of secondary treatment failure or an inadequate dose. These aspects which are analysed in the observational studies need to be verified by means of controlled clinical trials.

Resistance to treatment leads to additional costs due to an increase in dose, additional consultations, hospitalisation, change in treatment and addition or intensification of concomitant treatments[10]. Taking into account the growing concern to curb health care costs, it is of great interest to carry out drug cost analyses to assess the efficacy of the various bDMARDs in RA[11].

The aim of this study was to establish the use of health care resources in RA and the associated costs in patients treated with three bDMARDs: etanercept, infliximab and adalimumab.

METHOD

General design of the study

Observational studies can be used to carry out a financial assessment of health interventions[12]. The PRAXIS is an observational, retrospective, multicentre study on the use of bDMARDs and other health care resources linked to the treatment of RA, from which the costs per patient treated over a six month period are calculated for each of the bDMARDs being analysed.

Length of study

Data relating to the use of health care resources was collected over a period of 6 months (from 1 January to 30 June 2005).

Target population and selection criteria of patients and hospitals

Spanish patients with RA who have been undergoing treatment with one of the bDMARDs being analysed for at least a year. Inclusion criteria were as follows:

a) patients of both sexes; b) age of or above 18 years old; c) RA diagnosis; d) undergoing treatment with one of the following bDMARDs: etanercept with or without methotrexate, infliximab with methotrexate and adalimumab with or without methotrexate; and finally; and e) who have been undergoing treatment with one of the bDMARDs for one year or more, i.e. who began treatment on 1 January 2004 or before this date.

All hospitals which displayed interest in the research and which used the three abovementioned bDMARDs were included in the observational study. Furthermore, all of the participating hospitals required approval of the study protocol by their respective Clinical Research Ethical Committees (CEIC).

A total of 41 hospitals from all over Spain took part in the PRAXIS study, with 1,111 patients fulfilling the inclusion criteria.

Data collection and researchers

Data was collected from the pharmacy departments of the participating hospitals, assigning one or two health care professionals from each department to this task (the list of researchers is given at the end of the article).

Scope

In Spain, etanercept, infliximab and adalimumab are medicinal products used in hospitals, and the majority of health care resources required for patients treated with bDMARDs are used in this environment. Consequently, the study focused on Spanish National Health System (SNS) hospitals and only data about the use of health care resources were collected and costs of the disease were expressed as direct health care costs.

Use of resources

Data were obtained from the review of patient records using the following methods: an *ad hoc* notebook for reviewing patient records and a questionnaire on the use of bDMARDs. The following data were taken from the patient records: a) the demographic and clinical characteristics of the patients; b) the dose and regime of the bDMARDs; c) the concomitant treatments; d) if the current bDMARD replaced another previously administered drug and where relevant, the reason for the change; e) the number of consultations; f) if hospitalisation was required and where relevant, the length of stay and finally; and g) the laboratory and diagnostic tests carried out. Furthermore, each hospital was asked to fill out a questionnaire about the use of the bDMARDs on the following aspects: a) who carried out the reconstitution, administration and, where relevant, the monitoring of the intravenous infusion of the bDMARD; b) the hospital department in which these interventions were carried out; and c) the amount of time required for these interventions. Costs deriving from adverse drug events were not included in the cost analysis. The mean doses of etanercept, infliximab and adalimumab were calculated from the individual doses of 407, 311 and 260 patients.

Health care costs

Drug treatment costs were estimated from the purchase prices (laboratory sales price, LSP) calculated using the public retail prices[13] and, in the case of bDMARDs, from the mean doses obtained in the PRAXIS study. The unit costs of the other resources (consultations, hospitalisation, tests, health care personnel) were obtained from a Spanish database of health care costs[14] and other Spanish sources[15]. All of the costs are stated in euros (€) and were updated in July 2006.

The cost of the following concomitant treatments was assessed: a) disease-modifying anti-rheumatic drugs (DMARD) such as azathioprine, cyclosporine, chloroquine, hydroxychloroquine, lefunomide, methotrexate, gold salts and sulfasalazine; b) non-steroidal anti-inflammatories (NSAIDs) and analgesics; c) corticosteroids; and d) other drugs (such as omeprazole).

In order to estimate the cost of failed treatment with a previous bDMARD, the rates of change observed in the study were used, and it was established that the efficacy assessment would be carried out 4 months from the start of treatment. Therefore, when a change occurred due to inefficacy or toxicity, the new treatment would be administered for a further two months (until six months were completed)[15]. It was also assumed that an additional consultation would be carried out if there was a change in treatment due to inefficacy and that failure due to toxicity would incur a cost of € 1,160.00. This was based on a previously published study in Spain, which assessed the cost of infections linked to infliximab or etanercept[15].

Base case and sensitivity analysis

Mean values and unit costs of the resources required were used to carry out a cost analysis of the base case.

A sensitivity analysis consists of modifying the values of the variables in which there is uncertainty in order to check to what extent the results of the base case are affected. In order to check its robustness, various single-factor sensitivity analyses were carried out in the following cases: a) 95% confidence interval (95% CI) for the mean dose of the bDMARDs observed in PRAXIS; b) possible minimum and maximum number of doses of infliximab and adalimumab to administer over a period of 6 months; c) 95% CI of the number of doses of bDMARDs to administer in 6 months, in accordance with

the PRAXIS study; d) 95% CI for body mass (kg) of patients treated with infliximab in order to establish the mean dose; e) minimum and maximum unit costs of the health care resources and of the hospital in which the bDMARD is administered; f) 95% CI of the reconstitution time (minutes) of 1 vial of the bDMARD; and g) 95% CI for the administration time (minutes) of 1 vial of the bDMARD.

Budget impact for Spanish National Health System hospitals

Budget impact analysis is of particular relevance for making decisions within the SNS. A budget impact analysis of the replacement of bDMARDs with a drug which imply lower costs per patient was carried out on three theoretical hospital populations: 50, 100 and 200 patients (for small, medium and large hospitals respectively) which have similar characteristics to those included in the PRAXIS study.

The impact on hospital budgets (IHB) in the SNS was calculated as follows[16]:

$$IHB = (AC_p * [N_p - N_e]) + (AC_e * N_e) - (AC_p * N_p)$$

AC_p corresponds to the average cost per patient treated with the bDMARDs that led to greater costs; N_p is the current number of patients undergoing treatment with the bDMARDs that generated higher costs. AC_e and Ne are the average costs of a patient treated with the bDMARDs which would lead to lower costs and the number of patients treated with this drug instead of a more costly bDMARD respectively, within a new hypothetical setting.

