

Fatigue in Psoriatic Arthritis (PsA): Is it related to disease activity?

¹TL Lai, ¹CK Au, ³HY Chung, ²MC Leung, ²WL Ng, , ³CS Lau

¹Rheumatology team, Department of Medicine, Tseung Kwan O Hospital, Hong Kong

²Rheumatology team, Department of Medicine and Geriatrics, United Christian Hospital, Hong Kong

³Rheumatology & Clinical Immunology team, Department of Medicine, Queen Mary Hospital, Hong Kong

| | |
|---------------------------------|---|
| Declaration of Interests | No conflict of interest declared |
| Funding | Authors did not receive any funding for the present study |
| Correspondence to | Dr. TL Lai, Department of Medicine Tseung Kwan O Hospital, 2 Po Ning Lane, Hang Hau, Tseung Kwan O, Hong Kong |
| Email | laitl@ha.org.hk |
| Phone | 852-92298853 |
| Word Count | 3029 |
| No. of Table | 2 |
| No. of Figure | 1 |

Abstract

Aim Fatigue is commonly associated with psoriatic arthritis (PsA). However, information about its prevalence and associated factors is sparse. The primary objective was to find the prevalence and magnitude of PsA fatigue. The secondary objective was to explore its associated risk factors, particularly emphasis on the effect of disease-activity control.

Methods PsA patients that fulfilled CASPAR criteria were consecutively recruited from local Rheumatology clinics. Fatigue was assessed by a 13-item self-administered questionnaire (FACIT-F) (0-52). Data collected and analyzed included: demographic data, disease-activity data, comorbidities and the medications use.

Results 231 eligible PsA patients recruited. The mean FACIT-F score was 37.5 +/- 9.1. Severe fatigue, defined as FACIT-F score <30, was found in 49 (22.1%) of them. The univariate model identified these associated factors of fatigue: tender and swollen joint-count, dactylitis count, PASI score, pain and general health-perception, DAPSA score, HAQ, the use of cyclosporine, sulphasalazine and biologic agent. The final regression model identified DAPSA and PASI were closely associated with severe fatigue; $p=0.003$ and $p=0.04$ respectively. No associations with fatigue were found between age, gender, disease duration, comorbidities and medication use.

However, there were weak correlations between the magnitude of FACIT-F score, DAPSA and PASI with $r = -0.3$ and $r = -0.26$ respectively

Conclusion Severe fatigue was common in PsA patients, and its magnitude was closely correlated with DAPSA and PASI score, indicating its multifactorial nature. Achieving DAPSA and PASI remission could significantly alleviate the fatigue intensity to certain extent. However, treatment for PsA-related fatigue should adopt a multidisciplinary approach in addition to disease-activity control.

Keywords Disease activity, fatigue, psoriatic arthritis, skin psoriasis

Introduction

Fatigue is described as a feeling of “extreme weakness, substantial tiredness or persistent loss of vitality” and is one of the most frequent encountered complaints in patients with chronic rheumatic diseases.^{1,2} Possible explanations are controversial, with some investigators suggesting it as an unpleasant component of active rheumatic disorders, while others explaining it as a solely personal perception.^{2,3}

Psoriatic arthritis (PsA), which is characterized by arthritis and skin psoriasis, is one of the most prevalent rheumatic diseases in the world.⁴ Fatigue is an important

symptom in addition to joint pain and skin itchiness.⁵ A sense of tiredness, loss of energy and exhaustion not only decrease quality of life, but also affect academic or work performance, daily activity, exercise level and social interaction.^{2,3} Fatigue may even contribute to depression.⁵

Most PsA patients accepted that fatigue as a constant companion of psoriatic conditions, or as a side-effect of medication i.e. conventional or biologic disease modifying agents (DMARDs).^{2,3} Rheumatologists believe that fatigue results from chronic inflammation of the skin and joints via cytokine release.^{2,3} However, fatigue may also develop from the psychological stress of embarrassing cutaneous and nail conditions, joint deformities and functional incapacities.^{2,3,5}

