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Clinical science

Gender-specific differences in patients with psoriatic arthritis receiving ustekinumab or tumour necrosis factor inhibitor: real-world data

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Abstract

Objective: Investigate effects of gender on disease characteristics and treatment impact in patients with PsA.

Methods: PsABio is a non-interventional European study in patients with PsA starting a biological DMARD [bDMARD; ustekinumab or TNF inhibitor (TNFi)]. This *post-hoc* analysis compared persistence, disease activity, patient-reported outcomes and safety between male and female patients at baseline and 6 and 12 months of treatment.

Results: At baseline, disease duration was 6.7 and 6.9 years for 512 females and 417 males respectively. Mean (95% CI) scores for females *vs* males were: clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA), 32.3 (30.3, 34.2) *vs* 26.8 (24.8, 28.9); HAQ-Disability Index (HAQ-DI), 1.3 (1.2, 1.4) *vs* 0.93 (0.86, 0.99); total PsA Impact of Disease-12 (PsAID-12) score, 6.0 (5.8, 6.2) *vs* 5.1 (4.9, 5.3), respectively. Improvements in scores were smaller in female than male patients. At 12 months, 175/303 (57.8%) female and 212/264 (80.3%) male patients achieved cDAPSA low disease activity, 96/285 (33.7%) and 137/247 (55.5%), achieved minimal disease activity (MDA), respectively. HAQ-DI scores were 0.85 (0.77, 0.92) *vs* 0.50 (0.43, 0.56), PsAID-12 scores 3.5 (3.3, 3.8) *vs* 2.4 (2.2, 2.6), respectively. Treatment persistence was lower in females than males ($P \leq 0.001$). Lack of effectiveness was the predominant reason to stop, irrespective of gender and bDMARD.

Conclusions: Before starting bDMARDs, females had more severe disease than males and a lower percentage reached favourable disease states, with lower persistence of treatment after 12 months. A better understanding of the mechanisms underlying these differences may improve therapeutic management in females with PsA.

Trial registration: ClinicalTrials.gov, https://clinicaltrials.gov, NCT02627768

Keywords: PsA, disease activity, gender, real-world, persistence, disease impact, bDMARD

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Rheumatology key messages

- Baseline PsA disease activity, impact and function were poorer in females compared with males.
- Males with PsA had better 12-month responses and persistence with ustekinumab and TNFi than females.
- Disease course and treatment response seems to differ between female and male PsA patients.

Introduction

Epidemiological evidence suggests that the prevalence of PsA is similar across genders [1–3], but gender-related differences have not been thoroughly explored in PsA; a number of studies have analysed various aspects of the disease, from baseline characteristics and disease perception to treatment response [mostly to TNF inhibitors (TNFi)] and patient outcomes, in men and women separately. However, data are emerging of differences in the clinical expression of PsA, with men tending to develop more severe axial disease and women developing polyarticular disease [1, 4–7].

Furthermore, some studies have suggested gender-related differences in patient-reported measures of disease, in particular those related to pain [8]. PsA in women was found to lead to more severe limitation of their daily function than in men and to result in a higher level of work disability [1].

Men and women with PsA have shown different magnitudes of response to and retention of biologic DMARDs (bDMARDs), such as TNFi [9–13], indicating that women with PsA initiating TNFi are less likely to achieve remission or minimal disease activity/very low disease activity (MDA/VLDA) [14, 15]. The Danish registry DANBIO and the British BSRBR registry reported that women receiving TNFi more frequently develop side effects than men, possibly leading to an earlier discontinuation of these drugs in women [9, 11]. Results from the DANBIO registry showed that a higher proportion of female patients than male patients switched to another TNFi or stopped the first TNFi without starting a new TNFi [10].

Similar observations have been made across other rheumatic conditions: women with RA and AS have been shown to have shorter TNFi treatment retention than men [16–20]. In these studies, female gender was an independent predictor of shorter drug survival (regarded as a surrogate marker for efficacy) across different TNFi [16, 17]. Women received treatment for a significantly shorter time, and the main reason for switching treatment was inefficacy [18, 20]. Accumulating evidence in multiple rheumatic diseases indicates that gender may influence the likelihood of achieving the desired outcome with treatment.

The objective of this analysis of PsABio data was to establish whether there are gender-related differences at baseline as well as in response to and retention of biological treatment in patients with PsA treated with ustekinumab or TNFi in routine clinical practice and to analyse these differences in the context of previous research.

Methods

PsABio (NCT02627768) was a multinational, prospective, real-world, observational cohort study of patients with PsA who started ustekinumab (an IL-12/IL-23 inhibitor) or a TNFi as first-, second- or third-line bDMARD treatment. The study was designed to evaluate the persistence, effectiveness and tolerability of ustekinumab and TNFi. The study design, patient population and evaluations have been described elsewhere [21, 22].

