Clinical Characteristics of Potential “Difficult-to-treat” Patients with Psoriatic Arthritis: A Retrospective Analysis of a Longitudinal Cohort

Fabio Massimo Perrotta · Silvia Scriffignano · Francesco Ciccia · Ennio Lubrano

ABSTRACT

Introduction: The EULAR group recently published the definition of difficult-to-treat (D2T) patients for rheumatoid arthritis. However, a similar definition is lacking for patients with psoriatic arthritis (PsA), in which its multi-domain expression may impact the treatment response. The aim of the study was to characterize the potential D2T PsA patients, to assess the risk factors, and to determine the burden of disease.

Methods: Retrospective analysis of a longitudinal cohort of PsA patients attending a tertiary care center. At each visit, the patients underwent a complete physical examination and the clinical/laboratory data were collected. Data on comorbidities with the assessment of different comorbidity indices were also collected. Disease activity was assessed by using the DAPSA score and the MDA. The PsAID and HAQ-DI were also collected. We use the previous identified definition of D2T patients, applied to our PsA group and modified for this study.

Results: A total of 106 patients fulfilled the inclusion criteria and were evaluated. Of these, 36 (33.9%) patients fulfilled the criteria for the potential D2T patients. D2T patients showed a significantly higher BMI and higher prevalence of fibromyalgia. Furthermore, D2T patients showed a significantly higher median Functional Comorbidity Index and a significantly higher BSA, LEI, pain level, PsAID score, and HAQ-DI than non-D2T patients. Potential D2T patients also showed a significant delay in the time from diagnosis to first b/ts DMARDs treatment.

Conclusions: Our study firstly evaluated the presence of clinical characteristics of potential D2T patients and may contribute to future research on this intriguing aspect.

Keywords: Psoriatic arthritis; Treatment; Outcome measures
**Key Summary Points**

Difficult-to-treat (D2T) is a new concept to define patients with persistence of symptoms and/or signs despite failure of multiple drugs.

The EULAR task force recently published the D2T criteria for patients with rheumatoid arthritis, however, a shared definition of D2T patient in PsA is still lacking.

Our study firstly evaluated the presence of clinical characteristics of potential D2T PsA patients by applying modified D2T criteria.

The presence of fibromyalgia, higher BMI, and comorbidities were associated with potential D2T PsA patients.

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**INTRODUCTION**

Psoriatic arthritis (PsA) is a complex and chronic inflammatory disease characterized by an association of psoriasis and arthritis in which different manifestations run together during the disease course [1]. The achievement of the best possible disease control, such as disease remission or low disease activity, has been proposed as treatment targets and may be an achievable goal for PsA patients [2, 3]. However, some recent reports focused attention on the presence of residual disease activity [4], with the possibility of having a patient in remission in one domain (joints), but with active disease in other domains (e.g., skin or enthesis). The complexity of this multidomain disease may also impair the possibility of achieving an overall good control of symptoms, with the need of treatment changes which reduce treatment persistence [5]. In fact, despite significant improvements in the treatment of PsA, some patients may still present a high disease activity and burden of disease, leading to several treatment changes [6, 7].

This clinical scenario could be in keeping with the concept of “difficult to treat” (D2T) PsA. In these patients, a trial-by-error approach is usually implemented, following the published treatment recommendations [8], in the absence of accurate biomarkers.

Recently, the EULAR Task Force has defined the D2T criteria for patients with rheumatoid arthritis (RA) that can be used in clinical practice, clinical trials, and for future research. D2T is defined as patients with persistence of symptoms and/or signs despite failure of at least two biological or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) with different mechanisms of action (full definition in Table 1) [9]. However, a shared definition of D2T patient in PsA, and which factor(s) could contribute to this state, is still lacking. Inflammatory activity in one or more disease domains may persist due to multidrug resistance, clinical or immunologic mechanisms (including anti-drug antibodies), or other factors such as non-adherence. On the other hand, factors such as comorbidity and in particular fibromyalgia, anxiety, and depression may play a role, making a patient resistant to multiple treatment strategies [10–12]. In RA, a recent international survey showed the need for a more holistic approach for the D2T patient [13]. Therefore, the assessment of specific factors contributing to D2T patients in PsA could be of importance in order to evaluate more appropriate therapeutic strategies and an individualized management approach for those patients, which may include pharmacological as well as non-pharmacological therapies [14]. The aim of this study was to characterize potential D2T PsA patients, assess risk factors, and determine disease burden.

