Potential difficult-to-treat psoriatic arthritis real-world prevalence and contributing factors

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Abstract

Objective

The challenge of achieving low disease activity or remission in psoriatic arthritis (PsA) is an unmet need for many patients. Persistent disease activity in PsA may require treatment adjustments due to its complex pathogenesis and varied tissue involvement, highlighting the need for dedicated definitions. This study evaluates patients' frequency and contributing factors with potential "difficult-to-treat PsA (D2TPsA)", similar to the EULAR definition of D2T rheumatoid arthritis.

Methods

A retrospective study was conducted at two tertiary centres to define potential D2TPsA, defined as failure of ≥1 conventional synthetic disease-modifying anti-rheumatic drug (DMARD) and ≥2 biological or targeted synthetic DMARDs with different mechanisms of action.

Results

Of the 171 patients included in the study, 116 (67.8%) were women; the average age was 48.16 ±11.23 years. D2TPsA was detected in 33 patients (19.3%). This group exhibited a longer disease duration, higher disease burden (median number of tender and swollen joints, patient and physician global evaluation, morning stiffness, erythrocyte sedimentation rate and C-reactive protein, DAPSA), HLA-B27 positivity, and higher prevalence of peripheral involvement. Secukinumab usage and mean glucocorticosteroid dosage were significantly higher in the D2TPsA group. Comorbidities such as fibromyalgia (FM) and diabetes mellitus (DM) and the median number of comorbidities were significantly higher in D2TPsA. In multivariate analysis, FM, DM, and HLA-B27 positivity were independently associated with D2TPsA.

Conclusion

This study underscores the impact of comorbidities on PsA disease activity and emphasises the need for further research to differentiate treatment challenges influenced by comorbidities from true treatment resistance.

Key words
psoriatic arthritis, difficult-to-treat, biological therapy, comorbidities

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Introduction

Psoriatic arthritis (PsA) is a heterogeneous disease in which some may still be "active" even after controlling for disease activity in one area, leading to a change in treatment strategy. Although the European Alliance of Associations for Rheumatology (EULAR) has recently proposed a definition for difficult-to-treat (D2T) rheumatoid arthritis (RA) (1), a similar definition has not been published for PsA, which has a more heterogeneous phenotype, varied tissue involvement and efficacious biological or targeted synthetic disease-modifying anti-rheumatic drug (b/tsDMARD) options than RA.

The D2T concept was originally developed for RA, which consists of the presence of symptoms and signs despite the failure of at least two with different mechanisms of action (MOA) b/tsDMARDs after failing conventional synthetic DMARD (csDMARD) treatment as well as the management of signs and symptoms perceived as problematic by the rheumatologist and/or the patient (1). While Disease Activity Score 28-joint count erythrocyte sedimentation rate (DAS28ESR) is effective in assessing overall disease activity in RA, PsA relies on Disease Activity Score for Psoriatic Arthritis (DAPSA) (2) or Minimal Disease Activity (MDA) (3) for evaluating treatment response, both recognised and validated surrogate measures. Many disease activity instruments are valid for PsA, and different centers may use different measurement instruments for disease activity. However, it is important to note that limitations exist, particularly in these tools where subjective components may exert influence. MDA, lacking acute-phase reactants and spondylitis activity, is one such measure.

In observational studies, it has been found that approximately 30% of PsA patients cannot reach the target approved by the treat-to-target recommendation (4). Considering the diverse manifestations of PsA across multiple domains and the variability in definitions, axial involvement may be observed in 5–70% of patients (5). Notably, using csDMARDs does not offer additional benefits to individuals with axial participation in axial disease. Consequently, this factor might represent a significant constraint when applying the D2T proposal designed for RA to PsA. Given the absence of csDMARD indications for axial PsA (axPsA), utilising the concept of D2TPsA to define the condition based on unresponsiveness in two or more domains would not be appropriate. Prevalence of D2TPsA varies depending on the cohort and definition of D2T used by the authors of each respective study. The D2T concept has predominantly been formulated in the context of RA (6,7), and its prevalence is higher in PsA (8) compared to previous RA studies (32.6% *vs*. 16.7–23.7%). Therefore, there is a need for a more precise definition of the patient group classified as D2T in PsA. Identifying D2TPsA and determining potential predictive factors may guide which patients may develop this condition and whether these patients should be monitored more frequently.

