Relation between fatigue and ACR response in patients with psoriatic arthritis treated with TNFi therapy: a population-based cohort study

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Key Indexing Terms: Psoriatic arthritis / Fatigue / TNFi treatment

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Running head:

Fatigue remains a dominating symptom after TNFi treatment

ABSTRACT

Objective: The objective of this population-based cohort study was to investigate the association of fatigue with disease activity and drug survival in PsA patients 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 PsA patients in the period 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 measure (DAS28CRP), pain and health assessment questionnaire (HAQ) scores, tender joint count, 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, less patients achieved ACR responses and improvements in 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 followup.

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.

INTRODUCTION

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

PsA is an inflammatory disease characterized by inflammation of the joints, the 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, non-alcoholic fatty liver disease, diabetes and cardiovascular disease [12,13], with over 50% of PsA patients having more than one 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]. PsA patients continue to cite fatigue as one of the most challenging aspects of their disease as it decreases their health-related quality of life [19].

Fatigue in psoriasis has been associated with the impact 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 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 improve function, quality of life, 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 [22-24].

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 relation between ACR (American College of Rheumatology criteria) and fatigue response in PsA patients receiving their first TNFi. According to Danish law, informed consent and ethics approval were not required for the present study.

MATERIALS AND METHODS

Study design

Before initiating the study a systematic search for litereature was conducted. The study was conducted in accordance with the STROBE-startement (suppl. File S1) and based on a predefined protocol available on www.parkerinst.dk. The study was designed as a longitudinal registry study including data on patients registered in the Danish nationwide registry DANBIO [25]. Objective and study design were discussed with a PsA patient partner after informed consent. The results and conclusions of the study were relayed to the patient partner after the study was concluded.

Setting & data source

Data on patient characteristics, disease activity and drug survival was obtained from the DANBIO registry. Information on comorbidities according to the Charlson Comorbidity Index (CCI) 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 bDMARDs, can be considered representative of patients with PsA who are treated in routine care (www.danbio-online.dk).

Participants

All patients with PsA registered in DANBIO during the period from 2006 to 2015 receiving their first TNFi were identified and considered eliglible for participation in the study. Patients were excluded if they had erroneous baseline information, were not followed from the initiation of treatment, without consecutive follow-up visit registration, were participating in clinical trials, had been treated with other bDMARDs than TNFi, and those who did not record fatigue data.

VARIABLES AND OUTCOME MEASURES

Fatigue was assessed by a visual analogue scale (VAS), a scale composed to measure fatigue, pain and global health (VAS fatigue, VAS pain, VAS global health), on a scale from 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 in VAS fatigue. Variables extracted from DANBIO included: gender, age, date of visits, disease duration, smoking habbits, BMI (weight and height), ACR20/50/70, treatment duration, type of TNFi therapy, swollen joint count (SJC), tender joint count (TJC), C-reactive protein (CRP), health assessment questionnaire (HAQ), disease activity score (DAS28CRP), visual analogue scales (0-100 mm VAS) for doctor's global, patient's global, fatigue and pain, treatment information on conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and/or biologic DMARDs (bDMARDs). From the Danish National Patient Registry, information on comorbidities were extracted.

STATISTICAL ANALYSIS

Data analysis was performed in SPSS (version 25). Patients were grouped and compared based on severity of fatigue defined by median fatigue. Patient characteristics were presented by means with standard deviations. Statistical significance was determined with Mann-Whitney/χ^2-test. Two-sided P-values <0.05 were considered statistically significant. Mann-Whitney U was calculated to determine the significance of correlation between patients with depression/anxiety and their level of VAS fatigue. Kaplan-Meier plots, univariate, and multivariate Cox proportional hazard regression analyses were calculated adjusted 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); STR being either <0.5 or ≥ 0.5 [27]. The cut-off at 0.5 was chosen based on indirect evidence from RA, where this was the most discriminative cut-point. Kappa statistics were used to assess agreement between fatigue and ACR20/ACR50/ACR70, respectively, by the use of the Lund Efficacy Index (LUNDEX = (Fraction of starters still in the study at time T) x (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 (ITT) method developed for the observational

setting to account for both withdrawals from therapy and for missing response recordings at certain points of followup [28].

