



Residual symptoms and disease burden among patients with psoriatic arthritis: is a new disease activity index required?

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Received: 6 October 2018 / Accepted: 2 November 2018 / Published online: 13 November 2018
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Abstract

The aim of this study was to investigate residual symptoms or disease burden among patients with psoriatic arthritis (PsA) in remission or low disease activity (LDA) according to different outcome measures. A total of 126 patients with PsA were included and the following variables were assessed: Tender joint count (TJC), swollen joint count (SJC), patient's global assessment, physician's global assessment, pain, extra-articular manifestations, Psoriasis Area and Severity Index, Health Assessment Questionnaire, fatigue, Short Form-36, psoriatic quality of life, Hospital Anxiety and Depression Scale and C-reactive protein (CRP). Disease activity was measured using three different outcome measures including minimal disease activity (MDA), disease activity score for 28 joints (DAS28-CRP) and disease activity in psoriatic arthritis (DAPSA). The number (%) of patients who achieved remission or LDA was 9(14.1), 34(27.0) and 67(53.2) according to MDA, DAPSA and DAS28-CRP criteria, respectively, under usual care. SJC > 1 was seen in 3(8.8%) and 13(19.4%) of patients in remission or LDA as defined by the DAPSA and DAS28-CRP respectively. TJC > 1 was found at least 32.4% of patients with PsA in remission or LDA by any definition. 22.2–49.3% of patients with PsA in remission or LDA still suffered from clinically important fatigue. No patients in MDA had a substantial functional impairment while 2.9–19.4% of patients fulfilling remission or LDA according to the DAPSA and DAS28-CRP experienced functional disability. At least 22.2% of patients with PsA in remission or LDA by any description had higher risk for depression, and at least 11.1% for anxiety. Despite patients with PsA in remission or LDA by various definition, they may continue to experience pain, tender or swollen joints, fatigue, physiologic distress as well as functional impairment suggesting that there is a significant unmet need with regard to definition of remission or LDA in PsA.

Keywords Disease activity · Disease burden · Minimal disease activity · Psoriatic arthritis · Remission

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Introduction

Psoriatic arthritis (PsA), part of the concept of spondyloarthritis (SpA), is a complex inflammatory disease with various clinical manifestations including peripheral arthritis, axial disease, dactylitis, enthesitis, tenosynovitis, nail change, psoriasis, uveitis, and inflammatory bowel disease. Such peripheral, axial, and extra-articular involvement may occur separately or in combination with each other in the course of disease [1]. Some of the patients with PsA may also have high risk for developing cardiovascular disease and metabolic comorbidities (i.e., obesity, insulin resistance, fatty liver disease) [2].

In recent years, several clinical studies have highlighted the important role of treat-to-target (T2T) strategies to improve long-term clinical and radiographic outcomes in rheumatic diseases [3–7]. Tight Control of PsA (TICOPA)

was the first randomized controlled multicenter study comparing a T2T approach using a tight control strategy with adjustment of treatment according to the minimal disease activity (MDA) criteria against usual care in patients with early PsA (< 24 months). Patients in the tight control group reported better clinical outcomes in term of skin disease activity, physical function as well as quality of life from baseline to week 48. The proportion of patients achieving an ACR20, ACR50 and ACR70 responses were also higher in tight control group [5]. Then, the 2015 update European League Against Rheumatism (EULAR) treatment recommendations for PsA and the 2017 international task force recommendations for SpA and PsA defined treatment target as remission or, alternatively low disease activity (LDA), whereas the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommended T2T in all disease domains but no specific target was defined [6, 8, 9].

In rheumatic disease, monitoring outcome measures with a global assessment of disease activity is essential to determine the underlying disease process, follow the treatment response as well as achieve optimal patient outcomes. The PsA core domain set has been recently updated by the Outcome Measures in Rheumatology (OMERACT) and GRAPPA-PsA working group. A core set of outcome measures for clinical trials have classified into three concentric circle (core) including inner circle (peripheral joint activity, enthesitis, dactylitis, axial disease, skin disease activity, patient global assessment, pain, physical function, health-related quality of life, fatigue, systemic inflammation), middle circle (economic cost, emotional well-being, participation, structural damage) and outer circle or research agenda (stiffness, independence, treatment burden, sleep) [10]. Assessment of disease activity in PsA has been performed by a number of composite indices including the Psoriatic Arthritis Response Criteria (PsARC), the Disease Activity Score for 28 joints (DAS28) [11], the Psoriatic Arthritis Joint Activity Index (PsAJAI) [12], Disease Activity in Psoriatic Arthritis (DAPSA) [13], the Composite Psoriatic Disease Activity Index (CPDAI) [14], the MDA [15], the Psoriatic Arthritis Disease Activity Score (PASDAS) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis Composite Exercise (GRACE) and others [16]. Of these activity measures, only MDA and DAPSA have been endorsed by the international task force to define in treatment target [6].

With disease progress, PsA may cause fatigue, impaired physical function, reduced quality of life (QoL), increased psychological distress as well as loss of work productivity particularly in patients with uncontrolled disease activity. Until now, previous studies have reported that achieving remission or alternatively LDA has led to favorable effect on inflammatory marker, joint damage, radiologic progression and severity of skin involvement in PsA [5, 17]. However,

the impact of achievement of remission or LDA on physical function, quality of life and psychological status has not yet been sufficiently established. Therefore, the primary objective of this study was to examine residual symptoms or disease burden among patients with PsA achieving treatment target as defined by being in remission or LDA according to the three different definitions, including MDA, DAPSA and DAS28-CRP.

Material methods

Study population

Adult patients (aged ≥ 18 years) with PsA fulfilling the CASPAR classification criteria for PsA were included consecutively in this cross-sectional study [18]. This study protocol was approved by the local medical research ethics committee of Sakarya University (protocol number:16214662/050.01.04/90, date: 22.06.2016) and then a written consent form was obtained from all included patients.