Comorbidities play a role in D2T disease (9), and real-life data will guide evidence-based decisions and improve patient outcomes. Identifying reliable biomarkers predictive of treatment outcomes remains an active area of research. Although the concept of difficult treatment for RA has been widely studied, this concept has been discussed recently for PsA, and the high rate of patients in this group, despite increasing treatment options, supports the need for real-life data on this subject.

We aimed to evaluate the proportion of D2TPsA patients and possible related factors with the potential D2T disease.

Methods

A retrospective observational study was conducted in two tertiary centers from January 1, 2021, to July 1, 2023. Patients aged 18 years and over diagnosed with PsA according to the Classification for Psoriatic Arthritis (CASPAR) criteria (11) were included. Data presented were restricted to the last follow-up, and inclusion criteria were (1) age >18 years, (2) at least six months of follow-up. Potential D2TPsA was evaluated in patients who still do not achieve DAPSA remission or low disease activity despite receiving ≥1 cs-

DMARD and ≥2 b/tsDMARDs with a different MOA, similar to the EULAR RA definition.

Demographic and clinical characteristics

Patient demographics and disease characteristics, including sex, age, disease duration, level of education, smoking status, alcohol consumption, body mass index (BMI), and pattern of articular manifestations, were evaluated. Patients and their clinical radiological findings were assessed for PsA subtypes, and patients with the dominant subtype were included in that group. Additionally, they were evaluated in two general groups at any time according to axial or peripheral involvement.

Disease activity assessment

Disease activity was recorded based on the patient's values at the last follow-up visit. The clinical assessment encompassed the number of 68 tender joints (TJC) and 66 swollen joints (SJC), enthesitis, and dactylitis. The patient global assessment (PGA), pain assessment on a visual analogue scale (VAS), and the physician's global evaluation (PhGA) of disease activity on a VAS scale were also recorded. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were collected, and DAPSA was used for the activity. Enthesitis was assessed using the Leeds Enthesitis Index (LEI), and dactylitis was recorded as present/absent. Skin assessment was performed using body surface area (BSA). The comorbidities were recorded according to the Charlson Comorbidity Index (CCI); this data was self-reported by the patients or taken from the electronic healthcare record (10). Additionally, they were evaluated for fibromyalgia, thyroid disease, anxiety, and depression.

Radiological evaluation

Two specialist rheumatologists (GA and HC) evaluated radiographs, including pelvis, lumbar anteroposterior, lumbar lateral, cervical lateral, and sacroiliac views. Sacroiliitis, syndesmophytes, ischial enthesitis, and symphysitis were noted. The BASRI hip index was used to define hip joint involvement; index two and above was recorded as hip involvement. Irregular appearance in the region where tendons and ligaments attach to the bone in the pelvic x-ray was evaluated as ischial enthesitis.

Axial structural damage included sacroiliitis, syndesmophytes, ischial enthesitis, symphysitis, or hip joint involvement. Peripheral structural damage occurred when typical joint erosions and/or joint space narrowing were found on plain hand radiographs. Radiological evaluation was performed on patients with a radiograph taken within the last year at their previous visit.

Table I. Comparison of demographic and clinical characteristics of non-D2T and D2T PsA patients.

