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ORIGINAL RESEARCH

Impact of clinical domains other than arthritis on composite outcomes in psoriatic arthritis: comparison of treatment effects in the SEAM-PsA trial

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ABSTRACT

Objective We used the Study of Etanercept And Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis (SEAM-PsA) data set to examine the impact of presence of enthesitis, dactylitis, nail disease and/or psoriasis on treatment response in patients with early psoriatic arthritis (PsA).

Methods This post hoc analysis evaluated the effect of baseline Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index (EI), Leeds Enthesitis Index (LEI), Leeds Dactylitis Index (LDI), modified Nail Psoriasis Severity Index (mNAPSI) scores and body surface area (BSA) on composite outcomes of minimal disease activity (MDA) responses, Psoriatic Arthritis Disease Activity Score (PASDAS) low disease activity (LDA), PASDAS changes and Good Responses and Disease Activity Index for Psoriatic Arthritis (DAPSA) scores at Week 24.

Results Overall, 851 patients completed the SEAM-PsA trial and were included in the analysis. Baseline enthesitis (SPARCC EI>0 vs SPARCC EI=0 or LEI>0 vs LEI=0) was not associated with improved outcomes. Baseline dactylitis (LDI>0 vs LDI=0) was positively associated with improved MDA (OR: 1.4, p=0.0457), PASDAS LDA (OR: 1.8, p=0.0014) and Good Responses (OR: 1.6, p=0.0101) and greater reductions in PASDAS (estimate: −0.9, p<0.0001) and DAPSA scores (estimate: −3.8, p=0.0155) at Week 24. Similarly, baseline nail disease (mNAPSI >1 vs mNAPSI≤1) was positively associated with improved MDA (OR: 1.8, p=0.0233) and PASDAS LDA (OR: 1.8, p=0.0168) responses and greater reduction in PASDAS (estimate: −0.7, p=0.0005) at Week 24.

Conclusions Results from our analysis suggest that presence of dactylitis and nail disease, but not enthesitis, are associated with improved outcomes in patients with early PsA who were treated with methotrexate and/or etanercept.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Psoriatic arthritis (PsA) is associated with enthesitis, dactylitis, nail disease and psoriasis; however, the influence of these clinical domains to treatment response is unknown.

⇒ This study used the large data set from the Study of Etanercept And Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis randomised controlled trial to assess the potential impact of these clinical domains on treatment outcomes in patients with early PsA who had received therapy with methotrexate and/or etanercept for 24 weeks.

WHAT THIS STUDY ADDS

⇒ Results from the analysis suggest that presence of dactylitis and nail disease, but not enthesitis, are associated with improved treatment response in patients with early PsA who were treated with methotrexate and/or etanercept.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ These results inform treatment choice and how best to measure treatment response in PsA, which can present with multiple heterogeneous manifestations.

INTRODUCTION

Psoriatic arthritis (PsA) is an immune-mediated inflammatory disease characterised by clinical features involving the skin, nails, joints and spine.[1–5] Approximately 30% of patients with psoriasis develop PsA, with an annual incidence of 1%–3%.[1–4] PsA is associated with considerable disease burden as patients experience several symptoms, including peripheral and axial joint inflammation, enthesitis, dactylitis, nail disease and psoriasis.[3 5 6] The influence of these clinical domains on treatment response to methotrexate or tumour necrosis factor inhibitors as monotherapy or in combination in PsA is not known.

In the Study of Etanercept And Methotrexate in Combination or as Monotherapy in

Subjects with Psoriatic Arthritis (SEAM-PsA) randomised controlled trial (RCT; NCT02376790),[7] both etanercept monotherapy and methotrexate plus etanercept combination therapy were statistically significantly more effective than methotrexate monotherapy as assessed by the American College of Rheumatology ≥20% improvement (ACR ≥20) response and the minimal disease activity (MDA) response[8] at Week 24. No deaths occurred in the trial, and the incidences of adverse events and serious adverse events up to Week 48 were similar across the methotrexate monotherapy, etanercept monotherapy and methotrexate plus etanercept combination therapy groups.[7]

Analysing data from the SEAM-PsA RCT[7] may address uncertainties that remain about how best to measure disease activity and treatment response in PsA. We used this large data set to examine the potential impact of the presence of enthesitis, dactylitis, nail disease or psoriasis on treatment outcomes in patients with early PsA who were naïve to methotrexate or biological therapies and received either methotrexate or etanercept monotherapy or the combination therapy.

METHODS

Study design and patient population

SEAM-PsA was an international, 48-week, phase 3 RCT.[7 9] Adults with active PsA with ≥3 tender and ≥3 swollen joints (based on 68-joint counts and 66-joint counts, respectively) and an active psoriatic skin lesion at least 2 cm in diameter and who were naïve to methotrexate and biological therapies, had been randomised 1:1:1 to receive weekly oral methotrexate 20 mg or subcutaneous etanercept 50 mg, or the combination therapy weekly. The SEAM-PsA RCT was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient, and each participating site obtained protocol approval by an Institutional Review Board or independent ethics committee.

