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Sex Differences in the Effectiveness of First-Line Tumor Necrosis Factor Inhibitors in Psoriatic Arthritis: Results From the European Spondyloarthritis Research Collaboration Network

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Objective. Women with psoriatic arthritis (PsA) may have reduced tumor necrosis factor inhibitor (TNFi) effectiveness compared to men. We examined sex differences in treatment response and retention rates during 24 months of follow-up among patients with PsA initiating their first TNFi.

Methods. Data from patients with PsA across 13 European Spondyloarthritis Research Collaboration Network registries starting their first TNFi were pooled. Logistic regression was used to analyze the association between sex and treatment response using low disease activity (LDA) according to the Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) (<3.2) at six months as the primary outcome. Analyses were adjusted for age, country, conventional synthetic disease-modifying antirheumatic drug treatment, and TNFi start year. Retention rates were explored using the Kaplan–Meier estimator.

Results. We analyzed the treatment response of 7,679 patients with PsA (50% women) with available data on LDA at six months. At baseline, women and men had similar characteristics, including mean DAS28-CRP (women vs men, 4.4 [SD 1.2] vs 4.2 [SD 1.2]), though patient-reported outcome measures were worse in women. At six months, 64% of women and 78% of men had LDA (relative risk [RR] 0.82; 95% confidence interval [CI] 0.80–0.84). This difference was similar after adjustment (RR 0.83; 95% CI 0.81–0.85). TNFi retention rates were evaluated in 17,842 patients with PsA. Women had significantly lower retention rates than men at all time points (women 79%, 64%, and 50% vs men 88%, 77%, and 64% at 6, 12, and 24 months, respectively).

Conclusion. Despite comparable disease characteristics at baseline, women with PsA have reduced treatment response and retention rates to their first TNFi, highlighting the need to consider sex differences in PsA research and management.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy characterized by diverse clinical features, such as arthritis, enthesitis, dactylitis, and axial inflammation. The disease burden in PsA is substantial, often causing impaired function and reduced quality of life.[1,2] In terms of prevalence, PsA has been reported to affect both men and women equally.[3]

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The prognosis of patients with PsA has improved dramatically since the introduction of the first biologic disease-modifying antirheumatic drugs (bDMARDs) almost two decades ago. In clinical practice, of the available bDMARDs, tumor necrosis factor inhibitors (TNFi) are predominantly used, presumably because of available long-term outcome and safety data, physician familiarity, and potentially lower costs than for other bDMARDs due to the availability of TNFi biosimilars.[4] However, optimizing TNFi treatment remains challenging, and in routine practice, the loss of effectiveness in first-line TNFi after one year of treatment is estimated to range from 30% to 42%.[5] This significant variation in effectiveness highlights the importance of investigating factors, such as sex, that may influence treatment outcomes, ultimately guiding the development of individualized therapies.

Sex differences in the disease manifestation of PsA have been identified.[6,7] Women have significantly more peripheral arthritis and more frequently experience polyarticular involvement, whereas the oligoarticular pattern is more common in men.[8] Furthermore, women may be more prone to enthesitis and have higher tender joint counts, whereas men more commonly have axial involvement, severe psoriasis, and radiographic joint damage.[6,7] Moreover, women frequently report greater pain, functional limitations, depression, and poorer quality of life.[7] Sex differences may also extend to molecular pathways related to disease development; one study suggested that the expression of genetic risk factors associated with disease susceptibility could vary with sex.[9] These sex differences imply a distinct disease manifestation in men and women and may influence treatment effectiveness of TNFi.

Although accumulating evidence indicates that female sex is associated with reduced TNFi effectiveness,[10–17] some studies either present conflicting results[18–23] or reveal sex differences only in unadjusted analyses.[24–27] Given these contrasting findings, there's a need for more extensive and robust research to characterize sex differences in response to treatment. Insights from large observational cohort studies are important in determining whether sex differences in TNFi effectiveness exist and in accurately quantifying their magnitude. Awareness of this potential bias, if it exists, could improve outcomes for women with PsA. Incorporating this knowledge may contribute to optimization and tailoring of individualized treatment strategies, benefiting both men and women.

In this study, we analyzed data from large prospective observational cohorts from 13 European countries within the European Spondyloarthritis Research Collaboration Network (EuroSpA RCN). Our aim was to investigate potential sex differences in treatment response and retention rates during 24 months of follow-up in patients with PsA initiating their first TNFi.

PATIENTS AND METHODS

Data sources. We analyzed anonymized data from patients with PsA who started their first TNFi treatment in 13 European registries: National Biologics Treatment Registry (ATTRA; Czech Republic), Spanish Registry on Adverse Events of Advanced Therapies in Rheumatic Diseases (BIOBADASER; Spain), biorx.si (Slovenia), Danish Registry for Biologic Therapies in Rheumatology (DANBIO; Denmark), Gruppo Italiano di Studio sulla Early Arthritis (GISEA; Italy), Icelandic Registry for Biologic Therapies in Rheumatology (ICEBIO; Iceland), Norwegian Disease-Modifying Antirheumatic Drug Register (NOR-DMARD; Norway), Reuma.pt (Portugal), Register On antirheumatic and Biological therapy in FINland (ROB-FIN; Finland), Romanian Registry of Rheumatic Diseases (RRBR; Romania), Swiss Clinical Quality Management (SCQM; Switzerland), Swedish Rheumatology Quality (SRQ; Sweden), and Turkish Biologic Registry (TURKBIO; Turkey). These registries began data collection between 1999 and 2013 and provided data up to 2020. Data collection was conducted prospectively in accordance with each registry's protocol. In this study, we analyzed the data retrospectively and included variables predetermined in the study protocol.

Data access for external researchers is restricted because of logistical constraints. Acquiring permissions from each contributing registry and access to the secure server in Copenhagen is required. For inquiries about the data presented in this article, reasonable requests can be directed to the corresponding author.