Fatigue is difficult to manage as it often persists even after disease activity is well under control.^{1,2} The exact underlying mechanism of fatigue is still poorly understood, and the relevant research is scarce, especially in Asia.⁵ The majority of these trials were confined to Western populations and limited to skin psoriasis (PsO), regardless of arthritis and its comorbidities such as diabetes mellitus and ischaemic heart disease.² Moreover, variations in ethnicity, culture and living style might contribute to the wide range of fatigue severity in psoriatic disease.^{6,7,8} Thus, the primary aim of this study was to determine the magnitude and the prevalence of severe fatigue in Hong Kong Chinese PsA patients. The secondary aim was to explore its associated factors, particularly emphasis on the effect of PsA disease activity in the hopes of improving management.^{9,10}

Methodology

This was a multi-centre, cross-sectional observational study. The protocol was reviewed and approved by the Clinical Research Ethics Committee in our locality. The primary objective was to find the magnitude and the prevalence of fatigue in Hong Kong Chinese patients with PsA. The secondary objective was to investigate the associated factors of fatigue, particularly emphasis on the effect of PsA disease activity, in terms of DAPSA and PASI.^{9,10}

Subjects were recruited consecutively from the rheumatology clinics of Tseung Kwan O Hospital (TKOH), United Christian Hospital (UCH) and Queen Mary Hospital (QMH) from January 2019 to March 2020. All patients fulfilled the CLASSification criteria for Psoriatic ARthritis (CASPAR), were aged 18 years or above, had written consent. Patients excluded had: (1) ethnicity other than Chinese, (2) haemoglobin level less than 10, (3) history of depression or other psychiatric diseases, (4) history of carcinoma and (5) with stage 5 kidney disease. Relevant information was retrieved from the local electronic Central Management System (CMS).

Demographic and clinical data included age, sex, Body Mass Index (BMI) and disease duration. PsA disease activity parameters were measured: (1) tender (68) and swollen joint-count (66), (2) dactylitis-count, (3) Leeds Enthesitis Index (LEI), (4) PASI, (5) C-reactive Protein (CRP), (6) Erythrocyte Sedimentation Rate (ESR), (7) Health Assessment Questionnaire Disability Index (HAQ-DI), (8) pain score Visual Analog Scale (VAS, 0-100 mm), and (9) General Health (GH) score VAS, 0-

100 mm.^{4,5,9,11} Higher scores indicated more severe pain and worse general well-being. HAQ-DI assessed physical disability.^{9,11}

Other data recorded were: comorbid conditions (e.g. hypertension, ischaemic heart disease and diabetes mellitus), and use of conventional DMARDs (e.g. acitretin, methotrexate, sulphalsalazine, cyclosporine, and leflunomide), and biological agents i.e. Anti-TNF biologics and non-TNF biologics.⁹ DAPSA score was calculated, as the sum of the following components: (1) tender and swollen joint-count, (2) pain score/ 10, (3) GH score/ 10 and (4) CRP (mg/L)/ 10.¹⁰ DAPSA values below or equal to 4 is classified as arthritis remission, while values between 4.01 and 14, between 14.01 and 28, and above 28, are classified as low, moderate and high activity respectively.¹⁰ PASI score below or equal to 1 is defined as skin remission.¹² Kidney function was expressed as estimated Glomerular Filtration Rate (eGFR), using the Cockcroft-Gault formula.¹³

Fatigue was measured using the version 4 Traditional Chinese FACIT-F (Functional Assessment of Chronic Illness Therapy – Fatigue) questionnaire.^{14,15} It comprises 13 items with 5-point scales, total scores ranges from 0 to 52.^{14,15,16} Higher the score indicates lesser degree of fatigue.^{14,15,16} Severe or significant fatigue was defined as scores less than 30.^{14,15,16} Written consent from the FACIT organization was obtained for the formal use of validated Traditional Chinese language of the FACIT-F questionnaire.

Statistical analysis

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) 17.0 for Mac (Chicago, IL, US). All clinical and related parameters were expressed as median with interquartile range or percentages and mean +/- standard deviation (SD).

Severe or significant fatigue, was defined by a FACIT-F cutoff score less than 30.^{14,15} In univariate analyses, demographics and clinical variables differences between the two patient groups (with or without severe fatigue) were compared using the Student T-test or Mann-Whitney U test for variables as appropriate, and Chi-square test for categorical variables in univariate analyses. Subsequently, a logistic regression model was used to determine the associated factors of severe fatigue. Statistical significance was defined as a p-value of less than 0.05, two tailed.