Primary results of the SEAM-PsA RCT have been published previously.[7] This includes results for the primary endpoint of ACR 20 response; key secondary endpoint of MDA response; and additional endpoints of Psoriatic Arthritis Disease Activity Score (PASDAS), Disease Activity Index for Psoriatic Arthritis (DAPSA) score, changes from baseline in Leeds Dactylitis Index (LDI), Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index (EI), percentage of body surface area (BSA) affected by psoriasis (psoriasis-affected BSA) and modified Nail Psoriasis Severity Index (mNAPSI).[7]

Study outcomes at Week 24

The present post hoc analysis was conducted using the pooled SEAM-PsA population (ie, full analysis set (n=851) with pooled treatment arms of methotrexate monotherapy, etanercept monotherapy and methotrexate plus etanercept combination therapy) to evaluate the effect of the presence of enthesitis by SPARCC EI (>0 vs=0) and Leeds Enthesitis Index (LEI; >0 vs=0), dactylitis by LDI (>0 vs=0), nail disease by mNAPSI (>1 vs ≤1) and psoriasis-affected BSA (≥10% vs <10%) at baseline on key outcomes of MDA using SPARCC EI (assessment of 18 sites for tenderness with a score from 0 to 16)[6 10 11]; MDA using LEI (assessment of six sites for tenderness)[6 12]; PASDAS low disease activity (LDA; defined as 'Yes' if absolute PASDAS ≤3.2, otherwise 'No' or 'missing'); PASDAS Good Responses (defined as 'Yes' if absolute PASDAS ≤3.2 and PASDAS change from baseline ≤−1.6, otherwise 'No' or 'missing'); PASDAS changes; and DAPSA score changes at Week 24, controlled for the variables of prior non-biological disease-modifying antirheumatic drug (DMARD) use (Yes vs No), body mass index (BMI; >30 kg/m^2 vs ≤30 kg/m^2) and 66-swollen joint count. Missing data were imputed as non-responders for MDA using SPARCC EI or LEI; missing data were not imputed for PASDAS LDA, PASDAS Good Responses and PASDAS and DAPSA score changes.

Statistical analysis

Descriptive statistics for changes from baseline to Week 24 were summarised. A logistic model was used for MDA, PASDAS LDA and PASDAS Good Responses, predicted using baseline SPARCC EI, LEI, LDI, mNAPSI or psoriasis-affected BSA and controlled for prior non-biological DMARD use, baseline BMI, 66-swollen joint count and PASDAS for PASDAS LDA or Good Responses to determine ORs and 95% CIs. The analysis of covariance model was used for continuous outcomes of PASDAS and DAPSA changes from baseline, with the independent factors being baseline SPARCC EI, LEI, LDI, mNAPSI, or psoriasis-affected BSA, controlled for prior non-biological DMARD use, BMI and baseline 66-swollen joint count as covariates to determine estimates and SEs. Data for the effects of the control variables were also summarised. P values for both models were not adjusted for multiplicity and are considered nominal. The variable of swollen/tender joint counts using SPARCC EI, LEI, LDI, mNAPSI and psoriasis-affected BSA at baseline were also summarised descriptively.

RESULTS

Baseline patient demographics and disease activity

A total of 851 patients completed the SEAM-PsA trial (methotrexate monotherapy, n=284; etanercept monotherapy, n=284; and methotrexate plus etanercept combination therapy, n=283). Baseline demographics and disease characteristics were similar across the overall study population (table 1). Most patients were Caucasian (90.7%); mean (SD) age was 48.4 (13.1) years; and the proportion of men was 49.2% and women was 50.8%. Most patients were early in their disease course, with mean (SD) PsA duration of 3.2 (6.3) years (median of 0.6 years).

