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CLINICAL SCIENCE

Fatigue in patients with early rheumatoid arthritis undergoing treat-to-target therapy: predictors and response to treatment

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ABSTRACT

Objectives Fatigue is a frequent symptom in rheumatoid arthritis (RA) and has high impact on quality of life. We explored associations between disease activity and fatigue in patients with early RA during the initial 24 months of modern treat-to-target therapy and predictors of fatigue after 24 months of follow-up.

Methods Data were obtained from the treat-to-target, tight control Aiming for Remission in Rheumatoid Arthritis: a Randomised Trial Examining the Benefit of Ultrasound in a Clinical Tight Control Regime (ARCTIC) trial. Fatigue was measured on a visual analogue scale (VAS) from 0 to 100 mm and defined as clinically relevant if VAS was ≥20 mm. Baseline predictors of fatigue at 24 months were analysed by multivariable logistic regression.

Results 205 patients with fatigue data at baseline and 24 months were included. Median (25th, 75th percentiles) symptom duration was 5.4 months (2.8, 10.4), fatigue VAS 37.0 mm (13.0, 62.0) and mean Disease Activity Score (DAS) 3.4 (SD 1.1) at baseline. Prevalence of fatigue declined from 69% at baseline to 38% at 24 months. Fewer swollen joints (OR 0.92, 95% CI 0.87 to 0.98, p=0.006), lower power Doppler ultrasound score (OR 0.95, 95% CI 0.90 to 0.99, p=0.027) and higher patient global assessment (PGA) (OR 1.03, 95% CI 1.01 to 1.04, p<0.001) increased the risk of clinically relevant fatigue at 24 months. Not achieving remission at 6 months was associated with a higher risk of reporting fatigue at 24 months.

Conclusions Fatigue in patients with early RA was prevalent at disease onset, with a rapid and sustained reduction during treatment. Low objective disease activity and high PGA at baseline were predictors of clinically relevant fatigue at 24 months.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by joint inflammation with subsequent joint destruction and loss of function.[1] Up to 70% of patients with RA experience fatigue,[2] and patients have ranked fatigue as one of the most important disease-related outcomes in RA.[3 4] There is no generally accepted definition of RA-related fatigue, but the symptoms have been described 'as an overwhelming, debilitating, and sustained sense of exhaustion that decreases the ability to function and carry out daily activities'.[5]

Key messages

What is already known about this subject?
► Fatigue is common in patients with rheumatoid arthritis (RA). Knowledge about the causes of fatigue is limited, and associations between fatigue and disease activity are uncertain.

What does this study add?
► This study shows that there is an association between disease activity and fatigue, and that achieving early disease remission decreases the risk of fatigue. Baseline predictors of fatigue at 24 months are lower number of swollen joints, lower ultrasound power Doppler score and higher patient global assessment.

How might this impact on clinical practice or future developments?
► These results support the effect of early treat-to-target treatment on fatigue in a majority of patients with early RA and provide baseline predictors of fatigue at 24 months. A non-pharmacological approach to fatigue might be favourable in the presence of these predictors.

Fatigue is considered a multidimensional phenomenon involving disease processes, personal and social aspects,[2] and with implications for the patient's quality of life as well as increased societal costs related to reduced work productivity and frequent physician consultations.[6] Physical function, age, gender, mental health, pain, sleep disturbances and inflammation have been found to be associated with fatigue. However, none of these variables show a consistently strong relationship with fatigue across studies in systematic reviews, and the impact of inflammatory disease activity on fatigue has not been established.[6–9]

The goal in modern RA treatment is sustained remission and augmentation of long-term health-related quality of life through control of symptoms, prevention of structural damage, and participation in social and work-related activities.[10 11] In addition to the introduction of biological disease-modifying antirheumatic drugs (DMARDs), more aggressive treatment with higher doses of methotrexate, earlier initiation of DMARDs and tight control

strategies have led to a large proportion of patients with early RA reaching sustained remission.[11] However, fatigue in patients with early RA treated according to modern treatment strategies is still not well understood.

The objectives of this study were, first, to explore the longitudinal prevalence of fatigue in patients with early RA followed up in a treat-to-target strategy trial and to investigate the relationship between fatigue and disease activity. Second, we aimed to identify baseline predictors of unresolved fatigue after 24 months of follow-up and, finally, to assess the impact of early treatment response and remission on fatigue.

MATERIALS AND METHODS

Study design
Data were obtained from the Aiming for Remission in Rheumatoid Arthritis: a Randomised Trial Examining the Benefit of Ultrasound in a Clinical Tight Control Regime (ARCTIC) trial.[12] Participants were randomised 1:1 to a treat-to-target strategy with or without applying musculoskeletal ultrasonography in clinical examinations and treatment decisions. All patients were treated according to a predefined algorithm that started with a combination of methotrexate (15 mg/week escalated to 20–25 mg/week) and prednisolone (15 mg tapered to 0 mg) during the initial 7 weeks. The treatment target was remission defined as Disease Activity Score (DAS) in 44 joints of <1.6 and no swollen joints, with an additional target of no power Doppler signal in any examined joint in the ultrasound arm. Each patient was scheduled for 13 visits during the 2-year follow-up.[12]

Participants
Patients (18–75 years) who fulfilled the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for RA[13] were recruited from 11 Norwegian rheumatology centres between 2010 and 2013. All patients provided written consent, and all had symptom duration of less than 24 months, no prior DMARD use and indication for DMARD treatment at inclusion.[12]

Participant involvement
Two participants recruited from the ARCTIC trial were involved in the planning and interpretation of the analyses presented in this article.

