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REVIEW

TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden

G Kobelt, K Eberhardt, P Geborek

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Objectives: To evaluate costs, benefits, and cost effectiveness of tumour necrosis factor inhibitor treatment over one year in routine clinical practice.

Materials and methods: At four rheumatology units in southern Sweden treatment of 160 consecutive patients with RA was started with either etanercept or infliximab. The economic analysis was based on 116 patients with complete data who received treatment for at least one year. Details on drug treatment, functional capacity, disease activity, and laboratory values were available during the entire treatment. Information on resource use and QoL was collected at baseline and throughout the first year. The cost effectiveness analysis was based on changes in outcome and costs compared with the year before treatment. Cost per quality adjusted life year (QALY) gained was calculated for the entire sample and for patients with different levels of functional disability.

Results: During the first treatment year direct costs were reduced by 40%, but indirect costs did not change substantially. Patients' QoL improved on treatment—utility increased from an average of 0.28 to 0.65. Assuming that improvement occurred after three months' treatment, the cost per QALY gained is estimated as €43 500. If it occurs after six weeks, in parallel with clinical measures, the cost per QALY is €36 900. Sensitivity analysis, including all 160 patients, gave an estimated cost per QALY of €53 600. The cost per QALY increases for patient groups with less severe disease.

Conclusion: For this patient group, cost effectiveness ratios are within the generally accepted threshold of €50 000, but need to be confirmed with larger samples.

Whenever new treatments are introduced, their cost effectiveness has to be estimated from short term data from clinical trials. In chronic progressive diseases, cost effectiveness analysis generally involves estimating long term effects of treatments using disease models that incorporate disease symptoms and progression, as well as effects on costs and patients' quality of life (QoL). In rheumatoid arthritis (RA), a number of general economic models based on epidemiological data and observational studies have been proposed.^{1–3} All have shown a clear increase in costs with worsening physical disability, driven to a large extent by loss of work capacity. At the same time, patients' QoL—expressed as utility—has been shown to correlate highly with disease severity.^{2,4} Thus, treatments that delay progression could be expected to reduce the burden of RA by reducing some of the resource consumption, as patients remain for a longer time with mild disease, while at the same time increasing their QoL.

Over the past year a number of economic evaluations have been published in different countries, using such models to estimate the cost effectiveness of new treatments in RA based on clinical trials.^{5–9} These evaluations have shown that this hypothesis appears indeed correct, although none of the analyses found that savings were large enough to offset the cost of the new treatments. This leads to a number of critical questions: Does the clinical and QoL benefit justify the additional cost from the perspective of society, compared with other uses of these resources? Which patients should receive this treatment? And will the results in clinical practice differ from the clinical trials and early economic evaluation?

The question of whether reimbursement of expensive new treatments should be conditional upon showing similar benefits in clinical practice as in the models used at their introduction has been discussed over the past decade. In some special cases, the authorities have initiated follow up studies or patient registries, or they have urged companies to do so. The most well known case is multiple sclerosis, in particular the risk-sharing agreement between the National Health Service and companies in the United Kingdom. However, such studies are not currently required in any country.

Clinicians, on the other hand, have become increasingly interested in estimating consequences of treatment strategies used. Particularly in Sweden there is a long tradition of creating patient registries and special follow up studies. A nationwide registry for early RA was set up in 1995 and within this registry patients treated with the new biological drugs are currently specifically followed up. Since the introduction of the first biological drug in 1999, a regional observational follow up registry of patients given new treatments such as etanercept and infliximab has been implemented in southern Sweden (SSATG).¹⁰ Currently, this follow up registry includes over 90% of all patients in the area with prescriptions for these new agents.

Abbreviations: DAS28, 28 joint Disease Activity Score; DMARD, disease modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; NSAIDs, non-steroidal anti-inflammatory drug; QoL, quality of life; RA, rheumatoid arthritis; TNF, tumour necrosis factor

The current analysis aimed at evaluating RA related costs, benefits, and cost effectiveness of tumour necrosis factor (TNF) inhibitor treatment over one year, and extrapolating the analysis to the second year of treatment.