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Patients. The study identified all patients who, at initiation of their first TNFi, were aged ≥18 years and had a clinical diagnosis of PsA according to their treating rheumatologist. The primary cohort consisted of patients with an available Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) at six months and data on concomitant conventional synthetic disease-modifying antirheumatic drug (csDMARD) treatment. This cohort was defined to assess the effectiveness of TNFi treatment in achieving low disease activity (LDA). We chose the DAS28-CRP because it is a commonly used composite score in routine practice[28] and had the least missing data. The secondary cohorts included patients who had available data on other disease activity and response criteria scores (see outcome measures) at 6, 12, and 24 months. The retention cohort consisted of patients who had available data on TNFi retention, which were used to analyze the retention rate of TNFi over 24 months. The sensitivity cohort comprised patients with available DAS28-CRP at baseline. This cohort was established to assess the potential bias associated with missing DAS28-CRP measurements, particularly at six months.

Clinical variables. In this study, sex was reported as "male" or "female" according to the study protocols of the different registries within the EuroSpA RCN. The gender identity of patients is not recorded. However, the article refers to patients as "men" and "women" for simplicity and clarity. Baseline characteristics were age, country, disease duration (defined as years since diagnosis), concomitant csDMARD treatment (yes or no), type of TNFi, start year of TNFi, smoking status (current, never, or former), DAS28-CRP, patient global assessment (visual analog scale [VAS] 0–100 mm), CRP level (mg/L), swollen joint count in 28 joints, tender joint count in 28 joints (TJC28), 28-joint Disease Activity Index for Psoriatic Arthritis (DAPSA28), and pain (VAS 0–100 mm) and fatigue scores (VAS 0–100 mm).

Outcome measures. The study evaluated treatment response at three time windows after treatment initiation: 6 (days 90–270), 12 (days 271–545), and 24 (days 546–910) months of follow-up. The primary outcome was treatment response at six months of follow-up, evaluated by DAS28-CRP LDA (<3.2 points).[29] LDA at 12 and 24 months was considered a secondary outcome because the primary focus was the initial treatment effect in the first 6 months and to mitigate potential selection bias due to an increase in missing data at later follow-up. Other secondary outcomes included disease activity scores and response criteria assessed at 6, 12, and 24 months, including DAS28-CRP remission (<2.6),[29] DAPSA28 remission (≤4), and LDA (≤14),[30] and American College of Rheumatology 20%, 50%, and 70% response rates (ACR20, ACR50, and ACR70).[31] The probability of retaining TNFi treatment (ie, retention rate) was evaluated as the time from treatment initiation to discontinuation from any cause. Observations were censored at the last recorded visit if no registered stop date was available. In addition, observations were censored at the study termination (ie, after 24 months of follow-up).

Statistical analysis. The data from different countries were combined for analysis. Statistical analyses were performed using R V3.6.3 software (www.r-project.org). Summary statistics, such as mean, SD, median, interquartile range, and percentages, were calculated for demographic and patient characteristics.

Analyses of treatment response. Sex differences in treatment response were assessed by logistic regression. Covariates potentially influencing the outcome were selected a priori in the statistical analysis plan, and of these, variables with data availability >80% were used in the final model (see Missing data due to dropouts section). The final covariates included in the adjusted models were age and TNFi start year, treated as continuous variables, as well as country and concomitant csDMARD treatment, treated as categorical variables. The absolute risk difference (RD) and relative risk (RR) in treatment response (women vs men) were estimated, and bootstrap iterations (1,000 resamples) were performed to achieve valid SEs and confidence intervals (CIs). Both unadjusted and adjusted effects were assessed for all treatment outcomes.

The different components of the primary outcome (DAS28-CRP LDA) at baseline and six months were described. The analyses were stratified by country and calendar periods 1999 to 2008, 2009 to 2014, and 2015 to 2019. The cutoff values for these calendar periods were aligned with a previous study within the EuroSpA RCN.[32] These periods were selected because 2009 marked the year when the first three bDMARDs (adalimumab, etanercept, and infliximab) were well-established treatment options across European countries and 2015 was the year when the first interleukin-17A (IL-17A) inhibitor, secukinumab, was approved for PsA.[33]

Retention analysis. TNFi retention rates, pooled and stratified by country, were estimated using the Kaplan–Meier estimator for both sexes (women vs men). Log-rank tests were used to determine differences in retention rates between the sexes. Moreover, Cox proportional hazards models were used to calculate the weighted average of the hazard ratios (HRs) for TNFi treatment discontinuation over 24 months of follow-up. Women's unadjusted and adjusted HRs were compared with men's and calculated with their 95% CIs. The same covariates were included in the adjusted models as in the analyses of treatment responses. The Schoenfeld residual test was performed to evaluate the proportionality assumptions, and, if necessary, any violations were further investigated through visualization (residual plots, log–log plots) and resolved by stratifying the Cox regression model, as appropriate. Finally, sex differences in reasons for treatment discontinuation were explored using descriptive statistics and tested using the chi-square test. The reasons for discontinuation were classified as lack of efficacy, adverse events, other reasons, and remission.

Missing data due to dropouts. In this study, a higher number of patients had available data on retention rates compared to

treatment response. We assumed these data were missing completely at random; hence, we performed a complete case analysis for all treatment outcomes. To support this assumption for the primary analysis, we examined differences in baseline characteristics between patients with available DAS28-CRP measurements at six months (forming our primary cohort) and those for whom retention rates were available (forming our retention cohort). Moreover, to address potential selection bias due to missing data at follow-up, we compared the baseline characteristics of the primary cohort with those of patients with available DAS28-CRP measurements at baseline (forming our sensitivity cohort). Supplementary Figure 1 provides the definitions for the primary, retention, and sensitivity cohorts.

