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Objective: To explore the registration of enthesitis among biologic-naïve patients with psoriatic arthritis (PsA) initiating tumour necrosis factor inhibitor (TNFi) treatment across 12 European registries, compare the disease burden and patient-reported outcomes (PROs) between patients with and without enthesitis, and assess the enthesitis treatment response.

Method: Demographics, clinical characteristics, and PROs at first TNFi (TNFi-1) initiation (baseline) were assessed in patients with PsA, diagnosed by a rheumatologist, with versus without assessment of entheses and between those with versus without enthesitis. Enthesitis scores and resolution frequency were identified at follow-up.

Results: Of 10 547 patients in the European Spondyloarthritis (EuroSpA) Research Collaboration Network initiating TNFi, 1357 underwent evaluation for enthesitis. Eight registries included a validated scoring system for enthesitis. At baseline, 874 patients underwent entheses assessment [Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) 485 patients, Spondyloarthritis Research Consortium of Canada (SPARCC) 389 patients]. Enthesitis was detected by MASES in 170/485 (35%, mean score ± sd 3.1 ± 2.4) and by SPARCC in 236/389 (61%, 4 ± 3.4). Achilles enthesitis was most frequent, by both MASES (unilateral/bilateral 28%/9%) and SPARCC (48%/18%). MASES/SPARCC baseline and follow-up scores for TNFi-1 were available for 100/105 patients. Of these, 63 patients (63%)

(MASES) and 46 (43.8%) (SPARCC) achieved resolution of enthesitis. The site-specific enthesitis resolution was overall lower at SPARCC sites (peripheral; 63–80%) than at MASES sites (mainly axial; 82–100%) following TNFi-1. Disease activity and PROs were worse in patients with versus without enthesitis.

Conclusion: Entheseal assessments are only registered in a minority of patients with PsA in routine care. When assessed, enthesitis was common, and a substantial proportion demonstrated resolution following treatment with TNFi-1.

Psoriatic arthritis (PsA), diagnosed in 20–40% of patients with psoriasis, is a chronic, inflammatory disease that is phenotypically diverse, involving peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail disease (1–4). Inflammation at and immediately around the site of attachment of tendons, ligaments, or joint capsules to bones is termed enthesitis, a common clinical feature in patients with PsA that may be observed at any time during the disease course (5, 6). Depending on the cohort and outcome measurement instrument used, the prevalence of enthesitis in patients with PsA varies widely, between 27% and 66% (7–10). The presence of enthesitis in patients with PsA is associated with higher disease activity and often worse patient-reported outcomes (PROs) (9–11). The Outcome Measures in Rheumatology (OMERACT) has endorsed the assessment of enthesitis as one of the core domains in all clinical trials and longitudinal observational studies involving patients with PsA (12).

Clinical assessment of enthesitis is performed by eliciting tenderness at the peripheral and axial entheses, and validated enthesitis scoring systems addressing pre-defined anatomical areas of entheses have been developed. These include the Spondyloarthritis Research Consortium of Canada (SPARCC) and the Leeds Enthesitis Index (LEI), assessing the peripheral entheses, and the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), predominantly assessing the axial entheses (13, 14).

Notwithstanding the clinical significance of enthesitis, systematic assessment of entheses is frequently not performed in routine care and data on the burden of enthesitis among patients of PsA from routine clinical care are sparse (8–10). Furthermore, although most biological disease-modifying anti-rheumatic drugs (bDMARDs) demonstrate efficacy across the clinical domains in randomized clinical trials among patients with PsA (15–17), there is a paucity of real-world data on the effectiveness of bDMARDs on enthesitis (18, 19).

The European Spondyloarthritis (EuroSpA) Research Collaboration Network (RCN), a network of registries across Europe including patients with PsA, is a potential source of real-world data regarding enthesitis (20, 21). However, the registration practice and data availability on enthesitis have not been studied previously. Thus, we aimed to: (i) explore the registration practice and data availability of enthesitis in patients with PsA in routine care; (ii) describe the pattern (distribution of affected entheses) of enthesitis in these patients; (iii) assess the disease burden and PROs in patients with versus without enthesitis at initiation of the first tumour necrosis factor inhibitor (TNFi); and (iv) assess the change in enthesitis from baseline to follow-up after initiation of the first and second TNFi.

Method

Patients and study design

Prospectively collected data on patients with PsA included in registries participating in the EuroSpA RCN were analysed (20, 21). Biologic-naïve, adult patients with a clinical diagnosis of PsA, aged ≥ 18 years at initial diagnosis, who initiated a TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab) between 2010 and 2020, were identified from the following clinical registries (countries): AmSpA (Netherlands), ATTRA (Czechia), BSBR-AS (UK), biorx.si (Slovenia), DANBIO (Denmark), GISEA (Italy), ICEBIO (Iceland), ROB-FIN (Finland), RRBR (Romania), Reuma.pt (Portugal), SCQM (Switzerland), and TURKBIO (Turkey). The organization of and data collection practices across the EuroSpA registries have been described previously (21).

Enthesitis

Enthesitis was defined as registration of the domain either as (i) a clinical feature (ever/never), without any knowledge of time-point, or (ii) tenderness at any of the entheses included in the validated enthesitis scoring systems, including the SPARCC and/or MASES (Figure 1), with an enthesitis score from a clinical visit, i.e. with known time-point (13).