MATERIALS AND METHODS

Protocol

The development and approval of the clinical protocol has been reported.¹⁰ Four rheumatology centres participated in the present study (Helsingborg, Kristianstad, Trelleborg, and Lund). The centre in Lund recruits patients from primary, secondary, and tertiary care, but patients with RA are mostly recruited from primary care. The protocol was more comprehensive in Lund, recording detailed consumption of anti-TNF drugs and with closer follow up visits during the observation time. The quality control character of this observational study made it a part of the documentation required by the authorities in Sweden, and thus no formal ethical committee approval was required.

Patients

To be eligible for treatment with infliximab or etanercept, patients had to have a diagnosis of RA according to clinical judgment and have failed to respond to, or to be intolerant of, at least two disease modifying antirheumatic drugs (DMARDs), including methotrexate. Patients with any level of functional impairment and disability were offered treatment based on their current disease activity and/or unacceptable steroid requirement as judged by the treating doctor. In agreement with the guidelines of the Swedish Society of Rheumatology, no formal disease activity level other than the doctor's judgment was required and no restrictions on systemic or local glucocorticosteroid administration applied. Treatment of 160 patients with etanercept/infliximab was started between March 1999 and June 2000. Factors influencing choice of drug and dosage have been reported elsewhere.¹⁰ Patients who discontinued treatment were no longer followed up unless they started to receive one of the other study drugs. Only patients who continued to receive anti-TNF treatment for at least one year and had complete 12 month data were included in the current analysis.

Clinical data

At inclusion, age, diagnosis, disease duration, previous and current treatment with DMARDs, and current treatment with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) were recorded. Clinical data recorded included the validated Swedish version of the Health Assessment Questionnaire (HAQ)¹¹ and the 28 joint Disease Activity Score (DAS28).¹² During follow up, details of the use of anti-TNF treatments (Lund only), current systemic steroid and DMARD treatment and dosage, HAQ and DAS28 scores, and the use of NSAID and analgesics (recorded as yes/no/optional) were obtained at the mandatory visits at 3, 6, and 12 months (optional 0.5, 1.5, and 9 months) and thereafter every 3–6 months.

Health related QoL was collected during the first year using a generic preference based instrument, the EQ-5D,^{13–15} from the descriptive part of which utility values on a scale between 0 (death) and 1 (full health) for different health states can be developed. The visual analogue scale of EQ-5D was not used.

Economic data

Resource consumption and work capacity data for the year before treatment and the first anti-TNF treatment year were collected using a structured interview protocol. Only use strictly related to RA was recorded, and was limited to the most important resources in order to minimise the workload

for the clinics and to ensure that the data were of a high quality. The data thus comprised information on admission to hospital, surgical interventions, drug use, and short and long term work absence. Patients' out of pocket expenses and needs for community or informal care were not included.

Baseline data on drug use were assumed to reflect the situation for the year before the study. As no information on outpatient visits in the previous year was collected, computerised medical chart data for the patients from Lund were generalised to all patients. Patients from Lund accounted for more than 50% of the study cohort, and there was no significant difference between the Lund cohort and patients from the three other centres, with the exception of a somewhat longer disease duration and higher previous DMARD use. During the study, the mandatory follow up visits were used as a proxy for outpatient visits. For each administration of infliximab that did not coincide with a study visit, the cost of an outpatient visit was added (five visits). Drug use for the year before the study was calculated from the baseline data, using the mean cost of the four most prescribed anti-inflammatory and analgesic drugs in Lund. During the study detailed information on anti-TNF, DMARD, and prednisolone use was available. Valuation of direct resources was performed as in previous studies in Sweden,^{2–6} using unit costs available from the administration of the Lund hospital¹⁶ and the official drug list (FASS).¹⁷ Indirect costs were estimated by the human capital method using the average annual gross salary.¹⁸ Short term sick leave was based on the number of days of absence, and the loss of productivity was based on the proportion of full time work of patients aged <65.

Analysis

The main economic evaluation was based on patients who continued to receive anti-TNF treatment for at least 12 months and had complete data, as no data on resource consumption and utility were available for patients who discontinued treatment or were lost to follow up. A sensitivity analysis is presented including all 160 patients who started one of the treatments. In this analysis, we assumed that the withdrawals occurred regularly throughout the year and added the cost for six months of TNF inhibitor treatment at the initial dose, assuming no cost off set and no gains or losses of utility.