The analyses were carried out over one year, and theoretical rates ranging between 25 and 100% for replacing infliximab or adalimumab by etanercept were considered.

Statistical analysis

The statistical analysis was carried out using the "STATA" (StataCorp, College Station, TX: Stata Corporation) statistical package. The three bDMARDs were compared in all cases. The Student's t test was used to compare the means. The STATA prtest was used to compare proportions.

The calculation of the sample size required to establish differences was based on the comparison of the overall cost values of the three bDMARDs. Assessment was based on the following criteria: a) a relevant cost difference of € 300 between the bDMARDs, similar to that obtained in a previously published drug cost analysis[15]; b) a standard deviation of ± € 600; c) a $\alpha = 0.05$ risk for a bilateral hypothesis; and d) a $\beta = 0.05$ risk (power = 0.95). In accordance with these criteria, the estimated minimum sample size was 143 patients per group (a total of 429 patients).

RESULTS

Demographic and clinical characteristics of the population

The records of 1,111 patients who fulfilled the criteria from 41 Spanish hospitals were reviewed. Among these patients, 432 were treated with etanercept, 396 with infliximab and 283 with adalimumab. The hospitals which took part in the study were distributed as follows: Andalusia (n = 7), Aragon (n = 1), Asturias (n = 1), the Canary Islands (n = 1), Castile-La Mancha (n = 3), Castile and Leon (n = 2), Catalonia (n = 5), Extremadura (n = 2), Madrid (n = 5), Murcia (n = 3), Navarre (n = 1), the Basque Country (n = 1), and the Valencian Community (n = 9).

Table I shows no statistically significant differences in the majority of demographic characteristics (sex, body mass) or for the majority of characteristics between the three groups compared. Significant differences were observed in the age of patients treated with etanercept or infliximab (55.19 and 57.11 years; p = 0.034) and in the number of DMARDs previously administered to patients treated with etanercept, infliximab and adalimumab: 3.29; 2.94 (p = 0.004) and 2.96 (p = 0.01). Given that the other prognostic factors were similar and there were approximately three prior DMARDs for all treatments, it does not appear that the differences in age observed between the etanercept and infliximab samples are clinically relevant for interpreting the results.

Use of health care resources and clinical practice

Table II summarises the results for use of resources.

The mean doses of the bDMARDs were as follows: 48.90 mg of etanercept per week, 4.14 mg/kg of infliximab every eight weeks and 41.58 mg of adalimumab every two weeks (97.8, 138 and 104% respectively of the recommended doses). Furthermore, administration intervals were as follows: etanercept was administered every 1.00 weeks (95% CI 0.9916-1.0084); infliximab was administered every 7.61 weeks (95% CI 7.4698-7.7502), and adalimumab was administered every 1.98 weeks (95% CI 1.9468-2.0132). These results determined the treatment costs mentioned below.

Cost estimate

The unit costs used in the analysis are summarised in table III. Tables IV and V show the results of the cost analysis of the base case.

Table I. Demographic and clinical characteristics of the patients in the PRAXIS study

Ítem	*Etanercept*	*Infliximab*	*p*[a]	*Adalimumab*	*p*[b]
Demographic characteristics					
Total number of patients	432	396	–	283	–
Age in years (SE)	55.19 (13.23)	57.11 (12.68)	0.034	55.93 (13.58)	NS
Sex, % women	77.86	81.27	NS	77.30	NS
Body mass					
N	150	320	–	119	–
kg (SE)	67.19 (13.63)	67.92 (12.05)	NS	69.48 (14.74)	NS
Clinical characteristics					
Steinbrocker functional class					
N	78	84	–	54	–
Class I, % of patients	28.21	38.10	NS	14.81	NS
Class II, % of patients	34.62	40.48	NS	38.89	NS
Class III, % of patients	26.92	20.24	NS	40.74	NS
Class IV, % of patients	10.26	1.19	NS	5.56	NS
Positive rheumatoid factor					
N	425	388	–	272	–
Yes, % of patients	69.18	64.95	NS	72.06	NS
No, % of patients	17.88	25.00	NS	18.01	NS
Unknown % of patients	12.94	10.05	NS	9.93	NS
Number of years since diagnosis of rheumatoid arthritis					
N	389	364	–	265	–
Years (SE)	11.20 (6.63)	12.01 (7.01)	NS	11.32 (7.35)	NS
Number of DMARDs with which the patient is being or has been treated					
N	398	366	–	262	–
Number of DMARDs (SE)	3.29 (1.64)	2.94 (1.67)	0.004	2.96 (1.57)	0.010
Previous treatment with steroids					
N	425	386	-	278	–
Yes, % of patients	84.94	87.05	NS	89.21	NS
No, % of patients	10.82	9.84	NS	6.12	NS
Unknown % of patients	4.24	3.11	NS	4.68	NS

[a]Statistical differences between the results of etanercept and infliximab; [b]statistical differences between the results of etanercept and adalimumab. Abbreviations: SE: standard error of the mean; DMARDs: disease-modifying anti-rheumatoid drugs; N: number of observations; NS: non-statistically significant difference ($p < 0.05$).

The total six-monthly costs of a patient treated with etanercept, infliximab or adalimumab were € 6,662.84, € 7,240.77 and € 7,569.52 respectively. Therefore, the average savings per patient treated with etanercept for six months was € 577.94 compared to treatment with infliximab and € 906.68 compared to treatment with adalimumab (Tables IV and V).

The sensitivity analyses carried out confirmed the robustness of the base case in the majority of criteria considered, with six-monthly savings per patient which ranged between € 395.79 and € 644.32 compared to infliximab and between € 672.09 and € 1,159.46 compared to adalimumub (Table VI). Treatment with infliximab was less expensive than with etanercept and adalimumab when the minimum theoretical number of doses of infliximab was considered (3 doses in six months).

Impact on hospital budget

The reduction in costs for the patients treated with etanercept could lead to savings in the hospital budget which would range approximately between € 14,500 and € 231,100 if etanercept replaced infliximab and between € 22,600 and € 362,600 if etanercept replaced adalimumab, depending on the replacement rate and the size of the hospital population (Table VII).

