Health-Related Quality of Life in Early Rheumatoid Arthritis: Impact of Disease and Treatment Response

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Objective: To document the burden of early rheumatoid arthritis (RA) on health-related quality of life (HQL) and compare changes in HQL across 2 treatments.

Study Design: Analysis of HQL scores among patients enrolled in a multicenter, double-blind, randomized control trial of early RA treatment.

Patients and Methods: A total of 424 patients with early RA were randomized to 1 of 2 treatment groups: etanercept or methotrexate. Patients were treated and followed for 52 weeks. Health-related quality of life was assessed before and throughout treatment using the Medical Outcomes Study Short Form 36 Health Survey (SF-36) and the Health Assessment Questionnaire (HAQ). The HQL burden of RA was established by comparing SF-36 scale scores to general US population norms. The impact of treatment on HQL was determined by comparing scores on both SF-36 and HAQ scales.

Results: Before treatment, RA patients showed significant decrements in scores on all SF-36 scales and summary measures in comparison with age- and sex-matched general US population norms, multivariate analysis of variance (MANOVA) $F(8,2815) = 204.6$, $P < .0001$. After 52 weeks of treatment, 7 of 8 SF-36 scales and the physical summary measure remained significantly below the general US population norm, MANOVA $F(8,2815) = 41.9$, $P < .0001$. Patients randomized to etanercept showed significantly better HQL improvement earlier in treatment than patients randomized to methotrexate on the SF-36 physical summary, MANOVA $F(10,4230) = 6.1$, $P < .0001$, the SF-36 arthritis-specific health index, MANOVA $F(10,4230) = 8.5$, $P < .0001$, and the HAQ, MANOVA $F(10,4230) = 14.7$, $P < .0001$. At 52 weeks, there were no significant differences between treatment groups.

Conclusions: Rheumatoid arthritis places tremendous disease burden on patients' HQL. Successful treatment of early RA improved HQL. Etanercept showed a rapid HQL response.

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Rheumatoid arthritis (RA) is a chronic, progressive disease occurring in approximately 1% of the adult population in the United States.[1,2] The condition is characterized by joint pain, stiffness, and deformity in multiple regions, particularly the hands and feet. In addition, individuals with RA experience varying degrees of physical impairment, fatigue, fever, reactive depression, and weight loss.[3] Furthermore, RA places patients at greater risk of early death. Patients with RA have been found to die at 2 times the rate of control patients over a 10-year period.[2]

The progression of RA places an enormous burden on patients, their families, and society. The direct costs of care, including hospitalizations, doctor visits, medications, surgeries, physical and occupational therapy, and social services, are in the billions of dollars annually. As the disease progresses, patients experience increasing functional impairment, which often leads to work disability. It has been estimated that RA accounts for approximately $2.5 billion in lost wages annually.[4] The total cost of care for RA was estimated to consume 0.3% of the gross national product in 1994.[4]

The primary treatment objectives for RA are to reduce pain and to maintain physical and social function. Until recently, the aggressive treatment of RA consisted primarily of disease-modifying antirheumatic drugs (DMARDs). However, many patients treated with DMARDs do not achieve an adequate response,[5] and the prolonged use of DMARDs can lead to serious and potentially life-threatening adverse reactions.[6–8]

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A new class of specific biological response modifiers that competitively inhibit tumor necrosis factor-α (TNF-α inhibitors) has become available recently. One such agent, etanercept (Enbrel; Immunex, Seattle, WA), has been shown to be safe, well tolerated, and able to produce significant dose-dependent improvement in disease activity among RA patients who had an inadequate response to DMARDs.[9–12]

Measuring the efficacy of treatment in early RA is complex. Some of the clinical signs and symptoms of RA, such as swollen joints, elevated erythrocyte sedimentation rates, and elevated C-reactive protein levels, do not always correlate well with physical, social, and occupational function, a sense of well-being, or long-term outcomes.[13,14] Reductions in any 1 or all of these signs and symptoms do not necessarily mean that the patient feels better. Because a primary goal of RA treatment is to maintain patient functionality, it is important to use measures of functioning and well-being that provide a comprehensive assessment of the effectiveness of treatment. In the present study, a well-validated, self-administered, health-related quality-of-life (HQL) questionnaire, the Medical Outcomes Study Short Form 36 Health Survey (SF-36), was used to document the burden of RA on HQL. We sought to compare the impact on everyday functional status and well-being of a DMARD (methotrexate) and a biological agent (etanercept) as measured by the SF-36 and the Health Assessment Questionnaire (HAQ).

··· METHODS ···

Study Population

The study population consisted of 424 patients with early RA participating in a multicenter, double-blind, randomized trial comparing the efficacy of the administration of methotrexate tablets (rapidly escalated to 20 mg/week) plus subcutaneous placebo injections (n = 217) with subcutaneous injections of etanercept 25 mg twice weekly plus placebo tablets (n = 207). Study patients satisfied the following inclusion criteria: (1) a diagnosis of RA of 3 years or less; (2) no previous treatment with methotrexate; (3) active disease, characterized by 10 or more swollen and 12 or more tender joints; (4) erosions on baseline X rays of hands or feet or a positive serologic test for rheumatoid factor; and (5) stability on prednisone 10 mg or less per day. Nonsteroidal anti-inflammatory drugs were allowed, and a 4-week washout period was required to eliminate interference with DMARDs other than methotrexate. Patients were stratified by disease duration (less than 18 months and 18 to 36 months).

