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Relation Between Fatigue and ACR Response in Patients With Psoriatic Arthritis Treated With Tumor Necrosis Factor Inhibitor Therapy: A Population-based Cohort Study

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ABSTRACT. ***Objective.*** The objective of this population-based cohort study was to investigate the association between fatigue with disease activity and drug survival in patients with psoriatic arthritis (PsA) receiving their first tumor necrosis factor inhibitor (TNFi).

Methods. Data on patient characteristics, disease activity, and drug survival were obtained from the DANBIO database on all patients with PsA from 2006 through 2015. Information on comorbidities was obtained through linkage with the Danish National Patient Registry.

Results. A total of 880 patients were eligible for analyses. Patients with upper median fatigue scores had statistically significant higher disease activity measures (Disease Activity Score in 28 joints based on C-reactive protein), pain, and Health Assessment Questionnaire (HAQ) scores; tender joint counts; comorbidities (Charlson Comorbidity Index ≥ 2); and current smoking status at baseline compared to patients with lower median fatigue scores ($P < 0.05$). In the upper median fatigue group, fewer patients achieved American College of Rheumatology (ACR) responses and improvements in visual analog scale (VAS) fatigue compared to patients in the lower median fatigue group. Kaplan-Meier curves showed shorter drug survival in patients in the upper median fatigue group compared with the lower median fatigue group at 6-month follow-up.

Conclusion. Fatigue remains a dominating symptom after TNFi treatment, and is associated with higher baseline disease activity, pain, and HAQ scores; more comorbidities; and increased risk of TNFi treatment discontinuation in a cohort of Danish patients with PsA. The agreement between ACR and VAS fatigue responses is weak to moderate, suggesting heterogeneity between experienced fatigue and joint inflammation.

Key Indexing Terms: fatigue, psoriatic arthritis, TNFi treatment

Fatigue is defined as a persistent feeling of tiredness, lack of energy, and feeling worn out or exhausted.[1,2,3] It is often described as a phenomenon that interferes with physical and social functions and may lead to social withdrawal and longstanding sick leave.[4,5] Fatigue is seen in patients with various chronic diseases, including psoriatic arthritis (PsA).[6,7,8,9]

PsA is an inflammatory disease characterized by inflammation of the joints, surrounding ligaments and tendons, and skin.[10,11] Besides fatigue, PsA is also associated with pain[4] and a number of comorbidities, including obesity, metabolic syndrome, nonalcoholic fatty liver disease, diabetes, and cardiovascular disease,[12,13] with over 50% of patients with PsA having

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more than 1 comorbidity.[14,15] PsA affects approximately 0.3–1% of the general population worldwide[13,16] and 20–30% of patients with skin psoriasis.[14,17,18] Patients with PsA continue to cite fatigue as one of the most challenging aspects of their disease, as it decreases their health-related quality of life (QOL).[19]

Fatigue in psoriasis has been associated with the effect of the inflammatory cascade on the central nervous system. This may suggest a pathway that relays the immune signals that underlie psoriatic disease to the brain, resulting in negative symptoms such as fatigue.[19] This might explain why an often-used treatment such as tumor necrosis factor inhibitors (TNFi) targeting the inflammatory pathway should result in less fatigue.[3,10] Although TNFi treatment has been shown to be effective in treating PsA and improving function, QOL, and fatigue,[6,10] it still fails among half of PsA patients treated in routine care, resulting in patients discontinuing the medication because of lack of improvement.[20,21] TNFi efficacy trials in ankylosing spondylitis have shown distinct results with limited to marked improvement in fatigue.[22,23,24]

Existing knowledge indicates the need for further investigation into associations between fatigue, TNFi drug survival, treatment responses, and other patient-related factors including comorbidities.

The objective of this population-based cohort study was to investigate the association of fatigue with baseline characteristics, drug survival, and the relation between American College of Rheumatology (ACR) criteria and fatigue response in patients with PsA receiving their first TNFi.

METHODS

Study design. Before initiating the study, a systematic search for literature was conducted. The study was conducted in accordance with the STROBE statement (Supplementary Data 1, available with the online version of this article) and based on a predefined protocol available on The Parker Institute website (www.parkerinst.dk). It was designed as a longitudinal registry study including data on patients registered in the Danish nationwide registry DANBIO.[25] The objective and study design were discussed with a PsA patient research partner (PRP) after informed consent. The results and conclusions of the study were relayed to the PRP after the study was concluded.

