

Concise report

Impact of discordance between patient's and evaluator's global assessment on treatment outcomes in 14 868 patients with spondyloarthritis

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Abstract

Objectives. To assess the impact of 'patient's minus evaluator's global assessment of disease activity' (Δ PEG) at treatment initiation on retention and remission rates of TNF inhibitors (TNFi) in psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) patients across Europe.

Methods. Real-life data from PsA and axSpA patients starting their first TNFi from 11 countries in the European Spondyloarthritis Research Collaboration Network were pooled. Retention rates were compared by Kaplan–Meier analyses with log-rank test and by Cox regression, and remission rates by χ^2 test and by logistic regression across quartiles of baseline Δ PEG, separately in female and male PsA and axSpA patients.

Results. We included 14 868 spondyloarthritis (5855 PsA, 9013 axSpA) patients. Baseline Δ PEG was negatively associated with 6/12/24-months' TNFi retention rates in female and male PsA and axSpA patients ($P < 0.001$), with 6/12/24-months' BASDAI < 2 ($P \leq 0.002$) and ASDAS < 1.3 ($P \leq 0.005$) in axSpA patients, and with DAS28CRP(4) < 2.6 ($P \leq 0.04$) and DAPSA28 ≤ 4 ($P \leq 0.01$), but not DAS28CRP(3) < 2.6 ($P \geq 0.13$) in PsA patients, with few exceptions on remission rates. Retention and remission rates were overall lower in female than male patients.

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Conclusion. High baseline patient's compared with evaluator's global assessment was associated with lower 6/12/24-months' remission as well as retention rates of first TNFi in both PsA and axSpA patients. These results highlight the importance of discordance between patient's and evaluator's perspective on disease outcomes.

Key words: axial spondyloarthritis, psoriatic arthritis, TNF inhibitors, treatment outcomes

Rheumatology key messages

- Discordance between patient's and evaluator's global assessment negatively impacts retention and remission of TNFi in SpA.
- Remission criteria that objectively reflect disease activity should be included in patients with high discordance.
- TNFi retention and remission rates are overall lower for female than male patients with SpA.

Introduction

Discordance between patient's global assessment and physician's/evaluator's global assessment of disease activity at baseline is common [1, 2] and may reduce the likelihood of remission following tumour necrosis factor inhibitor (TNFi) treatment in patients with psoriatic arthritis (PsA) [2]. However, to our knowledge, the impact of such discordance on retention rates of TNFi treatment in PsA patients and on TNFi retention and remission rates in axial spondyloarthritis (axSpA) patients remains unexplored. Furthermore, it remains unknown whether the impact of such discordance on retention and remission rates may be influenced by gender in patients with spondyloarthritis.

In this study we aimed to assess the impact of baseline 'patient's minus evaluator's global assessment of disease activity' (Δ PEG), on retention and remission rates of first-time TNFi separately in female and male patients with PsA and axSpA across Europe.

Patients and methods

Patients

Anonymized data from PsA and axSpA patients who started their first TNFi between 2000 and 2017 were pooled from 11 registries participating in the European Spondyloarthritis Research Collaboration Network (EuroSpA) [3]: DANBIO (Denmark), NOR-DMARD (Norway), ATTRA (Czech Republic), SCQM (Switzerland), ROB-FIN (Finland), Reuma.pt (Portugal), TURKBIO (Turkey), ARTIS (Sweden), biorx.si (Slovenia), ICEBIO (Iceland) and RRBR (Romania). The study was approved by the respective national Data Protection Agencies and Research Ethical Committees according to legal regulatory requirements in the participating countries and was performed in accordance with the Declaration of Helsinki.