General Health Status Measures

The SF-36 was selected to measure generic health status,[15] because of its reliability and validity among both disease and general populations, and its usefulness in comparing the health burden of different conditions and the benefits of treatment.[16–24] The SF-36 consists of 36 items, 35 of which are aggregated to score 8 dimensions of health: physical functioning; role limitations as a result of physical health; bodily pain; general health perceptions; vitality; social functioning; role of emotions; and mental health. Each SF-36 scale was scored using norm-based methods that standardize the scores to a mean of 50 and a standard deviation (SD) of 10 in the general US population, with higher scores indicative of better health. Scores on the 8 SF-36 scales were further aggregated to produce physical and mental component summary (PCS and MCS) measures of health status. The PCS and MCS were also scored using norm-based methods.[24] In addition, an arthritis-specific health index (ASHI) was scored from the SF-36. The ASHI was developed by studying the responsiveness of the SF-36 scales to changes in clinical indicators of arthritis severity.[25,26]

Disease-Specific Measures

The HAQ was used to capture the specific effects of RA.[27] The HAQ consists of 24 questions concerning activities of daily living and mobility. Responses to each question were scaled from 0 (no difficulty) to 3 (unable to do) and then scored to produce the following 8 scales: dressing and grooming; arising; eating; walking; hygiene; reaching; gripping; and activities. Scores on the 8 HAQ scales were further aggregated into an overall summary disability index with scores ranging from 0 (no difficulty) to 3 (unable to do).

Both the SF-36 and the HAQ were self-administered at baseline (pretreatment) and at multiple follow-up times during treatment (2, 4, 8, 12, 16, 20, 26, 34, 42, and 52 weeks). Changes in SF-36 and HAQ scale scores were estimated in 2 ways. First, continuous change scores were derived by subtracting baseline scores from follow-up scores estimated at each time. For patients missing a follow-up score, the last observation was carried forward. Average changes in scores for a group based on the continuous change score have the advantage of reflecting the

magnitude of change in the metric of the scale; however, they mask the true proportion of patients with follow-up scores that differed from those at baseline.[28] Therefore, individual patients also were classified into 3 categories of change: (1) those whose follow-up scores did not change from baseline more than would be expected by chance ("same" group); (2) those whose follow-up scores improved from baseline more than would be expected by chance ("better" group); and (3) those whose follow-up scores declined from baseline more than would be expected by chance ("worse" group). Unlikely to be due to measurement error, changes large enough to be labeled better or worse have been shown to be relevant in terms of a wide range of clinical and social criteria.[24]

Burden of Early Rheumatoid Arthritis on Health-Related Quality of Life

General population normative data used to estimate the burden of early RA on HQL came from the 1990 National Survey of Functional Health Status (NSFHS), a national sample of noninstitutionalized US adults.[24,29,30] To make comparisons with the sample of early RA patients, the data from NSFHS were adjusted to the age, sex, and race of the early RA sample using separate least squares multiple regression models with each of the SF-36 scales and summary measures. Predicted normative scores for each SF-36 scale and summary measure were estimated for the general population, and the Student *t* test and multivariate analysis of variance (MANOVA) F statistics were used to test for significant differences between early RA patients and the adjusted norms. Burden comparisons were made with the combined samples of RA patients. Scores were estimated while patients were in an active state (pretreatment) and treated state (52 weeks posttreatment).

Impact of Treatment on Health-Related Quality of Life

Independent least squares multiple regression models were conducted to estimate adjusted mean scores for all SF-36 and HAQ scales and summary measures. Mean scores were adjusted for age, sex, and race. Student *t* tests were conducted to test for the significance of the difference in average change scores across the treatment groups and to test that changes in scores within treatment groups differed from zero. Comparisons of average and categorical change scores for all SF-36 and HAQ scales and summary measures were made with the 52-week outcome scores.

Multinomial (polytomous) logistic regression methods were used to compare categorical changes (better, same, worse) in SF-36 and HAQ scales and summary measures across treatment groups. Adjusted percentages for change categories were generated with statistical adjustments for age, sex, and race. Chi-square tests of significance were computed to determine whether the percentages across change categories differed across treatment groups. Comparisons of categorical change scores for all SF-36 and HAQ scales and summary measures were made with the 52-week outcome scores.

Treatment Comparison of Trends in Health-Related Quality of Life

Factorial analysis of variance (ANOVA) with repeated-measures and between-groups factors was conducted to compare the trends in average HQL scores between treatment groups over the 10 posttreatment assessments. An interaction term for Time × Treatment was included in the model to evaluate differential HQL response from baseline over the course of the 10 follow-up assessments. The HQL measures analyzed were the SF-36 PCS and MCS, the SF-36 ASHI, and the HAQ summary scale.