Setting and data source. Data on patient characteristics, disease activity, and drug survival were obtained from the DANBIO registry. Information on comorbidities according to the Charlson Comorbidity Index and psychiatric comorbidities was obtained through linkage with the Danish National Patient Registry. Results based on DANBIO data, which cover 98% of rheumatology patients treated with biologic disease-modifying antirheumatic drugs (bDMARDs), can be considered representative of patients with PsA who are treated in routine care (www.danbio-online.dk). According to Danish law, informed consent and ethics approval were not required for the present study.

Participants. All patients with PsA registered in DANBIO from 2006 to 2015 receiving their first TNFi were identified and considered eligible for participation in the study. Patients were excluded if they had erroneous baseline information, were not followed from the initiation of treatment, had no consecutive follow-up visit registration, were participating in clinical trials, had been treated with bDMARDs other than TNFi, and did not record fatigue data.

Variables and outcome measures. Fatigue was assessed by a visual analog scale (VAS), a measure of fatigue, pain, and global health (VAS fatigue, VAS pain, VAS global health, respectively), 0–100 mm, with 0 representing "no fatigue" and 100 representing "worst imaginable fatigue."[26] VAS fatigue 20/50/70 were calculated as at least 20%, 50%, or 70% relative improvement from baseline, respectively, in VAS fatigue. Variables extracted from DANBIO included sex, age, date of visits, disease duration, smoking habits, BMI (weight and height), ACR20/50/70, treatment duration, type of TNFi therapy, swollen joint count, tender joint count (TJC), C-reactive protein (CRP), health assessment questionnaire (HAQ), disease activity score (Disease Activity Score in 28 joints based on CRP), VAS (0–100 mm; physician global, patient global, fatigue, and pain), treatment information on conventional synthetic DMARDs (csDMARDs) and/or bDMARDs. Information on comorbidities was extracted from the Danish National Patient Registry.

Statistical analysis. Data analysis was performed in SPSS (v25; IBM Corp.). Patients were grouped and compared based on severity of fatigue defined by median fatigue. Patient characteristics were presented by means with SD. Statistical significance was determined with Mann-Whitney *U* test/2-tailed test. Two-sided *P* values < 0.05 were considered statistically significant. Mann-Whitney *U* test was calculated to determine the significance of correlation between patients with depression/anxiety and their level of VAS fatigue. Kaplan-Meier plots, and univariate and multivariate Cox proportional hazard regression analyses were calculated, adjusting for age, sex, and percentages of patients achieving relevant clinical responses. Moreover, for the assessment of associations between fatigue and inflammatory activity, patients were stratified based on number of swollen joint/tender joint ratio (STR), which was either < 0.5 or ≥ 0.5.[27] The cutoff at 0.5 was chosen based on indirect evidence from RA, where this was the most discriminative cutpoint. k statistics were used to assess agreement between fatigue and ACR20/50/70, respectively, by the use of the Lund Efficacy Index (LUNDEX = [Fraction of starters still in the study at time T] × [Fraction responding at time T])[28] method to ensure the integration of clinical response and persistence with therapy in a composite value. The LUNDEX adjustment is an intent-to-treat method developed for the observational setting to account for both withdrawals from therapy and missing response recordings at certain points of follow-up.[28]

RESULTS

During the study period, a total of 1980 patients were registered in DANBIO as having PsA, of which 1750 were treated with TNFi and thus were eligible for inclusion. Of these, 880 patients were included in the analysis, as they had reported useful data on fatigue (Figure 1).

The overall mean VAS fatigue for this patient group was 62.98 (SD 24.5). Patients were grouped based on median VAS fatigue of 67 mm. The 2 groups were defined as lower median fatigue (< 67) and upper median fatigue (≥ 67). Comparisons of the 2 groups showed that patients with upper median fatigue had statistically significant higher disease activity measure, VAS patient pain scores, HAQ scores, higher TJC, and current smoking status at baseline compared to those with lower median fatigue scores. Moreover, the group with upper median fatigue included significantly higher percentage of females, patients with CCI2, and patients with depression and/or anxiety, although the last did not reach statistical significance (Table 1). Patients with depression and/or anxiety had significantly higher VAS fatigue at baseline than patients without ($P = 0.03$).

