Understanding a clinical case:

Difficult-to-treat Psoriatic arthritis

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Kalamata 2024

Disclosures

None

Outline

- Clinical case
- The D2T concept
- Other studies - Definitions proposed in Bibliography
- Greek study

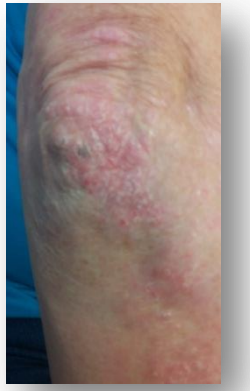
Clinical case

- Male 50 years old
  - Past history: none
  - Family history: none
  - Occupation: teacher
  - Habits: non-smoker
  - BMI: 31

BMI, body mass index

Clinical case

- Clinical
  - 2005: Psoriasis (topical treatment)
    - PASI: 2.8, BSA: 3%
  - 2019: Asymmetric oligoarthritis
    - 4 TJC/2 SJC
  - 2020: Enthesitis
    - LEI: 1
    - Laboratory
      - B-27: positive
      - ESR: 40 mm/h
      - CRP: 0,92 mg/dl



PASI, Psoriasis Area Severity Index; BSA, Body surface area; TJC, Tender joint count; SJC, Swollen joint count; LEI, Leeds enthesitis index; HLA-B27, Human leukocyte antigen B27; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein;

Clinical case

- Treated with
  - Methotrexate (8/2020-12/2020)

    (17.5mg/week)

- No improvement

- Clinical status
  - TJC: 6
  - SJC: 4
  - PASI: 3,8
  - LEI: 1
  - Complaining of low back pain
    - ASDAS: 2,5

TJC, Tender joint count; SJC, Swollen joint count; PASI, Psoriasis Area and Severity Index; LEI Leeds enthesitis index,

Clinical case

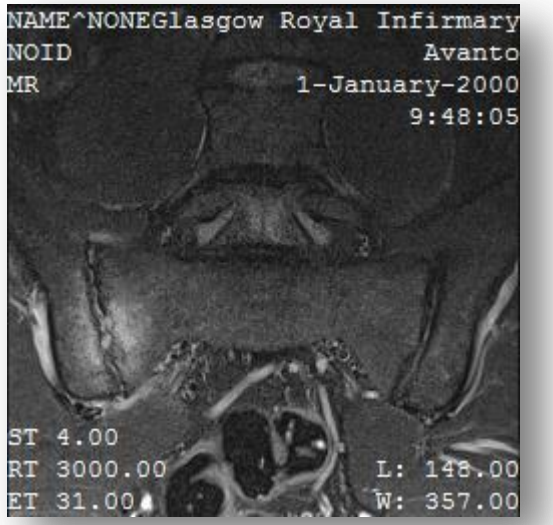
- Adalimumab (1/2021- 4/2021)
  - primary non-response
- 5/2021: Started on IL-17 inhibitor (Secukinumab)
  - He was doing well for 2 year until…

- In 6/2023
- Arthritis flare (DAPSA:16)
  - BSA 4%
  - Low back pain

DAPSA, Disease activity in Psoriatic arthritis; BSA, Body surface area

Clinical case

- **Low back pain**
  - On/off over the last two years
    - More intense in the last 3 months
    - Inflammatory back pain…



Clinical case

- Patient developed IBD (ulcerative colitis)

- Switched to tofacitinib (JAK-inhibitor)
  - Approved dose for ulcerative colitis

Response

IBD, Inflammatory bowel disease; JAK, Janus-kinase;