Assessments

Assessments included demographics, time since diagnosis, start and stop dates of first TNFi, visual analogue scales (0–100) of patient's and evaluator's global assessments (except for SCQM, biorx.si and RRBR

using a 0–10 Numeric Rating Scale) and CRP. Furthermore, in PsA patients, assessments at baseline (pre-treatment), 6, 12 and 24 months included 28 tender and swollen joint counts, 28-joint Disease Activity Score *with* CRP and patient's global assessment (DAS28CRP(4)) [4], DAS28CRP *without* patients' global assessment (DAS28CRP(3)) [4] as well as 28-joint Disease Activity Index for Psoriatic Arthritis (DAPSA28) [5], and in axSpA patients BASDAI [6] and Ankylosing Spondylitis Disease Activity Score (ASDAS) [7].

Statistics

All analyses were conducted separately for female and male PsA and axSpA patients. Retention rates after 6-, 12- and 24-months' treatment with first TNFi were assessed by Kaplan–Meier analyses, with comparison between baseline Δ PEG quartiles by log-rank test. The impact of baseline Δ PEG quartiles on 6-, 12- and 24-months' retention rates was also explored with Cox regression analyses, adjusted for age, time since diagnosis and current smoking (yes/no). Proportions of axSpA patients achieving BASDAI remission (defined in two ways, either as <2 , or as <2 with CRP <7 mg/l [8]) and ASDAS inactive disease (<1.3) [9], as well as proportions of PsA patients in DAS28CRP(4) remission (<2.6) [10], DAS28CRP(3) remission (<2.6) [4] and DAPSA28 remission (≤ 4) [5] after 6-, 12- and 24-months' treatment were compared across Δ PEG quartiles by χ^2 test. The impact of baseline Δ PEG quartiles on 6-, 12- and 24-months' remission rates was also explored in logistic regression models adjusted for age, time since diagnosis and current smoking (yes/no). Statistical analyses were performed with R version 3.4.3 and SPSS version 25. All analyses were available case analyses. No data imputation was performed.

Results

A total of 14 868 spondyloarthritis patients were included, thereof 5855 PsA and 9013 axSpA patients. For PsA patients, mean (s.d.) age of women ($n=2988$) and men ($n=2867$) were 49.3 (12.5) and 47.4 (11.7)

years, respectively, time since diagnosis was 6.6 (7.3) and 6.7 (7.2) years and median (25–75 percentiles) baseline Δ PEG 17 (0–38) and 10 (0–30), respectively, and for axSpA patients mean (s.d.) age of women ($n = 3639$) and men ($n = 5374$) was 42.7 (12.0) and 41.7 (12.0) years, respectively, and time since diagnosis was 5.1 (7.4) and 6.9 (8.7) years and median (25–75 percentiles) baseline Δ PEG 20 (3–42) and 15 (0–37).

Impact of baseline Δ PEG on TNFi retention

TNFi retention rates at 6-, 12- and 24-months' follow-up were significantly lower for higher quartiles of Δ PEG both in female and male PsA and axSpA patients (Table 1, Fig. 1).

Adjustment of the analyses for age, time since diagnosis and smoking consistently showed lower TNFi retention rates for higher quartiles of Δ PEG ($P \leq 0.01$). Findings for third and fourth Δ PEG quartiles in axSpA patients were similar (Supplementary Fig. S1, available at *Rheumatology* online).