Drug survival. In assessing the relationship between VAS fatigue and TNFi drug survival, our study showed that patients with higher baseline fatigue scores have shorter drug survival

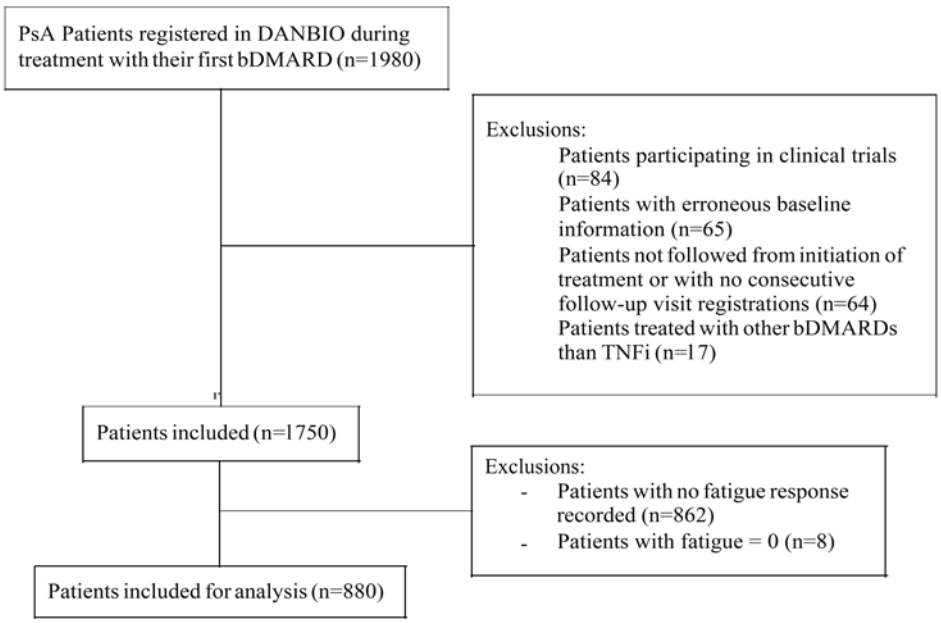


Figure 1. Flow diagram. bDMARD: biologic disease-modifying antirheumatic drug; PsA: psoriatic arthritis; TNFi: tumor necrosis factor inhibitors.

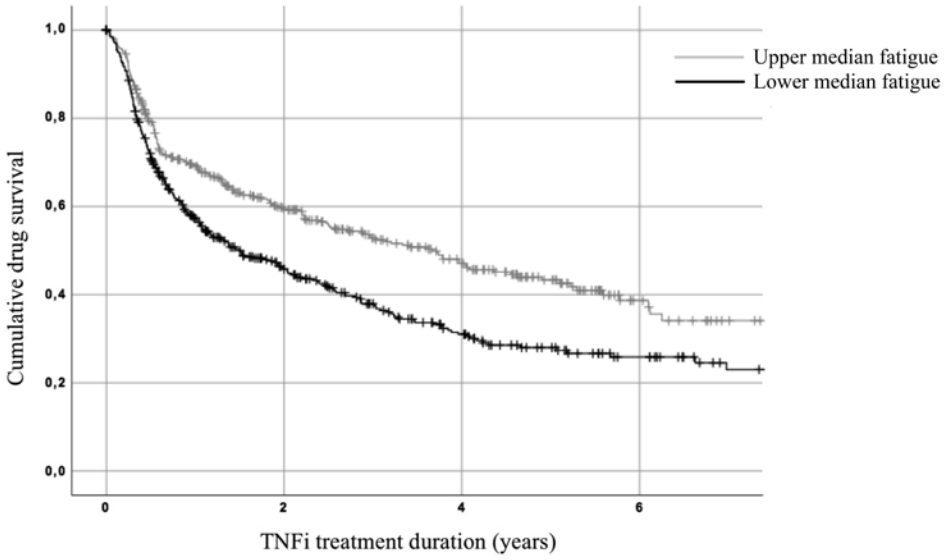
Table 1. Baseline characteristics of patients with PsA according to median fatigue stratification.