Results

A final of 231 eligible participants were recruited. Table 1 summarizes the baseline characteristics of all the participants. There were 80 females and 151 males, with mean age of 51.3 +/- 12.2 years. Mean BMI was 24.9 +/- 4.3 kg/m². The median duration of skin psoriasis was 14 (8, 22) years and the median duration of PsA was 5 (2, 10) years. Forty-two (18.2%) patients had diabetes mellitus and 10 (4.3%) had ischaemic heart disease. The median creatinine clearance was 93 (77, 112) ml/min. Thirty (13%) were active smoker, 14 (6.1%) were ex-smoker and 9 (3.9%) were chronic drinkers.

The median detected tender joint count (68) was 2 (0, 4) and swollen joint count (66) was 2 (0, 5). The median ESR level was 20 (10, 39) mm/hr and the median CRP level was 3.5 (3.1, 9.6) mg/L. Both tender enthesitis and tender dactylitis were relatively uncommon in the PsA participants at the time of survey, with prevalence of 18.6% (43/231) and 32.5% (75/231) respectively. Among them, the median LEI was 2 (1, 2) and the median dactylitis count was 2 (2, 4). 82.7% (191/231) of patients had skin psoriasis lesions. The median PASI score was 3.2 (1.2, 7.4) among those with skin lesions.

The median body pain VAS was 20 (2, 50) among them. While for patients' global health, the median VAS was 50 (20, 60). The median HAQ-DI was 0.13 (0, 0.63). The median DAPSA score was 13.3 (6, 20.5). Among all PsA participants, 33 (14.3%) of them was in DAPSA remission, with the score below or equal to 4. Eighty-six (37.2%) of them were in low arthritis activity with DAPSA score above 4-14. Eight-one (35.1%) of them were in moderate activity, with DAPSA score between 14-28 and 31 (13.4%) were in high activity with DAPSA score above 28.

Concerning the medications use, 88 (38.1%) were on a single conventional DMARD, 29 (12.6%) received dual DAMRDs. Thirteen of them (5.6%) were on leflunomide, 44 (19%) were on sulphasalazine, 19 (8.2%) were on cyclosporine, 4 (1.7%) were on acitretin and 82 (35.5%) were on methotrexate. Forty-five (19.5%)

were receiving biological agents, while 28 of them (62.2%) were receiving anti-TNF biologics.

The mean FACIT-F score was 37.5 +/- 9.1 and 21.2% (49/231) of all PsA participants were noted to have severe fatigue (FACIT-F score < 30). The mean age of those with severe fatigue was 50.3 +/- 12.7 years. Twenty-nine (59.2%) were men and 20 (40.8%) were women.

Univariate analysis found that (1) the use of DMARDs: leflunomide and cyclosporine, (2) self-perceived pain and GH scores, (3) HAQ-DI, (4) PASI and skin remission, (5) disease activity – tender and swollen joint-count, and dactylitis count, and (6) DAPSA score, were closely associated with severe fatigue in PsA. Table 2 summarizes the univariate analysis of associated factors for PsA-related fatigue.

Since the DAPSA score contains the components of tender and swollen joint-count, self-perceived pain and GH scores, they were all excluded from the subsequent logistic regression model. The final model identified that DAPSA and PASI score were the two significant associated factors with severe fatigue in PsA, with p-value of 0.003 and 0.04 respectively. In Spearman's rho correlation, the FACIT-F score showed a negative relationship with the DAPSA, with weak strength of association ($r=-0.3$; $p<0.001$). PASI also showed a weak strength of correlation with FACIT-F score with $r= -0.26$; $p<0.001$. Figure 1 shows the scatterplots of the relationship between FACIT-F, DAPSA and PASI in PsA cohorts.

No associations with severe fatigue were found with age, gender, BMI, renal function, inflammatory markers, the duration of psoriatic conditions, dactylitis-count, LEI, the medications use (either conventional DMARD or biologic agent), HAQ-DI and comorbid conditions in the final model.

Discussion

Fatigue is an important feature of chronic rheumatic diseases, however, it is often under-recognized, under-evaluated and under-treated by rheumatologists.^{1,2} The collected data confirmed that severe fatigue was common among Hong Kong Chinese PsA patients, with prevalence of 21.2%. The mean FACIT-F score was 37.5 +/- 9.1 among them. This distressing symptom was not only correlated with core disease domains, but also with their perceived pain and well-being.

