Early improvement of health-related quality of life during treatment with etanercept and adalimumab in patients with rheumatoid arthritis in routine practice

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Abstract

Objective

To assess health-related quality of life (HRQoL) in patients with rheumatoid arthritis (RA) treated with etanercept or adalimumab in routine clinical practice.

Methods

Patients with RA who started etanercept or adalimumab at Helsinki University Central Hospital or Lappeenranta Central Hospital during 2003-2006 were asked to participate in the study. In 97 patients, HRQoL was measured by the RAND 36-Item Health Survey 1.0 (RAND-36) at baseline and after three months of the treatment. HRQoL of the RA patients was compared to the Finnish age- and sex-matched general population values. In addition, changes in clinical parameters and disability index measured by the health assessment questionnaire (HAQ) were recorded.

Results

Treatment with etanercept and adalimumab increased the values in all domains of the RAND-36 during the first three months in routine practice. The improvement in both groups was statistically significant: with etanercept p=0.041 and with adalimumab p=0.019. The efficacy of etanercept and adalimumab in improving HRQoL during the first three months was comparable. The patients reported their best improvement in the subscales of bodily pain, role functioning/physical, energy, social functioning, and role functioning/emotional. Compared to the Finnish age- and sex-matched general population values, the HRQoL of the patients with RA was significantly lower at baseline and remained low at follow-up. The change in clinical parameters and the HAQ paralleled the improvement in HRQoL.

Conclusion

Treatment of patients with RA with etanercept and adalimumab in routine clinical practice provides clinically important and statistically significant improvement in HRQoL already in the first three months.

Key words

Rheumatoid arthritis, HRQoL, etanercept, adalimumab, RAND-36.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that causes pain, swelling and erosive destruction of joints. As a consequence, RA has a negative impact on patient's health-related quality of life (HRQoL) already in the early stages of disease. Many clinical measures are used in the assessment of disease activity and treatment outcome. From a patient's point of view, however, the primary goal of treatment of RA is to relieve pain, to restore functioning in daily living, and to improve the HRQoL. Patients with moderate to severe RA are often treated with tumour necrosis factor (TNF) inhibitors after the failure of traditional disease-modifying anti-rheumatic drugs (DMARDs). Three most often used TNF-inhibitors in RA treatment are adalimumab, etanercept and infliximab. Several randomized controlled studies (RCT) have reported significantly greater clinical improvement with TNF-inhibitors than with traditional DMARDs (1, 2). Besides the traditional clinical disease markers, the patient reported outcomes have also been emphasized recently. Some RCTs have shown that treatment with TNF-antagonists improves HRQoL of the RA patients (3, 4).

Several disease-specific and generic instruments exist for measuring patients' HRQoL. The Stanford Health Assessment Questionnaire (HAQ) is a good example of a disease-specific instrument that measures disability in RA patients (5). Generic HRQoL measurement instruments, such as the RAND 36-Item Health Survey 1.0 (RAND-36), make it possible to compare the HRQoL between different disease groups (6). A recent study showed that both disease-specific and generic instruments performed equally well when their validity, reliability and responsiveness were compared (7).

In RCTs, selected patient cohorts have to fulfill given inclusion and exclusion criteria and therefore they differ from those RA patients seen in daily clinical practice. Consequently, the results of RCTs are not easily generalized to the whole RA patient population. Therefore, we wanted to assess the early change in HRQoL of patients with active RA treated with etanercept or adalimumab in routine clinical practice.

Patients and methods

The study population comprises of 97 patients, who started either etanercept or adalimumab as their first biological treatment during 2003-2006 at Helsinki University Central Hospital or Lappeenranta Central Hospital. The patients were eligible for the study if they had active RA despite of previous treatment with various DMARDs including methotrexate and low dose of corticosteroids. The definition of active disease was >6 swollen joints, >6 tender joints, >45 min of morning stiffness, and an erythrocyte sedimentation rate (ESR) >30 mm/h or C-reactive protein (CRP) >28 mg/l or both. In addition, the patient ought to be in the American Rheumatism Association (ARA) functional class I to III (www.kaypahoito.fi/nivelreuma; Finnish current care guidelines for the management of rheumatoid arthritis). Etanercept was given at the dose of 25 mg subcutaneously twice weekly and adalimumab at the dose of 40 mg subcutaneously every other week. The current antirheumatic drug treatment was continued.

