Gain in Quality-adjusted Life-years in Patients with Rheumatoid Arthritis During 1 Year of Biological Therapy: A Prospective Study in Clinical Practice

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ABSTRACT. ***Objective.*** The quality-adjusted life-year (QALY) is used to measure outcome in rheumatoid arthritis (RA) studies; identification of drivers of a gain in QALY might help predict a treatment response. We investigated how changes in components of the Disease Activity Score-28 joints (DAS28) were associated with the European League Against Rheumatism (EULAR) and European Quality of Life 5 Dimensions (EQ-5D) responses; and what baseline variables predicted the change in QALY following 1 year of biological therapy.

Methods. Data were collected at baseline and after 3, 6, and 12 months of biological therapy in Danish patients with RA and included DAS28, sociodemographic data, comorbidity, Health Assessment Questionnaire (HAQ), and EQ-5D scored using the Danish algorithm. A cross-tabulation based on EULAR versus EQ-5D responses was performed, and the association of each DAS28 component across the EULAR/EQ-5D response groups was tested. Predictors of a change in QALY were assessed in a multiple regression model including baseline clinical and patient-reported data as explanatory variables.

Results. In total, 315 patients entered the study; 77% were women, 78% IgM rheumatoid factor-positive, with mean age 55 (SD 13) years, disease duration 10 (SD 8) years, mean DAS28 4.9 (SD 1.2), HAQ score 1.22 (SD 0.70), and EQ-5D score 0.60 (SD 0.19). Sixty-eight percent of patients gained QALY; the mean gain was 0.14 (SD 0.13). The patient global score was strongly correlated with both EULAR and EQ-5D responses. The gain in QALY increased with increasing patient global score and number of swollen joints, but not with C-reactive protein (CRP).

Conclusion. The subjective patient global score was the best baseline predictor of gain in QALY following biological therapy, while the objective CRP measure had no predictive value. It seems that no sharp demarcation between objective and subjective measures could be determined. (First Release July 1 2013; J Rheumatol 2013;40:1479–86; doi:10.3899/jrheum.121387)

Key Indexing Terms:
RHEUMATOID ARTHRITIS QUALITY-ADJUSTED LIFE-YEARS BIOLOGICAL THERAPY

The demand for costly biological therapies for the treatment of rheumatoid arthritis (RA) is increasing[1,2,3,4], and cost-effectiveness analyses are used to support the decision-making processes for their use. The quality-adjusted life-year (QALY) derived from measures of health-related quality of life (HRQOL) is an important outcome measure in such analyses, as it facilitates comparative analyses of cost-effectiveness of treatments.

A low cost per QALY gained is crucial for a new drug, and several national registries for patients with RA in Europe have demonstrated QALY gains for various biological therapies[5,6,7,8]. The majority of analyses have used simulation models to assess the cost-effectiveness, and thereby the QALY has not been derived using a measure of HRQOL, such as the European Quality of Life 5 Dimensions (EQ-5D) instrument. It is uncertain, moreover, which disease-related factors may influence the cost per QALY gained: such knowledge might help predict which patients are more likely to achieve the desired response. This question was briefly addressed in a study based on the Finnish ROB-FIN registry, where 76% of patients treated with infliximab achieved a QALY gain, and the cost per QALY gained was found to be lower in the patients who achieved an American College of Rheumatology (ACR50) response. Since the ACR response is not available at baseline, this finding cannot be used to predict a gain in QALY, and no other unambiguous predictors were identified[8].

Composite clinical disease activity measures, i.e., the Disease Activity Score-28 (DAS28) or Clinical Disease

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Activity Index (CDAI), correlate well with patient-reported HRQOL measures such as the EQ-5D and Medical Outcomes Study Short Form-36 (SF-36) in observational studies[9,10,11,12,13]. Because QALY are derived from HRQOL, this would indicate an association between the composite clinical disease activity measures and QALY, as well. The possible association would be expected to rely mainly on the patient-oriented elements of the indices, such as the tender joint count or the patient global score on a visual analog scale (VAS).

In this prospective, observational study of patients with RA initiating biological therapy, we investigated (1) the association between each component of the DAS28 and responses based on the European League Against Rheumatism (EULAR) criteria and EQ-5D as examples of a clinical versus a patient-reported outcome; and (2) what baseline variables are associated with the change in QALY following biological therapy in patients with RA.