Impact of baseline Δ PEG on achievement of remission

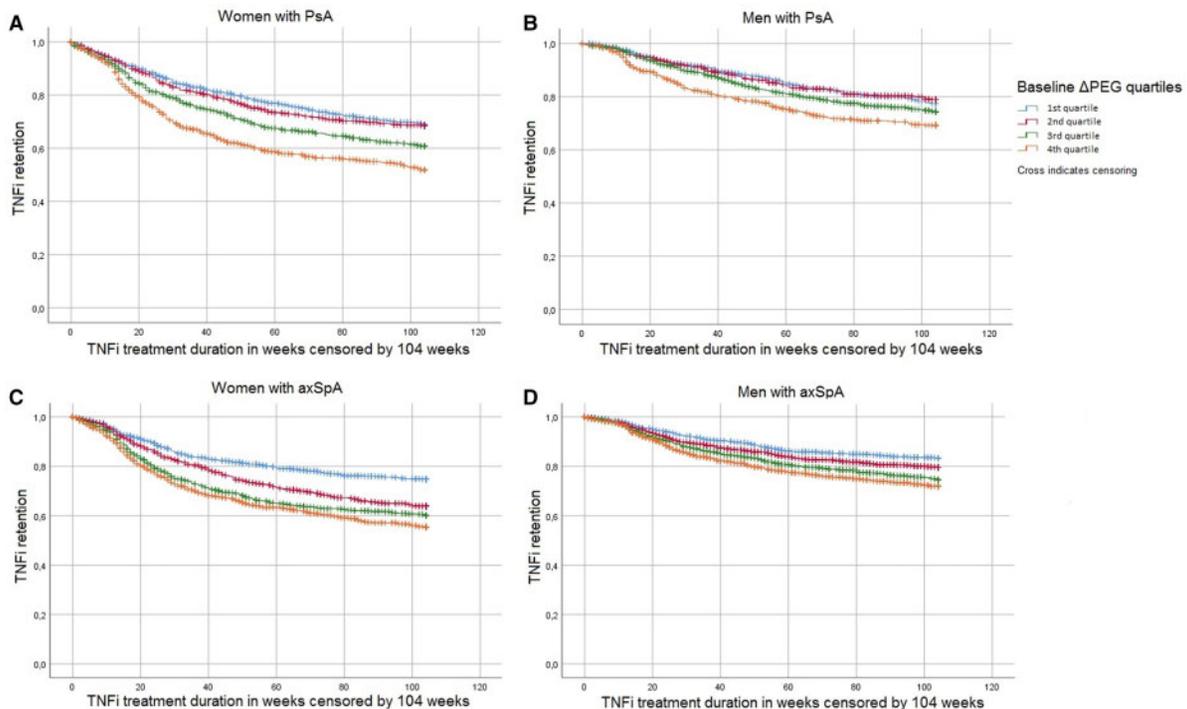
Proportions of PsA patients achieving DAPSA28 and DAS28(4)CRP—but not DAS28(3)CRP remission—and axSpA patients achieving BASDAI remission and ASDAS inactive disease were significantly lower for higher quartiles of baseline Δ PEG both in women and men after 6-, 12- and 24-months' follow-up, except for 12-months'

DAS28(4)CRP remission in men and 24-months' DAS28(3)CRP remission in women (Table 1). Adjustment for age, time since diagnosis and smoking in a logistic regression model did not change the significance of the above-mentioned patterns, with the following exceptions: 6- and 12-months' ASDAS inactive disease in female and 6-months' ASDAS inactive disease in male axSpA patients showed consistently lower point estimates for higher Δ PEG quartiles, but did not reach statistical significance (Supplementary Tables S1a and S1b, available at *Rheumatology* online).

Discussion

This longitudinal observational study including data from 11 European registries highlights the negative consequences of high baseline discordance between patient's and evaluator's global assessment (i.e. high baseline patient's compared with evaluator's global assessment, Δ PEG) for TNFi treatment outcomes in patients with PsA and axSpA. The higher the baseline Δ PEG, the lower were 6-, 12- and 24-months' TNFi drug retention as well as remission rates in both male and female PsA and axSpA patients, with few exceptions regarding remission rates. The study also highlights the importance of choice of remission criteria; baseline Δ PEG was negatively associated with achievement of 6-, 12- and 24-months' DAS28CRP(4) remission, which includes patient's global, but not with DAS28CRP(3) remission, which excludes patient's global. This is to our knowledge the first study

Fig. 1 TNFi retention rates across Δ PEG quartiles, censored by 104 weeks



(A) Women with PsA; (B) men with PsA; (C) women with axSpA; (D) men with axSpA.