Data were collected at baseline, then every 6 months up to 3 years, with a window of ±3 months to align with standard clinical practice. In addition to the main statistical analysis, exploratory analyses were performed on various patient subgroups. In the analysis presented here, male and female patients were compared for disease activity, patient-reported outcomes and treatment persistence.

The Baseline set included all eligible patients with baseline data and without major protocol deviations. The Safety set included all patients with baseline data and an additional three female and two male patients excluded from the baseline set [no valid baseline assessment (within 62 days prior to bDMARD start)] and any available follow-up data included in the 36-month data analysis. The effectiveness set-1 included all eligible patients from the Baseline set with any effectiveness follow-up data up to 12[+3] months (hereafter referred to as 12 months). The 'remainer' data analysis is based on a previously obtained effectiveness set that included two patients less, referred to as effectiveness set-2. Data on these two patients were not available at the time of previous analyses [21, 22]. 'Remainer' patient groups included all patients who remained on the initial treatment (ustekinumab or TNFi) and had a selected Month 12 visit (defined as a visit that took place within the Month 12 ± 3 visit window).

Patient-reported outcome effectiveness measures were reported. Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) scores reflect the sum of four measures: tender joint count of 68 joints (TJC68), swollen joint count of 66 joints (SJC66), Patient Global Assessment Visual Analogue Scale (PtGA VAS, in cm) and patient pain (PtP) VAS. cDAPSA remission is defined as a score of ≤4 [23, 24]. The MDA/VLDA criteria assess seven domains (cut-offs): TJC68 (≤1); SJC66 (≤1); enthesitis (Leeds Enthesitis Index [25]; ≤1); skin involvement (Psoriasis Area and Severity Index [≤1] or psoriasis body surface area [BSA; ≤3%]) [26]; HAQ score (≤0.5); PtGA VAS (≤20, VAS in mm); and PtP VAS (≤15). If five of seven domain cut-offs are reached, MDA has been achieved; if all seven are met, VLDA has been achieved. The PsA Impact of Disease-12 (PsAID-12) is a self-reported questionnaire that assesses the impact of PsA on patients' lives [27]. A rating of 0 (none/no difficulty/very well) to 10 (extreme/extreme difficulty/very poorly) is given for each question.

Data were also collected for the following variables: the presence of dactylitis, enthesitis, nail psoriasis and psoriasis

skin involvement (BSA) according to four categories (clear/almost clear skin, 10%) and the EuroQol- 5 Dimension [EQ-5D; descriptive across five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression)] and Fibromyalgia Rapid Screening Tool (FiRST; 6 fibromyalgia items, 5/6 indicates fibromyalgia presence).

Partially missing dates were imputed for analysis. These included start and stop days of previous treatments or of treatments within the study, laboratory sample dates and other dates (if incompletely known, day and/or month were imputed), the BASDAI and the PSAID-12 missing item scores were imputed according to the recommendations of the developers of the scales. We defined the risk window (the time between treatment initiation and 91 days after treatment stop) on the basis of which adverse events (AEs) were assigned to treatments. If information on AE relationship to treatment was missing, the AE was imputed as related to the bDMARD. The analysis included data from the baseline assessment, at 6(±3) months and at 12(±3) months.

Data were analysed by descriptive statistics including 95% CI. All inter-gender comparisons were descriptive. Intra-gender comparisons between ustekinumab and TNFi cohorts were done by logistic regression analysis, with propensity score adjustment for imbalanced baseline covariates and non-response imputation for stopping/switching biologic drugs.

Ethics approval

This study complied with ethics requirements as specified by the Independent Ethics Committee/Institutional Review board of each participating site (as detailed in [22]) and by local regulations in each country. Each participant signed a participation agreement/informed consent form in line with local regulations and trial sponsor policy, before data collection.

Results

In total, 991 patients, who signed the informed consent form, entered the study. The Baseline set included 929 patients (512 females and 417 males) and the Effectiveness set-1 included 895 patients; 439 started ustekinumab, and 456 started TNFi [21, 22] (Fig. 1).

Female patients were slightly older than male patients (mean age was 50.2 years for females *vs* 48.7 years for males); however, both genders had similar mean disease duration at baseline (6.7 years for females *vs* 6.9 years for males) and similar mean BMI (28.4 kg/m^2 for females *vs* 27.7 kg/m^2 for males) (Table 1). A higher proportion of female patients (42.7%) than male patients (24.4%) had a FiRST score ≥5, suggestive of chronic widespread pain. Similarly, females were proportionally more likely to have polyarticular disease and enthesitis, whereas males were proportionally more likely to have oligoarticular disease, dactylitis and psoriasis affecting >10% of body surface. In addition, a higher proportion of female patients than male patients had comorbidities and physician-confirmed axial involvement combined with peripheral joint disease (Table 1).