Resolution of enthesitis at the patient level was defined as an enthesitis score of 0 at follow-up, in patients who had an enthesitis score > 0 at baseline using either MASES or SPARCC. Resolution of enthesitis at the location-specific level was defined as the registration of the absence of enthesitis at follow-up in an enthesis registered with the presence of enthesitis at baseline. A change in the enthesitis score (increase or decrease in MASES or SPARCC score) was calculated at follow-up.
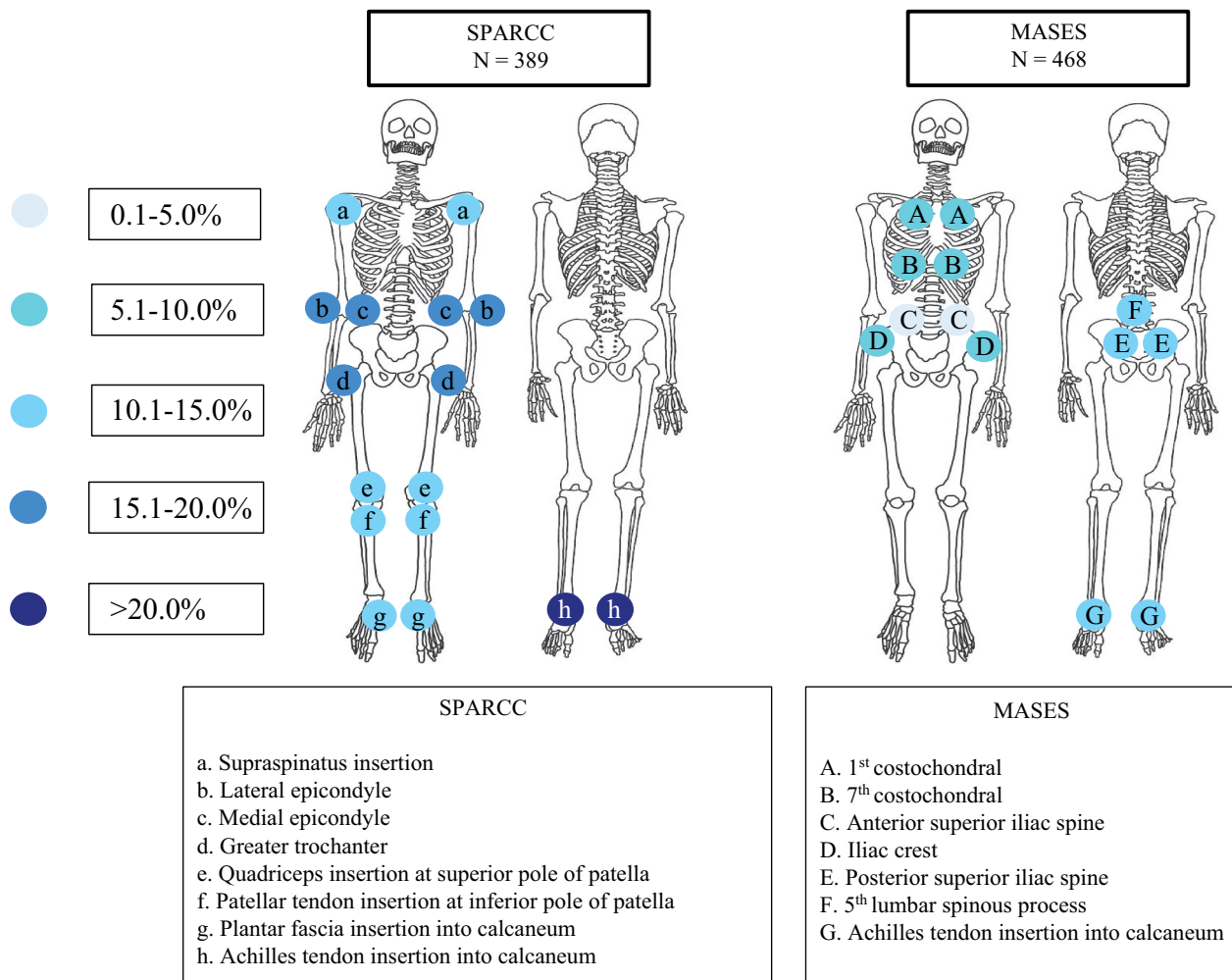
Figure 1. Distribution of enthesitis among patients evaluated with SPARCC and MASES at the initiation of the first tumour necrosis factor inhibitor (TNFi). SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis scoring system; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score. The colours of the circles indicate the proportion (percentage) of examined entheses with enthesitis at the initiation of the first TNFi. The letters in the circles refer to the individual entheses.

During data processing, all data managers were queried to ensure that missing entheseal assessment could be distinguished from active registration of no enthesitis.

Data sources

Study variables and statistical analyses for the study were planned a priori in a study protocol including a statistical analysis plan that was approved by investigators from all participating registries. Data sets from each registry were anonymized and uploaded securely to a common Euro-SpA server. Analyses were conducted on the pooled data as well as by registry. For analyses stratified by registry, only those registries that had a minimum of 50 patients with enthesitis scores were included.

