

Fatigue, Rheumatoid Arthritis, and Anti-Tumor Necrosis Factor Therapy: An Investigation in 24,831 Patients

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ABSTRACT. Objective. Fatigue is a common and distressing symptom in patients with rheumatoid arthritis (RA) and other rheumatic diseases. Reports have suggested profound improvements in fatigue after onset of anti-tumor necrosis factor- α (anti-TNF) therapy. In addition, physician and patient groups now identify fatigue as a very important symptom. However, data to support these observations are lacking. We evaluate the importance of fatigue in relation to other measures of clinical status, describe predictors of fatigue, and investigate fatigue levels in patients treated with anti-TNF therapy.

Methods. A total of 852 patients participated in a symptom-importance preference study. Additional analyses of fatigue and other clinical status variables were performed in up to 21,016 patients with RA and 3815 patients with osteoarthritis (OA) participating in the National Data Bank for Rheumatic Diseases.

Results. In ranking studies of the relative importance of fatigue compared with function, pain, cognition, gastrointestinal symptoms, and sleep, 8.0% of patients ranked fatigue as the most important variable, compared with 32.1% for function and 21.5% for pain. Multivariable studies of clinical change over 6 months found that changes in fatigue were weakly associated with changes in health status, in contradistinction to results for pain, function, and depression. Fatigue levels and fatigue predictors were similar in RA and OA patients. RA patients treated with anti-TNF therapy did not have lower fatigue scores compared with those not treated with this type of therapy.

Conclusion. Among RA patient self-report measures, fatigue is not ranked as important as functional disability, pain, or depression by most patients. This relative ranking is confirmed by examination of clinical improvement data. Fatigue levels and predictors of fatigue are essentially the same in RA and OA. Although anti-TNF therapy lowers fatigue levels, there is no evidence that this effect is greater for anti-TNF therapy than for other RA treatments. (J Rheumatol 2004;31:2115–20)

Key Indexing Terms:

FATIGUE

RHEUMATOID ARTHRITIS
ANTI-TUMOR NECROSIS FACTOR THERAPY

OSTEOARTHRITIS

The introduction of anti-tumor necrosis factor agents (anti-TNF) was associated with dramatic improvements in the clinical status of patients, documented according to American College of Rheumatology (ACR) improvement criteria¹, which include data concerning functional disability, pain, and patient global severity. Many rheumatologists also reported profound improvement in the level of fatigue, which is not included in ACR improvement criteria, after therapy with anti-TNF. Measures of fatigue have been

added to new clinical trials, and fatigue was shown to improve in response to adalimumab therapy². The US Food and Drug Administration has expressed interest in fatigue as a possible new domain of rheumatoid arthritis (RA) outcome, and fatigue is currently being considered in the revision of the ACR improvement criteria¹. Furthermore, patient interest and focus groups have identified fatigue as an important consideration in RA³, and articles on fatigue are in preparation.

While fatigue appears to be a variable whose time has come, there are few research data to support the concept that improvement in fatigue with anti-TNF therapy may be disproportionate to improvements in traditional measures of clinical status, such as functional disability and pain; nor that fatigue is a highly valued symptom by patients or that fatigue levels are greater in RA.

One of the first formal studies of fatigue in RA was reported by Belza, *et al* in 1993, who found that more than 60% of the variance in fatigue in RA was explained by demographic, psychosocial, and “disease-related” factors, the latter explaining two-thirds of the variance⁴. Disease-

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related factors included pain, poor sleep quality, limited physical activity, number of comorbidities, poor functional status, and duration of disease. The methodology of this study did not include direct measurement of the “inflammatory” component of RA. In 1996 we reported on fatigue in 1488 clinic patients⁵. We noted fatigue scores to be similar in RA and osteoarthritis (OA), and that about 90% of the explained variance in fatigue scores was due to pain, sleep disturbance, and depression. We also noted that in patients with RA no association was found in multivariable analyses between fatigue and inflammatory activity, assessed by erythrocyte sedimentation rate (ESR), joint count, and grip strength. We concluded that pain, functional loss, depression, and sleep disturbance, not inflammation, was the proximate cause of fatigue. These observations are in accord with epidemiologic studies of fatigue⁶⁻⁹ and with observations in patients with systemic lupus erythematosus¹⁰⁻¹² and with subsequent observations in RA^{13,14}.