**METHODS**

**Study Design and Participants**

We performed a retrospective analysis of a longitudinal cohort of PsA patients fulfilling the CLAssification criteria for Psoriatic ARthritis (CASPAR) criteria [15]. Patients were treated according to the current standard of care and
recruited from our tertiary care center devoted to diagnosis and assessment of spondyloarthritis from January 1, 2018 to January 1, 2021. Data presented were restricted to one single time-point (last follow-up).

Inclusion criteria were (1) age ≥ 18 years, (2) at least 12 months of follow-up (patients had to have been treated for at least 12 months in our center).

To define the potential D2T PsA patients, we used the EULAR criteria and we proposed some changes to better fit PsA patients (Table 1 shows the original definition for RA and changes for PsA) [9]. PsA patients who did not fulfil the D2T definition were used as the control group.

### Table 1 Definition of D2T patients

| EULAR definition of D2T rheumatoid arthritis | Potential definition of D2T psoriatic arthritis |
|---------------------------------------------|-----------------------------------------------|
| 1. Treatment according to European League Against Rheumatism recommendation and failure of ≥ 2 b/tsDMARDs (with different mechanisms of action)\(^a\) after failing csDMARD therapy (unless contraindicated)\(^b\) | 1. Treatment according to European League Against Rheumatism recommendation and/or GRAPPA recommendations and failure of ≥ 2 b/tsDMARDs (with different mechanisms of action)\(^a\) after failing csDMARD therapy (unless contraindicated)\(^b\) |
| 2. Signs suggestive of active/progressive disease, defined as ≥ 1 of: | 2. Signs suggestive of active/progressive disease, defined as ≥ 1 of: |
| a. At least moderate disease activity (according to validated composite measures including joint counts, for example, DAS28-ESR > 3.2 or CDAI > 10) | a. At least moderate disease activity (according to validated composite measures including joint counts, for example, DAPSA > 14 or not achieving the Minimal Disease Activity criteria (MDA)) |
| b. Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other) | b. Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other) |
| c. Inability to taper glucocorticoid treatment (below 7.5 mg/ day prednisone or equivalent) | c. Rapid radiographic progression (with or without signs of active disease)\(^c\) |
| d. Rapid radiographic progression (with or without signs of active disease)\(^c\) | d. Well-controlled disease according to above standards, but still having PsA symptoms that are causing a reduction in quality of life |
| e. Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life | |
| 3. The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient | 3. The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient |

All three criteria need to be present in D2T RA

All three criteria need to be present in D2T PsA

\(^b\) biological, CDAI clinical disease activity index, cs conventional synthetic, DAS28-ESR disease activity score assessing 28 joints using erythrocyte sedimentation rate, DMARD disease-modifying antirheumatic drug, mg milligram, RA rheumatoid arthritis, ts targeted synthetic

\(^a\)Unless restricted by access to treatment due to socioeconomic factors

\(^b\)If csDMARD treatment is contraindicated, failure of ≥ 2 b/tsDMARDs with different mechanisms of action is sufficient

\(^c\)Rapid radiographic progression: change in van der Heijde-modified Sharp score ≥ 5 points at 1 year
Data Collection