	Lower VAS Fatigue Median, n = 430	Upper VAS Fatigue Median, n = 450	*P*
Sex, female, n (%)	212 (49.3)	270 (60.0)	0.001
Age, yrs	48.0 ± 12.0	47.8 ± 12.2	0.10
BMI	27.6 ± 5.5	28.3 ± 6.0	0.10
Current smoking, n (%)	92 (43.8)	118 (56.2)	0.03
DAS28-CRP	3.9 ± 1.1	4.7 ± 1.1	< 0.001
CRP	12.8 ± 16.9	14.4 ± 22.2	0.02
Swollen joint count	2.8 ± 3.3	2.7 ± 3.2	0.001
Tender joint count	6.0 ± 5.0	9.0 ± 8.0	0.001
VAS patient pain global	52.3 ± 22.5	79.8 ± 16.2	< 0.001
VAS patient pain	45.8 ± 21.5	71.7 ± 17.8	< 0.001
HAQ score	0.83 ± 0.6	1.37 ± 0.6	< 0.001
Comorbidities, n (%)			
CCI = 0	284 (66.0)	278 (61.8)	0.19
CCI = 1	116 (27.0)	119 (26.4)	0.86
CCI ³ 2	30 (7.0)	53 (11.8)	0.02
PsO within 10 yrs, n (%)	170 (47.2)	190 (52.8)	0.42
Depression/anxiety within 10 years, n (%)	23 (39.7)	35 (60.3)	0.15

Data are shown as mean ± SD unless otherwise indicated. CCI: Charlson Comorbidity Index; CRP: C-reactive protein; DAS28-CRP: Disease Activity Score in 28 joints based on CRP; HAQ: Health Assessment Questionnaire; PsO: psoriasis; VAS: visual analog scale.

compared to patients with lower fatigue scores, as demonstrated by a Kaplan-Meier plot (Figure 2). The HR was 1.39 (95% CI 1.16–1.66) with a *P* value of < 0.001 (adjusted for age and sex), indicating significantly shorter drug survival in the upper fatigue group. At the 6-month follow-up, 291 (68%) patients in the lower median fatigue group and 282 (63%) patients in the upper median fatigue group remained in treatment. After 1 year, 50% of patients in the upper median fatigue group discontinued treatment, whereas the percentage in the lower median fatigue group was 40%. Throughout the years, assessed patients in the lower median fatigue group had on average longer drug survival.

Treatment response. Looking at the overall effects of treatment with TNFi at 6 months, our results showed that patients reaching 20%, 50%, and 70% improvement in ACR and VAS fatigue, respectively, are greater at 20% and much lower at 70% improvement. ACR20/50/70 responses at 6 months were 49%,



	0 years	1 year	2 years	3 years	4 years	5 years	6 years	7 years
Upper median fatigue	n=450	n=226	n=145	n=100	n=68	n=45	n=28	n=15
Lower median fatigue	n=430	n=258	n=187	n=132	n=99	n=62	n=26	n=13

Figure 2. TNFi drug survival. Kaplan-Meier plot is shown as the fraction of patients remaining on therapy during the observation period. The number of patients under observation at each timepoint is listed in the table under the graph. TNFi: tumor necrosis factor inhibitors.

35%, and 18%, respectively. VAS fatigue 20/50/70 responses were 57%, 39%, and 20%, respectively. The k value between ACR20/50/70 and VAS fatigue responses were 0.37, 0.40, and 0.48 ($P < 0.001$), respectively (Table 2).

Looking at the groups of lower and upper median VAS fatigue, the ACR20/50/70 responses at 6 months for lower median VAS fatigue group were 42.5%, 33.6%, and 19.4%, and for the upper median VAS fatigue group, the responses were 44.1%, 27.9%, and 13.2%, respectively. It is clear that more patients in the lower median VAS fatigue group reach 50% and 70% ACR improvement compared to patients in the upper median VAS fatigue group.

Treatment response: grouping based on fatigue and STR. Looking at the overall effect of TNFi treatment on ACR and VAS fatigue responses at the 6-month follow-up (Figure 3), patients showing the most improvement were those exhibiting more swollen joints. When subgrouping patients based on STR, our results showed that a higher number of patients with relatively more swollen joints (STR 0.5) reached improvements of 20%, 50%, and 70% for both VAS fatigue and ACR responses compared to patients with relatively more tender joints (STR < 0.5) when treated with TNFi (Figure 3). Fifteen percent of patients in the upper median fatigue group with STR 0.5 showed 70% improvement in fatigue when treated with TNFi, compared to the group with STR < 0.5, where only 8% showed improvement in VAS fatigue70. The same was seen for patients with lower median fatigue, where 27% of patients with STR 0.5 showed improvement in VAS fatigue70, compared to 16% in the group with STR < 0.5 (Figure 3).