Time-point definitions

The baseline date was defined as the registered date for the start of treatment with TNFi. A patient could

contribute more than one TNFi treatment series. Available data were collected for the first three TNFi treatment series (termed TNFi-1, TNFi-2, and TNFi-3). The baseline visit for each treatment was a registered visit from 30 days before to 30 days after the baseline date. In case more visits occurred within the given time interval, priority was given to a prior visit as close as possible in time to the baseline date. Follow-up visits for each treatment were registered visits at 6, 12, and 24 months, with the corresponding time windows being 90–270, 271–450, and 631–810 days from baseline.

Considering varying availability of data at the follow-up visits, follow-up data were combined to construct a 'combined follow-up visit' to maximize the available follow-up data. (i) If follow-up data were available only at the 6 or 12 or 24 month visit, the available visit was used for the combined follow-up visit. (ii) If data were available at all three visits (6, 12, and 24 months), or 6 and 12 months or 12 and 24 months, the data at the 12 month visit were used for the combined follow-up visit. (iii) If follow-up visits were available only at 6 and 24 months,

the visit at 6 months was prioritized. Only data from the same TNFi treatment series were combined. For each treatment, visits were included until 2 weeks after a registered stop date of the relevant TNFi.

Study outcomes

Primary outcomes included: (i) availability of clinical data on enthesitis, as defined above, in the participating clinical registries; and (ii) sites and distribution of enthesitis at baseline in patients with PsA who were initiated on TNFi-1.

Secondary outcomes included: patient characteristics, disease activity measures, and PROs at baseline of the TNFi-1 among patients with PsA with versus without enthesitis, and in those patients with a registration of either absence or presence of enthesitis, versus those who had no such registration. Additional secondary outcomes were an association of disease activity measures and PROs with the enthesitis scores at baseline of TNFi-1, and finally, the proportion of patients and entheses with resolution of enthesitis and change in enthesitis scores from baseline to follow-up for TNFi-1 and TNFi-2. No data from the TNFi-3 treatment series were included owing to low data availability.

Patient characteristics, disease activity measures, and PROs

Baseline data included age, sex, body mass index (BMI), disease duration, smoking status, data on comorbidities (cardiovascular disease, diabetes, and kidney disease) and extra-articular manifestations (uveitis, inflammatory bowel disease, psoriasis, and dactylitis), time from diagnosis to baseline of TNFi-1, and concomitant conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Disease activity was assessed by swollen joint count (SJC) (28 and 66 joints), tender joint count (TJC) (28 and 68 joints), Psoriasis Activity and Severity Index (PASI), MASES, SPARCC, composite disease activity indices including Disease Activity Score based on 28-joint count–C-reactive protein (DAS28-CRP) and erythrocyte sedimentation rate (ESR), Disease Activity in Psoriatic Arthritis (DAPSA-28), physician global assessment, and PROs [Health Assessment Questionnaire (HAQ), pain score, patient global score, and patient fatigue score].

Statistical analyses

Analyses were performed on observed data with no imputation of missing data. No statistical tests were performed for any data. For the primary analyses, descriptive statistics (medians with interquartile ranges or mean ± sd, according to the distribution of data) were applied. To analyse the association between enthesitis and functional disability and pain at initiation of TNFi-

1, four separate linear regression models with baseline HAQ and pain as independent variables and SPARCC and MASES as explanatory variables were constructed. All models included age, sex, and disease activity indices (SJC, TJC, CRP) as covariates.

Ethics and data protection

All participating registries obtained the necessary approvals in accordance with legal, compliance, and regulatory requirements from national Data Protection Agencies and/or Research Ethics Boards before the data transfer to the EuroSpA coordinating centre. This publication follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (22) and the Declaration of Helsinki.

Results

Registration practice across the participating registries

Of the 12 participating registries, eight included a validated scoring system for enthesitis. Registries in Switzerland, Slovenia, and Finland applied the MASES, and those in Denmark, Iceland, and Turkey used SPARCC to evaluate enthesitis. Both these scoring systems were used in Portugal. The LEI was used in Czechia. The remaining registries had inconsistent methods to register enthesitis, most frequently as a patient-level variable (ever/never).

Data availability regarding enthesitis

Among the 10 548 patients with PsA identified as initiating a TNFi, 4116 (39%) had a registration of either absence or presence of enthesitis recorded as a clinical feature or an enthesitis score at any timepoint. Of these, 1357 patients had undergone an assessment of entheses using MASES and/or SPARCC during treatment with a TNFi. Assessment by MASES and SPARCC was recorded in 1021 and 1166 patients, respectively, considering all visits (baseline and 6, 12, and 24 month follow-up). At the baseline of TNFi-1, 485 and 389 patients had recordings of MASES and SPARCC scores, respectively (Table 1), and these patients are referred to as the MASES and SPARCC cohorts. Of these, 274 and 197 patients were evaluated at one follow-up visit at least, by MASES and SPARCC, respectively. At the baseline of TNFi-2, the MASES and SPARCC scores were recorded for 114 and 164 patients, respectively. Among these patients, 70 and 73, respectively, were evaluated by MASES and SPARCC at least during one follow-up visit following initiation of TNFi-2. The numbers were lower for the TNFi-3 initiation, and data are therefore not reported.

Table 1. Patient characteristics, disease activity measures, and patient-reported outcomes at initiation of the first tumour necrosis factor inhibitor (TNFi-1) in the cohort stratified by MASES and SPARCC scores.

