Cost-effectiveness of infliximab in the treatment of rheumatoid arthritis in clinical practice

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Abstract

Objective

We evaluated the cost-effectiveness of infliximab therapy in Finnish RA patients in a real-life clinical setting and identified factors influencing it, using the national register of biological treatment (ROB-FIN).

Methods

A cost-utility analysis was performed, derived from EQ-5D, and related to HAQ score and disease activity using multiple regression. QALYs were calculated based on these utilities, using patient-level data up to the last control registered. Cost-effectiveness analyses included costs per ACR50 responder, and costs per low DAS28 score (<3.2) achieved, in combination with a clinically significant improvement (>1.2). The costs considered were direct medical costs of infliximab and cost of intravenous infusion. Patient-level costs were calculated based on dose and dosage frequency, and were related to the difference in QALYs resulting from infliximab therapy.

Results

The 297 patients had been treated with infliximab for an average of 21 months. The HAQ score and patient's global assessment improved significantly on infliximab therapy. More than two-thirds of the patients achieved a clinically important improvement in HAQ. A QALY gain occurred in 76%. 35% of these had an incremental cost-effectiveness ratio of ≤40,000 Euro/QALY gained, the median cost being 51,884 Euro. The cost per QALY gained was significantly lower for patients achieving an ACR50 response at 3, 12 and 24 months.

Conclusion

Treatment with infliximab and aiming at ACR50 response appears cost-effective, remembering the restrictions of an observational study set up. Current Care guidelines, which require sufficient disease control when deciding on continuing biological therapy, get support from these findings.

Key words

Biologicals, register, retrospective observational study.

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Introduction

Rheumatoid arthritis (RA), an autoimmune disease the natural course of which is characterized by chronic polyarticular synovial inflammation and progressive joint damage, affects approximately 0.8% of adults. Although the prevalence of RA is relatively low, its public health implications are significant. RA patients require access to a broad range of healthcare services, such as primary care and rheumatology service, physiotherapy, rehabilitation and orthopedic surgery. RA is associated with loss of function and working ability, resulting in a major economic and social burden.

In addition to the healthcare services mentioned above, pharmacological therapy forms one of the cornerstones of treatment. The introduction of biological antirheumatic drugs has significantly improved the prognosis and outcome of RA refractory to conventional therapies. The improvement comes at much higher drug costs, making cost-effectiveness analyses (CEAs, including cost-utility analyses, CUAs, a particular form of CEA) of the biologicals pertinent. In the absence of long-term effectiveness data, most published CEAs combine efficacy data from short-term randomized controlled trials (RCTs) with extrapolation and modelling based on observational data. Due to the essential differences between RCT and real-life clinical settings, questions and discussion have been raised regarding the sample representativeness of RCT patients and the discrepancy between efficacy and effectiveness, factors which may substantially influence CEA results (1-3). The patient inclusion criteria and flare design of the RCTs may increase responsiveness, which, in turn, may lead to overestimation of cost-effectiveness (2). In general, it is recognized that the effect of drugs tends to be better in controlled clinical trials than in a real-life clinical setting (1-4).

The purpose of the present study was to evaluate the cost-utility and cost-effectiveness of infliximab therapy in Finnish RA patients in a real-life clinical setting and to identify factors influencing it, using the national register of biological treatment, ROB-FIN, set up by the Finnish Society for Rheumatology (5-8). The concept of cost-utility and cost-effectiveness, in general and in the context of RA, have been reviewed in detail elsewhere (9, 10).