There were similarities and differences in baseline medication. Males were more likely to start ustekinumab or TNFi as the first line of bDMARD (54.7% males *vs* 46.9% females). They were slightly more likely to be receiving NSAIDs (63.1% males *vs* 59.4% females) and similarly likely to be receiving steroids (32.6% males *vs* 34.0% females). A numerically higher proportion of female patients were receiving antidepressants at baseline (8.0% females *vs* 2.6% males). The use of other analgesics was also slightly higher in females (29.7% females *vs* 25.9% males), whereas the proportions of patients receiving opioids were similar (5.1% females *vs* 4.8% males).

The proportions of females and males receiving any concomitant conventional DMARDs (cDMARDs) at baseline were similar (48.8% females *vs* 46.0% males); in particular for methotrexate at baseline (37.1% females *vs* 35.3% males).

At baseline, females had worse scores than males for a number of disease activity assessments (Table 2); notably, most of the 95% CIs did not overlap. Mean cDAPSA score was 32.3 (95% CI: 30.3, 34.2) for females and 26.8 (95% CI: 24.8, 28.9) for males. Mean HAQ-DI score was 1.3 (95% CI: 1.2, 1.4) for females *vs* 0.93 (95% CI: 0.86, 0.99) for males.

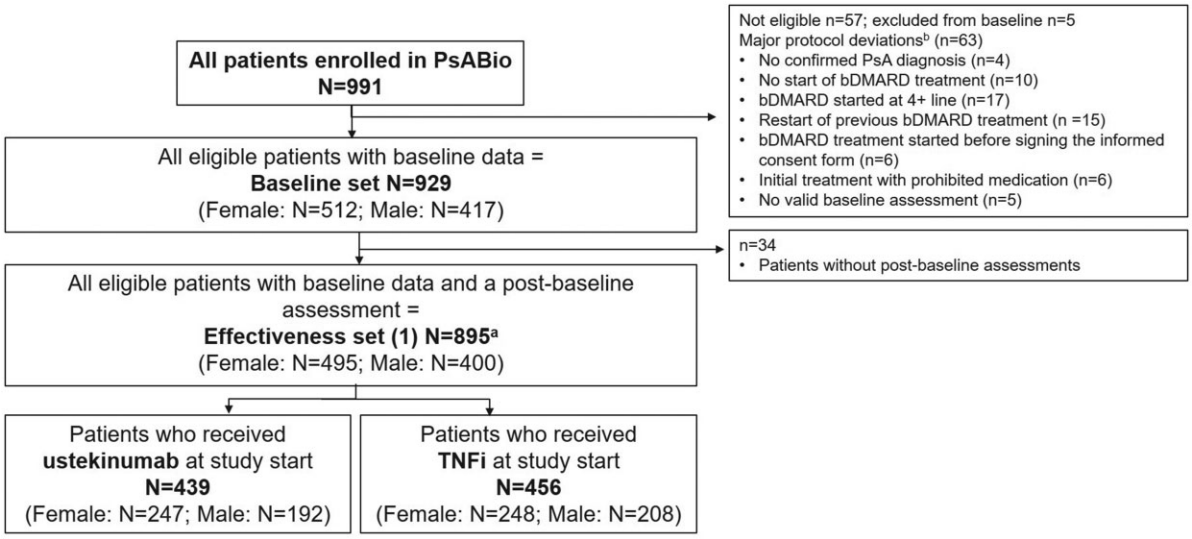

Figure 1. Summary of patients in analysis – all patients. [a]Note that Effectiveness set-1 comprises all patients in the latest data run, who had baseline data and a post-baseline assessment. See Methods and Supplementary Fig. S1, available at *Rheumatology* online. [b]Note that one patient may report more than one eligibility criteria. bDMARD: biological DMARD; TNFi: TNF inhibitor

Table 1. Patient demographics and disease characteristics at baseline – baseline set