Costs and quality of life for different levels of disability at baseline and after 12 months were explored by grouping patients according to their functional capacity, as had been done in earlier studies.^{1–2}

Cost effectiveness was calculated as the incremental cost per QALY gained during the first year in the follow up. In the base case analysis, the QALY gain was calculated assuming an improvement of utility after three months of treatment. Sensitivity analyses are also presented for a linear utility improvement over the first treatment year, as well as an improvement after six weeks, in parallel with the improvement of clinical measures.

Influence of disease activity (DAS28) and disease severity (HAQ) on utility was assessed by multiple regression analysis, controlling for age and sex.

RESULTS

A total of 160 patients with RA started to receive anti-TNF treatment—113 patients received etanercept and 47 patients received infliximab. During the follow up, nine patients were switched between the treatments for diverse reasons. For the current analysis, 12 month data were available for 116 patients who continued to receive treatment for the full year. Of these, 71 patients had completed two years of treatment at the time of this analysis, and 40 patients three years. The

Table 1 Patient characteristics

	Baseline Mean (SD)	12 Months Mean (SD)	24 Months Mean (SD)	36 Months Mean (SD)
Number of patients	116	116	71*	40*
Female, No (%)	87 (75)	87 (75)	55 (77)	33 (83)
Age (years)	56.6 (12.9)	56.6 (12.9)	55.5 (12.8)	54.3 (11.8)
Disease duration (years)	14.2 (9.1)			
DAS28*(0–10)	5.85 (1.08)	3.42 (1.32)	3.40 (1.22)	3.52 (1.44)
HAQ score* (0–3)	1.52 (0.61)	1.13 (0.73)	1.08 (0.75)	1.09 (0.62)
ESR (mm/1st h)	44.1 (26.5)			
CRP (g/l)	45.4 (37.8)			
Previous DMARDs (n)	4.2 (2.1)			
Current DMARDs (n)	0.9 (0.7)			

*Completers at the time of this analysis.

majority of the 116 patients received etanercept at baseline (85), as it was officially introduced in Sweden earlier than infliximab. During the first year, HAQ and DAS28 scores improved, and remained constant thereafter for patients who continued to receive treatment. Table 1 shows patient characteristics at baseline. Figure 1 shows the development over three years of HAQ, DAS28, and systemic steroid requirements.

Of the 44 patients not included in the analysis, 9 were excluded owing to missing data although they continued to

receive anti-TNF treatment, 1 patient moved away and was lost to follow up, 2 patients refused to continue the study, and 2 stopped treatment for unknown reasons. Ten patients discontinued owing to treatment failure and for 20 patients treatment was stopped owing to adverse events. Most adverse events were mild and transient and did not require intensive treatment or admission to hospital: 5 patients had an allergic/infusion reaction, 12 had miscellaneous events (myalgia, nausea, chills, anguish, diarrhoea, skin itching, lupus-like syndrome) that did not require extensive medical investigation. One patient was diagnosed with mesothelioma six weeks after infliximab initiation and treatment was withdrawn. Three patients died, but a relationship with anti-TNF treatment is uncertain. One patient died at home with a history of recent gastroenteritis, and a postmortem examination did not show any obvious cause of death. One patient with known serious atherosclerotic disease underwent gynaecological surgery owing to bleeding 11 months after etanercept initiation. Treatment was stopped one week before surgery. The postoperative phase was complicated by wound healing problems, myocardial infarction, progressive myocardial failure and death. Microscopy disclosed a uterine cervical carcinoma without signs of spreading. Finally, one of the patients who had stopped owing to treatment failure five months after starting etanercept was found to have a lymphoma (immunocytoma) of the breast after 12 months and died after 18 months.