Clinical assessment

Following complete history, physical and laboratory examination, visual analog scale (VAS)-pain, tender joint count (TJC), swollen joint count (SJC), patient's global assessment (PtGA), physician's global assessment (PhGA), the presence of extra-articular manifestations and acute phase reactants including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) were recorded at baseline visit. Health-related quality of life was assessed by the Short Form 36 (SF-36) and the Psoriatic Quality of Life (PsQoL) [19, 20]. Functional disability was evaluated with the Health Assessment Questionnaire (HAQ) [21]. Patients' physiological status or mental health was obtained with the Hospital Anxiety and Depression Scale (HADS) including the depression (HADS-D) and anxiety (HADS-A) subscales as well as SF-36 mental compound score [22]. In addition, fatigue was measured using the VAS-fatigue and skin disease activity assessed by the Psoriasis Area and Severity Index (PASI) [23].

Disease activity assessment

Three different disease activity measures including DAS28 based on CRP (DAS28-CRP), MDA and DAPSA criteria were used to define the degree of disease activity including remission(REM), low (LDA), moderate (MoDA) and high (HDA) disease activity.

The Minimal Disease Activity criteria was used as a first specific composite outcome measure in PsA

particularly for T2T domain. This outcome measure was validated using observational and interventional trial data [24]. It takes into consideration the assessment of multiple disease domains including; TJC ≤ 1 ; SJC ≤ 1 ; PASI ≤ 1 ; VAS-pain ≤ 1.5 ; PtGA ≤ 2 ; HAQ ≤ 0.5 ; tender enthesal points ≤ 1 . MDA was classified as achievement of 5 of these 7 criteria [15]. DAPSA is another validated, disease specific outcome measure in patients with PsA [13, 25]. It includes assessment of five variables, namely patient global and pain assessments on 0-to100-mmVAS, 68 TJC and 66 SJC, and CRP level. DAPSA score was calculated by a simple arithmetic sum of these variables (SJC + TJC + PtGA + VAS-pain + CRP). The DAS-28, widely used composite measures, initially developed and validated for RA, but nowadays it is also used to assess articular response or disease activity of patient with PsA in daily routine or PsA clinical trials [26, 27]. In this study, the DAS28-CRP was calculated by the following Eq. $0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.014 \times GH + 0.36 \times \ln(CRP + 1) + 0.96$.

The state of disease activity was defined as remission (DAPSA ≤ 4 , DAS28-CRP < 2.6), LDA (DAPSA ≤ 14 , DAS28-CRP ≤ 3.2), MoDA (DAPSA ≤ 28 , DAS28-CRP > 3.2 and ≤ 5.1) and HDA (DAPSA > 28 , DAS28-CRP > 5.1) according to the previously validated cut-off points [28].

Statistical analyses

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software v22 (IBM, Armonk, NY, USA). The normality of distribution of all data was analyzed using the Shapiro–Wilk test. Disease activity measures including MDA, DAPSA and DAS28-CRP were calculated for all participants. We divided the patients into subgroups as patients who met or did not meet MDA, DAPSA and DAS28-CRP remission or LDA (MDA5/7 or more positive, DAPSA ≤ 14 and DAS28 ≤ 3.2). But MDA could not be calculated in 62 patients with PsA due to missing data. Descriptive statistics were used to compute the mean, standard deviation (SD), median and interquartile range (IQR) for continuous variables and proportion for categorical variables. Student's *t* test for normally distributed data and Mann–Whitney *U* test for not normally distributed data were used to compare within subgroups. Chi square or Fisher's exact test was used to compare the difference between proportions. The relationship between parameters was analyzed using Pearson's and Spearman's correlation coefficients according to normality of distribution. A $p < 0.05$ was considered statistically significant.

Results

A total of 126 patients with PsA (mean age 46.0 ± 11.0 years, 41 male/85 female) were included in the analyses. The proportion of patients in remission or LDA was clearly different according to three composite measures. The number (%) of patients who achieved remission or LDA was 9 (14.1), 34 (27.0) and 67 (53.2) according to MDA, DAPSA and DAS28-CRP criteria, respectively, while those who had moderate or HDA was 92(73.0) and 59 (46.8) according to DAPSA and DAS28-CRP criteria, respectively under usual care. Demographic, clinical, and laboratory characteristics of patients are given in Table 1. Comparison of disease activity parameters within the subgroups of patients fulfilling and not fulfilling the MDA, DAPSA and DAS28-CRP remission or LDA criteria are summarized in Table 2.

Residual symptoms in remission or LDA

Residual symptoms and disease burden in patients with PsA in remission or LDA according to the three definitions are demonstrated in Table 3. There were only three

Table 1 Demographic and clinical characteristics of patients with PsA ($n = 126$) [data was given as, mean \pm SD, (median (IQR)) or n (%)]

Age, years	46.0 \pm 11.0
Male, n (%)	41 (32.5)
Symptom duration, year	7.5 (12.0)
TJC	2 (6.75)
SJC	1.0 (2.75)
VAS-pain (0–10)	5.0 (4.5)
VAS- fatigue (0–10)	5.0 (5.0)
PtGA (0–10)	5.0 (4.0)
PhGA (0–10)	5.0 (3.0)
DAS 28-CRP	3.1 (1.7)
DAPSA	22.0 (22.0)
HAQ	0.2 (0.7)
SF-36 physical component summary score	37.8 (18.1)
SF36 mental component summary score	46.1 (21.1)
PsAQoL	2.0 (5.0)
HADS depression	6.0 (5.3)
HADS anxiety	6.0 (5.2)
Elevated CRP (0–5 mg/L), n (%)	64 (50.8)

TJC tender joint count, SJC swollen joint count, VAS visual analog scale, PtGA patient's global assessment, PhGA physician's global assessment, DAS 28-CRP Disease Activity Score for 28 joints-C-reactive protein, DAPSA disease activity in psoriatic arthritis, HAQ Health Assessment Questionnaire, PsAQoL Psoriatic Quality of Life, SF-36 Short Form 36, HADS-D hospital anxiety and depression scale-depression, HADS-A hospital anxiety and depression scale-depression-anxiety

Table 2 Comparison of demographic and disease activity parameters within the subgroups of patients fulfilling and not fulfilling the MDA, DAPSA and DAS28-CRP remission or LDA criteria [median (IQR) if data is not otherwise specified]