MATERIALS AND METHODS

Patients and data collection. Danish outpatients with RA initiating biological therapy were recruited from 17 departments as part of this investigator-initiated, longitudinal study during the period November 2005 to July 2007. Clinical and patient-reported data were collected at baseline and after 3 months, 6 months, and 1 year of therapy in association with routine visits at the clinic. Clinical data were obtained by linking the social security number of each patient to the nationwide Danish DANBIO registry that includes prospective registration of more than 90% of Danish patients with RA receiving biological therapy[14]. Data collection included disease duration, 28 swollen and tender joint counts (SJC28, TJC28), C-reactive protein (CRP), patient global score on a VAS using the question: "In general, how would you rate the current impact of RA on your health?" (phrased in Danish), IgM-rheumatoid factor (IgM-RF) status, number of previous biological therapies, and concomitant use of methotrexate (MTX) and glucocorticoids. Patient-reported data were collected by self-questionnaires and included marital status, education, smoking behavior, body mass index, exercise habits, extraarticular features, joint surgery, and presence of comorbidities from a list of 17 chronic diseases. Finally, the validated Danish Health Assessment Questionnaire (HAQ) and EQ-5D[15] were completed.

The DANBIO registry was used to assess generalizability by comparing demographic and clinical characteristics of the study population and Danish RA patients in general initiating biological therapies during the study period November 2005 to July 2007.

The DANBIO registry is approved by the National Board of Health and the Danish Data Protection Agency. According to Danish law, no further approval was needed for this study.

EQ-5D. The EQ-5D is a generic preference-based health status instrument including 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression); in the original version it is divided into 3 levels of severity. In our study, we used 5 levels of severity (EQ-5D-5L; with no labels for state 2 and 4), as suggested by Kind[16] and developed further by others[17,18,19]. The recommended Danish scoring algorithm was used for scoring[15]. For scoring the intermediate levels 2 and 4, we applied a linear transformation of the scores for levels 1 and 3, and levels 3 and 5, respectively[20], because no recommended valuation set was available for the Danish EQ-5D-5L at the time of analysis[21]. The applied algorithm provided scores ranging from –0.68 to 1, where 1 corresponds to perfect health, 0 to death, and negative values to states worse than death.

Missing items in the EQ-5D were replaced by the median value of a given item, when a minimum of 4 of the 5 questions (80%) had been answered, otherwise the entire observation was excluded. Minimally important differences (MID) between 0.05 and 0.13 units have been proposed in the literature for patients with stable and early RA, respectively[22,23], and an even wider range when including other conditions[24]. As our study population consisted mainly of patients with longstanding RA, and because no MID studies were available for the Danish scoring algorithm, we assumed that score changes beyond 0.05 indicated clinically important differences.

QALY were calculated as the time-weighted average of EQ-5D scores from the followup period (area under the curve). Time-weighted scores were calculated with the available observations. If 1 observation (e.g., after 3 months) was missing, we calculated the gain using the data from baseline and the subsequent valid observations.

Clinical versus patient-reported outcomes. To investigate the relation between the clinical and patient-reported outcomes, patients were subgrouped according to their responses after 1 year according to EULAR and EQ-5D.

Patients achieving moderate or good EULAR responses were pooled ($EULAR_{response}$). Patients who discontinued therapy within the first year were considered EULAR nonresponders. In addition, patients were divided according to whether they had achieved a MID in EQ-5D using the cutoff value of 0.05[22].

We then performed a cross-tabulation of EULAR versus EQ-5D responses, yielding 4 possible combinations: (1) $EULAR_{no\ response}$/$EQ\text{-}5D_{no\ response}$, (2) $EULAR_{no\ response}$/$EQ\text{-}5D_{response}$, (3) $EULAR_{response}$/$EQ\text{-}5D_{no\ response}$, and (4) $EULAR_{response}$/$EQ\text{-}5D_{response}$. To investigate how each of the 4 DAS28 components was related to the EULAR/EQ-5D combinations, we developed 4 separate box plots testing the associations using ANOVA.

Statistical analyses. Statistical analyses were performed with Stata version 9.0 (StataCorp) and a p value ≤ 0.05 was chosen as the level of statistical significance. EQ-5D, HAQ, and the composite DAS28 and its components at 3 months, 6 months, and 1 year were compared with values from the prior visit using paired t tests. As a sensitivity analysis, missing data were replaced using the last observation carried forward (LOCF) method in case of missing visits or if the therapy was discontinued prior to 1 year.

