The Journal of Rheumatology 2022;49:885–93
doi:10.3899/jrheum.211037
First Release June 1 2022

The Journal of Rheumatology

Potential Impact of Sex and BMI on Response to Therapy in Psoriatic Arthritis: Post Hoc Analysis of Results From the SEAM-PsA Trial

Philip J. Mease[1], Dafna D. Gladman[2], Joseph F. Merola[3], Atul Deodhar[4], Alexis Ogdie[5], David H. Collier[6], Lyrica Liu[7], and Arthur Kavanaugh[8]

ABSTRACT. ***Objective.*** In this post hoc analysis, we examined the potential impact of sex and BMI on response in the Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis (SEAM-PsA) trial (NCT02376790), a 48-week, phase III, randomized controlled trial that compared outcomes with methotrexate (MTX) monotherapy, etanercept (ETN) monotherapy, and MTX+ETN combination therapy in patients with psoriatic arthritis (PsA) who were naïve to MTX and biologics.

Methods. We evaluated key outcomes at week 24 stratified by sex (male vs female) and BMI (kg/m^2; ≤ 30 vs > 30), including the American College of Rheumatology 20 (ACR20) criteria, minimal disease activity (MDA), very low disease activity (VLDA), and Psoriatic Arthritis Disease Activity Score (PASDAS). We analyzed data using descriptive statistics, normal approximation, logistic model, and analysis of covariance.

Results. A total of 851 patients completed the SEAM-PsA trial. Higher proportions of men than women who received MTX+ETN combination therapy achieved ACR20 (71.5% vs 58.3%; P = 0.02), MDA (45.8% vs 25.2%; P = 0.0003), and VLDA (19.1% vs 9.5%; P = 0.03), and men achieved better PASDAS (−3.0 vs −2.3; P = 0.0004). Patients with BMI ≤ 30 generally had better outcomes than those with BMI > 30 in some treatment arms for ACR20, MDA, VLDA, and PASDAS; however, there was no consistent pattern regarding the treatment arm in which the difference occurred.

Conclusion. Improved outcomes were observed more in men than in women for MDA and PASDAS with MTX+ETN combination therapy. Patients with BMI ≤ 30 had better outcomes than those with BMI > 30, with no clear pattern regarding treatment received. These findings suggest that contextual factors such as sex and BMI may affect response to PsA therapy.

Key Indexing Terms: body mass index, etanercept, methotrexate, psoriatic arthritis, sex

The study was funded by Immunex, a wholly owned subsidiary of Amgen Inc.

[1]P.J. Mease, MD, Director of Rheumatology Research, Swedish Medical Center/Providence St. Joseph Health, Seattle, Washington, and Clinical Professor, University of Washington, Seattle, Washington, USA; [2]D.D. Gladman, MD, FRCPC, Professor of Medicine, Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; [3]J.F. Merola, MD, Assistant Professor, Department of Dermatology and Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [4]A. Deodhar, MD, MRCP, Professor of Medicine and Medical Director of Rheumatology Clinics, Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, Oregon, USA; [5]A. Ogdie, MD, Associate Professor of Medicine, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [6]D.H. Collier, MD, Clinical Research Medical Director, Clinical Development, Amgen Inc., Thousand Oaks, California, USA; [7]L. Liu, PhD, Biostatistician, Global Biostatistics, Amgen Inc., Thousand Oaks, California, USA; [8]A. Kavanaugh, MD, Professor of Medicine, Division of Rheumatology, Allergy, and Immunology, University of California San Diego, La Jolla, California, USA.

PJM has received research grants and has served as a consultant or has been a speaker for AbbVie, Amgen, Boehringer Ingelheim, BMS, Celgene, Galapagos, Gilead, GSK, Janssen, Novartis, Pfizer, SUN Pharma, and UCB. DDG has received research grants from Amgen, AbbVie, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, and UCB; and has received consulting fees from Amgen, AbbVie, BMS, Celgene, Eli Lilly, Gilead, Galapagos, Janssen, Novartis, Pfizer, and UCB. JFM has received consulting fees from Merck, AbbVie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Celgene, Sanofi, Regeneron, Arena, SUN Pharma, Biogen, Pfizer, EMD Serono, Avotres, and Leo Pharma. AD has received research grants from AbbVie, GSK, Novartis, Pfizer, and UCB, and has received consulting fees from AbbVie, Amgen, Boehringer Ingelheim, BMS, Celgene, Gilead, GSK, Janssen, Novartis, Pfizer, and UCB. AO has received research grants from AbbVie, Novartis, and Pfizer to University of Pennsylvania and Amgen to FORWARD/NDB; has received consulting fees from AbbVie, Amgen, BMS, Celgene, CorEvitas, Gilead, Janssen, Eli Lilly, Novartis, Pfizer, and UCB; and reports receipt of royalties from Novartis (to spouse). DHC is an employee of and owns stock in Amgen. LL is an employee of and owns stock in Amgen. AK declares no conflicts of interest relevant to this work.

Address correspondence to Dr. P.J. Mease, Rheumatology Research, Swedish Medical Center/Providence St. Joseph Health, 601 Broadway, Seattle, WA 98122, USA. Email: pmease@philipmease.com.

Accepted for publication March 25, 2022.

Psoriatic arthritis (PsA) is a chronic inflammatory disease that involves both joint- and skin-related manifestations. In patients with psoriasis (PsO), about 30% develop PsA, with an annual incidence of 1% to 3%.[1,2,3] Patients with PsA experience many symptoms, including peripheral and axial joint inflammation, enthesitis, dactylitis, nail disease, and PsO.[2] PsA is associated with considerable disease burden, including physical function that is below that of age- and gender-matched norms,[4] pain, fatigue, and decreased work productivity.[5,6,7,8]

Effective PsA management requires not only timely diagnosis and treatment but also recognition that efficacy of treatments may be affected by contextual factors such as sex, weight, and BMI.[9,10] Similar numbers of men and women develop PsA, but differences between sexes may occur in PsA clinical expression and response to therapy.[10,11] Patients with PsA are more likely than the general population to be obese, which may reduce response to therapy.[9,10,12,13]

Various PsA treatments are currently in clinical use.[14] These include conventional synthetic disease-modifying antirheumatic drugs (csDMARDs; methotrexate [MTX], sulfasalazine, leflunomide, cyclosporine); biological therapies such as tumor necrosis factor inhibitors (TNFi; etanercept [ETN], adalimumab [ADA], infliximab, certolizumab pegol, and golimumab), interleukin (IL)-17 inhibitors (secukinumab and ixekizumab), the IL-12/23 inhibitor ustekinumab, the IL-23 inhibitor guselkumab, and abatacept; and targeted synthetic DMARDs (tsDMARDs) such as Janus kinase inhibitor (tofacitinib) and phosphodiesterase-4 inhibitor (apremilast).[14,15,16,17,18] Of these, MTX and TNFi are the most commonly used systemic therapies in PsA.