Assuming that the theoretical number of cases considered in the budget impact analysis (50, 100 or 200) corre-

Table II. Use of health care resources and clinical practice observed in the PRAXIS study (6 months)

Resource	*Etanercept*	*Infliximab*	*p*[a]	*Adalimumab*	*p*[b]
Mean dose of bDMARDs (frequency)	48,90 mg (weekly)	4,14 mg/kg (every 8 weeks)	–	41,58 mg (cada 2 semanas)	–
Mean number of bDMARD units (dose and frequency)	1,96 (25 mg weekly)	2,81 (of 100 mg every 8 weeks)	–	1,04 (of 40 mg every 2 weeks)	–
Concomitant treatments (%)					
N	425	394	–	283	–
DMARD					
Azathioprine	0,24	1,27	NS	0,71	NS
Cyclosporine	1,18	1 ,27	NS	1 ,41	NS
Chloroquine	0,71	0,76	NS	4,59	0,0007
Hidroxychloroquine	1,41	0,51	NS	1,06	NS
Leflunomide	13,88	16,50	NS	13,43	NS
Methotrexate	47,06	89,09	< 0,0001	65,72	< 0,0001
Gold salts	0,00	1,27	0,0198	0,35	NS
Sulfasalazine	0,24	0,00	NS	0,00	NS
NSAIDs/analgesics	61,65	57,11	NS	56,18	NS
Corticosteroids	27,06	23,10	NS	25,09	NS
Others	2,82	3,30	NS	5,65	NS
Change in the bDMARD (%)[c]					
N	421	388	–	280	–
A etanercept from	–	38,00	–	6,00	0,0104
A infliximab from	2,00	–	–	3,00	NS
A adalimumab from	12,00	23,00	–	–	–
Reason for the change in the previous bDMARD (%)					
N	421	388	–	280	–
Lack of efficacy	9,00	32,00	< 0,0001	5,00	NS
Toxicity	2,00	18,00	< 0,0001	1,00	NS
Mean number of consultations per patient (SE)					
Doctor (Rheumatology Dept.)	2,02 (1,13)	2,92 (1,59)	< 0,0001	1,94 (1,24)	NS
Doctor (Internal Medicine Dept.)	0,09 (0,42)	0,12 (0,51)	NS	0,17 (0,59)	0,0490
Doctor (Accident and Emergency Unit)	0,21(0,68)	0,16 (0,64)	NS	0,23 (0,94)	NS
Doctor (other departments)	0,63 (1,25)	0,53 (1,22)	NS	0,67 (2,23)	NS
Hospital nurse	0,40 (1,33)	2,36 (2,20)	< 0,0001	0,42 (2,33)	NS
Primary health care nurse	1,93 (9,38)	0,15 (2,35)	0,0002	0,51 (2,51)	0,0030
Hospitalisation rate (%)					
N	432	396	–	282	–
Rheumatology Dept.	0,70	1,50	NS	3,20	0,0112
Internal Medicine Dept.	1,90	1,30	NS	1,80	NS
Accident and Emergency Unit	3,20	2,00	NS	3,90	NS
Other departments	2,80	0,80	0,0295	6,40	0,0189
Mean No of days hospitalised (SE)					
Rheumatology Dept.	14,67 (5,51)	4,17 (2,71)	< 0,0001	10,44 (10,36)	< 0,0001
Internal Medicine Dept.	11,25 (5,87)	6,80 (8,31)	< 0,0001	7,00 (1,58)	< 0,0001
Accident and Emergency Unit	20,60 (41,97)	6,63 (4,31)	< 0,0001	8,82 (8,48)	< 0,0001
Other departments (mean)	7,78	5,67	–	6,64	–
Mean No of tests (SE)					
N	432	396	–	282	–
Thoracic radiograph	0,21(0,58)	0,19 (0,56)	NS	0,29 (0,71)	NS
Nuclear magnetic resonance	0,05 (0,25)	0,02 (0,12)	0,0261	0,05 (0,23)	NS
Echography	0,09 (0,38)	0,08 (0,30)	NS	0,08 (0,28)	NS
Tuberculin (Mantoux, PPD)	0,02 (0,15)	0,03 (0,21)	NS	0,04 (0,23)	NS
Anti-DNA antibodies and others	0,81 (1,19)	1,17 (1,35)	< 0,0001	0,72 (1,04)	NS
Hepatic function	1,79 (1,47)	1,66 (1,95)	NS	1,82 (1,38)	NS

(See the following page)

Table II. Use of health care resources and clinical practice observed in the PRAXIS study (6 months) (continuation)

Resource	*Etanercept*	*Infliximab*	*p*[a]	*Adalimumab*	*p*[b]
Full haemogram	2.01 (1.31)	2.64 (1.29)	< 0.0001	2.11 (1.40)	NS
Erthrocyte sedimentation rate	1.81 (1.16)	2.45 (1.27)	< 0.0001	1.81 (1.12)	NS
C-reactive protein (CRP)	1.68 (1.14)	2.42 (1.33)	< 0.0001	1.71 (1.18)	NS
Urea. creatinine. serum electrolytes	1.81 (1.24)	2.59 (1.44)	< 0.0001	1.98 (1.43)	NS
Other tests					
Urine analysis	0.10	0.24	–	0.34	–
General biochemistry	0.01	0.01	–	0.05	–
Coagulation	0.04	0.01	–	0.02	–
Cholesterol/lipids	0.05	0.02	–	0.01	–
Rheumatoid factor	0.08	0.06	–	0.12	–
Blood glucose	0.05	0.02	–	0.07	–
Proteinogram	0.03	0.04	–	0.05	–
Radiographs (excluding thorax)	0.15	0.14	–	0.13	–
Others	0.28	0.63	–	0.52	–
Reconstitution (%)					
Carried out by, N	37	36	–	34	–
Patient	82.57	0.00	< 0.0001	0.00	–
Pharmacist	0.00	5.39	< 0.0001	0.00	–
Nurse	17.22	94.61	0.0102	0.00	–
Auxiliary nurse	0.21	0.00	NS	0.00	–
Time taken to reconstitute 1 vial (minutes) (SE)	5.35 (3.85)	6.36 (4.80)	NS	–	–
Administration (%)					
Carried out by, N	34	34	–	25	–
Patient	85.00	0.00	< 0.0001	84.40	NS
Pharmacist	0.00	5.39	< 0.0001	0.00	NS
Nurse	14.78	94.61	< 0.0001	15.60	NS
Auxiliary nurse	0.22	0.00	NS	0.00	NS
Time taken to administer 1 vial (minutes) (SE)	3.60 (3.83)	120.82 (34.97)	–	4.32 (5.93)	–
Monitoring of administration (%)					
Carried out by, N	–	36	–	–	–
Patient	–	0.00	–	–	–
Pharmacist	–	0.00	–	–	
Nurse	–	100.00	–	–	–
Auxiliary nurse	–	0.00	–	–	–
Time taken to monitor 1 vial (minutes) (SE)	–	101.78 (61.95)	–	–	–
Place of administration and control (%)					
N	36	38	–	–	–
Patient's home	68.63	0.00	< 0.0001	64.40	NS
Health care centre	25.75	0.00	< 0.0001	25.76	NS
Outpatient hospital	3.11	83.46	< 0.0001	4.40	NS
Rheumatology Dept. (and others)	0.83	16.54	0.0242	0.88	NS