Variables	Overall n=171	Non-D2T n=138	D2T n=33	*p*-value
Sex, (female), n (%)	116 (67.8)	94 (68.1)	22 (66.7)	0.878
Age, year, mean ± SD	48.16 ± 11.2	48.4 ± 12.4	52.79 ± 12	0.072
Age disease onset, years, mean±SD	42.3 ± 11.9	42.7 ± 12	39.8 ± 11.4	0.955
Current smoking, n (%)	61 (35.7)	46 (33.3)	15 (45.3)	0.192
Alcohol consumption, drinkers n (%)	33 (19.3)	24 (17.4)	9 (27.3)	0.196
Education >8 years, n (%)	55 (49.1)	48 (50.5)	7 (41.2)	0.478
BMI (kg/m^2), mean ± SD	29.2 ± 5	28.9 ± 4.9	30.6 ± 5.1	0.150
PsA disease duration, year, median (IQR)	4 (10)	4 (9)	9.5 (9)	**0.019**
Psoriasis duration, year, median (IQR)	13 (20)	13 (20)	16.5 (14)	**<0.001**
PsA types				
Pure axial involvement, n (%)	22 (12.9)	21 (15.2)	1 (3)	
Polyarticular involvement, n (%)	67 (39.2)	49 (35.5)	18 (54.5)	0.077
Oligoarticular, n (%)	70 (40.9)	56 (40.6)	14 (42.4)	
Distal interphalangeal, n (%)	11 (6.4)	11 (8)	0 (0)	
Arthritis mutilans, n (%)	1 (0.7)	1 (0.6)	0 (0)	
Polyarticular involvement, n (%)	67 (39.2)	49 (35.5)	18 (54.5)	**0.044**
Peripheral involvement ± except pure axial, n (%)	144 (84.2)	112 (81.2)	32 (97)	**0.025**
Axial involvement±other types, n (%)	61 (35.7)	49 (35.5)	12 (36.4)	0.926
Enthesitis, ever, n (%)	78 (45.6)	65 (47.1)	13 (39.4)	0.425
Dactylitis, ever, n (%)	55 (32.2)	8 (24.2)	47 (34.1)	0.278
Nail involvement, ever, n (%)	65 (38)	51 (37)	14 (42.4)	0.565
RF positivity, n (%)	2 (1.2)	1 (0.7)	1 (3)	0.351
Anti-CCP positivity, n (%) n=148	6 (4.1)	5 (4)	1 (4.2)	1
ANA positivity, n (%) n=151	15 (10)	13 (10.6)	2 (7.1)	0.739
HLA-B27 positivity, n (%) n=84	14 (16.7)	8 (11.8)	6 (37.5)	**0.023**

ANA: antinuclear antibody; Anti-CCP: anti-cyclic citrullinated peptide; BMI: Body Mass index; RF: rheumatoid factor; PsA: psoriatic arthritis; HLA-B27: human leukocyte antigen B27; LEI: Leeds Enthesitis Index; SD: standard deviation. n: number of patients.
Bold values are significant at $p<0.05$.

Statistical analysis

PsA patients' characteristics, disease burden, and comorbidities were summarised with descriptive statistics and compared between D2T and non-D2T-PsA patients. Kolmogorov-Smirnov and Shapiro-Wilk normality tests were done to assess the distribution of continuous variables. An independent t-test or one-way analysis (ANOVA) of variance was used for continuous parameters, and the Mann-Whitney U- or Kruskal-Wallis test was used as an alternative. Fisher's exact (in case of expected value <5) or Pearson Chi-Square test was used to compare binary or categorical variables.

Relevant clinical or demographic factors were evaluated with univariate analysis, and those with $p<0.10$ were included in the multiple models in logistic regression. Disease activity variables such as TJC/SJC were not included in the multivariable model because they were high in the D2T group by definition, even though they were significantly high. Multivariate logistic regression was used to evaluate the factors associated with D2TPsA as the dependent variable, disease-related factors at the onset of PsA, and comorbidities independent variables. The statistical significance was considered $p<0.05$ in all results.

Statistical analyses were performed using the Statistical Package for the

Social Sciences software version 26.0 (IBM Corp, Armonk, NY, USA), which is a ready-packaged programme.

Ethical approval

Ethics committee approval for this study was received locally (Kirklareli Educational and Research Hospital, decision date: 01.12.2023, decision number P202300060). The study was conducted following the principles of the Declaration of Helsinki. Since our study was planned retrospectively, approval was obtained from the ethics committee without obtaining informed consent from the patients.

Results

Of the 171 patients included in the study, 116 (67.8%) were women, the mean±SD age was 48.16 ±11.23, the median (IQR) psoriasis duration was 13(20) years, and the PsA disease duration was 4(10) years. The mean BMI is 29.2±5 kg/m^2. Two (1.2%) patients were found to be rheumatoid factor (RF) positive, 6 (4.1%) patients were anti-cyclic citrullinated peptide (anti-CCP) positive, and 15 (10%) patients were antinuclear antibody (ANA) positive. Of the 151 PsA patients who were tested for ANA, 7 of these 15 patients had used SSZ at any time, and 5 of them had used biological treatment. Four patients were using neither TNFi nor SSZ, and no abnormalities were detected in the connective tissue examination of any of them. In addition, the ANA titre was found to be 1(+) in three patients and 3(+++) in one patient. Other demographic data and disease clinical characteristics of the patients are given in Table I.