Although MTX, as monotherapy or in combination regimens, is widely used to treat PsA, the evidence supporting its use in this disease setting is relatively limited. Further, no PsA randomized controlled trials (RCTs) have examined how sex and BMI may affect response to therapy in patients when directly comparing MTX with a TNFi or MTX in combination with a TNFi.

The Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis (SEAM-PsA) RCT[19] reported that both ETN monotherapy and MTX+ETN combination therapy were statistically significantly more effective than MTX monotherapy by the percentage of patients who were American College of Rheumatology 20% responders (ACR20) and had minimal disease activity (MDA) at week 24. Week 48 safety outcomes indicated that safety profiles were similar across the treatment groups.[19] In the present study, we used the large dataset from the SEAM-PsA RCT[19] to examine the potential impact of sex and BMI on response to MTX monotherapy, ETN monotherapy, or MTX+ETN combination therapy in patients with early PsA and who were naïve to treatment with MTX or biologics.

METHODS

Study design and patients. SEAM-PsA was a 48-week, phase III, multicenter RCT (ClinicalTrials.gov: NCT02376790). Trial details have been previously published.[19,20] Briefly, key patient eligibility criteria included those who were age ≥ 18 years at screening, met PsA diagnosis by Classification Criteria for Psoriatic Arthritis (CASPAR),[21] were naïve to ETN and other biologic agents, and had no prior MTX use for PsA (prior MTX treatment for PsO was allowed). Patients were randomized 1:1:1 to receive: (1) oral MTX to a target of 20 mg weekly plus subcutaneous (SC) placebo weekly, (2) SC ETN 50 mg weekly plus oral placebo weekly, or (3) oral MTX to a target of 20 mg weekly plus SC ETN 50 mg weekly.

The SEAM-PsA trial has been completed and 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.

Outcomes at week 24 adjusted by sex and BMI. The primary endpoint of the SEAM-PsA trial was the percentage of ACR20 responders at week 24; the key secondary endpoint was the percentage of patients with MDA at week 24. These results have been previously published.[19] In the current article, we report results from the SEAM-PsA trial examining the effect of MTX monotherapy, ETN monotherapy, and MTX+ETN combination therapy on key outcomes at week 24 stratified by sex (male vs female) and BMI (calculated as weight in kilograms divided by height in meters squared [kg/m^2]; ≤ 30 vs > 30), including ACR20; MDA; very low disease activity (VLDA); Psoriatic Arthritis Disease Activity Score (PASDAS); Disease Activity Index for Psoriatic Arthritis (DAPSA); the enthesitis outcome of the Spondyloarthritis Research Consortium of Canada (SPARCC); the nail outcome of the modified Nail Psoriasis Severity Index (mNAPSI); the PsO outcomes of PsO-affected body surface area (BSA) and static physician global assessment (sPGA); and the patient-reported outcomes (PROs) of Health Assessment Questionnaire–Disability Index (HAQ-DI), patient global assessment of disease activity (PtGA), patient global assessment of joint pain (PtGAJP), and the 36-item Short Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS).

For ACR20, MDA, and VLDA outcomes, we determined the percentage of patients achieving the outcome at week 24 using the full analysis set. This set included all randomized patients analyzed according to randomization assignment (intent-to-treat analysis; 284 in the MTX monotherapy arm, 284 in the ETN monotherapy arm, and 283 in the MTX+ETN combination therapy arm). For PASDAS, DAPSA, and PROs, we determined score change from baseline to week 24 using the full analysis set. For enthesitis, we determined score change from baseline to week 24 in SPARCC using the SPARCC enthesitis analysis set. This set included all randomized patients with nonzero SPARCC enthesitis at baseline (191 in the MTX monotherapy arm, 189 in the ETN monotherapy arm, and 196 in the MTX+ETN combination therapy arm). For nail outcomes, we determined score change from baseline to week 24 in mNAPSI using the mNAPSI analysis set. This set included all randomized patients with nonzero mNAPSI at baseline (185 in the MTX monotherapy arm, 206 in the ETN monotherapy arm, and 197 in the MTX+ETN combination therapy arm). For PsO outcomes in patients with baseline BSA ≥ 3% and ≥ 10%, we determined percentage improvement from baseline to week 24 in PsO-affected BSA and percentage of patients with a score of clear (0) or almost clear (1) in sPGA at week 24 in the full analysis set. Missing data were imputed as nonresponder data for ACR20 and MDA but not imputed for VLDA, PASDAS, SPARCC, mNAPSI, BSA, sPGA, and PRO scores.

Statistical analysis. We used descriptive statistics to examine outcomes within each treatment arm by sex (male vs female) or BMI category (≤ 30 vs > 30) and normal approximation to determine differences between males and females or BMI categories, using risk difference for dichotomous outcomes and *t* test for continuous outcomes. We used a logistic model for dichotomous outcomes and an ANCOVA model for continuous outcomes to examine the impact of the interaction of sex and treatment arms as well as the impact of the interaction of BMI and treatment arms by adjusting for prior use of a nonbiologic DMARD when comparing MTX monotherapy arm to the ETN arms. *P* values in all analyses were not adjusted for multiplicity and are considered nominal.

Statement of ethics and consent. The current analysis is a post hoc analysis of data from the SEAM-PsA trial in which none of the authors treated patients; ethical approval and informed consent are not required for this type of post hoc analysis.

RESULTS

Baseline patient demographics and disease activity. A total of 851 patients completed the SEAM-PsA trial; 284 in the MTX monotherapy arm, 284 in the ETN monotherapy arm, and 283 in the MTX+ETN combination therapy arm.[19] Patients across the study arms had similar baseline demographics (Supplementary Table 1, available with the online version of this article). Most patients were White (90.7%) and mean age was 48.4 years. Most patients were early in the course of their disease, with a mean PsA duration of 3.2 years (median 0.6 yrs). Slightly over half of the patients (54.0%) had BMI ≤ 30. As previously published,[19] patients in the treatment arms that received MTX achieved and maintained a mean MTX dose of > 18.8 mg (median 20 mg) per week.

Stratified by sex (Table 1), some baseline disease activity measures were slightly higher in women than men, especially with MTX+ETN combination therapy. Mean swollen joint count in 66 joints was significantly higher in women than men with MTX+ETN combination therapy (12.7 vs 9.8, $P = 0.008$) but similar in women and men with MTX monotherapy (12.0 and 14.1, respectively, $P > 0.05$) and ETN monotherapy (11.3 and 11.7, respectively, $P > 0.05$). Mean tender joint count in 68 joints was significantly higher in women than men with MTX+ETN combination therapy (22.7 vs 17.4, $P = 0.004$) but similar in women and men with MTX monotherapy (21.3 and 20.4, respectively, $P > 0.05$) and ETN monotherapy (19.4 and 18.4, respectively, $P > 0.05$). Mean SPARCC was higher in women than men with MTX monotherapy (4.4 vs 3.2, $P = 0.03$) and MTX+ETN combination therapy (4.8 vs 3.5, $P = 0.02$) but similar in women and men with ETN monotherapy (4.0 and 3.4, respectively, $P > 0.05$). However, mean BSA was significantly higher in men than women with MTX monotherapy (14.4 vs 11.3, $P = 0.04$) but similar in men and women with ETN monotherapy (12.0 and 9.4, respectively, $P > 0.05$) and MTX+ETN combination therapy (11.6 and 9.8, respectively, $P > 0.05$). Of note, PsA duration was similar in men and women across the treatment arms (Table 1).