RESULTS

During the study period a total of 1980 patients were registrered in DANBIO 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).

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 67 mm. The two groups were defined as lower median fatigue (<67) and upper median fatigue (≥ 67). Comparisions of the two 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 more females, a higher percentage of patients with CCI≥2 and a higher percentage of patients with depression and/or anxiety, although the latter did not reach statistical significance (table 1). Patients with depression/anxiety had significantly higher VAS fatigue at baseline than patients without (p=0.032).

Table 1:

Drug survival

Assessing the relationship between VAS fatigue and TNFi drug survival our study show shorter that patients with higher baseline fatigue scores have shorter drug survival compared to patients with lower fatigue scores demonstrated by a Kaplan-Meier plot (figure 2). The hazard ratio (HR) was 1.39 (95% CI 1.16-1.66) with a p-value of <0.001 (adjusted for age and gender), indicating significantly shorter drug survival in the upper fatigue group. At 6 months follow-up respectively, 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 it was 40% in the lower median fatigue group. Throughout the years assessed patients in the lower median fatigue group had on average longer drug survival.

Figure 2:

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. ACR 20, 50 and 70 responses at 6-month were 49%, 35% and 18% respectively. VAS fatigue 20, 50 and 70 responses were 57%, 39% and 20%, respectively. The kappa value between ACR 20, 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 ACR respons at 6 months for 20, 50 and 70% improvement for lower median VAS fatigue group were 42.5%, 33.6% and 19.4%, and for the upper median VAS fatigue group 44.1%, 27.9% and 13.2%. 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.

Table 2:

Treatment response; grouping based on fatigue & swollen / tender joint ratio

Looking at the overall effect of TNFi treatment on ACR and VAS fatigue responses at 6-month follow-up (figure 3), patients showing the most improvement were those exhibiting more swollen joints. When subgrouping patients based on swollen / tender joint ratio (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). 15% 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 improvements in 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 improvements. In fact, almost the same number of patients in the lower median fatigue group with STR<0.5 reached VAS fatigue 20, 50 and 70% compared with patients in the upper median fatigue group with STR≥0.5.

Figur 3:

Overall, as shown in table 2 fatigue responses at 6-month had low to moderate agreement with ACR responses, indicating that fatigue and ACR 20, 50 and 70% response represent different domains of the PsA disease. As expected, agreement was generally higer for the more strict criteria (ACR 70 and VAS fatigue 70). More interestingly, kappa-values were lowest in the most refractory patient group with high baseline fatigue and more tender than swollen joints.

DISCUSSION

In the present study, based on data from DANBIO, our results indicate a continuing challenge to treat fatigue as a symptom of disease. Though 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 ACR 20, 50 and 70% responses. Thus, the current study demonstrates the further need for investigation of 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, higher patient pain, and higher HAQ scores all in line with the hypothesis that fatigue is a relevant symptom to be targeted with anti-inflammatory 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], making it possible that some of the experienced fatigue may be due to other factors than caused by PsA.

Overall, when considering the patients' improvement in ACR and VASfatigue responses when treated with TNFi, this study showed a disproportional outcome that was more profound in patients with upper median fatigue, as we saw that less patients achieved 20% ACR and VASfatigue responses compared to patients with lower median fatigue (figure 3). This was also seen when examining 50 and 70% ACR and VASfatigue responses (figure 3). These results indicate that there may be an independent effect of fatigue severity 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 [22-24].