We examined a large sample of patients from the practices of over 950 rheumatologists to investigate several questions: (1) How do patients value fatigue, in relation to other measures of clinical status? (2) How important are fatigue symptoms in determining change in health status? (3) Is fatigue increased in RA compared with OA? (4) Are fatigue levels lower in anti-TNF treated patients? The results of this study should provide guidance whether anti-TNF therapy independently reduces fatigue, whether fatigue is a problem specific to RA in comparison with other rheumatic illnesses, and whether fatigue is a very important symptom to patients.

MATERIALS AND METHODS

Patient sample. Patients in this study were participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of RA outcomes. Patients are recruited from the practices of United States rheumatologists, and are followed with semiannual questionnaires¹⁵⁻¹⁸. This report concerns 3 overlapping patient samples from the NDB.

In July 2003, NDB participants who complete surveys by the Internet were given the opportunity to complete a series of optional questions relating to their preferences concerning the importance of clinical status measures. The first sample consisted of 852 RA patients who volunteered and completed the preference questionnaire (response rate = 85%). In the second sample, 17,625 patients were evaluated, including 12,217 RA patients who had complete data for at least 2 consecutive biannual questionnaires between 1999 and 2003. For each of the 12,217 patients, 2 randomly selected consecutive questionnaires were used in order to measure change scores over 6 months. There were no other selection criteria. Patients who completed shortened versions of the questionnaires or underwent telephone assessments were excluded from this group. In the third sample, 24,831 NDB participants were evaluated, including 21,016 with RA and 3815 with OA of the hip or knee. One random observation from each patient was selected from this group for analysis. There were no exclusions. Sample 3 includes all patients in samples 1 and 2.

Demographic and disease status variables. NDB participants are asked to complete semiannual, detailed 28-page questionnaires about all aspects of their illness. At each assessment, demographic variables are recorded, including sex, age, ethnic origin, education level, current marital status, and medical history. Disease status and activity variables collected include

the Stanford Health Assessment Questionnaire functional disability index (HAQ disability)^{19,20}, visual analog scale (VAS) for pain, global disease severity, and fatigue scales⁵, the Arthritis Impact Measurement Scales (AIMS) anxiety and depression scales^{21,22}, and the Rheumatoid Arthritis Disease Activity Index (RADAI)²³⁻²⁵. HAQ-II, a shortened, modified version of the HAQ with similar scaling but superior psychometric properties, was also evaluated²⁶. From the Medical Outcomes Study Short Form-36 (SF-36), a single question was used to determine health status change. Patients report their current health status as (a) much better than 6 months ago, (b) somewhat better than 6 months ago, (c) about the same as 6 months ago, (d) somewhat worse than 6 months ago, or (e) much worse than 6 months ago^{27,28}. Fatigue was measured using a double anchored VAS labeled on one end, “Fatigue is no problem” and on the other end, “Fatigue is a major problem.” The question read, “How much of a problem has fatigue or tiredness been for you IN THE PAST WEEK?” The range of the scale was 0–10.

Preference questionnaire. The following text constituted the preference questionnaire of this study.

Because you have arthritis or a pain disorder, you have special insight into illness. We want to ask you to share that insight by telling us how you value certain medical problems. The questions that follow are not about your arthritis or pain problem, but about the problems of all people. There are no right or wrong answers.

For the medical conditions in these questions, it is possible for their severity to be (a) none, (b) mild, (c) moderate, or (d) severe. In the following questions you are asked to consider only persons whose condition is moderate.

Rank each condition according to its severity by putting a number from 1 to 6 in each box. 6 is the worst (most severe) condition and 1 is the mildest. Do not use the same number twice: each condition should have a different number between 1 and 6.

Condition	Severity Ranking (1–6)
Moderate difficulty in daily function	
Moderate pain or discomfort	
Moderate fatigue	
Moderate sleep disturbance	
Moderate problems with memory and concentration	
Moderate stomach or digestive problems	

Statistical methods. Ordered logistic regression was used in analyses of patients’ preferences and health status changes. Results are reported as odds ratios (OR) for a 1-category change in health status for a 1-unit change in the dependent variable. The z-score serves as a relative measure of the strength of the predictor variable. General estimating equations were used to evaluate the effect of biologic therapy on fatigue scores. Data were analyzed using Stata version 8.0²⁹.