	Female $n = 512$	Male $n = 417$
Mean age, years (95% CI)	50.5 (49.4, 51.6)	48.7 (47.5, 49.9)
Mean BMI, kg/m^2 (95% CI)	28.4 (27.8, 29.0)	27.7 (27.3, 28.2)
Mean disease duration since initial diagnosis, years (95% CI)	6.7 (6.0, 7.4)	6.9 (6.2, 7.6)
PsA characteristics, *n* (%)		
Axial involvement[a] (pure or combined with peripheral joint disease)	189 (37.8)	140 (34.4)
Physician-confirmed pure	12 (2.3)	12 (2.9)
Physician-confirmed combined	134 (26.2)	91 (21.8)
Monoarticular PsA	6 (1.2)	7 (1.7)
Oligoarticular PsA	105 (21.0)	126 (31.0)
Polyarticular PsA	352 (70.4)	245 (60.2)
Enthesitis, *n* (%)	248 (49.1)	192 (46.9)
Dactylitis, *n* (%)	78 (15.5)	106 (26.2)
Skin involvement, *n* (%)		
Clear/almost clear skin	173 (39.1)	97 (25.8)
<3%	63 (14.2)	44 (11.7)
3–10%	141 (31.8)	140 (37.2)
>10%	66 (14.9)	95 (25.3)
Line of bDMARD treatment, *n* (%)		
First	240 (46.9)	228 (54.7)
Second	172 (33.6)	138 (33.1)
Third	100 (19.5)	51 (12.2)
cDMARD treatment, *n* (%)		
Previous exposure to any cDMARD	459 (89.6)	374 (89.7)
Ongoing exposure to any cDMARD at baseline	250 (48.8)	192 (46.0)
Ongoing exposure to methotrexate at baseline	190 (37.1)	147 (35.3)
Other treatments ongoing at baseline, *n* (%)		
NSAIDs	304 (59.4)	263 (63.1)
Glucocorticosteroids	174 (34.0)	136 (32.6)
Analgesics	152 (29.7)	108 (25.9)
Opioids	26 (5.1)	20 (4.8)
Antidepressants	41 (8.0)	11 (2.6)
FiRST score, mean (95% CI)	3.8 (3.6, 3.9)	2.8 (2.6, 3.0)
FiRST score ≥5, suggestive of fibromyalgia, *n* (%)	209 (42.7)	95 (24.4)
Comorbidities, *n* (%)		
Cardiovascular/metabolic syndrome[b]	204 (39.8)	157 (37.6)
Depression	48 (9.4)	28 (6.7)
Anxiety or panic disorders	29 (5.7)	9 (2.2)
Gastrointestinal disease or history of IBD	68 (13.3)	37 (8.9)

[a] Pure axial PsA is defined as having only axial involvement (evaluation by the investigator rheumatologist without imaging), whereas combined axial PsA includes axial involvement and ≥1 of distal interphalangeal joint involvement, monoarticular or oligoarticular PsA, and arthritis mutilans.
[b] Hypertension, myocardial infarction, congestive heart failure, stroke or transient ischemic attack, peripheral vascular disease, hyperlipidaemia, type 1 or 2 diabetes or angina pectoris.
b/cDMARD: biologic/conventional DMARD; FiRST: Fibromyalgia Rapid Screening Tool.

Mean EQ5D VAS (with higher values indicating better health) was 48.6 (95% CI: 46.5, 50.6) for females *vs* 53.8 (95% CI: 51.6, 56.0) for males. Total PsAID-12 score was 6.0 (95% CI: 5.9, 6.2) for females *vs* 5.1 (95% CI: 4.9, 5.3) for males (Table 2).

Patients of both genders demonstrated improvement of clinical outcomes at 6 months and at 12 months, compared with baseline; however, females experienced a less pronounced improvement of their disease than males (Table 2). The proportion of patients who reached MDA including VLDA was 21.0% at 6 months and 33.7% at 12 months for females, and 43.1% at 6 months and 55.5% at 12 months for males (Table 2; Fig. 2). The proportion of patients achieving cDAPSA LDA (including remission) was 43.8% for females *vs* 66.0% for males at 6 months, and 57.8% for females *vs* 80.3% for males at 12 months (Fig. 2).

Although at baseline males had a higher rate of dactylitis and nail psoriasis than females, and an only slightly lower rate of enthesitis, they had lower rates of enthesitis, dactylitis and nail psoriasis than females at 6 months; this difference became more pronounced at 12 months (Table 2; Fig. 2). Males had a lower HAQ-DI score at baseline and a greater improvement in HAQ-DI score at 6 months and at 12 months than females; the 95% CIs of the HAQ-DI change at 12 months did not overlap (Table 2). Females had a greater improvement of EQ5D VAS score over 12 months; however, their mean EQ5D VAS score at 12 months remained lower than that of males (61.5 for females *vs* 69.7 for males) (Table 2). The change from baseline in final PsAID-12 score was greater for males, as shown by non-overlapping 95% CIs (Table 2).

Male patients demonstrated higher treatment persistence than females ($P \leq 0.001$ log rank test; Fig. 3).