Methods

Patient selection

It is recommended by the Finnish Society for Rheumatology that patient selection for biological therapy in the treatment of RA should be based on the Finnish national Current Care guidelines (Käypä hoito, www.kaypahoito.fi) and the clinical judgment of a specialist. According to the Current Care guidelines, anti-tumor necrosis factor (anti-TNF) therapy is warranted if (1) the patient suffers from severe and continuously active disease (swollen joints and tender joints ≥6 and morning stiffness >45 min and/or erythrocyte sedimentation rate (ESR) ≥30 mm/h and/or C-reactive protein (CRP) ≥28 mg/l), (2) his/her response to combination therapy with conventional disease modifying antirheumatic drugs (DMARDs) (including methotrexate ≥15 mg/week) and low-dose predniso(lo)ne is unsatisfactory, but (3) he/she responds favorably to the biological drug, aiming at an American College of Rheumatology 50% (ACR50) (11) response after 3 months of therapy. For ROB-FIN register study participation, informed consent from the patient is required. The study was conducted with permission from local ethics committees and the national Data Protection authority. For inclusion in the present study, it was also required that (1) the patient had RA, (2) the patient started infliximab as the first-choice biological, (3) a baseline report and at least one subsequent report had been filed, and (4) the baseline Health Assessment Questionnaire (HAQ) score and patient's global assessment at commencement of infliximab therapy had been reported. No other inclusion or exclusion criteria were imposed.

Assessment of effects and costs

A CUA was performed in which utilities were appointed according to Kobelt *et al*. (12) (Table I). The utilities are derived from the five-dimensional

health state classification instrument EQ-5D, and have been related to HAQ score and disease activity using multiple regression. They are based on a survey of 616 patients with confirmed RA, carried out in 2002 by the department of rheumatology at Malmö University Hospital in Sweden. Quality-adjusted life years (QALYs) were calculated based on these utilities, using patient-level data up to the last control registered in ROB-FIN.

In Finland, infliximab therapy is, in practice, usually added to ongoing DMARD therapy (5). In the present study, it was therefore assumed that (1) infliximab therapy was added to a DMARD or DMARD combination, which had been optimized for the individual patient using a trial-and-error saw-tooth method according to our current clinical rheumatological practice, but which had not led to a satisfactory response, and (2) that the patient would have continued using a further optimized DMARD or DMARD combination had biological therapy not been available. Furthermore, the effect onset of infliximab therapy was assumed to occur two weeks after the commencement (13). The following assumptions were made for the patients had they not been treated with infliximab: (1) the disease activity, as measured by the patient's global assessment (mm visual analog scale, VAS), was assumed to stay at the baseline level, and (2) the HAQ score was assumed to progress 0.031 units/year (14). The changes in QALYs resulting from infliximab therapy were calculated based on these assumptions.

The costs considered in the present study consist of the direct medical costs as follows: cost of infliximab 622.22 Euro/100 mg (1Euro = approx. $1.5), and cost of intravenous infusion 211.73 Euro/administration (used in the communication with national drug pricing and reimbursement authorities; Schering-Plough, personal communication, 2007). Patient-level costs were calculated based on dose and dosage frequency, and they were related to the change in QALYs resulting from infliximab therapy. The costs and effects were not discounted in this retrospective study.

Table I. Utilities by functional capacity and disease activity (Kobelt *et al*. 2005, 12).

Functional state (HAQ)	Utility when global VAS <40 mm	Utility when global VAS ≥40 mm*
<0.6	0.780	0.709
0.6 to <1.1	0.704	0.568
1.1 to <1.6	0.676	0.441
1.6 to <2.1	0.562	0.446
≥2.1	0.408	0.213

*A global VAS ≥40 mm indicates high disease activity.

Table II. Baseline disease characteristics.

	Mean	Median	IQR	Range
Swollen joints	13	11	7 to 16	0 to 48
Tender joints	13	12	6 to 19	0 to 53
Patient's global assessment (mm VAS)	61	65	49 to 79	0 to 100
Pain (mm VAS)	61	65	47 to 80	0 to 100
ESR (mm/h)	41	37	20 to 58	0 to 134
CRP (mg/l)	43	32	14 to 60	0 to 250
Doctor's global assessment (mm VAS)	66	75	50 to 75	16 to 100

The OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) consensus recommends that economic analyses report QALY calculations in combination with more disease-specific outcome measures (10). Therefore, also two CEAs were performed: one in which the cost per ACR50 responder was calculated at 3, 12, 24 and 36 months, and one in which the cost per low disease activity score (DAS28, <3.2) achieved (15), in combination with a clinically significant improvement (>1.2), was calculated at the aforementioned control time-points.