	MDA (n=64)			DAPSA (n=126)			DAS28 (n=126)		
	MDA \geq 5/7	No MDA	p	DAPSA \leq 14	DAPSA > 14	p	DAS28 \leq 3.2	DAS28 > 3.2	p
N (% of all patients)	9 (14.1)	55 (84.9)	Na	34 (27.0)	92(73.0)	Na	67 (53.2)	59 (46.8)	Na
Age, year, mean \pm SD	43.3 \pm 10.5	47.8 \pm 11.1	0.267	40.2 \pm 9.7	48.3 \pm 10.9	<0.0001	42.4 \pm 10.2	50.1 \pm 10.7	<0.0001
Female, n (%)	1 (11.1)	42 (76.4)	0.0003	19 (55.9)	65(70.7)	0.118	41 (61.2)	44 (74.6)	0.109
Symptom duration, year	9.5 (17)	10 (12)	0.766	5.3 (10.5)	8.0(12.0)	0.599	7.0 (11.8)	8.0 (12.8)	0.852
TJC	0.1 (4.0)	2.0 (8.0)	0.254	0 (2.0)	3.1(8.0)	<0.0001	0 (2.0)	7.0 (9.0)	<0.0001
SJC	0 (0.55)	1.0 (4.0)	0.016	0 (0.1)	2(4.0)	<0.0001	0 (1.0)	2.0 (5.0)	<0.0001
VAS-pain	0 (0.50)	5.0 (4.0)	0.031	2 (3.0)	6.0(3.0)	<0.0001	3.0 (4.0)	7.0 (3.0)	<0.0001
PtGA on VAS	1.0 (2.5)	5.0 (4.0)	0.266	2.0 (3.0)	5.5(3.0)	<0.0001	3.0 (3.0)	6.0 (3.0)	<0.0001
PhGA on VAS	1 (1.5)	5.0 (3.0)	0.031	2.0 (2.0)	5.0(2.0)	<0.0001	3.0 (3.3)	5.0 (3.0)	0.001
CRP (mg/L)	3.2 (3.8)	5.1 (7.6)	0.050	3.4 (1.4)	7.8(9.5)	<0.0001	3.5 (5.4)	8.3 (14.6)	0.016
Dactylitis, n (%)	1 (11.1)	8 (14.5)	0.628	3(8.8)	10(10.9)	0.515	5 (7.5)	8 (13.6)	0.261
Tenosynovitis, n(%)	1 (11.1)	23 (41.8)	0.062	6 (17.6)	35(38.0)	0.030	19 (28.4)	22 (37.3)	0.655
Enthesitis, n (%)	1 (11.1)	31 (56.4)	0.026	7 (20.6)	42(45.7)	0.010	21 (31.3)	28 (47.5)	0.247
Inflammatory bowel disease, n (%)	0	0	Na	1 (2.9)	3(3.3)	0.706	2 (3.0)	2(3.4)	0.678
VAS-fatigue	2.0 (4.0)	6.0 (4.0)	0.063	3.0 (3.0)	6.0(3.0)	<0.0001	4.5 (4.0)	7.0 (3.0)	<0.0001
HAQ	0 (0)	0.25 (0.7)	0.016	0 (0.1)	0.4(0.7)	<0.0001	0.1 (0.3)	0.4 (0.8)	0.001
PsAQoL	0 (1.0)	2.0 (4.0)	0.165	0 (2.0)	3.0(4.0)	0.004	1.0 (4.0)	3.0 (4.0)	0.036
HADS-D	3.0 (4.0)	6.0 (6.3)	0.127	5.0 (6.0)	6.0(5.0)	0.268	5.0 (7.0)	6.0 (4.0)	0.335
HADS-A	3.0 (6.0)	6.0(6.3)	0.277	4.0(6.0)	7.0(5.0)	0.078	5.0 (6.0)	7.0 (4.5)	0.371
SF-36-Physical component summary score	56.2 (44.6)	37.8 (15.23)	0.027	53.0 (39.8)	35.7(16.1)	<0.0001	41.0 (24.4)	35.3 (17.8)	0.017
SF-36-Mental component summary score	61.7 (41.7)	45.4 (27.1)	0.136	54.7 (33.8)	44.5(19.6)	0.032	51.0 (26.3)	42.6 (18.0)	0.044

TJC tender joint count, SJC swollen joint count, VAS visual analog scale, PtGA patient's global assessment, PhGA physician's global assessment, HAQ Health Assessment Questionnaire, PsAQoL psoriatic quality of life, HADS-D hospital anxiety and depression scale-depression, HADS-A hospital anxiety and depression scale-depression-anxiety, SF-36 Short Form 36

patients with a TJC > 1 and no patient with one more swollen joints in patient with PsA achieving MDA. On the contrary, TJC > 1 was seen in 11 (32.4%) and 24 (35.8%) of patients; SJC > 1 was seen in 3 (8.8%) and 13 (19.4%) of patients in remission or LDA as defined by the DAPSA and DAS28-CRP, respectively. Residual symptoms were observed mainly in patient-reported outcomes (PRO): the proportion of patient with PtGA on VAS > 1, PhGA on VAS > 1 and VAS-pain > 4 described as clinically significant were found in nearly 11.1–22.2% of patients with PsA in MDA, %5.9–52.9 in DAPSA \leq 14 and 38.8–76.1% in DAS28-CRP \leq 3.2. Interestingly, elevated CRP(> 5 mg/L) was detected in 11.1% of patients in MDA, in 11.8% in DAPSA \leq 14 and in 38.8% in DAS28-CRP \leq 3.2. Clinically significant levels of fatigue defined as VAS-fatigue score > 4 was reported by 2 (22.2%), 9 (26.5%) and 33 (49.3%) patients with PsA in MDA, DAPSA and DAS28-CRP as defined remission or LDA, respectively.