A detailed medical history and physical examination were collected for all patients. Demographics and disease characteristics including gender, age, disease duration, level of education, and pattern of articular manifestations were evaluated. Laboratory parameters were also evaluated. Clinical assessment encompassed the number of 68 tender and 66 swollen joints, enthesitis, and dactylitis. Pattern of articular involvement was also collected as well as comorbidities and related manifestations. Enthesitis was assessed by using the Leeds Enthesitis Index (LEI) [16], and dactylitis as present/absent. Skin assessment was performed using body surface area (BSA). The Patient Global Assessment (PtGA), pain assessment on Visual Analogic Scale (VAS), and the physician’s global evaluation of disease activity on a VAS scale were also recorded [17]. Disease status and disease activity were assessed using the Minimal Disease Activity criteria (MDA) [18] and the Disease Activity score for Psoriatic Arthritis (DAPSA) [19]. The Patient Acceptable Symptom State (PASS) was also collected [20]. The Health Assessment Questionnaire Disability Index (HAQ-DI) and the Psoriatic Arthritis Impact of Disease (PsAID) [21] were evaluated as measures of function and quality of life. The Charlson Comorbidity Index (CCI) [22] and the Functional Comorbidity Index (FCI) [23] were also calculated. Presence of fibromyalgia was assessed following the ACR 2010 Fibromyalgia criteria [24]. Information on previous and current use of conventional synthetic, b/ts DMARDs was recorded as well as time from diagnosis to first b/ts DMARDs.

Ethical Approval

The study was approved by the institutional review board of the University of Molise (protocol n. 0001-017-2021) and performed according to the Helsinki Declaration. Written informed consent to use clinical data of all participants was obtained.

Statistical Analysis

Statistical analysis was performed using the “R” package. Normally distributed variables were summarized using the mean ± standard deviation (SD), and non-normally distributed variables by the median and interquartile range (IQR). Potential D2T PsA patients were compared with non-D2T patients with regards to baseline demographics and disease characteristics by descriptive statistics. Mann–Whitney test was performed accordingly. Comparisons between nominal variables were calculated using Chi-square test or Fisher test where appropriate. Two-tailed $p$ values were reported and $p$ values less than 0.05 were considered significant.

RESULTS

Of 174 PsA patients in our database, 106 fulfilled the inclusion criteria and were evaluated. Of these, 36 (33.9%) patients fulfilled the criteria for the potential D2T patients as reported in Table 1. Table 2 compares the baseline patient’s demographics and disease characteristics between potential D2T PsA patients vs. non-D2T patients. D2T patients showed a significantly higher BMI (27.7 vs. 25.7; $p = 0.03$) and higher prevalence of fibromyalgia (22.9 vs. 7.2%; $p = 0.02$). Furthermore, D2T patients showed a significantly higher median FCI than non-D2T patients. More frequently found comorbidities in our cohort were hypertension (18%), dyslipidemia (16.9%), metabolic syndrome (16.9%), diabetes mellitus (15%), cardiovascular diseases (14.1%), osteoarthritis (13.2%), and anxiety/depression (5.6%). Finally, D2T patients showed a significantly higher median FCI than non-D2T patients. More frequently found comorbidities in our cohort were hypertension (18%), dyslipidemia (16.9%), metabolic syndrome (16.9%), diabetes mellitus (15%), cardiovascular diseases (14.1%), osteoarthritis (13.2%), and anxiety/depression (5.6%). Finally, D2T patients showed a significantly higher baseline LEI, pain VAS, BSA, PsAID score, and HAQ-DI than non-D2T patients. No statistically significant differences were found in the other clinical aspect such as disease subset (predominant axial, peripheral or enthesitic), sex, age, and disease duration.

Table 3 shows the previous treatments, failed treatments, and time from diagnosis to first b/ts/DMARDs treatment in potential D2T and non-D2T PsA patients.
Table 2 PsA patients’ characteristics. The patients were stratified in non-D2T and D2T