In RA, measurement of fatigue provides several challenges due to its subjective nature and close relationship with cognitive and emotional dimensions [30]. Chaaracteristics of the experience and consequenses of fatigue are also likely to be unique in PsA patients, which imposes the need for specific assessment instruments and interpretation of VAS fatigue in the context of the individual PsA patient. Generic instruments may as the case is in PsA contain items that in PsA would capture the restrictions imposed by inflammation or disability [31], explaining the association between changes in VAS fatigue and ACR responses demonstrated in the current paper. On the other hand, fatigue in itself as a cognitive and emotional experience, can also be independent or indirectly related through central sensitisation 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 TNFi treatments effect on fatigue and ACR response might be related to the degree of inflammation as well as interacting 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 VASfatigue and ACR responses (figure 3). This is supported by the notion that fatigue can be associated with the impact of the inflammatory cascade on the central nervous system [19]. Moreover, it has been shown that

high concentrations of proinflammatory cytokines, such as tumor necrosis factor alpha, 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 the symptom of fatigue. As for this patient group, it creates further challenges for healthcare professionals as it suggests other underlying components than inflammation, which have to be taken into account when treating fatigue with anti-inflammatory medications. One possible explanation could be that fatigue in these patients is heterogeneuos and may be related to other conditions including widespread central pain sensitization, which may be associated to tender entheseal points [2, 30], explaining why TNFi treatment does not appear to have the same effect on the patients with STR<0.5 compared to the group with STR≥0.5 (figure 3).

We hypothesize that the patients reciding in the grouping of upper median fatigue and STR<0.5 showed disease characteristics of chronic widespread pain. They report a strong presence of fatigue but do 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 non-pharmacologically.

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 C-reactive proteins and concomitant methotrexate treatment [20] which together with our results indicates the importance of a strict therapy targeting also fatigue continuously favouring the combination therapy – especially for the inflammatory derived fatigue. Nonetheless, baseline fatigue and STR can serve as a good prognostic marker when trying to tailor interventions and expectations for the patient as well as the caregives thus stratifying care on the road towards personalized medicine.

Strength and limitations

LUNDEX adjusted responses were calculated to insure 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 droputs during the observational period.

The current study only included patients treated with TNFi. Recording of data in DANBIO was mandatory for patients treated with biological agents in Danish outpatient clinics why the population may be seen to represent the majority of patients considered a strength of the study. Though, patients in treatment with biologic agents also represent the part of patients with more severe symptoms which might have had an influence on the severity of other symptoms as well. Furthermore, only a subgroup of patients has complete patient-reported outcomes (PROs) recordings, which potentially could hamper the external validity of the findings due to selection bias.

Although it is difficult to disintangle the effects of fatigue from other diseases with the same symptom or other causes of fatigue, it has with accordance to table 1 shown to be of importance for treatment response and drug survival. Previous puplications have also shown that fatigue is one of the most troublesome symptoms for PsA patients as our patient partner also emfecised. Therefore we have not adjusted for potential residual confounding factors for fatigue in this study.

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

Conclusion

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 mechanism in PsA

needing different degrees of attention. Moreover, results suggest that treatment of fatigue needs to be based on patients' individual symptoms to reach a satisfying result.

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

REFERENCES

1. Orbai A. M., De Wit M., Mease P, Shea J. A., Gossec L., Ying Leung Y, et al. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. Ann Rheum Dis. 2017;(76):673–680.

2. Gudu T, Etchetoc A, De Wit M, Heiberg T, Maccarone M, Balanescu A, et al. Fatigue in psoriatic arthritis - a cross-sectional study of 246 patients from 13 countries. Joint Bone Spine 2016;83:439–443.

3. Druce KL, Jones GT, Macfarlane GJ, Basu N. Determining Pathways to Improvements in Fatigue in Rheumatoid Arthritis Results From the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Arthritis Rheumatol. 2015;67:2303-10.

4. Skoie I. M, Ternowitz T, Jonsson G, Norheim K, Omdal R. Fatigue in psoriasis: a phenomenon to be explored. Br J Dermatol. 2015;172:1196–1203.

5. Minnock P, Ringnér A, Bresnihan B, Veale D, FitzGerald O, McKee G. Perceptions of the Cause, Impact and Management of Persistent Fatigue in Patients with Rheumatoid Arthritis Following Tumour Necrosing Factor Inhibition Therapy. Musculoskeletal Care. 2017;15:23-35.

6. Husni ME., Merola FJ, Davin S. The psychosocial burden of psoriatic arthritis. Semin Arthritis Rheum. 2017;47:351–360.

7. Husted JA, Tom BD, Schentag CT, Farewell VT, Gladman DD. Occurrence and correlates of fatigue in psoriatic arthritis. Ann Rheum Dis. 2009;68:1553-8.