Residual disease burden in remission or LDA

Residual functional disability defined as a HAQ score > 0.5 was seen by 0% of patients in MDA vs 3–19.4% of patients in DAPSA \leq 14 and DAS28-CRP \leq 3.2. The HQoL data revealed that the SF-36 subscales of the physical component summary and mental component summary as well as the PsAQoL scores were slightly better in patients with PsA fulfilling MDA than in DAS28-CRP and DAPSA remission or LDA (Table 3). Moreover, 46.3% of patients in DAS28-CRP remission or LDA had high risk for depression and 20.9% for anxiety. 38.2% of patients in DAPSA remission or LDA had high risk for depression and 14.7% for anxiety. In contrast, among the patients achieving MDA, there were only two patients (22%) with high risk for depression and one patient (11.1%) with high risk for anxiety. Overall 20.6% of patients with PsA in remission or LDA had difficulty

Table 3 Residual symptoms and disease burden in patients with PsA in remission or low disease activity according to the three definitions [data was given as, mean \pm SD; median (IQR) or *n* (%)]

	MDA5/7 or more+	DAPSA \leq 14	DAS28 \leq 3.2
<i>N</i> (% of all patients)	9 (14.1)	34 (27.0)	67 (53.2)
Ages, year	43.3 \pm 10.5	40.2 \pm 9.7	42.4 \pm 10.2
Female, <i>n</i> (%)	1 (11.1)	19 (55.9)	41 (61.2)
Symptom duration, year	9.5 (17.0)	5.3 (10.5)	7.0 (11.8)
TJC > 1 <i>n</i> (%)	3 (33.3)	11 (32.4)	24 (35.8)
SJC > 1 <i>n</i> (%)	0	3 (8.8)	13 (19.4)
VAS-pain > 4 <i>n</i> (%)	1 (11.1)	2 (5.9)	26 (38.8)
PtGA on VAS > 1, <i>n</i> (%)	2 (22.2)	18 (52.9)	51 (76.1)
PhGA on VAS > 1, <i>n</i> (%)	2 (22.2)	18 (52.9)	50 (74.6)
Elevated CRP (> 5 mg/L) <i>n</i> (%)	1 (11.1)	4 (11.8)	26 (38.8)
Dactylitis, <i>n</i> (%)	1 (11.1)	3 (8.8)	5 (7.5)
Tenosynovitis, <i>n</i> (%)	1 (11.1)	6 (17.6)	19 (28.4)
Enthesitis, <i>n</i> (%)	1 (11.1)	7 (20.6)	21 (31.3)
Inflammatory bowel disease, <i>n</i> (%)	0	1 (2.9)	2 (3.0)
VAS-fatigue > 4, <i>n</i> (%)	2 (22.2)	9 (26.5)	33 (49.3)
HAQ > 0.5, <i>n</i> (%)	0	1 (2.9)	13 (19.4)
PsAQoL	0 (1.0)	0 (2.0)	1.0 (4.0)
SF-36-Physical component summary score	56.2 (44.6)	53.0 (39.8)	41.0 (24.4)
SF-36-Mental component summary score	61.7 (41.7)	54.7 (33.8)	51.0 (26.3)
HADS-D \geq 7, <i>n</i> (%)	2 (22.2)	13 (38.2)	31 (46.3)
HADS-A \geq 10, <i>n</i> (%)	1 (11.1)	5 (14.7)	14 (20.9)
VAS-difficulty in work > 4, <i>n</i> (%)	0	7 (20.6)	26 (38.8)

TJC tender joint count, SJC swollen joint count, VAS visual analog scale, PtGA patient's global assessment, PhGA physician's global assessment, HAQ Health Assessment Questionnaire, PsAQoL psoriatic quality of life, SF-36 short form 36, HADS-D hospital anxiety and depression scale-depression, HADS-A hospital anxiety and depression scale-depression-anxiety

in work (VAS > 4) by DAPSA and 38.8% by DAS28-CRP description.

DAPSA, DAS28 and MDA measures positively correlated with VAS-pain ($r=0.383$, $r: 493$ and $r: 604$, respectively, $p < 0.0001$), PtGA ($r=0.416$, $r: 0.514$ and $r: 0.582$ respectively, $p < 0.0001$), PhGA ($r=0.397$, $r: 0.494$ and $r: 0.543$, respectively, $p < 0.0001$), fatigue ($r=0.292$, $r: 0.437$ and $r: 0.553$, respectively, $p < 0.001$), TJC ($r=0.430$, $r: 0.807$ and $r: 0.558$ respectively, $p < 0.0001$), SJC ($r=0.467$, $r=0.688$ and $r: 0=405$ respectively, $p < 0.001$), BASDAI ($r=0.295$, $r=0.410$ and $r: 0=496$, respectively, $p < 0.001$), BASFI ($r=0.308$, $r=0.334$ and $r: 0=410$, respectively, $p < 0.001$), PsAQoL ($r=0.243$, $r=0.211$ and $r: 0=310$, respectively, $p < 0.05$), CRP ($r=0.523$, $r=0.345$ and $r=0.250$, respectively, $p < 0.05$), HAQ ($r=0.424$, $r=0.401$ and $r=0.411$, respectively, $p < 0.001$) and negatively correlated with SF36 physical component summary score ($r=-0.406$, $r=-0.353$ and $r=0.499$, respectively, $p < 0.0001$) and SF36 mental component summary score ($r=-0.296$, $r=-0.276$ and $r=0.371$, respectively, $p < 0.001$).

Discussion

In this study, we investigated residual symptoms and disease burdens among patients with PsA achieving treatment target as defined by being in remission or LDA by various definitions. Our results highlighted that despite patients with PsA in remission or LDA, some of them still experienced pain, tender or swollen joints, fatigue, physiologic distress as well as functional impairment.

Nowadays, many instruments are available to define a state of remission or LDA in T2T approach [29, 30]. However, there is still controversy about the best measure to use in PsA. There are several challenges in the assessment of disease activity in routine clinical practice. First, patients with PsA present different domain of disease including peripheral arthritis, dactylitis, axial disease, enthesitis, psoriasis, nail disease. For example, some patients may suffer from peripheral arthritis, dactylitis with severe psoriasis, other patients may experience mainly axial symptoms, enthesitis, little nail or skin disease. In addition,

disease outcome or progression may be variable in individual patients. Due to complex nature and heterogeneity of clinical course in PsA, there is no single instrument well describing the individual component of disease process for all patients. Second, it has been reported that there was a significant discordance in global assessment of disease activity particularly in state of remission between patient's and physician's perspective (PtGA > PhGA) [31]. Moreover, from a physician's perspective, nearly one-third of the patients with PsA who was an acceptable disease state did not meet the MDA criteria [32]. Finally, in general specifically developed and validated tools to assess the disease activity in PsA are also insufficient.