Fatigue
Fatigue was measured at all visits on a Visual Analogue Scale (VAS) ranging from 0 mm (fatigue is not a problem) to 100 mm (fatigue is a major problem).[14–16] The question was articulated, 'Have you had problems with fatigue during the last week'? Fatigue is recommended as a core outcome measure in clinical trials by the Outcome Measures in Rheumatology, ACR and the EULAR.[17 18]

As there are no standardised cut-offs for clinically relevant fatigue, we dichotomised fatigue in accordance with previous studies: <20 mm (no fatigue) and ≥20 mm (clinically relevant fatigue).[19–21] For the predictor analyses, the outcome was fatigue of ≥20 mm at 24 months. Additionally, we divided the fatigue VAS in <20, 20–39 and ≥40 mm corresponding to low or no fatigue, clinically relevant fatigue and high level of fatigue, respectively.[22–24] Fatigue was also assessed on a continuous scale. The percentage of participants who achieved a minimal clinically important improvement in fatigue VAS of ≥10 mm was assessed at 24 months.[25]

Clinical assessments
Disease activity was measured at all visits by DAS (range 0–10),[26] which incorporates assessment of tender joints (Ritchie Articular Index range 0–78), number of swollen joints (0–44), the patient global assessment (PGA) of disease activity on a VAS (VAS 0–100 mm) and erythrocyte sedimentation rate (ESR, mm/hour). DAS of <1.6 corresponds to remission; DAS of <2.4 corresponds to low disease activity; DAS of >2.4–3.7 corresponds to moderate disease activity; and DAS of >3.7 corresponds to high disease activity[27]. In addition, the Boolean-based ACR/EULAR remission,[28] Simplified Disease Activity Index remission[29] and Clinical Disease Activity Index remission[30] were assessed. Treatment response was evaluated by EULAR good/moderate response.[31]

The clinical evaluation also included C reactive protein (CRP, mg/L) and ultrasound examination of 32 joints at baseline and yearly in all patients (0–3 semiquantitative scoring of grey scale and power Doppler using an atlas for reference).[32 33]

Patient-reported outcomes and demographic measures
Sleep difficulty was assessed by a component of the Rheumatoid Arthritis Impact of Disease (RAID) on a Numerical Rating Scale (range 0–10, higher scores representing poorer outcome). Mental health was assessed by the 36-Item Short Form Survey Mental Component Summary Score consisting of the components mental health, vitality, role–emotional and social functioning (range 0–100, with lower scores indicating poorer outcome).[34] Physical function was assessed by Patient-Reported Outcome Information System (PROMIS) on a range of 20–100, translated to a T score with a mean of 50 and an SD of 10, where lower scores implied poorer outcome.[35] Patient-reported outcomes were acquired electronically at 0, 3, 6, 12, 16 and 24 months during study visits.[12] In addition, PGA was measured at all 13 visits. Baseline characteristics included age, gender, anti-CCP positivity, rheumatoid factor, body mass index (BMI) of ≥25 kg/m^2 and a comorbidity score measured by the Self-administered Comorbidity Questionnaire (score 0–45).[36] Education was dichotomised below/above 12 years.

Statistics
Data from the two study groups in ARCTIC were pooled for the current analyses as there were no statistically significant differences in primary or secondary endpoints between the two study groups.[12] Patients with complete fatigue data at baseline and 24 months were included. Missing fatigue data as well as other continuous variables between baseline and 24 months were imputed with last observation carried forward. Categorical variables missing at 24 months were imputed with worst outcome, and missing data before 24 months with last observation carried forward.[12] Continuous variables are described in means (SD), or medians (25th, 75th percentiles) as appropriate. Categorical variables are presented as frequencies (%).

We explored changes in median fatigue from baseline to 24 months and calculated the proportions of patients in the three fatigue categories at baseline and at 6 and 24 months. The correspondence between changes in fatigue VAS and changes in DAS according to categories was assessed.