Threshold values for statistical significance. All statistical comparisons were conducted using a two-sided test. For the primary and retention analyses, the significance level was set at 0.05. To adjust for multiple comparisons in the secondary outcomes, such as disease activity scores and response criteria, a Bonferroni correction was applied, resulting in a significance level of 0.0012. The calculation involved dividing 0.05 by 42, accounting for the number of secondary outcomes analyzed at three time points and considering both unadjusted and adjusted estimates (seven secondary outcomes × three time points × two estimated effects).

RESULTS

In the 13 EuroSpA RCN registries, 18,599 patients initiated their first TNFi treatment between 1999 and 2020. From these, 17,842 patients were included in the retention cohort, whereas

Table 1. Baseline characteristics of the primary cohort*

	Women (n = 3,811)		Men (n = 3,868)	
	Missing, %	Value	Missing, %	Value
Patient characteristics				
Age, mean (SD), y	0	50 (13)	0	48 (12)
Disease duration, median (IQR), y	34	4 (1–10)	35	4 (1–10)
Concomitant csDMARD,[a] no. (%)	0	2,867 (75)	0	2,968 (77)
TNFi, no. (%)	0		0	
Infliximab		808 (21)		870 (23)
Etanercept		1,355 (36)		1,290 (33)
Adalimumab		1,099 (29)		1,120 (29)
Certolizumab		218 (5.7)		200 (5.2)
Golimumab		331 (8.7)		388 (10)
Cohort characteristics, no. (%)				
TNFi start year	0		0	
1999–2008		873 (23)		902 (23)
2009–2014		1,538 (40)		1,584 (41)
2015–2020		1,400 (37)		1,382 (36)
Country	0		0	
Sweden		2,053 (54)		2,113 (55)
Denmark		659 (17)		598 (15)
Czech Republic		275 (7.2)		314 (8.1)
Norway		266 (7.0)		297 (7.7)
Portugal		171 (4.5)		157 (4.1)
Slovenia		105 (2.8)		124 (3.2)
Finland		84 (2.2)		89 (2.3)
Iceland		54 (1.4)		47 (1.2)
Switzerland		51 (1.3)		71 (1.8)
Romania		50 (1.3)		33 (0.9)
Turkey		43 (1.1)		25 (0.6)
Disease activity				
DAS28-CRP, mean (SD), units	23	4.4 (1.2)	24	4.2 (1.2)
SJC (0–28), median (IQR)	18	3 (1–6)	19	3 (1–6)
TJC (0–28), median (IQR)	18	6 (2–10)	19	4 (2–9)
PtGA, mean (SD), mm	18	63 (23)	18	57 (23)
CRP, median (IQR), mg/L	17	7 (3–17)	17	8 (3–19)
DAPSA28, mean (SD), units	27	32 (16)	27	29 (16)
VAS pain, mean (SD), mm	21	61 (23)	21	55 (23)
VAS fatigue, mean (SD), mm	56	62 (26)	56	53 (27)

* CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAPSA28, 28-joint Disease Activity Index in Psoriatic Arthritis; DAS28-CRP, Disease Activity Score in 28 joints using the C-reactive protein level; IQR, interquartile range; PtGA, patient global assessment; SJC, swollen joint count; TJC, tender joint count; TNFi, tumor necrosis factor inhibitor; VAS, visual analog scale.
[a] Such as methotrexate, leflunomide, sulfasalazine, or others.

7,679 patients who had available data on 6-month DAS28-CRP and concomitant csDMARD treatment were included in the primary cohort for treatment response analysis. Approximately half of the study participants were women. For further details regarding the definition of the cohorts and patient selections, please see Supplementary Figure 1.

Baseline characteristics of the three cohorts. The baseline characteristics of the primary cohort, including the proportions of participants with missing data, are presented in Table 1. Overall, baseline characteristics were generally similar between the sexes. However, whereas women scored similarly to men in the DAS28-CRP (mean 4.4 vs 4.2), they displayed slightly worse DAPSA28 (mean 32 vs 29), TJC28 (median 6 vs 4), patient global assessment (mean 63 vs 57 mm), VAS pain (mean 61 vs 55 mm), and VAS fatigue (mean 62 vs 53 mm) scores.

The baseline characteristics of the study population used for retention analyses with available data on age, sex, and retention are presented in Table 2. In total, 17,842 patients were included in the retention analysis, of whom 52% were women. The patient and disease characteristics of women in the primary cohort were consistent with those of women in the retention cohort, with one notable exception: women in the primary cohort were more frequently prescribed csDMARDs than those in the retention cohort (75% vs 68%). Similarly, the patient and disease characteristics of men in the primary cohort were comparable to those of men in the retention cohort, except for concomitant csDMARD