D2TPsA was detected in 33 (19.3%) patients, and this group had a longer disease duration. Although smoking status and alcohol consumption were higher in the D2T group, the difference was not statistically significant. Sex, age at diagnosis, BMI, marital status, educational levels, RF, anti-CCP, and ANA positivity rates were similar between the groups with and without D2TPsA (Table I). HLA-B27 positivity was higher in D2TPsA.

When PsA subtypes were compared, differences were observed between the polyarticular groups regarding D2T-disease (35.5% *vs*. 54.5%, p=0.044). A significant difference was detected in clinical features regarding peripheral involvement, with a proportion of 97% of the patients in the D2T group *versus* 81.2% in the nonD2T group (p=0.025) (Table I).

In the DT2PsA group, the median values of TJC, SJC, PGA, PhGA, morning stiffness, ESR, CRP, DAPSA, and BSA were higher (Table II).

Hypertension was the main comorbidity (32.7%). Additional comorbidities were obesity (32.1%), diabetes mellitus (DM) (17.5%), anxiety (13.4%), depression (12.2%), fibromyalgia (FM) (12.9%), and thyroid disease (12.9%). Among the comorbidities, FM, DM, and the median number of comorbidities were significantly higher in D2TPsA. In contrast, other comorbidities, such as anxiety or depression, and the number of one or more comorbidities were similar between the groups (Table III).

In comparing tumour necrosis factor inhibitor (TNFi) subgroups between groups, current or previous usage was similar for the two groups. Current secukinumab usage was significantly higher in the D2T group. Although GC usage was higher in this group, it was not statistically significant (p=0.051). However, when GC doses were compared, the mean dosage was significantly higher among patients using the D2T group (p=0.009). Only two patients are receiving ixekizumab, and one is receiving guselkumab, and no comparison was made between groups (Table IV). No difference was detected between the groups regarding peripheral and axial structural damage (Table V). In multivariate analysis, FM, DM, and HLA-B27 positivity were independently associated with potential D2T-PsA (Table VI).

In the D2T PsA group, those with DM exhibit a longer duration of psoriasis. The presence of enthesitis, PGA, and PhGA evaluations is significantly higher in these patients. PsA patients with DM, regardless of whether they

Table II. Comparison of disease activity characteristics of non-D2T and D2T PsA patients.

Variables	Overall n=171	Non-D2T n=138	D2T n=33	*p*-value
TJC (0-68), median (IQR)	1 (4)	0.5 (3)	3.5 (15)	**<0.001**
SJC (0-66), median (IQR)	0 (0)	0 (0)	0 (1)	**<0.001**
PhGA (0-100), median (IQR)	20 (20)	20 (20)	30 (35)	**<0.001**
PGA (0-100), median (IQR)	30 (30)	30 (30)	50 (55)	**<0.001**
Pain VAS (0-100), median (IQR)	30 (58)	30 (58)	50 (58)	**<0.001**
Morning stiffness, min, median (IQR)	0 (30)	0 (19)	22.5 (108)	**<0.001**
ESR, mm/h, median (IQR)	23 (23)	19 (22)	35.3 (21)	**0.001**
CRP, mg/dl, median (IQR)	4.8 (7.9)	3.8 (6.4)	9.4 (7)	**<0.001**
DAPSA, mean ± SD	17.9 (14.4)	11.5 (13.6)	24.6 (21.1)	**<0.001**
BSA, median (IQR)	1 (2)	1 (2)	0 (1)	**0.038**
LEI, median (IQR)	0 (1)	0 (1)	0.5 (2)	0.751

BSA: body surface area; CRP: C-reactive protein; DAPSA, Disease Activity Score for Psoriatic Arthritis; ESR: erythrocyte sedimentation rate; LEI: Leeds Enthesitis Index; TJC: tender joint count; PGA: patient global assessment; PhGA: physician global assessment.
Bold values are significant at p<0.05.

Table III. Comparison of comorbidity of non-D2T and D2T PsA patients.

