The Journal of Rheumatology 2024;51:378–89
doi:10.3899/jrheum.2023-0764
First Release February 15 2024

The Journal of Rheumatology

Patient-Reported Outcomes (PROs) and PRO Remission Rates in 12,262 Biologic-Naïve Patients With Psoriatic Arthritis Treated With Tumor Necrosis Factor Inhibitors in Routine Care

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ABSTRACT. ***Objective.*** To evaluate patient-reported outcomes (PROs) after initiation of tumor necrosis factor inhibitor (TNFi) treatment in European real-world patients with psoriatic arthritis (PsA). Further, to investigate PRO remission rates across treatment courses, registries, disease duration, sex, and age at disease onset.

Methods. Visual analog scale or numerical rating scale scores for pain, fatigue, patient global assessment (PtGA), and the Health Assessment Questionnaire–Disability Index (HAQ-DI) from 12,262 patients with PsA initiating a TNFi in 13 registries were pooled. PRO remission rates (pain ≤ 1, fatigue ≤ 2, PtGA ≤ 2, and HAQ-DI ≤ 0.5) were calculated for patients still on the treatment.

Results. For the first TNFi, median pain score was reduced by approximately 50%, from 6 to 3, 3, and 2; as were fatigue scores, from 6 to 4, 4, and 3; PtGA scores, from 6 to 3, 3, and 2; and HAQ-DI scores, from 0.9 to 0.5, 0.5, and 0.4 at baseline, 6, 12, and 24 months, respectively. Six-month Lund Efficacy Index (LUNDEX)–adjusted remission rates for pain, fatigue, PtGA, and HAQ-DI scores were 24%, 31%, 36%, and 43% (first TNFi); 14%, 19%, 23%, and 29% (second TNFi); and 9%, 14%, 17%, and 20% (third TNFi), respectively. For biologic-naïve patients with disease duration < 5 years, 6-month LUNDEX-adjusted remission rates for pain, fatigue, PtGA, and HAQ-DI scores were 22%, 28%, 33%, and 42%, respectively. Corresponding rates for patients with disease duration > 10 years were 27%, 32%, 41%, and 43%, respectively. Remission rates were 33%, 40%, 45%, and 56% for men and 17%, 23%, 24%, and 32% for women, respectively. For patients aged < 45 years at diagnosis, 6-month LUNDEX-adjusted remission rate for pain was 29% vs 18% for patients ≥ 45 years.

Conclusion. In 12,262 biologic-naïve patients with PsA, 6 months of treatment with a TNFi reduced pain by approximately 50%. Marked differences in PRO remission rates across treatment courses, registries, disease duration, sex, and age at onset of disease were observed, emphasizing the potential influence of factors other than disease activity on PROs.

Key Indexing Terms: epidemiology, fatigue, pain, psoriatic arthritis, tumor necrosis factor inhibitors

The EuroSpA Research Collaboration Network was financially supported by Novartis Pharma AG. Novartis had no influence on the data collection, statistical analyses, manuscript preparation, or decision to submit the manuscript.

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Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease, causing widespread inflammation, pain, fatigue, physical disability, and reduced quality of life.[1] In addition to musculoskeletal manifestations and psoriasis, PsA is associated with extramusculoskeletal manifestations such as uveitis and inflammatory bowel disease, and comorbidities including obesity, diabetes, hypertension, cardiovascular disease, and depression.[1]

PsA is initially treated with nonsteroidal antiinflammatory drugs, local corticosteroids, and/or conventional synthetic disease-modifying antirheumatic drugs (DMARDs), such as methotrexate. For patients with PsA with an insufficient response to these treatments, biologic DMARDs, including tumor necrosis factor inhibitors (TNFi) and other biologics (interleukin [IL]-17, IL-12/23, or IL-23 inhibitors), are recommended.[2,3]

Patient-reported outcomes (PROs) are important tools for the assessment of symptoms experienced by patients with PsA, such as pain, fatigue, and functional status, thereby supplementing the clinical examination.[4-6] Until now, the effect of TNFi treatment on PROs in patients with PsA has mainly been investigated in smaller real-world studies[7-9] and in randomized clinical trials,[10-13] with a focus on treatment response assessed at a group level. Larger real-world studies investigating PROs and PRO remission rates, that is, the proportion of individual patients who achieved very low scores of PROs (≤ 1 for pain, ≤ 2 for fatigue and patient global assessment of disease activity [PtGA], and ≤ 0.5 for the Health Assessment Questionnaire–Disability Index [HAQ-DI]) during TNFi treatment, are missing. Also, although previous studies suggest varying response to TNFi between patients stratified by sex and treatment courses, knowledge on the effect of TNFi on PROs in subgroups of patients with PsA are lacking.[8,14]

In 2017, the European Spondyloarthritis (EuroSpA) Research

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M.L. Hetland and M. Østergaard contributed equally to this work as co-senior authors.