Change in QALY was assessed by multiple regression analysis using baseline clinical and patient-reported data as explanatory variables. The baseline EQ-5D score was excluded from the model *a priori* because of a risk of multicollinearity, as was the baseline DAS28 (4 variables including CRP), because each component was included separately. The associations between the remaining baseline variables and change in QALY were tested in univariable analyses and those with a possible association ($p < 0.15$) were included in the multiple linear regression model. Age and sex were included regardless of the observed p value, because of a hypothesized age-and sex-associated difference in EQ-5D. In the final model, insignificant variables ($p > 0.05$) were removed by stepwise backward selection, except age and sex.

RESULTS

A total of 315 patients were recruited into the 1-year study; 85% were biological-naive at entry. Among them, 245 patients were receiving the same therapy, while 37 ended or switched therapy within 1 year. The remaining 33 patients had complete data only at the baseline visit (of whom 7 completed a minimum of 1 year of therapy, while 26 ended or switched therapy within a year) and were considered lost to followup. This left 282 patients, who were considered the study population. The median followup time from baseline was 377 days (interquartile range 308–429 days). The followup time for the patients who ended or switched therapy was 102 days (IQR 92–115). Table 1 shows baseline patient characteristics, and Figure 1 illustrates organization of patients from study entry.

Table 1. Baseline characteristics of the study population and patients lost to followup. Values are mean (SD) unless otherwise stated.

Characteristic	Study Population, n = 282	Lost to Followup, n = 33	p*
Women, %	77	73	0.56
Age, yrs	55 (13)	55 (14)	0.96
Disease duration, yrs	10 (8)	10 (9)	0.79
IgM rheumatoid factor-positive, %	78	79	0.96
DAS28	4.9 (1.2)	5.2 (1.2)	0.27
HAQ	1.22 (0.70)	1.40 (0.76)	0.17
EQ-5D	0.60 (0.19)	0.57 (0.18)	0.40
Concomitant methotrexate, %	74	58	0.05
Concomitant glucocorticoids, %	35	30	0.57
Biological therapies, %			0.02
Adalimumab	26	15	
Etanercept	28	18	
Infliximab	43	55	
Other	3	12	
Marital status (% married or cohabiting)	70	55	0.08
Education, %			0.45
None	21	27	
Vocational	32	36	
Higher	48	36	
Body mass index (BMI)			0.46
% with BMI < 25	52	61	
% with BMI ≥ 25	48	39	
Smoking, %			0.52
Never	31	33	
Current	29	37	
Previous	40	30	
Weekly exercise, %	43	30	0.18
Extraarticular manifestations, %	40	21	0.04
Comorbidity excluding RA, %			0.09
None	37	39	
1	35	18	
≥ 2	28	42	

* Chi-square test was used for comparison of proportions and ANOVA for continuous variables. DAS28: Disease Activity Score-28 joints; HAQ: Health Assessment Questionnaire; EQ-5D: European Quality of Life 5 Dimensions score; RA: rheumatoid arthritis.

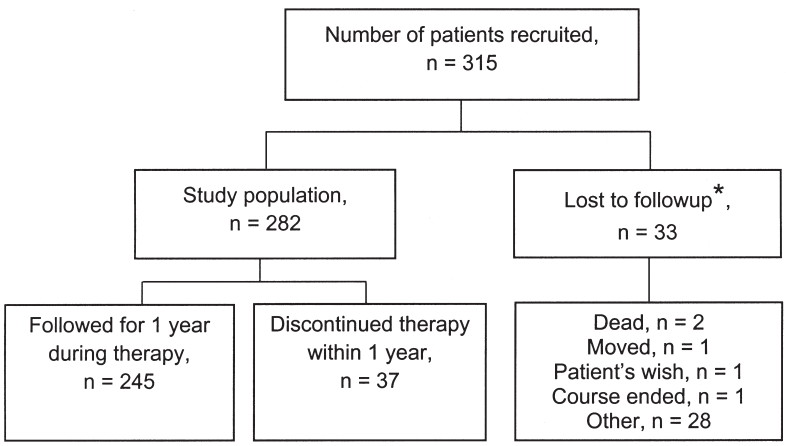

Figure 1. Distribution of the patients from study entry. *Number of patients completing only the baseline visit.