Fatigue is an abstract symptom, which varies across individuals, cultures and ethnicities.⁶ To date, there is no internationally consensus on its definition and use of measurement instruments. The 13-points FACIT-F scale was used because it had been validated in the 2007 Toronto PsA study, and it covered a broader range of fatigue-related manifestations.^{17,18} Other assessment tools for fatigue, including the Multidimensional Fatigue Inventory (MFI-20) scale, and the Fatigue Visual Analog Scale, are not specific to psoriatic diseases, except the modified Fatigue Severity Scale (FSS).^{9,11}

Data on the prevalence of severe fatigue in PsA is sparse. Using the fatigue VAS, FSS and SF-36 vitality scale, Skoie et al found that up to 50% of patients with skin psoriasis suffered from substantial fatigue.⁵ Using the modified FSS scores, Husted et al identified that 49.5% of PsA patients had at least moderate fatigue and 28.7% had severe fatigue.¹⁸ In 2016, Tobin et al reported that about 40% of PsA had fatigue, based on the VAS.¹⁹ Recently, Pilgaard et al found that severe fatigue was extremely common not only in PsA (approximately 27%), but also across Rheumatoid Arthritis (RA) (approximately 25%) and axial spondyloarthritis (axSpA) (approximately 28%), from the Danish National Rheumatology Registry (DANBIO).²⁰ Our results showed 21.2% prevalence of severe fatigue, consistent with previous studies.²⁰ This was also consistent across different fatigue assessment methods, cultures and ethnicities.^{5,18,19,20} Based on the above findings, fatigue phenomenon in PsA should not be neglected and under-estimated.

Information about the associated factors for PsA-related fatigue were found to be limited and inconsistent. A prospective observational study by Behrens et al found that a DMARD – leflunomide, could effectively reduce PsA patients' sense of fatigue, in addition to pain, skin and nail manifestations, and dactylitis.²¹ On the other hand, Husted et al identified that “ever used” methotrexate might provoke PsA-related fatigue.¹⁸ In univariate analysis of the present study, cyclosporine and sulphasalazine were found to be associated with severe fatigue, but not in the final regression model. Since the cumulative dose and the duration of DMARDs used were not recorded in all of them, their relationship with fatigue was not conclusive.

To most rheumatologists, fatigue is intimately related to the chronic inflammation of rheumatologic diseases.^{2,3} Much evidence, including randomized trials,

demonstrated that fatigue in RA was closely linked with joint inflammation.^{17,22} Biologic agents reduced RA-related fatigue, via cytokine inhibition.^{17,22} Bluthé et al postulated that Interleukin-1 (IL-1) cytokines and tumor necrosis factor-alpha (TNF-alpha) might play a key role in fatigue.²³ IL-1 and TNF-alpha crossed the blood-brain barrier in mice and induced the behavioral changes of immobility, loss of appetite and social exploration, which all share common symptoms with severe fatigue.²³ Studies about the effect of biologic agents on PsA fatigue are limited.²⁴ A meta-analysis of 7 randomized controlled trials concluded that anti-TNF biologics (adalimumab, certolizumab pegol), non-TNF biologics (secukinumab, ustekinumab) and apremilast had a small effect on fatigue at 24 weeks in PsA.²⁴ Consistently, our collected data did not find PsA fatigue having any correlation with the use of conventional DMARDs and biologic agents, which indicated that fatigue severity in PsA was not independently related to medications use, but more depended on the tight disease control with individual medication.

In 2016, Gudu et al highlighted that the intensity of fatigue in PsA was largely related to disease severity, including extent of skin involvement, tender joint-count and enthesitis.¹⁸ On the other hand, a large study (n=499) of PsA patients revealed that fatigue was more correlated to pain perception, gender, physical disability, medication use and emotional stress, than disease-related activities.¹⁸ Our data was consistent with both in that PsA-fatigue was correlated with its disease activities including tender joint-counts, and also pain and the general health perception, but not the gender, physical disability and medication use. Two respective studies by Skoie et al and Tobin et al had reported there were lack of correlations between fatigue magnitude and PASI in psoriatic patients.^{5,13} Although only weak correlations were found between fatigue severity and PASI score in the final model,

a significant numerically improvement of FACIT-F score was found in the subgroup analysis of skin remission patients (PASI \leq 1) versus skin non-remission patients (39.8 \pm 8.7 vs 36.5 \pm 9.2; $p=0.009$), indicated that cutaneous involvement did play the role in causing fatigue feeling in psoriatic conditions. Certainly, skin dryness and itchiness in poor controlled PsO can induce sleep deprivation, which can cause fatigue feeling.^{25,26}