LMØ has received a research grant paid to her employer from Novartis. KR has received a research grant paid to her employer from Novartis. SG has received a research grant paid to his employer from Novartis. SHR has received a research grant paid to his employer from Novartis. LJ has received consulting fees from Novartis, Eli Lilly, and Janssen. AGL has received consulting fees from AbbVie, Janssen, Eli Lilly, MSD, Novartis, Pfizer, Roche, and UCB. FI has received speaker fees from AbbVie, Eli Lilly, BMS, Sanofi, MSD, Roche, and Pfizer. JV has received consulting fees from AbbVie, argenx, Boehringer Ingelheim, Eli Lilly, Gilead, Octapharma, Pfizer, and UCB; speaking fees from AbbVie, Biogen, Boehringer Ingelheim, Eli Lilly, Gilead, MSD, Novartis, Pfizer, Roche, Sanofi, UCB, and Werfen; and grants from AbbVie. MJS has received speaker fees from AbbVie, Novartis, Pfizer, and Roche. BM has received speaking fees from AbbVie, Janssen, Novartis, and Pfizer and a research grant from Celgene. MPS has received speaker and consulting fees from Janssen, MSD, and Novartis. ZR has received speaker and consulting fees from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Biogen, Eli Lilly, Janssen, Medis, MSD, Novartis, Pfizer, and Sandoz Lek. BG has received speaker fees from Novartis. KE has received speaker fees from Novartis, Sobi, Eli Lilly, and Janssen. CC has received speaker fees and consulting fees from AbbVie, Amgen, Berlin Chemie, Boehringer Ingelheim, Ewopharma, Janssen, Eli Lilly, Novartis, Pfizer, and Sandoz. GJ has received research grants from AbbVie, Pfizer, UCB, GSK, and Amgen. MVS has received speaker fees from Novartis, UCB, Janssen; consulting fees from Novartis, UCB, AbbVie, Janssen; and research support from Novartis, UCB, and Janssen. JKW has received speaker fees from AbbVie and Amgen; and research support from AbbVie, Amgen, Eli Lilly, Novartis, and Pfizer. BM has received consulting fees and research support from Novartis. JZ has received speaker fees from AbbVie, Eli Lilly, BMS, and Sanofi. MJN has received a research grant from Novartis and speaker fees from AbbVie, Amgen, Eli Lilly, MSD, Novartis, and Pfizer. MT has received speaker and consulting fees from AbbVie, Boehringer Ingelheim, Eli Lilly, Medis, Novartis, Pfizer, and Sandoz Lek. HR has received consulting and/or speaking fees from AbbVie, Pfizer, and UCB, and support for congress from Janssen. CM has received speaker fees from AbbVie, Pfizer, Novartis, Eli Lilly, Ewopharma, Boehringer Ingelheim, and Sandoz. MLH has received research grants from AbbVie, Biogen, BMS, Celltrion, Eli Lilly, Janssen Biologics BV, Lundbeck Fonden, MSD, Medac, Novartis, Pfizer, Roche, Samsung Bioepis, and Sandoz. MØ has received research grants from AbbVie, BMS, Merck, Celgene, and Novartis; and speaker and/or consulting fees from AbbVie, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Hospira, Janssen, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi, and UCB. The remaining authors declare no conflicts of interest relevant to this article.

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Accepted for publication December 7, 2023.

Collaboration Network was established, allowing secondary use of real-world data from existing registries.[15] The present study was based on such data and aimed to (1) investigate the effects of TNFi treatment on PROs in patients with PsA, and (2) to explore differences in PRO remission rates across treatment courses, registries, disease duration, sex, and early vs later onset of disease.

METHODS

The EuroSpA Research Collaboration Network. The present study was based on data from the EuroSpA Research Collaboration Network, which includes data on patients with PsA from the following 13 registries (country, year of registry start): ATTRA (Czech Republic, 2002), DANBIO (Denmark, 2000), National Register of Biological Treatment in Finland (ROB-FIN; Finland, 1999), Icelandic Nationwide Database of Biologic Therapy (ICEBIO; Iceland, 2007), Italian Group for the Study of Early Arthritis (GISEA; Italy, 2008), Nowegian Disease-modifying Antirheumatic Drugs Register (NOR-DMARD; Norway, 2000), Rheumatic Diseases Portuguese Register (Reuma.pt; Portugal, 2008), the Romanian Registry of Rheumatic Diseases (RRBR; Romania, 2015), Slovenian Biologics Register (BioRx.si; Slovenia, 2008), Spanish Registry for Adverse Events of Biological Therapy in Rheumatic Diseases (BIOBADASER; Spain, 2000), Swedish Rheumatology Quality Register (SRQ; Sweden, 1999), Swiss Clinical Quality Management in Rheumatic Diseases (SCQM; Switzerland, 2006), and TURKBIO (Turkey, 2011).[16-28] Data were collected prospectively by the individual registries according to their respective protocols, either in a routine care environment or within a specific research context.[29] Thus, the number of PROs assessed and follow-up schedules differed between registries. The process of data transfer from the registries to the Research Collaboration Network included 3 steps: (1) data managers in each of the 13 registries received a list of variables that were predefined in the study protocol and created pseudonymized datasets, (2) datasets were securely uploaded to the EuroSpA server, and (3) datasets were harmonized and pooled to 1 dataset at the EuroSpA coordinating center.

Statement of ethics and consent. All participating registries obtained the necessary approvals in accordance with legal, compliance, and regulatory requirements from national data protection agencies and/or research ethics boards prior to the data transfer to the EuroSpA coordinating center.

Study population. Inclusion criteria for the present study were an initial clinical diagnosis of PsA at age 18 years or older, initiation of a TNFi as first biologic treatment during the period January 1, 2009, to December 31, 2018, and at least 1 visit (baseline, 6, 12, or 24 months) with a registered PRO while being treated with a TNFi. Patients who switched from a first to second TNFi and from a second to third TNFi, without non-TNFi biologic or targeted synthetic DMARD treatments in between, were included in the analyses of second and third TNFi, respectively. Treatment switches from originator to biosimilar or between biosimilar TNFi were disregarded. Data collection ended on November 4, 2019, which allowed all patients to have a minimum of 10 months of follow-up after starting their first TNFi treatment.

Data collection. At baseline for each TNFi, the following variables were extracted: age, years since diagnosis, sex, BMI (calculated as weight in kilograms divided by height in meters squared), smoking status (current, previous, never), physician global assessment (PGA), joint counts, C-reactive protein, erythrocyte sedimentation rate, and composite disease activity indices (Table 1). The following 4 PROs of interest were collected, if available, at baseline and at 6, 12, and 24 months of follow-up for first, second, and third TNFi treatments in patients who were still treated: patient's assessment of pain, fatigue,[30] and PtGA,[31] as well as the HAQ-DI score.[32] Three registries (RRBR, BioRx.si, and SCQM) used a 0-10 numeric rating scale for pain, fatigue, PtGA, and PGA, whereas the remaining registries used a visual analog scale (VAS) scale of 0-100. Scores on a VAS scale of 0-100 were converted to 0-10 by dividing by 10 and rounding to nearest integer; therefore, scores were harmonized on a common 0-10 scale. HAQ-DI was collected on a 0-3 scale. The visits at 6, 12, and 24 months were defined as registered visits in the periods of 90-270 days, 271-545 days, and 546-910 days after baseline, respectively. If > 1 visit was available in a period, the visit with registration of the most PROs was preferred. If a similar number of PROs were available, the visit closest in time to 6, 12, and 24 months was selected. Only medians for PROs reported by ≥ 50 patients are included in tables and figures.

Definition of PRO remission. There is no international consensus on cut-off values for PRO remission in patients with PsA. However, a study by Coates et al defined minimal disease activity (MDA) as patients fulfilling 5 of 7 criteria selected by an expert group.[33] Three of these criteria were VAS score for pain ≤ 15 mm, PtGA ≤ 20 mm, and HAQ-DI score ≤ 0.5. Based on these definitions of MDA, we defined PRO remission for each PRO as follows: pain ≤ 1, fatigue ≤ 2, PtGA ≤ 2, and HAQ-DI ≤ 0.5.