The study population and patients lost to followup were similar, with the exception that the individuals lost to followup were less likely to receive concomitant MTX, were more often prescribed infliximab, and had fewer extraarticular manifestations. Patients who discontinued therapy within 1 year (n = 37) had significantly worse baseline EQ-5D (mean 0.52 vs 0.61; p = 0.02) and HAQ scores (1.50 vs 1.17; p = 0.03) and were less educated (38% vs 18% with no education; p = 0.05), compared to patients completing 1 year of therapy, while the remaining baseline characteristics were similar (data not shown).

Table 2 shows a comparison of baseline demographic and clinical characteristics of the study population and all Danish RA patients who initiated biological therapies during the same period, according to DANBIO (n = 1163). A greater proportion of the study population received infliximab than did the patients in DANBIO (44% vs 25%).

The mean baseline EQ-5D (SD 0.60), HAQ (SD 1.22), and DAS28 (SD 4.9) scores showed significant and clinically relevant improvements after 3 months and the values remained stable for the duration of the study (Table 3). A similar pattern was seen when missing observations were replaced with the LOCF, although the observed improvements were slightly smaller. Using the LOCF method, the EQ-5D had thus improved by 0.11 (vs 0.13 without LOCF) after 1 year, the HAQ had decreased by 0.31 (vs 0.44), and the DAS28 by 1.5 (vs 1.8; Appendix).

Clinical versus patient-reported outcomes. In the study population, 61% were EULAR responders and 62% had achieved MID, according to the EQ-5D after 1 year. Classifying noncompleters as nonresponders, the proportion achieving a EULAR and EQ-5D response was 55%. Table 4 shows the cross-tabulation of EULAR and EQ-5D response after 1 year and Figure 2 illustrates the EULAR/EQ-5D categories for each component of the DAS28.

The mean reduction in swollen joints across the response groups ranged from 0 (in the $EULAR_{no\ response}$/$EQ\text{-}5D_{no\ response}$ group) to 6 (in the $EULAR_{response}$/$EQ\text{-}5D_{response}$ group), with clinically and statistically significant differences (2–5 swollen joints) in 3 of 6 possible comparisons

Table 2. Baseline characteristics of the patients recruited into the study in comparison with all Danish patients with RA starting biological therapy registered in DANBIO during the study period. Values are mean (SD) unless otherwise stated.

Characteristic	Patients Recruited, n = 315	DANBIO, n = 1163	p*
Women, %	77	73	0.56
Age, yrs	55 (13)	56 (13)	0.17
Disease duration, yrs	10 (9)	11 (10)	0.02
IgM rheumatoid factor-positive, %	78	77	0.65
DAS28	5.0 (1.2)	4.9 (1.3)	0.51
HAQ	1.24 (0.70)	1.28 (0.81)	0.39
Concomitant methotrexate, %	72	70	0.46
Concomitant glucocorticoids, %	35	37	0.38
Biological therapies, %			< 0.001
Adalimumab	25	33	
Etanercept	27	33	
Infliximab	44	25	
Other	4	9	

* Chi-square test was used for comparison of proportions and ANOVA for continuous variables. DAS28: Disease Activity Score-28 joints; HAQ: Health Assessment Questionnaire.

Table 3. Mean European Quality of Life 5 Dimensions (EQ-5D), Health Assessment Questionnaire (HAQ), and Disease Activity Score-28 joints (DAS28) for the study population at baseline, 3 months, 6 months, and 1 year (n = 282). Data are mean (SD).

Measure	n	Baseline	n	3 Months	n	6 Months	n	1 Year
EQ-5D (0–1)	275	0.60 (0.19)	191	0.71 (0.17)*	174	0.72 (0.16)	229	0.73 (0.15)
HAQ (0–3)	274	1.22 (0.70)	187	0.83 (0.72)*	163	0.85 (0.72)	228	0.78 (0.69)
DAS28	273	4.9 (1.2)	182	3.2 (1.3)*	157	3.1 (1.3)	225	3.1 (1.4)
Swollen joints (0–28)	281	6 (5)	224	2 (3)*	130	2 (3)	231	2 (3)
Tender joints (0–28)	280	10 (7)	224	4 (6)*	130	4 (6)	232	4 (6)
Patient global score, cm	274	5.9 (2.4)	222	3.3 (2.4)*	128	3.1 (2.6)	234	3.3 (2.7)
C-reactive protein, mg/l	279	23 (27)	227	10 (18)*	128	9 (9)	231	11 (19)

* Indicates statistically significant difference from previous visit (paired t test).