Our findings showed that severe PsA fatigue was significantly associated with DAPSA as well as PASI. DAPSA score is consisted of 5 components – (1) tender joint-count, (2) swollen joint-count, (3) CRP, (4) pain perception and (5) general health perception.¹⁰ This showed that the underlying cause of PsA-fatigue was multifaceted and that no single factor could fully explain it.^{18,29} Our collected data also found that the majority of severe fatigue patients were men (59.2%) of middle age, who were the main workforce of our society and the income producer of the families in a Chinese society. Understanding the way to tackle the fatigue feelings among them definitely can improve not only individual's work efficiency and quality of life, but also their families and the society. Since PsA fatigue magnitude was negatively correlated with DAPSA and PASI score, prompt disease activity control in arthritic and cutaneous conditions could definitely alleviate these unpleasant feelings to a certain extent.

However, there was not any association between DAPSA and PASI remission and the occurrence of severe fatigue among them, this finding reinforced the belief of the multifactorial nature of PsA-fatigue etiology. Achieving DAPSA and PASI remission in PsA could not completely eliminate their fatigue feelings. Furthermore, though the DAPSA and PASI were found to be closely associated with fatigue but

their magnitude correlation was actually weak. Their weak correlations indicated that neither DAPSA nor PASI was the perfect predictor for PsA-related fatigue. In addition to skin and joint examination, a more comprehensive assessment including psychological, emotional, physical and quality-of-life aspects, should be employed in predicting PsA-related fatigue. Furthermore, a multidisciplinary approach to management of fatigue is required, this may include psychological therapy and counselling which help to build and boost their psychological well-being. In view of its common prevalence and multidimensional nature, fatigue assessment should be routinely assessed in all our PsA patients.

Our study was one of only a few conducted internationally, to explore fatigue in PsA. Our findings provide useful information in understanding the psychological aspect of PsA patients, and hope to raise rheumatologists' awareness to this troublesome problem. Another strength of this study was that multiple confounding factors were considered, particularly comorbidities, the medication use and the use of DAPSA. The current data highlighted the importance of treating PsA to target in alleviating the fatigue magnitude.

There were a few limitations. Firstly, several potential confounding factors such as socioeconomic factors and sleep-related factors, were not considered in the present study. In previous studies, psychosocial adversity and social factors play pivotal roles in fatigue occurrence.^{6,18} Data on marital status, living environment, employment, and financial status assists understanding of the psychosocial factors of fatigue. Sleep disorders or sleep quality were not taken into account.²⁶ There is substantial symptom overlap between fatigue and sleep disorders.²⁶ Verhoeven et al had highlighted a high prevalence of pruritus (50%) among those with general skin

conditions.²⁷ Skin itchiness and joint pain in PsA patients worsen the sleeping quality, which may result in depressive symptoms, and exaggerate the fatigue feeling.^{22,25,26} Sleep related questionnaires such as the Global Sleep Assessment Questionnaire and itching measurement such as the 5-D itch scale, should be included in assessment.^{28,29}

Secondly, fibromyalgia was not specifically excluded.³⁰ A 2013 pilot study reported that 55% of PsA patients had concomitant fibromyalgia syndrome (FMS), in which a core symptom was severe fatigue.³⁰ Thirdly, variations in the magnitude of fatigue may be contributed by different degrees of HAQ-DI and pain level from subtypes of PsA such as predominant axial spondylitis and oligo-articular arthritis, which were not recorded in this study.

Finally, the limitation of a cross-sectional study is clear. The findings of association between fatigue magnitude, DAPSA and PASI score do not indicate the casual relationship. Longitudinal study with validated assessment tool is definitely required to examine the link between the change in PsA disease activity and fatigue magnitude.

Conclusion

Severe fatigue was prevalent in patients with PsA, its occurrence and magnitude was closely associated with the disease activity – DAPSA and PASI. It was not correlated with the age, gender, duration of psoriatic disease, medication use and comorbid conditions. Controlling disease activities in terms of DAPSA and PASI

could not completely eliminate PsA-related fatigue, but could relieve it to a certain extent.

PsA-related fatigue was multifaceted, not a single marker could predict its occurrence. In view of its complexity, more holistic and multidisciplinary approaches should be adopted to alleviate this burdensome symptom.