Table 2 shows resource consumption and utilities. For patients who continued to receive treatment, use of all types of resources decreased during the first year and consumption of anti-TNF treatments remained stable in the second year. The direct cost reduction was mostly due to a decrease in hospital care and surgery. The total number of orthopaedic procedures decreased from 63 events (56% per patient-year) in the year before the study to 32 events (28% per patient-year) during the treatment year. The corresponding numbers for major joint replacements (primary and revision) were 22% and 10%, for hand surgery 12% and 7%, and for other orthopaedic surgery 20% and 8%, respectively. Surgery related admission to hospital decreased from 857 days to 332 days for the sample. Admission to hospital in patients not undergoing surgery decreased from 593 days to 113 days. The number of acute care visits decreased by almost 50%, indicating a reduction in the need for local glucocorticosteroid injections. Outpatient visits increased owing to the use of the anti-TNF drugs. There was a slight increase in overall work capacity from 27% to 28%. For patients under 65 at baseline, work capacity increased from 31% to 33% during the first year of treatment, despite the fact that 2 patients retired (1.7%), increasing the proportion on normal retirement from 14.5% to 16.2%. Sick leave decreased from a mean of 1.6 (SD 5.0) days per patient to 1.1 (SD 2.6) days.

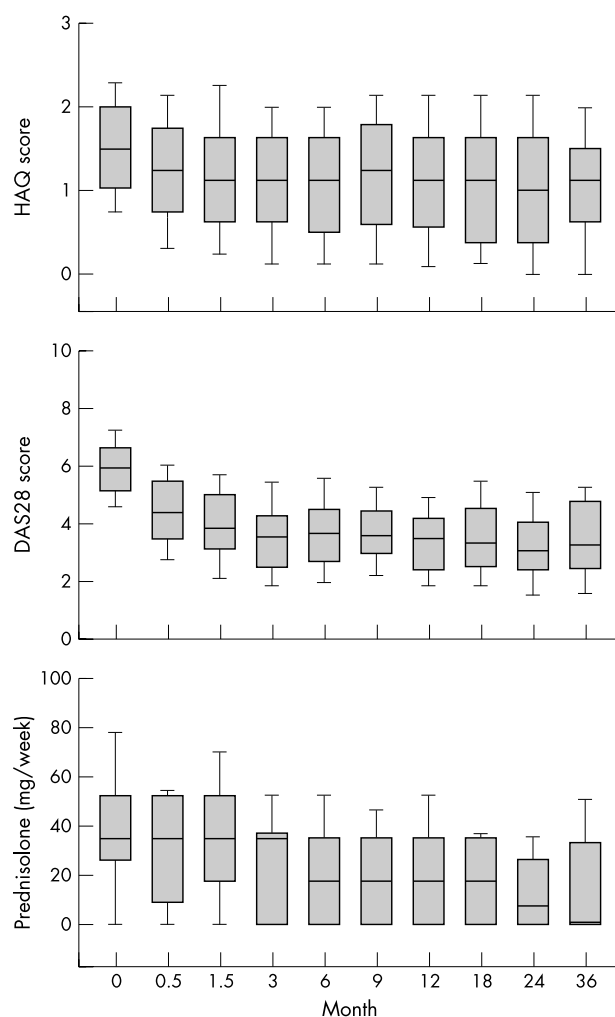


Figure 1 Development of functional disability (HAQ), disease activity (DAS28), and steroid use over time. The box plots represent the 10th, 25th, median, 75th, and 90th centiles.

Table 2 Mean costs per year (€, 2002) and utilities

	Baseline Mean (SD)	12 Months Mean (SD)	24 Months Mean (SD)
Utility	0.28 (0.33)	0.65 (0.23)	N/A
Work capacity, full sample (%)*	27	28	N/A
Work capacity, patients <65 (%)	31	33	N/A
Sick leave (days)	1.6 (5.0)	1.1 (2.6)	N/A
Indirect cost*	(17030)	(18110)	N/A
Total cost cortisone	97 (95)†	44 (52)	34 (44)
Total cost NSAID	21880	21739	87 (87)
Total cost analgesics	63 (51)†	51 (49)	54 (50)
Total cost DMARD	289 (734)†	109 (387)	98 (343)
Total cost hospital	3823 (7179)‡	1963 (3839)	N/A
Total cost surgery	569 (989)‡	356 (675)	N/A
Outpatient visits§	367	568¶	N/A
Acute care visits§	246	143	
Total cost anti-TNF treatment		14704	16202
		(3065)**	(3584)
Total costs	27447 (20933)	39630 (20829)	N/A

1 € = 9.05 SEK.