After 12 months, 730 patients (81.7%) remained on their initial bDMARD. When considering ustekinumab and TNFi treatment groups separately, a higher proportion of females in the ustekinumab group switched or stopped their initial treatment compared with males. The same pattern was seen for the TNFi group (Supplementary Fig. S1, available at *Rheumatology* online). The proportions of males and females achieving MDA/VLDA and cDAPSA low disease activity/remission at 12 months were similar across treatment groups, i.e. males receiving ustekinumab showed a similar level of improvement as males receiving TNFi, and the same pattern was seen for females (Supplementary Table S1 and Fig. S2A, available at *Rheumatology* online).

Previously published overall analysis reported that patients receiving ustekinumab were on average receiving a later line of bDMARD treatment, had more severe skin involvement and more chronic widespread pain than patients receiving TNFi [21, 22]. Separately for females and males, achievement of effectiveness endpoints was compared between treatment groups including propensity score adjustment for baseline covariates. No significant differences in effectiveness of ustekinumab *vs* TNFi were detected within genders (Supplementary Fig. S2B, available at *Rheumatology* online).

Overall safety data at 12 months have been reported previously [22]. The safety data reported at 36 months is in line with previous reports. The proportion of females with any AEs, treatment-related AEs and bDMARD discontinuation due to a treatment-related AE was slightly higher than males. The proportion of males with malignancies was slightly higher than females (Table 3).

Females were more likely to stop treatment compared with males [$n = 109/494$ (22.1%), $n = 50/399$ (12.5%), respectively]. Lack of efficacy was the most common reason to stop the initial treatment compared with safety in both males [$n = 42/50$ (84.0%), $n = 7/50$ (14.0%), respectively] and

Table 2. Patient outcomes at baseline, 6 months and 12 months by gender – Effectiveness set-1

	Baseline		6 months		12 months	
	Females $n = 495$	Males $n = 400$	Females $n = 495$	Males $n = 400$	Females $n = 495$	Males $n = 400$
Joint counts, mean (95% CI)						
Swollen 66	6.2 (5.4, 6.9)	5.6 (4.7, 6.4)	2.5 (2.1, 3.0)	1.7 (1.3, 2.1)	1.8 (1.4, 2.2)	1.2 (0.9, 1.5)
Tender 68	13.1 (12.0, 14.3)	10.1 (9.0, 11.2)	7.3 (6.3, 8.3)	4.7 (3.8, 5.6)	4.8 (4.1, 5.5)	3.2 (2.5, 4.0)
cDAPSA score, mean (95% CI)	32.3 (30.3, 34.2)	26.8 (24.8, 28.9)	18.2 (16.6, 19.8)	12.2 (10.7, 13.7)	13.8 (12.4, 15.1)	8.9 (7.6, 10.2)
Mean change (95% CI) in cDAPSA from BL, %	n/a	n/a	−32.8 (−46.9, −18.7)	−51.6 (−57.0, −46.2)	−49.2 (−54.2, −44.2)	−62.6 (−67.8, −57.4)
cDAPSA, *n* (%)						
Remission	5 (1.3)	13 (3.9)	49 (12.9)	94 (30.4)	65 (21.5)	110 (41.7)
Low	27 (6.8)	49 (14.7)	117 (30.9)	110 (35.6)	110 (36.3)	102 (38.6)
Moderate	153 (38.7)	145 (43.5)	144 (38.0)	75 (24.3)	93 (30.7)	34 (12.9)
High	210 (53.2)	126 (37.8)	69 (18.2)	30 (9.7)	35 (11.6)	18 (6.8)
MDA, *n* (%)	11 (2.8)	23 (7.5)	77 (21.0)	122 (43.1)	96 (33.7)	137 (55.5)
VLDA, *n* (%)	0	4 (1.2)	20 (5.1)	37 (12.5)	29 (9.8)	55 (21.4)
HAQ-DI score, mean (95% CI)	1.3 (1.2, 1.4)	0.93 (0.86, 0.99)	1.0 (0.94, 1.1)	0.60 (0.53, 0.66)	0.85 (0.77, 0.92)	0.50 (0.43, 0.56)
Mean (95% CI) change in HAQ-DI score from BL, %	n/a	n/a	−20.6 (−27.2, −14.1)	−33.9 (−42.4, −25.4)	−30.1 (−36.3, −23.9)	−46.8 (−54.2, −39.3)
Total PsAID-12, mean (95% CI)	6.0 (5.8, 6.2)	5.1 (4.9, 5.3)	4.2 (4.0, 4.4)	3.0 (2.7, 3.2)	3.5 (3.3, 3.8)	2.4 (2.2, 2.6)
Mean (95% CI) percent change in total PsAID-12 score from BL	n/a	n/a	−27.0 (−32.4, −21.5)	−39.9 (−44.9, −34.8)	−37.0 (−42.4, −31.7)	−52.3 (−57.5, −47.2)
EQ5D VAS score, mean (95% CI)	48.6 (46.5, 50.6)	53.8 (51.6, 56.0)	57.9 (55.8, 60.1)	65.8 (63.4, 68.3)	61.5 (58.9, 64.2)	69.7 (67.0, 72.5)
Mean (95% CI) percent change in EQ5D VAS score from BL	n/a	n/a	54.5 (42.2, 66.8)	45.3 (34.1, 56.5)	60.7 (44.9, 76.5)	54.8 (41.5, 68.1)
Enthesitis, *n* (%)	223 (50.6)	175 (47.8)	145 (34.8)	89 (25.8)	103 (31.3)	46 (15.6)
Dactylitis, *n* (%)	71 (16.1)	93 (25.5)	30 (7.1)	20 (5.8)	17 (5.2)	14 (4.8)
Skin involvement, *n* (%)						
Clear/almost clear skin	141 (36.9)	82 (24.4)	204 (58.6)	186 (61.6)	182 (68.7)	180 (66.7)
<3%	51 (13.4)	39 (11.6)	50 (14.4)	38 (12.6)	33 (12.5)	35 (13.0)
3–10%	128 (33.5)	129 (38.4)	85 (24.4)	64 (21.2)	46 (17.4)	51 (18.9)
>10%	62 (16.2)	86 (25.6)	9 (2.6)	14 (4.6)	4 (1.5)	4 (1.5)
Nail psoriasis, *n* (%)	163 (38.7)	177 (49.3)	121 (30.8)	121 (36.7)	89 (29.5)	109 (37.7)