8. Tobin AM, Sadlier M, Collins P, Rogers S, FitzGerald O, Kirby B. Fatigue as a symptom in psoriasis and psoriatic arthritis: an observational study. Br J Dermatol. 2017;176:827-828.

9. Michelsen B, Fiane R, Diamantopoulos AP, Soldal DM, Hansen IJ, Sokka T, et al. A comparison of disease burden in rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis. PLoS One. 2015;10.

10. Mease P, Lesperance T, Liu M, Collier D, Mason M, Deveikis S, et al. Changes in Treatment Patterns in Patients with Psoriatic Arthritis Initiating Biologic and Nonbiologic Therapy in a Clinical Registry. J Rheumatol. 2017;44:184-192.

11. Egeberg A, Kristensen LE, Thyssen JP, Gislason GH, Gottlieb AB, Coates LC, et al. Incidence and prevalence of psoriatic arthritis in Denmark: a nationwide register linkage study. Ann Rheum Dis. 2017;76:1591-1597.

12. Ogdie A, Schwartzman S, Husni ME. Recognizing and managing comorbidities in psoriatic arthritis. Curr Opin Rheumatol. 2015;27:118-26.

13. Cantini F, Niccoli L, Nannini C, Kaloudi O, Bertoni M, Cassarà E. Psoriatic arthritis: a systematic review. Int J Rheum Dis. 2010;13:300-17.

14. Boyd T, Kavanaugh A. Novel approaches to biological therapy for psoriatic arthritis. Expert Opin Biol Ther. 2016;16:173-186.

15. Ballegaard C, Højgaard P, Dreyer L, Cordtz R, Jørgensen TS, Skougaard M, et al. Impact of comorbidities on tumour necrosis factor inhibitor therapy in psoriatic arthritis: a population-based cohort study. Arthritis Care Res (Hoboken). 2018;70:592-599.

16. Gladman DD, Antoni C, Mease P, Clegg OD, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64:14–17.

17. Kristensen LE, Jørgensen TS, Christensen R, Gudbergsen H, Dreyer L, Ballegaard C, et al. Societal costs and patients' experience of health inequities before and after diagnosis of psoriatic arthritis: a Danish cohort study. Ann Rheum Dis. 2017;76:1495-1501.

18. Dandorfer SW, Rech J, Manger B, Schett G, Englbrecht M. Differences in the Patient's and the Physician's Perspective of Disease in Psoriatic Arthritis. Semin Arthritis Rheum. 2012;42:32-41.

19. Rosen J, Landriscina A, Friedman AJ. Psoriasis-Associated Fatigue: Pathogenesis, Metrics, and Treatment. Cutis. 2016;97:125-132.

20. Kristensen LE, Gulfe A, Saxne T, Geborek P. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. Ann Rheum Dis. 2008;67:364-9.

21. Glintborg B, Ostergaard M, Krogh NS, Andersen MD, Tarp U, Loft AG, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: results from the Danish Nationwide DANBIO Registry. Arthritis Rheum. 2013;65:1213-23.

22. Dougados M, Wen-Chan T, Saaibi DL, Bonin R, Bukowski J, Pedersen R. Evaluation of Health Outcomes with Etanercept Treatment in Patients with Early Nonradiographic Axial Spondyloarthritis. J Rheumatol. 2015;42:1835-1841.

23. Braun J, McHugh N, Singh A, Wajdula JS, Sato R. Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. Rheumatology (Oxford). 2007;46:999–1004.

24. Hammoudeh M, Zack DJ, Li W, Stewart MV, Koenig AS. Associations between inflammation, nocturnal back pain and fatigue in ankylosing spondylitis and improvements with etanercept therapy. J Int Med Res. 2013;41:1150-9.

25. Hetland ML. DANBIO - powerful research database and electronic patient record. Rheumatology (Oxford). 2011;50:69–77.

26. Hewlett S, Hehir M, Kirwan JR. Measuring Fatigue in Rheumatoid Arthritis: A Systematic Review of Scales in Use. Arthritis Rheum. 2007;57:429-39.

