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BRIEF REPORT

Fatigue Is Not Associated With Objective Assessments of Inflammation During Tocilizumab Treatment of Patients With Rheumatoid Arthritis

Hilde Berner Hammer,[1] Birte Agular,[2] and Lene Terslev[3]

Objective. In patients with rheumatoid arthritis (RA), the relation between fatigue and disease activity is not established, and our objective was to explore in post hoc analyses the associations between fatigue and subjective as well as objective assessments of inflammation during follow-up of patients with RA initiating biologic treatment.

Methods. In a Nordic multicenter study, patients with RA starting tocilizumab were examined for fatigue (Functional Assessment of Chronic Illness Therapy–Fatigue sum score) as well as patient-reported outcome measures (PROMs) (patient's global disease activity, joint pain, and Health Assessment Questionnaire Disability Index), clinical examinations (examiner's global disease activity, 28 tender/swollen joint counts), laboratory variables (erythrocyte sedimentation rate, C-reactive protein), and ultrasound assessments (semiquantitative scoring [0-3]) of gray scale and Doppler of 36 joints and 4 tendons) at baseline and 4, 12, and 24 weeks. The associations were explored by using nonparametric tests, including the Wilcoxon rank test, the Mann–Whitney *U* test, Spearman correlations, and a linear regression and linear mixed model.

Results. One hundred ten patients were included (83% female, mean [SD] age 55.6 [12.1] years, mean [SD] RA duration 8.7 [9.5] years, 81% anti–cyclic citrullinated peptide positive). Fatigue, PROMs, and clinical, laboratory, and ultrasound variables all decreased significantly during follow-up, already at 4 weeks ($P < 0.001$). Fatigue was both cross-sectionally and longitudinally associated with PROMs, whereas there were no or low associations with clinical, laboratory, or ultrasound assessments of inflammation. Baseline fatigue was predictive of PROMs at 12 and 24 weeks ($P < 0.05$ and $P < 0.001$, respectively) but not of any objective assessments.

Conclusion. Fatigue was primarily associated with subjective assessments of disease activity. Thus, the present study supports fatigue to reflect other aspects of RA disease activity than inflammation.

INTRODUCTION

Fatigue is common in patients with rheumatoid arthritis (RA) (1) and is evaluated among the patients as the second most important outcome, only surpassed by pain (2). Fatigue has been described to have a multifactorial explanation, with association with both inflammatory and psychosocial factors (3). Tumor necrosis factor α blocker treatment has been shown to reduce fatigue (4), suggesting that cytokine-mediated mechanisms may be important in the fatigue pathogenesis. However, in patients with established RA treated with biologic disease-modifying antirheumatic drugs (bDMARDs), fatigue was cross-sectionally found to be primarily associated with subjective and not objective assessments (including ultrasound) of disease activity (5).

To better understand the relationship between fatigue and disease activity in RA, there is a need for studies exploring the associations between fatigue and both patient-reported outcome measures (PROMs) and objective examinations of inflammation.

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[1]Hilde Berner Hammer, PhD, MD: Diakonhjemmet Hospital and University of Oslo, Oslo, Norway; [2]Birte Agular: Roche Pharmaceuticals, Copenhagen, Denmark; [3]Lene Terslev, PhD, MD: Rigshospitalet Glostrup, Glostrup, Denmark.

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On reasonable request, the authors are prepared to send relevant documentation or data.

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Address correspondence to Hilde Berner Hammer, PhD, MD, Diakonhjemmet Hospital, Department of Rheumatology, Box 23 Vinderen, N-0319 Oslo, Norway. Email: hbham@online.no.

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SIGNIFICANCE & INNOVATIONS

- In patients with rheumatoid arthritis (RA) initiating tocilizumab, fatigue was associated with patient-reported outcome measures during follow-up (both cross-sectionally and for changes).
- This is the first multicenter study that includes ultrasound for exploring associations between fatigue and objective assessments of inflammation. Fatigue had no or low associations with clinical assessments of disease activity or ultrasound examinations at baseline and during follow-up.
- Baseline fatigue was predictive of patient-reported outcomes at 12 and 24 weeks but was not predictive of clinical or ultrasound assessments.
- The present study supports fatigue to reflect other aspects of RA disease activity than inflammation.

Ultrasound is a sensitive imaging modality and is increasingly used in the clinics to evaluate inflammation in patients with RA by assessing the degree of synovitis (6). In addition, inflammatory markers, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are usually included in clinical examinations to reflect the degree of inflammation.