Although fewer patients in the upper median fatigue group achieved VAS fatigue and ACR improvements, patients with STR < 0.5 had a more beneficial treatment effect, indicated by more patients achieving VAS fatigue improvement. In fact, almost the same number of patients in the lower median fatigue

Table 2. k values assessing the agreement between fatigue and ACR20/50/70 as observed at 6 months.

		Lower VAS Fatigue Median				Upper VAS Fatigue Median		
STR < 0.5	n = 53	20	50	70	n = 86	20	50	70
	ACR, %	21.09	14.06	8.79	ACR, %	24.30	10.80	6.30
	VAS Fatigue, %	43.85	29.23	12.56	VAS fatigue, %	32.14	21.91	7.67
	k (*P*)	0.49 (< 0.001)	0.41 (0.004)	0.72 (< 0.001)	k (*P*)	0.29 (0.008)	0.40 (< 0.001)	0.24 (0.03)
STR ≥ 0.5	n = 81	20	50	70	n = 50	20	50	70
	ACR, %	51.59	42.42	24.07	ACR, %	52.14	41.08	17.38
	VAS fatigue, %	49.05	38.02	22.47	VAS fatigue, %	45.11	26.76	14.22
	k (*P*)	0.39 (0.001)	0.45 (< 0.001)	0.51 (< 0.001)	k (*P*)	0.49 (0.001)	0.45 (0.003)	0.47 (0.003)

ACR: American College of Rheumatology; STR: swollen/tender ratio; VAS: visual analog scale.

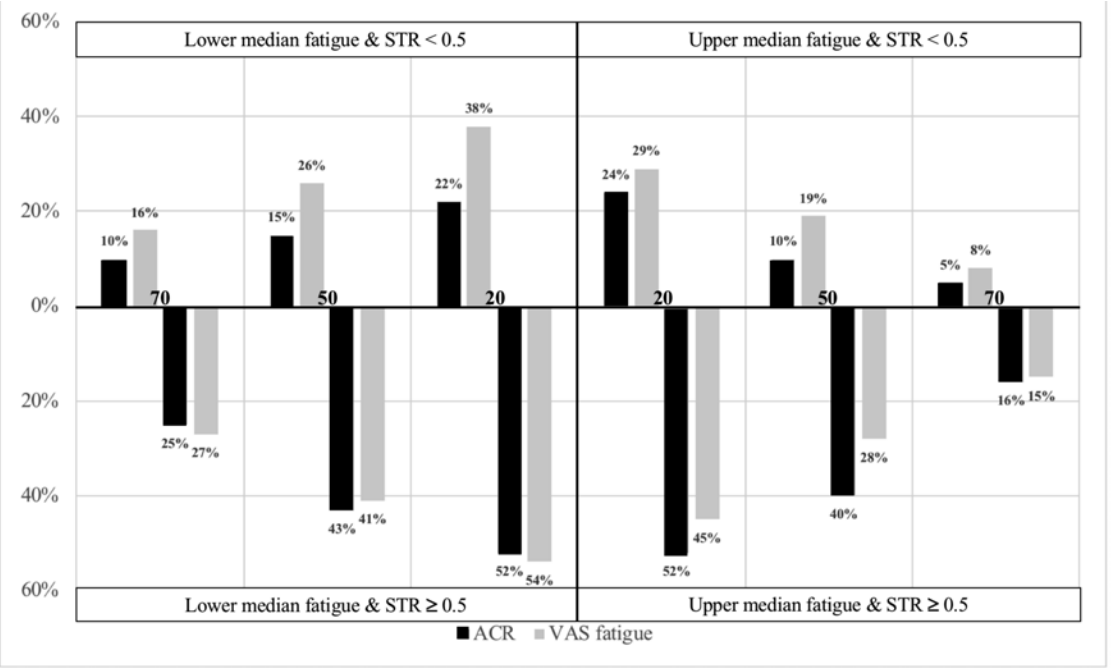


Figure 3. Effect of TNFi on ACR and VAS fatigue in patients with PsA, by STR and median VAS fatigue at 6 months. 2 × 2 table subgrouping patients based on upper and lower median fatigue, and STR < 0.5 and STR ≥ 0.5. Each subgroup contains number of patients with completed data; results are LUNDEX-corrected. Lower median fatigue and STR < 0.5 = 53, lower median fatigue and STR ≥ 0.5 = 81, upper median fatigue and STR < 0.5 = 86, and upper median fatigue and STR ≥ 0.5 = 50. The figure shows the effect of TNFi treatment on ACR and VAS fatigue, respectively, as percentages of patients reaching ACR20/50/70 and/or VAS fatigue 20/50/70 criteria when comparing baseline ACR and VAS fatigue with 6-month follow-up. ACR: American College of Rheumatology; PsA: psoriatic arthritis; STR: swollen/tender joint ratio; TNFi: tumor necrosis factor inhibitors; VAS: visual analog scale.