Ethics. The study was approved by the respective national data protection agencies and research ethics committees according to legal regulatory requirements in the participating countries and was performed in accordance with the Declaration of Helsinki.

The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[34]

Statistical analyses. Descriptive statistics (medians with IQRs) were applied for PRO scores and changes in PROs from baseline to 6, 12, and 24 months. For PRO remission, we report crude and Lund Efficacy Index (LUNDEX)–adjusted rates.[35] The LUNDEX-adjusted rate integrates clinical response with treatment retention using the equation: (fraction of starters still in the study at time T) × (fraction responding at time T). Drug retention rates were calculated with Kaplan-Meier estimation. In addition, metaanalyses across registries were performed for median PRO scores and crude PRO remission rates in registries with ≥ 20 patients with available data for the PRO and timepoint. No imputation of missing data was performed. All statistical analyses were performed in R version 3.6.1 (R Foundation).

RESULTS

Patients. We included data on 12,262 biologic-naïve patients with PsA starting treatment with a first TNFi in a real-world setting between January 1, 2009, and December 31, 2018. Among these patients, 4329 patients later initiated a second TNFi and 1240 patients a third TNFi. Considering the first TNFi treatment course, etanercept was the most frequently prescribed drug (35% of patients), followed by adalimumab (30%), infliximab (17%), golimumab (13%), and certolizumab pegol (7%). Similar prescription patterns were seen across treatment courses (Table 1).

The following median PRO scores were observed at baseline for first TNFi treatment: pain = 6 (IQR 4-8), fatigue = 6 (IQR 4-8), PtGA = 6 (IQR 4-8), and HAQ-DI = 0.9 (IQR 0.5-1.4). PRO scores at baseline were similar across first, second, and third treatment courses, with pain at 6, 6, and 7; fatigue at 6, 7, and 7; PtGA at 6, 6, and 7; and HAQ-DI 0.9, 1.0, and 1.0, respectively (Table 1). Baseline values for physician-reported outcomes, joint counts, blood tests, and composite disease activity indices were also comparable across treatment courses (Table 1).

PROs and changes from baseline at 6, 12, and 24 months of first, second, and third TNFi treatment. Figure 1 shows the median scores for pain, fatigue, PtGA, and HAQ-DI scores at baseline and at 6, 12, and 24 months after initiation of first, second, and third TNFi treatment in the overall cohort. For patients receiving

Table 1. Baseline characteristics of patients with psoriatic arthritis starting a first TNFi treatment between January 1, 2009, and December 31, 2018[a].

	First TNFi Treatment, n = 12,262		Second TNFi Treatment, n = 4329		Third TNFi Treatment, n = 1240	
	No. of Patients With Available Data	Median (IQR) or n (%)	No. of Patients With Available Data	Median (IQR) or n (%)	No. of Patients With Available Data	Median (IQR) or n (%)
Age at TNFi treatment initiation, yrs	12,262	49 (40-58)	4329	51 (41-59)	1240	50 (41-59)
Sex, men	12,262	5663 (48)	4329	1736 (40)	1240	434 (35)
Years since diagnosis	9498	3 (1-8)	3234	5 (2-9)	875	6 (3-10)
≤ 5		6072 (64)		1840 (57)		437 (50)
6-10		1656 (17)		699 (22)		242 (28)
> 10		1770 (19)		695 (22)		196 (22)
Age at diagnosis, yrs	9498	43 (33-52)	3234	43 (34-52)	875	42 (33-51)
< 45		5224 (55)		1772 (55)		490 (56)
≥ 45		4274 (45)		1462 (45)		385 (44)
BMI, kg/m^2	4578	27 (24-30)	1381	27 (24-31)	397	27 (24-31)
Current smokers	10,358	1758 (17)	3583	624 (17)	1054	196 (19)
First TNFi drug (year of EMA approval)	12,262		4329		1240	
Infliximab (1999)		2107 (17)		481 (11)		204 (16)
Etanercept (2000)		4182 (35)		1566 (37)		330 (27)
Adalimumab (2003)		3629 (30)		1360 (31)		315 (25)
Certolizumab pegol (2009)		811 (7)		319 (7)		138 (11)
Golimumab (2009)		1533 (13)		603 (14)		253 (20)
First TNFi initiation, yr	12,262		4329		1240	
2009-2014		7017 (57)		2042 (47)		560 (45)
2015-2018		5245 (43)		2287 (53)		680 (55)
PROs[b]						
Pain	9000	6 (4-8)	3053	6 (4-8)	896	7 (5-8)
Fatigue	4748	6 (4-8)	2007	7 (4-8)	634	7 (5-8)
PtGA	9577	6 (4-8)	3194	6 (5-8)	914	7 (5-8)
HAQ-DI	8484	0.9 (0.5-1.4)	2885	1.0 (0.5-1.5)	834	1.0 (0.6-1.5)
Physician-reported outcomes						
PGA	5956	4 (2-6)	1946	3 (2-5)	551	3 (2-5)
Joint counts						
SJC28	9189	2 (0-5)	3087	1 (0-4)	880	1 (0-3)
TJC28	9201	4 (1-9)	3090	4 (1-8)	880	4 (1-8)
SJC66	5377	3 (1-7)	1834	2 (0-5)	536	2 (0-5)
TJC68	5456	7 (3-13)	1871	6 (2-12)	549	6 (2-12)
Blood tests						
CRP, mg/L	8052	6 (3-14)	2742	4 (2-11)	798	4 (2-10)
ESR, mm/hr	7458	15 (7-29)	2263	12 (6-25)	612	13 (6-27)
Composite indices						
DAS28-CRP	7144	4.2 (3.3-5.0)	2430	3.9 (3.0-4.8)	704	4.0 (3.0-4.8)
DAS28-ESR	6342	4.3 (3.3-5.3)	1915	4.0 (3.0-5.0)	513	4.1 (3.0-5.1)
DAPSA28	6878	25 (17-37)	2361	23 (14-34)	698	24 (16-35)
DAPSA68	3853	25 (17-35)	1383	22 (15-32)	403	23 (16-34)