Content-Based and Norm-Based Interpretation of Results

To interpret the meaning of changes in HQL scores caused by treatment, the content of several SF-36 and HAQ items was examined. Specifically, the change from baseline to 52 weeks posttreatment was compared on the following items selected from SF-36 and HAQ scales that showed the greatest response to treatment: limitations in walking a block; limitations in climbing a flight of stairs; difficulty performing at work; feeling tired all or most of the time; severe or very severe pain; limitations in social activities; and difficulty gripping.

··· RESULTS ···

Patient Characteristics

Patient characteristics by treatment group are presented in **Table 1.** The mean age of participants randomized to methotrexate and etanercept was 49 and 51 years, respectively. Most participants in each treatment group were female and Caucasian, were positive for rheumatoid factor, and had RA for less than 18 months. Participants in both treatment groups were equal in average number of tender and swollen joints.

Table 1. Patient Characteristics

Demographic Variable	Methotrexate	Etanercept
Sample size (n)	217	207
Age, mean (range), y	49 (21–80)	51 (21–82)
Female (%)	75	74
Caucasian (%)	88	86
RA duration < 18 mo (%)	74	75
Rheumatoid factor positive (%)	89	87
Tender joint count (mean)	30	31
Swollen joint count (mean)	24	24

RA = rheumatoid arthritis.

Health-Related Quality-of-Life Burden of Early Rheumatoid Arthritis

Comparisons with adjusted general US population norms revealed that the HQL of early RA patients with active disease was significantly below normative values for all SF-36 scales and summary measures (**Table 2**). Differences were greatest in the SF-36 domains of physical functioning, role physical, bodily pain, and the physical summary measure, in which scores were more than 1.5 SD below normative values for early RA patients. Early RA patient scores were more than 1 SD below normative values on SF-36 scale domains of vitality and social functioning. Of interest was the finding that early RA also impacted emotional well-being, although to a lesser extent. Early RA scores on the role emotional, mental health, and mental summary domains were 8, 5, and 4 points lower, respectively, than normative values.

After 52 weeks of treatment, the HQL scores of early RA patients remained well below normative values for nearly all SF-36 scales and summary measures. Differences continued to be the greatest in the SF-36 domains of physical functioning, role physical, bodily pain, general health, vitality, and the physical summary measure, in which scores remained more than 0.5 SD below the general population norms. At 52 weeks, however, the mental health domains of the SF-36 had returned to normative values of the general population.

Table 2. Burden of Early RA: Combined Trial Samples Compared With US General Population Data

	Pretreatment		52 Weeks Posttreatment		General Population Norms*		Significance Testing: Pretreatment vs General Population		Significance Testing: Posttreatment vs General Population	
	Mean	SE	Mean	SE	Mean	SE	*t*	*P*	*t*	*P*
SF-36 scales										
Physical functioning	28.6	0.41	37.1	0.53	48.6	0.23	33.3	†	15.4	†
Role physical	30.9	0.34	40.0	0.52	49.0	0.24	31.9	†	12.4	†
Bodily pain	32.6	0.29	41.7	0.53	48.8	0.25	31.8	†	11.0	†
General health	39.1	0.40	42.8	0.45	48.8	0.24	15.5	†	9.8	†
Vitality	37.4	0.40	44.0	0.50	49.4	0.25	21.3	†	8.3	†
Social functioning	38.0	0.49	45.2	0.53	49.5	0.25	19.3	†	5.2	†
Role emotional	41.7	0.53	45.5	0.52	49.7	0.25	14.7	†	6.4	†
Mental health	44.9	0.45	49.5	0.43	49.7	0.25	9.4	†	0.2	NS
MANOVA F for 8 scales							204.4	†	41.9	†
SF-36 summary measures										
Physical summary	28.4	0.33	37.4	0.50	48.5	0.23	35.8	†	16.6	†
Mental summary	46.9	0.48	50.4	0.44	50.1	0.25	6.4	†	0.81	NS

RA = rheumatoid arthritis; SF-36 = Medical Outcomes Study Short Form 36 Health Survey; NS = not significant; MANOVA = multivariate analysis of variance.
*General US population norms were adjusted to the age, sex, and race characteristics of the trial sample.
†$P < .0001$.

Impact of Treatment on Health-Related Quality of Life

Scores improved significantly from baseline to 52 weeks for patients randomized to both treatment groups across all SF-36 scales and summary measures (**Table 3**). Both treatments had the greatest impact on SF-36 scales measuring physical health status. Scores improved by more than 9 points on average for the physical functioning, role physical, bodily pain, and physical summary scales; this change was as large as 1 full standard deviation on the norm-based scale score. Also, more than half of the patients in each treatment group improved more than would be expected by chance on these scales.