Table 4. European League Against Rheumatism (EULAR) response and minimally important difference according to European Quality of Life 5 Dimensions (EQ-5D; > 0.05) after 1 year (patients not completing 1 year of therapy were considered EULAR nonresponders, and the last observed EQ-5D-score was carried forward).

EULAR Response After 1 Year	Minimally Important Difference According to EQ-5D (> 0.05)			
	No Response	Response	Missing	Total
No response (%)	56 (51)	51 (47)	2 (2)	109
Moderate/good response (%)	45 (26)	123 (71)	5 (3)	173
Total (%)	101 (36)	174 (62)	7 (2)	282

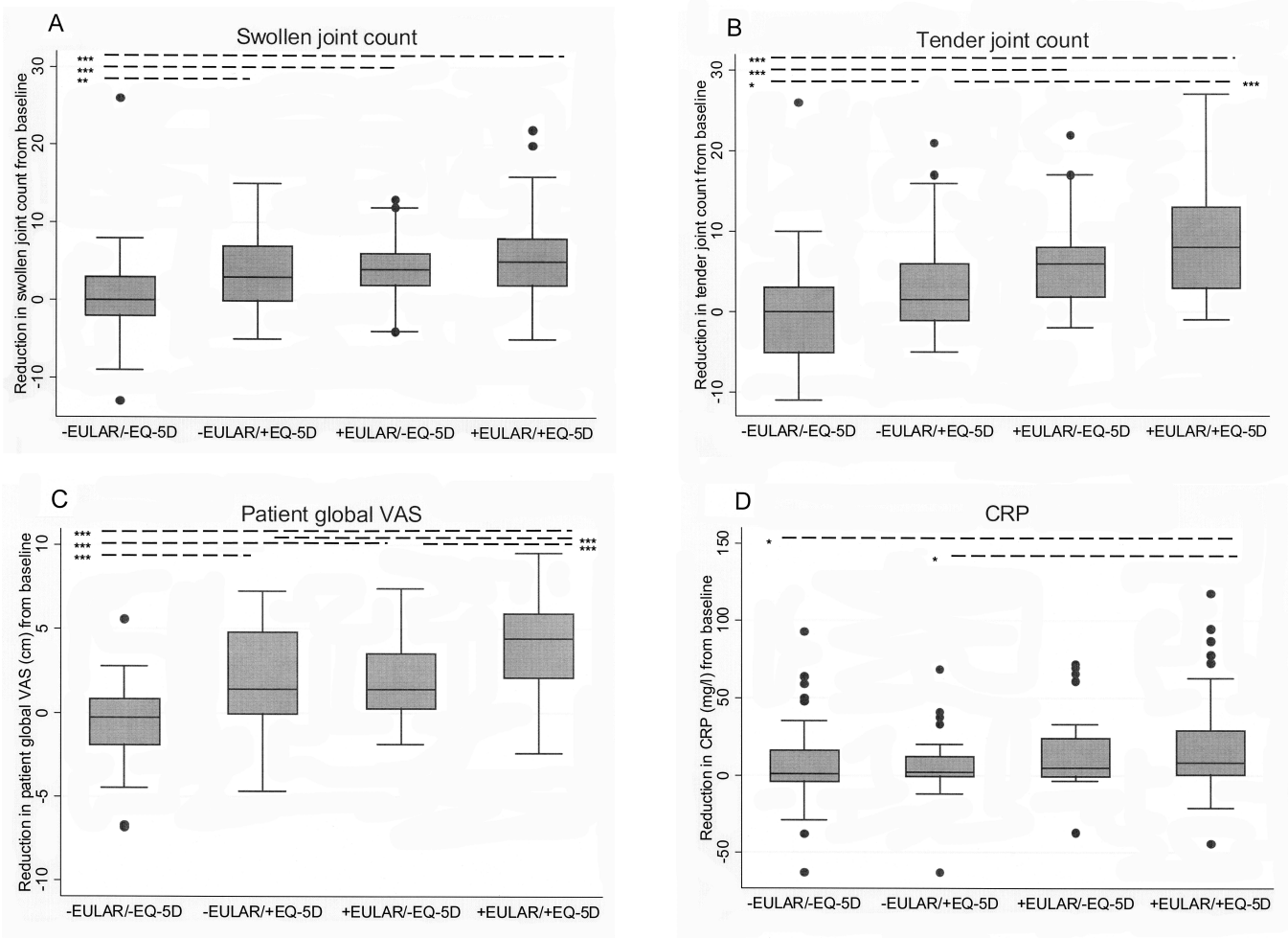

Figure 2. Plots of each DAS28 component by the combinations of EULAR and EQ-5D response. –EULAR/–EQ-5D: $EULAR_{no\ response}$/$EQ\text{-}5D_{no\ response}$; –EULAR/+EQ-5D: $EULAR_{no\ response}$/$EQ\text{-}5D_{response}$; +EULAR/–EQ-5D: $EULAR_{response}$/$EQ\text{-}5D_{no\ response}$; +EULAR/+EQ-5D: $EULAR_{response}$/$EQ\text{-}5D_{response}$. DAS28: 28-joint Disease Activity Score; VAS: visual analog scale; CRP: C-reactive protein; EULAR: European League Against Rheumatism; EQ-5D: European Quality of Life 5 Dimensions. *p < 0.05; **p < 0.01; ***p < 0.001.

(Figure 2A). Similar patterns, with the $EULAR_{no\ response}$/$EQ\text{-}5D_{no\ response}$ group having significantly smaller reductions, were also observed for tender joints and patient global score.

Thus, the mean reduction in tender joints ranged from –1 to 9 across the response groups. In addition, the $EULAR_{no\ response}$/$EQ\text{-}5D_{response}$ group could be discriminated from the $EULAR_{response}$/$EQ\text{-}5D_{response}$ group, leading to significant differences (3–9 tender joints) in 4 of 6 comparisons (Figure 2B). Similarly, the mean reduction in patient global score ranged from –0.7 to 4.0 cm across the response groups, and highly significant differences of 2.0–4.7 cm (p < 0.001)