27. Kristensen LE, Bliddal H, Christensen R, Karlsson JA, Gülfe A, Saxne T, et al. Is swollen to tender joint count ratio a new and useful clinical marker for biologic drug response in rheumatoid arthritis? Results from a Swedish cohort. Arthritis Care Res (Hoboken). 2014;66:173-9.

28. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. Arthritis Rheum. 2006;(54):600-6.

29. Skougaard M, Jørgensen TS, Rifbjerg-Madsen S. et al. In Psoriatic Arthritis fatigue is driven by inflammation, disease duration, and chronic pain: An observational DANBIO registry study. Jrheum. 2020; 47(4): 548-552.

30. Hewlett S, Cockshott Z, Byron M. et al. Patients' perception of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. Arthritis Rheum 2005;53:697-702.

31. Santos EJF, Duate C, da Silva JAP, Ferreira RJO. The impact of fatigue in rheumatoid arthritis and the challenges of its assessment. Rheumatology (Oxford). 2019;58(Suppl 5):v3-v9.

FIGURE LEGENDS

Figure 1 *Flow diagram*

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 der graph. TNFi; tumor necrosis factor inhibitors

Figure 3 *Effect of TNFi on ACR and VAS fatigue in PsA patients, by STR and Median VAS fatigue at 6-months*

2x2 table subgrouping patients based on upper and lower median fatigue, and STR<0.5 and STR≥0.5 N with completed data in each subgroup: Results are LUNDEX corrected. Lower median fatigue & STR<0.5=53; Lower median fatigue & STR ≥0.5=81; Upper median f fatigue & STR<0.5=86; Upper median f fatigue & STR≥0.5=50. The figure is showing the effect of TNFi treatment on ACR and VAS fatigue, respectively, as percentages of patients reaching ACR20/50/70 and/or VAS20/50/70 criterias when comparing baseline ACR and VAS fatigue with 6-month follow-up. VAS; visual analogue scale, STR; swollen / tender ratio, ACR; American College of Rheumatology criteria.