Enthesitis	MASES cohort (N = 485)				SPARCC cohort (N = 389)			
	Present		Absent		Present		Absent	
	n = 170	Avail	n = 315	Avail	n = 236	Avail	n = 153	Avail
Demographics								
Age (years)	46.9 ± 12.7	170	50.5 ± 12.8	315	46.6 ± 11.2	236	47.8 ± 11.6	153
Sex (male)	77 (45.3)	170	159 (50.5)	315	97 (41.1)	236	89 (58.2)	153
BMI (kg/m^2)	28 ± 5.5	131	26.8 ± 4.8	212	27.7 ± 4.5	60	27.4 ± 4.8	49
Current smoking	26 (19.8)	131	37 (15.5)	239	38 (19.3)	197	23 (21.9)	105
Years from symptom onset to diagnosis	2 (0–6.2)	120	1 (0–5)	217	2 (1–5)	144	1 (0–3)	121
Comorbidities (ever)								
Cardiovascular	30 (20.5)	146	54 (20.5)	264	2 (4.3)	47	0 (0)	82
Diabetes	9 (6.2)	146	16 (6.1)	264	5 (10.9)	46	5 (6.1)	82
Kidney disease	4 (2.7)	146	3 (1.1)	264	2 (4.4)	45	1 (1.2)	81
Extra-articular (ever)								
Uveitis	5 (3.4)	146	3 (1.1)	264	0	32	0	77
IBD	8 (5.5)	146	6 (2.3)	264	2 (4.4)	45	1 (1.2)	82
Psoriasis	108 (74)	146	202 (76.5)	264	28 (65.1)	43	61 (74.4)	82
Dactylitis	37 (33)	112	67 (35.3)	190	4 (12.5)	32	25 (32.5)	77
Years from diagnosis to TNFi-1 initiation	2 (1–8)	155	3 (1–8)	295	2 (1–6)	203	2 (1–6)	134
Infliximab	6 (3.5)	170	31 (9.8)	315	41 (17.4)	236	16 (10.5)	153
Etanercept	36 (21.2)		81 (25.7)		39 (16.5)		41 (26.8)	
Adalimumab	63 (37.1)		117 (37.1)		118 (50)		59 (38.6)	
Golimumab	50 (29.4)		74 (23.5)		21 (8.9)		25 (16.3)	
Certolizumab pegol	15 (8.8)		12 (3.8)		17 (7.2)		12 (7.8)	
Concomitant csDMARDs								
Methotrexate	69 (49.3)	140	158 (58.7)	269	121 (88.3)	137	99 (94.3)	105
Sulphasalazine	21 (16.3)	129	31 (15.3)	202	29 (24.2)	120	19 (43.2)	44
Leflunomide	22 (17.9)	123	37 (18.9)	196	16 (13.9)	115	11 (29.7)	37
Others	0	95	0	120	0 (0)	109	0 (0)	30
Concomitant NSAIDs at TNFi-1 initiation	96 (78)	123	135 (59.2)	228	56 (66.7)	84	58 (46)	126
Disease activity variables (baseline)								
SJC28 (0–28)	2 (0–4)	154	2 (1–6)	278	2 (0–3.8)	210	2 (0.2–4)	126
TJC28 (0–28)	4 (1–8)	154	3 (1–7)	279	4 (2–9)	213	2 (1–6)	128
SJC66 (0–66)	3 (0–4.5)	111	3 (1–6)	220	3 (1–5)	196	3 (1–7)	141
TJC68 (0–68)	6 (3–13)	117	4 (2–8)	224	8 (4–14)	214	5 (2–10)	144
PASI	0.6 (0–2.2)	16	0.8 (0–2)	35	0.8 (0–3)	21	0.8 (0–3.8)	30
Nail involvement	28 (33.7)	83	38 (36.5)	104	NA	0	NA	0
Dactylitis count	NA	0	NA	0	NA	0	NA	0
MASES	3.1 ± 2.4	170	0 (0)	315	2.3 ± 2.6	65	0.2 ± 0.6	119
SPARCC	2.8 ± 2.8	52	0.4 ± 1	132	4 ± 3.4	236	0 (0)	153
ESR (mm/h)	18.8 ± 18	158	22.2 ± 20	291	22.2 ± 18.1	61	26.3 ± 24.1	113
CRP (mg/L)	10.5 ± 16.9	166	10.4 ± 14.6	292	8.9 ± 16.6	224	12.1 ± 15.2	145
DAS28-CRP	4.4 ± 1.2	87	4.1 ± 1.2	197	4.2 ± 1	186	3.8 ± 1.2	110
DAS28-ESR	4.5 ± 1.3	83	4.4 ± 1.5	199	4.7 ± 1.1	47	4.1 ± 1.4	85
DAPSA68	30.7.4 ± 15	53	23.1 ± 12	123	29.8 ± 13.5	164	25.2 ± 13.2	105
DAPSA-28	32.5 ± 15.2	82	28.9 ± 17.2	188	28.9 ± 13.5	182	24.6 ± 15.8	108
BASDAI (mm)	61 ± 29	67	40 ± 30	114	68 ± 19	183	55 ± 23	73
BASDAI question 4 (mm)	63 ± 31	67	37 ± 34	114	69 ± 24	183	53 ± 32	73
Physician global (mm)	49 ± 19	162	46 ± 22	301	36 ± 18	208	42 ± 23	140
Patient-reported outcomes (baseline)								
Pain VAS (0–100)	69 ± 21	93	59 ± 24	217	68 ± 21	207	56 ± 26	121
Fatigue VAS (mm)	50 ± 34.6	3	44 ± 34.4	5	73 ± 23	157	63 ± 27	31
PGA VAS (mm)	69 ± 20	103	61 ± 24	243	74 ± 21	220	58 ± 27	140
HAQ	0.9 ± 0.6	120	0.8 ± 0.6	225	1.1 ± 0.6	195	0.8 ± 0.6	106