[a]Statistical differences between the results of etanercept and infliximab; [b]statistical differences between the results of etanercept and adalimumab; [c]change in bDMARD for whatever reason (lack of efficacy, toxicity or others). Abbreviations: SE: standard error of the mean; DMARDs: disease-modifying anti-rheumatoid drugs; bDMARDs: biological disease-modifying anti-rheumatic drugs; N: number of observations; NS: non-statistically significant difference ($p > 0.05$).

sponds to the size of the hospital (small, medium, large), the replacement of infliximab by etanercept in small, medium or large hospitals could lead to savings for each hospital of € 14,000-58,000, € 29,000-115,000 or € 58,000-231,000 respectively. Hypothetically if adalimumab was replaced by etanercept this could lead to savings of € 22,000-90,000, € 45,000-181,000 or € 90,000-362,000 for a small, medium or large sized hospital respectively (Table VII).

DISCUSSION

The observational studies help to estimate the actual use of the bDMARD drugs used to treat RA in clinical practice. The appearance of pharmacological resistance to treatment with these drugs has been described in the literature, in particular with infliximab, although this aspect must be studied further in adequately designed comparative clinical studies[7-9].

Table III. Unit costs used in the cost analysis of the PRAXIS study (euros –€– July 2006)

Resources	*Mean*	*Minimum-Maximum*	*Reference*
bDMARDs			
Etanercept (Enbrel, 4 vials of 25 mg)[a]	539.25	–	13
Infliximab (Remicade. 1 vial of 100 mg)[a]	604.43	–	13
Adalimumab (Humira, 2 syringes of 40 mg)[a]	1,116.12	–	13
Concomitant treatments			
Azathioprine (Imurel, fifty 50 mg tablets)[a]	11.27	–	13
Cyclosporine (Sandimmun Neoral, thirty 100 mg tablets)[a]	102.88	–	13
Chloroquine (Resochin, fifty 250 mg tablets)[a]	6.76	–	13
Hydroxychloroquine (Dolquine, thirty 200 mg tablets)[a]	11.44	–	13
Leflunomide (Arava, thirty 20 mg tablets)[a]	89.90	–	13
Methotrexate (M. Lederle, fifty 2.5 mg tablets)[a]	3.29	–	13
Gold salts (Riduara, thirty 30 mg tablets)[a]	14.58	–	13
Sulfasalazine (Salazopyrin, five hundred 500 mg tablets)[a]	29.45	–	13
Aceclofenac (Airtal, five hundred 100 mg tablets)[a]	126.93	–	13
Diclofenac (D. Aldo Union, forty 50 mg tablets)[a]	2.84	–	13
Ibuprofen (I. Alter, thirty 400 mg tablets)[a]	2.09	–	13
Naproxen (N. Ratiopharm, forty 500 mg tablets)[a]	6.23	–	13
Deflazacort (Dezacor, twenty 6 mg tablets)[a]	8.90	–	13
Prednisolone (Dacortin, sixty 5 mg tablets)[a]	3.01	–	13
Methylprednisolone (Urbason, thirty 4 mg tablets)[a]	2.98	–	13
Omeprazole (O. Alter, twenty-eight 20 mg tablets)[a]	8.04	–	13
Water for injection (one hundred 5 ml vials)[a]	20.53	–	13
Health care resources			
Doctor's consultation at the Rheumatology Dept.	45.16	36.13-57.22	14
Doctor's consultation at the Internal Medicine Dept.	57.58	31.59-108.31	14
Doctor's consultation at the Accident and Emergency Unit	36.69	–	14
Doctor's consultation at other departments	49.92	–	14
Nurse consultation in the hospital	24.65	21.88-26.42	14
Nurse consultation in Primary Health Care	16.28	10.48-22.66	14
Admission to Rheumatology Department (1 day)	374.55	168.92-592.56	14
Admission to Internal Medicine Department (1 day)	287.47	154.94-409.04	14
Admission to Accident and Emergency Unit (1 day)	476.79	414.75-562.99	14
Admission to other departments (1 day)	379.60	–	14
Outpatient visits	154.54	86.73-212.97	14
Visits to primary health care centre	20.48	18.78-22.18	14
Toxicity requiring change in treatment	1,160	–	15
Tests			
Thoracic radiograph	20.45	4.95-42.94	14
Nuclear magnetic resonance	355.89	100.05-620.21	14
Echography	37.25	–	14
Tuberculin (Mantoux. PPD)	4.00	2.89-5.10	14
Anti-DNA antibodies and others	17.90	12.34-22.61	14
Hepatic function	13.46	12.23-14.67	14
Full haemogram	13.00	10.36-16.95	14
Erthrocyte sedimentation rate	2.61	0.60-6.90	14
C-reactive protein (CRP)	10.30	2.42-44.73	14
Urea. creatinine. serum electrolytes	2.31	0.45-6.01	14
Urine analysis	3.71	1.72-6.01	14
General biochemistry	5.37	2.60-16.75	14
Coagulation	19.48	13.52-27.76	14
Cholesterol/lipids	6.84	0.48-51.04	14
Rheumatoid factor	8.52	2.42-24.19	14
Blood glucose	1.99	0.39-9.06	14
Proteinogram	4.51	–	14
Radiographs (excluding thorax)	16.73	14.05-18.13	14
Other tests (mean)	30.24	–	14
Personnel			14
Pharmacy (cost per hour)	33.49	–	14
Nursing (cost per hour)	23.07	–	14
Auxiliary Nursing (cost per hour)	11.79	–	14

[a]Public retail price, plus 4% VAT; the calculations of costs are based on laboratory sales prices (LSP).

Table IV. Average costs per patient in the PRAXIS study in accordance with the bDMARD used. Base case (6 months) (euros –€– July 2006).