Psoriatic arthritis may have a significant negative impact on the patients' life. So far, the clinical burden of PsA has been well documented by several studies [33–36]. However, there is relatively scant data reported on residual symptoms or disease burden in patients with PsA achieving different remission or LDA targets. In one observational cross-sectional study including 142 patients with PsA, nearly two-thirds of patients were reported to have residual disease activity mainly determined by joint disease and pain. Forty-eight percent of these patients met remission or LDA according to the clinical DAPSA [37]. In a study by Marin et al. it was found that nearly half of the patients with PsA who met MDA criteria experienced residual symptoms mainly on skin disease [38]. Another study by van Mens LJJ et al. assessed residual disease in patients with PsA in a real-life cohort achieving different composite scores, including clinical DAPSA (cDAPSA), DAPSA, very low disease activity (VLDA) and the MDA. They found that cDAPSA and DAPSA were fulfilled by more patients and patients fulfilling DAPSA and PASDAS for remission or LDA had a higher frequency of residual musculoskeletal disease than those fulfilling VLDA and the MDA skin/joint criteria [39]. The main difference between our study and these studies is that these studies only reported the residual symptoms of the principal domain of disease (i.e., pain, tender joint, swollen joint, skin disease), whilst our study also evaluated residual symptoms related to QoL, fatigue and physiologic distress in patients with PsA achieving remission or LDA according to the three different definitions, including MDA, DAPSA and DAS28-CRP. We observed that DAS28-CRP remission or LDA was achieved by the higher proportion of patients with PsA. Residual symptoms and disease burden were observed mainly in patient-reported outcomes (i.e., PtGA, PhGA, VAS-pain), joint disease, fatigue, as well as physiologic distress.

Progressive joint involvement occurring in a substantial proportion of patients with PsA may cause severe joint damage, functional impairment and reduced health-related quality life as well as work productivity loss in the later stages of the disease [40]. In most PsA clinical trials, following

after starting a biological therapy, a reduction of the baseline actively inflamed joint counts by $\geq 10\%$ to $\geq 30\%$ was defined as treatment target [41–43]. For these reasons, the primary goals in the treatment of PsA are to suppress the inflammatory process, protect joint deformity and also inhibition of radiographic progression. More recently two study indicated that low proportion (ranging from 7.4 to 8.8%) of patients with PsA fulfilling the MDA suffered from still a clinically significant number of tender and/or swollen joints [38, 44]. A study by van Mens LJJ et al. reported that among patients with PsA achieving clinical cDAPSA remission or LDA, 6% experienced swollen joints (SJC ≥ 1) and 12% experienced tender joints (TJC ≥ 1) [37]. Another data from a cross-sectional study showed that 11 (10%) patients with PsA fulfilling DAPSA remission had swollen joints and 18 (17%) patients had tender joints [39]. In this study, we found that at least 32.4% of patients with PsA in remission or LDA by any definition had more than one tender joint. In addition, while patient with PsA achieving MDA had no swollen joints, approximately 8.8–19.4% of patients fulfilling the DAPSA and DAS28-CRP remission or LDA had more than one swollen joints. These findings suggest that a significant proportion of patients with PsA in remission or LDA may continue to experience residual joint-related symptoms, which may affect adversely patient's daily activity and increase disease burden.

The fatigue is commonly encountered disabling symptom affecting several aspects of life in patients with inflammatory rheumatic diseases [45]. In updated PsA core set, fatigue was also included as a potential core domain to be assessed mandatory in all PsA clinical studies [10]. Data from large cross-sectional study indicated that moderate to severe fatigue was presented in nearly 28.7–49.5% of patients with PsA [34]. Another study investigating prevalence of fatigue across different patient populations demonstrated that severe fatigue was seen more frequently in patients with PsA (57%) than those with AS (45%), RA (41%), SLE (52%) and OA (35%) [45]. In present study, we demonstrated that 22.2–49.3% of patients with PsA who classified in remission or LDA still suffered from clinically important fatigue. This finding suggested that disease remission or LDA described by several composite measures might not always equate with full fatigue-free state in patients with PsA. Therefore, in these patients ongoing fatigue may seriously effect patient's quality of life and daily activities, even in remission or LDA.

Several studies reported that patients with PsA had a poorer functional impairment compared to healthy controls [33]. Furthermore, burden of disability in patients with PsA was found comparable with patients with RA [46]. More recently in a prospective study including 292 patients with PsA demonstrated that substantial functional disability (HAQ > 0.5) was demonstrated in 7% of patients in MDA and 22% of patients in DAPSA-LDA

[47]. Another study showed that 9.5% of patients with PsA who met MDA criteria had functional impairment [31]. In this study, no patients in MDA had a substantial functional impairment while 2.9–19.4% of patients fulfilling remission or LDA according to the DAPSA and DAS28-CRP experienced residual functional disability. These findings support functional impairment may persist in some of patients with PsA after achieving either DAPSA-LDA or DAS28-CRP LDA.

According to the accumulating data, PsA can also result in significant psychosocial burden in major of patients [35]. Furthermore, updated PsA core domain set by the GRAPPA-OMERACT Working Group has included the emotional well-being as a potential core domain in clinical studies [10]. In patients with PsA, the reported prevalence of psychologic symptoms including depression and anxiety measured by HADS tool, have been reported in 17.6–22.2% for depression and 29.7–36.6% for anxiety [36, 48]. Nevertheless, there is no data whether achieving remission or LDA as treatment goal can reduce psychologic burden in patients with PsA. In this study, we first documented that at least 22.2% of patients with PsA in remission or LDA by any description had higher risk for depression, and at least 11.1% of patients with PsA for anxiety. Assessment of psychologic burden of disease is important in PsA despite in remission or LDA. Since psychologic distress may not only negatively effect on patient's life, but also lead to poor treatment adherence and difficulty in coping with disease burden.