BL: baseline; cDAPSA: clinical Disease Activity Index for Psoriatic Arthritis; EQ5D: Euro Quality of Life questionnaire – 5 Dimensions; HAQ-DI: HAQ – Disability Index; MDA: minimal disease activity; n/a: not applicable; PsAID-12: Psoriatic Arthritis Impact of Disease-12; TNFi: TNF inhibitor; VAS: visual analogue scale; VLDA: very low disease activity.

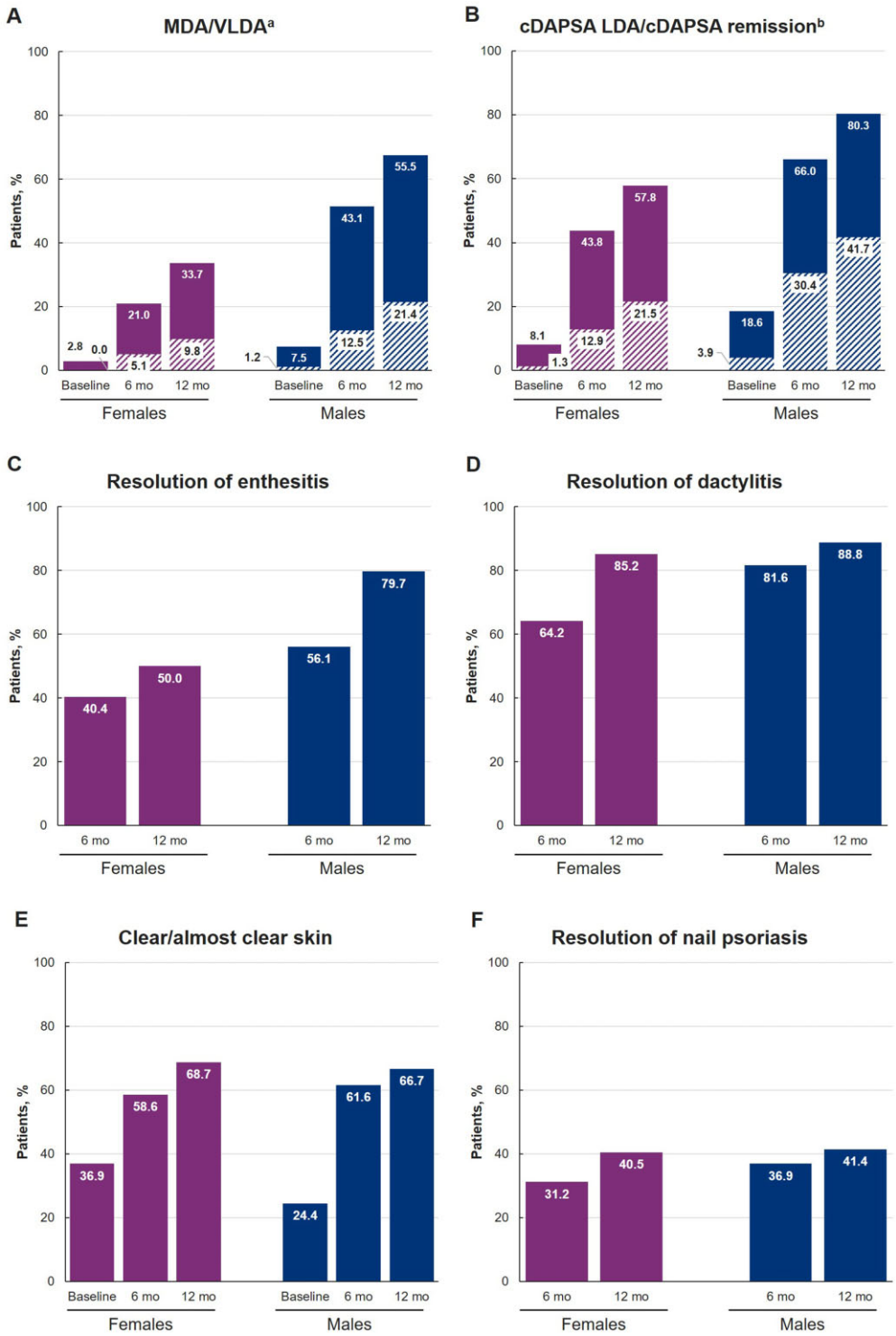

Figure 2. Observed proportion of male and female patients achieving treatment targets (A, B) and single item resolution (C–F) at 6 and at 12 months—Effectiveness set-1. [a]Solid bar represents MDA and hashed bar represents VLDA. [b]Solid bar represents cDAPSA LDA/remission (≤13) and hashed bar represents cDAPSA remission (≤4). cDAPSA: clinical Disease Activity Index for Psoriatic Arthritis; LDA: low disease activity; MDA: minimal disease activity; mo: months; TNFi: TNF inhibitor; VLDA: very low disease activity

females [$n = 78/109$ (71.6%), $n = 30/109$ (27.5%), respectively].

Discussion

The analysis of gender subgroup results of the PsABio study has expanded previously published observations that men and women with PsA have different experiences with the disease activity, clinical manifestations, impact on health-related quality of life, response to bDMARDs and drug persistence. Broadly, the differences we observed may be classified into those related to the disease and those related to the patient response to bDMARD treatment. At baseline, polyarticular PsA and enthesitis were more prevalent in female patients who