TABLE 1 Retention and remission rates of first TNFi in psoriatic arthritis and axial spondyloarthritis patients

		Psoriatic arthritis patients (n = 5855)									
		Women (n = 2988)					Men (n = 2867)				
TNFi retention rates	P-value	Retention rates (%; 95% CI) of first TNFi compared across baseline ΔPEEG quartiles									
		1st ΔPEEG quartile (-100 to 0)	2nd ΔPEEG quartile (1 to 17)	3rd ΔPEEG quartile (18 to 38)	4th ΔPEEG quartile (39 to 100)	1st ΔPEEG quartile (-100 to -1)	2nd ΔPEEG quartile (0 to 9)	3rd ΔPEEG quartile (10 to 30)	4th ΔPEEG quartile (31 to 100)	P-value	
6 months	<0.001	87% (85, 90%) n=815	85% (82, 88%) n=694	81% (78, 84%) n=739	74% (71, 77%) n=740	93% (91, 95%) n=648	93% (91, 95%) n=683	92% (90, 93%) n=865	86% (83, 89%) n=671	<0.001	
12 months	<0.001	79% (76, 82%) n=815	76% (73, 79%) n=694	70% (67, 74%) n=739	61% (57, 65%) n=740	88% (85, 90%) n=648	86% (84, 89%) n=683	83% (80, 85%) n=865	78% (75, 81%) n=671	<0.001	
24 months	<0.001	69% (66, 72%) n=815	69% (65, 72%) n=694	61% (57, 65%) n=739	52% (48, 56%) n=740	77% (74, 81%) n=648	79% (76, 82%) n=683	74% (71, 78%) n=865	69% (66, 73%) n=671	<0.001	
DAPSA28 remission (≤4)											
Proportions, % (95%CI), of patients achieving DAPSA28 remission compared across baseline ΔPEEG quartiles											
	P-value	1st ΔPEEG quartile (-100 to 0)	2nd ΔPEEG quartile (1 to 17)	3rd ΔPEEG quartile (18 to 38)	4th ΔPEEG quartile (39 to 100)	1st ΔPEEG quartile (-100 to -1)	2nd ΔPEEG quartile (0 to 9)	3rd ΔPEEG quartile (10 to 30)	4th ΔPEEG quartile (31 to 100)	P-value	
6 months	<0.001	21% (17, 25%) n=420	24% (19, 28%) n=413	12% (9, 15%) n=432	12% (9, 15%) n=457	42% (37, 47%) n=339	38% (33, 42%) n=399	30% (26, 34%) n=465	27% (23, 32%) n=412	<0.001	
12 months	0.002	23% (18, 27%) n=391	27% (22, 32%) n=352	16% (13, 20%) n=393	14% (11, 17%) n=400	41% (36, 46%) n=333	40% (35, 45%) n=359	34% (29, 38%) n=455	29% (25, 34%) n=383	0.002	
24 months	<0.001	27% (23, 32%) n=325	27% (22, 32%) n=290	19% (15, 23%) n=328	13% (9, 17%) n=329	46% (40, 51%) n=295	42% (36, 48%) n=300	33% (28, 37%) n=382	28% (23, 33%) n=309	<0.001	
DAS28(4)CRP remission (<2.6)											
Proportions, % (95%CI), of patients achieving DAS28(4)CRP remission compared across baseline ΔPEEG quartiles											
	P-value	1st ΔPEEG quartile (-100 to 0)	2nd ΔPEEG quartile (1 to 17)	3rd ΔPEEG quartile (18 to 38)	4th ΔPEEG quartile (39 to 100)	1st ΔPEEG quartile (-100 to -1)	2nd ΔPEEG quartile (0 to 9)	3rd ΔPEEG quartile (10 to 30)	4th ΔPEEG quartile (31 to 100)	P-value	
6 months	0.04	51% (47, 56%) n=492	48% (44, 53%) n=464	39% (34, 43%) n=460	36% (32, 41%) n=465	63% (58, 68%) n=378	67% (63, 71%) n=458	59% (55, 63%) n=506	59% (54, 63%) n=419	0.04	
12 months	0.21	53% (48, 57%) n=449	53% (48, 58%) n=397	43% (38, 47%) n=419	38% (33, 43%) n=409	68% (63, 71%) n=370	69% (63, 71%) n=404	63% (55, 63%) n=492	65% (54, 63%) n=389	0.21	
24 months	0.007	58% (53, 63%) n=358	58% (52, 63%) n=323	47% (42, 53%) n=349	37% (32, 43%) n=337	69% (64, 74%) n=324	72% (67, 77%) n=330	64% (59, 69%) n=408	60% (55, 66%) n=316	0.007	
DAS28(3)CRP remission (<2.6)											
Proportions, % (95%CI), of patients achieving DAS28(3)CRP remission compared across baseline ΔPEEG quartiles											
	P-value	1st ΔPEEG quartile (-100 to 0)	2nd ΔPEEG quartile (1 to 17)	3rd ΔPEEG quartile (18 to 38)	4th ΔPEEG quartile (39 to 100)	1st ΔPEEG quartile (-100 to -1)	2nd ΔPEEG quartile (0 to 9)	3rd ΔPEEG quartile (10 to 30)	4th ΔPEEG quartile (31 to 100)	P-value	
6 months	0.28	52% (48, 57%) n=507	53% (48, 57%) n=469	47% (43, 52%) n=469	48% (43, 52%) n=472	65% (60, 70%) n=386	69% (64, 73%) n=467	64% (60, 68%) n=517	68% (64, 73%) n=426	0.28	
12 months	0.77	54% (50, 59%) n=471	57% (52, 61%) n=409	53% (48, 57%) n=435	50% (45, 55%) n=420	70% (66, 75%) n=381	72% (67, 76%) n=411	69% (65, 73%) n=503	72% (68, 76%) n=396	0.77	
24 months	0.32	61% (56, 66%) n=374	60% (55, 65%) n=336	55% (50, 60%) n=367	52% (46, 57%) n=347	74% (69, 79%) n=331	76% (71, 80%) n=341	70% (66, 74%) n=425	73% (69, 78%) n=323	0.32	