Although this study is not able to clarify why patients with PsA in remission or LDA continue to report residual symptoms or disease burden, it raises several possibilities. One is that current definitions of remission or LDA in PsA may not be stringent enough and ongoing inflammation may lead to residual symptom or untoward patient outcomes. The other is that disease burden associated with functional status, psychologic distress, QoL, or fatigue in remission or LDA may be related to several factors other than disease activity or inflammation including; older age, disease duration, structural joint damage, sleep disturbance, comorbidities, socio-demographic characteristics of patients [49, 50]. Therefore, with taking into account these variables the definition of more comprehensive disease activity measures assessing individual aspect of disease in T2T approach in PsA needs to be further investigation.

A strength of our study is that to investigate residual symptoms or disease burden we examined not only the principle domains of PsA disease but also fatigue, mental health, functional disability and quality of life. Therefore, we provide more detailed information on pattern of residual symptoms in remission or LDA. On the other hand, a major limitation of this study is the cross-sectional design. The residue symptoms and disease burdens of patients were evaluated only in baseline visit.

Present study confirmed that despite in patient with PsA in remission or LDA by various definition, they may have still residual symptoms and/or disease burden in some clinical domains. These finding suggested that there is a significant unmet need with regard to definition of remission or LDA in T2T approach in PsA. In this regard, disease activity measures should not only assess major domain of clinical involvement, but also focus on assessment of unestimated residual symptoms in the several domains of disease. T2T approach also should aim to improvement in patient's overall health.

Author contributions GK is a corresponder author who has made substantial contribution to conception, design, interpretation of data and publication process. She has also participated in the review, drafting, and final approval of the manuscript. EK has made substantial contributions to the design, analysis and interpretation of data. He has drafted the manuscript for important intellectual content and also participated in final approval of the manuscript. KN has made substantial contributions to acquisition of data and drafting the article. He has approved the final version of the manuscript. AK has made substantial contributions to acquisition of data, drafting the article and approved the final version of the manuscript. IT has made substantial contributions to acquisition of data, revised article critically for important intellectual content and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest We have no conflicts of interest with respect to the authorship and/or publication of this article.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All subjects in this study have been informed for the study protocol and written informed consents have been obtained.

References

1. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P (2005) Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 64(suppl 2):14–17. <https://doi.org/10.1136/ard.2004.032482>
2. Nas K, Karkucak M, Durmus B, Karatay S, Capkin E, Kaya A, Ucmak D, Akar ZA, Cevik R, Kilic E, Kilic G, Ozgocmen S (2015) Comorbidities in patients with psoriatic arthritis: a comparison with rheumatoid arthritis and psoriasis. *Int J Rheum Dis* 18:873–879. <https://doi.org/10.1111/1756-185X.12580>
3. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, Kincaid W, Porter D (2004) Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 364:263–269. [https://doi.org/10.1016/S0140-6736\(04\)16676-2](https://doi.org/10.1016/S0140-6736(04)16676-2)
4. Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, Bykerk V, Dougados M, Emery P, Haraoui B, Gomez-Reino J, Kvien TK, Nash P, Navarro-Compan V, Scholte-Voshaar M, van Vollenhoven R, van der Heijde D, Stamm TA (2016) Evidence for treating rheumatoid arthritis