Patients were assessed clinically at baseline and after three months. We chose the three month time point for the analysis, because during that time the DMARD and corticosteroid therapy was stable allowing to see the effect of the added on biological therapy on the clinical and HRQoL outcome. On the first visit, demographic data including age, sex, disease duration, presence or absence of rheumatoid factor, and current use of DMARDs were collected. Disease activity was measured by tender joint count (of 68), swollen joint count (of 66), patient's assessment of pain (visual analogue scale = VAS), patient's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), ESR, and CRP. The Finnish version of the HAQ was used to assess patients' physical function (8). HRQoL was measured by the Finnish RAND-36 (9). This instrument covers 8 areas of health status, including physical functioning, role limitation due to physical health problems (here-

after called role functioning/physical), bodily pain, general health, energy, social functioning, role limitation due to personal emotional problems (hereafter called role functioning/emotional), and emotional well-being. An additional single item measures the change in perceived health during the last 12 months. The raw responses were recoded according to the original version of the RAND-36 (6), each item being scored on a 0-to-100 scale with higher scores indicating better quality of life.

Statistical analyses

Results are expressed as means or medians, with standard deviation (SD) or interquartile range (IQR) and 95% confidence intervals (CI). The between-group differences in change in the RAND-36 domains over the 3-month treatment period were compared by using a bootstrap-type ANCOVA with the baseline measurement as a covariate and by a multivariate Hotelling-type permutation test. The changes within groups were analysed by applying a permutation test or a Hotelling-type permutation test to related samples. The Hotelling *t*-squared test is a method to compare the means of all variables of interest simultaneously (in the present analysis the RAND-36 domains) while maintaining the chosen magnitude of Type I error. The effect size ("d") was calculated by using the method for paired samples: mean baseline scores minus mean follow-up scores, divided by the pooled standard deviation. The effect size of 0.20 was considered small, 0.50 medium and 0.80 large. Ninety-five per cent confidence intervals (95% CI) were obtained by bias-corrected bootstrapping (5000 replications). The Finnish general population values for the eight RAND-36 domains were weighted to match the gender and age distribution of the study population.

The study was performed according to the principles of the Declaration of Helsinki. The Ethics Committee of Helsinki University Central Hospital approved the protocol.

Results

In all, 97 patients with RA started biological treatment: 58 with etanercept and 39 with adalimumab. Table I presents the baseline demographic and clinical characteristics. The patients had a long-standing RA with median (IQR) disease duration of 15 (8 to 24) years. At baseline, the two study groups were comparable in regard to age, sex, disease duration, tender and swollen joint counts, as well as other clinical variables. The main treatment strategy before etanercept and adalimumab was the combination of DMARDs: methotrexate; sulfasalazine; and hydroxychloroquine (Table II). In 76% of the patients corticosteroids were used at baseline with the mean (SD) dose of 4.6 (3.4) mg. None of the patients had received biologicals earlier.

Table I. Baseline demographic and clinical characteristics. All values are median, except percentages.

Variable	Etanercept n=58	Adalimumab n=39	All n=97
Percentage female	74	76	75
Age, yrs (SD)	50 (14)	55 (11)	52 (13)
Years of RA (range)	16 (1-47)	17 (1-37)	17 (1-47)
Percentage of seropositive RA	79	67	74
Tender joint count, 0-68 (SD)	7 (5)	10 (7)	9 (6)
Swollen joint count, 0-66 (SD)	11 (10)	12 (10)	11 (10)
Patient assessment of pain, 100 mmVAS (SD)	55 (23)	57 (25)	56 (24)
Patient global assessment of disease activity, 100 mm VAS (SD)	59 (21)	58 (24)	59 (22)
Physician global assessment of disease activity, 100 mm VAS (SD)	46 (20)	43 (19)	44 (19)
ESR, mm/h (SD)	43 (25)	38 (23)	40 (24)
CRP, mg/l (SD)	34 (5)	29 (7)	31 (24)
HAQ (SD)	1.22 (0.68)	1.14 (0.72)	1.18 (0.7)

RA: rheumatoid arthritis; VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ: health assessment questionnaire; SD: standard deviation.

