LETTER TO THE EDITOR

THE ECONOMIC BURDEN OF BIOLOGICAL THERAPY IN RHEUMATOID ARTHRITIS IN CLINICAL PRACTICE: COST-EFFECTIVENESS ANALYSIS OF SUB-CUTANEOUS ANTI-TNFα TREATMENT IN ITALIAN PATIENTS

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Rheumatoid arthritis (RA), with a prevalence of 0.46%, is found in about 272,004 patients in Italy. The socioeconomic cost of rheumatoid arthritis in Italy in 2002 has been estimated at €1,600 million. Cost-effectiveness evaluations have been based on the concept that, with treatment, patients will not progress to the next level(s) of disease severity or will take a longer time to progress, thus avoiding or delaying the high costs and low utility associated with more severe disease. Many cost-effective studies have been based on the variation of Health Assessment Questionnaire (HAQ) in clinical trials. The objective of this study is to perform a cost-effective analysis of 86 patients with rheumatoid arthritis in therapy with adalimumab 40 mg every other week and etanercept 50 mg/week for two years in a population of patients observed in clinical practice. The group of patients in therapy with adalimumab had also taken methotrexate, mean dose 12.4±2.5 mg/week (22 patients) or leflunomide 20 mg/day (16 patients). The group of patients in therapy with etanercept had also taken methotrexate, mean dose 11.7±2.6 mg/week (24 patients) or leflunomide 20 mg/day (24 patients). Incremental costs and QALYs (quality adjusted life years) gains are calculated compared with baseline, assuming that without biologic treatment patients would remain at the baseline level through the year. Conversion HAQ scores to utility were based on the Bansback algorithm. The results after two years showed: in the group methotrexate+adalimumab the QALY gained was 0.62±0.15 with a treatment cost of €26,517.62 and a QALY/cost of €42,521.13. In the group methotrexate+etanercept the QALY gained was 0.64±0.26 with a treatment cost of €25,020.96 and a QALY/cost of €39,171.76. The result of using etanercept in association with methotrexate is cost-effectiveness with a QALY gained under the acceptable threshold of €50,000. These are important data for discussion from an economic point of view when we choose a biologic therapy for rheumatoid arthritis in clinical practice.

Rheumatoid arthritis (RA), with a prevalence of 0.46%, is found in 272,004 patients in Italy (1). The socioeconomic cost of rheumatoid arthritis in Italy in 2002 was estimated at €1,600 million. The social cost is made up of indirect costs of €1,210 million and direct medical costs of €380 million.

Key words: cost-effectiveness, TNFα blocking agents (adalimumab-etanercept)

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In this study we calculated the average annual cost for a patient with RA and show a significant range of cost variation depending on disease severity. The study shows a correlation between Health Assessment Questionnaire Disability Index and ACR Steinbrocker criteria, with a total social cost from €3,718.30 in the first group to €22,946 in the fourth group (2). The cost-effectiveness of treatments that have the potential to change the "natural history" of a chronic progressive disease has to be evaluated over the long term. The approach involves the use of disease models based on epidemiological data where costs and quality of life (utility) are related to the measure of disease severity and progression (3). In the models for rheumatoid arthritis (RA), disease severity has been based on functional status measured by the Health Assessment Questionnaire (HAQ) and the outcome has been expressed as quality-adjusted life years (QALYs) (4). Cost-effectiveness estimates have been based on the concept that, with treatment, patients will not progress to the next level(s) of disease severity or will take a longer time to progress, thus avoiding or delaying the high costs and low utility associated with more severe disease (5). When analysing observational data on patients treated with tumour necrosis factor inhibitors, it was found that disease activity had a significant impact on utility, independently from HAQ (6).

Etanercept and adalimumab are TNF antagonists that are administered subcutaneously. Both can be self-administered at home, provided that the patient has no functional limitations. Many cost-effective studies are based on variation of HAQ in clinical trials. The objective of this observational study was rather to perform a cost-effectiveness analysis of adalimumab treatment in comparison with etanercept in a population of patients with moderate to severe RA observed in clinical practice.

MATERIALS AND METHODS

This analysis focuses on the use of biological agents in treating patients with moderate to severe RA for whom at least two traditional DMARDs had failed. The aim of our study is to evaluate the economic burden of 86 patients with rheumatoid arthritis in therapy with adalimumab 40 mg every other week and etanercept 50 mg/week for two years.

All patients have been followed-up in our outpatients Clinic for Biological Therapy in the Hospital San Giovanni di Dio in Florence, and have been visited every 3 months for two years. In all patients we calculated at baseline and every 3 months DAS28 and HAQ.