Statistics

The data were analyzed with SPSS statistical software, version 14.0 (SPSS, Chicago, IL). Variable descriptives were checked to find any extreme values or errors in data input. Baseline demographics and disease characteristics were assessed using frequency calculations and descriptive statistics. Categorical data were analyzed with the Chi-square test. Between-groups comparisons were performed using the Kruskal-Wallis H test; in case of a statistically significant overall result, pairwise Mann-Whitney U testing was performed. Paired data were analyzed using the Friedman test; in case of a statistically significant overall result, Wilcoxon signed-rank testing was performed. Nonparametric tests were used due to skewed distributions of the data. The significance level was set at $p<0.05$ in all statistical testing. Two-tailed levels of significance were used throughout.

Results

Patient demographics

Two hundred and ninety-seven patients fulfilled the selection criteria above. Their mean age was 51 years (standard deviation 11 years, range 18 to 78 years). 69% (n=204) were women. The mean disease duration, calculated from the year of diagnosis, was 12 years (median 10 years, interquartile range (IQR) 6 to 17 years, range 0 to 47 years, n=220). 62% had seropositive and 24% had seronegative disease; in 14% this data was unknown or unspecified. The mean baseline HAQ score was 1.330 (median 1.250, IQR 0.750 to 1.875, range 0 to 3). Additional baseline disease characteristics are presented in Table II. Approximately half of the patients fulfilled the Current Care recommendations for commencement of anti-TNF therapy. The rest did not fulfil one or more of the clinical criteria (swollen joints, tender joints, acute phase reactant), indicating that some patients may be receiving therapy for particular reasons outside of the Current Care recommendations. For those who fulfilled the

recommendations, median (range) for swollen joints (54-joint count), tender joints (53-joint count), ESR (mm/h) and CRP (mg/l) were 14 (6 to 48), 16 (6 to 53), 50 (5 to 116) and 52 (4 to 250), respectively. For those who did not fulfil the recommendations, the corresponding values were 7 (0-35), 6 (0-40), 22 (0-134) and 16 (0-202), respectively.

The dosage of infliximab in the treatment of RA is 3 mg/kg at weeks 0, 2 and 6, and thereafter every 8 weeks (Summary of Product Characteristics). Dose escalation may be considered if a sufficient response is not achieved within 12 weeks or is lost subsequently. It is recommended that infliximab should be used in combination with methotrexate. In practice, due to the package size of 100 mg/vial, infliximab was given to the patients typically in doses of 200 mg (in two-thirds) or 300 mg (in one-fourth). At baseline, 96% (279/290) of the patients used at least one concomitant DMARD. The concomitant DMARDs were as follows: methotrexate 66% (n=190), hydroxychloroquine 26% (n=75), sulphasalazine 18% (n=53), leflunomide 14% (n=41), azathioprine 8% (n=24), sodium aurothiomalate 8% (n=24), cyclosporine 7% (n=20) and podophyllotoxin derivative 7% (n=19). 87% (n=251) used oral corticosteroid at baseline.

Outcome and costs

The functional ability (HAQ score) and patient's global assessment improved significantly as a result of infliximab therapy ($p<0.001$). The overall cross-sectional changes are shown in Fig. 1. More than two-thirds of the patients achieved a clinically important improvement in HAQ score (≥0.25) during infliximab therapy.

At the time of analysis, the patients had been treated with infliximab for an average of 21 months (median 18 months, range 1.5 to 78 months). QALY gain occurred in 76% (n=225). Due to the varying follow-up times of the patients in the register, the QALY difference was divided by the number of years that the patient had received infliximab therapy. On average, each year of infliximab therapy led to a QALY gain of 0.179, equivalent to 65 days of perfect health (0.179×365). The median utility was 0.446 at baseline and 0.704 at all follow-up time-points up to five years.