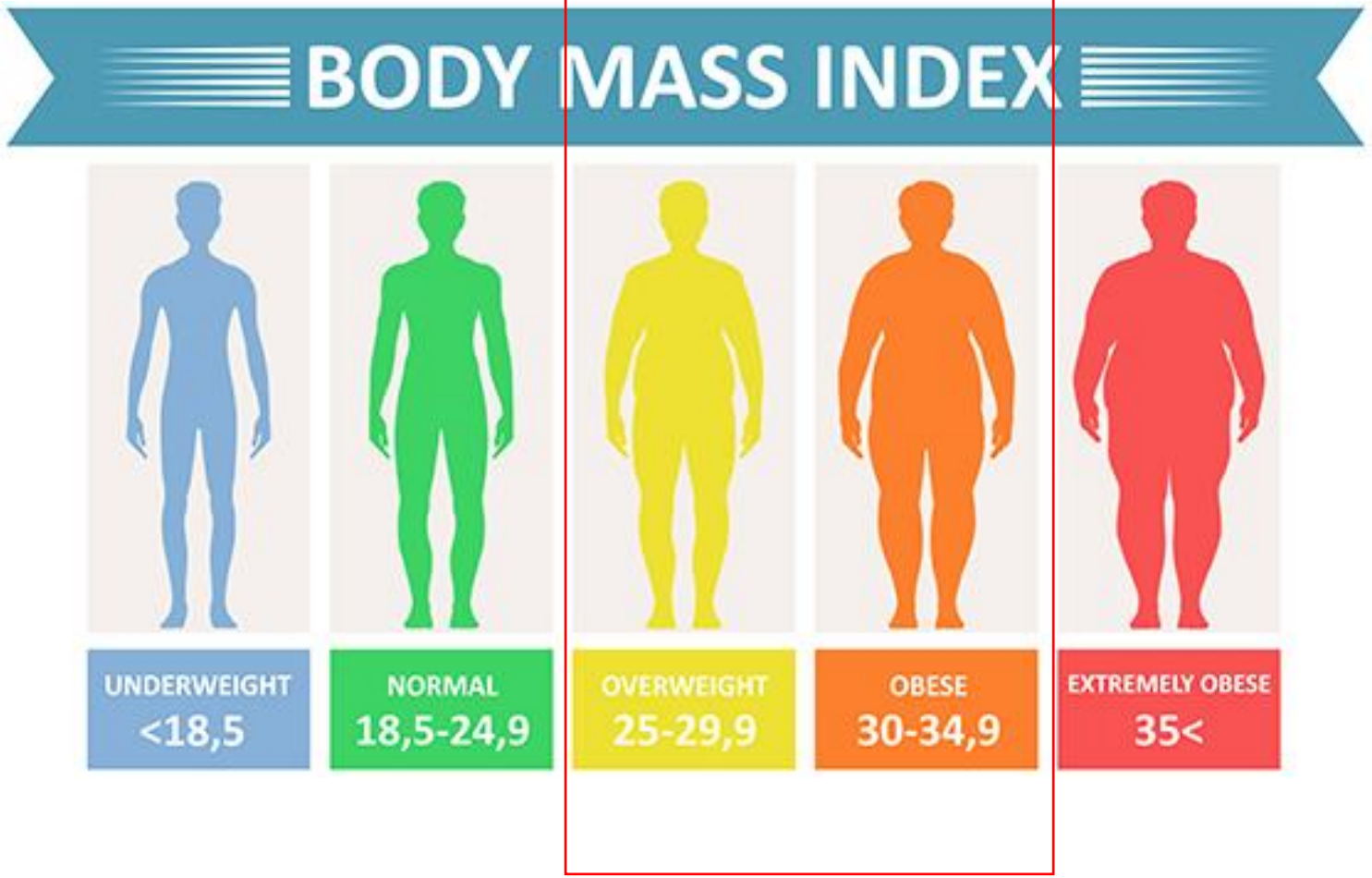
Clinical case – The aftermath

Patient received

- 1 conventional DMARD
  - Methotrexate
- 3 biological DMARDs with different mechanism of action
  - Adalimumab (TNFi)
  - Secukinumab (anti-IL-17 inhibitor)
  - Tofacitinib (JAK-inhibitor)

DMARD(s), Disease modifying anti-rheumatic drug(s); TNFi, Tumor necrosis factor inhibitor; JAK, Janus-kinase

Obesity
Definitions



PsA
Data from Greece

MEDITERRANEAN JOURNAL OF RHEUMATOLOGY | 34 4 2023

ORIGINAL PAPER

Disease Profile and Achievement of Therapeutic Goals in a Modern, Nationwide Cohort of 923 Patients with Psoriatic Arthritis