Three registries (RRBR, BioRx.si, and SCQM) used a 0-10 numeric rating scale for pain, fatigue, PtGA, and PGA, whereas the remaining registries used a scale of 0-100. Scores on a 0-100 scale were converted to 0-10 by dividing by 10 and rounding to nearest integer. [a] By 2009, all relevant TNFi products were marketed and the patients included in this cohort had the same treatment options as patients treated today; however, after 2009, other biologic treatment options, which can replace TNFi drugs, have been marketed. [b] The scales for the patient-reported outcomes and PGA were 0-10, except for the HAQ-DI scale, which was 0-3. BioRx.si: Slovenian Biologics Register; CRP: C-reactive protein; DAPSA28: Disease Activity Index for Psoriatic Arthritis in 28 joints; DAPSA68: Disease Activity Index for Psoriatic Arthritis in 68 joints; DAS28-CRP: Disease Activity Score in 28 joints based on CRP; DAS28-ESR: Disease Activity Score in 28 joints based on ESR; EMA: European Medicines Agency; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire–Disability Index; PGA: physician global assessment of disease activity; PRO: patient-reported outcome; PtGA: patient global assessment of disease activity; RRBR: Romanian Registry of Rheumatic Diseases; SCQM: Swiss Clinical Quality Management in Rheumatic Diseases; SJC28: swollen joint count of 28 joints; SJC66: swollen joint count of 66 joints; TJC28: tender joint count of 28 joints; TJC68: tender joint count of 68 joints; TNFi: tumor necrosis factor inhibitor.

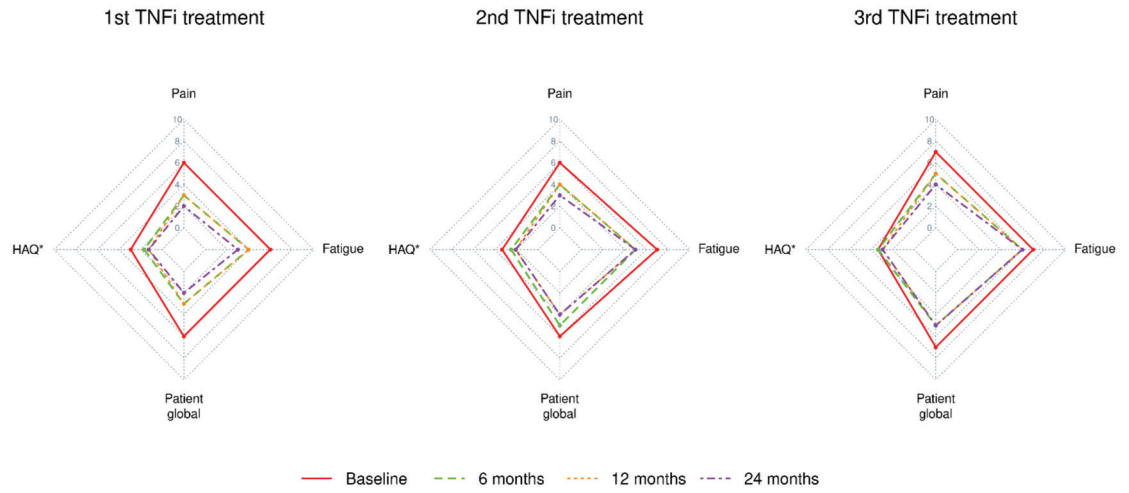


Figure 1. Radar charts illustrating the median scores for patient-reported outcomes at baseline and at 6, 12, and 24 months after initiation of a first TNFi (baseline, N = 12,626), second TNFi (baseline, n = 4329), and third TNFi (baseline, n = 1240). * HAQ was scored on a scale ranging from 0-3. HAQ: Health Assessment Questionnaire–Disability Index; patient global: patient global assessment of disease activity; TNFi: tumor necrosis factor inhibitor.

their first TNFi treatment, there was a marked improvement in median PRO scores from baseline to 6 months. Median pain score decreased from 6 to 3, whereas fatigue score decreased from 6 to 4, and PtGA score from 6 to 3. Improvements were also seen for patients receiving their second and third TNFi treatments, but to a smaller degree. Similarly, larger changes in individual patients in PROs from baseline were observed for first TNFi treatment compared to later-line treatment courses; most markedly in pain scores (Supplementary Figure S1, available with the online version of this article).

The distribution of individual pain scores changed markedly from baseline to 6 months after initiation of a first TNFi treatment, whereas distributions at 12 months and 24 months were similar to those at 6 months (Figure 2A). Figure 2B,C shows that 12% of patients who reported high pain at baseline[9,10] also reported high pain at 6 months. Conversely, in patients who reported pain at baseline in the range 6 to 7, ≤ 2% reported high pain[9,10] at 6 months (Figure 2B,C). Similar patterns were seen for fatigue, PtGA, and HAQ-DI (Supplementary Figure S2A-C, available with the online version of this article).

PRO remission rates after 6, 12, and 24 months of first, second, and third TNFi treatment. After 6 months of a first TNFi treatment, the crude remission rate for pain score (ie, pain score ≤ 1) was 29% in the overall cohort. The estimated remission rate based on metaanalysis was 30% (95% CI 26-34), whereas the LUNDEX-adjusted remission rate was 24%. Six-month crude remission rate for fatigue (fatigue score ≤ 2) was 37%, whereas the metaanalysis-based rate was 43% (95% CI 32-54) and the LUNDEX-adjusted remission rate was 31%. For patient global remission (PtGA ≤ 2), the crude 6-month remission rate was 43%, the metaanalysis-based estimate 45% (95% CI 39-51), and the LUNDEX-adjusted remission rate 36%. Crude 6-month HAQ-DI remission rate (HAQ-DI ≤ 0.5) was 52%, the metaanalysis-based estimate 54% (95% CI 46-52) and the LUNDEX-adjusted remission rate 43%.

After 12 months and 24 months of a first TNFi, the crude remission rates increased slightly, whereas the LUNDEX-adjusted PRO remission rates had decreased (Table 2; Supplementary Figure S3, available with the online version of this article).