Table 1 Demographics and baseline disease activity

Characteristics	Methotrexate monotherapy N=284	Etanercept monotherapy N=284	Methotrexate+etanercept combination therapy N=283	All patients N=851
Age in years, mean (SD)	48.7 (13.1)	48.5 (13.5)	48.1 (12.7)	48.4 (13.1)
Sex, n (%)				
Male	124 (43.7)	151 (53.2)	144 (50.9)	419 (49.2)
Female	160 (56.3)	133 (46.8)	139 (49.1)	432 (50.8)
White race, n (%)	255 (89.8)	252 (88.7)	265 (93.6)	772 (90.7)
PsA duration in years, mean (SD) (no. of patients assessed)	3.6 (6.9) (231)	3.1 (6.0) (222)	3.0 (6.0) (231)	3.2 (6.3) (684)
Median (Q1, Q3) (no. of patients assessed)	0.9 (0.1, 3.3) (231)	0.6 (0.1, 3.0) (222)	0.5 (0.1, 3.0) (231)	0.6 (0.1, 3.0) (684)
Prior use of non-biological DMARD, n (%)	38 (13.4)	26 (9.2)	43 (15.2)	107 (12.6)
Body mass index (kg/m^2), mean (SD) (no. oTypesetter to amendf patients assessed)	30.6 (7.1) (284)	30.4 (6.6) (283)	30.0 (6.7) (283)	30.3 (6.8) (851)
Swollen joint count (66 joints), mean (SD) (no. of patients assessed)	12.9 (9.9) (284)	11.5 (9.6) (283)	11.2 (9.1) (282)	11.9 (9.6) (849)
Tender joint count (68 joints), mean (SD) (no. of patients assessed)	20.9 (15.0) (284)	18.8 (14.5) (283)	20.0 (15.3) (282)	19.9 (14.9) (849)
mTSS, mean (SE) (no. of patients assessed)	2.8 (0.1) (269)	3.0 (0.1) (273)	2.7 (0.1) (274)	2.8 (0.1) (816)
PASDAS, mean (SE) (no. of patients assessed)	6.1 (0.1) (282)	6.1 (0.1) (279)	6.0 (0.1) (280)	6.1 (0.04) (841)
DAPSA, mean (SE) (no. of patients assessed)	46.5 (1.4) (283)	43.4 (1.4) (281)	43.8 (1.4) (281)	44.6 (0.8) (845)
SPARCC EI				
Patients with ≥0 at baseline, n (%)	191 (67.3)	189 (66.5)	196 (69.3)	576 (67.7)
Mean (SE) for patients with ≥0 at baseline (no. of patients assessed)	5.7 (0.3) (191)	5.5 (0.3) (189)	5.9 (0.3) (196)	5.7 (0.2) (576)
LEI				
Patients with ≥0 at baseline, n (%)	284 (100)	283 (99.6)	281 (99.3)	848 (99.6)
Mean (SE) for patients with ≥0 at baseline (no. of patients assessed)	1.5 (0.1) (284)	1.6 (0.1) (283)	1.7 (0.1) (282)	1.6 (0.1) (849)
LDI				
Patients with >0 at baseline, n (%)	98 (34.5)	96 (33.8)	90 (31.8)	284 (33.4)
Mean (SE) for patients with >0 at baseline (no. of patients assessed)	164.9 (26.9) (98)	147.6 (20.8) (96)	138.2 (23.9) (90)	150.6 (13.9) (284)
mNAPSI				
Patients with >0 at baseline, n (%)	185 (65.1)	206 (72.5)	197 (69.6)	588 (69.1)
Mean (SE) for patients with >0 at baseline (no. of patients assessed)	3.4 (0.2) (183)	3.5 (0.2) (205)	3.6 (0.2) (195)	3.5 (0.1) (583)
Psoriasis-affected BSA, % mean (SD)	12.7 (18.8)	10.8 (14.7)	10.7 (15.6)	11.4 (16.4)
Patients with ≥10% psoriasis-affected BSA at baseline, n (%)	99 (34.9)	97 (34.2)	90 (31.8)	286 (33.6)
Mean (SE) for patients with ≥10% psoriasis-affected BSA at baseline	30.3 (2.3)	25.9 (1.7)	27.3 (2.0)	27.9 (1.2)
sPGA, mean (SD) (no. of patients assessed)	2.6 (1.1) (281)	2.6 (1.0)	2.5 (1.0) (283)	2.6 (1.0) (848)
HAQ-DI, mean (SE) (no. of patients assessed)	1.3 (0.0) (283)	1.1 (0.0)	1.2 (0.0) (282)	1.2 (0.0) (849)
Patient global assessment (0–100), mean (SE) (no. of patients assessed)	60.7 (1.3) (283)	62.9 (1.3) (284)	61.0 (1.2) (282)	61.5 (0.7) (849)
Patient global assessment of joint pain (0–100), mean (SE) (no. of patients assessed)	56.1 (1.3) (283)	56.5 (1.3) (284)	55.7 (1.3) (282)	56.1 (0.7) (849)
SF-36 PCS, mean (SE) (no. of patients assessed)	35.6 (0.5) (282)	37.8 (0.5) (284)	37.4 (0.6) (282)	36.9 (0.3) (848)
SF-36 MCS, mean (SE) (no. of patients assessed)	45.2 (0.7) (282)	45.1 (0.7) (284)	46.3 (0.7) (282)	45.5 (0.4) (848)
SF-36 Domains, mean (SE) (no. of patients assessed)				
Physical function	42.1 (1.5) (282)	48.5 (1.5) (284)	49.0 (1.5) (282)	46.5 (0.9) (848)