Table 2. Baseline characteristics of the retention cohort*

	Women (n = 9,279)		Men (n = 8,563)	
	Missing, %	Value	Missing, %	Value
Patient characteristics				
Age, mean (SD), y	0	50 (13)	0	48 (12)
Disease duration, median (IQR), y	26	3 (1–8)	26	4 (1–9)
Concomitant csDMARD,[a] no. (%)	14	5,439 (68)	12	5,284 (70)
TNFi, no. (%)	0		0	
Infliximab		1,779 (19)		1,708 (20)
Etanercept		3,326 (36)		2,953 (35)
Adalimumab		2,840 (31)		2,708 (32)
Certolizumab		501 (5.4)		374 (4.4)
Golimumab		833 (9.0)		820 (9.6)
Cohort characteristics, no. (%)				
TNFi start year	0		0	
1999–2008		1,975 (21)		2,038 (24)
2009–2014		3,829 (41)		3,558 (42)
2015–2020		3,475 (38)		2,967 (35)
Country	0		0	
Sweden		3,442 (37)		3,246 (38)
Denmark		1,564 (17)		1,278 (15)
Italy		1,300 (14)		1,129 (13)
Norway		499 (5.4)		499 (5.8)
Switzerland		478 (5.2)		451 (5.3)
Czech Republic		436 (4.7)		480 (5.6)
Portugal		367 (4.0)		372 (4.3)
Spain		350 (3.8)		362 (4.2)
Iceland		212 (2.3)		152 (1.8)
Finland		202 (2.2)		242 (2.8)
Slovenia		187 (2.0)		204 (2.4)
Turkey		190 (2.0)		107 (1.2)
Romania		52 (0.6)		41 (0.5)
Disease activity				
DAS28-CRP, mean (SD), units	45	4.3 (1.3)	45	4.1 (1.2)
SJC (0–28), median (IQR)	26	2 (0–6)	28	2 (0–5)
TJC (0–28), median (IQR)	26	5 (2–10)	28	4 (1–8)
PtGA, mean (SD), mm	26	63 (23)	27	57 (24)
CRP, median (IQR), mg/L	37	6 (3–15)	36	8 (3–18)
DAPSA28, mean (SD), units	47	30 (16)	47	28 (16)
VAS pain, mean (SD), mm	30	61 (33)	32	55 (24)
VAS fatigue, mean (SD), mm	65	63 (26)	66	53 (27)

* CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAPSA28, 28-joint Disease Activity Index in Psoriatic Arthritis; DAS28-CRP; Disease Activity Score in 28 joints using the C-reactive protein level; IQR, interquartile range; PtGA, patient global assessment; SJC, swollen joint count; TJC, tender joint count; TNFi, tumor necrosis factor inhibitor; VAS, visual analog scale.
[a] Such as methotrexate, leflunomide, sulfasalazine, or others.

treatment (77% vs 70%). However, the sex difference for concomitant csDMARD treatment remained consistent at 2% within each cohort. Finally, the patient and disease characteristics of women and men in the primary cohort were similar to those of women and men in the sensitivity cohort (Supplementary Table 1).

Treatment response. *Primary cohort.* In the primary cohort, women had a 64% probability of having DAS28-CRP LDA at six months, in comparison to 78% for men. This indicates an 18% lower probability for women to have LDA compared to men (RR 0.82, 95% CI 0.80–0.84), with a 14–percentage point difference in risk (RD 0.14, 95% CI 0.12–0.16). This was similar in the adjusted analysis (RR 0.83, 95%CI 0.81–0.85; RD 0.13, 95% CI 0.11–0.15) (Table 3). Additional information about the DAS28-CRP at the beginning of the study and six months later, as well as its components, are presented in Supplementary Table 2. In comparison to men, women had less improvement in the TJC28 and CRP components.

Subgroup analyses. When stratified by country, the subgroup analyses revealed varying effects of sex on LDA. Several countries showed a reduced probability of LDA in women (Portugal, Denmark, Sweden, and Norway), whereas others did not (Slovenia, Romania, Turkey, and Finland). Some countries with smaller sample sizes also showed a similar trend (ie, reduced probability of LDA in women), although without reaching statistical significance (Switzerland, Iceland, and the Czech Republic), as shown in Table 3. Similar to the primary analysis, significant effects of sex on LDA were observed regardless of TNFi start period (1999–2008, 2009–2014, and 2015–2019; Supplementary Table 3).

The other disease activity scores revealed similar results to the primary analysis at 6, 12, and 24 months for all secondary outcomes, except for DAPSA28 LDA, in which there were no differences present between the sexes at any time point (Table 4). Notably, at six months, the greatest unadjusted RR was observed in DAPSA28 remission (RR 0.53, 95% CI 0.48–0.57), and the smallest unadjusted RR was observed in ACR20 (RR 0.86, 95% CI 0.80–0.91). At later time points during follow-up, the effect sizes of the secondary outcomes and the number of participants remaining in the analyses, especially women, diminished (data not shown).

Treatment persistence. *Retention cohort analysis.* Over a two-year study period, 6,479 (37%) of 17,842 patients discontinued their first TNFi treatment. Women had significantly lower retention rates at all time points ($P < 0.001$), with a 12-month retention rate of 64% (95% CI 63%–65%) compared to 77% (95% CI 76%–78%) for men and 6- and 24-month retention rates of 79% (95% CI 78%–80%) and 50% (95% CI 49%–51%) and 88% (95% CI 87%–89%) and 64% (95% CI 63%–65%) for women and men, respectively. Figure 1 illustrates these differences in retention rates for women and men over the two-year follow-up period. Additional subgroup analyses revealed similar trends in individual countries, although in countries with a small number of study participants, differences were not statistically significant (Figure 2).

Data regarding reasons for treatment discontinuation were available for 5,878 of the 6,479 patients (91%) who stopped treatment. The most common reason for treatment discontinuation was lack of efficacy (2,939 patients; 50%), followed by adverse events (1,629; 28%), other reasons (1,208; 21%), and remission (102; 1.7%). Women discontinued treatment slightly more often because of adverse events and lack of efficacy, whereas men stopped more frequently because of remission and other reasons (see Supplementary Table 4).