(continued)

TABLE 1 Continued

		Axial spondyloarthritis patients (n=9013)									
		Women (n = 3639)					Men (n = 5374)				
TNFi retention rates	Retention rates of first TNFi (%; 95%CI) compared across baseline ΔPEQ quartiles	Proportions, % (95%CI), of patients achieving ASDAS<1.3 compared across baseline ΔPEQ quartiles									
		1st ΔPEQ quartile (-100 to 2)	2nd ΔPEQ quartile (3 to 20)	3rd ΔPEQ quartile (21 to 42)	4th ΔPEQ quartile (43 to 100)	1st ΔPEQ quartile (-100 to -1)	2nd ΔPEQ quartile (0 to 15)	3rd ΔPEQ quartile (16 to 37)	4th ΔPEQ quartile (38 to 100)	P-value	P-value
6 months	88% (86, 90%) n=908	84% (82, 87%) n=915	78% (75, 81%) n=907	76% (73, 79%) n=909	94% (92, 95%) n=1220	91% (89, 92%) n=1487	89% (88, 91%) n=1338	87% (85, 89%) n=1329	<0.001	<0.001	
12 months	81% (78, 84%) n=908	74% (71, 77%) n=915	67% (64, 70%) n=907	64% (61, 68%) n=909	88% (86, 90%) n=1220	86% (84, 88%) n=1487	83% (81, 85%) n=1338	79% (77, 82%) n=1329	<0.001	<0.001	
24 months	75% (72, 78%) n=908	64% (61, 67%) n=915	60% (57, 64%) n=907	55% (52, 59%) n=909	83% (81, 86%) n=1220	80% (77, 82%) n=1487	75% (72, 77%) n=1338	72% (69, 75%) n=1329	<0.001	<0.001	
ASDAS<1.3		Proportions, % (95%CI), of patients achieving ASDAS<1.3 compared across baseline ΔPEQ quartiles									
		1st ΔPEQ quartile (-100 to 2)	2nd ΔPEQ quartile (3 to 20)	3rd ΔPEQ quartile (21 to 42)	4th ΔPEQ quartile (43 to 100)	1st ΔPEQ quartile (-100 to -1)	2nd ΔPEQ quartile (0 to 15)	3rd ΔPEQ quartile (16 to 37)	4th ΔPEQ quartile (38 to 100)	P-value	P-value
6 months	28% (23, 33%) n=313	24% (19, 28%) n=293	23% (18, 27%) n=289	17% (14, 21%) n=449	40% (36, 45%) n=507	41% (36, 45%) n=527	34% (30, 38%) n=446	31% (27, 35%) n=625	0.005	0.001	
12 months	27% (22, 33%) n=266	23% (18, 29%) n=221	23% (18, 29%) n=233	15% (12, 19%) n=370	41% (37, 46%) n=427	41% (37, 46%) n=458	33% (28, 37%) n=403	31% (27, 35%) n=508	0.002	0.001	