Potential baseline predictors of fatigue of ≥20 mm at 24 months of follow-up were explored by univariable logistic regression, and a p value of less than 0.10 was required for the variable to be included in the subsequent multivariable analysis. Continuous variables were tested for linearity. A multivariable prediction model was built using backward stepwise selection

requiring a p value of <0.05 to keep the covariate in the model. All models were adjusted for age and gender. Variables excluded from the final model were re-entered one by one and kept in the model if they changed the coefficient of any other variable by more than 20%. Potential interactions between variables in the final model were analysed by including interaction terms one by one. Joint pain VAS, PROMIS physical function and RAID sleep were excluded from analyses due to high correlation with PGA (r=0.83, r=−0.67 and r=0.58, p<0.001, respectively) at baseline, but separate analyses of a model including these variables were also performed. DAS was not included as a composite measure, but the components were included separately. As CRP and ESR are closely related, we included CRP in the analyses in favour of ESR. ORs were calculated to explore the associations between early treatment response or remission and fatigue after 24 months of treatment. Robustness analyses were performed using only complete case data, and sensitivity analyses were performed for patients with fatigue of ≥20 mm at all time points from baseline to 24 months.

All analyses were performed using Stata/IC V.14.0 and 16.0.

RESULTS

Baseline characteristics

Of the 230 patients analysed for the primary outcome in the ARCTIC trial, 205 had complete fatigue data at baseline and 24 months and were included in the current analyses. There were no statistically significant differences in baseline variables between the subset of 205 and the full set of 230 patients. Less than 5/205 (2.4%) of the observations for any variables were imputed at any time point during the 24 months of follow-up. Baseline demographics and disease characteristics are presented in table 1. Fatigue was highly prevalent at baseline with 142/205 (69%) reporting fatigue of ≥20 mm, and median fatigue was 37.0 mm (25th, 75th percentiles 13.0, 62.0). Mean DAS of 3.4 (SD 1.1) corresponded to moderate disease activity level at baseline.

Changes in fatigue from baseline to 24 months

There was a rapid and sustained reduction in fatigue with the largest reduction observed within the first 3 months (figure 1 and online supplemental figure 1). Median fatigue was 37 mm (25th, 75th percentiles 13.0, 62.0) at baseline and 9 mm (25th, 75th percentiles 2.0, 34.0) at 24 months, and mean fatigue was 39 mm (SD 27.9) and 21 mm (SD 24.5) at baseline and 24 months, respectively.

At baseline, 142/205 (69%) reported a fatigue score of ≥20 mm, compared with 77/205 (38%) at 24 months (p<0.001) (figure 2). A total of 57% of the patients had a minimal clinically important improvement in fatigue (≥10 mm) at 24 months, and the proportion of patients reaching minimal clinically important improvement according to baseline fatigue of <20, 20–40 and >40 mm were 11%, 64% and 84%, respectively, displaying that a majority of patients with moderate and high fatigue achieved an improvement corresponding to minimal clinically important improvement.

Changes in fatigue and disease activity

There was a parallel reduction in fatigue and disease activity as 80% of the patients had moderate or high disease activity according to DAS (>2.4) at baseline and 9% at 24 months, while 69% of patients reported clinically relevant fatigue (≥20 mm) at baseline and 38% at 24 months (figure 2). At baseline, 95/205 (46%) had a fatigue score of 40 mm or higher, and this proportion

Table 1 Baseline demographics and disease characteristics

Variable	Patients n=205
Age (years)	52.2 (13.4)
Female gender	126 (61.5)
Education >12 years	123 (60)
Symptom duration (months)	5.4 (2.8, 10.4)
Anti-CCP positive	169 (82.4)
RF positive	142 (69.3)
Comorbidity score (SCQ)	4.0 (2.0, 7.0)
Depression	11 (5.4)
Fibromyalgia	1 (0.5)
BMI ≥25	111 (54.7)
DAS	3.4 (1.1)
Swollen joint count*	9.0 (4.0, 14.0)
Tender joint count, RAI†	6.0 (4.0, 12.0)
ESR	19.0 (11.0, 31.0)
C reactive protein	7.0 (3.0, 18.0)
Patient global assessment (VAS) score	48.8 (24.4)
Physician global assessment (VAS) score	39.2 (20.0)
Ultrasound power Doppler score (0–96)	7.0 (3.0, 14.0)
van der Heijde Modified Sharp Score (0–480)‡	4.5 (1.5, 9.0)
Fatigue VAS	37.0 (13.0, 62.0)
Joint pain VAS	42.6 (23.4)
PROMIS physical function score	39.5 (8.6)
SF-36 MCS score	49.4 (10.6)
Sleep (RAID)	3.8 (3.0)

Values are presented as mean (SD), n (%) or median (25th, 75th percentiles). SD: 95%.
DAS: 44 joints (0–10), <1.6 (remission), ≥1.6–2.4 (low disease activity), >2.4–3.7 (moderate disease activity), >3.7 (high disease activity). ESR (mm/hr): 1-140. PROMIS: 20–100. MCS score: 0–100, RAID: 0–10. SCQ: 0–45. VAS (mm) score: 0-100.
*Assessment of 44 joints (0–44).
†RAI score: 0–78.
‡Including erosion score and joint space narrowing score.
BMI, body mass index; CCP, cyclic citrullinated peptide; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; MCS, mental component summary; PROMIS, Patient-Reported Outcome Information System; RA, rheumatoid arthritis; RAI, Ritchie Articular Index; RAID, Rheumatoid Arthritis Impact of Disease; RF, rheumatoid factor; SCQ, Self-administered Comorbidity Questionnaire; SF-36, 36-Item Short Form Survey; VAS, Visual Analogue Scale.

was reduced to 39/205 (19%) at 24 months (figure 2). There was a corresponding increase in patients with low or no fatigue from baseline to 24 months; 63/205 (31%) of the patients scored <20 mm on the fatigue scale at baseline, compared with 128/205 (62%) at 24 months. In concurrence, 10/205 (5%) were in DAS remission at baseline vs 156/205 (76%) at 24 months (figure 2).