To explore whether fatigue is primarily associated with subjective or objective assessments of disease activity, data from a recently published Nordic study of patients with RA initiating tocilizumab as their first bDMARD were used (7). The study included a comprehensive assessment of fatigue as well as PROMs, clinical examinations, and ultrasound assessments. Our aims were to explore the cross-sectional and longitudinal associations between the level of fatigue and PROMs as well as clinical, laboratory, and ultrasound assessments of disease activity in people with RA.

PATIENTS AND METHODS

Patients (≥18 years old) with active RA according to the revised (1987) American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR)/ACR (2010) criteria (moderate to severe RA with a Disease Activity Score in 28 Joints [DAS28] with ESR > 3.2) with inadequate response or intolerance to conventional synthetic disease-modifying antirheumatic drugs were included (7). Inclusion and exclusion criteria were as previously described (8). In this post hoc analysis, only the subgroup of patients from the main study (TOZURA) who were assessed by ultrasound were included (7). All assessments (PROMs and clinical, laboratory, and ultrasound assessments) were performed at baseline and after 4, 12, and 24 weeks.

Protocols, amendments, and informed consent documentation of the studies were approved by the respective local independent ethics committees (Norwegian Ethical Committee 2013/1857/REK South-East; ClinicalTrials.gov identifier: NCT02046616). All patients provided written informed consent according to the Declaration of Helsinki.

Assessment of fatigue. Fatigue was assessed by use of the symptom-specific measure the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) (9), version 4. This questionnaire was developed to assess chronic illness therapy with special emphasis on fatigue in the past 7 days and consists of five dimensions: physical well-being (seven items), social/family well-being (seven items), emotional well-being (six items), functional well-being (seven items), and additional concerns (13 items). Thus, FACIT-F has a total of 40 items, with a score range of 0 to 160 (www.facit.org). This FACIT-F score is referred to as the fatigue sum score or FACIT-F sum score. In addition, the last 13 items (additional concerns) were explored as an isolated fatigue score because this score may be used as a short form of the FACIT-F (range 0-52) (10) and is included in several studies to explore fatigue (10,11). We also calculated the Trial Outcome Index (TOI) (9). This score includes the sum of the physical well-being, functional well-being, and additional concerns subscales (range 0-108).

Each of the questions is categorically answered by using the scales 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much. Higher score values indicate more favorable conditions (ie, less fatigue). The FACIT-F questionnaire has been translated into the different Nordic languages, and these were used in the present study.

PROMs. The patient's global assessment of disease activity (PGA) and joint pain were scored on visual analog scales (VAS) (0-100). In addition, the patients completed the Health Assessment Questionnaire Disability Index (HAQ-DI) (12).

Clinical and laboratory assessments. The 28 joints included in the DAS28 were assessed for tenderness and swelling by rheumatologists or trained study nurses depending on the study site, and the tender joint count (TJC) and swollen joint count (SJC) were calculated. The examiner's global assessments (EGAs) were scored by VAS (0-100).

Tocilizumab is an interleukin 6 inhibitor that inhibits the production of acute phase proteins. Because the Clinical Disease Activity Index (CDAI) (13) has been recommended as a clinical composite score during tocilizumab treatment, we included the CDAI as the clinical score (SJC [28] + TJC [28] + PGA + EGA).

ESR was examined locally at each hospital laboratory, whereas serum samples were sent to a central study laboratory for examination of CRP.

Ultrasound examination. The ultrasound examinations included gray scale (GS) and power or color Doppler scored semiquantitatively on a four-point scale (0 = no, 1 = minor, 2 = moderate, 3 = major presence of GS or Doppler) of 36 joints

(wrists [radiocarpal, midcarpal, radioulnar joints scored separately], metacarpophalangeal 1-5, proximal interphalangeal 2-3, elbow, knee, tibiotalar, and metatarsophalangeal 1-5 as well as the extensor carpi ulnaris and tibialis posterior tendons) according to Outcome Measures in Rheumatology (OMERACT) and the Norwegian ultrasound atlas (14,15). A sum score for all joints and tendons was calculated at the patient level separately for GS and for Doppler. The ultrasonographers were blinded to the PROMs, clinical assessments, and laboratory markers of the patients during the entire study. The intrarater reliability for the ultrasonographers at the involved centers had a median (range) intraclass correlation coefficient of 0.89 (0.79-0.96) (7).