Continued

Table 1 Continued

Characteristics	Methotrexate monotherapy N=284	Etanercept monotherapy N=284	Methotrexate+etanercept combination therapy N=283	All patients N=851
Role physical	44.6 (1.5) (282)	48.5 (1.5) (284)	50.2 (1.5) (282)	47.8 (0.9) (848)
Bodily pain	36.3 (1.1) (282)	39.8 (1.1) (284)	39.3 (1.1) (282)	38.5 (0.6) (848)
General health	46.1 (1.1) (282)	48.1 (1.3) (284)	47.1 (1.2) (282)	47.1 (0.7) (848)
Vitality	40.2 (1.2) (282)	43.1 (1.3) (284)	42.0 (1.2) (282)	41.8 (0.7) (848)
Social function	58.3 (1.6) (282)	62.7 (1.6) (284)	63.3 (1.6) (282)	61.4 (0.9) (848)
Role emotional	65.8 (1.7) (282)	65.4 (1.7) (284)	70.0 (1.6) (282)	67.1 (1.0) (848)
Mental health	60.3 (1.3) (282)	60.8 (1.3) (284)	62.5 (1.2) (282)	61.2 (0.7) (848)

BSA, body surface area; DAPSA, disease activity index for psoriatic arthritis; DMARD, disease-modifying antirheumatic drug; HAQ-DI, health assessment questionnaire-disability index; LDI, leeds dactylitis index; LEI, leeds enthesitis index; MCS, mental component summary; mNAPSI, modified nail psoriasis severity index; mTSS, van der heijde modified total sharp score; PASDAS, psoriatic arthritis disease activity score; PCS, physical component summary; PsA, psoriatic arthritis; Q1, first quartile; Q3, third quartile; SF-36, medical outcomes study short form-36 questionnaire; SPARCC EI, spondyloarthritis research consortium of canada enthesitis index; sPGA, static physician global assessment.

MDA, PASDAS LDA, PASDAS Good Responses, PASDAS and DAPSA score outcomes at Week 24

A descriptive summary of outcomes of interest at Week 24 is presented in table 2. Overall, 34.7% (268/773) of patients achieved MDA using SPARCC EI and 35.7% (276/773) using LEI at Week 24. Overall, 46.3% (351/758) of patients had PASDAS LDA and 44.3% (332/750) had PASDAS Good Responses at Week 24.

Table 2 Descriptive summary of select outcomes at Week 24 on therapy (combined arms of methotrexate monotherapy, etanercept monotherapy or methotrexate plus etanercept combination therapy)

Outcome	All patients N=851
MDA using SPARCC EI, n/N1 (%) (SE)	268/773 (34.7) (0.017)
MDA using LEI, n/N1 (%) (SE)	276/773 (35.7) (0.017)
PASDAS LDA,* n/N1 (%) (SE)	351/758 (46.3) (0.018)
PASDAS Good Responses,† n/N1 (%) (SE)	332/750 (44.3) (0.018)
PASDAS changes from baseline to Week 24, median (Q1, Q3)	−2.4 (−3.6, −1.3)‡
DAPSA changes from baseline to Week 24, median (Q1, Q3)	−22.3 (−36.0, −11.4)§

*PASDAS LDA status at a specified week defined as 'Yes' if absolute PASDAS ≤3.2, otherwise as 'No' or as 'missing' if PASDAS score is missing.
†PASDAS Good Responses at a specified week defined as 'Yes' if absolute PASDAS score ≤3.2 and PASDAS score change from baseline ≤−1.6, otherwise as 'No' or as 'missing' if PASDAS score or change from baseline is missing.
‡Number of subjects with observed data for PASDAS change from baseline to Week 24 was 750.
§Number of subjects with observed data for DAPSA change from baseline to Week 24 was 760.
DAPSA, disease activity index for psoriatic arthritis; DMARD, disease-modifying antirheumatic drug; LDI, leeds dactylitis index; LEI, leeds enthesitis index; MDA, minimal disease activity; N1, number of subjects with non-missing response at a specified week; n, number of MDA using SPARCC EI responders or number of MDA using LEI responders or number of subjects with PASDAS status = 'Yes'; N, number of subjects in the full analysis set; PASDAS, psoriatic arthritis disease activity score; PASDAS LDA, psoriatic arthritis disease activity score low disease activity; Q1, quartile 1; Q3, quartile 3; SPARCC EI, spondyloarthritis research consortium of canada enthesitis index.

Median (Q1, Q3) PASDAS change from baseline to Week 24 was −2.4 (−3.6, −1.3), and median (Q1, Q3) DAPSA score change was −22.3 (−36.0, −11.4).

Effect of baseline clinical domains on outcomes of MDA, PASDAS LDA and PASDAS Good Responses at Week 24

The effects of baseline clinical domains of SPARCC EI, LEI, LDI, mNAPSI and psoriasis-affected BSA on MDA, PASDAS LDA and PASDAS Good Responses at Week 24 are presented in figure 1 and online supplemental table 1. The effects of the control variables are also presented in online supplemental table 1.