Cost	*Etanercept*	*Infliximab*	*Diferencia*[d]	*Adalimumab*	*Diferencia*[e]
Treatment with the bDMARDs					
Cost according to frequency	231.59[a]	1,507.97[b]	–	534.45[c]	–
Six-monthly cost subtotal	*5,558.26*	*5,790.59*	*-232.33*	*6,670.00*	*-1,111.74*
Concomitant treatments					
DMARDs	13.00	14.90	-1.90	15.51	-2.51
NSAIDs/analgesics	8.00	7.41	0.59	7.29	0.71
Corticosteroids	7.64	6.52	1.12	7.09	0.55
Others	0.48	0.56	-0.08	0.96	-0.48
Six-monthly cost subtotal	*29.13*	*29.40*	*-0.27*	*30.85*	*-1.72*
bDMARD failure					
Change of treatment to etanercept	-	-29.74[f]	29.74	-23.82[f]	23.82
Change of treatment to infliximab	1.66	-	1.66	-7.33[g]	8.99
Change of treatment to adalimumab	68.66	68.75[g]	-0.09	-	68.66
Extra consultations due to lack of efficacy	4.18	14.43	-10.25	2.42	1.76
Toxicity requiring change in bDMARD treatment	24.80	209.28	-184.48	8.29	16.51
Six-monthly cost subtotal	*99.30*	*262.72*	*-163.42*	*-20.45*	*119.75*
Consultations					
Rheumatology Dept.	91.22	131.87	-40.64	87.61	3.61
Internal Medicine Dept.	5.18	6.91	-1.73	9.79	-4.61
Accident and Emergency Unit	7.70	5.87	1.83	8.44	-0.73
Other Medical Departments	31.45	26.46	4.99	33.45	-2.00
Hospital nurse	9.86	58.17	-48.31	10.35	-0.49
Primary health care nurse	31.42	2.44	28.98	8.30	23.12
Six-monthly cost subtotal	*176.84*	*231.72*	*-54.88*	*157.94*	*18.90*
Hospitalisation					
Rheumatology Dept.	38.16	23.66	14.49	124.80	-86.64
Internal Medicine Dept.	59.89	24.68	35.21	35.68	24.21
Accident and Emergency Unit	318.30	63.86	254.44	164.04	154.27
Other medical departments	82.07	16.30	65.78	160.96	-78.88
Six-monthly cost subtotal	*498.42*	*128.50*	*369.92*	*485.47*	*12.95*
Tests					
Thoracic radiographs	4.29	3.89	0.41	5.93	-1.64
Nuclear magnetic resonance	17.79	7.12	10.68	17.79	0.00
Echography	3.35	2.98	0.37	2.98	0.37
Tuberculin (Mantoux, PPD)	0.08	0.12	-0.04	0.16	-0.08
Anti-DNA antibodies and others	14.50	20.94	-6.44	12.89	1.61
Hepatic function	24.09	22.34	1.75	24.50	-0.40
Full haemogram	26.13	34.32	-8.19	27.43	-1.30
Erthrocyte sedimentation rate	4.72	6.39	-1.67	4.72	0.00
C-reactive protein (CRP)	17.30	24.93	-7.62	17.61	-0.31
Urea, creatinine, serum electrolyte	4.18	5.98	-1.80	4.57	-0.39
Urine analysis	0.39	0.91	-0.52	1.28	-0.89
General biochemistry	0.04	0.07	-0.03	0.27	-0.23
Coagulation	0.81	0.15	0.66	0.48	0.33
Cholesterol/lipids	0.35	0.12	0.23	0.10	0.25
Rheumatoid factor	0.65	0.47	0.18	1.03	-0.38
Blood glucose	0.10	0.03	0.07	0.15	-0.05
Proteinogram	0.14	0.17	-0.04	0.24	-0.10
Radiographs (excluding thorax)	2.44	2.41	0.03	2.14	0.30
Other tests (mean)	8.40	18.94	-10.54	15.66	-7.26
Six-monthly cost subtotal	*129.76*	*152.28*	*-22.52*	*139.92*	*-10.16*
Administration of the bDMARDs					
Six-monthly cost TOTAL	*171.14*	*645.55*	*-474.42*	*105.79*	*65.35*
Six-monthly cost totals	*6,662.84*	*7,240.77*	*-577.94*	*7,569.52*	*-906.68*

[a]Weekly; [b]every 8 weeks; [c]every 2 weeks; [d]difference between etanercept and infliximab; [e]difference between etanercept and adalimumab; [f]failures with initial bDMARD are treated with a less expensive rescue bDMARD; [g]failures in the initial bDMARD are treated with a more expensive rescue bDMARD. Abbreviations: DMARDs: disease-modifying anti-rheumatoid drugs; bDMARDs: biological disease-modifying anti-rheumatic drugs.

Table V. Results of the PRAXIS study cost analysis: base case (6 months)

Cost	*Etanercept*	*Infliximab*	*Difference*[a]	*Adalimumab*	*Difference*[b]
Treatment with the bDMARDs	5,558.26 (83.4%)	5,790.59 (79.9%)	-232.33 (3.5%)	6,670.00 (88.1%)	-1,111.74 (-4.7%)
Concomitant treatments	29.13 (0.4%)	29.40 (0.4%)	-0.27 (0%)	30.85 (0.4%)	-1.72 (0%)
bDMARD failure	99.30 (1.5%)	262.72 (3.6%)	-163.42 (-2.1%)	-20.45 (-0.3%)	119.75 (1.8%)
Consultations	176.84 (2.6%)	231.72 (3.2%)	-54.88 (-0.6%)	157.94 (2.1%)	18.90 (0.5%)
Hospitalisation	498.42 (7.5%)	128.50 (1.8%)	369.92 (5.7%)	485.47 (6.4%)	12.95 (1.1%)
Tests	129.76 (1.9%)	152.28 (2.1%)	-22.52 (-0.2%)	139.92 (1.8%)	-10.16 (0.1%)
Administration of the bDMARDs	171.14 (2.5%)	645.55 (8.9%)	-474.42 (-6.4%)	105.79 (1.4%)	65.35 (1.1%)
Six-monthly cost totals	*6,662.84*	*7,240.77*	*-577.94*	*7,569.52*	*-906.68*

[a]Difference between etanercept and infliximab; [b]difference between etanercept and adalimumab. Abbreviations: bDMARDs: biological disease-modifying anti-rheumatic drugs.