George E. Fragoulis[1]*, Charalampos Papagoras[2]*, Sousana Gazi[3], Evangelia Mole[3], Michael Krikelis[3], Paraskevi V. Voulgari[4], Evripidis Kaltsonoudis[4], Nikolaos Koletsos[4], Pelagia Katsimpri[5], Dimitrios Boumpas[5], Dimitrios Katsifis[5], Nikolaos Kougkas[6], Theodoros Dimitroulas[6], Petros P. Sfikakis[1], Maria G. Tektonidou[1], Chrysoula Gialouri[1], Dimitrios P. Bogdanos[7], Theodora Simopoulou[7], Christos Koutsianas[8], Eugenia Mavrea[8], Gkikas Katsifis[9], Konstantinos Kottas[9], Maria Konsta[10], Matthoula Tziafalia[10], Evangelia Kataxaki[11], Eleni Kalavri[12], Kalliopi Klavdianou[12], Eleftheria P. Grika[13], Charalampos Sfontouris[13], Dimitrios Daoussis[14], George Iliopoulos[14], Ilias Bournazos[15], Dimitrios Karokis[15], Konstantinos Georganas[15], Dimos Patrikos[15], Dimitrios Vassilopoulos[8]

PsA
Data from Greece

- 923 patients (55% females)
  - median (IQR) age of 57 (48-65) years

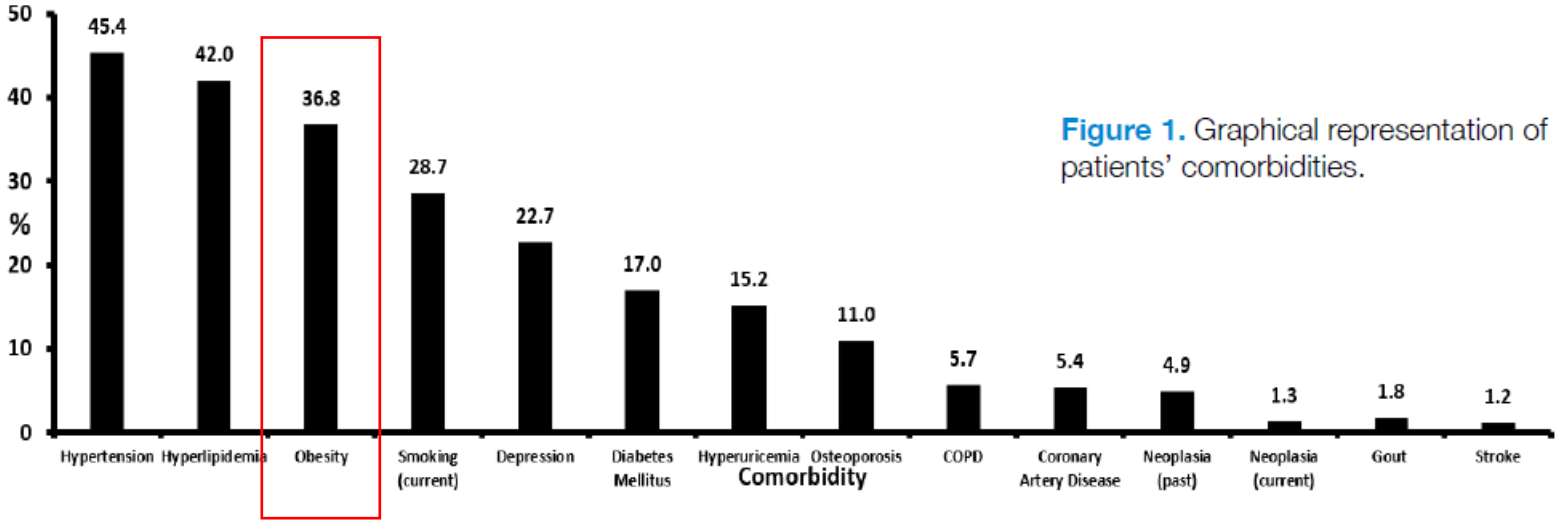


Figure 1. Graphical representation of patients' comorbidities.