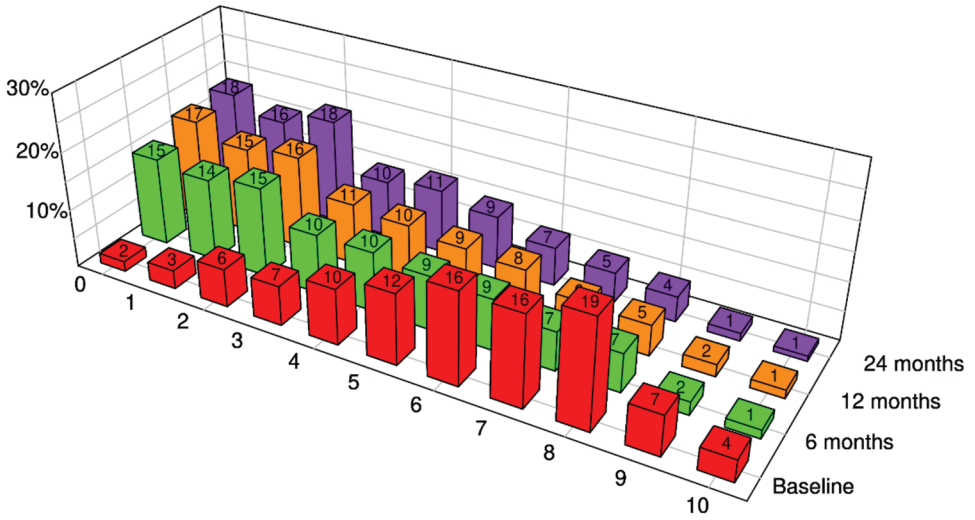
Crude and LUNDEX-adjusted remission rates were lower for the second and third TNFi (Supplementary Figure S3, available with the online version of this article), as were the estimates based on metaanalysis (data not shown).

PROs across registries. Across the 13 registries, PRO registration varied considerably. Twelve registries had registrations of ≥ 2 PROs and 6 registries had registrations of all 4 PROs of interest. Also, variations in patient characteristics, baseline disease activity, and PROs were observed. The median age at initiation of TNFi treatment ranged from 41 to 52 years, age at PsA diagnosis ranged from 36 to 49 years, and median pain scores ranged from 5 (NOR-DMARD) to 8 (TURKBIO; Supplementary Table S1 and Supplementary Table S2, available with the online version of this article). Figure 3 shows PROs per registry for the first TNFi treatment at baseline and at 6, 12, and 24 months. For all 13 registries, an improvement in PROs was seen after the initiation of a first TNFi treatment when compared to baseline; however, the magnitude of the improvements differed between registries. Similarly, PRO remission rates differed, exemplified by LUNDEX-adjusted pain remission rates at 6 months, ranging from 13% (GISEA) to 31% (TURKBIO).

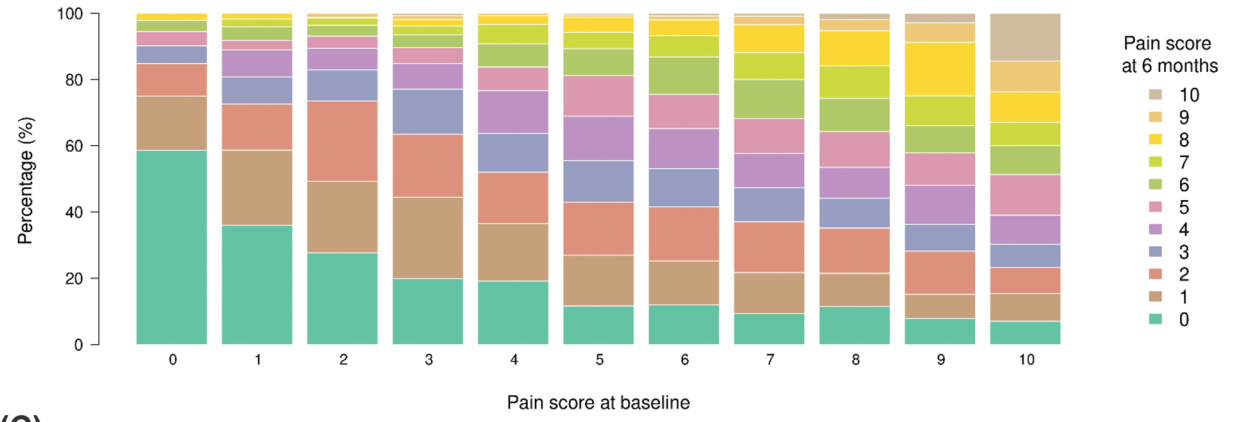
PRO remission rates across disease duration, sex, and age at disease onset. To explore differences in PRO remission rates, the overall cohort was stratified according to (1) disease duration (≤ 5 yrs, 6-10 yrs, and > 10 yrs), (2) sex (men, women), and (3) age at disease onset (< 45 yrs, ≥ 45 yrs).

Patients with medium and long disease duration (6-10 yrs and > 10 yrs) at initiation of first TNFi had numerically higher LUNDEX-adjusted pain remission rates than patients with short disease duration (28% and 27%, respectively, vs 22% at 6 months); this pattern was also seen for fatigue and PtGA,

(A)



(B)



(C)

Pain scores at baseline	Pain scores at 6 months after start of 1st TNFi treatment										
	0	1	2	3	4	5	6	7	8	9	10
0	59%	16%	10%	5%	0%	4%	3%	0%	2%	0%	0%
1	36%	23%	14%	8%	8%	3%	4%	2%	2%	0%	0%
2	28%	22%	24%	9%	7%	4%	3%	2%	0%	1%	0%
3	20%	25%	19%	14%	8%	5%	4%	3%	2%	1%	1%
4	19%	17%	16%	12%	13%	7%	7%	6%	3%	1%	0%
5	12%	15%	16%	13%	13%	12%	8%	5%	5%	1%	1%
6	12%	13%	16%	12%	12%	10%	11%	6%	5%	1%	1%
7	9%	12%	15%	10%	10%	11%	12%	8%	8%	3%	1%
8	11%	10%	14%	9%	9%	11%	10%	10%	11%	3%	2%
9	8%	7%	13%	8%	12%	10%	8%	9%	16%	6%	3%
10	7%	8%	8%	7%	9%	12%	9%	7%	9%	9%	14%

Figure 2. Pain scores during first TNFi treatment. (A) Three-dimensional bar chart of the relative frequency (y-axis) of pain (mm given on x-axis) among all patients with PsA at baseline, 6, 12, and 24 months after initiation of first TNFi treatment (z-axis). (B) Stacked bar chart showing the distribution of patients with PsA pain scores at 6 months dependent on how the same patients scored at initiation of TNFi treatment (baseline). (C) Percentages as illustrated in stacked bar chart. PsA: psoriatic arthritis; TNFi: tumor necrosis factor inhibitor.

Table 2. LUNDEX-adjusted PRO remission rates at 6, 12, and 24 months after first TNFi treatment start across time since diagnosis, sex, and age at diagnosis.