Data are shown as mean ± sd, frequency (percentage), or median (interquartile range).
MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis score; N, number of patients who underwent entheseal assessment; n, number of patients who had presence or absence of enthesitis; Avail, number of patients with available data; BMI, body mass index; IBD, inflammatory bowel disease; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; NSAID, non-steroidal anti-inflammatory drug; SJC, swollen joint count; TJC, tender joint count; PASI, Psoriasis Area and Severity Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, Disease Activity Score based on 28-joint count; DAPSA-68, Disease Activity in PSoriatic Arthritis including 68 joints; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; VAS, visual analogue scale; PGA, patient global assessment; HAQ, Health Assessment Questionnaire.

Patient characteristics, disease activity measures, and PROs in patients with versus without enthesitis at the initiation of TNFi-1

Patient characteristics and disease activity measures were comparable between the patients who underwent assessment of entheses using the MASES or SPARCC at any time-point during treatment with a TNFi and the 9190 patients who did not have an entheseal assessment registered (Supplementary Table S1a).

Table 1 describes the patient characteristics, disease activity measures, and PROs at baseline of TNFi-1 in patients who had an assessment of entheses using MASES and SPARCC, stratified by the presence versus absence of enthesitis. The mean age of patients registered with enthesitis by MASES was 46.9 ± 12.7 years and by SPARCC was 46.6 ± 11.2 years. More women had enthesitis compared to men (MASES: 54.7% vs 45.3%; SPARCC: 58.9% vs 41.1%). The median duration between diagnosis of PsA and initiation of TNFi-1 was shorter among patients with enthesitis (2 years) compared to those without enthesitis (3 years) in the MASES cohort. The most used TNFi-1 in both patients with and without enthesitis was adalimumab (MASES: 37.1% for both; SPARCC: 50% and % and 38.6%, respectively). The use of concomitant NSAIDs at TNFi-1 initiation was also higher in the group with enthesitis (MASES: 78%; SPARCC: 66.7%) compared to those without enthesitis (MASES: 59.2%; SPARCC: 46%). The mean disease activity in PsA (DAPSA) was higher among patients with enthesitis (MASES: 30.74 ± 15; SPARCC: 29.8 ± 13.5) compared to those without enthesitis (MASES: 23.14 ± 12; SPARCC: 25.2 ± 13.2). Similar findings were observed in the individual registries (Supplementary Table S1b). PROs were numerically higher among patients with enthesitis compared to those without in both MASES and SPARCC cohorts (Table 1).

Enthesitis scores and distribution of enthesitis among patients at the initiation of TNFi-1

The mean baseline enthesitis scores in the MASES and SPARCC cohorts were 3.1 ± 2.4 and 4 ± 3.4, respectively. Women had higher mean enthesitis scores compared to men, by both MASES (3.7 ± 2.7 vs 2.4 ± 1.6) and SPARCC (4.5 ± 3.6 vs 3.2 ± 2.8). In the registries assessing enthesitis by MASES, Achilles tendon entheses (unilateral 27.6%; bilateral 8.5%), posterior superior iliac spine (unilateral 24.8%; bilateral 10%), and fifth lumbar spinous process (13%) were the most affected. In the registries with SPARCC scores, Achilles tendon (unilateral 47.8%; bilateral 18%), lateral epicondyle (unilateral 35.5%; bilateral 14.7%), and greater trochanter (unilateral 31.7%; bilateral 13.1%) were the most affected entheses (Table 2 and Figure 1).

Correlation between enthesitis scoring systems and PROs

In the linear regression models with MASES as an explanatory variable, HAQ and pain demonstrated significant positive associations with tender joint count (p < 0.0001 for both) and negative associations with male gender (p = 0.0003 and 0.03), while no association between MASES and HAQ or pain was observed. In the models including SPARCC, both HAQ and pain had a significant positive association with baseline SPARCC score (p = 0.007 and 0.008, respectively) and TJC (p = 0.049 and 0.011, respectively), whereas HAQ had a significant negative association with male gender (p = 0.0003) (Table 4).

Effectiveness of TNFi in resolution and change in enthesitis at follow-up

For TNFi-1, assessment of entheses by MASES and SPARCC at baseline was performed in 274 and 197 patients, respectively. Of these, 100 and 105 patients, respectively, had enthesitis. At the follow-up visit, in the MASES and SPARCC cohorts, 63 (63%) and 46 (43.8%) of the patients still on treatment, respectively, demonstrated resolution of enthesitis (Table 3). Among patients initiating TNFi-2, enthesitis was observed in 26 of the 70 patients evaluated by MASES and 42 of the 73 patients assessed by SPARCC. Resolution of enthesitis following TNFi-2 was observed in 30.8% and 28.6% of the patients still on treatment, by MASES and SPARCC, respectively. There were no major differences in the resolution of enthesitis at different entheses following TNFi therapy, among either those who underwent assessment by MASES or those assessed by SPARCC (Supplementary Table S2). Among the patients who underwent assessment of entheses using MASES at the initiation of TNFi-1 (n = 266), complete resolution of enthesitis was noted in > 80% of patients at all the entheses, except for the left Achilles tendon insertion (74.3%). Patients who underwent SPARCC assessment of entheses at the initiation of TNFi-1 (n = 197) demonstrated an overall lower rate of site-specific enthesitis resolution (43.8–63%).