*Baseline and 12 months' status for the entire cohort, extrapolated to annual costs. Work capacity is expressed as full time equivalent—that is, full time work represents 100%, part time work actual percentage, and not working 0%; †usage at baseline, extrapolated to costs for the previous year; ‡retrospective data, previous year; §mean number of visits of the Lund cohort; ¶including visits for administration of infliximab; **use during study year.

Direct costs in the first year were reduced by 40% or €2250, thereby offsetting part of the cost of TNF inhibitor treatment. Total cost offsets amounted to €2520 or 10%, resulting in an incremental cost for TNF inhibitor treatment of €12 200.

Patients QoL improved with treatment, with utility increasing from an average of 0.28 to 0.65, a change of 0.37. Assuming that the improvement in utility occurs after three months of treatment (base case), the QALY gain for the first year can be estimated at 0.28, resulting in a cost per QALY gained of €43 500. If the utility improves gradually and in a linear fashion over the year, patients gain on average 0.19 QALYs, resulting in a cost per QALY gained of €64 100. When utility improves at six weeks (simultaneously with HAQ and DAS28) (fig 1), the QALY gain is 0.33 and the resulting cost per QALY) is €36 900. When only direct costs are included in the analysis, the respective incremental cost effectiveness ratios are €44 500 per QALY. The intention to treat analysis, including all 160 patients who started treatment, results in a cost per QALY of €53 600 for the first treatment year. The utility gain is larger in patients with more severe disease at baseline, and as a consequence, the

cost per QALY is lower for patients with higher HAQ scores (table 3).

Table 4 shows costs and utilities at the different levels of functional capacity defined in earlier studies.² Patients' HAQ levels improve during the study, and more patients are in benign levels of the disease. Although costs remain relatively constant (excluding anti-TNF treatment costs), utility is higher for patients at the same HAQ levels after treatment than for patients at these levels at baseline. Both HAQ and DAS28 correlated significantly with utility in this sample showing regression coefficients of 0.155 and 0.265 at baseline compared with 0.085 and 0.222 respectively at 12 months, and both remained significant when included in a multiple regression (table 5).

DISCUSSION

As far as we know the current study is the first to assemble comprehensive health economic data for patients with RA treated with anti-TNF drugs in clinical practice. Several of the findings need special attention.

Firstly, the study included a special patient group with longstanding disabling disease, refractory to treatment, resulting in very low EQ-5D scores at inclusion. Indeed, our earlier cross sectional studies have shown higher utility values at all levels of disability,^{1,2} despite a similar age and sex distribution (table 4). One explanation is the significant negative effect of disease activity (illustrated by DAS28) on utilities, which was not included in earlier studies. DAS28 is a continuous variable and has no simple cut off levels to designate high/medium/low levels of disease activity. However, compilation from different studies suggests that patients included in several clinical trials have DAS28 values above 5.¹⁹ Thus the high DAS28 scores at baseline may partly explain the low utility scores at the start of the study. It is, however, interesting to note that after 12 months' treatment patients' utilities at different levels of disability closely resemble those found in the earlier studies. One logical explanation for this finding may be that after treatment, these patients' disease activity is similar to that of any general sample of patients with RA. Consequently, conclusions must be drawn with great caution when comparing the actual patient material with established models and results from clinical trials.

The improvement in utility over one year is large, and is one of the major drivers in the cost effectiveness analysis. Despite the impact of the high disease activity mentioned, the possibility cannot be entirely excluded that patients overstated their problems at baseline, in order to be enrolled in the study with the new treatments. More likely, however, these patients were truly patients with the most severe disease. Patients enrolled currently seem to have somewhat

Table 3 Cost per QALY gained with one year treatment (€)

	No	Incremental cost (€)*	QALY gain*	Cost/QALY (€)
Direct costs only	116	12455	0.28	44500
Base case†	116	12184	0.28	43500
Improvement linear	116	12184	0.19	64100
Improvement after 6 weeks	116	12184	0.33	36900
Drop outs included	160	10727	0.2	53600
Patients with HAQ <0.6 at baseline	8	14131	0.11‡	128500
Patients with HAQ 0.6<1.1 at baseline	21	11131	0.18‡	61800
Patients with HAQ 1.1<1.6 at baseline	30	15241	0.25‡	61000
Patients with HAQ 1.6<2.1 at baseline	36	11176	0.30‡	37300
Patients with HAQ ≥2.1 at baseline	21	6888	0.16‡	43000

1 € = 9.05 SEK.