Large and significant improvements between both treatment groups were also observed for the social functioning and vitality scales, and the SF-36 ASHI. The average change in scores was more than 6 points, which is more than 0.5 standard deviation on the norm-based scale score, and the proportion of

Table 3. Average and Categorical Changes in HQL Scores From Baseline to 52 Weeks

	Etanercept					Methotrexate						
	Average Change		Categorical Change			Average Change		Categorical Change			Significance Tests*	
	Mean	SE	%W	%S	%B	Mean	SE	%W	%S	%B	*t*	χ^2
SF-36 scales												
PF	9.7†	0.8	10	28	62	10.4†	0.8	12	29	59	0.62	0.73
RP	10.8†	0.9	9	39	52	9.9†	0.9	11	38	51	0.66	0.49
BP	10.5†	0.8	10	26	64	10.1†	0.7	13	28	59	0.31	0.41
GH	4.5†	0.7	12	58	30	3.4†	0.7	14	58	28	1.13	0.50
VT	7.9†	0.8	13	35	52	6.8†	0.8	16	36	48	0.88	1.49
SF	8.4†	0.9	14	37	49	8.1†	0.9	17	37	46	0.10	1.03
RE	4.0‡	1.1	15	52	33	4.7‡	1.0	14	52	34	0.51	0.25
MH	4.4†	0.8	7	66	27	5.8†	0.8	6	62	32	1.22	2.47
SF-36 summaries												
PCS	10.7†	0.8	14	20	65	9.6†	0.8	19	20	61	0.84	3.05
MCS	3.6‡	0.8	13	57	30	4.1†	0.8	14	55	32	0.39	0.87
ASHI	8.2†	1.0	22	20	58	8.1†	1.0	25	20	55	0.01	0.61
HAQ scales												
Activity	-.76†	0.06	6	38	56	-.74†	0.06	12	35	53	0.37	4.98
Arising	-.71†	0.06	5	35	60	-.77†	0.06	5	36	59	0.78	0.16
Dressing	-.71†	0.06	5	34	61	-.89†	0.06	4	29	67	2.18§	4.04
Eating	-.47†	0.04	4	64	32	-.16†	0.04	10	70	20	4.93"	24.39"
Grip	-.81†	0.07	3	48	49	-.78†	0.07	2	52	46	0.36	2.69
Hygiene	-.69†	0.07	7	40	53	-.67†	0.07	10	40	50	0.21	0.69
Reach	-.74†	0.06	5	38	57	-.75†	0.06	7	35	58	0.09	1.59
Walking	-.62†	0.06	6	38	56	-.66†	0.06	5	37	58	0.47	1.02
HAQ summary												
HAQ	-.73†	0.05	4	25	71	-.76†	0.05	5	30	65	0.46	3.53

HQL = health-related quality of life; W = worse; S = same; B = better; SF-36 = Medical Outcomes Study Short Form 36 Health Survey; PF = physical functioning; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role emotional; MH = mental health; PCS = physical component summary; MCS = mental component summary; ASHI = arthritis-specific health index; HAQ = Health Assessment Questionnaire.

*Significance testing between treatment groups: *t* test for mean differences, χ^2 for categorical change.

Change in HQL differs from 0 within treatment group.

†$P < .001$.

‡$P < .01$.

§$P < .05$.

"$P < .0001$.

patients who improved more than would be expected by chance across treatment groups ranged from 46% to 58% on these scales. To a lesser extent than physical scales, treatment significantly improved the emotional well-being of patients as detected by the SF-36 mental health, mental summary, and role emotional scales. The average change in scores ranged from 3.6 to 5.8 points and the proportion of patients who improved more than would be expected by chance was less than 35% on these scales.

Across all HAQ scales and the summary index, scores improved significantly from baseline to 52 weeks for patients randomized to both treatment groups (Table 3). With the exception of the eating scale, scores improved by more than 0.61 on average and nearly half or more of the patients in each treatment group improved more than would be expected by chance on all HAQ scales and the summary index.

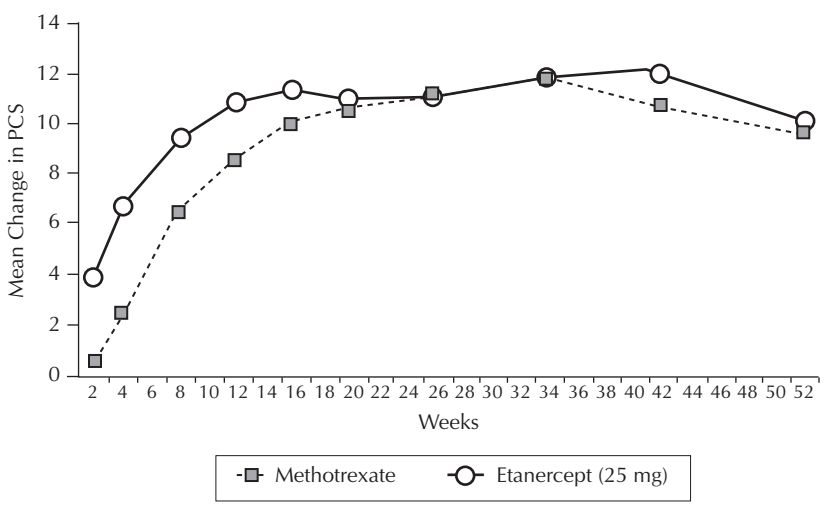
Treatment Comparison of Trends in Health-Related Quality of Life