Table II. Use of DMARDs and corticosteroids at baseline.

Variable	Etanercept (%) n=58	Adalimumab (%) n=39	All n=97
Drugs:			
Methotrexate	31 (53)	22 (56)	53 (55)
Cyclosporine-A	10 (17)	6 (16)	16 (17)
Azathioprine	2 (3)	1 (3)	3 (3)
Podophyllotoxin	13 (22)	9 (24)	22 (23)
Leflunomide	11 (19)	11 (28)	22 (23)
Sulfasalazine	17 (29)	9 (23)	26 (27)
Gold salts, i.m. or p.o.	4 (7)	3 (8)	7 (7)
Hydroxychloroquine	18 (31)	11 (29)	29 (30)
Corticosteroids	52 (76)	33 (75)	85 (76)
Treatment strategy:			
No drugs	1 (2)	0	1 (1)
Single DMARD	6 (10)	6 (15)	12 (12)
Single DMARD with corticosteroids	10 (17)	10 (26)	20 (21)
Corticosteroids alone	6 (10)	2 (5)	8 (8)
Combination of DMARDs	7 (12)	2 (5)	9 (9)
Combination of DMARDs with corticosteroids	28 (48)	19 (49)	47 (48)

DMARD: disease-modifying anti-rheumatic drug, i.m.: intramuscular, p.o.: per os.

HRQoL

The RAND-36 data at baseline and the change in values after three months of treatment are shown in Table III. The Hotelling-type permutation test for related samples performed in eight domains simultaneously showed that in both treatment groups the improvement in the RAND-36 domains was statistically significant: with etanercept p=0.041 and with adalimumab p=0.019.

Table III. RAND-36 domains at baseline and the change in values after three months of treatment.

Domain	Baseline		Change at month 3			
	Etanercept Mean (SD)	Adalimumab Mean (SD)	Etanercept Mean (95% CI)	*p*-value	Adalimumab Mean (95% CI)	*p*-value
Physical functioning (PF)	43.4 (25.6)	46.0 (26.8)	7.5 (3.0 to 12.0)	0.002	6.5 (-0.1 to 13.2)	0.056
Role physical (RP)	27.3 (38.2)	32.2 (37.2)	8.8 (-1.6 to 19.2)	0.12	1.8 (-10.4 to 14.0)	0.82
Pain (BP)	36.3 (17.8)	37.7 (19.9)	13.1 (7.6 to 18.6)	<0.001	13.9 (4.8 to 22.9)	0.003
General health (GH)	44.7 (22.0)	41.6 (16.8)	2.4 (-1.6 to 6.3)	0.24	7.3 (1.8 to 12.8)	0.011
Vitality (VT)	47.9 (23.4)	45.7 (24.2)	7.4 (2.1 to 12.8)	0.004	6.8 (-1.7 to 15.2)	0.11
Social functioning (SF)	61.2 (30.3)	65.2 (27.8)	9.2 (2.4 to 15.9)	0.013	2.7 (-8.3 to 13.7)	0.67
Role emotional (RE)	53.9 (46.5)	53.5 (44.2)	11.6 (0.7 to 22.6)	0.039	0.4 (-14.4 to 15.3)	0.92
Mental Health (MH)	68.4 (19.8)	67.3 (19.3)	3.7 (-0.4 to 7.7)	0.073	2.3 (-4.9 to 9.6)	0.52

Both biologicals improved the HRQoL of RA patients in similar manner during the first three months (p=0.30). The etanercept group reported significant improvement in physical functioning, energy, social functioning, role functioning/emotional, and emotional wellbeing, whereas the adalimumab group in general health. Both groups reported a significant change from baseline to three months in dimension of bodily pain.