MDA using SPARCC EI at Week 24

Baseline SPARCC EI was negatively associated with achievement of MDA using SPARCC EI (OR (95% CI): 0.5 (0.4 to 0.7), p<0.0001) as was baseline LEI (OR (95% CI): 0.5 (0.4 to 0.7), p<0.0001) (figure 1 and online supplemental table 1). Baseline LDI was positively associated with achieving MDA using SPARCC EI (OR (95% CI): 1.4 (1.0 to 2.0), p=0.0457) as was baseline mNAPSI (OR (95% CI): 1.8 (1.1 to 2.9), p=0.0233). However, baseline psoriasis-affected BSA was not associated with MDA using SPARCC EI (p=0.6733).

MDA using LEI at Week 24

Baseline SPARCC EI was negatively associated with achievement of MDA using LEI (OR (95% CI): 0.6 (0.4 to 0.8), p=0.0004) as was baseline LEI (OR (95% CI): 0.5 (0.4 to 0.7), p<0.0001) (figure 1 and online supplemental table 1). Baseline LDI was positively associated with achieving MDA using LEI (OR (95% CI): 1.5 (1.0 to 2.0), p=0.0270) as was baseline mNAPSI score (OR (95% CI): 1.7 (1.1 to 2.8), p=0.0278). However, baseline psoriasis-affected BSA was not associated with MDA using LEI (p=0.3991).

PASDAS LDA at Week 24

Baseline SPARCC EI was negatively associated with achievement of PASDAS LDA (OR (95% CI): 0.6 (0.4

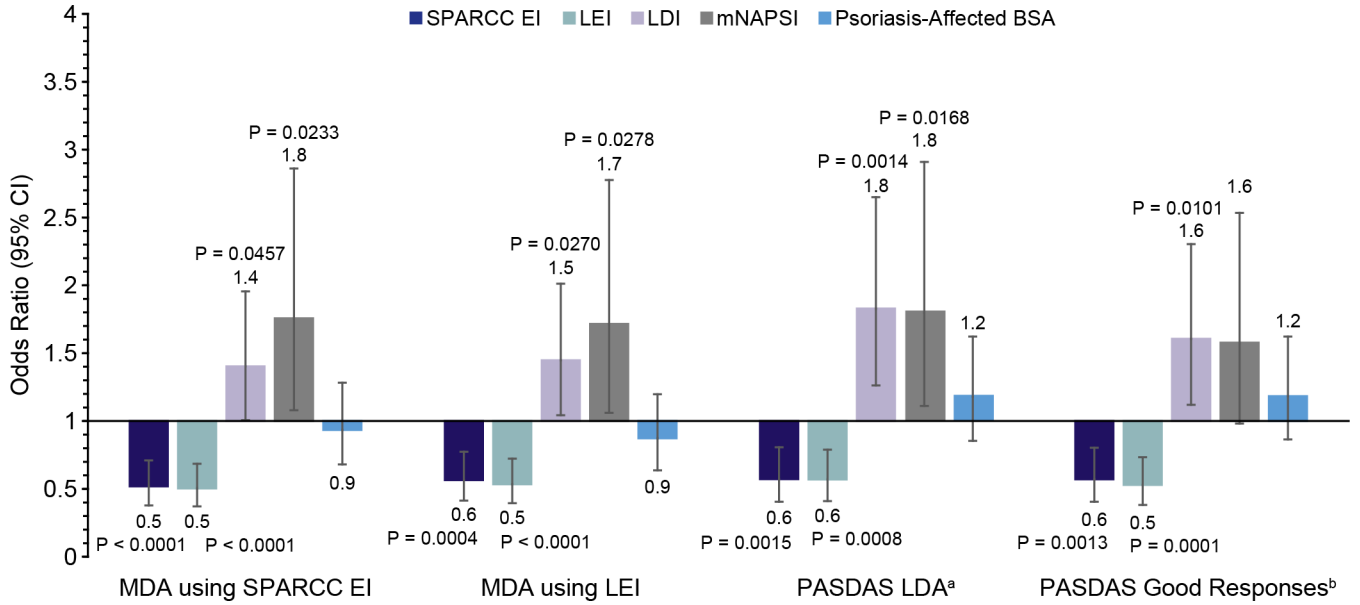

Figure 1 Effect of baseline clinical domains on outcomes of MDA, PASDAS LDA and PASDAS Good Responses at Week 24. N=851; number of subjects in the full analysis set. Data were analysed based on logistic model adjusted for prior non-biological DMARD use, baseline BMI status (≤30 kg/m^2 or >30 kg/m^2), and baseline 66-swollen joint count for each clinical domain status evaluated (baseline enthesitis, LDI, mNAPSI or psoriasis-affected BSA). P values were unadjusted for multiplicity and are considered nominal. P≤0.05 are shown. [a]PASDAS LDA status at Week 24 defined as 'Yes' if absolute PASDAS score ≤3.2, otherwise as 'No', or as 'missing' if PASDAS score is missing. [b]PASDAS Good Responses at Week 24 defined as 'Yes' if absolute PASDAS score ≤3.2 and PASDAS score change from baseline ≤−1.6, otherwise as 'No', or as 'missing' if PASDAS or PASDAS change from baseline is missing. BMI, body mass index; BSA, body surface area; DMARD, disease-modifying antirheumatic drug; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; mNAPSI, modified Nail Psoriasis Severity Index; PASDAS, Psoriatic Arthritis Disease Activity Score; PASDAS LDA, Psoriatic Arthritis Disease Activity Score low disease activity; SPARCC EI, Spondyloarthritis Research Consortium of Canada Enthesitis Index.