Risk for discontinuation of a first TNFi. Among 17,842 patients included in the retention cohort, 15,598 patients contributed to the Cox regression analyses for treatment discontinuation of their first TNFi over a two-year time period. In total, 2,274

Table 3. Sex and association with DAS28-CRP LDA at six months in patients with PsA (women vs men), overall and stratified by country*

			Unadjusted		Adjusted	
Country	No. of patients	Women, %	Risk difference	Relative risk	Risk difference	Relative risk
Portugal	328	52	0.27 (0.17 to 0.35)	0.70 (0.61 to 0.80)	0.25 (0.17 to 0.33)	0.72 (0.64 to 0.81)
Denmark	1,257	52	0.22 (0.17 to 0.26)	0.73 (0.68 to 0.79)	0.21 (0.16 to 0.26)	0.74 (0.69 to 0.79)
Sweden	4,166	49	0.14 (0.11 to 0.16)	0.82 (0.79 to 0.85)	0.13 (0.10 to 0.16)	0.83 (0.79 to 0.86)
Norway	563	47	0.12 (0.051 to 0.20)	0.84 (0.75 to 0.93)	0.11 (0.038 to 0.19)	0.86 (0.77 to 0.95)
Switzerland	122	42	0.12 (−0.011 to 0.27)	0.87 (0.72 to 1.01)	0.11 (−0.024 to 0.24)	0.88 (0.74 to 1.03)
Iceland	101	53	0.079 (−0.093 to 0.27)	0.90 (0.69 to 1.14)	0.093 (−0.067 to 0.26)	0.88 (0.69 to 1.10)
Czech Republic	589	47	0.051 (−0.014 to 0.12)	0.94 (0.86 to 1.01)	0.051 (−0.020 to 0.12)	0.94 (0.86 to 1.03)
Slovenia	229	46	0.031 (−0.085 to 0.15)	0.96 (0.80 to 1.12)	0.023 (−0.081 to 0.14)	0.97 (0.82 to 1.12)
Romania	83	60	0.025 (−0.19 to 0.24)	0.98 (0.69 to 1.37)	0.022 (−0.19 to 0.22)	0.98 (0.71 to 1.36)
Turkey	68	63	0.003 (−0.19 to 0.18)	1.00 (0.81 to 1.28)	0.014 (−0.16 to 0.21)	0.99 (0.78 to 1.22)
Finland	173	49	0.014 (−0.15 to 0.11)	1.02 (0.86 to 1.23)	0.000 (−0.12 to 0.13)	1.00 (0.84 to 1.18)
Pooled	7,679	50	0.14 (0.12 to 0.16)	0.82 (0.80 to 0.84)	0.13 (0.11 to 0.15)	0.83 (0.81 to 0.85)

* Values are the absolute relative risk and relative difference with the 95% confidence interval unless indicated otherwise. Countries are ordered from most significant adjusted relative risk to least significant relative risk. The adjusted models in the analyses included age, conventional synthetic disease-modifying antirheumatic drugs, and tumor necrosis factor inhibitor start year for the separate countries. DAS28-CRP, Disease Activity Score in 28 joints using the C-reactive protein level; LDA, low disease activity.

Table 4. Sex and the association with secondary outcomes in patients with psoriatic arthritis (women vs men)*

	6 mo			12 mo			24 mo		
	n	Unadjusted	Adjusted	n	Unadjusted	Adjusted	n	Unadjusted	Adjusted
DAS28-CRP remission									
RR	7,679	0.70 (0.67 to 0.73)[a]	0.71 (0.68 to 0.74)[a]	4,868	0.73 (0.69 to 0.76)[a]	0.75 (0.71 to 0.78)[a]	2,348	0.80 (0.75 to 0.84)[a]	0.81 (0.76 to 0.86)[a]
RD		0.19 (0.17 to 0.21)[a]	0.18 (0.16 to 0.21)[a]		0.19 (0.16 to 0.22)[a]	0.17 (0.15 to 0.20)[a]		0.16 (0.12 to 0.19)[a]	0.15 (0.11 to 0.18)[a]
DAS28-CRP LDA									
RR	7,679	0.82 (0.80 to 0.85)[a]	0.83 (0.81 to 0.85)[a]	4,868	0.83 (0.80 to 0.86)[a]	0.84 (0.81 to 0.87)[a]	2,348	0.87 (0.83 to 0.90)[a]	0.88 (0.84 to 0.91)[a]
RD		0.14 (0.12 to 0.16)[a]	0.13 (0.11 to 0.15)[a]		0.14 (0.12 to 0.17)[a]	0.13 (0.11 to 0.16)[a]		0.12 (0.084 to 0.15)[a]	0.11 (0.077 to 0.14)[a]
DAPSA28 remission									
RR	7,373	0.53 (0.48 to 0.57)[a]	0.55 (0.50 to 0.59)[a]	4,621	0.55 (0.50 to 0.61)[a]	0.58 (0.53 to 0.64)[a]	2,197	0.71 (0.62 to 0.80)[a]	0.74 (0.66 to 0.84)[a]
RD		0.16 (0.14 to 0.18)[a]	0.15 (0.13 to 0.17)[a]		0.16 (0.14 to 0.19)[a]	0.15 (0.12 to 0.17)[a]		0.12 (0.079 to 0.16)[a]	0.11 (0.065 to 0.14)[a]
DAPSA28 LDA									
RR	7,373	0.98 (0.93 to 1.03)	0.98 (0.92 to 1.04)	4,621	1.02 (0.94 to 1.08)	1.01 (0.94 to 1.08)	2,197	0.95 (0.86 to 1.04)	0.94 (0.85 to 1.04)
RD		0.008 (−0.014 to 0.030)	0.009 (−0.015 to 0.031)		0.006 (−0.032 to 0.024)	0.002 (−0.030 to 0.024)		0.021 (−0.019 to 0.063)	0.028 (−0.015 to 0.071)
ACR20									
RR	7,276	0.86 (0.80 to 0.91)[a]	0.88 (0.83 to 0.93)[a]	5,701	0.83 (0.77 to 0.89)[a]	0.85 (0.80 to 0.91)[a]	4,212	0.84 (0.76 to 0.93)[a]	0.91 (0.84 to 0.99)
RD		0.059 (0.037 to 0.082)[a]	0.050 (0.028 to 0.070)[a]		0.066 (0.042 to 0.090)[a]	0.056 (0.035 to 0.080)[a]		0.045 (0.019 to 0.073)[a]	0.024 (0.003 to 0.046)
ACR50									
RR	7,386	0.69 (0.64 to 0.74)[a]	0.72 (0.67 to 0.77)[a]	5,749	0.72 (0.66 to 0.79)[a]	0.75 (0.69 to 0.81)[a]	4,233	0.74 (0.66 to 0.83)[a]	0.81 (0.72 to 0.90)[a]
RD		0.097 (0.077 to 0.12)[a]	0.086 (0.068 to 0.10)[a]		0.083 (0.061 to 0.10)[a]	0.074 (0.054 to 0.095)[a]		0.062 (0.038 to 0.086)[a]	0.044 (0.022 to 0.066)[a]
ACR70									
RR	7,601	0.58 (0.52 to 0.65)[a]	0.61 (0.54 to 0.68)[a]	5,897	0.63 (0.55 to 0.71)[a]	0.66 (0.59 to 0.74)[a]	4,271	0.66 (0.56 to 0.77)[a]	0.73 (0.63 to 0.84)[a]
RD		0.078 (0.063 to 0.093)[a]	0.070 (0.054 to 0.086)[a]		0.069 (0.051 to 0.086)[a]	0.062 (0.044 to 0.079)[a]		0.056 (0.035 to 0.076)[a]	0.042 (0.024 to 0.061)[a]