Adipose tissue
An inflammatory tissue

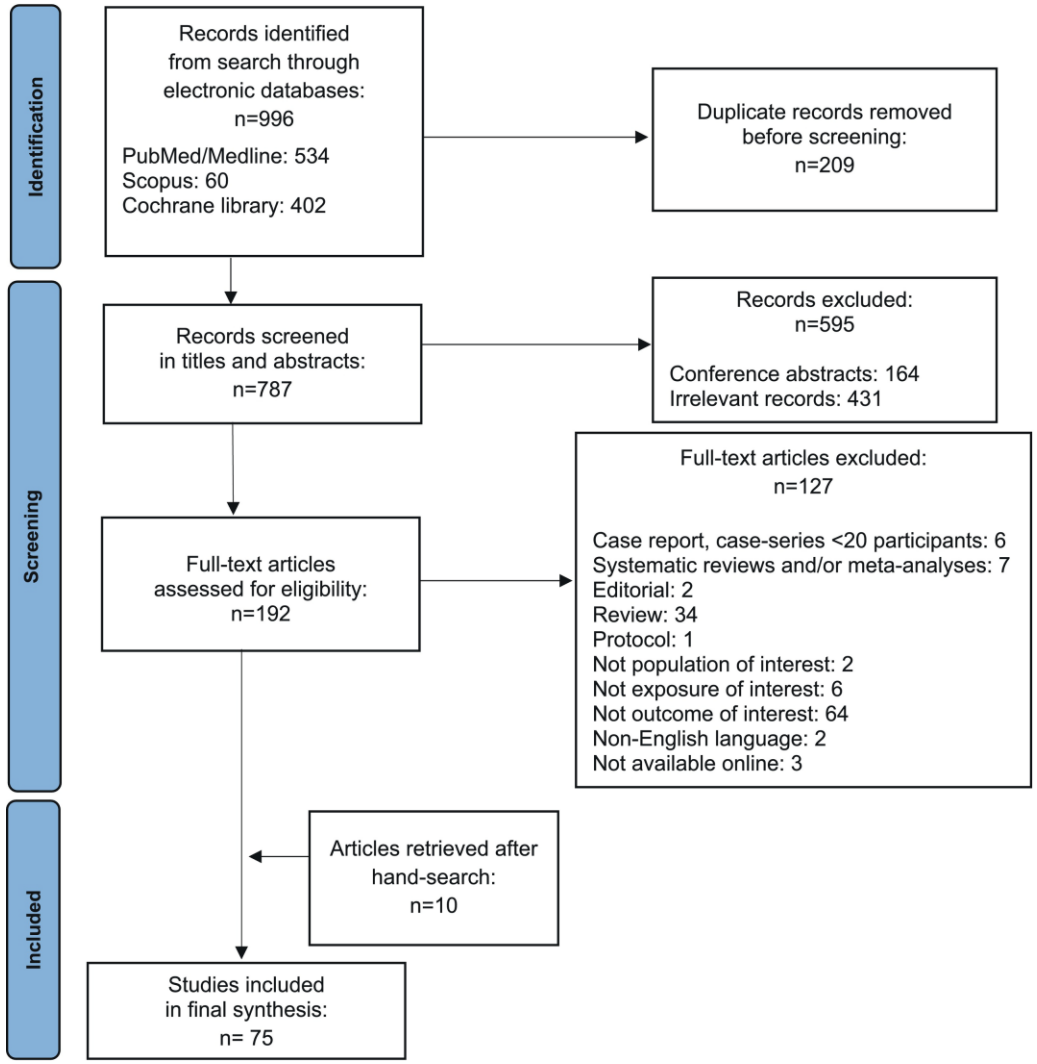
- Adipose tissue
  - Adipocytes + Immune cells (B cells, T cells, Macrophages etc)
    - Lean state: homeostatic role
    - Obesity: Other cells (e.g Th17) take over
      - ✓ Producing inflammatory cytokines (e.g IL-17, TNF etc)
      - ✓ Macrophages are polarized towards M1 (more inflammatory..)
      - ✓ Alterations in adipokines