The group of patients in therapy with adalimumab had also taken a mean dose of methotrexate 12.4±2.5 mg/week (22 patients) or leflunomide 20 mg/day (16 patients). The group of patients in therapy with etanercept had also taken a mean dose of methotrexate 11.7±2.6 mg/week (24 patients) or leflunomide 20 mg/day (24 patients). All patients (86) were also in treatment with a mean dose of prednisolone, 5.2±2.6 mg/day.

Disease progression

Transition probabilities for the first 2 years were assessed on the basis of the observed transitions in the clinical trial for patients with an HAQ measurement at the beginning and at the end of each year. Transition probabilities beyond the trial are based on the average reported annual progression of HAQ (0.03). The primary outcome measure QALYs was derived from utility values calculated from a relationship with the Health Assessment Questionnaire (HAQ).

Model

Health-related quality of life

At every 6-month-point in the model, the patients' HRQoL (Health-related quality of life) scores were evaluated by simple linear transformation from the HAQ-DI score. This allowed to carry out a cost-utility analysis and, by combining HRQoL with life expectancy, a quality-adjusted life year (QALY) and single index utility was produced. All adalimumab trials used the Health Utility Index-III (HUI-3) as an indirect measure of health utility. An analysis of adalimumab trial data of almost 2,000 patients permitted the transformation from HAQ to HUI-3 (HUI-3 utility = 0.76–0.286 HAQ-DI+0.056 FEMALE, R2=0.49). This transformation was necessary because the etanercept and infliximab trials did not report any health utility measures. In addition, the HUI-3 has been validated as a good measurement for severe diseases. Incremental costs and QALY gains were calculated in relation to baseline, assuming that without biologic treatment the patients would remain at the baseline level throughout the year.

Utility

Utility scores were necessary in order to adjust patient survival for quality of life and consequently generate QALYs. A mechanism was incorporated in the model to map utilities from a disease severity measure (HAQ score). The assumption of this calculation is that we accept HAQ score as an indication of severity of the

Table I. *b-DMARDs naive patients: 12 months treatment.*

After one year of treatment	qaly gained	dev stnd	Cost/treatment	QALY/cost
All patients (86 pts)	**0.25**	**0.12**	**13,110.34**	**52,159.94**
L+E (24 pts)	0.25	0.11	13,089.22	51,583.13
L+A (16 pts)	0.17	0.08	13,837.60	79,469.34
M+A (22 pts)	0.29	0.08	13,258.86	45,294.24
M+E (24 pts)	0.26	0.16	12,510.48	47,658.97

Incremental costs and QALY gains are calculated compared with baseline, assuminq that without biologic treatment patients would remain at the baseline level througout the year. Conversion HAQ scores to utility based on Bansback (2005.)

Table II. *b-DMARDs naive patients: 24 months treatment.*

After two years of treatment	qaly gained	dev stnd	Cost/ treatment	QALY/cost
All patients (86 pts)	**0.57**	**0.22**	**26,211.17**	**46,307.58**
L+E (24 pts)	0.54	0.22	26,178.44	48,832.78
L+A(16 pts)	0.42	0.16	27,675.20	65,484.06
M+A (22 pts)	0.62	0.15	26,517.72	42,521.13
M+E (24 pts)	0.64	0.26	25,020.96	39,171.76

Incremental costs and QALY gains are calculated compared with baseline, assuminq that without biologic treatment patients would remain at the baseline level througout the year. Conversion HAQ scores to utility based on Bansback (2005).

condition and, therefore, a reliable link with utility values. It should be noted that this is standard practice in most RA published models to date. Conversion HAQ scores to utility were based on Bansback algorithm (7).

RESULTS

After one year of treatment (Table I), for all 86 patients we observed a QALY gain of 0.25±0.12 with a treatment cost of €13,110.34 and a QALY/cost ICER (incremental cost-effectiveness ratio) of €52,159.94. In the group leflunomide+etanercept the QALY gained was 0.25±0.11 with a treatment cost of €13,089.22 and a QALY/cost of €51,583.13.

In the group leflunomide+adalimumab the QALY gained was 0.17±0.08 with a treatment cost of €13,837.60 and a QALY/cost of €79,469.34. In the

group methotrexate+adalimumab the QALY gained was 0.29±0.08 with a treatment cost of €13,258.86 and a QALY/cost of €45,294.24. In the group methotrexate+etanercept the QALY gained was 0.6±0.16 with a treatment cost of €13,258.86 and a QALY/cost of €47,658.97.

The result after two years (Table II) of treatment for all 86 patients showed a QALY gained of 0.57±0.22 with a treatment cost of €26,211.17 and a QALY/cost ICER of €46,307.58. In the group leflunomide+etanercept the QALY gained was 0.54±0.22 with a treatment cost of €26,178.44 and a QALY/cost of €48,832.78. In the group leflunomide+adalimumab the QALY gained was 0.42±0.16 with a treatment cost of €26,178.44 and a QALY/cost of €65,484.06. In the group methotrexate+adalimumab the QALY gained was 0.62±0.15 with a treatment cost of €26,517.62 and a QALY/cost of €42,521.13. In the group methotrexate+etanercept the QALY gained was 0.64±0.26 with a treatment cost of €25,020.96 and a QALY/cost of €39,171.76.