Discussion

In this cohort of patients with PsA across 12 European countries, registration of enthesitis was inconsistent both within and across clinical registries. In all registries, it was possible to register enthesitis either as a dichotomous clinical feature, without mentioning a time-point, or as an enthesitis score from a clinical visit. However, only about one-third of patients had any recording of enthesitis and even fewer had entheseal assessment performed using validated scores. Among the patients who underwent assessment of entheses

Table 2. Distribution of enthesitis by MASES and SPARCC scoring systems among all patients at the initiation of the first tumour necrosis factor inhibitor (TNFi-1).

| | Number (%) of patients (all patients) | | Enthesitis score (patients with enthesitis) | | |
	Enthesitis score > 0	Enthesitis score = 0	All	Males	Females
MASES (N = 485)	170 (35)	315 (65)	3.1 ± 2.4	2.4 ± 1.6	3.7 ± 2.7
SPARCC (N = 389)	236 (60.7)	153 (39.3)	4.0 ± 3.4	3.2 ± 2.8	4.5 ± 3.6

Distribution of enthesitis in MASES cohort

Cohort		Pooled	Males	Females
Site	Side	(N = 468)[†]	(N = 226)	(N = 242)
1st Costochondral	Left[‡]	40 (8.5)	12 (5.3)	28 (11.6)
	Right[‡]	43 (9.2)	13 (5.8)	30 (12.4)
	Bilateral[‡]	36 (7.7)	11 (4.9)	25 (10.3)
7th Costochondral	Left	37 (7.9)	12 (5.3)	25 (10.3)
	Right	37 (7.9)	12 (5.3)	25 (10.3)
	Bilateral	32 (6.8)	10 (4.4)	22 (9.1)
Anterior superior iliac spine	Left	20 (4.3)	9 (4)	11 (4.5)
	Right	19 (4.1)	6 (2.7)	13 (5.4)
	Bilateral	15 (3.2)	6 (2.7)	9 (3.7)
Iliac crest	Left	27 (5.8)	11 (4.9)	16 (6.6)
	Right	25 (5.3)	8 (3.5)	17 (7)
	Bilateral	21 (4.5)	7 (3.1)	14 (5.8)
Posterior superior iliac spine	Left	59 (12.6)	16 (7.1)	43 (17.8)
	Right	57 (12.2)	13 (5.8)	44 (18.2)
	Bilateral	47 (10)	10 (4.4)	37 (15.3)
5th lumbar spinous process		61 (13)	22 (9.7)	39 (16.1)
Achilles tendon	Left	59 (12.6)	29 (12.8)	30 (12.4)
	Right	70 (15)	29 (12.8)	41 (16.9)
	Bilateral	40 (8.5)	15 (6.6)	25 (10.3)

Distribution of enthesitis in SPARCC cohort

Cohort		Pooled	Males	Females
Site	Side	(N = 389)	(N = 186)	(N = 203)
Achilles tendon	Left	90 (23.1)	27 (14.5)	63 (31)
	Right	96 (24.7)	29 (15.6)	67 (33)
	Bilateral	70 (18)	18 (9.7)	52 (25.6)
Supraspinatus insertion	Left	47 (12.1)	15 (8.1)	32 (15.8)
	Right	49 (12.6)	16 (8.6)	33 (16.3)
	Bilateral	36 (9.3)	11 (5.9)	25 (12.3)
Lateral epicondyle	Left	68 (17.5)	27 (14.5)	41 (20.2)
	Right	70 (18)	23 (12.4)	47 (23.2)
	Bilateral	57 (14.7)	20 (10.8)	37 (18.2)
Medial epicondyle	Left	59 (15.2)	24 (12.9)	35 (17.2)
	Right	61 (15.7)	24 (12.9)	37 (18.2)
	Bilateral	49 (12.6)	19 (10.2)	30 (14.8)
Greater trochanter	Left	59 (15.2)	20 (10.8)	39 (19.2)
	Right	64 (16.5)	22 (11.8)	42 (20.7)
	Bilateral	51 (13.1)	17 (9.1)	34 (16.7)
Plantar fascia	Left	48 (12.3)	23 (12.4)	25 (12.3)
	Right	57 (14.7)	23 (12.4)	34 (16.7)
	Bilateral	38 (9.8)	17 (9.1)	21 (10.3)
Quadriceps insertion	Left	41 (10.5)	9 (4.8)	32 (15.8)
	Right	41 (10.5)	9 (4.8)	32 (15.8)
	Bilateral	30 (7.7)	6 (3.2)	24 (11.8)
Patellar tendon insertion	Left	41 (10.5)	12 (6.5)	29 (14.3)
	Right	44 (11.3)	11 (5.9)	33 (16.3)
	Bilateral	34 (8.7)	9 (4.8)	25 (12.3)

Data are shown as n (%) or mean ± sd.
[†]One of the registries did not have the entheses marked separately.
[‡]Left, left alone; Right, right alone; Bilateral, both left and right.
MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis scoring system; N, number of patients assessed for enthesitis; n, number of patients who had enthesitis at each enthesis; bilateral, enthesitis at left, right, or both entheses.