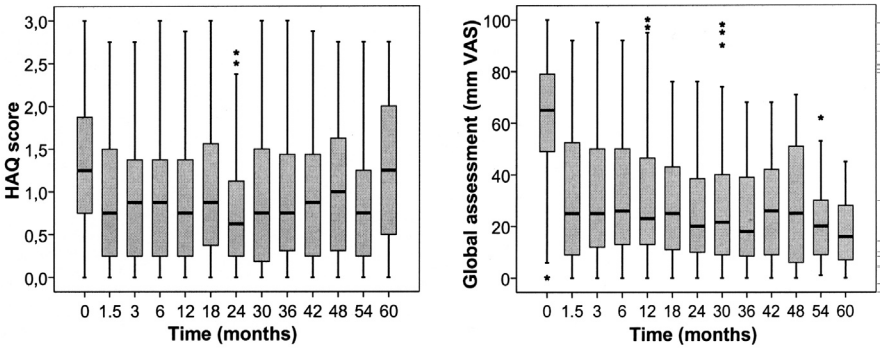
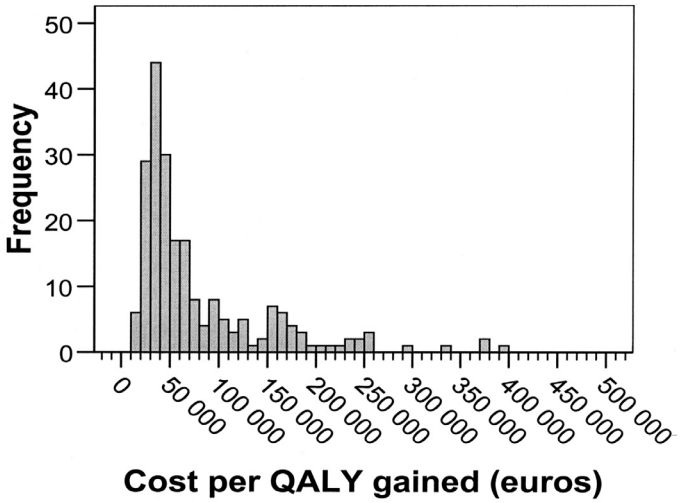


Fig. 1. Overall cross-sectional change in HAQ score (left) and patient's global assessment (right) as a function of infliximab treatment duration. The horizontal line in the box represents the median. The box encloses the middle half of the sample, *i.e.*, the interquartile range. The whiskers extend to the minimum and maximum values, excluding deviating values represented by the stars.

Fig. 2. Frequencies of patients as a function of cost per QALY gained. Ten patients had a cost per QALY gained of >500,000 Euro (omitted from the figure for clarity).



35% (n=79) of the patients with QALY gain had an incremental cost-effectiveness ratio of ≤40,000 Euro/QALY gained (see *Discussion*). The median cost per QALY gained was 51,884 Euro (IQR 36,193 Euro to 112,404 Euro, range 15,157 Euro to 3,677,806 Euro; mean 153,121 Euro). From Figure 2 it is obvious that a small number of patients with a very high cost per QALY gained have a major impact on the cost-utility result. A closer look at the patients with the most extreme cost per QALY gained revealed that their HAQ scores and/or global VAS fluctuated during the course of the treatment. However, these patients had significant improvements in *e.g.*, their joint counts.

ACR50 response rates at 3, 12, 24 and 36 months were 43% (89/207), 51% (94/183), 63% (56/89) and 66% (40/61), respectively. The higher response percentages at later time-points are partly due to elimination of non-responders; those who had discontinued infliximab therapy before the relevant time-point due to inadequate response or any other reason are not included in the calculations. The calculations therefore represent cross-sectional outcomes. The total cumulative cost per ACR50 response at 3, 12, 24 and 36 months was 14,795 Euro, 26,803 Euro, 38,269 Euro and 52,871 Euro, respectively.

The cross-sectional proportions of patients achieving a low DAS28 score (<3.2) in combination with a clinically significant improvement (>1.2) at 3, 12, 24 and 36 months were 41% (63/155), 42% (53/127), 62% (41/66) and 58% (26/45), respectively. The total cumulative cost per response was 15,463 Euro, 32,376 Euro, 38,197 Euro and 59,557 Euro, respectively.