| PsA patients | Overall, n = 106 | Non-D2T n = 70 (66.1%) | D2T n = 36 (33.9%) | p value |
|--------------|------------------|------------------------|-------------------|---------|
| Demographic, physical characteristics | | | | |
| Sex (male), n (%) | 47/70 (67.1) | 21/36 (58.3) | | 0.370 |
| Age, median (IQR) | 58.5 (46.5–67.7) | 58 (52–67) | | 0.657 |
| Weight (kg), median (IQR) | 73 (65.5–84) | 79 (70–83) | | 0.235 |
| Height (cm), median (IQR) | 1.69 (1.6–1.7) | 1.68 (1.6–1.7) | | 0.298 |
| BMI (kg/h²), median (IQR) | 25.7 (22.8–29.0) | 27.7 (24.5–30.6) | | 0.032 |
| Clinical PsA characteristics | | | | |
| Disease duration (months), median (IQR) | 67 (24–156) | 81 (30–120) | | 0.668 |
| PsA subset | | | | |
| Axial, n (%) | 7/63 (11.1) | 1/34 (2.9) | | 0.163 |
| Monoarticular, n (%) | 5/63 (7.9) | 0/34 (0) | | |
| Oligoarticular, n (%) | 21/63 (33.3) | 11/34 (32.3) | | |
| Polyarticular, n (%) | 21/63 (33.3) | 19/34 (55.8) | | |
| Enthesitis, n (%) | 8/63 (12.7) | 3/34 (8.8) | | |
| Prevalent DIP involvement, n (%) | 1/63 (1.6) | 0/34 (0) | | |
| Axial involvement, n (%) | 7/63 (11.1) | 1/34 (2.9) | | |
| Peripheral involvement, n (%) | 56/63 (88.9) | 33/34 (97.1) | | 0.162 |
| Uveitis present or past, n (%) | 3/69 (4.3) | 2/36 (5.5) | | 0.537 |
| Crohn’s disease, n (%) | 0/69 (0) | 1/36 (2.7) | | 0.342 |
| Ulcerative colitis, n (%) | 0/69 (0) | 0/36 (0) | | 1 |
| Psoriasis at the visit moment, n (%) | 35/65 (53.8) | 27/32 (84.3) | | < 0.001 |
| BSA, median (IQR) | 0.25 (0–1.2) | 1 (1–4.2) | | < 0.01 |
| PASS yes, n (%) | 66/70 (94.2) | 8 (22.2) | | < 0.01 |
| Patient Global Assessment, median (IQR) | 2 (1–5) | 6 (5–8) | | < 0.01 |
| Patient pain on VAS, median (IQR) | 2.5 (1–5) | 7 (5–8) | | < 0.01 |
| Dactylitis, n (%) | | | | |
| Past or present | 18/62 (29) | 11/36 (30.5) | | 0.873 |
| CRP (mg/dl), median (IQR) | 0.2 (0.2–0.4) | 0.2 (0.2–0.6) | | 0.288 |
| DAPSA, median (IQR) | 7.1 (3–12) | 17.2 (12.3–26) | | < 0.01 |

PsA function and impact

△ Adis
Table 2 continued

| PsA patients | Overall, n = 106 |  |  |
|--------------|-----------------|---|---|
|              | Non-D2T n = 70 (66.1%) | D2T n = 36 (33.9%) | p value |
| PsAID, median (IQR) | 1.91 (0.8–4.7) | 5.30 (2.9–8.2) | < 0.001 |
| HAQ-DI, median (IQR) | 0.25 (0–0.6) | 1 (0.5–1.4) | < 0.001 |

Comorbidities indices

| Comorbidities indices |  |  |
|-----------------------|---|---|
| CCI, median (IQR) | 0 (0–0) | 0 (0–1) | 0.179 |
| FCI, median (IQR) | 0 (0–1) | 1 (0–1) | 0.021 |
| CCI ≥ 1, n (%) | 14/96 (20.3) | 11/36 (30.6) | 0.241 |
| FCI ≥ 1, n (%) | 25/69 (36.2) | 21/36 (58.3) | 0.030 |
| Presence of fibromyalgia, n (%) | 5/69 (7.2) | 8/36 (22.9) | 0.022 |