* Values are the absolute RR and RD with the 95% confidence interval unless indicated otherwise. The adjusted models included country, age, conventional synthetic disease-modifying antirheumatic drugs, and TNFi start year. ACR20, 50, 70, American College of Rheumatology 20%, 50%, and 70% improvement criteria; DAPSA28, 28-joint Disease Activity Index in Psoriatic Arthritis; DAS28-CRP, Disease Activity Score in 28 joints using the C-reactive protein level; LDA, low disease activity; RD, risk difference; RR, relative risk; TNFi, tumor necrosis factor inhibitor.

[a] Statistically significant with $P < 0.0012$ (Bonferroni).

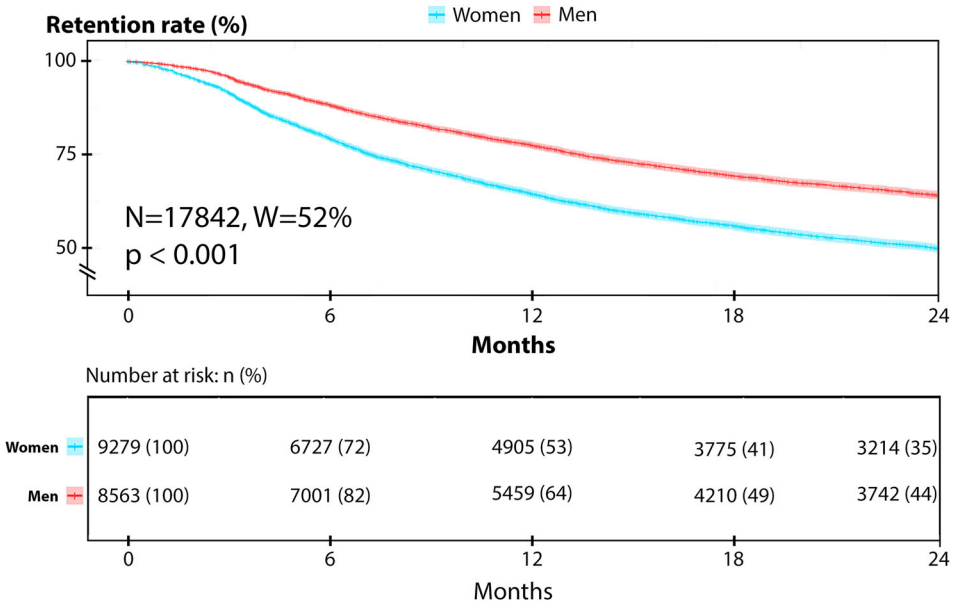

Figure 1. Sex differences in 24-month retention rates in first-line tumor necrosis factor inhibitors in patients with psoriatic arthritis in the European Spondyloarthritis Research Collaboration Network (Kaplan–Meier estimator, log-rank test). The number of patients and the percentage of women are provided.