Table 3. Effectiveness of the first tumour necrosis factor inhibitor (TNFi) evaluated as change in MASES and SPARCC scores and resolution of enthesitis at follow-up.

| | TNFi-1 | | TNFi-2 | | TNFi-1 | | TNFi-2 | |
| | MASES (N = 274) | | MASES (N = 70) | | SPARCC (N = 197) | | SPARCC (N = 73) | |
Timeline	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Enthesitis present	n = 100	n = 100	n = 26	n = 26	n = 105	n = 105	n = 42	n = 42
Mean ± sd	3 ± 2.2	1.1 ± 1.9	3.7 ± 2.7	2.5 ± 3.1	4.2 ± 3.4	2.4 ± 3.3	4.8 ± 3.6	3.4 ± 3.6
Median (IQR)	2 (1–4)	0 (0–1)	2.5 (2–4)	1 (0.2–2.8)	3 (2–5)	1 (0–4)	4 (2–6.8)	2 (1–5)
Change (follow-up)								
Mean ± sd	0.6 ± 1.9		0.3 ± 1.8		0.9 ± 2.9		0.6 ± 3	
Median (IQR)	0 (0–1)		0 (0–0)		0 (0–2)		0 (0–1)	
Resolution (follow-up)								
Number (%)	63 (63)		8 (30.8)		46 (43.8)		12 (28.6)	

MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis score; N, number of patients who underwent evaluation of entheses; n, number of patients who had enthesitis as per the scoring systems; sd, standard deviation; IQR, interquartile range.

Table 4. Linear regression models for association between clinical variables and patient-reported outcomes with enthesis scores at baseline.

| | Independent variables | Pain | | | HAQ | | |
		Estimate	se	p	Estimate	se	p
MASES	MASES	0.915	0.588	0.121	−0.004	0.015	0.77
	Age	−0.159	0.098	0.106	0.004	0.002	0.07
	Gender (male)	−5.208	2.338	0.026*	−0.213	0.058	<0.001*
	SJC-28	0.402	0.297	0.177	0.014	0.007	0.05
	TJC28	1.159	0.241	<0.001*	0.040	0.006	<0.001*
	CRP	0.177	0.074	0.017*	0.003	0.002	0.057
SPARCC	SPARCC	1.152	0.429	0.008*	0.031	0.011	0.007*
	Age	−0.026	0.129	0.839	0.005	0.003	0.112
	Gender (male)	−3.987	2.863	0.165	−0.283	0.077	<0.001*
	SJC28	0.044	0.501	0.930	0.015	0.014	0.287
	TJC28	0.724	0.285	0.011*	0.015	0.008	0.049*
	CRP	0.173	0.095	0.070	0.004	0.002	0.075

HAQ, Health Assessment Questionnaire; se, standard error; SJC28, swollen joint count including 28 joints; TJC28, tender joint count including 28 joints; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis score; MASES and SPARCC, explanatory variables; Pain and HAQ, independent variables.
*p < 0.05.

using a validated scoring system at the initiation of a first TNFi, enthesitis was observed in a large proportion. Enthesitis was noted more commonly in women compared to men, and patients with enthesitis initiated TNFi earlier in the disease course than those without enthesitis. Patients with enthesitis demonstrated an overall higher disease activity and poorer PROs compared to those without enthesitis. Baseline HAQ and pain had a positive association with baseline SPARCC enthesitis scores. Complete remission of enthesitis was observed after initiation of TNFi-1 in approximately 63% and 44% of patients assessed by MASES and SPARCC, respectively.

As in the current study, significant gaps in the registration of enthesitis have previously been reported in the Danish DANBIO registry (10). This emphasizes the need for a more rigorous assessment of entheses in routine care by rheumatologists. In our study, we also found a wide variability in the assessment of entheses in the countries participating in the EuroSpA collaboration. Many patients in our study had enthesitis registered as a dichotomous variable, without any time-point. Only eight registries in the EuroSpA research collaboration network applied assessment of entheses using validated scoring indices. In a 2021 systematic review exploring outcome measures used in 27 PsA registries or cohorts, enthesitis was reported in 21 registries, of which 12 had registration using MASES or LEI (23). Clinical trials have also used varied entheseal assessment methods, with some being dichotomous and others using validated indices (24–29). This heterogeneity in assessing enthesitis impedes comparison between trials and cohorts.

The Achilles tendon was the most commonly affected enthesis, both in the patients who underwent assessment with the SPARCC and in those assessed with the MASES. This is in agreement with the Toronto PsA cohort and the Assessment of SpondyloArthritis international Society (ASAS) PerSpA data, but not with the CorEvitas registry data, in which lateral epicondyle was the most affected enthesis (8, 30, 31). A Turkish multi-centre study reported the Achilles tendon, followed by the fifth lumbar spinous process, as the most affected entheses (32). This concurs with findings among patients who underwent entheseal assessment using the MASES in our study.