Stratified by BMI (Table 2), some baseline disease activity measures differed between BMI categories, with the BMI ≤ 30 category being associated with less disease activity but with no discernable association with the treatments. Swollen joint count, tender joint count, and SPARCC were significantly lower in the BMI ≤ 30 category than the BMI > 30 category with MTX monotherapy and MTX+ETN combination therapy but similar in the BMI categories with ETN monotherapy (Table 2). The opposite results were observed for sPGA, with significantly lower sPGA in the BMI ≤ 30 category than the BMI > 30 category with ETN monotherapy and similar sPGA for the BMI categories with MTX monotherapy and MTX+ETN combination therapy.

Table 1. Baseline disease activity by sex.

	MTX Monotherapy, N = 284			ETN Monotherapy, N = 284			MTX+ETN Combination Therapy, N = 283		
	Male	Female	*P*, Male vs Female[a,b]	Male	Female	*P*, Male vs Female[a,b]	Male	Female	*P*, Male vs Female[a,b]
PsA duration, yrs	3.8 (0.7)	3.6 (0.6)	–	3.8 (0.6)	2.3 (0.5)	–	3.1 (0.5)	2.8 (0.6)	–
SJC66	14.1 (1.1)	12.0 (0.6)	–	11.7 (0.8)	11.3 (0.8)	–	9.8 (0.6)	12.7 (0.9)	0.008
TJC68	20.4 (1.5)	21.3 (1.1)	–	18.4 (1.2)	19.4 (1.3)	–	17.4 (1.1)	22.7 (1.4)	0.004
PGA, 0–100	57.0 (1.8)	59.8 (1.5)	–	57.5 (1.6)	59.3 (1.4)	–	56.1 (1.4)	59.9 (1.6)	–
CRP, mg/L	10.9 (1.5)	10.2 (1.2)	–	11.3 (1.4)	10.1 (1.1)	–	7.8 (0.8)	9.6 (1.2)	–
SPARCC enthesitis	3.2 (0.4)	4.4 (0.4)	0.03	3.4 (0.3)	4.0 (0.4)	–	3.5 (0.3)	4.8 (0.4)	0.02
sPGA	2.6 (0.1)	2.6 (0.1)	–	2.7 (0.1)	2.5 (0.1)	–	2.6 (0.1)	2.4 (0.1)	–
sPGA status, n (%)									
< 2	22 (7.7)	26 (9.2)	–	16 (5.6)	24 (8.5)	–	22 (7.8)	30 (10.6)	–
≥ 2	101 (35.6)	132 (46.5)	–	135 (47.5)	109 (38.4)	–	122 (43.1)	109 (38.5)	–
BSA, %	14.4 (1.8)	11.3 (1.4)	0.04	12.0 (1.3)	9.4 (1.2)	–	11.6 (1.4)	9.8 (1.2)	–
BSA									
< 3%, n (%)	40 (14.1)	52 (18.3)	–	51 (18.0)	54 (19.0)	–	51 (18.0)	55 (19.4)	–
≥ 3%, n (%)	84 (29.6)	108 (38.0)	–	100 (35.2)	79 (27.8)	–	93 (32.9)	84 (29.7)	–
HAQ-DI	1.1 (0.1)	1.4 (0.1)	< 0.0001	1.0 (0.1)	1.3 (0.1)	0.0001	1.0 (0.1)	1.3 (0.1)	< 0.0001
PtGA, 0–100	57.3 (2.0)	63.3 (1.8)	0.02	61.9 (1.9)	64.1 (1.8)	–	57.9 (1.7)	64.1 (1.8)	0.01
PtGAJP, 0–100	53.6 (1.8)	58.0 (1.8)	–	53.9 (1.9)	59.4 (1.8)	0.04	51.9 (1.7)	59.5 (1.9)	0.003
SF-36 PCS	36.9 (0.8)	34.6 (0.6)	0.02	38.4 (0.7)	37.2 (0.7)	–	39.5 (0.8)	35.2 (0.8)	0.0001
SF-36 MCS	47.1 (1.1)	43.7 (1.00)	0.02	46.2 (1.0)	43.9 (1.1)	–	47.7 (0.9)	44.8 (1.0)	0.03

Values are expressed as mean (SE) unless otherwise stated. [a] *P* values are nominal. [b] Only *P* values ≤ 0.05 are shown. BSA: body surface area; CRP: C-reactive protein; ETN: etanercept; HAQ-DI: Health Assessment Questionnaire–Disability Index; MTX: methotrexate; MCS: Mental Component Summary; PCS: Physical Component Summary; PGA: physician global assessment; PsA: psoriatic arthritis; PtGA: patient global assessment of disease activity; PtGAJP: patient global assessment of joint pain; SE: standard error; SF-36: 36-item Short Form Health Survey; SJC66: swollen joint count in 66 joints; SPARCC: Spondyloarthritis Research Consortium of Canada; sPGA: static physician global assessment (of psoriasis); TJC68: tender joint count in 68 joints.

Table 2. Baseline disease activity by BMI (kg/m²).