	No. of Patients	Months Treated		
		6	12	24
		No. of Patients in Remission (LUNDEX-adjusted rate, %)		
Pain remission (≤ 1)				
All	12,262	2297 (24)	1839 (22)	978 (18)
Sex				
Men	5863	1436 (33)	1164 (30)	621 (25)
Women	6399	861 (17)	675 (16)	357 (12)
Years since diagnosis				
≤ 5	6072	1022 (22)	813 (20)	534 (18)
6-10	1656	323 (28)	292 (27)	188 (21)
> 10	1770	355 (27)	285 (24)	170 (19)
Age at diagnosis, yrs				
< 45	5224	1130 (29)	927 (27)	588 (22)
≥ 45	4274	570 (18)	463 (16)	304 (14)
Fatigue remission (≤ 2)				
All	12,262	1736 (31)	13264 (27)	557 (23)
Sex				
Men	5863	1030 (40)	803 (36)	355 (32)
Women	6399	706 (23)	461 (19)	202 (15)
Years since diagnosis				
≤ 5	6072	838 (28)	576 (25)	302 (22)
6-10	1656	221 (33)	187 (31)	97 (26)
> 10	1770	235 (32)	163 (27)	97 (25)
Age at diagnosis, yrs				
< 45	5224	803 (34)	578 (30)	309 (26)
≥ 45	4274	491 (25)	348 (22)	175 (20)
PtGA remission (≤ 2)				
All	12,262	3507 (36)	2842 (32)	1636 (28)
Sex				
Men	5863	2041 (45)	1732 (41)	986 (36)
Women	6399	1466 (27)	1119 (24)	651 (20)
Years since diagnosis				
≤ 5	6072	1587 (33)	1310 (30)	867 (26)
6-10	1656	507 (40)	461 (37)	331 (33)
> 10	1770	559 (41)	458 (36)	309 (32)
Age at diagnosis, yrs				
< 45	5224	1694 (41)	1429 (38)	953 (32)
≥ 45	4274	959 (28)	800 (25)	554 (23)
HAQ-DI remission (≤ 0.5)				
All	12,262	3895 (43)	3029 (38)	1627 (31)
Sex				
Men	5863	2330 (56)	1896 (51)	1013 (42)
Women	6399	1565 (32)	1133 (27)	614 (21)
Years since diagnosis				
≤ 5	6072	1863 (42)	1446 (37)	891 (30)
6-10	1656	520 (45)	443 (41)	312 (35)
> 10	1770	541 (43)	429 (38)	252 (30)
Age at diagnosis, yrs				
< 45	5224	1890 (50)	1507 (45)	959 (37)
≥ 45	4274	1034 (34)	811 (29)	496 (23)

HAQ-DI: Health Assessment Questionnaire–Disability Index; LUNDEX: Lund Efficacy Index; PRO: patient-reported outcome; PtGA: patient global assessment of disease activity; TNFi: tumor necrosis factor inhibitor.

whereas HAQ-DI remission rates seemed similar across disease duration (45% and 43%, respectively, vs 42% at 6 months). Similar findings were present for the second and third TNFi (Figure 4, Table 2; Supplementary Tables S3–5, available with the online version of this article).

Men had numerically higher LUNDEX-adjusted PRO remission rates than women for all PROs after 6, 12, and 24 months of a first TNFi (Figure 4, Table 2). A similar pattern was seen for second and third TNFi courses (Supplementary Tables S3-5, available with the online version of this article).