24 months	29% (23, 35%) n=225	24% (18, 30%) n=197	27% (21, 33%) n=205	16% (11, 20%) n=284	45% (40, 50%) n=369	41% (36, 45%) n=406	39% (33, 44%) n=335	31% (27, 35%) n=444	0.002	0.001	
BASDAI<2		Proportions, % (95%CI), of patients achieving BASDAI<2 compared across baseline ΔPEQ quartiles									
		1st ΔPEQ quartile (-100 to 2)	2nd ΔPEQ quartile (3 to 20)	3rd ΔPEQ quartile (21 to 42)	4th ΔPEQ quartile (43 to 100)	1st ΔPEQ quartile (-100 to -1)	2nd ΔPEQ quartile (0 to 15)	3rd ΔPEQ quartile (16 to 37)	4th ΔPEQ quartile (38 to 100)	P-value	P-value
6 months	44% (39, 49%) n=517	31% (28, 35%) n=525	27% (23, 31%) n=535	26% (22, 29%) n=625	57% (54, 61%) n=796	50% (47, 53%) n=955	44% (41, 47%) n=866	40% (37, 43%) n=921	<0.001	<0.001	
12 months	45% (41, 50%) n=487	32% (27, 36%) n=479	29% (24, 33%) n=471	24% (21, 28%) n=522	59% (55, 62%) n=734	51% (48, 55%) n=892	44% (40, 47%) n=812	41% (38, 44%) n=833	<0.001	<0.001	
24 months	48% (43, 53%) n=385	33% (28, 38%) n=395	30% (25, 34%) n=386	21% (17, 25%) n=406	60% (56, 63%) n=621	54% (50, 57%) n=759	44% (40, 47%) n=665	40% (37, 44%) n=686	<0.001	<0.001	
BASDAI<2 and CRP<7mg/l		Proportions, % (95%CI), of patients achieving BASDAI<2 and CRP<7mg/l compared across baseline ΔPEQ quartiles									
		1st ΔPEQ quartile (-100 to 2)	2nd ΔPEQ quartile (3 to 20)	3rd ΔPEQ quartile (21 to 42)	4th ΔPEQ quartile (43 to 100)	1st ΔPEQ quartile (-100 to -1)	2nd ΔPEQ quartile (0 to 15)	3rd ΔPEQ quartile (16 to 37)	4th ΔPEQ quartile (38 to 100)	P-value	P-value
6 months	33% (29, 37%) n=527	23% (20, 27%) n=541	21% (18, 24%) n=557	20% (17, 23%) n=641	43% (40, 47%) n=822	40% (37, 44%) n=973	33% (30, 36%) n=885	32% (29, 35%) n=927	<0.001	<0.001	
12 months	31% (26, 35%) n=486	21% (18, 25%) n=500	21% (17, 24%) n=488	17% (14, 20%) n=529	45% (42, 49%) n=752	39% (36, 43%) n=905	35% (32, 38%) n=824	31% (28, 34%) n=828	<0.001	<0.001	
24 months	32% (28, 37%) n=404	23% (19, 27%) n=408	24% (19, 28%) n=394	16% (13, 20%) n=415	46% (42, 50%) n=626	41% (38, 44%) n=772	33% (29, 36%) n=672	31% (28, 35%) n=681	<0.001	<0.001	