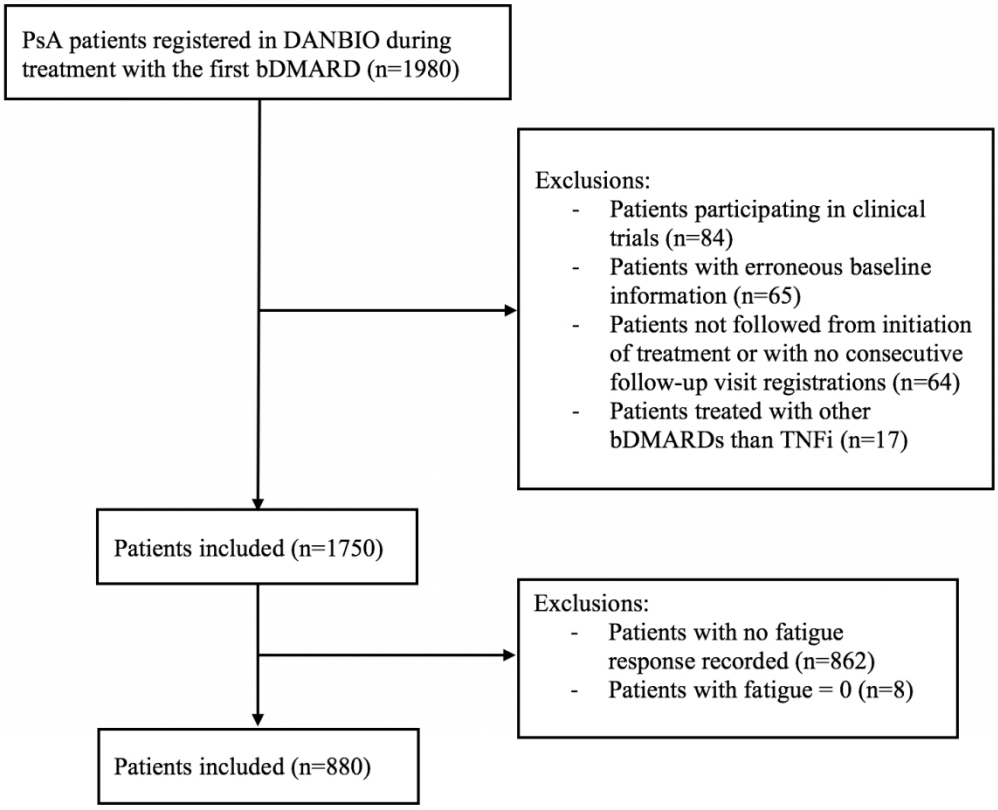

Figure 1. Flow diagram

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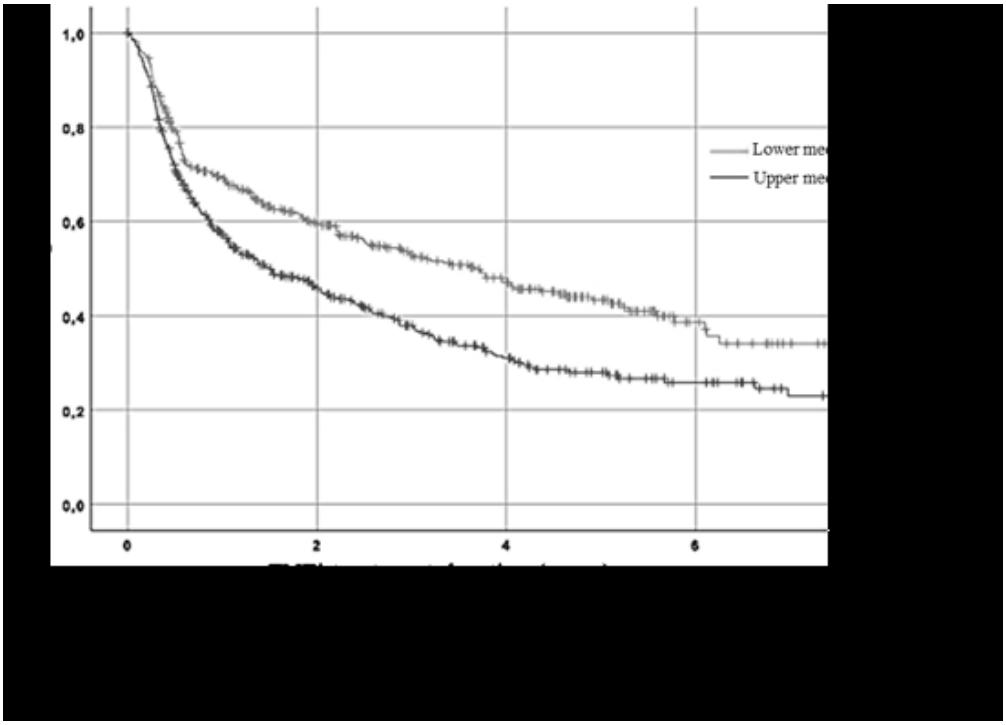