Comparison of patient groups with regard to cost-utility

Discriminant analysis indicated that the subgroups with QALY gained at ≤40,000 Euro, QALY gained at >40,000 Euro, and no QALY benefit differed most with regard to baseline HAQ score, global VAS and pain (which correlated highly with global VAS). Indeed, Table III shows clear differences between these subgroups. The baseline HAQ score was significantly higher in the group with QALY gained at ≤40,000 Euro than in the other groups, indicating more severe functional limitation (p<0.001). Correspondingly, the disability class and functional state as grouped according to Kobelt *et al*. (12) were clearly worse in this group. The baseline global VAS was also significantly higher in the group with QALY gained at ≤40,000 Euro than in the other groups, indicating higher disease activity (p<0.001). As a result, the baseline utility score, as appointed according to Kobelt *et al*. (12), was significantly lower in this group (p<0.001). Conversely, the median cost per QALY gained was 112,509 Euro for the patients with mild to moderate difficulty at baseline (HAQ score <1, 0 means no difficulty), 50,216 Euro for patients with moderate to severe disability (HAQ score ≥1 but <2), and 38,156 Euro for patients with severe to very severe disability (HAQ score ≥2).

Group comparisons also revealed that a larger proportion of the patients with QALY gained at ≤40,000 Euro were women (85% *vs*. 62% and 65% in the other subgroups, respectively, p<0.005). Significant differences in baseline joint counts, acute phase reactants, age or disease duration were not found.

The median dose of infliximab was 200 mg in all groups. However, a relatively small proportion of the patients in the group with QALY gained at ≤40,000 Euro used doses higher than 200 mg. Of the patients with QALY gained at ≤40,000 Euro, QALY gained at >40,000 Euro, and no QALY benefit, proportions using >200 mg infliximab were 13% (10/79), 35% (51/146) and 29% (21/72), respectively (median dose). A somewhat larger proportion of patients with QALYs gained used concomitant methotrexate.

Table III. Comparison of baseline characteristics in patients with QALY gained at ≤40,000 Euro, QALY gained at >40,000 Euro, and no QALY benefit.

	≤40,000 Euro/QALY gained (n=79)	>40,000 Euro/QALY gained (n=146)	No QALY benefit (n=72)
HAQ score, mean	1.728	1.245	1.066
Disability class, % (n)			
Mild to moderate	4 (3)	35 (51)	50 (36)
Moderate to severe	57 (45)	49 (71)	35 (25)
Severe to very severe	39 (31)	16 (24)	15 (11)
Functional state (HAQ) as grouped according to Kobelt *et al*. 2005, % (n)			
<0.6	0 (0)	16 (23)	39 (28)
0.6 to <1.1	9 (7)	27 (40)	18 (13)
1.1 to <1.6	34 (27)	27 (39)	10 (7)
1.6 to <2.1	27 (21)	19 (28)	22 (16)
≥2.1	30 (24)	11 (16)	11 (8)
Global assessment, mm VAS (mean)	74	61	48
Global assessment ≥40 mm, % (n)	100 (79)	88 (129)	56 (40)
DAS28 score, % (n)			
Low (<3.2)	0 (0/63)	3 (3/115)	7 (4/54)
High (>5.1)	75 (47/63)	64 (73/115)	59 (32/54)
Mean	5.9	5.5	5.2
Utility score, mean	0.384	0.513	0.591
Methotrexate usage (concomitantly throughout infliximab therapy), % (n)	72 (55/76)	77 (111/145)	57 (40/70)

The Current Care recommendations for commencement of anti-TNF therapy were fulfilled in 54% (40/74) of those with QALY gained at ≤40,000 Euro, 46% (64/138) of those with QALY gained at >40,000 Euro, and 47% (32/68) of those with no QALY benefit (not significant). ACR50 response at 3 months after commencement of infliximab therapy was reached in 64% (34/53) of those with QALY gained at ≤40,000 Euro, 42% (45/108) of those with QALY gained at >40,000 Euro, and 22% (10/46) of those with no QALY benefit (p<0.001) (Table IV).

The cost per QALY gained was significantly lower for patients achieving an ACR50 response at 3, 12 and 24 months after commencement of infliximab therapy, compared with those not achieving this response (median 42,960 Euro *vs*. 62,141 Euro, p=0.02; 44,366 Euro *vs*. 76,598 Euro, p<0.001; and 41,646 Euro *vs*. 61,791 Euro, p=0.007, respectively). It was also somewhat lower for those patients fulfilling the Current Care recommendations for commencement of anti-TNF therapy (median 50,278 Euro *vs*.57,253 Euro for those not fulfilling the recommendations), but the difference was not statistically significant. Similar results were also seen regarding costs for patients reaching low DAS28 activity in combination with a clinically significant improvement, the numbers, however, not reaching statistical significance (Table IV).