The Treatment × Time interaction term in the repeated-measures factorial ANOVA was significant for the SF-36 physical summary scale, $F(10,4230) = 6.06$, $P < .0001$, the SF-36 ASHI, $F(10,4230) = 8.51$, $P < .0001$, and the HAQ summary measure, $F(10,4230) = 14.69$, $P < .0001$. For all 3 scales, mean changes in scores from baseline were significantly better for patients in the etanercept group during the first 12 weeks of the trial compared with the methotrexate group (see **Figures 1–3**). From week 16 through week 52, no significant differences were found between the 2 treatment groups on these scales. The Treatment × Time interaction term in the repeated-measures factorial ANOVA was not significant for the SF-36 mental summary scale, $F(10,4230) = 1.54$, $P = .2158$. Changes in the SF-36 mental summary scale were similar across treatment groups over time (**Figure 4**).

Content-Based Interpretation of Results

As a basis for interpreting the changes in HQL scores from baseline to 52 weeks, the content of selected questionnaire items (those most subject to change) was examined. As shown in **Figure 5**, the percentage of patients in both treatment groups reporting limitations in walking 1 block dropped from 65.4% at baseline to 35.9% at 52 weeks posttreatment. From baseline to 52 weeks posttreatment, the percentage reporting limitations in climbing a flight of stairs dropped from 74.7% to 43.3%; the percentage reporting difficulty performing at work declined from 89.6% to 52.9%; the percentage feeling tired all or most of the time dropped from 43.6% to 19.3%; and the percentage of patients reporting severe or very severe pain declined from 43.1% to 9.8%. The percentage of patients reporting that their health interfered with social activities dropped from 59.4% to 28.5% from baseline to 52 weeks. Lastly, the percentage of patients reporting some difficulty gripping declined from 92.4% at baseline to 57.6% at follow-up.

Figure 1. Mean Changes in SF-36 PCS Scores Over 52 Weeks by Treatment



SF-36 = Medical Outcomes Study Short Form 36 Health Survey; PCS = physical component summary.

··· DISCUSSION ···

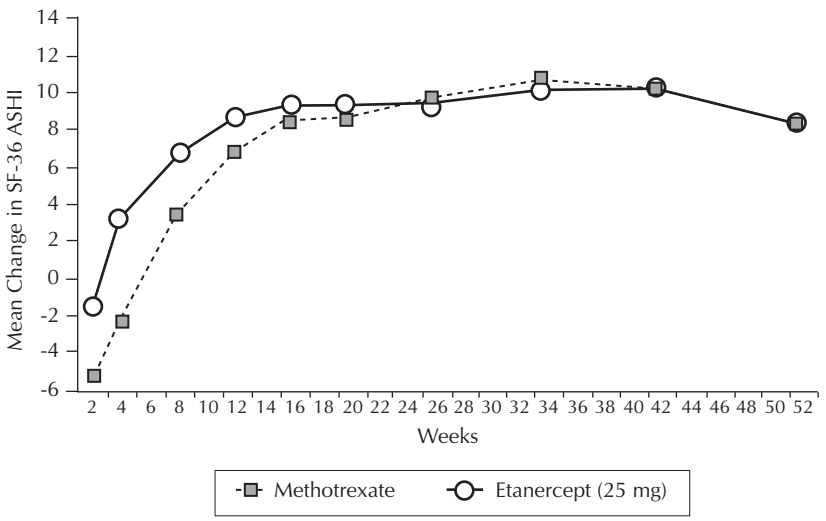
In this study, HQL measures were helpful in quantifying the burden of early RA on patients' functioning and well-being. Overall, early RA patients reported substantially diminished functioning and well-being, compared with age-, sex-, and race-adjusted norms from the general US population. The burden was observed primarily on measures of physical, role, and social functioning; pain; and vitality. Although treatment diminished the bur-

den substantially, early RA patients who underwent treatment remained well below the general population norms on these measures. Comparisons with other chronic conditions[24,30] suggest that the burden of early RA documented in this study should be considered clinically significant. For example, the profile of SF-36 scale scores of early RA patients in this study was equal to or worse than the profile of age-, sex-, and race-adjusted scores reported by patients with congestive heart failure and diabetes.[24,30]

The results showed that HQL scores for both treatment groups improved significantly during the trial. However, the pattern of results indicated that not all HQL scales were equally responsive to treatment. As would be expected for a condition with important physical implications, HQL scales assessing pain and physical health status were more responsive to treatment than HQL scales assessing mental health status. For example, the largest average change scores and the largest percentage of patients who improved more than expected by chance were observed for SF-36 physical functioning, role physical, bodily pain, and physical summary scales, and all HAQ scales. The disease-specific scoring of the SF-36 (ASHI) also was found to be highly responsive to both treatments. The changes in scores on these scales were slightly higher than those observed in other 52-week HQL trials of RA[31,32] and clearly reached the suggested minimum values of clinical importance.[33]