to 0.8), p=0.0015) as was baseline LEI (OR (95% CI): 0.6 (0.4 to 0.8), p=0.0008) (figure 1 and online supplemental table 1). Baseline LDI was positively associated with achieving PASDAS LDA (OR (95% CI): 1.8 (1.3 to 2.6), p=0.0014) as was baseline mNAPSI (OR (95% CI): 1.8 (1.1 to 2.9), p=0.0168). However, baseline psoriasis-affected BSA was not associated with PASDAS LDA (p=0.3157).

PASDAS Good Responses at Week 24

Baseline SPARCC EI was negatively associated with achievement of PASDAS Good Responses (OR (95% CI): 0.6 (0.4 to 0.8), p=0.0013) as was baseline LEI (OR (95% CI): 0.5 (0.4 to 0.7), p=0.0001) (figure 1 and online supplemental table 1). Baseline LDI was positively associated with achieving PASDAS Good Responses (OR (95% CI): 1.6 (1.1 to 2.3), p=0.0101). Baseline mNAPSI showed a trend toward positive association with PASDAS Good Responses (OR (95% CI): 1.6 (1.0 to 2.5), p=0.0592), whereas psoriasis-affected BSA was not associated with PASDAS Good Responses (p=0.2926) (figure 1 and online supplemental table 1).

Effect of clinical domains on PASDAS and DAPSA changes from baseline to Week 24

The effects of the presence of enthesitis, dactylitis, nail disease and psoriasis-affected BSA on PASDAS and DAPSA score changes at Week 24 are presented in figure 2 and online supplemental table 2. The effects of the control variables are also presented in online supplemental table 2.

PASDAS changes at Week 24

Controlling for prior DMARD use, BMI, 66-swollen joint count and PASDAS, there was no association between changes in PASDAS from baseline to Week 24 and presence of enthesitis using either SPARCC EI or LEI (figure 2 and online supplemental table 2). However, PASDAS changes from baseline to Week 24 were associated with baseline LDI (estimate (SE): −0.9 (0.1); p<0.0001), mNAPSI (estimate (SE): −0.7 (0.2); p=0.0005) and psoriasis-affected BSA (estimate (SE): −0.3 (0.1); p=0.0098) after controlling for baseline factors noted above.

DAPSA score changes at Week 24

Controlling for prior DMARD use, BMI, 66-swollen joint count and DAPSA scores, there were no associations between DAPSA score changes from baseline to Week 24 and the presence of enthesitis (using either SPARCC EI or LEI), mNAPSI or psoriasis-affected BSA (figure 2 and online supplemental table 2). DAPSA score changes from baseline to Week 24 were significantly associated with LDI (estimate (SE): −3.8 (1.6); p=0.0155) after controlling for baseline factors noted above.