RESULTS

Demographic and clinical characteristics. The 852 patients with RA who completed the Internet preference surveys concerning clinical status measures were 54.6 years old (SD 11.4): 20.3% were men (Table 1). They had slightly less severe RA than the usual RA sample, indicated by their HAQ score of 0.9 (SD 0.7), pain 3.5 (SD 2.8), and fatigue 4.1 (SD 2.9). As these results are, in part, a function of increased education, the 51.9% college-graduate level found in this Internet-based sample may explain the slight severity decrease that was noted. By comparison, when all NDB RA patients (n = 21,016) were studied, the mean age

Table 1. Characteristics of RA patients completing preference survey.

Variable	N	Mean
Age, yrs	852	54.62 ± 11.36
Sex, % male	856	20.3
Education, yrs	856	14.88 ± 2.05
Education category, n, %	856	
0–8	3	0.35
8–11	6	0.70
12	169	19.74
13–15	234	27.34
≥ 16	444	51.87
Disease duration, yrs	813	13.7*
HAQ (0–3)	856	0.91 ± 0.7
HAQ2 (0–3)	856	0.87 ± 0.62
Pain (0–10)	856	3.5 ± 2.76
Fatigue (0–10)	856	4.07 ± 2.93
Global severity (0–10)	856	2.98 ± 2.35
Physical component score (SF 36)	856	34.17 ± 10.37
Mental component score (SF 36)	856	47.66 ± 12.61
EQ5D 5SF mapped utility (0–1)	856	0.66 ± 0.21
Any DMARD or biologic, %*	856	86.68
Biologic agents, %*	856	52.22
No DMARD or biologic, %*	856	13.32

* Includes etanercept, infliximab, adalimumab, and anakinra.

was 60.6 years (SD 13.2), 22.9% were men, 24.5% were college graduates, and the mean HAQ, pain and fatigues scores were 1.1 (SD 0.7), 4.0 (SD 2.8), and 4.5 (SD2.9), respectively.

Patient preferences: ranking of symptom importance. Fatigue was ranked 5th of the 6 symptoms (Figure 1). Overall, 8.0% of patients ranked fatigue as the most important symptom, slightly above sleep problems (7.1%), but

less than functional status (32.1%), pain (21.5%), cognition (21.5%), and gastrointestinal (GI) symptoms (9.8%) (Figure 1). Fatigue remained in 5th place at 11.6% when rankings by first or 2nd position were analyzed (Figure 2).

Current fatigue levels, but not levels of other clinical variables, predicted a first-place symptom-importance ranking for fatigue. In a multivariable-ordered logistic regression analysis, with fatigue first-place ranking as the dependent variable and VAS fatigue, HAQ, pain, depression, age, and sex as the independent variables, only the VAS fatigue score predicted the ranked position for fatigue importance (OR 1.2, 95% CI 1.1 to 1.2, $p < 0.001$). When fatigue was dichotomized at a value of 6, the multivariable OR was 1.8 (1.3 to 2.5).

The ranking of fatigue was not related to use of anti-TNF agents (OR 1.1, 95% CI 0.9 to 1.4, $p = 0.477$) or prednisone use (OR 1.1, 95% CI 0.9 to 1.5, $p = 0.358$).

Patient data: ranking of symptom importance. The above analyses present reported patient preferences. We next examined actual clinical data in 12,217 RA patients in the NDB (Sample 2) to determine if the overall placement of fatigue noted in the preference survey was consistent with actual patient clinical outcome data. A change or difference score was calculated for each clinical variable from 2 questionnaires administered 6 months apart. This change score was then used to determine the extent to which the measured change predicted the patient's estimate of change in health status over a 6-month period. The strength of the relationship, then, represents a measure of the strength of the association of the change in the clinical variable with overall health status change. In agreement with the preference survey data, scores for HAQ and pain were most