group with STR < 0.5 reached VAS fatigue 20/50/70 compared with patients in the upper median fatigue group with STR ≥ 0.5.

Overall, as shown in Table 2, fatigue responses at 6 months had low to moderate agreement with ACR responses, indicating that both fatigue and ACR20/50/70 response represent different domains of the PsA disease. As expected, agreement was generally higher for the stricter criteria (ACR70 and VAS fatigue70). More interestingly, k values were lowest in the most refractory patient group with high baseline fatigue and more tender vs swollen joints.

DISCUSSION

In the present study, based on data from the DANBIO registry, our results indicate a continuing challenge to treat fatigue as a symptom of disease. Although TNFi showed an effect on fatigue, a considerable percentage of patients still experienced fatigue as one of the dominating symptoms after TNFi treatment. Higher levels of fatigue at baseline were associated with increased risk for TNFi treatment discontinuation. Moreover, fatigue responses at 6 months had low to moderate agreement with ACR20/50/70 responses. Thus, the current study demonstrates the further need for investigation on the associations between fatigue, disease activity, and drug survival to possibly predict and understand treatment response to TNFi.

Looking at baseline characteristics, upper median fatigue was associated with higher disease activity, patient pain, and HAQ scores, all in line with the hypothesis that fatigue is a relevant symptom to be targeted with antiinflammatory treatment.[29] This is in line with the study by Tobin, *et al*[8] showing that there appears to be an incremental increase in fatigue with increased disease severity and joint involvement.

In addition, upper median fatigue was also associated with more comorbidities, current smoking status, and higher occurrence of depression and/or anxiety[7,8]; it is therefore possible that some of the experienced fatigue may be due to factors other than PsA.

Overall, when considering the patients' improvement in ACR and VAS fatigue responses when treated with TNFi, this study showed a disproportionate outcome that was more profound in patients with upper median fatigue, as we saw that fewer patients achieved 20% ACR and VAS fatigue responses compared to patients with lower median fatigue. This was also seen when examining 50% and 70% ACR and VAS fatigue responses (Figure 3). These results indicate that there may be an independent effect of fatigue severity that is causing more difficulties in treating fatigue as a symptom.

Underlying differences in disease characteristics are important for physicians to be aware of when treating fatigue as a symptom of disease.[21] The physician's evaluation of disease activity may not fully reflect the implicit burden of PsA for the patients.[18] It has been suggested that fatigue may predominantly reflect psychosocial distress, including an inability to cope with disease, rather than a true indicator of inflammatory disease.[7] As a consequence,

it is necessary to understand the patient's perception of PsA in more detail and relate it to the physician's point of view.[18] When considering the effects of TNFi treatment, it is important to keep previous research in mind, which shows varying effects of TNFi treatment on fatigue.[22,23,24]

In RA, measurement of fatigue provides several challenges due to its subjective nature and close relationship with cognitive and emotional dimensions.[30] Characteristics of the experience and consequences of fatigue are also likely to be unique in patients with PsA, imposing the need for specific assessment instruments and interpretation of VAS fatigue in the context of the individual PsA patient. Generic instruments may, as is the case in PsA, contain items that would capture the restrictions imposed by inflammation or disability,[31] explaining the association between changes in VAS fatigue and ACR responses demonstrated in the present study. On the other hand, fatigue in itself is a cognitive and emotional experience; therefore, it can also be independent or indirectly related through central sensitization, leading to the disconnect between ACR responses and changes in VAS fatigue, as seen in the data presented.