The follow-up and response to infliximab therapy in the different cost-utility groups are presented in detail in Table IV.

The cost-utility was similar in a subgroup of patients diagnosed ≤3 years before commencement of infliximab (n=30, mean age 48 years, mean HAQ score at baseline 1.242), compared with those diagnosed >3 years before commencement (data not shown). Overall, baseline patient and disease characteristics were similar in these groups. However, as shown in Figure 3, a proportion of the patients diagnosed >3 years before commencement of infliximab therapy had developed disability more severe than that seen in the cohort diagnosed ≤3 years earlier.

Discussion

Infliximab therapy significantly improves the clinical signs and symptoms of severe and active RA in patients refractory to conventional DMARD therapy (5, 13). It also significantly improves the functional ability, as seen in

Table IV. Follow-up and comparison of changes from baseline in patients with QALY gained at ≤40,000 Euro, QALY gained at >40,000 Euro, and no QALY benefit.

	≤40,000 Euro/ QALY gained	>40,000 Euro/ QALY gained	No QALY benefit
Number of patients			
3 months	79	142	66
12 months	61	109	40
24 months	38	57	15
36 months	23	36	9
HAQ change, mean (n)			
3 months	-0.870 (55)	-0.383 (120)	0.088 (47)
12 months	-1.045 (50)	-0.300 (103)	0.233 (36)
24 months	-1.074 (34)	-0.397 (52)	0.302 (12)
36 months	-1.131 (22)	-0.430 (34)	0.286 (7)
HAQ clinically important improvement (≥0.25)[1], % (n)			
3 months	89 (49/55)	72 (84/116)	25 (10/40)
12 months	94 (47/50)	67 (66/98)	20 (6/30)
24 months	97 (33/34)	65 (31/48)	22 (2/9)
36 months	91 (20/22)	68 (21/31)	17 (1/6)
Global VAS change, mean (n)			
3 months	-48 (57)	-31 (117)	-10 (48)
12 months	-52 (52)	-29 (104)	-6 (36)
24 months	-54 (34)	-31 (52)	-10 (13)
36 months	-52 (22)	-37 (34)	-9 (7)
ACR50 response % (n)			
3 months	64 (34/53)	42 (45/108)	22 (10/46)
12 months	77 (37/48)	51 (51/100)	17 (6/35)
24 months	80 (24/30)	61 (28/46)	31 (4/13)
36 months	73 (16/22)	69 (22/32)	29 (2/7)
Low DAS28 (<3.2) % (n)			
3 months	61 (28/46)	43 (41/95)	24 (9/37)
12 months	60 (24/40)	44 (37/84)	42 (11/26)
24 months	65 (15/23)	53 (24/45)	92 (11/12)
36 months	63 (12/19)	68 (19/28)	50 (3/6)
DAS28 change, mean (n)			
3 months	-2.7 (40)	-2.0 (83)	-1.2 (33)
12 months	-2.7 (33)	-2.0 (73)	-0.9 (23)
24 months	-3.1 (18)	-2.4 (39)	-1.8 (11)
36 months	-3.3 (14)	-2.8 (25)	-1.2 (6)
DAS28 clinically significant improvement (>1.2)[2], % (n)			
3 months	90 (36/40)	74 (61/83)	46 (15/33)
12 months	85 (28/33)	66 (48/73)	35 (8/23)
24 months	100 (18/18)	80 (31/39)	90 (9/10)
36 months	86 (12/14)	92 (23/25)	50 (3/6)
Reason for discontinuation of infliximab therapy, % (n)			
insufficient effectiveness	6 (5)	22 (32)	39 (28)
adverse event	8 (6)	10 (15)	17 (12)
remission	1 (1)	3 (4)	0 (0)
other or unspecified	24 (19)	22 (32)	18 (13)
lost to follow-up[3]	20 (16)	10 (14)	4 (3)
none (*i.e.* still on infliximab)	41 (32)	34 (49)	22 (16)
Follow-up time, months (mean)	26	23	14