Women had worse mean MASES and SPARCC scores than men. This difference between the sexes was maintained across individual entheses, depicting an overall higher burden of enthesitis among women, as reported in previous studies (10, 33–35). In contrast, a study evaluating the differences between sexes, comparing clinical findings and ultrasound examination at the joints and entheses in patients with PsA, demonstrated women to have more clinical findings of enthesitis than men, whereas men had significantly higher sonographic inflammatory enthesitis scores compared to women (35). This discrepancy between clinical examination and ultrasonography may partly be explained by the well-recognized higher prevalence of fibromyalgia in women and previous studies reporting significantly higher clinical enthesitis scores among patients with concomitant fibromyalgia (36). Data on fibromyalgia were, unfortunately, not available in our study.

Composite disease activity measures were found to be associated with enthesitis scores in our study, i.e. patients with enthesitis had less favourable outcomes than those without enthesitis. A similar association was noted for PROs and enthesitis scores. This is in accordance with the observations from the Psoriatic Arthritis-International Database, in which enthesitis was a significant risk factor for patients not achieving the minimal disease activity state (37). In another cross-sectional survey of 3200 patients with PsA from nine countries comparing clinician- and patient-reported outcomes among those with versus without enthesitis, the former group experienced worse outcomes than the latter. Physicians expressed more dissatisfaction with the overall lack of efficacy and lack of pain control with the treatment provided among patients with enthesitis compared to those without enthesitis (11).

Data on response with treatment in patients with PsA in real-life settings are sparse, as are data on the resolution of peripheral versus axial enthesitis. A study from the Toronto PsA clinic cohort reported resolution of enthesitis in 86% of patients within a year of initiation of therapy, regardless of the medication used (38). In our study, following TNFi-1, a higher rate of overall enthesitis resolution was noted among patients assessed using MASES (63%) compared to those assessed by SPARCC (44%). This was also reflected in the site-specific resolution of enthesitis, wherein axial enthesitis demonstrated a higher rate of resolution than peripheral enthesitis. This may suggest that axial entheses respond better to TNFi compared to peripheral entheses. It is, nevertheless, important to recognize that the patients assessed were different. Moreover, a lower baseline MASES compared to SPARCC may contribute to the observed disparity.

Several clinical trials of TNFi in patients with PsA have explored the effect of therapy on enthesitis as either a secondary or an exploratory endpoint. The only study designed with enthesitis as a primary end-point was the ACHILLES trial, in which 204 patients with active axial spondyloarthritis or PsA and heel enthesitis were randomized to receive secukinumab or placebo, followed by secukinumab. The study, however, did not demonstrate the superiority of secukinumab over placebo, according to the percentage of patients achieving clinical resolution of Achilles tendon enthesitis in the affected foot assessed by the LEI (approximately 42% vs 31%, respectively; not statistically significantly different) (38). In the SEAM-PsA trial, resolution of enthesitis was noted in 53% of 173 patients on etanercept monotherapy, which is comparable to the findings in this current study (26). The GO-VIBRANT study of intravenous golimumab in PsA demonstrated enthesitis resolution in around 63% of patients assessed by the LEI, at week 52 (39). In the CRESPA trial of golimumab involving patients with very early peripheral spondyloarthritis, a 25% drop in enthesitis assessed by modified MASES, along with a significant reduction in enthesitis scores among patients on golimumab compared to placebo, was demonstrated at weeks 8, 16, and 24 (40).

A major strength of this study is the real-world analysis of prospectively collected data on the treatment of enthesitis with TNFi across different countries in Europe, providing important evidence for the effectiveness of TNFi on enthesitis from a real-world setting. The results must, however, be interpreted considering the limitations of this study. One of the major limitations is the high number of patients with no data on the evaluation of entheses. The patients who underwent a detailed evaluation of entheses could have had more severe symptoms, consequently leading to a selection bias. This missingness of data can potentially lead to misrepresentation of the true burden of this clinical domain. Nevertheless, the patients who underwent assessment of entheses seemed to be a representative sample of the overall study population in this study, as shown in Supplementary Table S1. The fallacies associated with clinical assessment of enthesitis add to this uncertainty. Competent awareness and training among clinicians on the importance of this clinical domain may result in a more consistent assessment of enthesitis in

patients with PsA. Registries should facilitate the evaluation and registration of enthesitis at each visit. An important limitation is the lack of data on coexisting fibromyalgia, as the presence of fibromyalgia or nociplastic pain can distort the clinical examination findings significantly. This limitation could potentially have been overcome if data from imaging modalities such as ultrasound or magnetic resonance imaging had been available. Imaging can be very helpful in differentiating true enthesitis from tenderness due to other causes (41). Unfortunately, no data on imaging or coexistent fibromyalgia were available in the registries. The effectiveness of TNFi in the investigated cohort may not be representative of all patients treated in clinical practice. Furthermore, limited data on enthesitis and its resolution hindered a robust analysis of effectiveness following the initiation of the second and third TNFi.

Conclusion

This study highlights the deficiencies in clinical assessment and treatment of enthesitis in patients with PsA in the real-world setting. Based on our data, enthesitis appears to be present in a high proportion of patients with PsA and the presence of enthesitis is associated with a higher overall disease burden. Axial entheses are affected in a lower proportion of patients with PsA compared to peripheral entheses. Following initiation of a first TNFi, a sizable proportion of PsA patients with enthesitis achieves complete resolution.

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Supplementary material

Additional supplementary material may be found in the online version of this article. Please note that the editors are not responsible for the content or functionality of any supplementary material supplied by the authors. Any queries should be directed to the corresponding author.

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