Figure 2. TNFi drug survival

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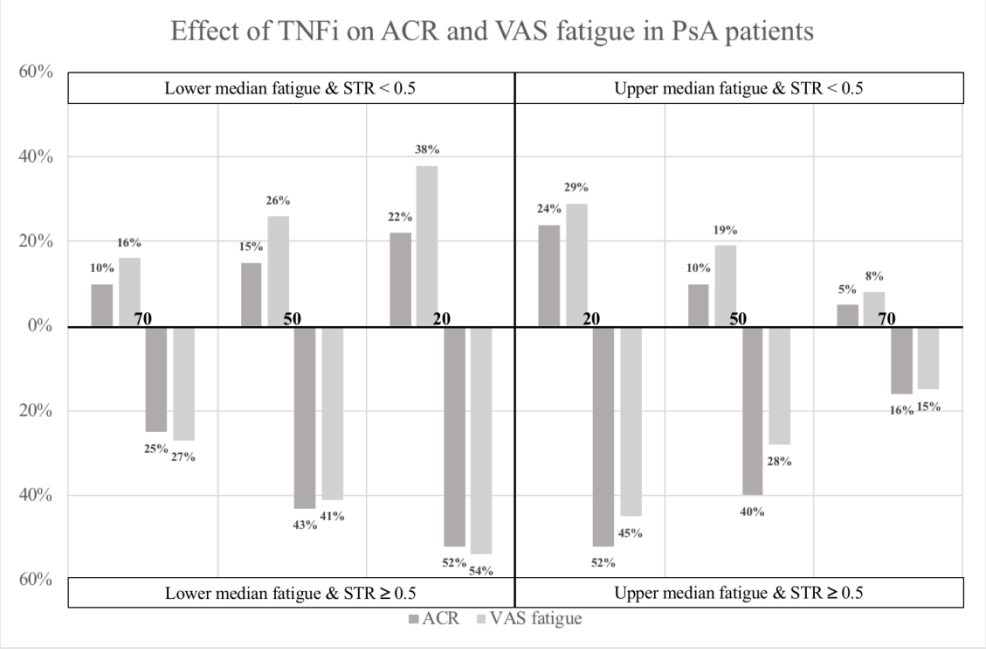

Figure 3. Effect of TNFi on ACR and VAS fatigue in PsA patients, by STR and Median VAS fatigue at 6-months

330x218mm (144 x 144 DPI)

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

		Lower VAS fatigue median (n=430)	Upper VAS fatigue median (n=450)	P-value
Gender, female n (%)		212 (49.3%)	270 (60.0%)	0.001
Age, mean ± SD		48.0 ± 12.0	47.8 ± 12.2	0.100
BMI, mean ± SD		27.6 ± 5.5	28.3 ± 6.0	0.100
Current smoking, n (%)		92 (43.8%)	118 (56.2%)	0.034
DAS28CRP, mean ± SD		3.9 ± 1.1	4.7 ± 1.1	<0.001
CRP, mean ± SD		12.8 ± 16.9	14.4 ± 22.2	0.022
Swollen joint count, mean ± SD		2.8 ± 3.3	2.7 ± 3.2	0.001
Tender joint count, mean ± SD		6.0 ± 5.0	9.0 ± 8.0	0.001
VAS pt pain global, mean ± SD		52.3 ± 22.5	79.8 ± 16.2	<0.001
VAS patient pain, mean ± SD		45.8 ± 21.5	71.7 ± 17.8	<0.001
HAQ score, mean ± SD		0.83 ± 0.6	1.37 ± 0.6	<0.001
Comorbidities, n (%)	**CCI = 0**	284 (66.0%)	278 (61.8%)	0.187
	CCI = 1	116 (27.0%)	119 (26.4%)	0.858
	CCI ≥ 2	30 (7.0%)	53 (11.8%)	0.015
PSO within 10 years, n (%)		170 (47.2%)	190 (52.8%)	0.418
Depression/anxiety within 10 years, n (%)		23 (39.7%)	35 (60.3%)	0.147

Data are shown as mean ± SD unless otherwise indicated. VAS; Visual Analogue Scale, DAS28CRP; disease activity score on 28 joints and c-reactive protein, HAQ; Health Assessement Questionnaire, CCI; Charlson Comorbidity Index, PSO; psoriasis.

Table 2 K*appa values assessing the agreement between fatigue and ACR20/ACR50/ACR70 as observed at 6-months.*

	Lower VAS fatigue median				Upper VAS fatigue median			
STR<0.5	*	**20**	**50**	**70**	***	**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%
	Kappa (p-value)	0.489 (0.000)	0.409 (0.004)	0.724 (0.000)	**Kappa (p-value)**	0.291 (0.008)	0.398 (0.000)	0.244 (0.031)
STR≥0.5	**	**20**	**50**	**70**	****	**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%
	Kappa (p-value)	0.394 (0.001)	0.447 (0.000)	0.507 (0.000)	**Kappa (p-value)**	0.493 (0.001)	0.446 (0.003)	0.468 (0.003)

*VAS; visual analogue scale, STR; swollen/tender ratio, ACR; American College of Rheumatology criteria. *n=53; **n=81; ***n=86; ****n=50.*