The proportion of patients with fatigue was highest among the patients with moderate to high disease activity both at baseline with 122/165 (74%) and 24 months with 14/18 (78%).

A fraction of the patients in DAS remission reported fatigue: 4/10 (40%) at baseline and 45/156 (29%) at 24 months, while some patients with moderate or high DAS (>2.4) did not report fatigue: 43/165 (26%) at baseline and 4/18 (22%) at 24 months (figure 2).

Baseline predictors of fatigue

Sleep disturbances, Mental Component Summary Score, physical function and PGA at baseline were predictors of fatigue at 24 months, in addition to low number of swollen joints and low ultrasound power Doppler score (table 2). In the multivariable
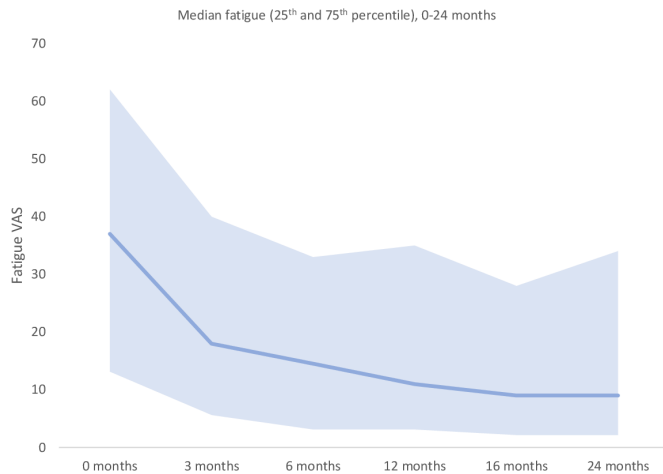
Figure 1 Change in median fatigue VAS (0–100 mm) over 24 months. Percentiles (25th and 75th) illustrated by the shaded area. VAS, Visual Analogue Scale.

analyses, number of swollen joints (OR=0.92, 95% CI 0.87 to 0.98, p value of 0.006), ultrasound power Doppler score (OR=0.95, 95% CI 0.90 to 0.99, p value of 0.027) and PGA (OR per mm=1.03, 95% CI 1.01 to 1.04, p<0.001) were significant predictors of reporting fatigue at 24 months, when controlling for the other factors in the model, as described in table 2.

Similar results were observed in robustness analyses in complete case data and sensitivity analyses for patients with sustained, clinically relevant fatigue from baseline to 24 months (data not shown).

Moreover, neither BMI, depression as a comorbidity (online supplemental table 1), methotrexate dosage (online supplemental table 2) nor the extent of adverse events (online supplemental table 3) were associated with fatigue in our data.

Associations between fatigue and early treatment response or remission at 6 months

There was no significantly decreased risk of reporting fatigue of ≥20 mm at 24 months for patients who achieved EULAR good/moderate response at 3 months (OR=0.62, 95% CI 0.28, 1.34,
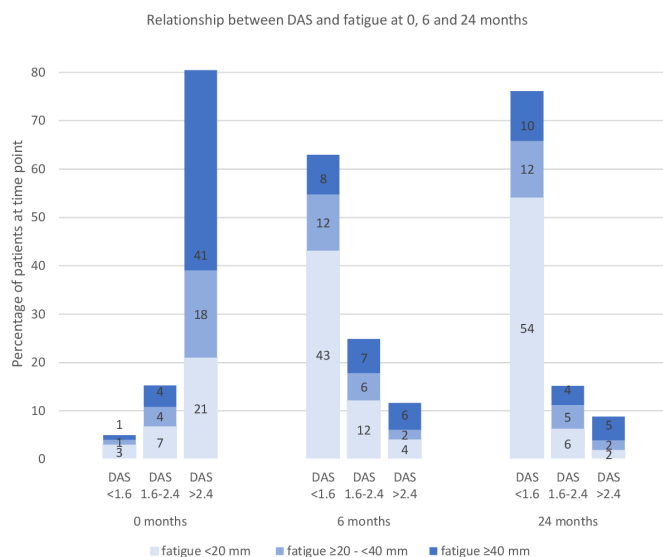

Figure 2 Percentage of patients in fatigue categories <20, ≥20–<40 and ≥40 mm according to DAS categories <1.6, 1.6–2.4 and >2.4 at 0, 6 and 24 months. DAS, Disease Activity Score.

p value of 0.277) (table 3). However, there was a significantly decreased risk of reporting fatigue of ≥20 mm at 24 months for patients who achieved remission at 6 months by all listed remission criteria (table 3).