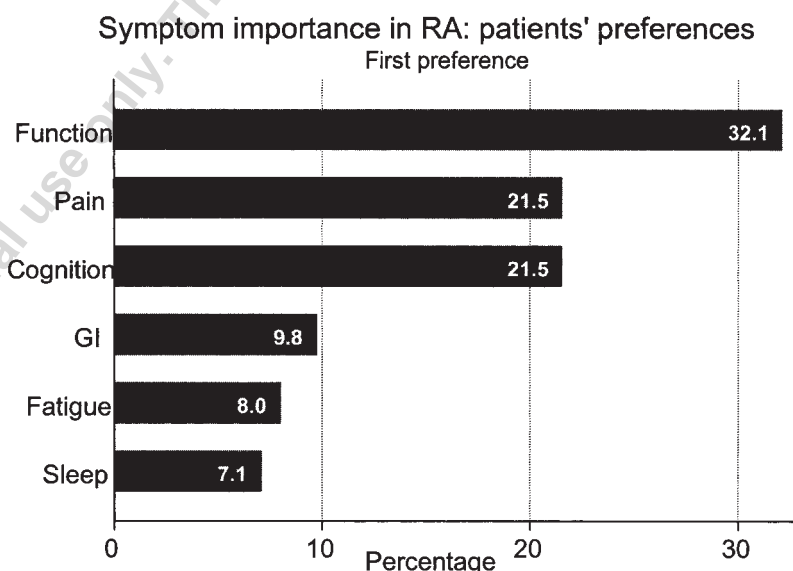


Figure 1. Percentage of patients (n = 852) ranking clinical problems on y-axis as most important.

strongly associated with change in health status (Table 2) in the multivariable model as well as in the univariate analyses, as shown by their much higher z-scores. Change in fatigue score was weakly associated with change in health status in the multivariable analysis, but more strongly associated with change in status in the univariate analysis.

Do patients who take biologic anti-TNF agents have lower fatigue scores? Regression analyses were performed in the 852 patients who completed the preference questionnaire and then, separately, in 17,625 RA patients from the NDB (Sample 2) to study possible differences in fatigue scores between patients treated with anti-TNF and those not treated with anti-TNF (Table 3). Analyses were first performed adjusting for age and sex and then repeated adjusting for age, sex, HAQ, and pain. The coefficients of the regression analyses represent the difference in fatigue scores between patients treated with anti-TNF and those not treated with anti-TNF. No association was seen between use of biologic agents and fatigue scores, regardless of the patient group or covariates that were included.

Are fatigue scores higher in RA than in OA (Sample 3)? The mean fatigue score in the RA patient group was 4.8. The difference in fatigue scores between patients with RA and those with OA was studied by regression analysis, controlling for HAQ, pain, depression, age, and sex (Table 4A). Fatigue scores were 0.17 (95% CI 0.09 to 0.25) units higher (3.6% higher) in the 21,016 RA patients than in the 3815 OA patients. In contrast to diagnostic category (RA vs OA), which had little association with fatigue score, scores for

pain, depression, and HAQ, as well as age were strongly associated with fatigue score. These analyses were repeated separately (Tables 4B and 4C) for patients with RA and OA, with similar results.

DISCUSSION

We believe that fatigue is a very important symptom, as supported by our inclusion of a fatigue VAS in a questionnaire completed by all patients in our clinics in standard care for more than a decade³⁰. Few measures identify patients with distress as well as do high levels of fatigue, and it is not our purpose in this report to denigrate fatigue measurement, but rather to place it properly within the context of patient measurement and importance.

Although fatigue is a distressing symptom in RA, as in all illnesses, it appears to be far from the most important symptom in most patients. Scores for function, pain, cognition, and GI symptoms are rated "most important" by more patients (Figure 1). When these "preferences" are tested in the clinical setting (Table 2), the results are similar: function and pain predominate as determinants of change in health status. The relative loss of effectiveness of fatigue in multivariable analyses compared to univariate analyses suggests that fatigue is highly correlated with other clinical variables and is not a key independent predictor of outcome.