Bold values represent those statistically significant

Table 3 Time from diagnosis to first b/ts/DMARDs treatment in PsA, failed treatments, and previous treatments in our PsA group

| PsA patients | Overall, n 106 |  |  |
|--------------|-----------------|---|---|
|              | Non-D2T n = 70 (66.1%) | D2T n = 36 (33.9%) | p value |
| Time from diagnosis to first b/ts DMARDs; median (IQR); months | 24 (9–52) | 54 (36–68) | < 0.01 |
| Patients who failed b/ts DMARDs treatments, n (%) |  |  |
| ≥ 1 b/ts DMARDs | 30 (42.8) | 36 (100) | < 0.01 |
| ≥ 2 b/ts DMARDs | 6 (8.5) | 36 (100) | < 0.01 |
| ≥ 3 b/ts DMARDs | 3 (4.2) | 24 (66.6) | < 0.01 |
| Previous treatments |  |  |
| csDMARDs, n (%) | 50 (71.4) | 34 (94.4) |  |
| Anti-TNF, n (%) | 30 (42.8) | 30 (83.3) |  |
| Anti-IL12/23, n (%) | 2 (2.8) | 5 (13.8) |  |
| Anti-IL17, n (%) | 14 (20) | 19 (52.7) |  |
| Anti-PDE4 | 4 (5.7) | 6 (16.6) |  |
The number of failed b/tsDMARDs was statistically significantly higher in potential D2T than in non-D2T PsA patients. Following the definition, all D2T patients failed ≥ 2 b/tsDMARDs with different mechanisms of action, while only 8.5% of non-D2T patients failed ≥ 2 b/tsDMARDs. Interestingly, potential D2T patients showed a significant delay in the time from diagnosis to first b/ts DMARDs treatment, suggesting an important role for the early treatment in the management of patients.

DISCUSSION

To our knowledge, this is the first study assessing the clinical characteristics of potential D2T patients in PsA based on the recently established D2T definition published for RA and modified for PsA [11]. Although there is no consensus on the definition of D2T patients in PsA, this study may contribute to this intriguing topic, which is considered an unmet need in clinical practice. For this reason, we applied the EULAR definition of D2T for RA, modified to fit disease characteristics and disease activity of PsA patients, in order to evaluate the possibility of such a proposal. We are aware that demographic, clinical, and disease characteristics are significantly different between the two diseases (in particular the presence of multiple articular and extra-articular manifestations, response to steroids and other treatments and presence of comorbidities), however, we believe that the EULAR definition may be applied even to PsA patients, helping to identify those more difficult to treat.

In our study, multiple factors contributing to potential D2T PsA patients were identified. As expected, the presence of psoriasis, significantly higher scores of BSA, HAQ-DI, PsAID, PtGA and pain, as well as a lower rate of patients in PASS, were found among DT2 patients, suggesting a higher burden of disease. Moreover, other interesting factors were found. Of these factors, the presence of fibromyalgia, higher BMI, and comorbidities were associated with potential D2T PsA patients.

Furthermore, a significant time delay from diagnosis to first b/ts DMARDs treatment, suggesting a key role for the early treatment, possibly in the “window of opportunity” should lead to better outcomes [25].

In a previous study on D2T RA patients, fibromyalgia was also identified as an associated factor [13]. Furthermore, different studies on PsA patients suggest that fibromyalgia and comorbidities may have a significant impact on disease activity, function, and quality of life [26]. Our results are in keeping with these studies.

The clinically most interesting associated factors are both unmodifiable (such as fibromyalgia and to a certain extent, comorbidities) and modifiable (BMI, early treatment). In this light, better attention to those aspects might reduce the possibility for a PsA patient to be D2T. Interestingly, in our study, the clinical subset seems to not be associated with a potential D2T patients.

Our study has some limitations: first, we use a definition for D2T patients borrowed from RA; second, the study design did not allow the assessment of some important aspects such as adherence and patient’s perspective of their treatment. This may, for a certain extent, have an impact on the study results.

CONCLUSION

Although the previous discussed limits, our study firstly evaluated the presence of clinical characteristics of potential D2T patients and may contribute to future research on this intriguing aspect.

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Authorship. All named authors meet the International Committee of Medical Journal
Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Authorship Contributions.** All authors have made substantial contributions to all of these sections: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content and final approval of the version to be submitted.

**Disclosures.** Fabio Massimo Perrotta, Silvia Scriffignano, Francesco Ciccia, and Ennio Lubrano have nothing to disclose.

**Compliance with Ethics Guidelines.** 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 was obtained from all individual participants included in the study. The study was approved by the Institutional Review Board of the University of Molise.

**Data Availability.** The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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