Table VI. Results of the PRAXIS study cost analysis: sensitivity analysis (6 months)

Settings	*Difference etanercept-infliximab*	*Difference etanercept-adalimumab*
Base case	-577.94	-906.68
Sensitivity analysis		
95% CI of the mean dose of the bDMARD (mg)		
Lower limit of 95% CI	-414.52	-824.91
Upper limit of 95% CI	-741.35	-988.46
Possible minimum and maximum numbers of doses during 6 months of treatment with infliximab and adalimumab		
Minimum number of doses	422.77	-672.09
Maximum number of doses	-772.31	-1.159.46
Number of doses over 6 months, in accordance with the 95% CI of the intervals observed for administration of bDMARD		
Lower limit of 95% CI	267.64	-675.57
Upper limit of 95% CI	207.95	-790.57
95% CI of the body mass of the patients treated with infliximab (kg)		
Lower limit of 95% CI	-488.73	-906.55
Upper limit of 95% CI	-666.47	-906.82
Minimum and maximum unit costs of the health care resources (€)		
Minimum costs	-644.32	-863.04
Maximum costs	-521.68	-951.90
Minimum and maximum unit costs of the centre administering treatment (€)		
Minimum costs	-395.79	-914.50
Maximum costs	-735.70	-899.66
95% CI of the reconstitution time (minutes) of 1 vial		
Lower limit of 95% CI	-599.07	-931.95
Upper limit of 95% CI	-557.00	-881.62
95% CI of the administration time (minutes) of 1 vial		
Lower limit of 95% CI	-599.65	-877.03
Upper limit of 95% CI	-556.50	-936.50

CI 95% confidence interval; bDMARDs: biological disease-modifying anti-rheumatic drugs.

Table VII. Results from the analysis of the impact on hospital budgets (IHB) with respect to etanercept prescribed (the treatment which led to the fewest costs) instead of infliximab or adalimumab, in patients with rheumatoid arthritis of the type included in the PRAXIS study

bDMARDs which would be replaced by etanercept	*Number of patients being treated with previous bDMARD (Np)*	*% for theoretical replacement*	*Number of patients who would change treatment to etanercept (Ne)*	*Coste anual por patient treated with bDMARDs who would change treatment (ACp)*	*Annual cost per patient treated with etanercept (ACe)*	*Net cost for the hospital (IHB)**
Infliximab	50	25%	13			-€ 14,448.40
		50%	25			-€ 28,896.80
		100%	50			-€ 57,793.59
	100	25%	25			-€ 28,896.80
		50%	50	€ 14,481.55	€ 13,325.68	-€ 57,793.59
		100%	100			-€ 115,587.19
	200	25%	50			-€ 57,793.59
		50%	100			-€ 115,587.19
		100%	200			-€ 231,174.37
Adalimumab	50	25%	13			-€ 22,667.10
		50%	25			-€ 45,334.20
		100%	50			-€ 90,668.39
	100	25%	25			-€ 45,334.20
		50%	50	€ 15,139.04	€ 13,325.68	-€ 90,668.39
		100%	100			-€ 181,336.79
	200	25%	50			-€ 90,668.39
		50%	100			-€ 181,336.79
		100%	200			-€ 362,673.57

IHB = (ACp[Np-Ne])+(ACe*Ne)-(ACp*Np).
Abbreviations: ACe: annual cost per patient treated with etanercept; ACp: annual cost per patient treated with infliximab or adalimumab; IHB: impact on hospital budget; bDMARDs: biological disease-modifying anti-rheumatic drugs (etanercept, infliximab or adalimumab); Ne: number of patients who could theoretically change treatment to etanercept (Np): Number of patients being treated with previous bDMARD (infliximab or adalimumab).

Given that the objective established for the PRAXIS study (use of resources and costs linked to treatment with the three bDMARDs) is clearly influenced by the relation between the recommended doses and those actually used in clinical practices, the results helped establish that the mean doses of etanercept, infliximab and adalimumab were 97.8, 138 and 104% respectively, of the recommended doses. This would appear to indicate the following: a) a small number of patients treated with etanercept receive a weekly dose of 25 mg (the minimum recommended dose); b) a significant number of patients treated with infliximab receive higher doses to those recommended in their data sheets; and c) a small number of patients treated with adalimumab are treated with the maximum recommended dose.

In the base case of the analysis, the mean cost of the six-monthly treatment with bDMARDs of a patient with rheumatoid arthritis in Spain is estimated at € 6,662.84 with etanercept, € 7,240.77 with infliximab (€ 577.94 more) and € 7,569.52 with adalimumab (€ 906.68 more). These results were robust for the majority of the sensitivity analyses carried out, with six-monthly savings per patient which ranged between € 395.79 and € 644.32 compared to infliximab and between € 672.09 and € 1,159.46 compared to adalimumub. There was only an additional cost with etanercept (€ 422.77 per patient) compared to infliximab, when considering the minimum theoretical number of doses of this drug (3 doses in six months) and not the mean number of doses in clinical practice, estimated from the PRAXIS study.

This study has strengths and weaknesses related to its design and development. Among its weaknesses is its retrospective design, which led to the loss of some data, which were not available in a small number of patients' records. As a result, the analyses had to be carried out taking into account the patients available in each case. However, one of the strengths of the study is the fact that the results obtained could be seen in clinical practice, and could therefore be applied to similar populations to that used in the PRAXIS study. Another strength of the study was the robustness of the results in the large majority of

the sensitivity analyses carried out, mainly based on the 95% CI limits of the mean values obtained in the study.

Although adverse drug events (ADE) recorded in patient records were included, these were not taken into account when assessing the cost of the disease since neither the study design nor the sample size were adequate to assess the frequency with which the ADE appeared, or differences in the severity of these with the bDMARDs.

It is to be noted that the budget impact analysis of hypothetically replacing infliximab or adalimumab with etanercept was carried out over a period of 1 year in order to adapt it to the SNS's budget. However, it should be borne in mind that the results of the first six months may not necessarily be the same as those for the subsequent six months, and that this factor could favour or negatively affect the etanercept option.