were observed between the response groups ($p < 0.001$) in 5 of 6 comparisons (Figure 2C). In contrast, the mean reduction in CRP (ranging from 6.0 to 16.5 mg/l across the response groups) was able to distinguish only the $EULAR_{response}$/$EQ\text{-}5D_{response}$ from the EULAR nonresponders (Figure 2D).

All EULAR responders had significant reductions in swollen and tender joints, CRP, and patient global scores compared to baseline, irrespective of the EQ-5D status. The EULAR nonresponders with an EQ-5D response also had significant reductions in all components, while those with no EQ-5D response experienced a worsening in patient global score of 0.7 ($p = 0.01$).

Regression analyses. The mean baseline EQ-5D score of 0.60 increased to the time-weighted mean score (QALY) of 0.69 during the treatment period; the mean gain in QALY was 0.10 (SD 0.15). Sixty-eight percent of the patients gained QALY: the mean gain in QALY was 0.14 (SD 0.13). For EULAR responders, the gain in QALY was 0.15 (SD 0.14), while EULAR nonresponders gained 0.10 (SD 0.11).

Age, sex, CRP, patient global score, swollen and tender joint counts, HAQ, extraarticular manifestations, and exercise were included in the multiple linear regression model. The HAQ, CRP, tender joint count, and exercise were excluded in that order, resulting in a final model including age, sex, patient global score, swollen joint count, and extraarticular manifestations (Table 5). The gain in QALY after 1 year of biological therapy increased with increasing baseline patient global score and number of swollen joints, and patients with 2 or more extraarticular manifestations gained more QALY compared with those without such manifestations.

DISCUSSION

In our study of patients with RA treated with biologic therapies in routine care, we found that among the 4 DAS28 components, the patient global score at baseline was most strongly correlated with both EULAR and EQ-5D responses after 1 year, and it was also a baseline predictor of the achieved gain in QALY after 1 year of therapy.