Versini et al Autoimm Rev 2014

PsA
Obesity – 3 problems…

- ⇧ BMI
  - ⇧ risk of PsA Development in patients with Psoriasis or in healthy individuals
  - ⇧ risk of not reaching outcomes
  - ⇧ risk of not maintaining favorable outcomes

Effect of BMI in treatment efficacy b-ts-DMARDs



- Effect more pronounced for TNFi across IA
- IL 17i and IL-23i: less affected

Drug category	RA	PsA	SpA
Abatacept			
JAK inhibitors			
IL-17 inhibitors			
IL-23 inhibitors			
IL-6R inhibitors			
Rituximab			
TNF inhibitors			

Fragoulis G et al Ther Adv M. Dis 2018
DiMinno et al Arthr Care & Res 2013

PsA

IBD Treatment

Approved Drugs	
Ulcerative colitis	**Crohn's Disease**
TNFi	
Infliximab	Infliximab
Adalimumab	Adalimumab
Golimumab	Certolizumab
IL-23i	
Ustekinumab	Ustekinumab
Risankizumab (pre-reg)	Risankizumab
Guselkumab (pre-reg)	
JAKi	
Upadacitinib	Upadacitinib
Tofacitinib	

Whitlock SM et al J Am Acad Derm 2018
Feagan BG et al Lancet 2017

Is that a case of Difficult-to-treat Psoriatic arthritis?

The D2T concept – Is there a standard definition?

- No official definition suggested by EULAR
- EULAR survey: D2T status should be defined as failure of at least 2 bDMARDs with different mechanism of action (1)
- GRAPPA Scope literature review: differences in how D2T is defined and used in literature (2)

(1) Marzo-Ortega H. et al.. Ann Rheum Dis. 2023

(2) Singla S et al. RMD Open. 2024

Studies up to May 2024

- What studies are we aware of?
  - Philippoteaux et al (Seminars in Arthr & Rheum 2023), (France)
  - Perrotta et al (Rheumatol Ther 2022), (Italy)
  - Vassilakis et al (Rheumatology Oxford 2024), (Greece)

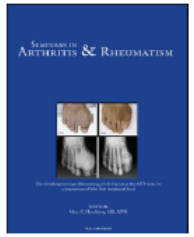
Other studies – French study (1)

Seminars in Arthritis and Rheumatism 63 (2023) 152275

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit



Characteristics Of Difficult-To-Treat Psoriatic Arthritis: A Comparative Analysis☆

Cécile Philippoteaux [a,*], Anne Marty-Ane [a], Emeline Cailliau [b], Julien Labreuche [b], Peggy Philippe [a], Bernard Cortet [a], Julien Paccou [a], Rene-Marc Flipo [a], Jean-Guillaume Letarouilly [c]

[a] *Rheumatology Department, Lille University Hospital, Lille, France*
[b] *Biostatistics Department, Lille University Hospital, Lille, France*
[c] *Rheumatology Department, Lille University, Lille University Hospital, FHU PRECISE, Lille, France*

Other studies – French study (2)

Proposed definition of D2T PsA

- D2T PsA: failure of at least 2 b/tsDMARDs with different mechanism of action

- Very D2T PsA: failure of at least 2 b/tsDMARDs in less than 2 years of follow-up.
- 150 PsA patients were included

    49 D2T PsA and 101 non-D2T PsA

Philippoteaux C et al. Semin Arthritis Rheum. 2023.

Other studies – French study (3)

Results

- D2T patients: higher prevalence of **axial involvement** (p=0.030), **axial and/or peripheral structural damage** (p=0.007) at baseline and more bDMARDs discontinuation due to poor dermatological control (p=0.005).

peripheral structural damage at baseline: predictive factor for D2T PsA [OR: 2.57 (1.16 to 5.69; p=0.020)].