- to target: results of a systematic literature search update. *Ann Rheum Dis* 75:16–22. <https://doi.org/10.1136/annrheumdis-2015-207526>
5. Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, Meads DM, Emery P, Conaghan PG, Helliwell PS (2015) Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* 386:2489–2498. [https://doi.org/10.1016/S0140-6736\(15\)00347-5](https://doi.org/10.1016/S0140-6736(15)00347-5)
 6. Smolen JS, Schols M, Braun J, Dougados M, FitzGerald O, Gladman DD, Kavanaugh A, Landewe R, Mease P, Sieper J, Stamm T, Wit M, Aletaha D, Baraliakos X, Betteridge N, Bosch FVD, Coates LC, Emery P, Gensler LS, Gossec L, Helliwell P, Jongkees M, Kvien TK, Inman RD, McInnes IB, Maccarone M, Machado PM, Molto A, Ogdie A, Poddubnyy D, Ritchlin C, Rudwaleit M, Tanew A, Thio B, Veale D, Vlam K, van der Heijde D (2018) Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis* 77:3–17. <https://doi.org/10.1136/annrheumdis-2017-211734>
 7. Nas K, Kilic E, Cevik R, Bodur H, Ataman S, Ayhan F, Akgul O, Akinci A, Altay Z, Capkin E, Dagli AZ, Duruoz T, Gurer G, Gogus F, Garip Y, Kacar C, Kamanli A, Kaptanoglu E, Kaya T, Kocabas H, Ozdemirel EA, Ozel S, Sezer I, Sunar I, Yilmaz G (2018) Management of psoriatic arthritis: Turkish League Against Rheumatism (TLAR) Expert Opinions. *Arch Rheum* 33:108–127. <https://doi.org/10.5606/ArchRheumatol.2018.6946>
 8. Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, Emery P, Landewe R, Oliver S, Aletaha D, Betteridge N, Braun J, Burmester G, Canete JD, Damjanov N, FitzGerald O, Haglund E, Helliwell P, Kvien TK, Lories R, Luger T, Maccarone M, Marzo-Ortega H, McGonagle D, McInnes IB, Olivieri I, Pavelka K, Schett G, Sieper J, van den Bosch F, Veale DJ, Wollenhaupt J, Zink A, van der Heijde D (2016) European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 75:499–510. <https://doi.org/10.1136/annrheumdis-2015-208337>
 9. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, Bautista-Molano W, Boehncke WH, Campbell W, Cauli A, Espinoza LR, FitzGerald O, Gladman DD, Gottlieb A, Helliwell PS, Husni ME, Love TJ, Lubrano E, McHugh N, Nash P, Ogdie A, Orbai AM, Parkinson A, O'Sullivan D, Rosen CF, Schwartzman S, Siegel EL, Toloza S, Tuong W, Ritchlin CT (2016) Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis. *Arthritis Rheumatol* 68:1060–1071. <https://doi.org/10.1002/art.39573>
 10. Ogdie A, de Wit M, Callis Duffin K, Campbell W, Chau J, Coates LC, Eder L, Elmamoun M, FitzGerald O, Gladman DD, Goel N, James J, Kalyoncu U, Latella J, Lindsay C, Mease PJ, O'Sullivan D, Steinkoenig I, Strand V, Tillett W, Orbai AM (2017) Defining outcome measures for psoriatic arthritis: a report from the GRAPPA-OMERACT Working Group. *J Rheumatol* 44:697–700. <https://doi.org/10.3899/jrheum.170150>
 11. Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, Van Riel PL (2006) Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. *Ann Rheum Dis* 65:1373–1378. <https://doi.org/10.1136/ard.2006.051706>
 12. Gladman DD, Tom BD, Mease PJ, Farewell VT (2010) Informing response criteria for psoriatic arthritis. I: discrimination models based on data from 3 anti-tumor necrosis factor randomized studies. *J Rheumatol* 37:1892–1897. <https://doi.org/10.3899/jrheum.091172>
 13. Eberl G, Studnicka-Benke A, Hitzelhammer H, Gschnait F, Smolen JS (2000) Development of a disease activity index for the assessment of reactive arthritis (DAREA). *Rheumatology* 39:148–155
 14. Coates LC, Helliwell PS (2016) Defining low disease activity states in psoriatic arthritis using novel composite disease instruments. *J Rheumatol* 43:371–375. <https://doi.org/10.3899/jrheum.150826>
 15. Coates LC, Fransen J, Helliwell PS (2010) Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 69:48–53. <https://doi.org/10.1136/ard.2008.102053>
 16. Helliwell PS, FitzGerald O, Fransen J, Gladman DD, Kreuger GG, Callis-Duffin K, McHugh N, Mease PJ, Strand V, Waxman R, Azevedo VF, Beltran Ostos A, Carneiro S, Cauli A, Espinoza LR, Flynn JA, Hassan N, Healy P, Kerzberg EM, Lee YJ, Lubrano E, Marchesoni A, Marzo-Ortega H, Porru G, Moreta EG, Nash P, Raffayova H, Ranza R, Raychaudhuri SP, Roussou E, Scarpa R, Song YW, Soriano ER, Tak PP, Ujfalussy I, de Vlam K, Walsh JA (2013) The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). *Ann Rheum Dis* 72:986–991. <https://doi.org/10.1136/annrheumdis-2012-201341>
 17. Kavanaugh A, van der Heijde D, Beutler A, Gladman D, Mease P, Krueger GG, McInnes IB, Helliwell P, Coates LC, Xu S (2016) Radiographic progression of patients with psoriatic arthritis who achieve minimal disease activity in response to golimumab therapy: results through 5 years of a randomized, placebo-controlled study. *Arthritis Care Res (Hoboken)* 68:267–274. <https://doi.org/10.1002/acr.22576>
 18. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, Group CS (2006) Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 54:2665–2673. <https://doi.org/10.1002/art.21972>
 19. Husted JA, Gladman DD, Farewell VT, Long JA, Cook RJ (1997) Validating the SF-36 health survey questionnaire in patients with psoriatic arthritis. *J Rheumatol* 24:511–517
 20. McKenna SP, Doward LC, Whalley D, Tennant A, Emery P, Veale DJ (2004) Development of the PsAQoL: a quality of life instrument specific to psoriatic arthritis. *Ann Rheum Dis* 63:162–169
 21. Fries JF, Spitz P, Kraines RG, Holman HR (1980) Measurement of patient outcome in arthritis. *Arthritis Rheum* 23:137–145
 22. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. *Acta Psychiatr Scand* 67:361–370
 23. Fredriksson T, Pettersson U (1978) Severe psoriasis—oral therapy with a new retinoid. *Dermatologica* 157:238–244
 24. Coates LC, Helliwell PS (2010) Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. *Arthritis Care Res (Hoboken)* 62:965–969. <https://doi.org/10.1002/acr.20155>
 25. Schoels M, Aletaha D, Funovits J, Kavanaugh A, Baker D, Smolen JS (2010) Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. *Ann Rheum Dis* 69:1441–1447. <https://doi.org/10.1136/ard.2009.122259>
 26. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL (1995) Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 38:44–48
 27. Gladman DD, Mease PJ, Healy P, Helliwell PS, Fitzgerald O, Cauli A, Lubrano E, Krueger GG, van der Heijde D, Veale DJ, Kavanaugh A, Nash P, Ritchlin C, Taylor W, Strand V (2007) Outcome measures in psoriatic arthritis. *J Rheumatol* 34:1159–1166
 28. Schoels MM, Aletaha D, Alasti F, Smolen JS (2016) Disease activity in psoriatic arthritis (PsA): defining remission and