DISCUSSION

In this inception cohort of patients with early RA, clinically relevant fatigue of ≥20 mm was highly prevalent at treatment onset. There was an overall rapid and sustained reduction in fatigue corresponding to the reduction in disease activity, and the majority of patients were in remission or low disease activity with no clinically relevant fatigue at 24 months. Prediction analyses demonstrated that few swollen joints, low power Doppler ultrasound score and high PGA at baseline increased the risk of reporting fatigue at 24 months. In addition, not reaching remission at 6 months increased the risk of reporting fatigue at 24 months.

Differences in fatigue measures, cut-offs and study designs create some challenges in the comparison of fatigue across studies. We saw a lower baseline level of fatigue in the present analyses than in comparable studies by Rat et al,[20] Scott et al[37] and Gossec et al,[38] where patients with early RA reported mean fatigue level of 47.8 (SD 28.2) and mean fatigue of >50 and >60 mm, respectively. Furthermore, the reduction in fatigue during the 24 months of follow-up was greater in the ARCTIC cohort than in a longitudinal register study by Druce et al,[21] where mean fatigue VAS was above 50 mm at baseline and at 1 and 4 years of follow-up, and smaller reductions in fatigue were observed in studies on patients with early RA as well as in patients with established RA.[19 23 24] Mean fatigue at 24 months in the ARCTIC cohort was similar to the level of fatigue (mean 20.5 mm (SD 0.02)) in Norwegian healthy controls reported by Slatkowsky-Christensen et al, supporting that the overall level of fatigue in the ARCTIC cohort at 24 months was at the same level as a normal population.[39] In agreement with previous research, our findings suggest that fatigue is prevalent in patients with early RA in about two of three patients, and that the prevalence is similar to what has been observed in established RA.[19 20 24 40]

We found that the improvement in fatigue over time corresponded to the reduction in disease activity, indicating a treatment response. There was a higher proportion of patients with high fatigue among patients with the highest disease activity at all assessed time points, which implies a positive relationship between the two factors. At the same time, our analyses showed that some patients in DAS remission reported fatigue and that some patients with high disease activity experienced low or no fatigue. Proinflammatory cytokines involved in the inflammatory responses in RA have been suggested to trigger fatigue,[6 41 42] and some trials have indicated an association between disease activity and fatigue.[24 43–45] However, other studies show that in some cases, fatigue persists even though inflammation and disease activity are low.[22 46 47]

The predictor analyses support that fatigue is a multidimensional phenomenon.[2] The multivariable analyses indicated that low inflammatory disease activity represented by few swollen joints and low ultrasound power Doppler score, and high scores of PGA at baseline were associated with a higher risk of fatigue at 24 months of follow-up. It could seem contradictory that we observed a positive association between fatigue and disease activity as well as between early remission and unresolved fatigue at 24 months, and at the same time found little inflammation at baseline to predict fatigue at 24 months. One explanation could be that there were two subsets of fatigue: patients where high

Table 2 Baseline predictors of clinically relevant fatigue (≥20 mm) at 24 months

	Fatigue ≥20 mm at 24 months, n=77/205			
	Univariable analysis		Multivariable analysis	
Variables	OR (95% CI)	P value	OR (95% CI)	P value
Female gender	1.52 (0.84 to 2.74)	0.167	1.30 (0.67 to 2.53)	0.441
Age	0.99 (0.98 to 1.02)	0.844	1.01 (0.99 to 1.03)	0.465
Education >12 years	0.63 (0.35 to 1.12)	0.112		
Anti-CCP positivity	1.46 (0.67 to 3.16)	0.341		
BMI ≥25	0.91 (0.52 to 1.61)	0.794		
Swollen joint count*	0.92 (0.88 to 0.97)	**0.001‡**	0.92 (0.87 to 0.98)	**0.006**
Tender joint count (RAI)	1.01 (0.96 to 1.05)	0.737		
Patient global assessment (VAS) score	1.01 (1.00 to 1.03)	**0.016‡**	1.03 (1.01 to 1.04)	**<0.001**
C reactive protein	0.99 (0.97 to 1.00)	0.146		
Ultrasound power Doppler score†	0.93 (0.88 to 0.99)	**0.022‡**	0.95 (0.90 to 0.99)	**0.027**
PROMIS physical function	0.96 (0.93 to 0.99)	**0.021‡**		
SF-36 MCS	0.96 (0.94 to 0.99)	**0.007‡**		
RAID sleep	1.16 (1.05 to 1.27)	**0.003‡**		

P values <0.05 in bold. MCS score: 0–100. PROMIS score: 20–80. RAI score: 0–78. RAID: NRS score: 0–10. VAS (mm): 0–100.