	MTX Monotherapy, N = 284			ETN Monotherapy, N = 284			MTX+ETN Combination Therapy, N = 283		
	BMI, ≤ 30	BMI, > 30	$P^{a,b}$, BMI ≤ 30 vs > 30	BMI, ≤ 30	BMI, > 30	$P^{a,b}$, BMI ≤ 30 vs > 30	BMI, ≤ 30	BMI, > 30	$P^{a,b}$, BMI ≤ 30 vs > 30
PsA duration, yrs	3.9 (0.6)	3.4 (0.6)	–	2.8 (0.4)	3.5 (0.7)	–	3.9 (0.6)	1.9 (0.4)	0.01
SJC66	11.1 (0.7)	14.9 (0.9)	0.001	11.2 (0.7)	11.9 (1.0)	–	10.1 (0.6)	12.7 (1.0)	0.02
TJC68	18.4 (1.2)	23.6 (1.3)	0.003	17.3 (1.1)	20.7 (1.3)	–	18.0 (1.1)	22.6 (1.5)	0.01
PGA, 0–100	57.1 (1.6)	60.2 (1.7)	–	58.2 (1.5)	58.7 (1.6)	–	56.6 (1.4)	59.8 (1.6)	–
CRP, mg/L	9.6 (1.4)	11.5 (1.3)	–	10.5 (1.5)	11.1 (1.1)	–	8.0 (1.0)	9.6 (0.9)	–
SPARCC enthesitis	3.3 (0.3)	4.4 (0.4)	0.03	3.6 (0.3)	3.8 (0.4)	–	3.6 (0.3)	4.8 (0.4)	0.04
sPGA	2.5 (0.1)	2.7 (0.1)	–	2.5 (0.1)	2.8 (0.1)	0.02	2.5 (0.1)	2.5 (0.1)	–
sPGA status									
< 2, n (%)	24 (8.5)	24 (8.5)	–	25 (8.8)	15 (5.3)	–	27 (9.5)	25 (8.8)	–
≥ 2, n (%)	120 (42.3)	113 (39.8)	–	128 (45.1)	116 (40.8)	–	133 (47.0)	98 (34.6)	–
BSA, %	12.3 (1.5)	13.1 (1.7)	–	10.9 (1.2)	10.4 (1.2)	–	10.2 (1.1)	11.5 (1.6)	–
BSA									
< 3%, n (%)	42 (14.8)	50 (17.6)	–	58 (20.4)	47 (16.5)	–	62 (21.9)	44 (15.5)	–
≥ 3%, n (%)	104 (36.6)	88 (31.0)	–	95 (33.5)	84 (29.6)	–	98 (34.6)	79 (27.9)	–
HAQ-DI	1.2 (0.1)	1.4 (0.1)	0.03	1.1 (0.1)	1.3 (0.1)	0.003	1.1 (0.1)	1.3 (0.1)	0.002
PtGA, 0–100	58.3 (2.0)	63.2 (1.7)	–	63.2 (1.9)	62.6 (1.8)	–	61.0 (1.7)	60.9 (1.8)	–
PtGAJP, 0–100	54.9 (1.8)	57.4 (1.8)	–	55.0 (1.9)	58.3 (1.8)	–	55.0 (1.8)	56.5 (1.8)	–
SF-36 PCS	37.1 (0.7)	33.9 (0.7)	0.001	38.7 (0.7)	36.7 (0.7)	0.04	38.3 (0.7)	36.2 (0.8)	–
SF-36 MCS	45.6 (1.0)	44.7 (1.1)	–	46.1 (1.0)	44.0 (1.1)	–	45.3 (0.9)	47.5 (1.0)	–

Values are expressed as mean (SE) unless otherwise stated. [a] *P* values are nominal. [b] Only *P* values ≤ 0.05 are shown. BSA: body surface area; CRP: C-reactive protein; ETN: etanercept; HAQ-DI, Health Assessment Questionnaire–Disability Index; MCS: Mental Component Summary; MTX: methotrexate; PCS: Physical Component Summary; PGA: physician global assessment; PsA: psoriatic arthritis; PtGA: patient global assessment of disease activity; PtGAJP: patient global assessment of joint pain; SE: standard error; SF-36: 36-item Short Form Health Survey; SJC66: swollen joint count in 66 joints; SPARCC: Spondyloarthritis Research Consortium of Canada; sPGA: static physician global assessment (of psoriasis); TJC68: tender joint count in 68 joints.

Of note, PsA duration was similar for the BMI categories with MTX monotherapy and ETN monotherapy but significantly higher in the BMI ≤ 30 category than the BMI > 30 category with MTX+ETN combination therapy (Table 2).

Patient outcomes at week 24 stratified by sex. Descriptive analyses of data stratified by sex within each treatment arm at week 24 showed that both sexes had similar outcomes for ACR20, MDA, VLDA, and PASDAS measures with MTX monotherapy and ETN monotherapy (Figure 1). With MTX+ETN combination therapy, men had significantly better outcomes than women, as determined by the proportion of patients achieving ACR20 (71.5% vs 58.3%, $P = 0.02$), MDA (45.8% vs 25.2%, $P = 0.0003$), and VLDA (19.1% vs 9.5%, $P = 0.03$; Figure 1A). Men also had significantly better outcomes than women for PASDAS with MTX+ETN combination therapy (Figure 1B), with change in PASDAS from baseline to week 24 of –3.0 vs –2.3 ($P = 0.0004$). No differences were observed between the sexes for DAPSA, SPARCC enthesitis score, mNAPSI nail outcome, PsO-affected BSA, or sPGA for MTX monotherapy, ETN monotherapy, and MTX+ETN combination therapy (data not shown). Also, no differences were observed between the sexes for the PROs of HAQ-DI, PtGA, PtGAJP, SF-36 PCS, and SF-36 MCS (Supplementary Table 2, available with the online version of this article).

Modeling analyses of the outcomes between treatment arms at week 24 stratified by sex showed that men had a significantly more favorable response than women with MTX+ETN combination therapy for MDA and PASDAS (Figure 2). Within each treatment arm, there was no difference between the least squares estimate for males and females (male minus female) in the MTX monotherapy and the ETN monotherapy arms; this difference was 0.2 in the MTX+ETN combination therapy arm (Figure 2A). When compared with MTX monotherapy, the treatment difference estimate for achieving MDA at week 24 for men vs women was 0.2 ($P = 0.02$) for MTX+ETN combination therapy, whereas there was no difference ($P = 0.86$) with ETN monotherapy (Figure 2A). Within each treatment arm the difference between the least squares estimate for males and females was 0.2 with MTX monotherapy, 0.1 with ETN monotherapy, and –0.7 with MTX+ETN combination therapy (Figure 2B). When compared with MTX monotherapy, the treatment difference estimate for achieving PASDAS at week 24 for men vs women was –0.9 ($P = 0.002$) with MTX+ETN combination therapy, whereas there was no difference ($P = 0.96$) with ETN monotherapy (Figure 2B). No differences between the sexes were detected for ACR20, VLDA, DAPSA, SPARCC enthesitis score, mNAPSI nail outcome, PsO-affected BSA, or sPGA across treatment arms (data not shown).