Strengths of the study include the nationwide recruitment of patients across 17 centers in Denmark, and the fact that it was carried out in a clinical setting. Moreover, the study population was similar on most clinical and demographic variables to other Danish patients initiating biological therapy and registered in the nationwide DANBIO registry[14] during the same time period. The study population also had similar baseline demographic, clinical, and patient-reported values as other RA patients treated with biological therapies in routine care, as reported from the Swedish SSATG[6], the Dutch DREAM[25], and the Finnish ROB-FIN[8] registries. This result suggests that our findings may be generalizable to patients with RA treated in routine care with biologicals in countries with a public healthcare system similar to the Danish model. In contrast, a study of the British Society for Rheumatology Biologics Register (BSRBR) has reported a longer disease duration and worse baseline DAS, HAQ, and EQ-5D scores[5]. In this comparison, it should be noted that our study used the new 5-level version of the EQ-5D and applied the Danish value set, whereas the British study used the standard 3-level version of the EQ-5D and the UK value set. This may influence the comparability of scores from the 2 studies.

An observational study model, in contrast to a randomized controlled trial, requires a few assumptions, the most important of which is that the subjects would have remained at a constant (baseline) level had they not been given the study treatment. Another is that no deaths and no important deterioration would be likely to occur during the study period, causing QALY loss. In our procedure, we find that both assumptions were met, and ample data on tumor necrosis factor (TNF) blockade in RA support this. A speculated deterioration in RA would lead to an underestimation of the observed QALY gain.

Other possible limitations to the observational design included the patients lost to followup, which may generate a possible bias if this group is systematically different from the study population. However, sensitivity analyses using the LOCF gave no evidence of such bias.

We had expected the improvements in patient global score and tender joint count would be more prominent in the EQ-5D than in the EULAR response, and vice versa for the reduction in swollen joint counts and CRP. This was based on an assumption that the patient global score and tender joint count could be considered the subjective elements of the EULAR criteria, and would thus be more strongly associated with the patient-reported and thus subjective EQ-5D as opposed to the objective CRP and swollen joint count. However, we found a tendency toward larger improvements only in the patient global score (2.2 and 2.7 vs 2.0 and 2.5 cm) when the EULAR in contrast to the EQ-5D response was held constant, and larger improvements in tender joint count (6 and 7 vs 3) were observed when the EQ-5D response was held constant. For the swollen joint count (2 and 4 vs 1 and 3) and CRP (8 and 11

Table 5. Multiple linear regression with change in quality-adjusted life-years (QALY) as the outcome and clinical and patient-reported variables as explanatory variables. Number of observations = 206; adjusted $R^2 = 0.14$.

Gain in QALY (units of 0.10)	Coefficient (95% CI)
Sex (female)	–0.26 (–0.69; 0.17)
Age (years/10)	0.06 (–0.10; 0.21)
Swollen joint count (0–28)	0.04 (0.01; 0.08)
Patient global score (cm)	0.16 (0.08; 0.24)
Extraarticular manifestations (1)	0.30 (–0.11; 0.70)
Extraarticular manifestations (2 or more)	1.05 (0.29; 1.81)
Constant	–0.54 (–1.56; 0.48)

vs 0 and 3) the improvements tended to be larger when the EQ-5D response was held constant. No significant differences were detected comparing the 2 groups with conflicting EULAR/EQ-5D responses.

These findings suggest that the patient global score may be more associated with the patient-reported (EQ-5D) than with the clinical (EULAR) outcome, while tender and swollen joint counts and the CRP seem to be more strongly associated with the clinical EULAR response. Surprisingly, the CRP values showed the weakest associations with the 2 outcomes.

In the regression model, a higher baseline patient global score, a higher swollen joint count, and the presence of 2 or more extraarticular manifestations predicted a gain in QALY after 1 year of treatment. This finding may reflect the likely scenario that patients with very active or severe disease have more room for improvement. This does not imply, however, that such patients will have a more favorable final status than those with less active or less severe disease at baseline, a conclusion not supported by our observational data. A similar interpretation was suggested by the Finnish authors of a cost-effectiveness study of 297 patients with RA treated with infliximab[8]. In a discriminant analysis of subgroups with QALY gained at ≤ 40,000 Euro, QALY gained at > 40,000 Euro, and no QALY benefit, the baseline patient global score and HAQ were significantly higher in the most cost-effective subgroup (all expenses were connected with treatment)[8]. To our knowledge, no other studies have investigated this issue, but the correlation between composite disease activity measures and HRQOL has been demonstrated[9,10,11,12], and 2 studies have reported an association of the VAS for pain with the HAQ score[26,27]. One observational study included extraarticular features and reported an association between presence of these and a higher HAQ score[11], but we were not able to identify any other clinical studies showing an influence of extraarticular disease on the effect of RA treatment.