To illustrate the change in the RAND-36, we calculated the effect size of each domain with the definition that 0.20 was a small, 0.50 a medium and 0.80 a large effect size. Effect sizes of all domains are located in the area of positive outcome and the domain of pain had the highest effect size with both drugs (Fig. 1). The largest differences in HRQoL between RA patients and age-and gender-matched general population were in the physical domains of the RAND-36 (Fig. 2). Although the improvement in the RAND-36 was significant in both treatment groups, the HRQoL of RA patients failed to reach the level of general population after three months of treatment.

Clinical outcome

The improvement in all clinical variables during three months was significant in both treatment groups. Disability index, measured by the HAQ, decreased significantly in patients with etanercept but not in the adalimumab group (Table IV).

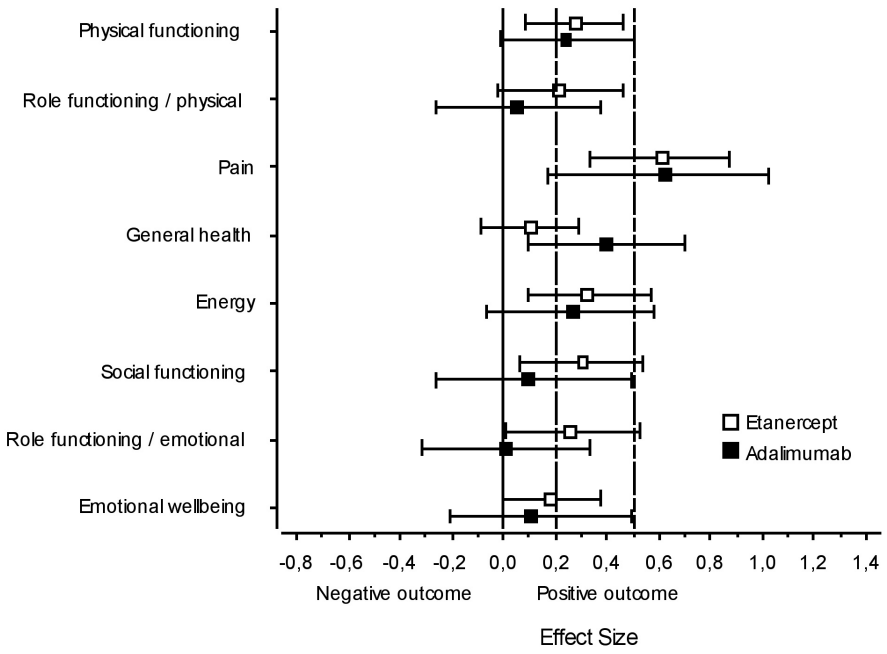

Fig. 1. Effect size for change from baseline to month 3 in all RAND-36 domains.

Discussion

This study examined the HRQoL of patients with long-standing RA treated with etanercept or adalimumab in routine practice. We demonstrated a rapid increase in the HRQoL during biological treatment already in three months. Both biologicals showed equal efficacy in improving the HRQoL. The improvement in HRQoL was parallel with the clinical outcome variables. Improvement in the HAQ was significant in patients treated with etanercept. A similar trend, although not statistically significant, was observed in the smaller adalimumab group, as well.

Measuring the HRQoL as an outcome measure in clinical trials has been increasingly popular since 1990s (10, 11). In RA patients, besides maintaining physical function, an important goal of treatment is to restore the HRQoL. Many clinical studies confirm that treatment with biologicals improves the HRQoL of RA patients, reflected by better physical function, less fatigue, and improved emotional and mental health (12). To measure HRQoL, we used the RAND-36 questionnaire, which contains the same items as the short form 36-item questionnaire (SF-36) (13) but with a slightly different scoring system. The results are nonetheless comparable (6).