DISCUSSION

This is the first Italian observational study that primarily evaluated quality of life and cost-effectiveness analysis of TNFα antagonists (adalimumab and etanercept) in a population with RA. The data of patients in therapy with two subcutaneous anti-TNFα antagonists showed that the optimum DMARDs association is with methotrexate. The cost of leflunomide in Italy is €641.01 in the first year of therapy and €620.56 in the second year, but the addition of monitoring brings the total cost from €691.84 to €819.21. On the other hand, the annual cost of methotrexate is €62.28 and with monitoring can reach a cost of €217.26 a year. The difference between methotrexate and leflunomide with a better cost-effectiveness was also shown in monotherapy (8). We evaluated only methotrexate and leflunomide DMARD because they are the most frequently prescribed drugs in association with anti-TNFα in clinical practice.

The administration of anti-TNFα as second line therapy is regarded as cost-effective compared to other well-accepted therapies with comparable cost-utility ratio <50,000/QALY gained (9). The data in literature showed different results for etanercept and adalimumab. The effective annual cost of two TNFα blocking agents plus methotrexate is respectivly €12,665 for etanercept and €12,258 for adalimumab. Moreover, a fixed cost of €688.36 for monitoring must be added.

The cost-effectiveness of adalimumab appears to be similar to the pooled etanercept results with a cost between €35,000 and €42,000 per year in a study of the Swedish population (7). In addition, a study of the USA population showed similar data (10). The two papers showed that the annual healthcare cost was significantly less than for infliximab patients. Also a switch from infliximab to adalimumab in patients with RA who have responded to infliximab is feasible with economic advantage (11).

The cost of adalimumab plus methotrexate per QALY was US $47,157 excluding productivity losses, and $19,663 including productivity losses. The cost-effectiveness of sequenced therapy initiated with adalimumab plus methotrexate extensively dominated both infliximab-plus-methotrexate-initiated and etanercept sequences. These data were evaluated in three different studies on early arthritis in a recent paper (12)

Also a recent paper on patients of Dutch Rheumatoid Arthritis Monitoring evaluated by HAQ for 12 months showed that adalimumab and etanercept are more or less equally favourable compared to infliximab in the first year of treatment (13). We have not compared patients treated with sub-cutaneous TNF-α antagonists with patients in infliximab therapy because the data from the literature showed that infliximab dose escalation incurred a 25% increase in mean one year cost (14).

More data from literature showed that etanercept was cost-effective. The comparison of etanercept with infliximab in the Dutch population showed a cost respectively of $12,648 *vs* $18,046 (15). Also, a retrospective study of health plan costs related to RA revealed that etanercept was associated with a lower drug and outpatient cost (4.1%) than both infliximab (17.4%) and adalimumab (12%) (16).

Furthermore, the incremental cost-effectiveness analysis of Birmingham Rheumatoid Arthritis Model (ICER) for etanercept used was £24,000 per QALY, which was substantially lower than for adalimumab (£30,000 per ICER). The data of meta-analyses were

evaluated by the National Institute for Health and Clinical Excellence (NICE) using ACR20-50-70 (17). A study of 160 patients with RA, followed-up for one year, showed an increase of QALY from 0.28 to 0.65 with data similar to those in our study (18).

An analysis was made of the use of health care resources and the associated costs for patients with RA, treated with three different biological anti-TNFα, in the Spanish National Health System Hospitals, covering 1,111 patients from 41 Spanish hospitals. This showed that the use of etanercept achieved a patient saving of €577.94 compared to infliximab and €906.00 for adalimumab. The study also showed that treatment with etanercept reduced hospital costs (19). The optimum cost-effective association in our study was etanercept-methotrexate. Also, the data from the TEMPO trial on 616 patients in a Markow model over two years showed an increased total cost of €14,221 in comparison with monotherapy with methotrexate and led to a QALY gain of 0.38. When the treatment was continued for 10 years, incremental costs were €42.148 for a QALYgain of 0.91. The cost per QALY gained was €37,331 and €46,494 repectively, with a cost-effectiveness ratio under a threshold of 50,000/QALY in 88% (20). This is the first economic study on Italian outpatients treated with sub-cutaneous anti-TNFα. The study included functional status, making a model better adapted to estimate the cost-effectiveness of treatment with a marked effect on disease activity. The benefit of using the association of etanercept-methotrexate is cost-effectiveness with a QALY/gained under the acceptable threshold of €50,000 in our observational study. This is an important finding for discussion and the decision of choice from the economic point of view when we start biological therapy for rheumatoid arthritis in clinical practice.

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