Patient outcomes at week 24 stratified by BMI. Analyses of data stratified by BMI within each treatment arm at week 24 showed that patients with BMI ≤ 30 generally had better outcomes than those with BMI > 30 in some treatment arms for ACR20, MDA, VLDA (Figure 3A), PASDAS (Figure 3B), and BSA (Figure 3C,D). There was no consistent pattern regarding the

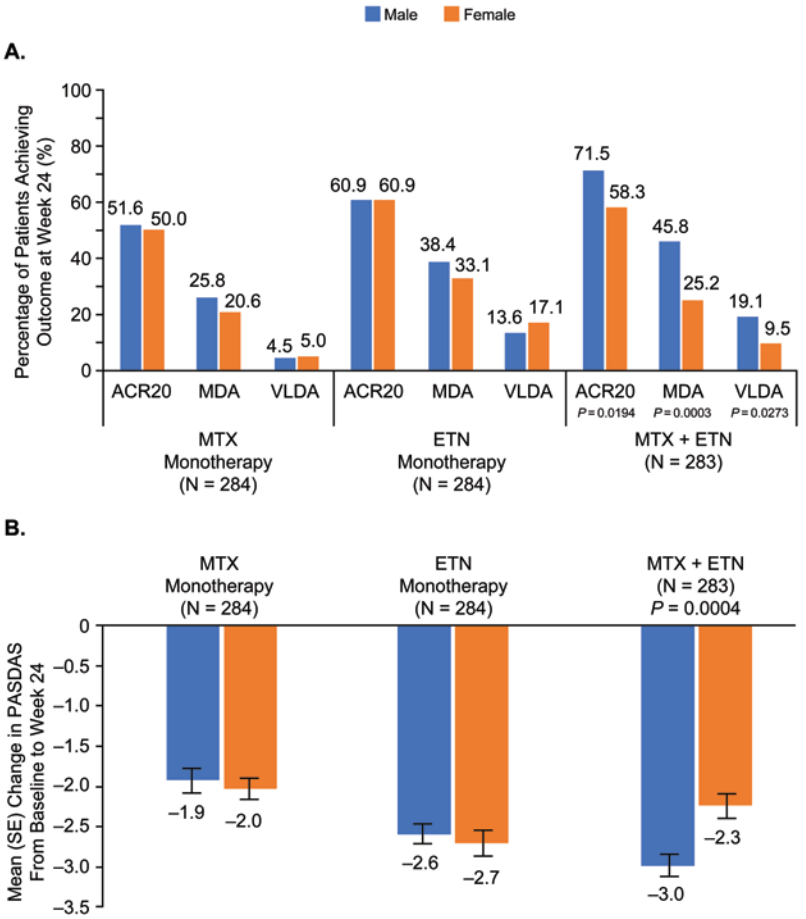

Figure 1. (A) Effect of MTX monotherapy, ETN monotherapy, and MTX+ETN combination therapy on the percentage of patients achieving ACR20, MDA, VLDA at week 24 by sex, and (B) mean change in PASDAS from baseline to week 24 by sex. N = no. of patients in the full analysis set. Descriptive statistics were used to examine outcomes within each treatment arm. *P* values were estimated from the normal approximation and are nominal; only *P* values ≤ 0.05 are shown. ACR: American College of Rheumatology; ETN: etanercept; MDA: minimal disease activity; MTX: methotrexate; PASDAS: Psoriatic Arthritis Disease Activity Score; SE: standard error; VLDA: very low disease activity.

treatment arm in which the difference occurred. No differences were observed between BMI categories for DAPSA, SPARCC enthesitis score, or mNAPSI nail outcome across treatment arms (data not shown). No significant differences were observed between BMI categories for the PROs of HAQ-DI, PtGA, PtGAJP, SF-36 PCS, and SF-36 MCS with ETN monotherapy and MTX+ETN combination therapy (Supplementary Table 3, available with the online version of this article). For MTX monotherapy, no significant differences were observed between BMI categories for PtGA, SF-36 PCS, and SF-36 MCS; however, significant differences were observed in mean change from baseline to week 24 in HAQ-DI score (−0.5 vs −0.3; $P = 0.006$, respectively) and PtGAJP score (−24.5 vs −16.8; $P = 0.03$) between patients with BMI ≤ 30 and those with BMI > 30 (Supplementary Table 3).

Modeling analyses of outcomes between treatment arms at week 24 stratified by BMI in patients with baseline BSA ≥ 3% showed that patients had similar responses for sPGA across the treatment arms regardless of BMI category (Figure 4A). Analyses of outcomes between treatment arms at week 24 stratified by BMI in patients with baseline BSA ≥ 10% showed that patients with BMI ≤ 30 than those with BMI > 30 had a more favorable response for sPGA with MTX+ETN combination therapy (Figure 4B). When compared with MTX monotherapy, the treatment difference estimate for achieving sPGA score of clear or almost clear at week 24 for BMI ≤ 30 vs BMI > 30 was 0.27 ($P = 0.047$) with MTX+ETN combination therapy vs 0.04 ($P = 0.75$) with ETN monotherapy. No differences between BMI categories were detected for ACR20, MDA, VLDA, PASDAS, DAPSA, SPARCC enthesitis score, or mNAPSI nail outcome across treatment arms (data not shown).

DISCUSSION

We used the large dataset from the SEAM-PsA RCT[19] to examine the potential impact of sex and BMI on response to MTX monotherapy, ETN monotherapy, or MTX+ETN combination therapy in patients with early PsA. After 24 weeks of treatment and with the results stratified by sex (male vs female) and BMI (≤ 30 vs > 30) within each treatment arm, responses for the outcomes of ACR20, MDA, VLDA, and PASDAS were comparable between men and women with MTX and ETN monotherapy. With MTX+ETN combination therapy, men had significantly better outcomes than women. However, the response with ETN monotherapy was slightly higher than that with MTX monotherapy for these outcomes. As such, ETN monotherapy appears to work for both men and women, although the magnitude of improvement is slightly lower than that for MTX+ETN combination in men in select outcomes. Stratified by BMI between treatment arms, patients with BMI ≤ 30 than those with BMI > 30 had a more favorable response for sPGA with MTX+ETN combination therapy vs MTX monotherapy. No differences between the sexes or BMI