*Incremental costs and QALY gains are calculated compared with baseline, assuming that without TNF inhibitor treatment patients would remain at the baseline level throughout the year; †base case assumption for QALY gain: improvement of utility after three months.

Table 4 Costs and utilities at different levels of functional impairment

	Costs and utilities by levels of functional disability by HAQ				
	<0.6	0.6<1.1	1.1<1.6	1.6<2.1	≥2.1
<i>Baseline</i>					
Number of patients	8	21	30	36	21
Mean HAQ score	0.38	0.90	1.34	1.83	2.35
Mean DAS28	5.45	5.44	6.05	6.11	6.08
Mean utilities	0.680	0.455	0.299	0.174	0.063
Mean costs (€)	4350	19200	20550	36250	40850
<i>12 Months</i>					
Number of patients	29	24	33	16	14
Mean HAQ score	0.19	0.88	1.31	1.81	2.33
Mean DAS28	2.48	3.61	3.49	3.63	4.66
Mean utilities	0.829	0.686	0.634	0.576	0.270
Mean costs (€)	19140	38800	48100	49500	44000
<i>Epidemiological cohort, Lund*</i>					
Mean utilities	0.717	0.636	0.611	0.422	0.235

*See Kobelt *et al.*^{1,2}

milder disease and therefore higher utility scores (unpublished data). This can only be verified over time, when larger datasets become available.

Use of all types of direct resources decreased markedly during the first year, driven by the reduction in admission to hospital. Surgical interventions were reduced by half, with a lower proportion of major interventions, and one question that should be asked is whether this is a true effect of the treatment. Indeed, it might be possible that treatment is only started once planned elective surgery has been performed, thus increasing the number of interventions in the year before treatment artificially, or that interventions are postponed beyond the first year. In the latter case, one would expect an increase in interventions after the first year again. This was, however, not the case when studying patients from Lund (n = 100). Surgical procedures fell from 43% in the year before the study to 26% in the first treatment year and 14% and 18% in the second and third years, respectively. The corresponding figures for major joint replacement were 12, 9, 5, and 8%, for hand surgery 16, 8, 1, and 0%, and for other RA surgery 14, 8, 5, and 4%. The question whether there was an increase in surgery before the study cannot be answered with

this study group. We therefore compared our results with the proportion of interventions that were done in the 10 year follow up study in Lund.^{1,2} Although this was an inception cohort where over 70% of patients at baseline and over 50% of patients after 10 years had an HAQ of less than 1.1, the advantage of these data is that they were collected at the same clinic as the current study. For the entire cohort, the average proportion of surgical interventions during follow up years 3 to 10 was 16%. When only patients with an HAQ of 1.1 and higher are included, the proportion increases to 24%, and for patients with an HAQ of 1.6 and above, the proportion is 40%. For these latter patients, the proportion was around 80% during the fifth and sixth years of follow up. These proportions are comparable with those in the year before the current study, and it would appear that the reduction in surgeries is indeed an effect of the treatment.

As expected, savings in indirect costs are limited in a patient group of this age with severe disease where over 50% of patients have been on long term sick leave. These patients will not easily be reincorporated into the workforce within a short timeframe. Also, a number of patients reached retirement age during the year, while others obtained

Table 5 Correlations between utilities and DAS28 and/or HAQ at baseline and after 12 months

	Non-standardised coefficients		Standardised coefficient		p Value
	B	Std error	β	T	
<i>1A DAS28 at baseline</i>					
(Constant)	1.199	0.126		9.491	<0.001
DAS28-0	-0.155	0.021	-0.501	-7.246	<0.001
<i>1B DAS28 at 12 months</i>					
(Constant)	0.944	0.055		17.058	<0.001
DAS28-12	-0.085	0.015	-0.484	-5.534	<0.001
<i>2A HAQ at baseline</i>					
(Constant)	0.690	0.057		12.198	<0.001
HAQ-0	-0.265	0.035	-0.511	-7.630	<0.001
<i>2B HAQ at 12 months</i>					
(Constant)	0.898	0.031		28.799	<0.001
HAQ-12	-0.222	0.024	-0.677	-9.324	<0.001
<i>3A HAQ, DAS28 at baseline</i>					
(Constant)	1.233	0.177		10.544	<0.001
HAQ-0	-0.190	0.036	-0.365	-5.299	<0.001
DAS28-0	-0.112	0.21	-0.362	-5.255	<0.001
<i>3B HAQ, DAS28 at 12 months</i>					
(Constant)	0.982	0.045		21.621	<0.001
HAQ-12	-0.186	0.026	-0.584	-7.178	<0.001
DAS28-12	-0.036	0.014	-0.203	-2.494	<0.05