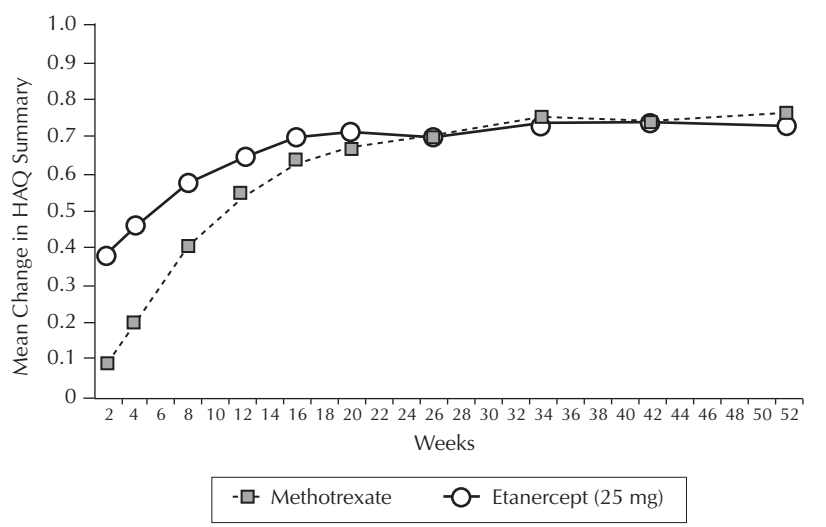
Notably, treatment did improve the emotional well-being of patients as measured by the SF-36 mental health, role emotional, and mental summary scales. Changes were significant from baseline over the 52-week follow-up and the improvement was more than what was observed in other 52-week HQL trials of RA.[31,32] However, the improvement in emotional

Figure 2. Mean Changes in SF-36 ASHI Scores Over 52 Weeks by Treatment



SF-36 = Medical Outcomes Study Short Form 36 Health Survey; ASHI = arthritis-specific health index.

Figure 3. Mean Changes in HAQ Summary Scores Over 52 Weeks by Treatment



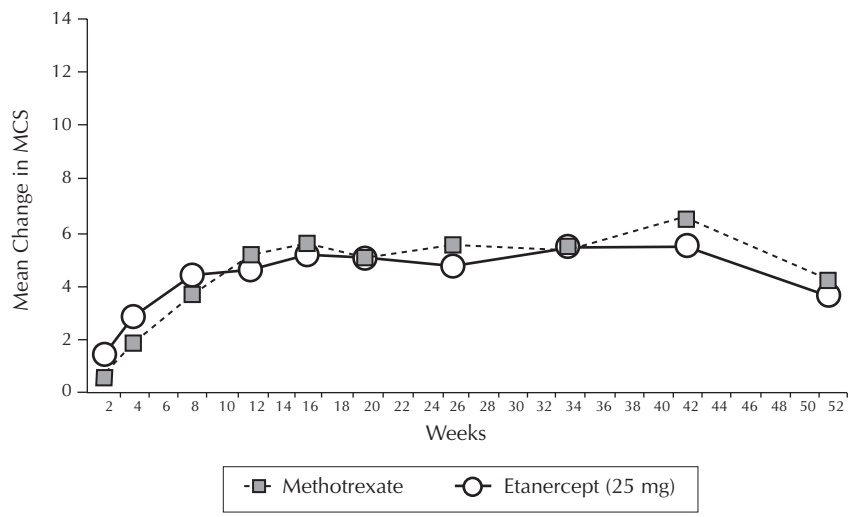
SF-36 = Medical Outcomes Study Short Form 36 Health Survey; HAQ = Health Assessment Questionnaire.

well-being was less than that noted in the physical and pain domains.

These findings have importance for the treatment of early RA patients. It is clear from the age distribution of this population that these individuals would likely be in the work force, years from retirement eligibility. However, in terms of physical health status, they appear to be more comparable to those aged 75 years and older in the general US populaton. [24,30] Effective treatment alleviates much of this burden and would be expected to reduce problems in performing work and other duties.