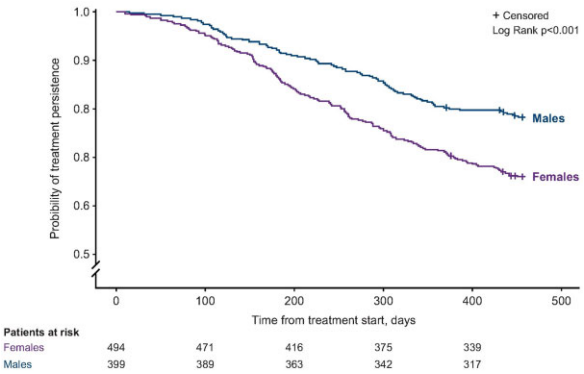

Figure 3. Treatment persistence during 12-months

Table 3. Adverse events at 36 months – Safety set[a]

Patients, *n* (%)	Female *n* = 515	Male *n* = 419
Any AE[b]	221 (42.9)	166 (39.6)
Any treatment-related AE	126 (24.5)	84 (20.0)
Any SAE	43 (8.3)	33 (7.9)
Any treatment-related SAE	10 (1.9)	10 (2.4)
Any treatment-related AE leading to withdrawal of bDMARD	55 (10.7)	28 (6.7)
Any neoplasm AE (sensitivity analysis no lag time)	9 (1.7)	12 (2.9)
Benign	4 (0.8)	2 (0.5)
Non-melanoma skin cancer	3 (0.6)	1 (0.2)
Malignancy exc non-melanoma skin cancer	3 (0.6)	7 (1.7)
Unknown/undefined	0	2 (0.5)
Any neoplasm AE (12-month lag time)	7 (1.4)	7 (1.7)
Benign	3 (0.6)	1 (0.2)
Non-melanoma skin cancer	2 (0.4)	1 (0.2)
Malignancy exc non-melanoma skin cancer	2 (0.4)	4 (1.0)
Unknown/undefined	0	1 (0.2)
Death	1 (0.2)	2 (0.5)

[a] Safety set included all patients who had baseline data and an additional three female and two male patients excluded from baseline set [no valid baseline assessment (within 62 days prior to bDMARD start)].
[b] AEs do not include neoplasms unless stated.
AE: adverse event; bDMARD: biologic DMARD; SAE: serious adverse event.