Dependent variable: 1A, 2A, 3A; utility at baseline: 1B, 2B, 3B; utility at 12 months.

invalidity pensions. Thus, although sick leave was reduced by half a day on average, overall work capacity increased only slightly during this study. This seemingly limited impact must, however, be seen in the light of the particularly severe disease in this patient group and the limitation of the calculations to patients in employment. Although in principle the costs of unpaid work should be included in a social perspective, there are major problems related to their measurement, valuation, and interpretation. Also, data collection in the study was limited, and therefore did not include this information. Similarly, no data on the effect of treatment on patients' ability to perform activities of daily living and the need for informal care were available, and costs may therefore be underestimated.

The cost per QALY gained is estimated to range between €36 900 and €53 600 during the first year, depending on the assumptions. However, it must be noted that cost effectiveness ratios are calculated based on the change of costs and utilities from baseline, rather than on a comparison with patients receiving other RA treatments. This is not standard practice in economic evaluation, and the numbers must therefore be considered with caution. In the absence of a direct comparison group in a study, it is often possible to collect data separately for an untreated group with the same baseline criteria. However, in this particular case, this was impossible, as most patients of the region with this level of disease severity were included in the follow up registry.

We have also chosen to present the main analysis for patients who continued to receive treatment, owing to the limited information available for patients who withdrew from the study. For the intention to treat analysis, we have included treatment costs, but no other costs or cost offsets, nor any change in utility. The rationale is that, although there is likely to be a gain in utility during the months on treatment even for patients who stopped, this might be off set by a disutility if withdrawal is due to adverse events. Similarly, there might have been a reduction in costs during the months of treatment, but this might be off set owing to the cost of treating adverse events. However, it is likely that our assumption is very conservative, as none of the adverse events required intensive treatment or admission to hospital. No patient in this cohort stopped treatment owing to infection; most patients stopped treatment because of mild symptoms, and all allergic/infusion reactions were self limiting with supportive care and day time observation. Costs due to adverse events were thus minimal. The overall reduction in admission to hospital further supports the notion that adverse events were not a major contributor to costs.

However, the three deaths that occurred within this study illustrate the problem of comorbidity in longstanding RA. It has not been possible to attribute these events to the treatment in a pre-post observational study with a limited number of patients over a limited time frame and without a control group. The results of an economic evaluation might be very different if all comorbidity encountered in a population with longstanding disease had to be attributed to a new treatment, but such an evaluation would require a strictly controlled randomised comparative study. Current adherence to treatment with anti-TNF drugs in the SSATG register remains remarkably consistent with the one previously reported.¹⁰ Of patients with RA starting treatment with etanercept, 82% continued to receive treatment after one year, 75% after two years and 72% after three years. The respective numbers for infliximab are 68%, 59%, and 56%. During these years, cumulative withdrawals due to adverse events were 10%, 13%, and 17% for etanercept and 21%, 31%, and 33% for infliximab (February 2003, 302 etanercept and 582 infliximab treatments started, unpublished data). This

suggests that adverse events, although contributing to comorbidity and withdrawal of these drugs, remain relatively limited and occur primarily during the first treatment year.

Despite a follow up of patients for up to three years, the cost effectiveness of treatment cannot be estimated beyond the first year, as no resource consumption or utilities measurements were available. Nevertheless, considering that both HAQ and DAS28 remain at their 12 month level during the second (and third) year for patients who continue treatment, one can speculate that costs and utilities also remain stable. With this assumption, the cost per QALY gained with treatment during two years would be €37 500, suggesting that the cost effectiveness ratio might be maintained beyond one year.