*Assessment of 44 joints (0–44)

†Range 0–96

‡Variables with univariable p values <0.10

BMI, body mass index; CCP, cyclic citrullinated peptide; 95% CI, 95% confidence interval; MCS, Mental Component Summary; NRS, Numerical Rating Scale; OR, odds ratio; PROMIS, Patient-Reported Outcome Information System; RAI, Ritchie Articular Index; RAID, Rheumatoid Arthritis Impact of Disease; SF-36, 36-Item Short Form Survey; VAS, Visual Analogue Scale.

inflammatory disease activity was the cause of fatigue and for whom early, intensive treatment improved fatigue, and patients with fatigue at baseline for whom fatigue could have been triggered by different factors that were not affected by DMARD treatment.[23 48] These factors might be captured by PGA, and further research is warranted on the relationship between fatigue and PGA. In the 38% of the patients who reported clinically relevant fatigue at 24 months, the source of fatigue might not have been adequately addressed. Associations between comorbidities such as depression and fibromyalgia and fatigue have been documented in prior studies[8 49] but were not confirmed in our data. Non-pharmacological interventions to relieve fatigue are tailored physical activity, behavioural modification, treatment of pain or depression, and improving sleep.[8]

Our results indicate that achievement of treatment target at 6 months reduced the risk of fatigue at 24 months, and similar results were observed by Scott *et al*, who found that fatigue was significantly lower in patients with RA in an intensive treat-to-target strategy compared with patients who received standard treatment.[24 37]

This study has limitations. There is a lack of standardised fatigue measures and definitions in RA, and we used global, unidimensional fatigue VAS in the present analyses. Fatigue VAS does not yield detailed information; however, fatigue VAS is validated as more sensitive to change than some multidimensional measures and has high reliability, construct, content and face validity.[14–16 50] Furthermore, it is one of the most frequently applied measures of fatigue in RA.[16] The lack of standardised cut-offs for fatigue VAS generates uncertainties regarding the prevalence and severity of fatigue, including the extent of residual fatigue, and complicates comparison of results across studies.

A strength of this study is the longitudinal, prospective and multivariable analyses which have been recommended.[7] In addition, data from the ARCTIC trial provided a unique opportunity to explore fatigue in patients with early RA followed by modern treat-to-target strategies, and to our knowledge, this is the first

Table 3 ORs of fatigue ≥20 mm at 24 months according to EULAR response at 3 months, DAS remission, ACR/EULAR Boolean remission, SDAI remission and CDAI remission at 6 months

		Fatigue ≥20 mm at 24 months	
	Classification n/N (%)	OR (95% CI)	P value
Response at 3 months			
EULAR good/moderate response	170/199 (85)	0.62 (0.28 to 1.34)	0.227
Remission at 6 months			
DAS 44 remission	124/197 (63)	0.31 (0.17 to 0.57)	**<0.001**
ACR/EULAR Boolean remission	78/197 (40)	0.30 (0.16 to 0.58)	**0.002**
SDAI remission	90/197 (46)	0.23 (0.12 to 0.43)	**<0.001**
CDAI remission	92/197 (47)	0.19 (0.10 to 0.36)	**<0.001**

EULAR good/moderate response defined as DAS ≤2.4 and a decrease by >1.2, DAS ≤2.4 and a decrease by >0.6 and ≤1.2, or a DAS >2.4 and ≤3.7 and decreases by >1.2 and >0.6 and ≤1.2, or a DAS >3 and a decrease by >1.2. DAS (44 joints, ESR) remission defined as DAS <1.6. ACR/EULAR Boolean remission criteria defined as swollen joints ≤1, tender joints ≤1, CRP ≤10 and PGA ≤10. SDAI: defined as SDAI ≤3.3. CDAI: remission defined as CDAI ≤2.8. P values <0.05 in bold.

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; SDAI, Simplified Disease Activity Index.

study that have explored associations in patients with early RA between fatigue and ultrasound, biochemical and clinical assessments, in addition to a comprehensive assessment of patient-reported outcome measures.

In conclusion, this study showed that the majority of patients with early RA treated according to current EULAR treatment recommendations experienced a rapid and sustained reduction of fatigue. However, patients who did not reach remission at 6 months were at risk of experiencing fatigue at the 2-year follow-up, which could be of importance to clinicians in identifying patients at risk of long-term fatigue. In addition, there was a higher risk of fatigue in patients with RA with low objective disease activity measures and high patient reported global assessment of disease at baseline, and a non-pharmacological approach to fatigue in these patients might be considered.

Competing interests All authors have completed the International Committee of Medical Journal Editors uniform disclosure form at www.icmje.org/disclosure-of-interest/ (available on request from the corresponding author). KH, JS, NPS, SL and LBN declare no conflict of interest. EM received personal fees as leader for the national rheumatology nurses in the Norwegian Nurses Organisation. HBH received personal honoraria from Abbvie, Lilly, Pfizer and Novartis, and participated in a data safety monitoring board or advisory board for Novartis and Lilly. TU received consultancy honorarium from Lilly and Pfizer. TKK received consultancy honorariums from AbbVie, Amgen, Biogen, Celltrion, Eli Lilly, Gilead, Mylan, Novartis, Pfizer, Sandoz, Sanofi, Egis, Evapharma, Ewopharma, Hikma and Oktal. EAH received consulting fees from Abbvie, Novartis, Pfizer, Gilead, Eli Lilly, Galapagos and Janssen. A-BA received consultancy honorariums from AbbVie, Eli Lilly, Novartis, Pfizer and UCB.