were also almost twice more likely to have FiRST score ≥5, indicative of chronic widespread pain. The observation that they received NSAIDs slightly less frequently than male patients may indicate that patients and/or their prescribing physicians perceive PsA-related pain differently in females and males. This may also be supported by the less favourable outcomes among female patients, reflected by more frequent switching and greater use of antidepressants. To our knowledge, this is the first report of gender differences in non-DMARD medication. In the context of clinical and patient-reported outcomes following ustekinumab or TNFi treatment, although both gender subgroups showed improvement at 6 and 12 months, female patients remained in a worse disease state than male patients (i.e. lower rates of MDA/VLDA and cDAPSA low disease activity/remission among females compared with males). Although male patients started with lower (i.e. better) HAQ-DI and total PsAID-12 scores at baseline, they showed a greater improvement in both scores at 12 months than females, increasing the gap between the genders rather than closing it. Finally, female patients in our study entered on later lines of bDMARD treatment than males, suggesting that their previous biologic treatment(s) may have been unsuccessful. In addition, they stopped or switched the bDMARD earlier than male patients in the study, which may represent the recognized phenomenon of decreasing effectiveness in subsequent bDMARD lines. Females were more likely than males to stop treatment; this was due to effectiveness reasons, but also to some degree safety signals, in line with observations in the DANBIO registry [13]. Lack of effectiveness was the most common reason to stop treatment, irrespective of gender.

These results add to the accumulating evidence of gender-specific differences in PsA [1, 4, 10, 12] and other rheumatic conditions [28–30]. Females are more likely to have polyarticular disease [4, 30] and experience more chronic pain than males. A recent study that observed differences in reporting of pain [8] hypothesized that women may have a different perception of disease. Our observations on prior and baseline medications (e.g. use of analgesics) may also point towards a different interpretation of the genesis of disease expression by health care providers/rheumatologists.

The chronic widespread pain identified with the FiRST tool could rather be an epiphenomenon, typically occurring in females, and should not preclude potent anti-inflammatory treatment for female patients. The results of this study suggest that treatment approaches for females are not fully successful, and broader/more comprehensive therapeutic strategies including sufficient and lasting anti-inflammatory DMARDs are needed for female patients, probably earlier in the disease course.

Poor prognostic factors, including dactylitis, enthesitis, polyarticular disease and progressive disability have been reported to be more common in females, suggesting a need for more intensive treatment management [1, 13]. Results from the DANBIO registry indicated that females had worse physical function compared with males after 12 months of treatment. In addition, inflammatory markers (e.g. CRP and SJC) were less affected in females compared with males [13]. Female sex hormones may contribute to enhanced immunogenicity and pro-inflammatory disease and could in part contribute to gender differences in the clinical characteristics of PsA [1]. Although dactylitis was not more common in females in our study, greater prevalence of enthesitis, polyarticular disease and higher HAQ scores in females are all in agreement with previous studies.

It may be that enthesitis and polyarticular disease are a patient's way of expressing pain and the higher levels at baseline in females compared with males may be linked to the higher levels of fibromyalgia and chronic pain (FiRST questionnaire) seen in females. However, to fully understand if pain is linked to a higher enthesitis score, a mediation analysis would need to be undertaken which could be difficult to interpret when outcomes are highly correlated [as is the case for patient reported outcomes (PROs)].

This study benefited from a number of strengths as it was a large prospective real-world cohort study (conducted across 91 sites in eight European countries) and as such, patients were selected in a less rigid way than those enrolling in randomized controlled trials. The responses to treatment by gender were not limited to just one type of medication (i.e. they included two different modes of action of biologic therapy, ustekinumab or TNFi) and are thus more widely applicable. Limitations include the fact that the results shown here were

generated from a *post-hoc* analysis, as investigating gender-related differences was not a primary study objective. In addition, in consensus with a routine care setting, there was no strict medication protocol and the choice of bDMARD was made independently before enrolment by each patient's rheumatologist.

More studies are needed, to illuminate further the disappointing treatment results for female patients compared with their male counterparts. This study can make rheumatologists aware that women with PsA have a substantially worse experience with their disease both in terms of disease activity (i.e. increased disease duration and severity) and patient-reported outcomes, at the start of treatment with bDMARDs. The between-gender differences have consequences for treatment response and treatment persistence, and physicians should consider changing the current practice of treatment, particularly for female patients with PsA.

Conclusion

These real-world data from PsABio on gender differences suggest that, at the start of biologic treatment, females have a worse clinical picture of PsA than males. Although treatment improvements were seen in both genders, a lower percentage of women reached a favourable disease state of low or minimal disease activity at one year, and more women stopped/switched biologic due to both lower effectiveness of the treatment and AEs. A better understanding of the mechanisms underlying these differences may improve therapeutic management in females with PsA.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

No data are available. Access to anonymised individual participant-level data will not be provided for this trial as it meets one or more of the exceptions described on https://yoda.yale.edu/ under 'Data Use Agreement—Janssen Pharmaceuticals DUA'.

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