Disclaimer

The authors did not receive any funding for the present study.

Acknowledgements

The authors would like to thank all the participants for their contribution and time to the project, and to express our appreciation to our rheumatology specialty nurses and clerks: Ms. Cheryl Cheng, Ms. Ann Kwok, Ms. Lee, Ms. Cheung, Ms. Gladys Kwok, Ms. Manly Tang and Ms. Anna Lee, for their continued support to this time-consuming task. We would also like to thank Dr. Cynthia Chan for her invaluable advice on editing and proofreading.

References

1. Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. *Curr Opin Neurol* 1996;9:456-60.
2. Overman CL, Kool MB, Da Silva JA, Geenen R. The prevalence of severe fatigue in rheumatic diseases: an international study. *Clin Rheumatol* 2016;35(2):409-15.
3. Prins JB, van der Meer JW, Bleijenberg G. Chronic fatigue syndrome. *Lancet* 2006;367(9507):346-55.
4. Leung YY, Li EK, Leung MH, Kun EWL, Tam LS. Psoriatic arthritis in Hong Kong. *Hong Kong J Dermatol Venereol* 2007;15:62-6.
5. Skoie IM, Ternowitz T, Jonsson G, Norheim K, Omdal R. Fatigue in psoriasis: a phenomenon to be explored. *Br J Dermatol* 2015;172(5):1196-1203.
6. Bhui KS, Dinos S, Ashby D, Nazroo J, Wessely S, White PD. Chronic fatigue syndrome in an ethnically diverse population: the influence of psychosocial adversity and physical inactivity. *DMC Med* 2011;9:26.

7. Cordero ED, Loreda JS, Murray KE, Dimsdale JE. Characterizing fatigue: The effects of ethnicity and acculturation. *J Appl Biobehav Res* 2012;17(1):59-78.
8. Dinos S, Khoshaba B, Ashby D, et al. A systemic review of chronic fatigue, its syndromes and ethnicity: prevalence, severity, co-morbidity and coping. *Int J Epidemiol* 2009;38(6):1554-1570.
9. Wong PCH, Leung YY, Li EK, Tam LS. Measuring disease activity in psoriatic arthritis. *Int J Rheumatol* 2012;2012:839425.
10. Schoels MM, Aletaha D, Alasti, Smolen JS. Disease activity in psoriatic arthritis (PsA): defining remission and treatment success using the DAPSA score. *Ann Rheum Dis* 2016;75:811-818.
11. Mease PJ. Measures of Psoriatic Arthritis. *Arthritis Care Res* 2011;63 Suppl 11:64-85.1.
12. Coates LC, Helliwell PS. Defining low disease activity states in psoriatic arthritis using novel composite disease instruments. *J Rheumatol* 2016;43:371-5.
13. Botev R, Mallié JP, Couchoud C, Schück O, Fauvel J-P, Wetzels JFM, Lee N, De Santo NG, Cirillo M. Estimating glomerular filtration rate: Cockcroft-Gault and modification of diet in renal disease formulas compared to renal inulin clearance. *Clin J Am Soc Nephrol* 2009;4(5):899-906.

14. Webster K, Cella D, Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. *Health Qual Life Outcomes* 2003;1:79.
15. Chandran V, Bhella S, Schentag C, Gladman DD. Functional assessment of chronic illness therapy-fatigue scale is valid in patients with psoriatic arthritis. *Ann Rheum Dis* 2007;66:936-939.
16. Wang SY, Zang XY, Liu JD, Gao M, Cheng M, Zhao Y. Psychometric properties of the functional assessment of chronic illness therapy-fatigue (FACIT-fatigue) in Chinese patients receiving maintenance dialysis. *J Pain and Symptom Manage* 2015;49(1):135-143.
17. Huyser BA, Parker JC, Thoreson R, Smarr KL, Johnson JC, Hoffman R. Predictors of subjective fatigue among individuals with rheumatoid arthritis. *Arthritis Rheum* 1998;41(12):2230-7.
18. Husted JA, Tom BD, Schentag CT, Farewell VT, Gladman DD. Occurrence and correlates of fatigue in psoriatic arthritis. *Ann Rheum Dis* 2009;68(10):1553-8.
19. Tobin AM, Sadlier M, Collins P, Rogers S. Fatigue as a symptom in psoriasis and psoriatic arthritis: an observational study. *Br J Dermatol* 2016;doi:10.1111/bjd15258.