Variables	Overall n=171	Non-D2T n=138	D2T n=33	*p*-value
Comorbidity present *vs*. absent, n (%)	107 (52.6)	80 (60.9)	23 (69.7)	0.347
Number of comorbidities, median (IQR)	1 (2)	1 (1)	1 (2)	**0.047**
Hypertension, n (%)	56 (32.7)	42 (30.4)	14 (42.4)	0.187
Diabetes mellitus, n (%)	30 (17.5)	16 (11.6)	14 (42.4)	**<0.001**
Thyroid disease, n (%)	22 (12.9)	20 (14.5)	2 (6.1)	0.255
Depression, n (%)	21 (12.2)	17 (12.3)	4 (12.2)	1
Anxiety, n (%)	23 (13.4)	18 (13)	5 (15.1)	0.532
Fibromyalgia, n (%)	22 (12.9)	12 (8.7)	10 (30.3)	**0.001**

n: number of patients. Bold values are significant at p<0.05.

Table IV. Comparison of treatment non-D2T and D2T PsA patients.

Variables	Overall n=171	Non-D2T n=138	D2T n=33	*p*-value
Methotrexate, n (%)	105 (61.8)	83 (60.6)	22 (66.7)	0.519
Methotrexate dosage, mg/week, mean (SD)	16.6 (3.2)	16.2 (2.6)	16.7 (3.9)	0.606
Leflunomide, n (%)	55 (32.2)	43 (31.2)	12 (36.4)	0.565
Leflunomide dosage, mg/day mean (SD)	19.7 (3.4)	18.4	19.5	0.408
Sulfasalazine, n (%)	18 (10.5)	15 (10.9)	3 (9.1)	1
GCs, n (%) n=123	48 (39)	34 (27.6)	14 (56)	0.051
GCs dosage, mg/day, mean ± SD	2.31 (2.2)	1.98 (0.2)	3.14 (0.5)	**0.009**
Biological therapy, n (%)	90 (52.6)	57 (41.3)	33 (100)	**<0.001**
TNFi, n (%)	53 (31)	41 (29.7)	12 (36.4)	0.458
Secukinumab , n (%)	25 (14.6)	10 (7.2)	15 (45.5)	**<0.001**
Ustekinumab, n (%)	2 (1.2)	1 (0.7)	1 (3.2)	NA
Ixekizumab, n (%)	9 (5.3)	6 (3.8)	3 (9.1)	0.368
Guselkumab, n (%)	1 (0.6)	1	0	NA
≥2 biological use, n (%)	65 (38)	32 (23.2)	33 (100)	**<0.001**
≥3 biological use, n (%)	35 (20.5)	16 (11.6)	19 (57.6)	**<0.001**

GCs: glucocorticoids; NA: not applicable; n: number of patients; TNFi: TNF alpha inhibitors. Bold values are significant at $p<0.05$.

Table V. Comparisons of radiographic characteristics of PsA patient group with and without D2T.

Variables	Overall n=171	Non-D2T n=138	D2T n=33	*p*-value
Peripheral structural damage, n (%) n=119	26 (21.8)	22 (22.2)	4 (20)	1
Axial structural damage, n (%), n=104	64 (61.5)	52 (60.5)	12 (66.7)	0.623
Sacroiliitis, n (%) n=79	19 (24.1)	15 (21.7)	4 (40)	0.242
Presence of syndesmophyte, n (%) n:66	30 (45.5)	23 (45.1)	7 (46.7)	0.925
Presence of hip involvement, n (%) n=79	21 (26.9)	18 (29)	3 (18.8)	0.408
İschial enthesitis, n (%) n:79	13 (16.5)	12 (17.9)	1 (8.3)	0.79
Presence of symphysitis, n (%) n=79	6 (7.6)	6 (9)	0	NA

NA: not applicable; n: number of patients.

are D2T, tend to be older and are diagnosed at an older age. Additionally, concomitant hypertension is more frequently detected in patients with diabetes. However, in the non-D2T group, patients with diabetes have higher BMI and ESR (Supplementary Table S1). Radiographic findings reveal that the presence of cervical syndesmophytes is detected more frequently in diabetic patients within the non-D2T PsA group (100% *vs*. 30.4%, $p=0.037$, data not shown). In the D2T FMS group, the TJC is higher, whereas the disease duration is found to be longer in the non-FMS group (Suppl. Table S2).