When subgrouping patients based on STR and baseline fatigue, our findings suggested that differences in effect of TNFi treatments on fatigue and ACR response might be related to the degree of inflammation as well as the interaction with background fatigue (Figure 3).[8] We assumed that disease was driven by a stronger inflammatory component in patients with relatively more swollen joints (STR ≥ 0.5), as these patients showed improved effect of treatment on both VAS fatigue and ACR responses (Figure 3). This is supported by the notion that fatigue can be associated with the effect of the inflammatory cascade on the central nervous system.[19] Moreover, it has been shown that high concentrations of proinflammatory cytokines, such as TNF-α, play a role in the pathogenesis of psoriasis and PsA, including fatigue and depression.[8]

Subgrouping of patients based on STR also showed that the same was not the case for patients with relatively more tender joints (STR < 0.5; Figure 3), as these patients showed less effect of TNFi treatment on fatigue. As for this patient group, it creates further challenges for healthcare professionals, as it suggests underlying components other than inflammation, which have to be taken into account when treating fatigue with antiinflammatory medications. One possible explanation could be that fatigue in these patients is heterogeneous and may be related to other conditions including widespread central pain sensitization, which in turn may be associated with tender entheseal points,[2,30] explaining why TNFi treatment does not appear to have the same effect on patients with STR < 0.5 compared to the group with STR ≥ 0.5 (Figure 3).

We hypothesize that the patients belonging to the upper median fatigue group and STR < 0.5 showed disease characteristics of chronic widespread pain. They reported a strong presence of fatigue but did not seem to have as much improvement from the TNFi treatment. In these patients, comprehensive treatment warrants further need for alternative strategies pharmacologically as well as nonpharmacologically.

Adding to the challenge of treating fatigue is the fact that patients suffering from a higher degree of fatigue showed shorter drug survival (Figure 2). Treatment continuation has previously been associated with high levels of CRP and concomitant methotrexate treatment[20]; together with our results, this indicates the importance of a strict therapy targeting fatigue continuously with combination therapy—especially for inflammatory-derived fatigue. Nonetheless, baseline fatigue and STR can serve as good prognostic markers when trying to tailor interventions and expectations for the patient as well as the caregiver, thus stratifying care on the road toward personalized medicine.

This study has its strengths and limitations. LUNDEX-adjusted responses were calculated to ensure that the reported data was indicative of patients who not only remained on TNFi treatment but also met certain response criteria under the observational period for the treatment groups of lower and upper median fatigue. The LUNDEX-corrected percentages all decreased as a consequence of missing data from dropouts during the observational period.

The current study included only patients treated with TNFi. Recording of data in DANBIO was mandatory for patients treated with biological agents in Danish outpatient clinics. One strength of this study is that the study population may be seen to represent the majority of patients. However, patients receiving treatment with biologic agents also represent patients with more severe symptoms, which might have had an influence on the severity of other symptoms as well. Further, only a subgroup of patients has complete patient-reported outcome responses, potentially hampering the external validity of the findings due to selection bias.

Although it is difficult to disentangle the effects of fatigue from PsA vs fatigue from other diseases or from causes not related to disease, it has shown to be important in treatment response and drug survival (Table 1). Previous publications have also shown that fatigue is one of the most troublesome symptoms for patients with PsA, as our PRP also emphasized. Therefore, we have not adjusted for potential residual confounding factors for fatigue in this study.

Nonetheless, fatigue remains of great importance to patients, leading to decreased QOL, as described by the PRP. The current findings provide new insights into the effect of treatment and how physicians might focus on different mechanisms to treat fatigue as a symptom of PsA.

In conclusion, fatigue remains a dominating symptom after TNFi treatment and is associated with higher baseline disease activity, more comorbidities, smoking, higher pain and HAQ scores, and increased risk of TNFi treatment discontinuation in a cohort study of Danish patients with PsA. The agreement between ACR responses and VAS fatigue responses is weak to moderate, suggesting heterogeneity between experienced fatigue and joint inflammation. Our results suggest that fatigue might be seen as a distinct symptom or disease domain caused by diverse mechanisms in PsA, needing different degrees of attention. Moreover, results suggest that, to reach a long-term result, treatment of fatigue needs to be based on patients' individual symptoms.

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We wish to acknowledge our PRP for valuable discussion during the study. The PRP described a decrease in QOL, based on her own experience with the symptom of fatigue. During a conversation with the PRP, it was made clear that the investigation into cause and possible treatment was of importance to the general feeling of well-being. It was also important to the PRP that there be more focus on the general misconception that fatigue is tiredness, rather than an overwhelming life-intruding feeling of extreme exhaustion resulting from mental and/or physical exertion or illness.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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