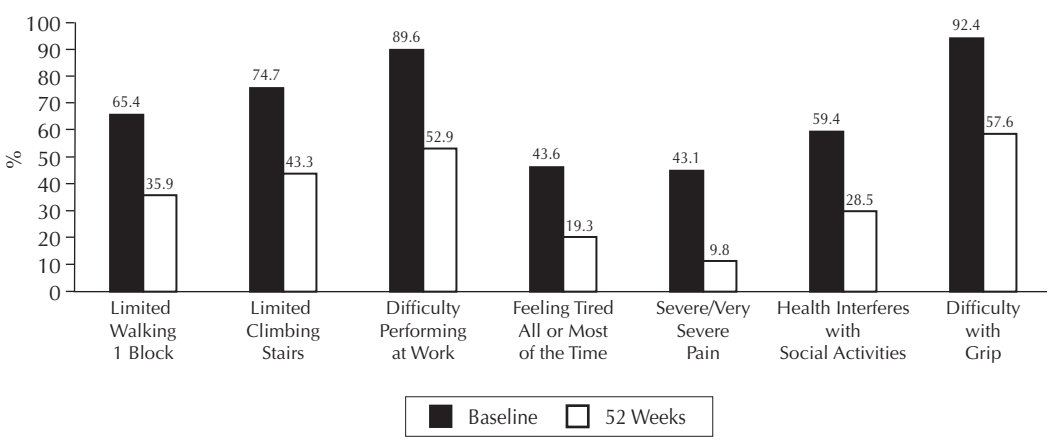
The results of this study provide insight into the pattern of HQL scores that can be expected between 2 different treatments—etanercept and methotrexate—during the course of a 1-year regimen. Although both treatments achieved similar HQL outcomes by the end of 52 weeks, patients randomized to etanercept responded much faster to treatment in HQL terms than patients randomized to methotrexate. Through the third month of treatment, patients in the etanercept group enjoyed significantly better physical health status than patients in the methotrexate group. The rapid improvement in HQL scores favoring etanercept over methotrexate coincided with the clinical outcomes.[12] During the first 6 months of the trial, a significantly greater proportion of patients in the etanercept group had improved disease activity, as measured by the American College of

Figure 4. Mean Changes in SF-36 MCS Scores Over 52 Weeks by Treatment



SF-36 = Medical Outcomes Study Short Form 36 Health Survey; MCS = mental component summary.

Figure 5. Impact of Treatment on HQL: Item Analysis for Overall Treatment Response (Combined Trial Samples, n = 424)



HQL = health-related quality of life.

Rheumatology improvement criteria, and erosion scores were significantly lower than those observed among patients in the methotrexate group.

The advantage of using HQL measures in assessing the rapidity of treatment response is that these are patient-based measures. Patients report their experiences and perceptions. Upon initial treatment of a newly diagnosed patient, the first few months are critical in establishing regimen compliance and persistence. If the patient does not experience positive treatment effects over an extended period, this lack of improvement can lead to a perceived failure of therapy and to the patient discontinuing treatment, foregoing the as-yet-unapparent benefits. Almost half the patients assigned to the etanercept group achieved reported improvement in less than 2 months, whereas the group receiving methotrexate took as long as 6 months (according to the HAQ measure) to achieve a comparable level of HQL impact.

While the results of this study and others[12,34] have shown the benefit of TNF–α inhibitors in improving the signs and symptoms of RA and lowering the risk of joint damage, particularly early in the disease, cost is a major barrier to adopting TNF–α inhibitors as standard treatment for all patients with RA. It is estimated that TNF–α inhibitors cost $10,000 to $12,000 a year per patient.[35] Furthermore, published information on the benefits of TNF–α inhibitors are limited to patients with advanced signs and symptoms of RA. It is reasonable to assume that the benefits of TNF–α inhibitors would generalize to patients with less advanced RA. However, studies are necessary to establish the value of aggressive therapy with TNF–α inhibitors. Study end points could include reductions in the need for long-term care, decreased healthcare resource utilization, and decreased disability caused by progressive joint damage.[35]

One limitation of this study is that all data were collected as part of a randomized clinical trial. As such, our findings may not accurately represent those of the entire population of patients with early RA or their treatment response in routine practice. However, the characteristics of the population in the present study are comparable to those reported for the early RA patient population, and likely are generalizable to clinical rheumatology practice.

··· CONCLUSIONS ···

Early RA places a tremendous disease burden on patients' HQL, in both the physical and emotional aspects of function and well-being. This impact is comparable to that of diabetes or congestive heart failure and should be assessed further for its clinical, social, and economic implications. Successful treatment of early RA improves patient-reported HQL as measured by both generic (SF-36) and disease-specific (HAQ) measures of functioning and well-being. Patient-reported HQL improvements during the early stages of treatment were significantly larger for patients randomized to etanercept than for those treated with methotrexate, indicating a rapid response to this treatment. The implications of this rapid response should be further investigated in terms of patient compliance, persistence, and cost effectiveness.

··· REFERENCES ···

1. Harris ED. Rheumatoid arthritis. Pathophysiology and implications for therapy. *N Engl J Med* 1990;322:1277-1289.

2. Wolfe F. The burden of rheumatoid arthritis. *Am J Manag Care* 1999;14(5 suppl):S852-S859.

3. Karlson EW, Katz JN, Liang MH. Chronic rheumatic disorders. In: Spilker B, ed. *Quality of Life in Clinical Trials.* 2nd ed. Philadelphia, PA: Lippincott-Raven; 1996:1029-1037.

4. Yelin E. The costs of rheumatoid arthritis: Absolute, incremental, and marginal estimates. *J Rheumatol Suppl* 1996;44:47-51.

5. Matsuda Y, Yamanaka H, Higami K, Kashiwazaki S. Time lag between active joint inflammation and radiological progression in patients with early rheumatoid arthritis. *J Rheumatol* 1998;25:427-432.