The predominant determinants of fatigue are pain, depression, and functional loss (Tables 4A–4C), in agreement with our previous reports in a smaller clinical sample. These tables also show that levels of fatigue are only 3.6%

Table 2. Multivariable ordered logistic regression of 6-month change in health status on HAQ, pain, depression, fatigue, and sleep in 12,217 patients with RA. The OR represents the odds ratio for a 1-category change in health status for a 1-unit change in the dependent variable. The z-score serves as a relative measure of the strength of the predictor variable. Health status change is categorized as (a) much better than 6 months ago, (b) somewhat better than 6 months ago, (c) about the same as 6 months ago, (d) somewhat worse than 6 months ago, (e) much worse than 6 months ago.

Variable	OR (95% CI) Multivariable Analysis	Z-score	p	OR (95% CI) Univariate Analyses	Z-score	p
HAQ (0–3)	2.64 (2.32 to 3.01)	14.62	< 0.001	4.22 (3.82 to 4.68)	27.65	< 0.001
Pain (0–10)	1.17 (1.15 to 1.20)	15.84	< 0.001	1.25 (1.23 to 1.27)	29.06	< 0.001
Depression (0–10)	1.20 (1.15 to 1.25)	8.54	< 0.001	1.35 (1.30 to 1.39)	17.99	< 0.001
Fatigue (0–10)	1.04 (1.02 to 1.06)	4.07	< 0.001	1.16 (1.14 to 1.17)	19.23	< 0.001
Sleep problem (0–10)	1.03 (1.01 to 1.05)	3.29	< 0.001	1.09 (1.08 to 1.11)	13.09	< 0.001

Table 3. Regression of fatigue on biologic therapy use. The coefficients represent the change in fatigue score associated with use of biologic agents.

Covariates	Method	Patients	Obs.	Coeff (95% CI)	p
Age, sex	OLS	852	852	−0.20 (−0.20 to 0.59)	0.325
Age, sex, HAQ, pain	OLS	852	852	−0.10 (−0.40 to 0.21)	0.531
Age, sex	GEE	17,625	77,973	−0.04 (−0.09 to 0.02)	0.174
Age, sex, HAQ, pain	GEE	17,062	75,007	−0.03 (−0.02 to 0.07)	0.224

OLS: ordinary least squares regression. GEE: generalized estimating equations.

Table 4A. Multivariate regression of fatigue on RA diagnosis controlling for pain, HAQ, age, and sex in 24,831 RA and OA patients.

Variable	OR (95% CI)	Z-score	p
Pain (0–10)	0.39 (0.37 to 0.40)	60.18	< 0.001
Depression (0–10)	0.41 (0.39 to 0.42)	45.41	< 0.001
HAQ (0–3)	0.79 (0.74 to 0.84)	30.50	< 0.001
Age, yrs	–0.01 (–0.02 to –0.01)	–13.67	< 0.001
Sex, 1 = male	–0.26 (–0.33 to –0.20)	–7.82	< 0.001
RA, 1 = RA	0.17 (0.09 to 0.25)	4.27	< 0.001
Constant	1.88 (1.71 to 2.04)	22.44	< 0.001

$R^2 = 0.46$.

Table 4B. Multivariable regression of fatigue on pain, depression, HAQ, age, and sex in 21,016 patients with RA.

Variable	OR (95% CI)	Z-score	p
Age, yrs	–0.02 (–0.02 to –0.01)	–13.87	< 0.001
Sex, 1 = male	–0.28 (–0.35 to –0.21)	–7.69	< 0.001
HAQ (0–3)	0.75 (0.71 to 0.81)	26.96	< 0.001
Pain (0–10)	0.39 (0.38 to 0.41)	56.01	< 0.001
Depression (0–10)	0.40 (0.38 to 0.42)	41.04	< 0.001
Constant	2.17 (2.02 to 2.31)	28.88	< 0.001

$R^2 = 0.46$.

higher in RA than in OA. We believe that evidence of similar levels of fatigue in RA and OA is generally incompatible with a hypothesis that RA inflammation is a proximate cause of fatigue in RA. The data, particularly in light of the experience of patients with OA, suggest that pain, functional loss, and depression are the primary bases for fatigue rather than inflammation. This is in agreement with our previous observation that ESR was poorly correlated with RA disease activity, and consistent with community studies

Table 4C. Multivariate regression of fatigue on pain, depression, HAQ, age, and sex in 3815 patients with OA.