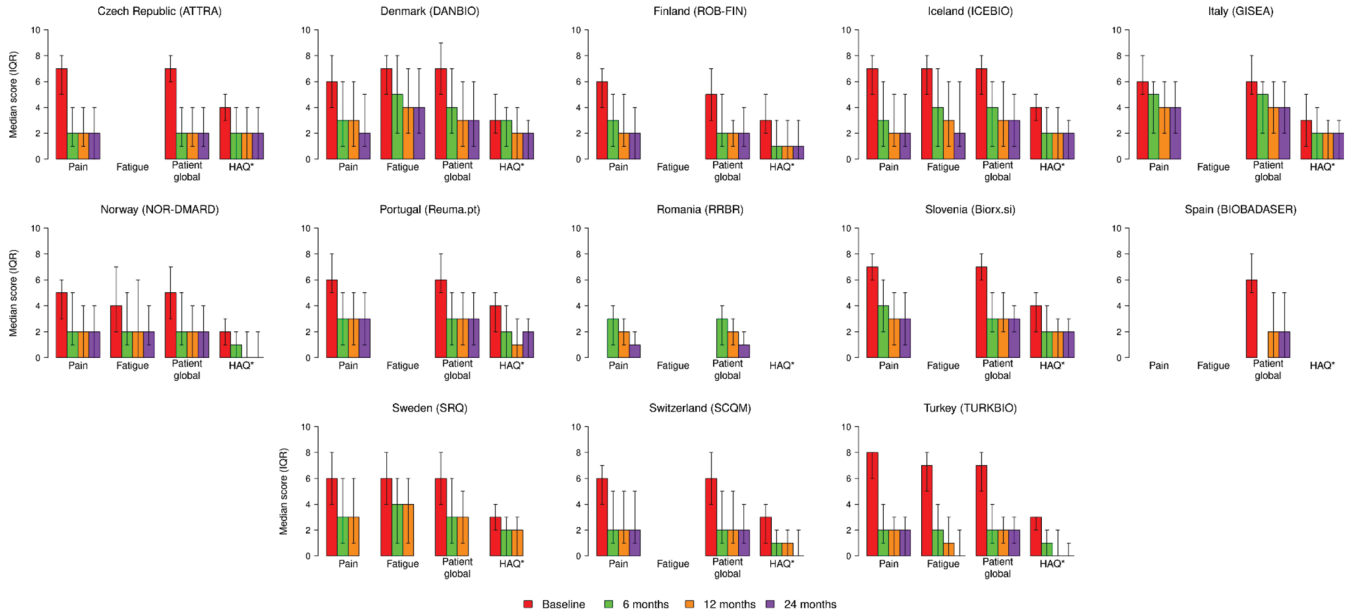


Figure 3. Pain, fatigue, patient global, and HAQ by registry for patients with PsA at baseline and 6, 12, and 24 months after initiation of first TNFi treatment. For BIOBADASER, pain and HAQ were not collected. For ROB-FIN, GISEA, Reuma.pt, RRBR, BioRx.si, and BIOBADASER, fatigue was not collected; the remaining missing median PROs were not calculated due to available PRO data for < 50 patients. Three registries (RRBR, BioRx.si, and SCQM) used a 0-10 numeric rating scale for pain, fatigue, patient global assessment, and physician global assessment, whereas the remaining registries used a 0-100 scale. Scores on a 0-100 scale were converted to 0-10 by dividing by 10 and rounding to nearest integer. * HAQ was scored on a scale ranging from 0-3. HAQ scores were multiplied by 3.3 to fit the 0-100 scale in this figure. BIOBADASER: Spanish Registry for Adverse Events of Biological Therapy in Rheumatic Diseases; BioRx.si: Slovenian Biologics Register; GISEA: Italian Group for the Study of Early Arthritis; HAQ: Health Assessment Questionnaire–Disability Index; ICEBIO: Icelandic Nationwide Database of Biologic Therapy; NOR-DMARD: Nowegian Disease-modifying Antirheumatic Drugs Register; patient global: patient global assessment of disease activity; PRO: patient-reported outcome; PsA: psoriatic arthritis; Reuma.pt: Rheumatic Diseases Portuguese Register; ROB-FIN: National Register of Biological Treatment in Finland; RRBR: Romanian Registry of Rheumatic Diseases; SCQM: Swiss Clinical Quality Management in Rheumatic Diseases; SRQ: Swedish Rheumatology Quality Register; TNFi: tumor necrosis factor inhibitor.

In patients with early onset of disease (< 45 yrs at diagnosis), the LUNDEX-adjusted pain remission rate was higher than in patients with later onset of disease (29% vs 18% at 6 months after initiation of first TNFi); this pattern was seen for all 4 PRO measures in first, second, and third TNFi courses (Figure 4, Table 2; Supplementary Tables S3–5, available with the online version of this article).

Drug retention rates. Retention rates for the overall cohort decreased with increasing number of TNFi treatment courses, whereas retention rates in the stratified cohort displayed the same trend as observed for PRO remission rates, with lower retention in women, patients with short disease duration, and patients with later onset of disease (Supplementary Table S6, available with the online version of this article).

DISCUSSION

Based on prospectively collected PROs from > 12,000 patients with PsA treated across Europe, the present study reports, for the first time to our knowledge, the effect of TNFi on PROs and PRO remission rates in a large real-world cohort. At baseline, PRO values were high, demonstrating a large disease burden. We observed that 6 months of treatment with a first TNFi reduced the pain score by approximately 50% and led to the remission of pain (defined as pain score ≤ 1 on a 0-10 scale) in approximately 25% of patients. Similar treatment responses and remission rates were seen for fatigue, PtGA, and HAQ-DI scores. Interestingly, we observed marked differences in all PROs and PRO remission rates across treatment courses, registries, disease duration, sex, and age at onset of disease, suggesting that PRO values are influenced by multiple factors.

Although pain and fatigue are recognized as the most disabling symptoms by patients with PsA,[36] surprisingly few studies have addressed the effect of treatment on the individual PROs outside of randomized controlled trials (RCTs). In RCTs, benefit of TNFi treatment on PROs in PsA has been shown,[10-13,37] but concern has been raised about the extrapolation of results from RCTs to real-world patients because of the strict inclusion and exclusion criteria applied in RCTs.[38,39] Here we provide evidence from a large multinational cohort of patients treated in routine care registries that improvement in PROs can be expected during TNFi treatment, which is in accordance with the few smaller studies on real-world data.[7-9]

We found that the effects of a second and third TNFi drug on PRO scores were smaller than those observed for the first TNFi treatment. This finding was expected, since patients who switch to a second or third TNFi belong to a selected group of patients with poor initial response or secondary loss of response to a first TNFi and likely have a worse response to TNFi treatment