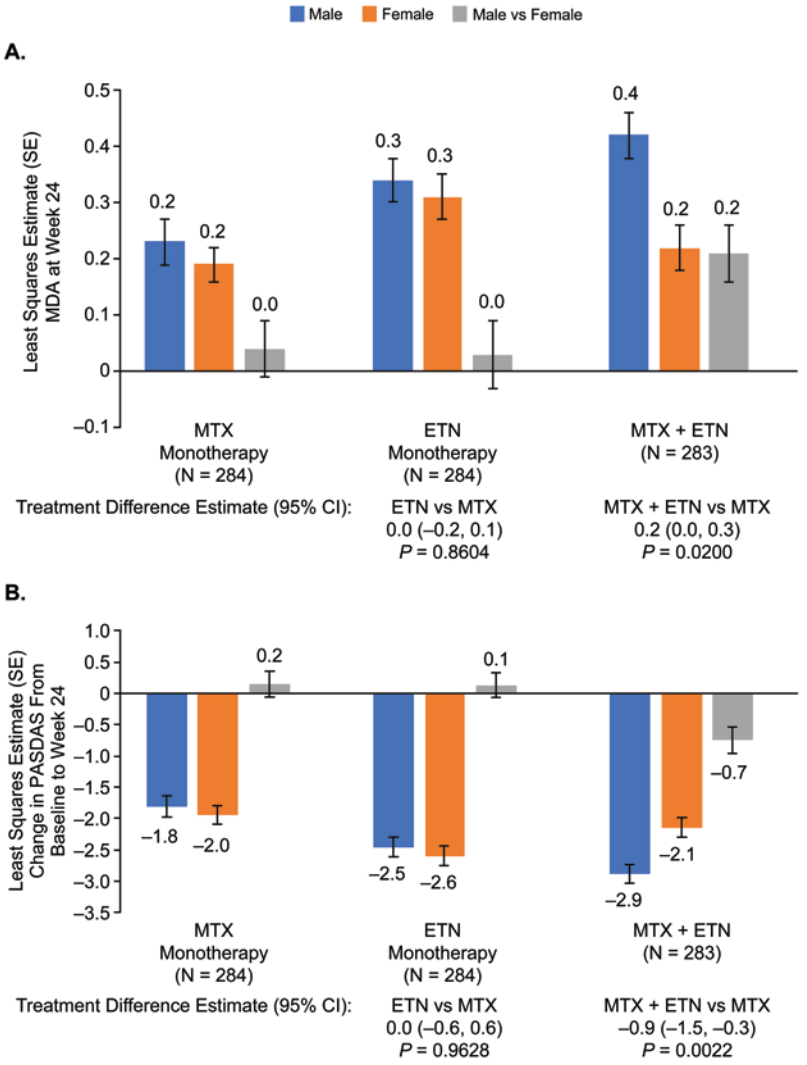

Figure 2. Effect of MTX monotherapy, ETN monotherapy, and MTX+ETN combination therapy on MDA and PASDAS at week 24 by sex (modeling analyses). (A) Least squares estimate MDA at week 24. (B) Least squares estimate change in PASDAS from baseline to week 24. N = no. of patients in the full analysis set. The mean differences between BMI categories were estimated from the normal approximation. For MDA, treatment differences and *P* values for comparison with MTX monotherapy were based on logistic model adjusted for prior nonbiologic DMARD use, baseline BMI status (kg/m^2; ≤ 30 or > 30), gender, and treatment*gender interaction term. For PASDAS change, treatment differences and *P* values for comparison with MTX monotherapy were based on ANCOVA model adjusted for prior nonbiologic DMARD use, baseline BMI status (≤ 30 or > 30), and treatment*gender interaction term. *P* values are for the treatment difference in ETN arms to MTX monotherapy for the difference of male vs female and are nominal with no adjustments for multiplicity. DMARD: disease-modifying antirheumatic drug; ETN: etanercept; MDA: minimal disease activity; MTX: methotrexate; PASDAS: Psoriatic Arthritis Disease Activity Score; SE: standard error.

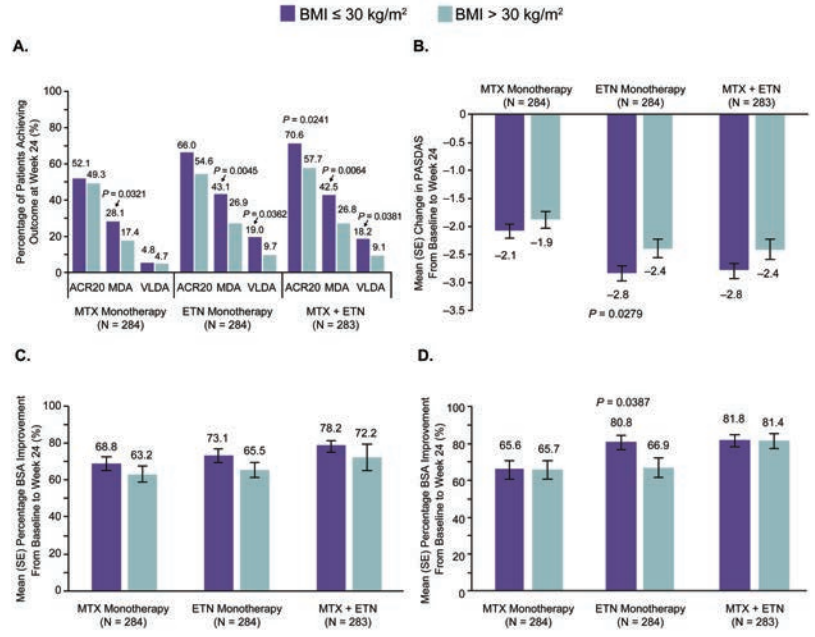

Figure 3. Effect of MTX monotherapy, ETN monotherapy, and MTX+ETN combination therapy on ACR20, MDA, VLDA, PASDAS, and BSA at week 24 by BMI category (descriptive statistics). (A) Percentage of patients achieving ACR20, MDA, and VLDA at week 24. (B) Mean change in PASDAS from baseline to week 24. (C) Mean percentage of BSA improvement from baseline to week 24 in patients with baseline BSA ≥ 3%. (D) Mean percentage of BSA improvement from baseline to week 24 in patients with baseline BSA ≥ 10%. N = no. of patients in the full analysis set. Descriptive statistics were used to examine outcomes within each treatment arm. *P* values were estimated from the normal approximation and are nominal; only *P* values ≤ 0.05 are shown. ACR: American College of Rheumatology; BSA: body surface area; ETN: etanercept; MDA: minimal disease activity; MTX: methotrexate; PASDAS: Psoriatic Arthritis Disease Activity Score; SE: standard error; VLDA: very low disease activity.