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REFERENCES

1 Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *The Lancet* 2016;388:2023–38.
2 Hewlett S, Chalder T, Choy E, *et al*. Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology* 2011;50:1004–6.
3 Gossec L, Dougados M, Rincheval N, *et al*. Elaboration of the preliminary rheumatoid arthritis impact of disease (raid) score: a EULAR initiative. *Ann Rheum Dis* 2009;68:1680–5.
4 Hewlett S, Carr M, Ryan S, *et al*. Outcomes generated by patients with rheumatoid arthritis: how important are they? *Musculoskeletal Care* 2005;3:131–42.
5 Seifert O, Baerwald C. Impact of fatigue on rheumatic diseases. *Best Pract Res Clin Rheumatol* 2019;33:101435.
6 Druce KL, Basu N. Predictors of fatigue in rheumatoid arthritis. *Rheumatology* 2019;58:v29–34.
7 Nikolaus S, Bode C, Taal E, *et al*. Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review. *Arthritis Care Res* 2013;65:1128–46.
8 Pope JE. Management of fatigue in rheumatoid arthritis. *RMD Open* 2020;6:e001084.
9 Uhlig T, Provan SA. Treating fatigue in rheumatoid arthritis: does patient age matter? *Drugs Aging* 2018;35:871–6.
10 Smolen JS, Breedveld FC, Burmester GR, *et al*. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international Task force. *Ann Rheum Dis* 2016;75:3–15.
11 Smolen JS, Landewé RBM, Bijlsma JWJ, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.
12 Haavardsholm EA, Aga A-B, Olsen IC, *et al*. Ultrasound in management of rheumatoid arthritis: Arctic randomised controlled strategy trial. *BMJ* 2016;354:i4205.
13 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League against rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8.
14 Wolfe F. Fatigue assessments in rheumatoid arthritis: comparative performance of visual analog scales and longer fatigue questionnaires in 7760 patients. *J Rheumatol* 2004;31:1896.
15 Hewlett S, Hehir M, Kirwan JR. Measuring fatigue in rheumatoid arthritis: a systematic review of scales in use. *Arthritis Rheum* 2007;57:429–39.
16 Hewlett S, Dures E, Almeida C. Measures of fatigue: Bristol rheumatoid arthritis fatigue multi-dimensional questionnaire (BRAF MDQ), Bristol rheumatoid arthritis fatigue numerical rating scales (BRAF NRS) for severity, effect, and coping, Chalder fatigue questionnaire (CFQ), checklist individual strength (CIS20R and CIS8R), fatigue severity scale (FSS), functional assessment chronic illness therapy (fatigue) (FACIT-F), multi-dimensional assessment of fatigue (Maf), multi-dimensional fatigue inventory (MFI), pediatric quality of life (PedsQL) multi-dimensional fatigue scale, profile of fatigue (Prof), short form 36 vitality Subscale (SF-36 VT), and visual analog scales (vas). *Arthritis Care Res* 2011;63 Suppl 11:S263–86.
17 Kirwan JR, Minnock P, Adebajo A, *et al*. Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. *J Rheumatol* 2007;34:1174–7.
18 Aletaha D, Landewe R, Karonitsch T, *et al*. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. *Ann Rheum Dis* 2008;67:1360–4.
19 Rodríguez-Muguruza S, Combe B, Guillemin F, *et al*. Predictors of fatigue and persistent fatigue in early rheumatoid arthritis: a longitudinal observational study, data from the ESPOIR cohort. *Scand J Rheumatol* 2020;49:259–66.
20 Rat A-C, Pouchot J, Fautrel B. Factors associated with fatigue in early arthritis: results from the ESPOIR cohort. *Arthritis Care Res* 2012;64:1061–9.
21 Druce KL, Jones GT, Macfarlane GJ, *et al*. The longitudinal course of fatigue in rheumatoid arthritis: results from the Norfolk arthritis register. *J Rheumatol* 2015;42:2059–65.
22 Olsen CL, Lie E, Kvien TK, *et al*. Predictors of fatigue in rheumatoid arthritis patients in remission or in a low disease activity state. *Arthritis Care Res* 2016;68:1043–8.
23 Hammer HB, Michelsen B, Sexton J, *et al*. Fatigue is cross-sectionally not associated with objective assessments of inflammation, but changes in fatigue are associated with changes of disease activity assessments during biologic treatment of patients with established rheumatoid arthritis. *Clin Rheumatol* 2021;40:1739–49.
24 Holdren M, Schieir O, Bartlett SJ, *et al*. Improvements in fatigue lag behind disease remission in early rheumatoid arthritis: results from the Canadian early arthritis cohort. *Arthritis Rheumatol* 2021;73:53-60.

25 Strand V, Boers M, Idzerda L, *et al*. It's good to feel better but it's better to feel good and even better to feel good as soon as possible for as long as possible. response criteria and the importance of change at OMERACT 10. *J Rheumatol* 2011;38:1720–7.