It was difficult to compare the results with those from other studies due to the lack of similar studies. In 2005 in Spain, the Costs and Quality of Life Study Group for Rheumatoid Arthritis of the Spanish Society of Rheumatology (SER) published the results of a cost analysis for a cohort of patients with RA who received treatment in 10 rheumatology departments in Spanish SNS hospitals[3]. In this study, the average annual cost per patient was estimated at € 3,845 (between € 318 and € 36,783) and in the case of patients treated with bDMARDs, the average annual cost per patient amounted to € 5,111 (between € 1,616 and € 15,345)[3]. The main conclusion drawn in the SER study was that there was wide variability in the costs observed. It should be pointed out that the figures for both studies cannot be compared since they refer to average and mean costs respectively. However, the maximum annual limit of the SER study (€ 15,345 per patient) would be similar to the annual costs per patient observed in the PRAXIS study, which would range between a minimum of € 13,326 with etanercept and a maximum of € 15,138 with adalimumab.

It is possible to compare the distribution of costs per patient with RA between the SER study and the PRAXIS study. In the first study drug treatment costs implied 56% of the total costs. However, it must be borne in mind that this figure includes all of the RA drugs, and not only the cost of the bDMARDs, which are more expensive, and therefore these corresponded to 80-88% of the total cost in the present study.

In another Spanish study, published in 2003[2], the mean cost per patient and year was estimated at 10,419 dollars in 2001, similar to the costs observed in the present study (given in euros in July 2006).

In a recently published retrospective study of the costs linked to RA carried out on 1,647 patients over 10 months in the United States[17], very similar results to those obtained in this study were found. There were higher drug and outpatient costs for infliximab and adalimumab (55 and 12% respectively) than for etanercept. These differences were partly due to increases in the doses of bDMARDs compared to the mean initial doses: 17.4% for infliximab, 11.2% for adalimumab and 4.1% for etanercept.

The results are indicative of a recently published systematic review of the medical literature, carried out by Spanish rheumatologists[18]. The aim of the review was to assess the proportion of patients with RA being treated with infliximab and etanercept who require an increased dose. They reviewed 1,801 references; 16 studies including a total of 8,510 patients were selected from these. Among these patients 44% of those treated with infliximab and 17.5 of those treated with etanercept required an increased dose. It was necessary to reduce the dose interval for 8.3% of patients treated with infliximab.

Both the retrospective study carried out in the United States[17] and the systematic review carried out by Ariza et al.[18] confirm the main finding of our study: the mean doses of infliximab and adalimumab actually used in clinical practice were 138 and 104% respectively of the recommended doses.

It is to be pointed out that in a recent systematic review[19] which analysed the efficacy and cost-effectiveness of etanercept, infliximab and adalimumab in the treatment of rheumatoid arthritis, at the recommended dose the number of patients that it would be necessary to treat (NNT) (95% CI) to obtain an ACR20 response (a 20% improvement in painful and inflamed joints, in accordance with the American College for Rheumatology criteria) was as follows: 2.1 (1.9 to 2.4) for etanercept, 3.2 (2.7 to 4.0) for infliximab and 3.6 (3.1 to 4.2) for adalimumab. The same trend (favouring etanercept over infliximab and adalimumab) was seen for the NNT to obtain an ACR50 response (improvement of 50% in joints): 3.1 (2.7 to 3.6); 5.0 (3.8 to 6.7) and 4.2 (3.7 to 5.0) respectively[19].

According to the results of the PRAXIS study, the treatment of rheumatoid arthritis with etanercept compared to treatment with infliximab and adalimumab could reduce hospital costs. However, these results must be confirmed in a pragmatic, randomised clinical trial, which compares the efficacy, tolerance and use of health care resources with the three biological disease-modifying anti-rheumatic drugs[12].

Anex I

Hospital	*Investigadors*
1. Hospital de Alcorcón, Madrid	Patricia Sanmartín Fenollera
	Inés Gil Navarro
	María Luisa de Carlos Soter
	Montserrat Pérez Encinas
2. Hospital del Bierzo, León	Miriam Rodríguez María
3. Hospital Carlos Haya, Málaga	María Ángeles Rosado
	Rosa Romero Jiménez
	Paula Pérez Puente
4. Hospital General Universitario de Elche	Rosa Antón Torres
5. Hospital de Figueres, Gerona	Virginia Gol Vallés
	Montiel Faus
	Inmaculada Coma
6. Hospital de Galdakao, Vizcaya	Oihana Mora Atorrasagasti
	María José Martínez Bengoechea
	Ana María de Juan Arroyo
	Estíbaliz Franco
	Javier Peral Aguirregina
	Ana Iglesias
	Unai Lentxundi
	Itxasne Gabilondo Zelaia
7. Consorcio Hospital General Universitario, Valencia	Alejandro Bernalte Sesé
	Javier Guevara Serrano
	Raquel Minuesa Sánchez
8. Hospital de Guadalajara	Ana Álvarez Díaz
	Eva Martín Alcalde
	Marta Blasco Guerrero
	Miriam Heredia Benito
	Paula de Juan García Torres
	Susana Canales Ugarte
	Gema Marcos Pérez
	Alicia Lázaro López
9. Hospital General Universitario de Alicante	Juan Pablo Ordovás Baines
	Pepa Polache Vengud
	Francisco Martínez Granados
	Teresa Martínez Lazcano
10. Hospital Universitario Central de Asturias, Oviedo	Miguel Al-Kassam Martínez
	Maribel Magaña Pintado
	Ana Olebem Blanco
	Carmen Rosado
	María Paz Sacristán de Lame
	Lucía Velasco Roces
11. Hospital Infanta Cristina, Badajoz	Juan Francisco Rangel Mayoral
12. Hospital Universitario Insular de Gran Canaria	Lourdes García Reina
	Carlos Vidal López
13. Hospital Universitario Dr. Josep Trueta, Girona	Rocío Gil Partal
	Maria Ángeles Bobis Casas
14. Hospital Universitario La Fe, Valencia	Julia Hernández Martín
	Eva Romá Sánchez
	Emilio Monte Boquet
	Laura Domeñech Moral
15. Hospital La Paz, Madrid	Yolanda Larrubia Marfil
	Elena Villamañan Bueno
	María Ángeles Campos Fernández de Sevilla
16. Hospital La Princesa, Madrid	Concepción Martínez Nieto
17. Hospital Lluís Alcanyís, Xátiva	Teresa Faus Soler
	Guillermo Sangrador García
18. Hospital Miguel Servet, Zaragoza	Mercedes Arenere Mendoza
	Herminia Navarro Aznárez
19. Hospital General Universitario Morales Meseguer, Murcia	Joaquín Plaza Aniorte
20. Hospital Mútua de Terrassa	María Ángeles Parada
21. Hospital de Mérida, Badajoz	Jesús Luis Fernández
	Yolanda González Gudiño
22. Hospital de Móstoles, Madrid	Susana Lorenzo Giménez
	Rosa Catalá Pizarro