QALYs are an area under the curve, and when only two measurements are available as in this study, some assumptions have to be made about the rate of improvement of utilities throughout the year. As utility correlates with both disability (HAQ) and disease activity (DAS28), improvement in these measures was used to predict the timing of the utility improvement. However, in the base case a conservative estimate was used, with utility improving after three months, despite the clear improvement in disability and disease activity already after six weeks and maintenance of these levels thereafter (fig 1). If the improvement in QoL is assumed to be simultaneous with improvements in disability and disease activity, the QALY gain increases by 18% and the cost effectiveness ratio is reduced by 14%.

A cost effectiveness ratio will not itself provide information about whether a treatment is cost effective or not. A treatment strategy can only be judged to be cost effective in relation to other strategies, or other uses of the resources. One approach often used to put results into perspective is to compare them with those obtained in other fields, or other studies. More recently, results have been evaluated using the net benefit approach. Net benefit is defined as the monetary value of incremental effects minus incremental cost, and if the net benefit is greater than the willingness to pay for this benefit, the treatment being evaluated should be adopted. However, as there is currently no defined willingness to pay for a QALY, several approaches have been used to deduce this threshold. Recent studies used the threshold value for saving lives used by the Swedish road authority in investment decisions and estimated the value of a QALY at \$60 000.^{20 21} Similar amounts (€35–55 000) can be deduced from recent reimbursement decisions in Sweden. In the United Kingdom, recent recommendations for treatments by the National Institute of Clinical Excellence (NICE) seem to suggest a threshold of about £30 000 (€45 000).²² Authors in the United States have estimated the threshold at \$100 000 (€95 000 €) based on an estimate of the value of lives saved.²³

Using a willingness to pay for a QALY of €60 000, anti-TNF treatment in this cohort appears acceptable under most assumptions, except when utility improvement is assumed to be linear (table 3). Generally, one would expect cost effectiveness ratios to be higher for less severe disease, as the potential for improvement is smaller. This was found to be the case in this cohort, despite the limited sample size in each group. The cost per QALY is, however, driven mostly by the higher utility gain of patients with more severe disease, while the incremental cost at the different levels of HAQ varies. This is partly owing to a different mix of the two anti-TNF treatments in each group, and partly to differences in costs of admission to hospital. Nevertheless, the estimates indicate that over one year, anti-TNF treatment is more cost effective in patients with more advanced disease. However, in view of the small number of patients in each group, and the possibility that the gain in

utility is overstated, no firm conclusion can be drawn from these estimates.

In all health economic studies the quality of data collection is essential. Our study was observational and based on clinical practice, implying the possibility of compliance problems. However, both patients and responsible health professionals were very motivated and aware of the importance of the accuracy of information. To improve data quality the amount of information gathered was minimised to the absolute essential, implying some assumptions about costs. The study recorded current RA drug use at study enrolment as valid for the pretreatment year, because detailed data on past drug use can only be collected from patients for a short period of time. Computer search of medical records in Lund was used to ascertain data, because patients in this centre were similar to patients from the other centres. Thus, costs of the most current NSAID and analgesics during the year before treatment of the Lund patients were generalised to all patients. The same approach could not be used to estimate the cost of outpatient visits during the treatment year(s), as the treatment protocol in Lund was more intensive than in the other clinics. The number of visits planned in the standard protocol was therefore used.

The reduction in acute care visits (table 2), generally required for local steroid injections, during the first treatment year supports the notion that the four standard protocol visits are a fair estimation of outpatient visit needs during anti-TNF treatment.

In earlier studies, the clinical outcome was based on the HAQ. Functional disability has been shown in several studies to correlate with both costs and quality of life.²⁻⁴ However, the current analysis shows that in patients with longstanding and disabling, as well as active disease, disease activity may exert an additional negative impact on QoL, leading to low utility values. Therefore the analysis is limited to the period of time for which data are available rather than extrapolating to the longer term as in previous studies. This may underestimate the cost effectiveness of treatment, because it ignores a possible effect of treatment on progression in the longer term, as might be suggested by the continuing small numbers of surgical procedures beyond the first year in the Lund patients. However, as more data on subgroups of patients with severe and active disease become available, it may be possible to make more accurate estimates of the QALY gain over several years and assess long term effects with the new treatments.

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