26 van der Heijde DM, van 't Hof MA, van Riel PL, *et al*. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990;49:916–20.

27 Salaffi F, Ciapetti A. Clinical disease activity assessments in rheumatoid arthritis. *Int J Clin Rheumtol* 2013;8:347–60.

28 Felson DT, Smolen JS, Wells G, *et al*. American College of Rheumatology/European League against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011;70:404–13.

29 Aletaha D, Ward MM, Machold KP, *et al*. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum* 2005;52:2625–36.

30 Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. *Rheum Dis Clin North Am* 2006;32:9–44.

31 van Gestel AM, Haagsma CJ, van Riel PL, AMv G, PLCMv R. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum* 1998;41:1845–50.

32 Haavardsholm EA, Østergaard M, Hammer HB, *et al*. Monitoring anti-TNFalpha treatment in rheumatoid arthritis: responsiveness of magnetic resonance imaging and ultrasonography of the dominant wrist joint compared with conventional measures of disease activity and structural damage. *Ann Rheum Dis* 2009;68:1572–9.

33 Hammer HB, Bolton-King P, Bakkeheim V, *et al*. Examination of intra and interrater reliability with a new ultrasonographic reference atlas for scoring of synovitis in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70:1995–8.

34 Ware J, Ma K, Keller SD. SF-36 physical and mental health summary scales: a user's manual 1994;8:23–8.

35 Cella D, Riley W, Stone A, *et al*. The patient-reported outcomes measurement information system (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. *J Clin Epidemiol* 2010;63:1179–94 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2965562/pdf/nihms203741.pdf doi:10.1016/j.jclinepi.2010.04.011

36 Sangha O, Stucki G, Liang MH, *et al*. The self-administered comorbidity questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum* 2003;49:156–63.

37 Scott D, Ibrahim F, Hill H, *et al*. The clinical effectiveness of intensive management in moderate established rheumatoid arthritis: the titrate trial. *Semin Arthritis Rheum* 2020;50:1182–90.

38 Gossec L, Ahdjoudj S, Alemao E, *et al*. Improvements in fatigue in 1536 patients with rheumatoid arthritis and correlation with other treatment outcomes: a post hoc analysis of three randomized controlled trials of abatacept. *Rheumatol Ther* 2017;4:99–109.

39 Slatkowsky-Christensen B, Mowinckel P, Loge JH, *et al*. Health-Related quality of life in women with symptomatic hand osteoarthritis: a comparison with rheumatoid arthritis patients, healthy controls, and normative data. *Arthritis Rheum* 2007;57:1404–9.

40 Overman CL, Kool MB, Da Silva JAP, *et al*. The prevalence of severe fatigue in rheumatic diseases: an international study. *Clin Rheumatol* 2016;35:409–15.

41 Norheim KB, Jonsson G, Omdal R. Biological mechanisms of chronic fatigue. *Rheumatology* 2011;50:1009–18.

42 Landmark-Høyvik H, Reinertsen KV, Loge JH, *et al*. The genetics and epigenetics of fatigue. *Pm R* 2010;2:456–65.

43 Madsen SG, Danneskiold-Samsøe B, Stockmarr A, *et al*. Correlations between fatigue and disease duration, disease activity, and pain in patients with rheumatoid arthritis: a systematic review. *Scand J Rheumatol* 2016;45:255–61.

44 Thyberg I, Dahlström O, Thyberg M. Factors related to fatigue in women and men with early rheumatoid arthritis: the Swedish TIRA study. *J Rehabil Med* 2009;41:904–12.

45 Uhlig T, Lie E, Norvang V, *et al*. Achievement of remission and low disease activity definitions in patients with rheumatoid arthritis in clinical practice: results from the NOR-DMARD study. *J Rheumatol* 2016;43:716–23.

46 Druce KL, Jones GT, Macfarlane GJ, *et al*. Patients receiving anti-TNF therapies experience clinically important improvements in RA-related fatigue: results from the British Society for rheumatology biologics register for rheumatoid arthritis. *Rheumatology* 2015;54:964–71.

47 Curtis JR, Shan Y, Harrold L, *et al*. Patient perspectives on achieving treat-to-target goals: a critical examination of patient-reported outcomes. *Arthritis Care Res* 2013;65:1707–12.

48 Provan SA, Michelsen B, Sexton J, *et al*. Trajectories of fatigue in actively treated patients with established rheumatoid arthritis starting biologic DMARD therapy. *RMD Open* 2020;6:e001372.

49 Walter MJM, Kuijper TM, Hazes JMW, *et al*. Fatigue in early, intensively treated and tight-controlled rheumatoid arthritis patients is frequent and persistent: a prospective study. *Rheumatol Int* 2018;38:1643–50.

50 Santos EJF, Duarte C, da Silva JAP, *et al*. The impact of fatigue in rheumatoid arthritis and the challenges of its assessment. *Rheumatology* 2019;58:v3–9.