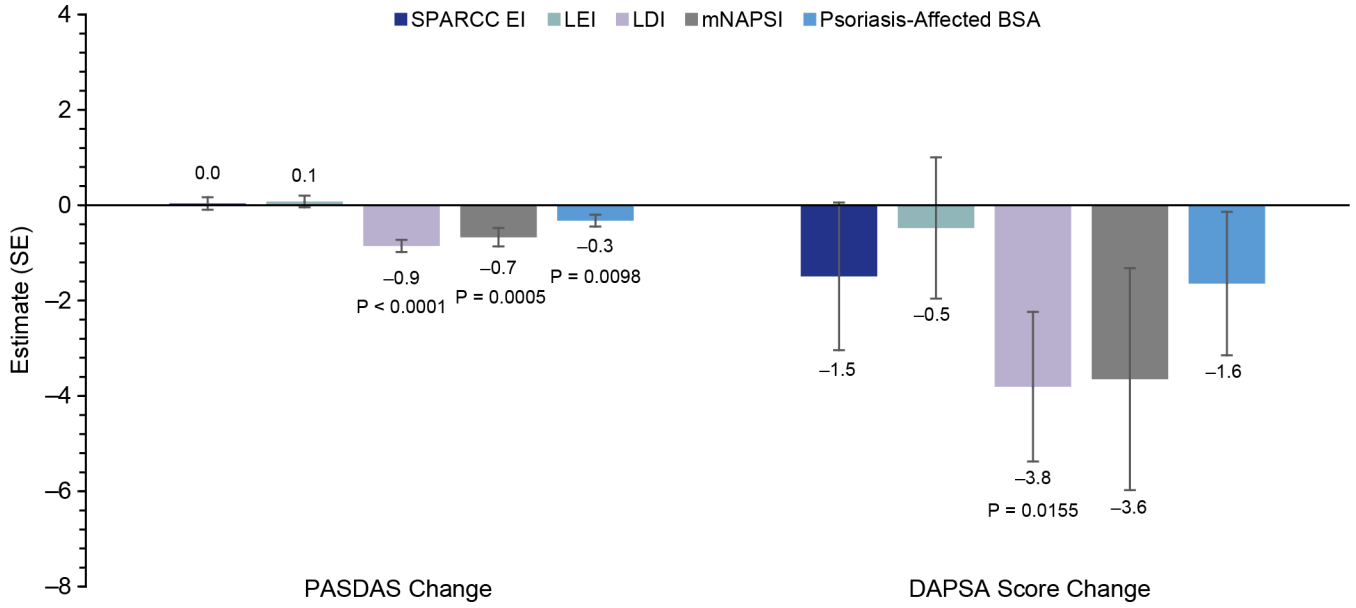

Figure 2 Effect of baseline clinical domains on outcomes of PASDAS change and DAPSA score change from baseline to Week 24. N=851; number of subjects in the full analysis set. Data were analysed based on analysis of covariance model adjusted for prior non-biological DMARD use, baseline BMI status (≤30 kg/m^2 or >30 kg/m^2), and baseline 66-swollen joint count, and for each clinical domain status evaluated (baseline enthesitis, LDI, mNAPSI or psoriasis-affected BSA). P values were unadjusted for multiplicity and are considered nominal. P≤0.05 are shown. BMI, body mass index; BSA, body surface area; DAPSA, Disease Activity Index for Psoriatic Arthritis; DMARD, disease-modifying antirheumatic drug; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; mNAPSI, modified Nail Psoriasis Severity Index; PASDAS, Psoriatic Arthritis Disease Activity Score; SPARCC EI, Spondyloarthritis Research Consortium of Canada Enthesitis Index.

Baseline swollen/tender joint counts using baseline SPARCC EI, LEI, LDI, mNAPSI scores and psoriasis-affected BSA

The presence of enthesitis, dactylitis, nail disease or psoriasis-affected BSA had no apparent association with baseline swollen joint counts (table 3). Median (Q1, Q3) tender joint counts were numerically higher in patients with enthesitis by SPARCC EI or LEI and dactylitis by LDI (table 3).

Table 3 Median swollen/tender joint count by baseline SPARCC EI, LEI, LDI, mNAPSI and psoriasis-affected BSA status

Clinical domain	Number of subjects in full analysis set, N	Number of subjects with observed data, n	Swollen joint count (66-joint count) at baseline median (Q1, Q3)	Tender joint count (68-joint count) at baseline median (Q1, Q3)
Baseline SPARCC EI				
>0	576	575	10 (6, 16)	19 (11, 33)
=0	273	272	7 (4, 12)	9 (6, 16)
Baseline LEI				
>0	480	479	10 (7, 17)	21 (12, 36)
=0	368	367	7 (4, 12)	10 (6, 16)
Baseline LDI				
>0	284	284	13 (7, 19)	21 (11, 34)
=0	565	563	8 (5, 13)	13 (7, 23)
Baseline mNAPSI				
>1	467	467	9 (5, 16)	16 (9, 29)
≤1	116	116	9 (5, 15)	18 (9, 29)
Baseline psoriasis-affected BSA				
≥10%	286	286	9 (5, 15)	13 (8, 23)
<10%	565	563	9 (6, 15)	16 (9, 29)

BSA, body surface area; LDI, leeds dactylitis index; LEI, leeds enthesitis index; mNAPSI, modified nail psoriasis severity index; Q1, quartile 1; Q3, quartile 3; SPARCC EI, spondyloarthritis research consortium of canada enthesitis index.

DISCUSSION

In our analysis, presence of enthesitis (SPARCC EI or LEI) was associated with lower odds of achieving MDA, PASDAS LDA and PASDAS Good Responses. Presence of dactylitis (LDI) was associated with higher odds of achieving MDA, PASDAS LDA and PASDAS Good Responses and greater reductions in PASDAS or DAPSA scores at Week 24. Presence of nail disease (mNAPSI) was associated with higher odds of achieving MDA and PASDAS LDA and a trend toward positive association with PASDAS Good Responses. Presence of nail disease was also associated with greater reductions in PASDAS changes at Week 24 but was not associated with DAPSA score changes at Week 24. Also, joint count was not different by mNAPSI status. Overall, psoriasis-affected BSA (≥10% vs <10%) was not associated with achievement of MDA, PASDAS LDA and PASDAS Good Responses or DAPSA score changes at Week 24. However, psoriasis-affected BSA ≥10% was associated with greater reductions in PASDAS. We evaluated MDA using both SPARCC EI and LEI. Both measures have been used to evaluate MDA in a number of PsA trials with no measure appearing superior to the other.[13] This is consistent with findings from our analysis.