- treatment success using the DAPSA score. *Ann Rheum Dis* 75:811–818. <https://doi.org/10.1136/annrheumdis-2015-207507>
29. Mease PJ, Coates LC (2018) Considerations for the definition of remission criteria in psoriatic arthritis. *Semin Arthritis Rheum* 47:786–796. <https://doi.org/10.1016/j.semarthrit.2017.10.021>
 30. Coates LC, FitzGerald O, Merola JF, Smolen J, van Mens LJJ, Bertheussen H, Boehncke WH, Callis Duffin K, Campbell W, de Wit M, Gladman D, Gottlieb A, James J, Kavanaugh A, Kristensen LE, Kvien TK, Luger T, McHugh N, Mease P, Nash P, Ogdie A, Rosen CF, Strand V, Tillett W, Veale DJ, Helliwell PS (2018) Group for Research and Assessment of Psoriasis and Psoriatic Arthritis/Outcome Measures in Rheumatology consensus-based recommendations and research agenda for use of composite measures and treatment targets in psoriatic arthritis. *Arthritis Rheumatol* 70:345–355. <https://doi.org/10.1002/art.40391>
 31. Desthieux C, Granger B, Balanescu AR, Balint P, Braun J, Canete JD, Heiberg T, Helliwell PS, Kalyoncu U, Kvien TK, Kiltz U, Niedermayer D, Otsa K, Scrivo R, Smolen J, Stamm TA, Veale DJ, de Vlam K, de Wit M, Gossec L (2017) Determinants of patient–physician discordance in global assessment in psoriatic arthritis: a multicenter European Study. *Arthritis Care Res (Hoboken)* 69:1606–1611. <https://doi.org/10.1002/acr.23172>
 32. van Mens LJJ, Turina MC, van de Sande MGH, Nurmohamed MT, van Kuijk AWR, Baeten DLP (2018) Residual disease activity in psoriatic arthritis: discordance between the rheumatologist’s opinion and minimal disease activity measurement. *Rheumatology (Oxford)* 57:283–290. <https://doi.org/10.1093/rheumatology/kex183>
 33. Husted JA, Gladman DD, Farewell VT, Cook RJ (2001) Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. *Arthritis Rheum* 45:151–158. [https://doi.org/10.1002/1529-0131\(200104\)45:2%3C151::AID-ANR168%3E3.0.CO;2-T](https://doi.org/10.1002/1529-0131(200104)45:2%3C151::AID-ANR168%3E3.0.CO;2-T)
 34. Husted JA, Tom BD, Schentag CT, Farewell VT, Gladman DD (2009) Occurrence and correlates of fatigue in psoriatic arthritis. *Ann Rheum Dis* 68:1553–1558. <https://doi.org/10.1136/ard.2008.098202>
 35. Husni ME, Merola JF, Davin S (2017) The psychosocial burden of psoriatic arthritis. *Semin Arthritis Rheum* 47:351–360. <https://doi.org/10.1016/j.semarthrit.2017.05.010>
 36. Freire M, Rodriguez J, Moller I, Valcarcel A, Tornero C, Diaz G, Armendariz Y, Paredes S (2011) Prevalence of symptoms of anxiety and depression in patients with psoriatic arthritis attending rheumatology clinics. *Reumatol Clin* 7:20–26. <https://doi.org/10.1016/j.reuma.2010.03.003>
 37. van Mens LJJ, van de Sande MGH, Fluri IA, Atiqi S, van Kuijk AWR, Baeten DLP (2017) Residual disease activity and treatment adjustments in psoriatic arthritis in current clinical practice. *Arthritis Res Ther* 19:226. <https://doi.org/10.1186/s13075-017-1424-8>
 38. Marin J, Acosta Felquer ML, Ferreyra Garrot L, Ruta S, Rosa J, Soriano ER (2016) Patients with psoriatic arthritis fulfilling the minimal disease activity criteria do not have swollen and tender joints, but have active skin. *J Rheumatol* 43:907–910. <https://doi.org/10.3899/jrheum.151101>
 39. van Mens LJJ, van de Sande MGH, van Kuijk AWR, Baeten D, Coates LC (2018) Ideal target for psoriatic arthritis? Comparison of remission and low disease activity states in a real-life cohort. *Ann Rheum Dis* 77:251–257. <https://doi.org/10.1136/annrheumdis-2017-211998>
 40. Kane D, Stafford L, Bresnihan B, FitzGerald O (2003) A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. *Rheumatology* 42:1460–1468. <https://doi.org/10.1093/rheumatology/keg384>
 41. Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, Birbara C, Thomson GT, Perdok RJ, Medich J, Wong RL, Gladman DD (2009) Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). *Ann Rheum Dis* 68:702–709. <https://doi.org/10.1136/ard.2008.092767>
 42. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, Zrubek J, Mudivarthi S, Mack M, Visvanathan S, Beutler A (2009) Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 60:976–986. <https://doi.org/10.1002/art.24403>
 43. Feletar M, Brockbank JE, Schentag CT, Lapp V, Gladman DD (2004) Treatment of refractory psoriatic arthritis with infliximab: a 12-month observational study of 16 patients. *Ann Rheum Dis* 63:156–161
 44. Haddad A, Thavaneswaran A, Ruiz-Arruzo I, Pellett F, Chandran V, Cook RJ, Gladman DD (2015) Minimal disease activity and anti-tumor necrosis factor therapy in psoriatic arthritis. *Arthritis Care Res (Hoboken)* 67:842–847. <https://doi.org/10.1002/acr.22529>
 45. Overman CL, Kool MB, Da Silva JA, Geenen R (2016) The prevalence of severe fatigue in rheumatic diseases: an international study. *Clin Rheumatol* 35:409–415. <https://doi.org/10.1007/s10067-015-3035-6>
 46. Sokoll KB, Helliwell PS (2001) Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. *J Rheumatol* 28:1842–1846
 47. Wervers K, Vis M, Tchetverikov I, Gerards AH, Kok MR, Appels CWY, van der Graaff WL, van Groenendael J, Korswagen LA, Veris-van Dieren JJ, Hazes JMW, Luime JJ, The behalf of C (2018) Burden of psoriatic arthritis in different definitions of disease activity: comparing minimal disease activity and disease activity index for psoriatic arthritis. *Arthritis Care Res (Hoboken)*. <https://doi.org/10.1002/acr.23571>
 48. McDonough E, Ayearst R, Eder L, Chandran V, Rosen CF, Thavaneswaran A, Gladman DD (2014) Depression and anxiety in psoriatic disease: prevalence and associated factors. *J Rheumatol* 41:887–896. <https://doi.org/10.3899/jrheum.130797>
 49. Kavanaugh A, Fransen J (2006) Defining remission in psoriatic arthritis. *Clin Exp Rheumatol* 24(6 Suppl 43):S–S83
 50. Brikman S, Furer V, Wollman J, Borok S, Matz H, Polachek A, Elalouf O, Sharabi A, Kaufman I, Paran D, Elkayam O (2016) The effect of the presence of fibromyalgia on common clinical disease activity indices in patients with psoriatic arthritis: a cross-sectional study. *J Rheumatol* 43:1749–1754. <https://doi.org/10.3899/jrheum.151491>