- 17 PsA (11.3%) patients were categorized as Very D2T PsA. When compared to non-D2T group, proportion of obesity was higher (p=0.015) and axial involvement was more common in the Very D2T group (p=0.020).

Philippoteaux C et al. Semin Arthritis Rheum. 2023.

Other studies – Italian study (1)

Rheumatol Ther (2022) 9:1193–1201
https://doi.org/10.1007/s40744-022-00461-w

BRIEF REPORT

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

Other studies – Italian study (2)

Proposed definition of D2T PsA

- D2T status: failure of at least 2 b/tsDMARDs (with different mechanisms of action) after failing csDMARD therapy (unless contraindicated)
- 106 PsA patients were included

    36 D2T PsA and 70 non-D2T PsA

Perrotta FM et al.. Rheumatol Ther. 2022.

Other studies – Italian study (3)

Results

- D2T patients: 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 Functional Comorbidity Index and a significantly higher BSA, LEI, pain level, PsAID score, and HAQ-DI than non-D2T patients.

Perrotta FM et al.. Rheumatol Ther. 2022

Greek study

> Rheumatology (Oxford). 2024 May 17:keae263. doi: 10.1093/rheumatology/keae263.
Online ahead of print.

Identification and characteristics of patients with potential difficult-to-treat Psoriatic Arthritis: exploratory analyses of the Greek PsA registry

Konstantinos D Vassilakis [1], Charalampos Papagoras [2], Nikolaos Fytanidis [2], Sousana Gazi [3], Evangelia Mole [3], Michael Krikelis [3], Paraskevi V Voulgari [4], Evripidis Kaltsonoudis [4], Nikolaos Koletsos [4], Dimitrios Boumpas [5], Pelagia Katsimpri [5], Dimitrios Katsifis-Nezis [5], Theodoros Dimitroulas [6], Nikolaos Kougkas [6], Maria Boutel [6], Petros P Sfikakis [1], Maria G Tektonidou [1], Chrysoula Gialouri [1], Dimitrios Bogdanos [7], Theodora Simopoulou [7], Christos Koutsianas [8], Evgenia Mavrea [8], Gkikas Katsifis [9], Konstantinos Kottas [9], Maria Konsta [10], Matthoula Tziafalia [10], Evangelia Kataxaki [11], Eleni Kalavri [12], Kalliopi Klavdianou [12], Eleftheria P Grika [13], Charalampos Sfontouris [13], Dimitrios Daoussis [14], George Iliopoulos [14], Ilias Bournazos [15], Dimitrios Karokis [15], Konstantinos Georganas [15], Dimos Patrikos [15], Dimitrios Vassilopoulos [8], George E Fragoulis [1]

Affiliations + expand

PMID: 38759119 DOI: 10.1093/rheumatology/keae263

Vassilakis KD et al. Rheumatology (Oxford) 2024

Our analysis– Methods (1)

- Data were retrieved from the multicentre registry of patients with PsA that is ongoing in Greece, under the auspices of the Greek Rheumatology Society

- Cross-sectional analysis of patients who had their visit to participating rheumatology clinics/practices in Greece between 1/1/2022 and 31/12/2022.

Fragoulis et al. MJR 2023
Vassilakis KD et al. Rheumatology (Oxford) 2024

Our analysis – Methods (2)

Our D2T PsA definition:

1. **At least 6 months of follow-up**
2. **Failure of at least 1 csDMARDs (unless contraindicated) and**
3. **Failure of at least 2 bDMARDs/tsDMARDs (except from apremilast) with a different mechanism of action and**
4. **Patients had either at least moderate disease activity (MODA -defined as DAPSA>14) and/or were not in MDA (main definition).**

- For this analysis, the following patients were excluded: patients whose disease activity by DAPSA was < 14 and MDA was not available or patients that were in MDA, but DAPSA was not available.