To our knowledge, this is the first observational study about the early HRQoL response to etanercept and adalimumab treatment in routine practice. Several

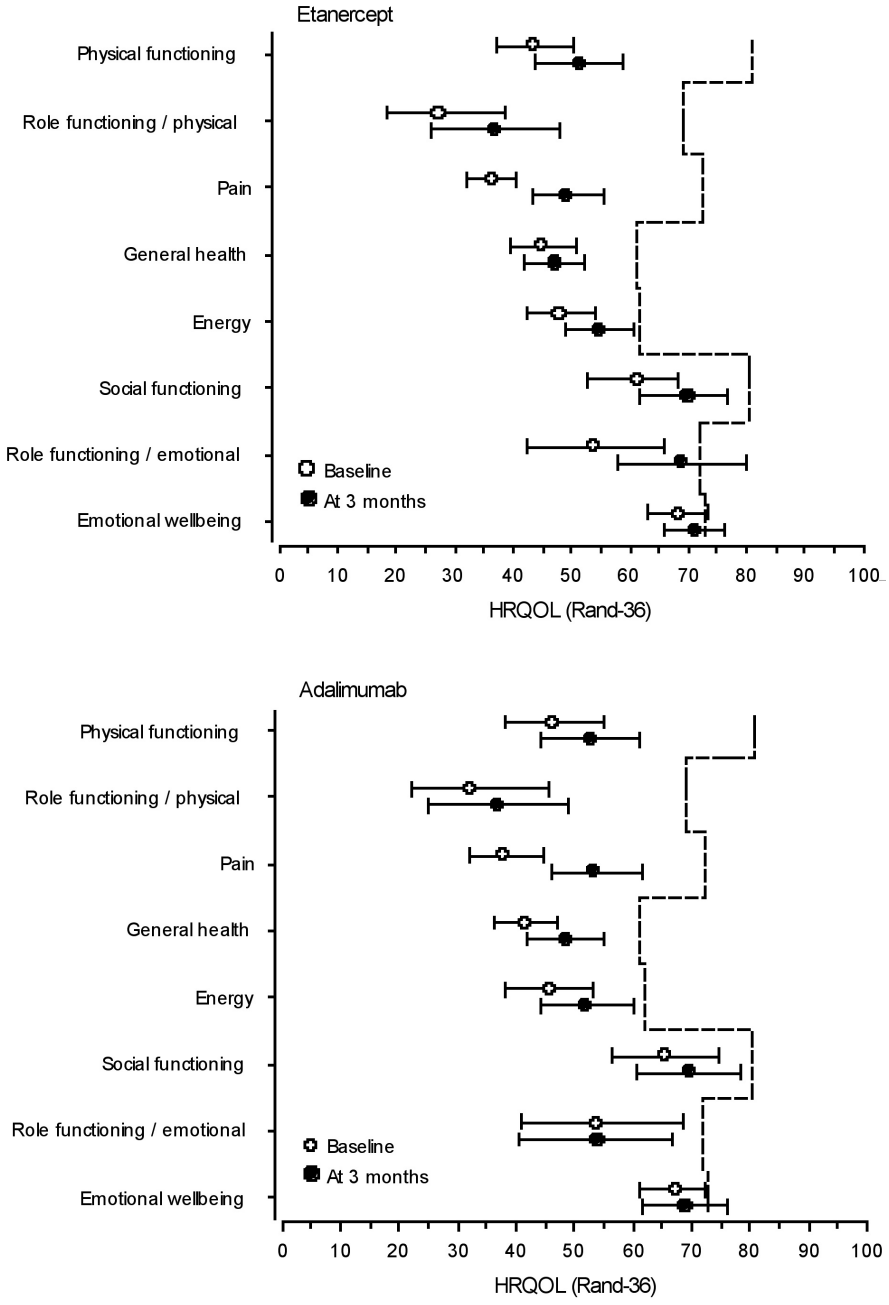

Fig. 2. The RAND-36 domains of treatment groups at baseline (○) and at 3 months (●) compared to the age- and gender-matched general population (---).