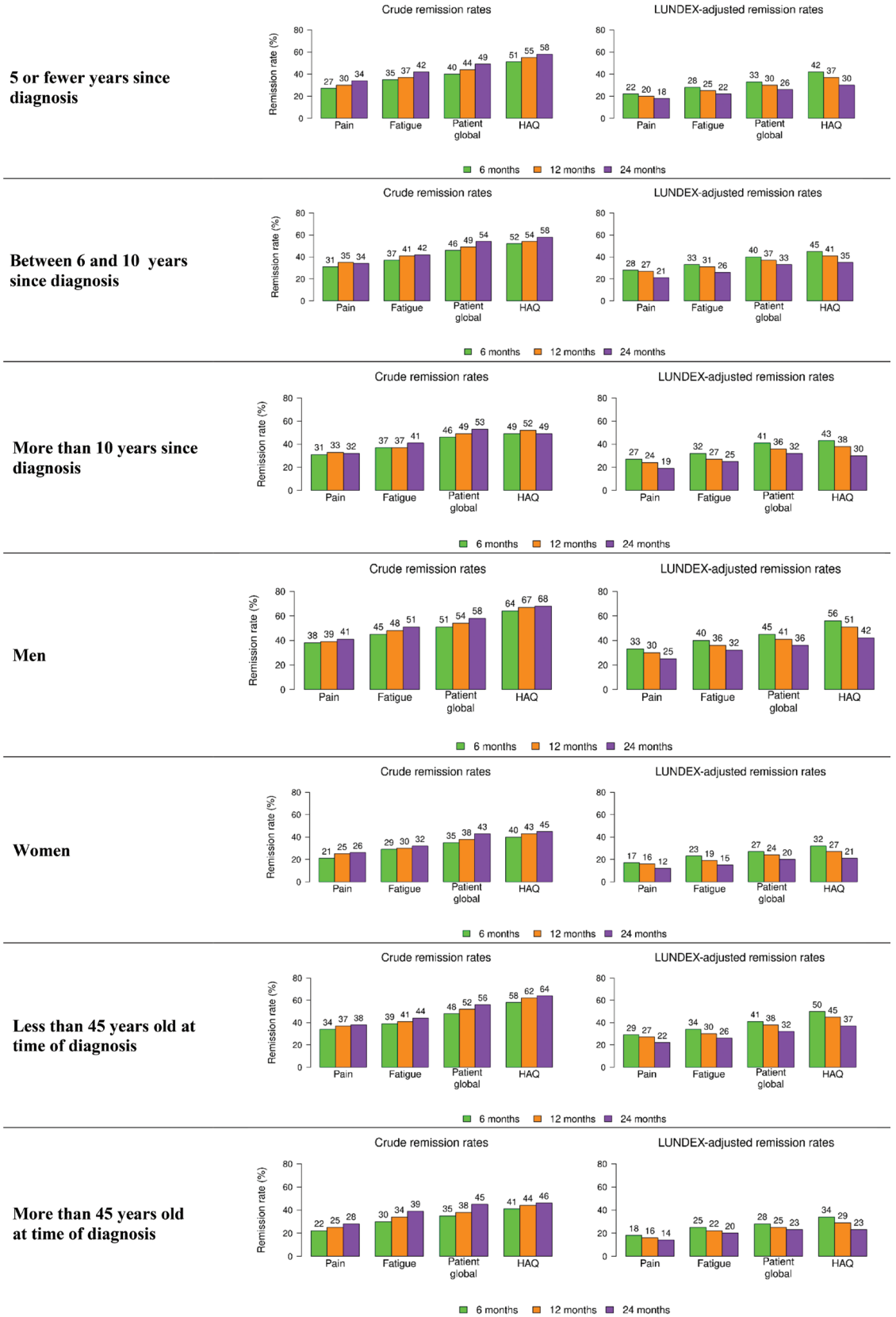


Figure 4. PRO remission rates (%) at 6, 12, and 24 months after first TNFi treatment initiation across sex, time since diagnosis, and age at diagnosis. Left panel: crude remission rates; right panel: LUNDEX-adjusted remission rates. Definitions of remission: pain score ≤ 1, fatigue score ≤ 2, patient global score ≤ 2, HAQ score ≤ 0.5. HAQ: Health Assessment Questionnaire–Disability Index; LUNDEX: Lund Efficacy Index; patient global: patient global assessment of disease activity; PRO: patient-reported outcome; TNFi: tumor necrosis factor inhibitor.

in general.[8,40] Our finding is in accordance with the results of a real-world study from the United Kingdom including 141 patients with PsA treated with TNFi and a follow-up period of ≥ 3 years, which also showed that patients with poor response to the first TNFi experienced less benefit and more adverse events in the following TNFi treatment course.[8]

We observed that patients with a high pain score (≥ 9) at baseline had a lower PRO response to the first TNFi treatment after 6 months (12% reported pain ≥ 9 at 6 months) than in patients with a baseline pain score < 7 (≤ 2% reported pain ≥ 9 at 6 months). A similar observation has been made in axial spondyloarthritis, where patients with extremely high PRO scores had worse response to TNFi than patients with more favorable PRO scores at baseline.[41,42] We hypothesize that these observations are a result of comorbidities such as chronic widespread pain or fibromyalgia, which are known to be frequent in patients with PsA and diminish treatment response.[43,44] It is one of the limitations of our study that no data on comorbidities were available for analyses. An additional limitation is the differences between registries in the number of PROs assessed and follow-up schedules, which caused substantial variation in the number of patients that could be included in the various analyses. Linde et al have previously published details on the organization, inclusion criteria, and data collection across registries participating in the EuroSpA Collaboration.[29] Registry differences add to the inherent limitation of missing outcome data in registry research, which is also evident in our study as pain assessment after 6 months of treatment with the first TNFi was available in 68% of patients, with decreasing data availability as follow-up increased (60% at 12 months and 42% at 24 months). This may lead to a bias toward lower PROs if patients with a good response to TNFi treatment are overrepresented in our study because of a higher motivation to comply with their physician appointments. However, a bias in the opposite direction could also have been introduced as patients with disease flares in need of treatment intensification would be more likely to have a hospital visit scheduled. Differences in treatment outcomes in patients with PsA across countries have been documented in several previous papers from the EuroSpA Collaboration and other groups.[15,45,46] Country-specific guidelines and recommendations for TNFi treatment of patients with PsA may have influenced our results and contributed to the observed differences between registries. Of specific importance to PROs, differences in the exact wording of the questions, including the recall period used, may also have contributed to the observed differences between registries.

To our knowledge, there is no consensus for the definition of PRO remission; ideally the definition of PRO remission should be based on a validated combination of PRO measures describing the most important disease features seen from the patients' perspective.[47] Lacking validated PRO remission cut-offs, we based our definitions on those previously reported for MDA in patients with PsA.[33]

With the applied definitions of PRO remission, the majority of patients with PsA in the present study did not reach PRO remission during treatment with a TNFi, which suggests an unmet need for further treatment options from the patient perspective. Of note, the crude rates reported are based on patients who were receiving treatment at the time of assessment. This implies that despite PRO scores > 2 on scale of 0 to 10, the treating rheumatologist generally found the treatment effect satisfactory, since the TNFi was continued in most cases. Thus, the low PRO remission rates could also point to a need for better strategies to manage pain and disease impact in patients with this complex disease.

Our finding of higher PRO remission rates in men is in accordance with a European study showing that women were less likely to reach the treatment target according to the Disease Activity Index for Psoriatic Arthritis (DAPSA).[48] In contrast, the higher PRO remission rates among patients with medium and long disease duration (> 5 years) at initiation of TNFi treatment, when compared to patients with shorter disease duration, was an unexpected finding, as a previous study reported better treatment outcomes with regard to PROs for patients treated at an early point in their disease.[49] We observed that patients diagnosed prior to 45 years of age were more likely to reach PRO remission after 6 months of a first TNFi treatment when compared to patients > 45 years at diagnosis. This finding adds to studies describing different phenotypes of PsA according to age at onset of disease.[50,51] Currently, very limited data on treatment outcomes in these phenotypes are available and our findings suggest worse treatment outcomes in later-onset PsA.

Overall, striking differences in PRO remission rates across treatment courses, registries, sex, disease duration, and age at onset of disease were seen. This may suggest that disease control (ie, suppression of inflammation) is achieved to a lesser degree in certain groups of patients. However, it may also be interpreted in light of the emerging distinction between disease impact, as experienced by the patient and measured with PROs, and disease activity caused by inflammation and measured by joint counts and inflammatory markers.[52]

In conclusion, this study showed a marked improvement in PROs in > 12,000 patients with PsA during TNFi treatment. Although large improvements at the group level were seen, only one-quarter of patients reached pain remission, pointing to an unmet need for improvements in treatment and pain management from the patient perspective. In addition, female sex, shorter disease duration, and older age at diagnosis were associated with lower PRO remission rates.

DATA AVAILABILITY

The data in this article were collected in the individual registries and made available for secondary use through the EuroSpA Research Collaboration Network (https://eurospa.eu/#registries).

ACKNOWLEDGMENT

On behalf of the EuroSpA Scientific Committee, the authors acknowledge Novartis Pharma AG and IQVIA for supporting the EuroSpA Research Collaboration Network.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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