Our analysis – Methods (3)

Sensitivity analyses:

- MODA definition - irrespective of MDA status

  Failure of at least 1 csDMARDs (unless contraindicated) and 2 bDMARDs/tsDMARDs as above and had DAPSA>14

- MDA definition - irrespective of DAPSA value

  Failure of at least 1 csDMARDs (unless contraindicated) and 2 different b/tsDMARDs as above and not be in MDA

Our analysis – Methods (4)

Main definition	a. failure to at least 1 csDMARDs^ and at least 2 bDMARDs/tsDMARDs* with a different mechanism of action AND b. having at least moderate disease activity (MODA -defined as DAPSA>14), and/or not being MDA
Alternate definition #1 (MODA definition1)	a. failure to at least 1 csDMARDs^ and at least 2 bDMARDs/tsDMARDs* with a different mechanism of action AND b. DAPSA>14,
Alternate definition #2 (MDA definition2)	a. failure to at least 1 csDMARDs^ and at least 2 different b/tsDMARDs* with a different mechanism of action. AND b. Not being in MDA

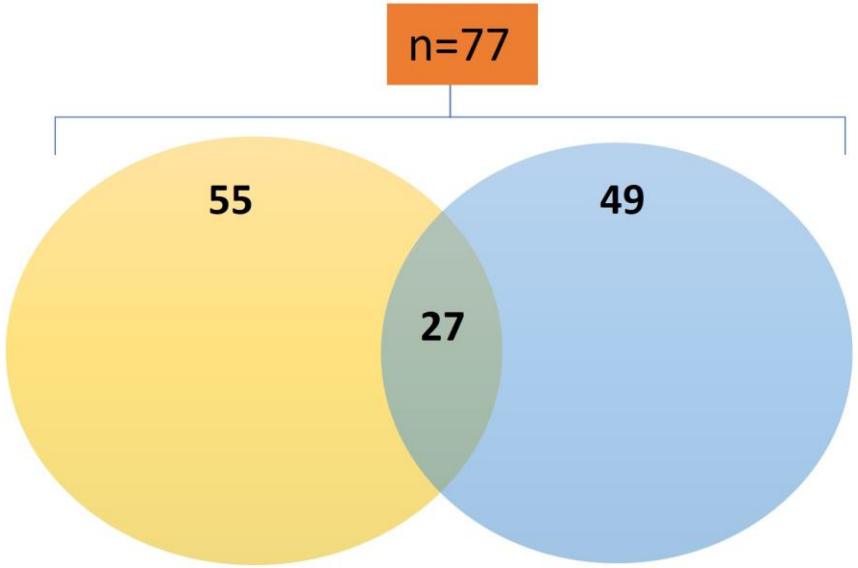
Table-1: Definitions for potential D2T PsA patients, used in this study. In all definitions, patients need to have at least 6 months of disease duration.

1. irrespective of MDA status, 2. irrespective of DAPSA value, * except from apremilast, ^unless contraindicated

bDMARD: biologic DMARD, csDMARD: conventional synthetic DMARD, DAPSA: disease activity Psoriatic Arthritis, MDA: minimal disease activity, MODA: moderate disease activity, tsDMARDs: targeted synthetic DMARD

Vassilakis KD et al. Rheumatology (Oxford) 2024

Our analysis – Understanding the sample



Number of D2T patients not being in MDA OR having DAPSA> 14

Number of D2T patients not being in MDA AND having DAPSA> 14

Number of D2T patients with DAPSA> 14

Number of D2T patients not being in MDA

Vassilakis KD et al. Rheumatology (Oxford) 2024

Our analysis – Results (’’Main definition’’)

Among 738 patients in the registry, 467 patients were included in the main definition analysis.

77 (16.5%) D2T and 390 (83.5%) non-D2T

D2T patients, compared to the non-D2T group, were more likely to have:

- **extensive psoriasis**, defined as BSA>3% (OR: 5.05, 95% CI: 2.22-11.47, p<0.0001).
- a greater **BMI** (OR: 1.07, 95% CI: 1.01-1.13, p=0.023) and
- **IBD ever** (OR: 1.22, 95% CI: 1.25-31.06, p=0.026).

Vassilakis KD et al. Rheumatology (Oxford) 2024

Our analysis – Results (MODA definition)

Among 738 patients in the registry, 728 patients were included in the MODA definition analysis.