Discussion

This study reveals that approximately 20% of patients fall into the D2T group, facing greater management challenges due to comorbidities such as DM and FM and more frequent peripheral disease, HLA-B27 positivity, and GC dosage.

Despite significant advancements in understanding the pathogenetic mechanisms of PsA, which have led to a wide array of therapeutic options, the efficacy of the available drugs may still be suboptimal (11). Distinguishing between D2T and treatment-resistant diseases is crucial, especially with the increasing availability of biological treatment options for PsA. Due to the multidomain nature of the disease, higher rates of D2T disease may have been detected, unlike RA studies (12–14), because the response is obtained in one area (*e.g*. joint entheses and spine), at the same time, activity continues in another area (*e.g*. skin and nails).

Furthermore, our research suggests that D2TPsA is associated with a higher prevalence of peripheral involvement. When we retrospectively evaluated our study's peripheral and axial structural damage, we did not detect any differences between patient groups. Although we found similar D2T PsA rate, the D2T disease rate was higher in the HLA-B27-positive patient group. This discrepancy may be explained by the fact that the HLA-B27 rate is less frequent in axPsA than in axial spondyloarthritis (15). Our results contrast with other studies that D2TPsA link it more often to axial involveent, axial and peripheral structural damage at baseline, and more bDMARD discontinuation due to poor dermatological control (8). In multivariate analysis, Philippoteaux *et al*. found that peripheral structural damage at baseline was a predictive factor for D2TPsA. The researchers introduced a more stringent subgroup definition for very early D2TPsA, defined as failure of ≥2 b/ts-DMARDs with less than two years of follow-up, and showed that 11.3% of patients were categorised as very early D2T PsA. Very early D2TPsA patients noted a higher prevalence of obesity and axial involvement in this group compared to the non-D2T group (8).

Table VI. Evaluation of factors associated with D2T PsA in multivariate analysis.

	Univariate analysis				Multivariable analysis			
Variables	OR	%95 CI lower	%95 CI upper	*p*-value	OR	%95 CI lower	%95 CI upper	*p*-value
HLA-B27 positivity	4.500	1.286	15.745	**0.019**	6.297	1.231	32.222	**0.027**
Presence of diabetes mellitus	5.618	2.366	13.343	**<0.001**	12.144	2.271	64.936	**0.004**
Presence of fibromyalgia	4.565	1.766	11.800	**0.002**	14.376	2.995	69.014	**0.001**

CI: confidence interval. OR: odds ratio; HLA-B27: human leukocyte antigen B27. Bold values are significant at $p<0.05$.

The fact that the ANA positivity rate was around 10 % in our study was interpreted as being secondary to the patients' treatments. In the literature, rates of over 132 of 232 (57%) PsA patients have been reported for ANA positivity in biologically naïve PsA patients when a titre of 1:100 is accepted. The ANA measured in our study is from any period and may be related to using bDMARDs or SSZ (16).

We found higher FMS, BSA, PGA, Pain VAS, and GCs dosages in D2TPsA patients. Similar to our results, Perrotta *et al*. evaluated 106 PsA patients, with 33.9% identified as potential D2T PsA patients, finding that D2T patients exhibited higher BMI, FMS, Functional Comorbidity Index, BSA, LEI, pain VAS, Psoriatic Arthritis Impact of Disease score, and Health Assessment Questionnaire Disability Index compared to non-D2T patients (9). In a study conducted by Cincinelli *et al*., a lower rate (2.9%) of D2T cases among 269 PsA patients, with D2T patients presenting higher rates of osteoarthritis, FMS, and GCs therapy. Furthermore, D2T patients showed significantly higher PGA and VAS pain (17). In these studies, the D2TPsA rate may be low, as 88.5% of the patients in this study reached MDA, and the median DAPSA was 4.21.

Another study of 200 patients evaluated retrospectively 15% of D2TPsA cases meet the D2TPsA definition adapted from the EULAR D2TRA criteria, associating D2T disease with resistance to methotrexate and prolonged breaks in treatment (18). However, variations in D2T prevalence across studies raise questions about the heterogeneity of PsA and the impact of different population characteristics.