(See the following page)

Anex I (continuation)

Hospital	*Investigadores*
23. Hospital de Navarra, Pamplona	Juana Alfaro Basarte
24. Hospital Parc Taulí, Sabadell	Nuria Rudi Sola
25. Hospital de Puerto Real, Cádiz	Carmen Martínez Díaz
26. Hospital de Sagunto	Joaquín Borrás Blasco
	Amparo Sánchez Pedroche
27. Hospital de Salamanca	Dominica Morán González
28. Hospital Universitario San Cecilio, Granada	Antonio Salmerón García
	Miguel Damas Fernández-Fígares
	Francisco Rodríguez Lucas
29. Hospital de San Jorge, Huesca	María Aránzazu Alcácera López
30. Hospital Clínico Universitario San Juan, Alicante	María Ángeles Pardo López
31. Hospital de la Santa Creu i Sant Pau, Barcelona	María Luisa Sala Esteban
	María Antonia Cortés
	Nuria Sabaté Frías
32. Hospital Santa María del Rosell de Cartagena	Lucía Villamayor Blanco
33. Hospital Severo Ochoa. Leganés, Madrid	María Ramalla Jiménez de Llano
	María Amparo Lucena Campillo
	Elena García Benayas
34. Hospital Torrecárdenas, Almería	María José Tarín Remohi
	Inmaculada Alferer
	Arancha Pou Alonso
	Esther Fernándes
	Marta Meleón Ruiz
	Emilio Molina
	Antonio Sánchez Arcos
	Susana Cifuentes Cabello
35. Hospital de Valme, Sevilla	Isabel Martínez Alonso
	María Miguel del Corral
36. Hospital de la Vega Baja. Orihuela, Alicante	Ana García Monsalve
	Pilar Campillos Alonso
	Pedro García Salom
37. Hospital Universitario Virgen de la Arrixaca, Murcia	María José Sánchez Garre
38. Hospital Virgen de la Concha, Zamora	José Roldán González
39. Hospital Virgen de la Salud, Toledo	José M. Martínez Sesmero
	Paloma Moya Gómez
	María Fernández Arevag
40. Hospital Clínico Virgen de la Victoria, Málaga	José Manuel Fernández Ovies
41. Hospital Virgen del Rocío, Sevilla	Amparo Lluch Colomer
	María Espinosa Bosch
	Roberto Marín Gil

References

1. Carmona L, Ballina J, Gabriel R, Laffon A on behalf of the EPISER Study Group. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. Ann Rheum Dis 2001; 60: 1040-5.
2. Lajas C, Abásolo L, Bellajdel B, Hernández-García C, Carmona L, Vargas E, et al. Costs and predictors of costs in rheumatoid arthritis: a prevalence-based study. Arthritis Rheum 2003; 49: 64-70.
3. Ruiz-Montesinos MD, Hernández-Cruz B, Ariza-Ariza R, Carmona L, Ballina J, Navarro-Saravia F, y Grupo de Estudio de Costes y Calidad de Vida en Artritis Reumatoide de la Sociedad Española de Reumatología. Análisis de costes en una cohorte de enfermos con artritis reumatoide atendidos en área especializada de reumatología en España. Reumatol Clin 2005; 1: 193-9.
4. Resumen de características del producto: Enbrel (etanercept) vial de 25 mg. Berkshier: Wyeth Europe Ltd; 2001.
5. Resumen de características del producto: Remicade (infliximab) vial de 100 mg. Leiden: Centocor BV; 1999.
6. Resumen de características del producto: Humira (adalimumab) vial de 40 mg. Kent: Abbott Laboratories Ltd; 2003.
7. Finckh A, Simard JF, Gabay C, Guerne PA, SCQM physicians. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis 2006; 65: 746-52.
8. Zink A, Listing J, Kary S, Ramlau P, Stoyanova-Scholz M, Babinsky K, et al. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis 2005; 64: 1274-9.
9. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid

arthritis patients in southern Sweden. Arthritis Rheum 2006; 54: 600-6.
10. Barton P, Jobanputra P, Wilson J, Bryan S, Burls A. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumor necrosis factor in rheumatoid arthritis. Health Technol Assess 2004; 8 (11).
11. Navarro F. Análisis económico en un servicio de reumatología: análisis de costes en artritis reumatoide. Rev Esp Reumatol 2002; 1 (Supl. 2): 45-6.
12. Rubio-Terrés C, Sacristán JA, Badía X, Cobo E, García Alonso F, por el Grupo ECOMED. Métodos utilizados para realizar evaluaciones económicas de intervenciones sanitarias. Med Clín (Barc) 2004; 122: 578-83.
13. Base de datos de medicamentos. Consejo General de Colegios Oficiales de Farmacéuticos. Disponible en URL: http://www.portalfarma.com/home.nsf (consulta: septiembre, 2006).
14. Gisbert R, Brosa M. Base de datos de costes sanitarios. Versión 2.2. Barcelona: Soikos; 2005.
15. Hernández-Cruz B, Rubio-Terrés C, Ariza-Ariza R, Domínguez-Gil Hurlé A, Navarro-Sarabia F. Evaluación económica de etanercept frente a infliximab-metotrexato en el tratamiento de la artritis reumatoide resistente a fármacos antirreumáticos modificadores de la enfermedad. Pharmacoeconomics Spanish Research Articles 2004; 1 (2): 73-85.
16. Brosa M, Gisbert R, Rodríguez JM, Soto J. Principios, métodos y aplicaciones del análisis del impacto presupuestario en el sector sanitario. Pharmacoeconomics Spanish Research Articles 2005; 2: 65-78.
17. Bullano MF, McNeely BJ, Fu YF, Quimbo R, Burawski LP, Yu EB, et al. Comparison of costs associated with the use of etanercept, infliximab and adalimumab for the treatment of rheumatoid arthritis. Man Care Interface 2006; 19: 47-53.
18. Ariza-Ariza R, Navarro-Sarabia F, Hernández-Cruz B, Rodríguez-Arboleya R, Navarro-Compan V, Toyos J. Dose escalation of the anti-TNF-α agents in patients with rheumatoid arthritis. A systematic review. Rheumatology (Oxford) 2007; 46: 529-32.
19. Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess 2006; 10: 1-248.