Statistical methods. The variables were not normally distributed (detrended normal Q-Q plot), and nonparametric statistics were used. Correlations were assessed by Spearman's ρ, and correlation coefficients were defined as follows: no, <0.2; low, 0.2 to 0.3; moderate, >0.3 to <0.5; substantial, 0.5 to 0.7; and high associations, >0.7. Differences between groups were explored by using Mann–Whitney *U* tests, and changes from baseline were explored by using Wilcoxon signed rank tests. At baseline, patients were divided into quartiles according to fatigue sum score. In addition, at all visits the patients were divided in two groups: having a fatigue sum score level less than or equal to the median (ie, higher fatigue) or having a fatigue sum score level greater than the median (ie, lower fatigue); differences between these two groups were explored for levels of PROMs and clinical, laboratory, and ultrasound assessments. Linear regression was used to assess the associations between baseline fatigue sum scores (adjusted for age, sex, and disease duration) and PROMs and clinical or ultrasound scores at 12 and 24 weeks' follow-up. A linear mixed model (adjusted for age, sex, and disease duration) was used to assess the relationship between changes in fatigue sum scores and changes in PROMs and clinical and ultrasound scores across the visits. This was done separately for each disease activity measure, treating fatigue as the dependent variable. Significance was defined as $P < 0.05$, and all calculations were performed by using SPSS Statistics version 27 (IBM Corp) or Stata version 16 (StataCorp).

RESULTS

A total of 110 patients (mean [SD] age 55.6 [12.1] years, mean [SD] RA disease duration 8.7 [9.5] years, 83% female, 81% anti–cyclic citrullinated peptide positive) were examined (7). Only patients continuing tocilizumab treatment were included in the follow-up analyses (4 weeks: n = 102; 12 weeks: n = 95; 24 weeks: n = 91). Discontinuation was caused by side effects or insufficient response to medication. Fatigue sum scores, PROMs, clinical and laboratory variables, and ultrasound scores all improved significantly from baseline, already after 4 weeks ($P < 0.001$).

There were no significant differences in fatigue sum scores between men and woman at any visits and no significant correlations between fatigue sum score levels and age or disease duration at baseline or during follow-up.

Associations across baseline quartiles of fatigue. Figure 1 illustrates the associations at baseline across quartiles of fatigue sum scores and PROMs, clinical assessments, and ultrasound assessments. Increased sum scores of the FACIT-F questionnaire indicated reduced levels of fatigue. With increasing quartiles of FACIT-F sum scores (ie, decreasing levels of fatigue), there were decreasing levels of PGA VAS, joint pain VAS, and HAQ-DI ($P < 0.001$ for all), whereas there were no significant associations between quartiles of fatigue sum scores and any of the clinical or ultrasound assessments.

Fatigue levels during follow-up. Median (interquartile range) FACIT-F sum scores were 104 (86-123) at baseline, 117 (101-136) at 4 weeks, 126 (109-139) at 12 weeks, and 129 (112-142) at 24 weeks, showing significant increase of the score (ie, reduced fatigue) during the study ($P < 0.001$).

Correlations between the subscales of fatigue during follow-up. The fatigue sum score of (FACIT-F) had different levels of correlations with the subscales, with highest association with the additional concerns subscale (which is frequently used as the short form of the FACIT-F). The median (range) correlation coefficients during follow-up between the FACIT-F sum score and subscales were as follows: additional concerns, 0.94 (0.92-0.94); physical well-being, 0.84 (0.77-0.85); emotional well-being, 0.59 (0.55-0.72); social/family well-being, 0.56 (0.42-0.61); and functional well-being, 0.88 (0.86-0.91) (all $P < 0.001$).

Associations between fatigue and PROMs and clinical and ultrasound assessments. Patients with higher levels of fatigue (ie, median or lower levels of FACIT-F sum scores) compared with patients with lower levels of fatigue (ie, higher than the median FACIT-F sum score) had significantly higher levels of PGA VAS (mean [SD]: 62 [21] vs 46 [20] at baseline [$P < 0.001$]; 42 [21] vs 26 [18] at 4 weeks [$P < 0.001$]; 33 [26] vs 14 [13] at 12 weeks [$P < 0.001$]; and 26 [23] vs 11 [11] at 24 weeks [$P < 0.001$]). In addition, patients in the group with the highest levels of fatigue had higher levels of joint pain VAS (mean [SD]: 63 [21] vs 47 [22] at baseline [$P < 0.001$]; 44 [24] vs 24 [20] at 4 weeks [$P < 0.001$]; 32 [26] vs 12 [14] at 12 weeks [$P < 0.001$]; and 24 [24] vs 11 [13] at 24 weeks [$P = 0.004$]) as well as higher levels of HAQ-DI (mean [SD]: 1.5 [0.5] vs 0.9 [0.6] at baseline [$P < 0.001$]; 1.3 [0.5] vs 0.5 [0.5] at 4 weeks [$P < 0.001$]; 1.0 [0.6] vs 0.4 [0.5] at 12 weeks [$P < 0.001$]; and 0.9 [0.6] vs 0.2 [0.4] at 24 weeks [$P < 0.001$]). However, the patients with the highest levels of fatigue did not have higher levels of clinical or ultrasound assessments during follow-up (data not shown).