In our study, current treatment with secukinumab was significantly higher in the D2T group, influenced by the first-line use of TNFi and second-line use of interleukin (IL)-17A inhibitors, IL12-23, anti-IL-23, apremilast aligning with reimbursement rules. JAK inhibitors have been included in the new reimbursement system, and we do not have any patients using them in this retrospective evaluation. However, for a patient to be included in the D2T group, he/she must have used at least two b-DMARDs (which act through different mechanisms). As a result, since the patient's current medication was likely to be secukinumab, it was not included in the regression analysis.

This study suggests that comorbidities such as FMS and DM may contribute to treatment resistance in PsA patients. These comorbidities can complicate the management of PsA and make patients resistant to multiple treatment strategies. In another study conducted on this subject, no significant difference was found in comorbidities such as obesity, smoking status, fibromyalgia, or depression (8). This implies that not all challenges in managing PsA are solely due to resistance to treatment; the nature of the disease may play a significant role.

Comorbidities, such as FMS, can contribute to treatment resistance, complicating management strategies and highlighting the importance of distinguishing between D2T and difficult-to-manage diseases. The term "difficult-to-treat" encompasses diseases that are resistant to treatment and challenging to manage. It is crucial to differentiate between patients with D2TPsA and those with difficult-to-manage disease, as comorbidities, particularly FMS, can blur this distinction. For instance, disease activity parameters such as high scores on the number of tender joints may be attributed to fibromyalgia rather than inflammatory disease activity, indicating unresponsiveness to treatment. Moreover, diabetic patients often report higher patient-physician global assessment values due to increased pain, likely exacerbated by diabetic neuropathy. This heightened pain perception may inflate DAPSA scores, potentially contributing to the higher incidence of patients classified as difficult-to-treat within this group.

A recently published international survey defines D2TPsA as including failure of at least two b/tsDMARD classes. It has been suggested that 'refractory PsA' be defined as 'failure of all available classes of b/tsDMARDs', that failure to achieve ≥1 csDMARDs should also be taken into account, that composite measures should be used, and that low disease activity should be taken as the treatment target. Additionally, consideration of radiographic progression and structural changes, axial disease, functional limitation, comorbidities, and non-musculoskeletal symptoms is emphasised. There is no consensus on D2TPsA or difficult-to-manage PsA (19).

This work has several limitations, including the inherent limitations of retrospective observational studies. The most significant limitation is the absence of baseline patient characteristics, which hinders the evaluation of predictive factors for D2TPsA. Additionally, the limitations of the study include the lack of recorded reasons for discontinuing bDMARDs and the absence of images regarding erosion and radiological damage for all patients. Furthermore, since the disease group with pure axial involvement was not excluded, evaluating the activity of these patients with DAPSA would not be appropriate.

Conclusion

The assessment and management of patients with PsA who need to achieve treatment targets after multiple treatment strategies are complex and include evaluating the potential concepts of D2T PsA and difficult-to-manage PsA. A validated definition of D2TPsA is necessary, and further comprehensive studies are needed to differentiate between patients who struggle to achieve treatment goals due to comorbidities and those who are genuinely refractory to treatment.

Key points

- ***What is already known about this subject?***
  A small number of existing observational cohort studies have shown several potential factors that predict D2TPsA, but these are inconsistent between studies.
- ***What does this study add?***
  FM, DM, and HLA-B27 positivity emerged as independent predictors of D2T PsA in this study.
- ***How might this impact clinical practice?***
  When defining D2T PsA, it will be essential to distinguish between patients who do not respond to treatment due to comorbidities and patients with true refractory disease.