20. Pilgaard T, Hagelund L, Staliknecht SE, Jensen HH, Esbensen BA. Severity of fatigue in people with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis – Results of a cross-sectional study. *PLoS ONE* 14(6):e0218831.
21. Behrens F, Finkenwirth C, Pavelka K, et al. Leflunomide in psoriatic arthritis: results from a large European prospective observational study. *Arthritis Care Res* 2013;65(3):464-70.
22. Strand V, Scott DL, Emery P, et al. Physical function and health related quality of life: analysis of 2-year data from randomized, controlled studies of leflunomide, sulfasalazine, methotrexate in patients with active rheumatoid arthritis. *J Rheumatol* 2005;32(4):590-601.
23. Bluthé RM, Layé S, Michaud B, Combe C, Dantzer R, Parnet P. Role of interleukin-1beta and tumor necrosis factor-alpha in lipopolysaccharide-induced sickness behavior: a study with interleukin-1 type 1 receptor-deficient mice. *Eur J Neurosci* 2000;12(12):4447-56.
24. Reygaerts T, Mitrovic S, Fautrel B, Gossec L. Effects of biologics on fatigue in psoriatic arthritis: a systemic literature review with meta-analysis. *Joint Bone Spine* 2018;85(4):405-410.
25. Jackson ML, Bruck D. Sleep abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: a review. *J Clin Sleep Med* 2012;8(6):719-728.

26. Arnold LM. Understanding fatigue in major depressive disorder and other medical disorders. *Psychosomatics* 2008;49:185-90.
27. Verhoeven EW, Kraaimaat FW, van de Kerkhof PC, et al. Prevalence of physical symptoms of itch, pain and fatigue in patients with skin diseases in general practice. *Br J Dermatol* 2007;156:1346-9.
28. Roth T, Zammit G, Kushida C. A new questionnaire to detect sleep disorders. *Sleep Med* 2002;3(2):99-108.
29. Elam S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. *Br J Dermatol* 2010;162(3):587-593.
30. Magrey MN, Antonelli M, James N, Khan MA. High frequency of fibromyalgia in patients with psoriatic arthritis: a pilot study. *Arthritis* 2013;doi:10.1155/2013/762921.

Table 1. Demographics and characteristics of PsA patients (231).

| | Number (%) | Mean (+/- SD) |
|---|--------------------|----------------|
| M/F ratio | 151/80 (65.4/34.6) | |
| Age (years) | | 52.3 +/- 12.2 |
| Body mass index, BMI (kg/m ²) | | 24.9 +/- 4.3 |
| Duration of psoriasis (years), median | | 14 (8, 22) |
| Duration of PsA (years) | | 5 (2, 10) |
| Diabetes mellitus | 42 (18.2) | |
| Ischaemic heart diseases | 10 (4.3) | |
| <i>Disease activity</i> | | |
| Swollen joint count (0-66), median | | 2 (0, 5) |
| Tender joint count (0-68), median | | 2 (0, 4) |
| DAPSA score, median | | 13.3 (6, 20.5) |
| Patients with DAPSA remission (<=4) | 33 (14.3) | |
| Patients with low DAPSA activity (4-14) | 86 (37.2) | |
| Patients with moderate DAPSA (14-28) | 81 (35.1) | |
| Patients with high DAPSA (>28) | 31 (13.4) | |
| Patients with dactylitis, median | | 0 (0, 2) |
| Leeds Enthesitis Index (0-6), median | | 0 |
| Positive skin condition | 191 (82.7) | |
| PASI score (0-72), n=191, median | | 3.2 (1.2, 7.4) |
| Severe skin condition (PASI>10) | 29 (12.6) | |
| ESR (mm/hr), median | | 20 (10, 39) |
| CRP (mg/dl), median | | 3.5 (3.1, 9.6) |
| Creatinine clearance (ml/min), median | | 93 (77, 112) |
| <i>Medication use</i> | | |