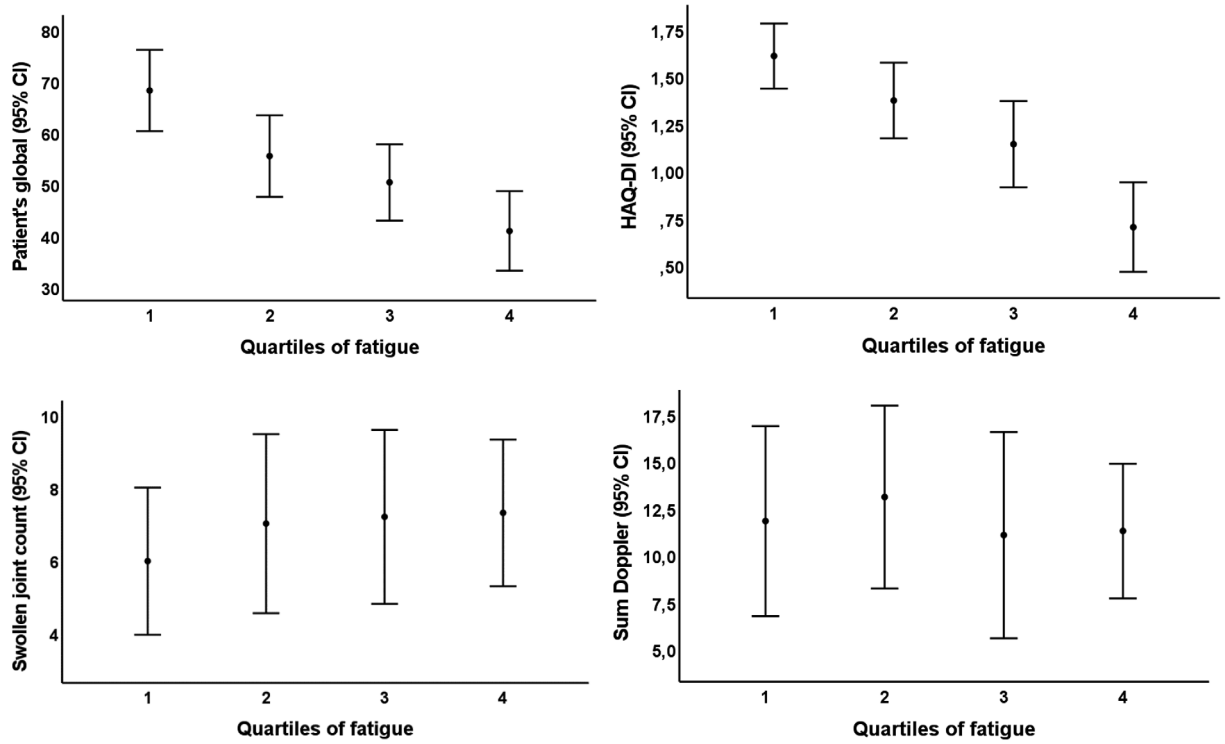

Figure 1. Quartiles of fatigue at baseline (assessed by the Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT-F] sum score, in which higher quartiles reflect lower levels of fatigue) compared with baseline levels of patient-reported outcome measures (patient's global disease activity visual analog scale [VAS] [0-100] and Health Assessment Questionnaire Disability Index [HAQ-DI]), swollen joint count, and Doppler sum score. CI, confidence interval.

The fatigue sum score (FACIT-F) was associated with PROMs both cross-sectionally at all visits and for changes during the study (Tables 1 and 2). However, as shown in the tables, the fatigue sum score had no significant or low correlations with clinical or ultrasound assessments (neither cross-sectionally at all visits nor for changes during the study). In addition, there were no significant correlations between the baseline fatigue sum score and CRP/ESR (correlation coefficients of −0.11/−0.02).