References

1. NAGY G, ROODENRIJS NMT, WELSING PM *et al*.: EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021; 80(1): 31-35. https://doi.org/10.1136/annrheumdis-2020-217344
2. SCHOELS M, ALETAHA D, FUNOVITS J *et al*.: Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. *Ann Rheum Dis* 2010; 69(8): 1441-47. https://doi.org/10.1136/ard.2009.122259
3. COATES LC, FRANSEN J, HELLIWELL PS: Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 2010; 69(1): 48-53. https://doi.org/10.1136/ard.2008.102053
4. GOSSEC L, MCGONAGLE D, KOROTAEVA T *et al*.: Minimal disease activity as a treatment target in psoriatic arthritis: a review of the literature. *J Rheumatol* 2018; 45(1): 6-13. https://doi.org/10.3899/jrheum.170449
5. LUBRANO E, CHAN J, QUEIRO-SILVA R *et al*.: Management of axial disease in patients with psoriatic arthritis: an updated literature review informing the 2021 GRAPPA Treatment Recommendations. *J Rheumatol* 2023; 50(2): 279-84. https://doi.org/10.3899/jrheum.220309
6. HECQUET S, COMBIER A, STEELANDT A *et al*.: Characteristics of patients with difficult-to-treat rheumatoid arthritis in a French single-centre hospital. *Rheumatology* (Oxford) 2023; 62(12): 3866-74. https://doi.org/10.1093/rheumatology/kead143
7. GIOLLO A, ZEN M, LAROSA M *et al*.: Early characterization of difficult-to-treat rheumatoid arthritis by suboptimal initial management: a multicentre cohort study. *Rheumatology* (Oxford) 2023; 62(6): 2083-89. https://doi.org/10.1093/rheumatology/keac563
8. PHILIPPOTEAUX C, MARTY-ANE A, CAILLIAU E *et al*.: Characteristics of difficult-to-treat psoriatic arthritis: a comparative analysis. *Semin Arthritis Rheum* 2023; 63: 152275. https://doi.org/10.1016/j.semarthrit.2023.152275
9. PERROTTA FM, SCRIFFIGNANO S, CICCIA F, LUBRANO E: Clinical characteristics of potential "difficult-to-treat" patients with psoriatic arthritis: a retrospective analysis of a longitudinal cohort. *Rheumatol Ther* 2022; 9(4): 1193-201. https://doi.org/10.1007/s40744-022-00461-w
10. CHARLSON ME, POMPEI P, ALES KL, MACKENZIE CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40(5): 373-83. https://doi.org/10.1016/0021-9681(87)90171-8
11. CIGOLINI C, FATTORINI F, GENTILESCHI S, TERENZI R, CARLI L: Psoriatic arthritis: one year in review 2022. *Clin Exp Rheumatol* 2022; 40(9): 1611-19. https://doi.org/10.55563/clinexprheumatol/x3sfxe
12. NOVELLA-NAVARRO M, RUIZ-ESQUIDE V, TORRES-ORTIZ G *et al*.: A paradigm of difficult-to-treat rheumatoid arthritis: subtypes and early identification. *Clin Exp Rheumatol* 2023; 41(5): 1114-19. https://doi.org/10.55563/clinexprheumatol/7mscci
13. TAKANASHI S, KANEKO Y, TAKEUCHI T: Characteristics of patients with difficult-to-treat rheumatoid arthritis in clinical practice. *Rheumatology* (Oxford) 2021; 60(11): 5247-56. https://doi.org/10.1093/rheumatology/keab209
15. FELD J, CHANDRAN V, HAROON N, INMAN R, GLADMAN D: Axial disease in psoriatic arthritis and ankylosing spondylitis: a critical comparison. *Nat Rev Rheumatol* 2018; 14(6): 363-71. https://doi.org/10.1038/s41584-018-0006-8
16. SILVY F, BERTIN D, BARDIN N *et al*.: Antinuclear antibodies in patients with psoriatic arthritis treated or not with biologics. *PLoS One* 2015; 10(7): e0134218. https://doi.org/10.1371/journal.pone.0134218
17. CINCINELLI G, FERRITO M, PANDOLFI M *et al*.: AB1138 Difficult- to- treat psoriatic arthritis: analysis of a single- center cohort from northern Italy. *Ann Rheum Dis* 2023; 82: 1799-800. https://doi.org/10.1136/annrheumdis-2023-eular.3948
18. SINGLA S, RIBEIRO A, TORGUTALP M, MEASE PJ, PROFT F: Difficult-to-treat psoriatic arthritis (D2T PsA): a scoping literature review informing a GRAPPA research project. *RMD Open* 2024; 10(1): e003809. https://doi.org/10.1136/rmdopen-2023-003809
19. MARZO-ORTEGA H, HARRISON SR, NAGY G *et al*.: Time to address the challenge of difficult to treat psoriatic arthritis: results from an international survey. *Ann Rheum Dis* 2024; 83(3): 403-04. https://doi.org/10.1136/ard-2023-225087