The regression model fit was not optimal, because the R^2 value was 0.14, which indicates that other important factors remain to be identified. In an attempt to include the baseline EQ-5D score as an explanatory variable, the R^2 was, surprisingly, not increased, but because it is a major contributor to the outcome (gain in QALY), this approach was considered unsuitable.

In our study, 68% of the patients gained QALY, with a mean gain of 0.14. The ROB-FIN study of 297 Finnish patients treated with infliximab in routine care used methods comparable to ours[8]. However, the QALY was derived using the patient global score and not the EQ-5D or another HRQOL measure. They reported a QALY gain in 76% of the patients, with a mean of 0.179 QALY per year[8], which is in accord with our findings.

Other studies based on European registries used methods that varied greatly, which limits comparability to our results. For example, the majority used computer simulation models to analyze cost-effectiveness, and none used the EQ-5D to derive the QALY.

In a Swedish study of 637 patients treated with infliximab based on the STURE registry, a Markov model based on the HAQ score was used to yield an estimated QALY gain of 1.019, with a mean followup of 5.1 years, or 0.20 QALY per year compared to nonbiological treatment[7]. Another Swedish study[28] based on the SSATG registry in patients treated with TNF inhibitor used a discrete-event simulation algorithm to model a QALY gain of 2.5 over 5 years and 4.4 over 10 years (0.50 and 0.44 QALY per year, respectively). No comparator group was included in that study. Based on the same registry, the authors showed an incremental effect of rituximab versus second-line TNF inhibitor of 0.20 QALY over 2.4 years of treatment (0.08 QALY per year)[29]. A study from the BSRBR reported a lifetime gain in QALY of 1.5583 for patients given TNF inhibitors compared to traditional disease-modifying antirheumatic drug therapy. The results were based on a simulation model and the QALY was derived using a validated mapping of EQ-5D from the HAQ[5].

The subjective patient global score was found to be most strongly associated with the EULAR and EQ-5D responses, and it was also the best baseline predictor of the gain in QALY achieved after 1 year of therapy, while the objective

APPENDIX. Mean European Quality of Life 5 Dimensions (EQ-5D), Health Assessment Questionnaire (HAQ), and Disease Activity Score-28 joints (DAS28) values at baseline, 3 months, 6 months, and 1 year for all patients entering the study (n = 315) with replacement of missing data using the last observation carried forward method. Values are mean (SD).

	n	Baseline	n	3 Months	n	6 Months	n	1 Year
EQ-5D (0–1)	308	0.59 (0.19)	311	0.67 (0.18)*	313	0.68 (0.17)	315	0.70 (0.17)*
HAQ (0–3)	306	1.24 (0.70)	308	0.99 (0.73)*	311	0.98 (0.7)	314	0.93 (0.74)*
DAS28	304	5.0 (1.2)	306	3.9 (1.5)*	309	3.7 (1.54)*	313	3.5 (1.5)*
Swollen joints (0–28)	312	6 (5)	312	3 (4)*	312	3 (4)	313	3 (4)*
Tender joints (0–28)	311	10 (7)	311	5 (7)*	311	6 (7)	313	5 (7)*
Patient's global score (cm)	306	6.0 (2.4)	311	4.1 (2.7)*	311	4.1 (2.8)	314	3.8 (2.8)*
CRP (mg/l)	312	23 (27)	314	13 (21)*	314	14 (18)	315	12 (18)*

* Indicates statistically significant difference from previous visit (paired t test). CRP: C-reactive protein.

CRP measure had no predictive value. It seems, however, that no sharp demarcation between "objective" and "subjective" variables could be derived.

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Gain in Quality-adjusted Life-years in Patients with Rheumatoid Arthritis During 1 Year of Biological Therapy: A Prospective Study in Clinical Practice

Linde L, Sørensen J, Østergaard M, Lund Hetland M. Gain in quality-adjusted life-years in patients with rheumatoid arthritis during 1 year of biological therapy: a prospective study in clinical practice. The fourth author's name should be listed as Hetland ML. We regret the error.
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