Associations between TOI and PROMs and clinical and ultrasound assessments. During follow-up, the TOI had substantial correlations (*r*), with all the PROMs (median [range]: PGA VAS, $r = -0.51$ [−0.45 to −0.54]; joint pain, $r = -0.52$ [−0.47 to −0.56]; and HAQ-DI, $r = -0.64$ [−0.62 to −0.64]). However, there were no significant correlations between TOI and clinical or ultrasound examinations (data not shown), except the finding of a low association at 24 weeks with EGA ($r = -0.23$) and TJC ($r = -0.23$).

Linear regression analysis with baseline fatigue. Linear regression analyses showed that the baseline fatigue sum score was predictive of PGA VAS both at 12 and 24 weeks'

Table 1. Spearman's correlations between fatigue (assessed by FACIT-F sum score) and patient-reported outcome measures, clinical and laboratory assessments, and ultrasound examinations during follow-up

	Baseline fatigue	4-week fatigue	12-week fatigue	24-week fatigue
Patient's global VAS	−0.46**	−0.41**	−0.50**	−0.48**
Joint pain VAS	−0.43**	−0.50**	−0.54**	−0.41**
HAQ-DI	−0.59**	−0.59**	−0.60**	−0.62**
28 tender joint count	−0.07	−0.19	−0.12	−0.22*
28 swollen joint count	0.14	0.12	0.20*	0.19
Examiner's global VAS	0.05	0.05	−0.03	−0.15
GS sum score	0.09	0.20*	0.24*	0.13
Doppler sum score	0.06	0.01	0.13	0.02

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; GS, gray scale; HAQ-DI, Health Assessment Questionnaire Disability Index; VAS, visual analog scale.
*$P < 0.05$; **$P < 0.001$.

Table 2. Spearman's correlations between changes from baseline to 4, 12, and 24 weeks of fatigue (assessed by FACIT-F sum score) and patient-reported outcome measures, clinical assessments, and ultrasound examinations

Change from baseline	4 weeks	12 weeks	24 weeks
Δ patient's global VAS	−0.59**	−0.56**	−0.59**
Δ joint pain VAS	−0.60**	−0.50**	−0.52**
Δ HAQ-DI	−0.43**	−0.44**	−0.61**
Δ 28 tender joint count	−0.29*	−0.30*	−0.24*
Δ 28 swollen joint count	−0.15	−0.17	−0.06
Δ examiner's global VAS	−0.14	−0.27*	−0.15
Δ GS sum score	−0.10	−0.17	−0.12
Δ Doppler sum score	−0.21*	−0.14	−0.10

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; GS, gray scale; HAQ-DI, Health Assessment Questionnaire Disability Index; VAS, visual analog scale.
*$P < 0.05$; **$P < 0.001$.

follow-up (β [95% confidence interval (CI)]: −0.24 [−0.45 to −0.04], $P = 0.021$, and − 0.30 [−0.53 to −0.07], $P = 0.01$, respectively). The baseline fatigue sum score was also predictive of joint pain at 12 and 24 weeks' follow-up (β [95% CI]: −0.28 [−0.48 to −0.09], $P = 0.006$, and − 0.26 [−0.48 to −0.04], $P = 0.021$, respectively) as well as HAQ-DI (β [95% CI]: −14.8 [−22.0 to −7.6], $P < 0.001$, and − 14.6 [−21.9 to −7.3], $P < 0.001$, respectively). However, the baseline fatigue sum score was not associated with clinical assessments, CDAI, or ultrasound sum scores at 12 or 24 weeks (data not shown).

Changes in fatigue versus changes in PROMs and clinical and ultrasound measures. The relationship between changes in fatigue and changes in the disease activity measures, as assessed by the standardized regression coefficient (β [95% CI]), was highly significant for PGA (−0.60 [−0.68 to −0.52]), joint pain (−0.59 [−0.68 to −0.50]), HAQ-DI (−0.48 [−0.57 to −0.39]), TJC (−0.26 [−0.34 to −0.17]), and EGA (−0.22 [−0.33 to −0.12]), with $P < 0.001$ for all. For ultrasound GS and Doppler sum scores, the relationship was less pronounced (−0.12 [−0.21 to −0.02], $P = 0.016$, and − 0.12 [−0.22 to −0.03], $P = 0.010$, respectively), and there was no relation with SJC (−0.06 [−0.15 to 0.04], $P = 0.245$).