55 (7.55%) D2T and 673 (92.45%) non-D2T

D2T patients, compared to the non-D2T group, were more likely to :

- have **extensive psoriasis**, defined as BSA>3% (OR: 4.89, 95% CI: 1.89=12.64, p=0.001)
- be of **female gender** (OR: 3.03, 95% CI: 1.08-8.47, $p=0.034$)

Vassilakis KD et al. Rheumatology (Oxford) 2024

Our analysis – Results (MDA definition)

Among 738 patients in the registry, 393 patients were included in the MDA definition analysis.

49 (12.47%) D2T and 344 (87.53%) non-D2T

D2T patients, compared to the non-D2T group, were more likely to have:

- **extensive psoriasis**, defined as BSA>3% (OR: 3.28, 95% CI: 1,36-7,90, p=0.008) at diagnosis
- **axial disease ever** (OR: 2.23, 95% CI: 1.04-4.77, p=0.040)

Vassilakis KD et al. Rheumatology (Oxford) 2024

Discussion– Psoriasis (1)

- More extensive psoriasis in patients with D2T PsA (main, MODA, MDA analyses) (1)
- In agreement with Italian study; higher BSA score (2)
- French study: discontinuation due to poor dermatological response in D2T group (3)

(1) Vassilakis KD et al. Rheumatology (Oxford) 2024
(2)Perrotta FM et al.. Rheumatol Ther. 2022
(3) Philippoteaux C et al. Semin Arthritis Rheum. 2023.

Discussion – BMI and IBD (2)

- Higher BMI in individuals with D2T PsA
- Similar findings about BMI in Italian Study (1)

- IBD more common in D2T PsA
- confidence intervals were quite large owing to the low number of cases - not unexpected since the frequency of IBD is <5% in the setting of PsA (2)

(1) Vassilakis KD et al. Rheumatology (Oxford) 2024
(2)Perrotta FM et al.. Rheumatol Ther. 2022
(3) Fragoulis GE, et al.. Mediterr J Rheumatol. 2023

Discussion – Sensitivity analyses (3)

- D2T PsA patients more commonly females (MODA sensitivity analysis) (1)
- In agreement with systematic review: female patients display a higher disease burden and worse treatment outcomes compared to males with PsA (2)

- Axial disease ever more common in D2T group (MDA sensitivity analysis) (1)
- Axial disease at baseline was also found more frequently in D2T patients, in the French study (3)

(1) Vassilakis KD et al. Rheumatology (Oxford) 2024
(2) Coates L, Gossec L.. Joint Bone Spine [Internet]. 2023
(3) Perrotta FM et al.. Rheumatol Ther. 2022

Discussion - Depression vs Fibromyalgia (4)

- Occurrence of depression higher in D2T group in univariate analysis (but not in multivariate)
- Common comorbidity in the setting of PsA, about 20% (1-2)
- Italian study (9) which found fibromyalgia to be more common in D2T patients (3)
- it is sometimes difficult to distinguish depression from fibromyalgia (4)

(1)Zhao SS et alClin Rheumatol. 2019
(2) Fragoulis GE et al. Ther Adv Musculoskelet Dis. 2020.
(3) Perrotta FM et al.. Rheumatol Ther. 2022
(4) Zhao SS et al.. Clin Rheumatol. 2019.

Discussion - Limitations (5)

- Definitions for D2T PsA are lacking
  - Might explain the discrepancies between studies
- Comorbidities, like depression, are reported based on treatment received
  - cannot be excluded that fibromyalgia, could be the culprit
- No data about whether bDMARDs/tsDMARDs were co-administered with csDMARDs
- No data about HAQ
- D2T PsA is a dynamic state

Discussion – Strengths and Conclusion (6)

- The largest study in the field
- One definition and two alternatives suggested
- D2T PsA is not uncommon in real life settings and that certain patient (female gender, obesity) and disease (extensive skin disease, axial involvement, history of IBD) characteristics were associated with its occurrence.
- These findings could be helpful in the ongoing effort for better defining D2T PsA and more importantly for designing management strategies to decrease its incidence.

Thank you for your attention