| | | |
|---------------------------------------|-----------|----------------|
| Patients on single conventional DMARD | 88 (38.1) | |
| Patients on dual conventional DMARDs | 29 (12.6) | |
| Methotrexate | 82 (35.5) | |
| Sulphasalazine | 44 (19) | |
| Lefluonamide | 13 (5.6) | |
| Cyclosporine | 19 (8.2) | |
| Patients on biologics | 45 (19.5) | |
| Patients on anti-TNF biologics | 28 (12.1) | |
| <i>Quality-of-life measurement</i> | | |
| FACIT-F score (0-52) | | 37.5 +/- 9.1 |
| Severe fatigue (FACIT-F < 30) | 49 (21.2) | |
| HAQ (0-3), median | | 0.13 (0, 0.63) |
| Pain VAS (0-100 mm), median | | 20 (2, 50) |
| General health VAS (0-100 mm), median | | 50 (20, 60) |

| Parameter | Patients with severe fatigue N= 49 | Patients without severe fatigue N = 182 | P value |
|---|---------------------------------------|--|---------|
| <i>Sex</i> | | | 0.31 |
| Male, No. (%) | 29 (59.2) | 122 (67) | |
| Female, No. (%) | 20 (40.8) | 60 (33) | |
| Age in years, mean +/- SD | 50.4 +/- 12.7 | 51.6 +/- 12 | 0.52 |
| Body mass index (kg/m ²), mean +/- SD | 24.8 +/- 5.5 | 24.9 +/- 3.9 | 0.90 |
| Duration of PsO, median | 12 (10, 23) | 14 (7, 22) | 0.92 |
| Duration of PsA, median | 4 (2, 10) | 5 (2, 10) | 0.75 |
| Diabetes mellitus, No. (%) | 7 (14.3) | 35 (19.2) | 0.43 |
| Ischaemic heart disease, No. (%) | 2 (4.1) | 8 (4.4) | 0.92 |
| Creatinine clearance (ml/min), median | 89 (76, 120) | 94 (78, 110) | 0.19 |
| <i>Disease activity</i> | | | |
| Swollen joint-count (0-66), median | 4 (1, 8) | 2 (0, 5) | 0.03 |
| Tender joint-count (0-68), median | 3 (1, 8) | 2 (0, 4) | 0.01 |
| Dactylitis count, median | 0 (0, 3) | 0 (0, 1) | 0.02 |
| LEI (0-6), median | 0 (0, 1) | 0 | 0.11 |
| PASI score (0-72), median | 4.2 (1.2, 10.7) | 2.1 (0.3, 5.6) | 0.01 |
| PASI score <= 1, No. (%) | 10 (20.4) | 65 (35.7) | 0.04 |
| ESR (mm/hr), median | 18 (11, 47) | 20 (10, 35) | 0.62 |
| CRP (mg/L), median | 4.6 (3.1, 11.1) | 3.5 (3.1, 9.5) | 0.44 |
| DAPSA score, median | 18.3 (11.4, 29.9) | 11.3 (5.3, 18) | 0.002 |
| DASPA score <= 4, No. (%) | 3 (6.1) | 30 (16.5) | 0.07 |
| <i>Medication use</i> | | | 0.64 |
| On single conventional DMARD, No. (%) | 11 (47.8) | 30 (43.5) | |
| On dual conventional DMARDs, No. (%) | 3 (13) | 10 (14.5) | |
| Methotrexate, No. (%) | 15 (30.6) | 67 (36.8) | 0.42 |

| | | | |
|---|-------------------|-------------|---------|
| Sulphasalazine, No. (%) | 15 (30.6) | 29 (15.9) | 0.02 |
| Lefluonamide, No. (%) | 0 (0) | 13 (7.1) | 0.06 |
| Cyclosporine, No. (%) | 9 (18.4) | 10 (5.5) | 0.004 |
| Acitretin, No. (%) | 0 (0) | 4 (2.2) | 0.30 |
| Patients on biologic agent, No. (%) | 4 (8.2) | 41 (22.5) | 0.02 |
| Patients on anti-TNF biologics, No. (%) | 3 (6.1) | 25 (13.7) | 0.15 |
| <i>Quality-of-life measurement</i> | | | |
| HAQ (0-3), median | 0.75 (0.13, 1.13) | 0 (0, 0.38) | < 0.001 |
| Pain VAS, median | 50 (15, 70) | 10 (0, 43) | < 0.001 |
| General health VAS, median | 60 (40, 80) | 40 (20, 60) | < 0.001 |

Table 2. Univariate analysis of PsA patients with and without severe fatigue.

Figure 1. Scatterplots showing the relationship between FACIT-F, DAPSA and PASI score in PsA patients (n=231).