The presence of enthesitis is usually associated with higher disease activity[14–16]; however, in our analysis, the presence of enthesitis (SPARCC EI or LEI) was associated with lower odds of achieving MDA, PASDAS LDA and PASDAS Good Responses but not with PASDAS and DAPSA score changes. Enthesitis scores are included in deriving MDA, which may confound the results. It is also possible that enthesitis, in the context of the patient population with early PsA evaluated in our analysis, may mostly be due to allodynia with heightened sensitivity to pain at sites of entheseal insertions, and not true enthesitis. Such pain may be slower to improve. Alternatively, enthesitis may denote more severe disease which is more resistant to therapeutic response. Any of these possibilities may account for the association of worse baseline enthesitis with lower odds of achieving MDA, PASDAS LDA and PASDAS Good Responses as observed in our analysis. This would be consistent with an earlier study that reported a poor correlation of clinical assessments of pain at entheseal insertions with ultrasound evidence of enthesitis.[17] A more recent study has reported a low association of joint tenderness with imaging signs of inflammation in patients with PsA, suggesting that pain at the joint may be influenced by other factors not related to local inflammation.[18] With regards to the composite outcomes such as changes in PASDAS, the percentage contribution of each clinical domain such as enthesitis is increased where that clinical domain is prominent in the composite outcome measure.[19] This may explain the lack of association between presence of enthesitis and PASDAS changes.

LDI is calculated from a combination of quantifiable increase in circumference of involved digits due to swelling and the score for tenderness,[20] both of which can improve with treatment. This would be consistent with our analysis that presence of dactylitis (LDI) was associated with higher odds of achievement of MDA, PASDAS LDA and PASDAS Good Responses and greater reductions in PASDAS and DAPSA scores from baseline to Week 24.

Nail psoriasis is a recognised common feature of PsA and is associated with high disease burden and enthesitis in particular.[21–23] This would be consistent with our findings that presence of nail disease (mNAPSI) was associated with higher odds of achieving MDA and PASDAS LDA and greater reductions in PASDAS at Week 24. Our results also suggest that nail disease showed a trend toward positive association with PASDAS Good Responses. These findings are also consistent with the report of nail disease as a predictor of good outcomes in axial PsA.[24] However, no biological explanation for this association has been provided. Additionally, it is unclear why presence of nail disease was not associated with DAPSA score changes in our analysis.

Overall, psoriasis-affected BSA was not associated with achievement of MDA, PASDAS LDA and PASDAS Good Responses or DAPSA score changes at Week 24. However, psoriasis-affected BSA was associated with a greater reduction in PASDAS; probably because PASDAS indirectly incorporates a measure of skin disease as patient's global assessment of disease activity (visual analog scale).

Clinically, it is important to fully evaluate all clinical domains and to consider affected domains when choosing therapy and assessing response to treatment. Some clinical domains may be more sensitive in predicting decreasing inflammatory joint responses than others. An earlier post hoc analysis of data from the SEAM-PsA trial evaluated the effect of sex and BMI on treatment outcomes.[25] Significantly improved treatment outcomes in men, more than in women, were observed for MDA and PASDAS in patients who received methotrexate plus etanercept combination therapy, with no differences observed in patients who received methotrexate alone or etanercept alone.[25] Patients with BMI ≤30 kg/m^2 generally showed better treatment outcomes than those with BMI >30 kg/m^2, regardless of treatment received.[25] Results from the current post hoc analysis suggests that the presence of dactylitis and nail disease are associated with improved treatment outcomes, whereas presence of enthesitis is not. These findings suggest that contextual factors such as sex, BMI and clinical domains may affect response to PsA therapy.

The major strength of our analysis is that we used the large data set from the SEAM-PsA RCT to address the uncertainties of the best means to measure disease activity and treatment outcomes in PsA. However, our analysis has a few limitations. Generalisability may be a key limitation as the treatment-naïve population enrolled in the SEAM-PsA RCT may not reflect the experiences of typical patients with moderate or severely active PsA. However, these results are likely most relevant to patients with early active PsA disease. Another limitation is the possible confounding of the data due to the variable

contributions of specific clinical measures to the differing composite outcome measures. A further limitation is that no adjustments for multiplicity were made and therefore the statistically significant differences indicated by the p values should be viewed from this perspective. Additionally, our analysis is based on pooled data from patients with early PsA treated with methotrexate and/or etanercept and does not address the impact of each individual treatment on predictors of response, which would require much larger patient populations in each treatment group.

In conclusion, findings from our analyses of data in patients with early PsA treated with methotrexate and/or etanercept for 24 weeks in the SEAM-PsA RCT suggest that presence of dactylitis and nail disease are positively associated with improved disease activity outcomes. However, presence of enthesitis and psoriasis-affected BSA ≥10% does not appear to be associated with improved disease outcomes. Further research is needed to confirm the preliminary findings that presence of dactylitis and to some extent nail disease but not enthesitis or psoriasis-affected BSA, may be predictive of improved outcomes in patients with early PsA treated with methotrexate and/or etanercept.

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