1) patients with baseline HAQ score ≥0.25, *i.e.*, who can improve by at least 0.25.
2) patients with baseline DAS28 score >1.2, *i.e.*, who can improve by more than 1.2.
3) no report for >1 year.

the present study. In early RA, disability is mainly a consequence of pain and inflammatory synovitis (14). Within the first three years of disease onset, 70% of RA patients develop radiographic damage of the joints despite treatment with conventional DMARDs (16). It markedly contributes to the disability in the later stages of the disease, accounting for approximately 25% of the disability in established RA (14). Demographic factors such as high age, female gender and low socio-economic and educational status, and high measures of disease activity and inflammation, such as pain, fatigue and elevated CRP/ESR, are also associated with higher HAQ scores (14).

No unambiguous patient or disease characteristics were identified in the present study that could predict the cost-utility of infliximab therapy in an individual patient. The finding that patients with QALY gained at ≤40,000 Euro had a higher baseline HAQ score and global VAS, and thereby lower initial utility, is mainly a reflection of the methodology used. With the starting point being worse, there is more room for improvement to occur, a fact that appears to lead to better cost-utility. The flare-up design in RCTs may contribute to the same CUA effect in such studies. The eventual preventive effect of anti-TNF therapy on disability progression would require a longer follow-up time to influence CUA concerned with change in utility based on HAQ as a result of an intervention. Prevention of functional impairment and disability is indeed an essential long-term aim of the treatment. According to the current treatment consensus, early treatment of RA is the best way to prevent damage to the joints and subsequent disability, although reducing the progression of damage in later disease will also help to prevent further functional loss and maintain function. Some of the patients in the present cohort may have developed permanent damage and deformities of the joints and subsequent disability due to longstanding progressive RA before the biologicals became available; such deformities are not reversible with pharmacological therapy. It can therefore be supposed that CUA results based on HAQ improve when the concepts of early and controlled care are widely assumed in the care of RA patients.

As female gender has been found to be a predictor of disability in RA patients (14), it was not surprising that the largest proportion of females was found in the group of patients with QALY gained at ≤40,000 Euro, that is, the group which also had the highest baseline HAQ scores. The dosage of infliximab may affect the cost-utility; treatment

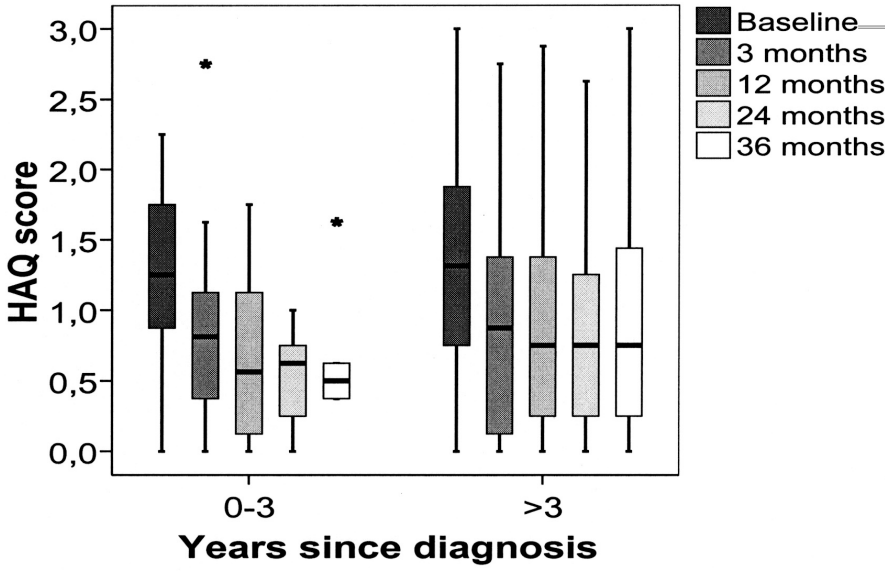


Fig. 3. Comparison of HAQ scores in patients diagnosed ≤3 years and >3 years before commencement of infliximab therapy.

of a "light" patient may inherently be more cost-effective than treatment of a "heavy" patient, owing to the lower absolute dose of infliximab. It was disclosed that dose escalation of infliximab, with a higher dose and/or shortened dosing interval, is not currently widely practiced in Finland. Such a practice could change the CUA and CEA results.