P-values retention rates: Kaplan-Meier analyses with log-rank test; P-values remission rates: χ^2 test. n: numbers available; ASDAS: Ankylosing Spondylitis Disease Activity Score; DAS28(3)CRP: 28-joint disease activity score with CRP and three variables (excluding patient's global); DAS28(4)CRP: 28-joint disease activity score with CRP and four variables (including patient's global); ΔPEQ: patient's minus evaluator's global assessment; TNFi: TNF inhibitor.

to identify Δ PEG as an independent predictor of TNFi retention in PsA and axSpA patients. Adjustment for age, time since diagnosis and smoking did not change these findings.

We found higher Δ PEG in female than male PsA and axSpA patients, which is in accordance with previous findings in PsA [1, 2]. Retention and remission rates were overall lower for female than male patients. In RA patients, high Δ PEG has been found associated with depression, fibromyalgia and polysymptomatic distress, but not with elevated joint inflammation, as evaluated by ultrasonography [11]. In a recent cross-sectional study on PsA patients Δ PEG was found to be independently associated with higher fatigue, lower self-perceived coping and impaired social participation [12]. Importantly, patients with elevated Δ PEG who do not achieve remission or who have had short treatment adherence to several TNFi may benefit from being identified and offered additional treatment approaches, e.g. social mapping, evaluation of depression and anxiety, and instruction in coping strategies and stress-management [12, 13].

Our study underscores that choice of remission criteria in PsA patients with high Δ PEG may have great impact on evaluation of treatment response. DAS28CRP(4) is more commonly used than DAS28CRP(3) in RA as well as PsA. However, in patients with high Δ PEG, DAS28CRP(3), which does not include patient's global assessment, may be a more suitable alternative.

Our study is in accordance with a smaller study on PsA patients where Δ PEG was found to be a negative predictor for achievement of 3- and 6-months' DAS28ESR(4) and 32-joint DAPSA remission. In that study, however, 12- and 24-months' outcomes, DAS28CRP(3) and retention rates were not evaluated [2].

Limitations of our study include lack of data regarding extra-articular manifestations in PsA patients (e.g. enthesitis, dactylitis and skin involvement) and the use of 28 and not 66/68 joint counts. This may have led to overestimation of remission rates in the PsA patients. Furthermore, DAS28 was developed for RA and not PsA, but has been validated in PsA patients in a clinical trial [14]. Also, there is no consensus as yet on the best cut-off for BASDAI remission in axSpA. Consequently, the two BASDAI remission cut-offs used in this study have not been validated, although one of them was recently used in another study [8]. However, the consistent findings for both these remission definitions as well as for ASDAS inactive disease support the validity and robustness of the results.

The major strength of this study is the longitudinal observational design including >14 000 patients with spondyloarthritis from 11 European countries. To our knowledge, this is the first study to assess the impact of baseline Δ PEG on TNFi retention rates in PsA and axSpA patients. It is also the first study to assess the impact of baseline Δ PEG for achievement of remission in axSpA patients as well as for achievement of 12- and 24-months' remission in patients with PsA.

In conclusion, high baseline patient's compared with evaluator's global assessment was associated with lower

6-, 12- and 24-months' retention and remission rates of first TNFi in female and male PsA and axSpA patients, except for DAS28CRP(3) remission in PsA. The study highlights the negative impact of high baseline Δ PEG on treatment outcomes in PsA and axSpA patients as well as the importance of including remission criteria that objectively reflect disease activity, particularly in the evaluation of PsA patients with high baseline Δ PEG.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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