RCTs have assessed HRQoL of RA patients in their extension studies. Mathias et al assessed the HRQoL of RA patients treated with etanercept in a RCT where the SF-36 data was available for only a subset of patients (n=48) and the scores of physical and mental components were calculated. Both scores improved significantly after 26 weeks in patients who received 25 mg etanercept twice a week (14). Mittendorf *et al*. reported results from an extension of adalimumab RCT in patients with long-standing RA where HRQoL was measured using SF-36, FACIT-Fatigue and HUI3. In 26 weeks, patients treated with adalimumab reported statistically significant improvement in all HRQoL measures (4). Abatacept, selective T-cell co-stimulation modulator, has shown to improve the HRQoL in RA patients with inadequate response to methotrexate and also in RA patients with inadequate response to ≥3 months of therapy with TNF-inhibitors (15).

In our study, the HAQ scores improved significantly in the group of etanercept patients already in three months with the median (IQR) change of 0.25 (0.13 to 0.6). Kosinski *et al*. has suggested that improvement in HAQ score of 0.13-0.24 can be considered as clinically significant (16). The HAQ index has been utilized in economic evaluations in RA cohorts. The measurement of HRQoL, however, forms the basis of cost-utility analysis (17-19).

Our study population included patients with long-standing severe RA with a mean disease duration of 17 years and with very active disease despite having been treated with various DMARDs as monotherapy or in combinations, frequently also with a low dose of corticosteroids. This population may not be representative of RA patients in general. The improvement of HRQoL over a short period in late-stage RA patients suggests that the results would have been even better if treatment would be started in earlier phases of RA. Recently, a RCT of early RA was published, where the combination treatment with adalimumab and methotrexate significantly improved physical domains of the SF-36 already after 12 weeks of treatment and the domain of vitality improved to the level of US general population (20).

From a methodological point of view, the best way to compare the efficacy of etanercept and adalimumab would be a randomized head-to-head study. Until now, no such study has been performed and it is unlikely that it will ever be performed, because there is a lack of funding possibilities. Therefore, observational studies may be the only source of information for the comparison of different biologicals. In our study, etanercept and adalimumab were equally effective in improving the HRQoL and clinical variables in patients with RA. Although the patients were not randomized into two study groups, the baseline demographic and clinical variables were similar. In a recent study by Kievit *et al*., where the efficacy of three biologicals: etanercept, adalimumab, and infliximab was compared, etanercept and adalimumab revealed better outcomes compared to infliximab. In the SF-36 physical component scale,

Table IV. Change in clinical parameters from baseline to three months. All values are median (IQR).

	Etanercept n=58	Adalimumab n=39	All n=97
Tender joint count (0- 68)	4 (1.5; 9.5)	5 (2; 9)	5 (2; 11)
Swollen joint count (0-66)	3 (2; 7)	5 (2; 11)	4 (2; 8)
Patient's assessment of pain, 100 mmVAS	23 (15; 36)	21 (9; 54)	23 (13; 42)
Patient's global assessment of disease activity, 100 mmVAS	25 (12; 40)	30 (15; 50)	28 (14; 42)
Physician's global assessment of disease activity, 100 mmVAS	15 (8; 29)	25 (8; 40)	17 (8; 31)
ESR, mm/h	10 (3; 30)	10 (6; 26)	10 (5; 27)
CRP, mg/l	10 (3; 30)	20 (7; 32)	14 (4; 30)
HAQ	0.25 (0.12; 0.5)	0.25 (0.13; 0.6)*	0.25 (0.13; 0.6)

All changes being statistically significant except* the change in HAQ in patients treated with adalimumab.
ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ: health assessment questionnaire; VAS: visual analogue scale; IQR, interquartile range.

etanercept and adalimumab were equally effective paralleling the results of our study (21).

The RAND-36 scores indicated that patients with long-standing RA are especially impaired in physical domains – role functioning/physical, pain, physical functioning, and general health but less in emotional domains. That finding is similar to earlier studies of the HRQoL in patients with rheumatic diseases (22).

Although several measures of quantitative assessment of rheumatic diseases exist, they are rarely used in routine clinical practice (23). Adding a measure of HRQoL to the evaluation of a RA patient could add valuable information also in routine care.

Overall, this evaluation of the HRQoL in patients with long-standing RA treated with etanercept or adalimumab in routine practice showed that the improvement is considerable already after three months of treatment.

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