In principle, CUAs allow health-economical comparisons of vastly different types of interventions for the same condition, but also across different conditions. It is therefore often considered the gold standard for reporting cost-effectiveness in the literature and to healthcare policy-makers. Most (but not all, 17) of the published cost-effectiveness analyses of anti-TNF therapy in RA have utilized this method (12, 18-24). However, comparison of the results of different studies is difficult due to differing outcome measures, comparators, time horizons, discount rates, attribution of costs etc. Depending on the setting, methodology and assumptions, results from published CUAs of anti-TNF therapy report costs which range from <10,000 Euro to >150,000 Euro per QALY gained and thus cover the range from cost-effective to not cost-effective (12, 18-23).

No clear-cut price per QALY gained exists which would define cost-effectiveness unambiguously. In practice, up to £35,000 (approximately 50,000 Euro) may be acceptable (25). An often cited cost-effectiveness threshold is $50,000 (approximately 35,000 Euro), although up to $100,000 may be considered reasonable (18, 26). In general, savings in both direct and indirect costs have been found to offset some of the drug costs due to anti-TNF therapy (12, 18-21). In the present study, which considered only direct drug and administration costs of infliximab in a routine care patient cohort, the cost-utility was in the same range or slightly more high-priced compared with most earlier published CUAs.

Attention has been drawn to the profound methodological challenges and limitations inherent in utility assessment and CUAs, recently so in the context of RA (27, 28). CEAs based on disease-specific clinical outcomes measured in "natural units" seem more robust and face-valid and are substantiated from this point of view. Moreover, HAQ scores, and consequently utilities based on these, are influenced by several factors not alterable by pharmacological therapy (14, 29). This might also necessitate CEAs in order to assess more fully the obtainable treatment effects.

The CEA of the present study, in which the cost per ACR50 responder was calculated, reflects the treatment decisions in Finland in accordance with the Current Care guidelines better than the CUA based on HAQ score and global VAS. Patients may achieve ACR50 response and are thereby warranted continuation of biological therapy according to the national Current Care guidelines irrespective of whether there is an improvement in HAQ score and global VAS. However, since the other components of the ACR response criteria set are not incorporated in the utilities, they go unnoticed in the CUA.

As ACR50 response does not necessarily mean that the disease activity is low, also DAS28 was incorporated in the present study. A significant degree of convergence was seen between the cost-utility and the measures of effectiveness, as DAS28 improvements and ACR50 response rates were better in the patients with QALY gain, compared to those with no QALY benefit, with the best results seen in the group with QALY gained at ≤40,000 Euro (Table IV). The global VAS was a component in all composite indexes in the present study (utility, ACR50 and DAS28). Notwithstanding, treatment responses were seen in all cost-utility groups, which would have gone unnoticed had only cost-utility been studied.

The validity of CEAs/CUAs based on RCTs has been questioned (2), but those based on observational data are not uncomplicated either. The unblinded, open-label setting may influence the response to therapy, and in addition, there is flexibility in the treatment strategy regarding *e.g.*, concomitant therapies and dosages, as no rigid study protocol is imposed. In the present study, patients were followed up to their last registered control, and no assumptions were made of their subsequent disease progression; the study therefore applies a per-protocol type of principle, while RCTs are analyzed according to the intention-to-treat principle. Therefore, the results may be sensitive to treatment discontinuations and prevailing treatment practices. The current national recommendation for continuation of biological therapy is, for financial reasons, that the patient should achieve at least ACR50 response at 3 months after commencement of anti-TNF therapy. In the present study 43% of the patients achieved this response. The majority (84%) of those who did not achieve it

continued to receive infliximab beyond 3 months. This indicates that these types of official recommendations are not strictly followed, as the patients are treated mainly on medical and not financial indications; in Finland, they seem to receive biologicals if some improvement is seen. Significant improvement can occur even if ACR50 response is not reached.

In conclusion, based on the present study, treatment with infliximab and aiming at or reaching ACR50 response appears cost-effective, remembering the restrictions of an observational study set up when elucidating results. Current Care guidelines, which require sufficient disease control when deciding on continuing biological therapy, get support from the findings in this study.

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