DISCUSSION

This is the first longitudinal multicenter study to include a comprehensive ultrasound examination as an objective assessment of inflammation for exploring the association between fatigue and disease activity. In this Nordic study of patients with RA initiating tocilizumab, we found fatigue in post hoc analyses to have strong positive associations with all the PROMs, whereas there were no cross-sectional and only weak longitudinal associations between fatigue and clinical, laboratory, and ultrasound assessments of disease activity. In addition, baseline fatigue was found to predict all the PROMs at 12 and 24 weeks but none of the objective assessments of disease activity.

A previous study of patients with RA found negative correlations between fatigue (assessed by FACIT-F) and DAS28, CDAI, TJC, and SJC (correlations of −0.73 to −0.83), which were stronger associations than in our study. But likewise, they found no significant correlation with ESR (11). A recent single-center study found no cross-sectional associations between fatigue and ultrasound scores (5), similar to the present study, whereas change in fatigue during bDMARD treatment was found to be associated with change in objective assessments of disease activity, including ultrasound (5). This is to some degree in contrast with our findings because we found no or weak associations between change in fatigue and change in the objective assessments, including ultrasound, during follow-up. However, the previous study (5) used only a numeric rating scale (range 0-10) for fatigue, and the results, therefore, may not be directly comparable with our study because we used an established comprehensive questionnaire for fatigue. Thus, the present study adds to the increasing number of studies showing fatigue primarily to be associated with subjective, but not objective, assessments of disease activity (1,5,11,16).

The FACIT-F sum score was found to have different levels of correlation with its subscales. However, the frequently used short form of FACIT-F consisting of the additional concerns (13 items) had high correlations with the FACIT-F sum score. This suggests that studies including either the total FACIT-F sum score or the short form of FACIT-F would give similar results and supports use of the short form to reduce the load for patients.

We included the TOI, which is found to be an efficient summary index of physical/functional outcomes and is commonly used as an end point in clinical trials (9). The TOI score is responsive to change in physical/functional outcomes, sometimes more than the FACIT-F sum score, which includes social and emotional well-being, which are not as likely to change quickly in response to treatment. However, in the present study, the TOI score was only associated with the PROMs and not with any of the objective assessments of disease activity. Thus, the TOI was not found to reflect the inflammatory activity in patients with RA.

Fatigue is a major complaint in patients with RA (1) and is frequent despite effective control of the inflammatory activity, as also demonstrated in our study. This troublesome complaint should be treated adequately, and several nonpharmacological treatments of fatigue have been explored, showing reduction of fatigue by physical activity and psychosocial interventions (17). Thus, health personnel treating patients with RA with fatigue should be aware of treatment options, such as different forms of self-management.

The high positive associations between fatigue and PGA may, with increasing fatigue, cause higher levels of clinical composite scores (ie, DAS28 and CDAI) and thus affect the ability to obtain clinical composite score remission. When treating to target

using a clinical composite score as the target, an important pitfall is that this score may reflect subjective complains and not inflammation (18).

A study limitation is the relatively low number of patients. Despite including more than 100 patients, it may be insufficient to fully eliminate an association between fatigue and objective assessments of disease activity. Another potential limitation may be the high number of ultrasonographers involved in the study. However, a high intrarater agreement was found between the ultrasonographers, as previously published (7), and the ultrasonographers sought to assess the same patients during follow-up. The patients included in the present study had established RA, and thus our results may be different from that for patients with recent-onset RA. In addition, because the fatigue score is a PROM, it could be expected that the FACIT-F scores were highly associated with the other PROMs. However, the present objectives were to explore the associations between fatigue and subjective as well as objective assessments. Strengths of our study were the inclusion of several centers as well as a follow-up design. Furthermore, we used a validated questionnaire for assessing fatigue and a well-described ultrasound scoring of synovitis including an atlas of the different scores in all the examined joints (15).

In conclusion, fatigue as well as clinical, laboratory, and ultrasound assessments improved significantly during tocilizumab treatment of patients with established RA. Fatigue was found to be substantially associated to PROMs, both cross-sectionally at all visits and for changes from baseline during follow-up. However, fatigue had no or weak associations with clinical and ultrasound examinations during follow-up. The cross-sectional lack of association between fatigue and objective assessments of inflammation suggests that antiinflammatory treatment alone is not sufficient to treat fatigue. However, further studies should explore this issue and preferably include patients with shorter disease duration also.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. XXX had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Hammer, Agular, Terslev
Acquisition of data. Hammer, Terslev
Analysis and interpretation of data. Hammer, Agular, Terslev

ROLE OF THE STUDY SPONSOR

Roche Pharmaceuticals had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Roche Pharmaceuticals.

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