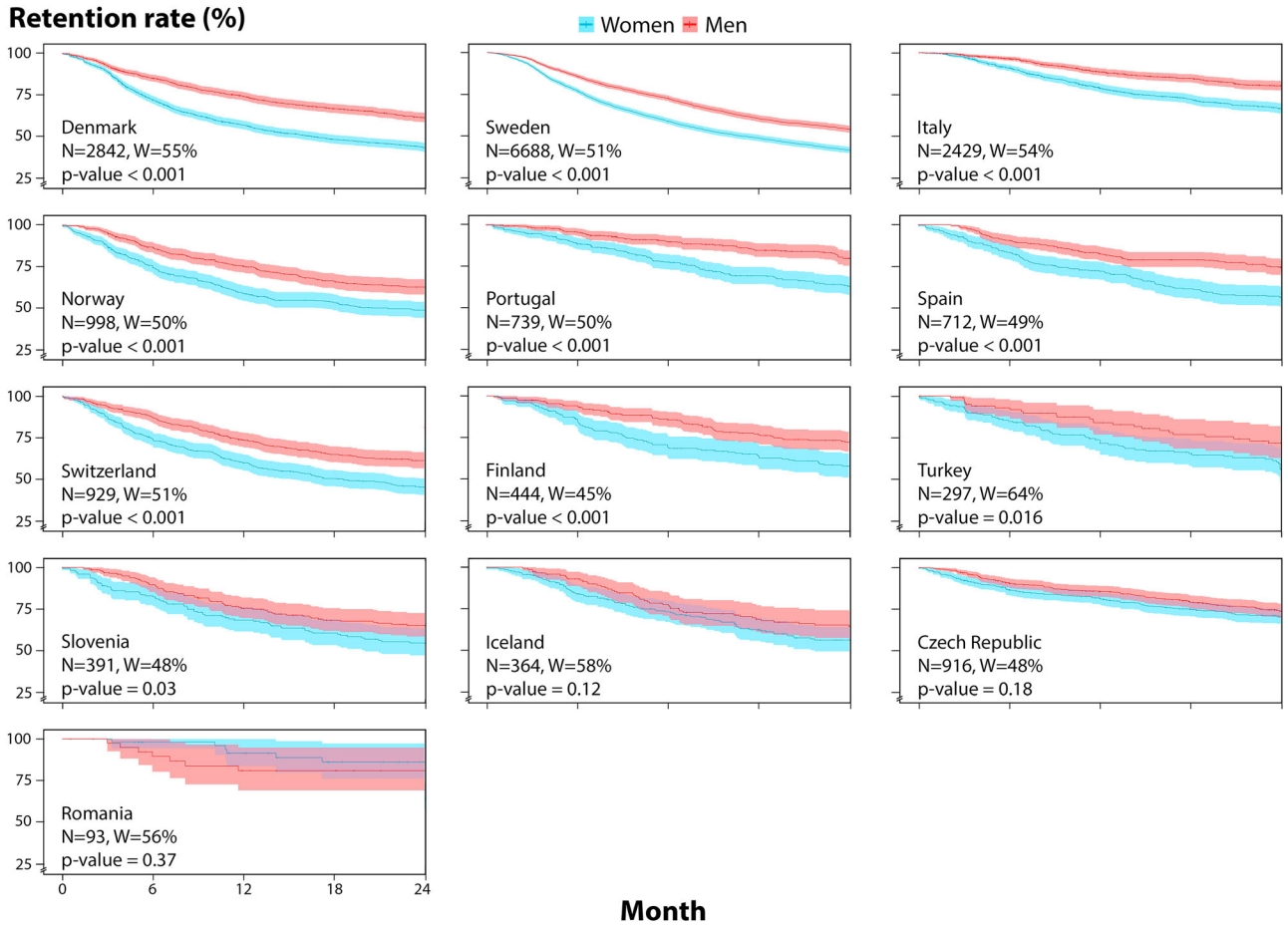

Figure 2. Sex differences in 24-month retention rates in first-line tumor necrosis factor inhibitors in patients with psoriatic arthritis, stratified by country (Kaplan–Meier estimator, log-rank test). Countries are ranked from most significant to least significant. The number of patients and the percentage of women are provided.

observations were deleted because of missingness in concomitant csDMARD treatment. Women had a 60% higher risk of discontinuation at two-years' follow-up compared to men (unadjusted HR 1.60, 95% CI 1.52–1.69). After adjustment for age, country, concomitant csDMARD treatment, and TNFi start year, the risk remained significantly higher (HR 1.57, 95% CI 1.49–1.66). When we stratified the analyses by calendar periods, we observed that the risk of discontinuation for women compared to men increased slightly during subsequent time periods (1999–2008 [HR 1.49, 95% CI 1.33–1.67], 2009–2014 [HR 1.60, 95% CI 1.48–1.73], and 2015–2019 [HR 1.65, 95% CI 1.51–1.81]; all $P < 0.001$). After adjustment for age, country, and concomitant csDMARD treatment, a similar trend was observed for 1999 to 2008 (HR 1.45, 95% CI 1.29–1.63), 2009 to 2014 (HR 1.60, 95% CI 1.47–1.73), and 2015 to 2019 (HR 1.61, 95% CI 1.47–1.77) (all $P < 0.001$).

DISCUSSION

This study, using data from 13 European countries, is the largest to date in quantifying sex differences in treatment response and retention rates among patients with PsA initiating their first TNFi. Our analyses, encompassing more than 17,000 participants, revealed that women consistently had reduced treatment effectiveness compared to men. This disparity was evident in DAS28-CRP LDA at six months, in which women displayed an 18% lower response compared to men, and also persisted across various other treatment outcomes despite adjustment for country, age, concomitant csDMARD treatment, and TNFi start year. Furthermore, throughout the two-year study period, women experienced a 60% increased risk of discontinuing TNFi treatment. These findings emphasize the relevance of the results to both clinical practice and future research.

Our study addresses a notable discrepancy in the literature concerning sex differences in response to TNFi treatment. Whereas previous studies have shown contrasting results[18–23] or have identified sex differences only in unadjusted analyses,[24–27] our findings align with those studies indicating that women have a reduced probability of responding to TNFi treatment compared to men.[34–39] The real-world data used in this study encompass a highly diverse patient population, representative of a significant portion of Europe, which strengthens the generalizability and applicability of our findings to clinical practice.

Interestingly, recent studies have discovered similar sex differences in patients treated with IL-17 inhibitors in a real-world setting and in post hoc analyses of randomized controlled trials (RCTs) of Janus kinase inhibitors after three months of treatment.[8,40] However, a real-world study on apremilast did not identify sex differences in retention rates.[41] In addition, the preliminary findings from post hoc analyses of the EXCEED RCT suggested that women receiving an IL-17 inhibitor experienced a better clinical response than those treated with a TNFi. This difference was not observed in men.[42] These findings highlight the need for further research to determine whether sex differences in treatment response are a class effect or a general finding for all therapeutic agents.