6. Elkayam O, Yaron M, Zhukovsky G, Segal R, Caspi D. Toxicity profile of dual methotrexate combinations with gold, hydroxychloroquine, sulphasalazine and minocycline in rheumatoid arthritis patients. *Rheumatol Int* 1997;17:49-53.

7. Mavrikakis M, Papazoglou S, Sfikakis PP, Vaiopoulos G, Rougas K. Retinal toxicity in long term hydroxychloroquine treatment. *Ann Rheum Dis* 1996;55:187-189.

8. Bendix G, Bjelle A. A 10 year follow up of parenteral gold therapy in patients with rheumatoid arthritis. *Ann Rheum Dis* 1996;55:169-176.

9. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999;130:478-486.

10. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N Engl J Med* 1997;337:141-147.

11. Moreland LW, Margolies G, Heck LW, Jr, et al. Recombinant soluble tumor necrosis factor receptor (p80)-Fc fusion protein: Toxicity and dose finding trial in refractory rheumatoid arthritis. *J Rheumatol* 1996;23:1849-1855.

12. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586-1592.

13. Pincus T, Brooks RH, Callahan LF. Prediction of long-term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. *Ann Intern Med* 1994;120:26-34.

14. Terry RB, Singh G. Quality of life measures in the treatment of arthritis in clinical practice. *New Stand Arthritis Care* 1996;5(3):2-6.

15. Ware JE, Sherbourne CD. The Medical Outcomes Study (MOS) 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care* 1992;30:473-483.

16. McHorney CA, Ware JE, Lu JFR, Sherbourne CD. The Medical Outcomes Study (MOS) 36-item short-form health survey (SF-36): III. Tests of data quality, scaling assumptions and reliability across diverse patient groups. *Med Care* 1994;32:40-66.

17. McHorney CA, Ware JE, Raczek AE. The Medical Outcomes Study (MOS) 36-item short-form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;31:247-263.

18. Brazier JE, Harper R, Jones NMB. Validating the SF-36 Health Survey questionnaire: New outcome measure for primary care. *BMJ* 1992;305:160-164.

19. Katz JN, Larson MG, Phillips CB, Fossel AH, Liang MH. Comparative measurement sensitivity of short and longer health status instruments. *Med Care* 1992;30:917-925.

20. Osterhaus JT, Townsend RJ, Gandek B, Ware JE. Measuring functional health status and well-being of patients with migraine headache. *Headache* 1994;34:337-343.

21. Phillips RC, Lansky DJ. Outcomes management in heart valve replacement surgery: Early experience. *J Heart Valve Dis* 1992;1:42-50.

22. Okamoto LJ, Noonan M, DeBoisblanc BP, Kellerman DJ. Fluticasone propionate improves quality of life in patients with asthma requiring oral corticosteroids. *Ann Allergy Asthma Immunol* 1996;5:455-461.

23. Coulehan JL, Schulberg HC, Block MR, Madonia ML. Treating depressed primary care patients improves their physical, mental and social functioning. *Arch Intern Med* 1997;157:1113-1120.

24. Ware JE, Kosinski M, Keller SD. *SF-36 Physical and Mental Health Summary Scales: A User's Manual.* Boston, MA: Health Assessment Lab; 1994.

25. Ware JE, Keller SD, Hatoun HT, Kong SX. The SF-36 Arthritis Specific Health Index (ASHI): I. Development and cross validation of scoring algorithms. *Med Care* 1999;37:MS40-MS50.

26. Keller SD, Ware JE, Hatoun HT, Kong SX. The SF-36 Arthritis Specific Health Index (ASHI): II. Tests of validity in four clinical trials. *Med Care* 1999;37:MS51-MS60.

27. Fries JP, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137-145.

28. Ware JE, Bayliss MS, Rogers WH, Kosinski M, Tarlov AR. Differences in 4-year health outcomes for elderly and poor, chronically ill patients treated in HMO and fee-for-service systems. *JAMA* 1996;276:1039-1047.

29. McHorney CA, Kosinski M, Ware JE. Comparisons of the cost and quality of norms for the SF-36 Health Survey collected by mail versus telephone interview: Results from a national survey. *Med Care* 1994;32:551-567.

30. Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36 Health Survey Manual and Interpretation Guide.* Boston, MA: The Health Institute, New England Medical Center; 1993.

31. Tugwell P, Wells G, Strand V, et al. Clinical improvement as reflected in measures of function and health related quality of life following treatment with leflunomide compared with methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;43:506-514.

32. Scott DL. Leflunomide improves quality of life in rheumatoid arthritis. *Scand J Rheumatol* 1999;28(suppl 11):23-29.

33. Kosinski M, Zhao SZ, Dedhiya S, Osterhaus JT, Ware JE. Determining minimally important changes in generic and disease specific health related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arthritis Rheum* 2000;43:1478-1487.

34. Lipsky PE, van der Heijde DM, St. Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000;343:1594-1602.

35. Klippel JH. Biologic therapy for rheumatoid arthritis. *N Engl J Med* 2000;343:1640-1641.