Variable	OR (95% CI)	Z-score	p
Age, yrs	–0.01 (–0.01 to 0.00)	–1.79	0.073
Sex, 1 = male	–0.16 (–0.33 to 0.01)	–1.90	0.058
HAQ (0–3)	1.04 (0.90 to 1.18)	14.87	< 0.001
Pain (0–10)	0.36 (0.32 to 0.39)	22.22	< 0.001
Depression (0–10)	0.46 (0.42 to 0.51)	19.73	< 0.001
Constant	1.01 (0.58 to 1.44)	4.65	< 0.001

$R^2 = 0.45$.

indicating that fatigue is associated with distress rather than physical illness^{6–9}. Similar observations have been made in systemic lupus erythematosus^{10–12}.

It is likely that the change in fatigue levels noted in clinical trials of anti-TNF and other agents reflects general improvement in pain, function, and psychological status rather than any direct interference with cytokines controlling fatigue. In regression analyses (Table 2), fatigue contributes only slightly to overall clinical change when sleep is removed from the model. These data suggest that if fatigue is added to improvement criteria for RA, it will change significantly in response to therapy, but will contribute little additional information to clinical models such as the Core Data Set, which includes joint evaluation, pain, function, global assessments, and laboratory data.

As it was the observation that fatigue was dramatically improved with anti-TNF therapy that led to the current upsurge of interest in fatigue, we note that our data offer no support for differences in fatigue levels among RA patients treated with anti-TNF therapy compared with those not

Symptom importance in RA: patients' preferences

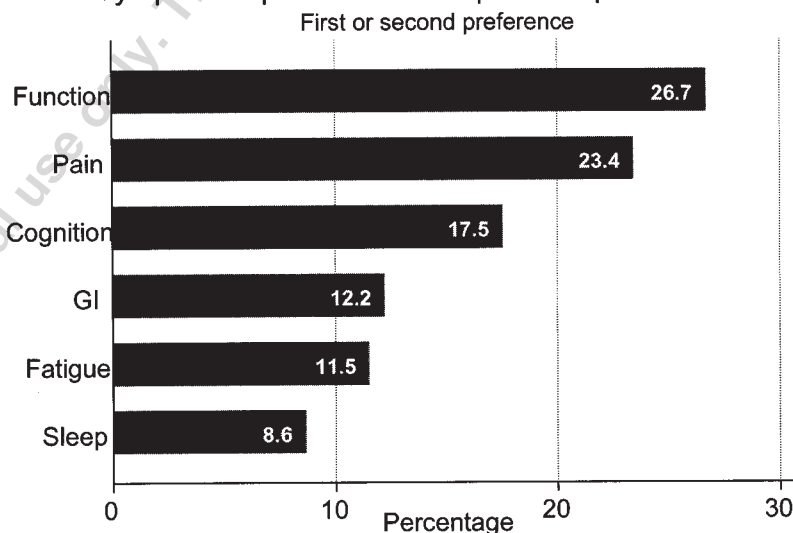


Figure 2. Percentage of patients (n = 852) ranking clinical problems on y-axis as most important or second most important.

treated with such therapy (Table 3). This observation is true overall and is also true in models that adjust for differences in clinical severity.

Despite our observations regarding the relative importance of fatigue, there is a group of patients (~12%) for whom fatigue is among the most important of symptoms, which is in agreement with our clinical experience. These observations emphasize the need to pay attention to fatigue.

It may be thought that the use of a VAS rather than a more complex fatigue questionnaire is a limitation to our observations. However, we show elsewhere that the VAS scale performs as well as or better than complex, multi-question scales³¹. A potential limitation (or perhaps a strength) of our study is that the results are based on observational data. However, we have seen analyses of clinical trial data that also show a limited role for fatigue scores. We think it is particularly important that the multivariable importance of fatigue in clinical trials be understood before the symptom is widely adopted and considered as a separate RA outcome domain.

In summary, among RA patient self-report measures, fatigue is given a low ranking compared to other measures by patients, and this ranking is confirmed by examination of clinical improvement data over 6 months. Fatigue levels are essentially the same in RA and OA, and the predictors of fatigue are the same in both disorders. There is no evidence that anti-TNF therapy preferentially alters fatigue levels.

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