When analyzing treatment response (ie, DAS28-CRP LDA) by country, we observed some heterogeneity in the results. Several countries demonstrated significantly reduced responses in women; some were potentially underpowered, revealing numerically lower treatment responses without reaching statistical significance, whereas others showed no sex differences. We speculate that countries without observed sex differences in response (Turkey, Finland, Romania, and Slovenia) may be potentially underpowered or have distinct patient populations. For instance, women from Turkey had the youngest average age and the second shortest disease duration of all countries, whereas women from Romania had the highest average CRP level at baseline (data not shown), which could have contributed to their better response.[20]

The treatment response disparities observed between men and women with PsA may be attributed to various biologic factors. As previously noted, women exhibit a distinct clinical PsA disease manifestation compared to men.[7] Hormonal differences between the sexes could influence immune responses: whereas androgens and progesterone have an immunosuppressive action, estrogens can exert both immunostimulatory and anti-inflammatory effects.[43] Moreover, genetic associations between sex steroid signaling and other autoimmune diseases have been reported,[43] suggesting a potential connection between these hormonal differences and disease development. Finally, sex and hormones can affect gut microbiota,[43,44] which may be closely linked to PsA pathophysiology through the modulation of immune responses and inflammation.[45] These factors could significantly impact disease severity and treatment response, emphasizing the need for further research to elucidate their interplay with PsA.

In contrast to our treatment response analysis, the retention rate analysis revealed consistent findings across all 13 countries. Women had lower retention rates in 10 countries, and in the remaining 3, their rates were numerically lower compared to men. This consistency suggests high external validity and aligns with prior literature.[16,17,24,36] A potential explanation for women's lower persistence of TNFi treatment might be sex differences in pharmacokinetics, including the absorption, distribution, metabolism, and excretion of therapeutic agents, which could lead to higher TNFi concentrations in women, potentially leading to increased adverse events.[46] This would be consistent with our findings that women discontinued their treatment more often than men because of adverse events (29% vs 25%; Supplementary Table 4), an observation in line with the literature.[12,14]

Sex differences similar to those in PsA have also been observed in rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA)[47,48] and may share a common underlying mechanism. To better understand the factors driving these differences, future

studies should investigate whether the same pathophysiologic mechanisms driving sex differences are present in PsA, axSpA, and RA. This exploration could provide valuable insights into the shared and distinct features of these conditions and their potential influence on treatment outcomes.

Our study has several major strengths, including the analysis of a large number of participants from diverse patient populations across numerous European countries and the robustness of our main results, confirmed through extensive subgroup analyses and various defined secondary cohorts. Nevertheless, certain limitations should be acknowledged. First, we observed a lower proportion of patients with available treatment response data compared to retention rate data. Moreover, within those with treatment response data, there was a distinction between patients with available baseline DAS28-CRP and those with six-month follow-up data. This raises the possibility of selection bias due to missingness. However, the baseline characteristics of the primary cohort and retention cohort, as well as the primary cohort and sensitivity cohort, were largely similar, making the assumption that the data were missing completely at random more plausible. One notable exception was the increased concomitant csDMARD prescriptions in the primary cohort compared to the retention cohort. Despite this, the differences between the sexes remained the same. Because the primary comparison is between sexes in treatment response rather than a comparison of treatment response between the retention and primary cohorts, we do not expect this to lead to selection bias. If the data were missing completely at random, then the results are expected to be unbiased.[49] Finally, the analysis of multiple secondary cohorts, defined by the availability of secondary outcomes, consistently revealed sex differences in favor of men, with the exception of DAPSA28 LDA, reducing the likelihood that the sex differences observed in the primary cohort were a result of selection bias.

Second, we hypothesize that patients experiencing worse outcomes might have been more likely to change treatment (eg, switch to another DMARD), and they were consequently excluded from the treatment response analyses, particularly at later follow-up time points. Because women experienced worse outcomes on average, they may have been more affected than men, potentially leading to an underestimation of the actual difference in treatment response. We mitigated this risk by selecting six months as the primary end point for our main analyses.

Third, although the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) - Outcome Measures in Rheumatology (OMERACT) working group endorses the use of the 66/68 joint scores for arthritis evaluation in PsA, no consensus exists on the preferred composite score for measuring disease activity.[28] Our study relied on the DAS28-CRP to define treatment response because of limited availability of high-quality data on 66/68 joint scores. As such, our estimates may not fully capture the effect of sex on treatment response because some studies suggest that women are more likely to have distal interphalangeal joints affected than men.[9] Future studies employing optimal joint numbers as outcomes may reveal even greater sex differences. Moreover, although this study focused on the articular domains of the disease, subsequent studies should examine the presence of sex differences using multidomain composite scores, such as the Composite Psoriatic Disease Activity Index. This approach could provide deeper insights into the implications of sex differences across various aspects of the disease.

Finally, we lacked data on core domains of PsA, such as arthritis patterns, enthesitis, dactylitis, axial disease, or psoriasis severity. Sex differences in these core domains have been described[7] and could potentially explain the sex differences in treatment response. However, our study lacked data on these domains. In addition, we lacked data on comorbidities (eg, fibromyalgia and depression).[7] Future studies should therefore focus on how these factors influence treatment response and retention rates to gain a better understanding on this topic.

In conclusion, our study across 13 European countries in patients with PsA treated with their first TNFi demonstrated that women experienced reduced treatment effectiveness compared to men. Further analyses confirmed that women had lower TNFi retention rates over a two-year follow-up period. These differences may be attributed to various biologic variations between the sexes. Future studies should investigate tailored treatment strategies that not only consider clinical manifestations (eg, enthesitis, polyarticular vs oligoarticular arthritis) but also analyze outcomes separately for men and women. This approach will help inform clinicians on how to optimize treatment plans and ultimately improve patient outcomes.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Prof. van der Horst-Bruinsma had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Hellamand, van de Sande, Ørnbjerg, Klausch, Santos, Loft, Glintborg, Østergaard, Lindström, Wallman, Michelsen, Fagerli, Castrejón, Gudbjornsson, Rotar, Díaz-González, Iannone, Codreanu, Nissen, Möller, Hetland, van der Horst-Bruinsma.

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Analysis and interpretation of data. Hellamand, van de Sande, Klausch, van der Horst-Bruinsma.

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Novartis Pharma AG did not have any influence on the data collection, statistical analyses, manuscript preparation, or the decision to submit the manuscript for publication. Publication of the article was not contingent upon approval by Novartis Pharma AG.

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