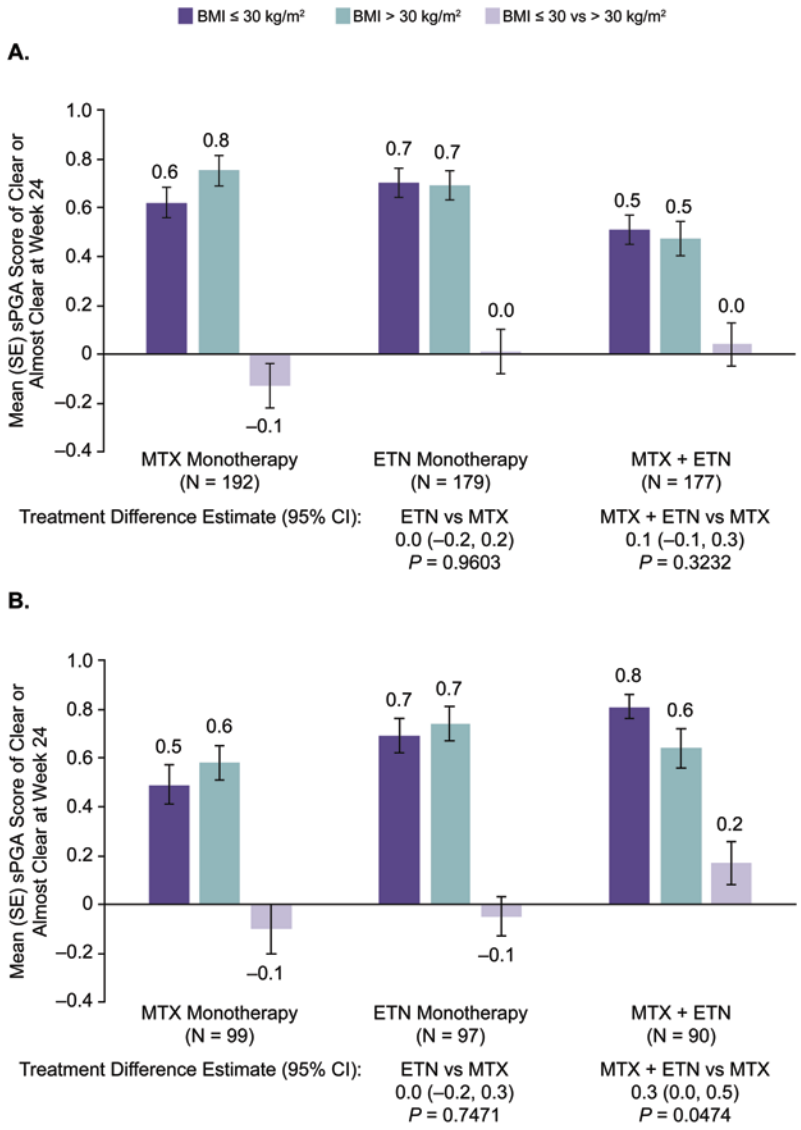

Figure 4. Effect of MTX monotherapy, ETN monotherapy, and MTX+ETN combination therapy on sPGA score at week 24 by BMI category (descriptive statistics for baseline BSA ≥ 3% and modeling analyses for baseline BSA ≥ 10%). (A) Achieving an sPGA score of clear (0) or almost clear (1) at week 24 in patients with baseline BSA ≥ 3%. (B) Achieving an sPGA score of clear (0) or almost clear (1) at week 24 in patients with baseline BSA ≥ 10%. N = no. of patients in the full analysis set with BSA ≥ 3% or ≥ 10% at baseline. The mean differences between BMI categories were estimated from the normal approximation. Treatment differences and *P* values for comparison with MTX monotherapy were based on logistic model adjusted for prior nonbiologic DMARD use, baseline BMI status (kg/m²; ≤ 30 or > 30) and treatment*BMI status interaction term. *P* values are for the treatment difference in ETN arms to MTX monotherapy for the difference of BMI ≤ 30 vs > 30 and are nominal with no adjustments for multiplicity. BSA: body surface area; DMARD: disease-modifying antirheumatic drug; ETN: etanercept; MTX: methotrexate; SE: standard error; sPGA: static physician global assessment.

categories were detected for some of the outcomes, including DAPSA, SPARCC enthesitis score, mNAPSI nail outcome, or PsO outcomes of PsO-affected BSA and sPGA across treatment arms. No significant differences were observed between sexes for PROs across treatment arms. No significant differences were observed between BMI categories for the PROs across treatment arms, except with MTX monotherapy, where patients in the BMI ≤ 30 category showed greater improvements in HAQ-DI and PtGAJP scores than those in the BMI > 30 category.

A previous study reported greater baseline disease severity in women than men, including higher tender joint count, patient global assessment, HAQ-DI, PsA pain, and enthesitis.[22] Further, higher efficacy overall was demonstrated in men vs women at week 52 of treatment with secukinumab vs ADA.[22] We observed similar results with MTX+ETN combination therapy in our study, with better outcomes seen in men for some disease measures, including ACR20, MDA, VLDA, and PASDAS. The results from our study could partly be explained by the fact that women had overall higher disease activity than men at baseline with MTX+ETN combination therapy. However, overall, the basis for the differences between men and women in disease severity or in response to treatment is not fully understood. In general, women tend to have a higher degree of central sensitization, which may at least partly account for the higher disease activity at baseline as well as after treatment. Results from an earlier study[23] alluded to the potential for disease activity measures with subjective elements to be driven, at least partly, by central sensitization rather than true differences in inflammatory disease states, implying that the higher disease activity observed in women in our study might not reflect the true inflammatory disease. However, biological-based factors may also play a role in the differences in disease severity and response to treatment between men and women, including the difference in sex hormones and their effects on the immune system and inflammatory responses.[24] Estrogens are viewed as enhancers of immune response, and androgens, progesterone, and glucocorticoids as natural suppressors of immune response.[25] Recent data suggest that

estrogens may regulate the activity of regulatory T cells.[26] More work is warranted to understand the factors that drive the differences between men and women in PsA disease severity or in treatment response.

In our analysis, differences between the 2 BMI categories were detected mainly with ETN, either as monotherapy or in combination with MTX. Patients with BMI ≤ 30 generally had better outcomes than those with BMI > 30. Results from prior studies support the observation from our analysis that lower BMI might be associated with more favorable outcomes in patients with PsA. A cohort study at a single center showed that overweight patients (BMI = 25–30) and obese patients (BMI > 30) with PsA were less likely to achieve sustained MDA compared with those of normal weight (BMI < 25).[27] In 557 patients with 36.2% classified as overweight and 35.4% classified as obese, patients in the higher BMI categories were likely to achieve sustained MDA than those in the lowest BMI category (overweight: odds ratio [OR] 0.66, $P = 0.003$; obese: OR 0.53, $P < 0.0001$).[27] Another study showed differential risk factors that may drive the inflammatory process in PsA, with obesity linked with late-onset PsO and PsA, whereas normal weight was associated with an earlier onset of PsA.[28] A study that analyzed the frequency of obesity and occurrence of obesity-associated factors in a cohort of patients with PsA showed that obesity is common in psoriatic disease.[29] A case series study that analyzed the relationship between obesity and PsA showed that obesity at age 18 years increases the risk of developing PsA.[30]

Other prior studies support the observation from our analysis that both men and lower BMI might be associated with more favorable treatment outcomes in patients with PsA. A cohort study that investigated the effect of obesity in response to TNFi in the DANBIO and ICEBIO registries showed that obesity was associated with higher disease activity and seemed to diminish response and adherence to TNFi in PsA.[13] Further, male gender was strongly associated with greater TNFi treatment effectiveness.[10] A CorEvitas (formerly known as Corrona) rheumatoid arthritis registry study showed that sex, obesity, and baseline disease activity are important predictors of achieving remission and/or low disease activity among patients with PsA initiating TNFi.[9]

Our analysis has a few limitations. The key limitation is the generalizability of results, as the treatment-naïve population enrolled in the SEAM-PsA RCT may not reflect experiences of typical patients with severe or moderate PsA. However, our results are likely most relevant to patients with relatively early, active PsA. Another limitation is the lack of a placebo group in the SEAM-PsA trial. This is important because including a placebo arm could help contextualize the results of this trial with prior RCTs in PsA, as it is well known that active comparator trials, without placebo, result in higher responses since all patients have higher "expectation bias," knowing they are all receiving active treatment.[31,32] However there are ethical issues regarding prolonged placebo exposure in patients with active disease, especially with early PsA. A further limitation is the post hoc nature of our analysis. Additionally, even though adjustments were made for differences in some baseline characteristics in the modeling analyses (Figure 2 and Figure 4), these adjustments were not made for the descriptive analyses (Figure 1 and Figure 3). Another limitation is that our analysis did not evaluate whether the same effective MTX dose was achieved for men and women or whether obese patients required a higher MTX dose to achieve the same effect. The targeted dose per the study protocol was 20 mg weekly, and as previously published, patients in the MTX arms achieved and maintained a mean MTX dose of > 18.8 mg (median 20 mg) per week.[19]

In conclusion, results from our analysis show significantly more improved outcomes in men than in women for MDA and PASDAS with MTX+ETN combination therapy. Patients with BMI ≤ 30 generally showed better outcomes than those with BMI > 30, with no clear pattern regarding treatment received. These findings suggest that contextual factors such as sex and BMI may affect response to PsA therapy.

ACKNOWLEDGMENT

Julie Wang (Amgen Inc.) and Martha Mutomba (on behalf of Amgen Inc.) provided medical writing support.

DATA SHARING POLICY

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Eder L, Haddad A, Rosen CF, et al. The incidence and risk factors for psoriatic arthritis in patients with psoriasis: a prospective cohort study. Arthritis Rheumatol 2016;68:915-23.
2. Menter A. Psoriasis and psoriatic arthritis overview. Am J Manag Care 2016;22:s216-24.
3. Ogdie A, Weiss P. The epidemiology of psoriatic arthritis. Rheum Dis Clin North Am 2015;41:545-68.
4. Singh JA, Strand V. Spondyloarthritis is associated with poor function and physical health-related quality of life. J Rheumatol 2009;36:1012-20.
5. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med 2017;376:957-70.
6. Tillett W, Shaddick G, Askari A, et al. Factors influencing work disability in psoriatic arthritis: first results from a large UK multicentre study. Rheumatology 2015;54:157-62.
7. Boehncke WH, Menter A. Burden of disease: psoriasis and psoriatic arthritis. Am J Clin Dermatol 2013;14:377-88.
8. Kavanaugh A, Helliwell P, Ritchlin CT. Psoriatic arthritis and burden of disease: patient perspectives from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey. Rheumatol Ther 2016;3:91-102.
9. Ogdie A, Palmer JL, Greenberg J, et al. Predictors of achieving remission among patients with psoriatic arthritis initiating a tumor necrosis factor inhibitor. J Rheumatol 2019;46:475-82.
10. Højgaard P, Ballegaard C, Cordtz R, et al. Gender differences in biologic treatment outcomes–a study of 1750 patients with psoriatic arthritis using Danish Health Care Registers. Rheumatology 2018;57:1651-60.
11. Eder L, Thavaneswaran A, Chandran V, Gladman DD. Gender difference in disease expression, radiographic damage and

disability among patients with psoriatic arthritis. Ann Rheum Dis 2013;72:578-82.
12. Singh S, Facciorusso A, Singh AG, et al. Obesity and response to anti-tumor necrosis factor-α agents in patients with select immune-mediated inflammatory diseases: a systematic review and meta-analysis. PLoS One 2018;13:e0195123.
13. Højgaard P, Glintborg B, Kristensen LE, Gudbjornsson B, Love TJ, Dreyer L. The influence of obesity on response to tumour necrosis factor-α inhibitors in psoriatic arthritis: results from the DANBIO and ICEBIO registries. Rheumatology 2016;55:2191-9.
14. Ogdie A, Coates LC, Gladman DD. Treatment guidelines in psoriatic arthritis. Rheumatology 2020;59 Suppl 1:i37-i46.
15. Gottlieb A, Merola JF. Psoriatic arthritis for dermatologists. J Dermatolog Treat 2020;31:662-79.
16. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020;79:700-12.
17. Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol 2016;68:1060-71.
18. Singh JA, Guyatt G, Ogdie A, et al. Special article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. Arthritis Care Res 2019; 71:2-29.
19. Mease PJ, Gladman DD, Collier DH, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase III trial. Arthritis Rheumatol 2019;71:1112-24.
20. Mease PJ, Gladman DD, Samad AS, et al. Design and rationale of the study of etanercept and methotrexate in combination or as monotherapy in subjects with psoriatic arthritis (SEAM-PsA). RMD Open 2018;4:e000606.
21. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665-73.
22. Wright G, Nash P, Coates L, et al. Comparison of secukinumab versus adalimumab efficacy by sex in psoriatic arthritis from a phase 3b, double-blinded, randomized, active-controlled study [abstract]. Arthritis Rheumatol 2020;72 Suppl 10:0507.
23. Mease PJ. Fibromyalgia, a missed comorbidity in spondyloarthritis: prevalence and impact on assessment and treatment. Curr Opin Rheumatol 2017;29:304-10.
24. Nie J, Li YY, Zheng SG, Tsun A, Li B. FOXP3+ Treg cells and gender bias in autoimmune diseases. Front Immunol 2015;6:493.
25. Cutolo M, Sulli A, Capellino S, et al. Sex hormones influence on the immune system: basic and clinical aspects in autoimmunity. Lupus 2004;13:635-8.
26. Singh RP, Bischoff DS. Sex hormones and gender influence the expression of markers of regulatory T cells in SLE patients. Front Immunol 2021;12:619268.
27. Eder L, Thavaneswaran A, Chandran V, Cook RJ, Gladman DD. Obesity is associated with a lower probability of achieving sustained minimal disease activity state among patients with psoriatic arthritis. Ann Rheum Dis 2015;74:813-7.
28. Eder L, Abji F, Rosen CF, Chandran V, Gladman DD. The association between obesity and clinical features of psoriatic arthritis: a case-control study. J Rheumatol 2017;44:437-43.
29. Queiro R, Lorenzo A, Tejón P, Coto P, Pardo E. Obesity in psoriatic arthritis: comparative prevalence and associated factors. Medicine 2019;98:e16400.
30. Soltani-Arabshahi R, Wong B, Feng BJ, Goldgar DE, Duffin KC, Krueger GG. Obesity in early adulthood as a risk factor for psoriatic arthritis. Arch Dermatol 2010;146:721-6.
31. Enck P, Klosterhalfen S, Weimer K, Horing B, Zipfel S. The placebo response in clinical trials: more questions than answers. Philos Trans R Soc Lond B Biol Sci 2011;366:1889-95.
32. Merola JF, Ogdie A. SEAM-PsA: seems like methotrexate works in psoriatic arthritis? Arthritis Rheumatol 2019;71:1027-9.