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" (ΔPEG) 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 Chi-Square test and by logistic regression across quartiles of baseline ΔPEG, separately in female and male PsA and axSpA patients.

Results

We included 14,868 spondyloarthritis (5855 PsA, 9013 axSpA) patients. Baseline ΔPEG 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 ($p\leq0.002$) and ASDAS<1.3 ($p\leq0.005$) in axSpA patients, and with DAS28CRP(4)<2.6 ($p\leq0.04$) and DAPSA28≤4 ($p\leq0.01$), but not DAS28CRP(3)<2.6 ($p\geq0.13$) in PsA patients, with few exceptions on remission rates. Retention and remission rates were overall lower in female than male patients.

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

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 tumor 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" (ΔPEG), 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 C-reactive protein (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 Bath Ankylosing Spondylitis Disease Activity Index (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 ΔPEG quartiles by log-rank test. The impact of baseline ΔPEG 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 2 ways, either as <2, or as <2 with CRP <7mg/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 ΔPEG quartiles by Chi-square test. The impact of baseline ΔPEG 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 (SD) age of women (n=2988) / men (n=2867) were 49.3 (12.5) / 47.4 (11.7) years, time since diagnosis 6.6 (7.3) / 6.7 (7.2) years and median (25-75 percentiles) baseline ΔPEG 17 (0-38) / 10 (0-30), respectively, and for axSpA patients mean (SD) age of women (n=3639) / men (n=5374) 42.7 (12.0) / 41.7 (12.0) years, time since diagnosis 5.1 (7.4) / 6.9 (8.7) years and median (25-75 percentiles) baseline ΔPEG 20 (3-42) / 15 (0-37).

Impact of baseline ΔPEG on TNFi retention

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

Adjustment of the analyses for age, time since diagnosis and smoking consistently showed lower TNFi retention rates for higher quartiles of ΔPEG ($p \leq 0.01$). Findings for 3rd and 4th ΔPEG quartiles in axSpA patients were similar (supplementary figure 1).

Impact of baseline ΔPEG 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 ΔPEG 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 ΔPEG quartiles, but did not reach statistical significance (supplementary tables 1a-b).

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, ΔPEG) for TNFi treatment outcomes in patients with PsA and axSpA. The higher baseline ΔPEG 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 ΔPEG 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 to identify ΔPEG 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 ΔPEG 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 ΔPEG 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 PsA patients with ΔPEG ≥30 compared to <30 were found to be more frequently in DAPSA but not DAS28ESR remission, most likely explained by psychological rather than physical domains of health, like fatigue and lower self-perceived coping.[12] Importantly, patients with elevated ΔPEG 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 ΔPEG 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 ΔPEG 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 ΔPEG 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 more than 14,000 patients with spondyloarthritis from 11 European countries. To our knowledge, this is the first study to assess the impact of baseline ΔPEG on TNFi retention rates in PsA and axSpA patients. It is also the first study to assess the impact of baseline ΔPEG 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 ΔPEG 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 ΔPEG.

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Key messages

- Discordance between patient's and evaluator's global 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.

REFERENCES

1 Lindstrom Egholm C, Krogh NS, Pincus T, Dreyer L, Ellingsen T, Glintborg B, et al. Discordance of global assessments by patient and physician is higher in female than in male patients regardless of the physician's sex: data on patients with rheumatoid arthritis, axial spondyloarthritis, and psoriatic arthritis from the DANBIO Registry. *J Rheumatol* 2015;42:1781-5.

2 Michelsen B, Kristianslund EK, Hammer HB, Fagerli KM, Lie E, Wierod A, et al. Discordance between tender and swollen joint count as well as patient's and evaluator's global assessment may reduce likelihood of remission in patients with rheumatoid arthritis and psoriatic arthritis: data from the prospective multicentre NOR-DMARD study. *Ann Rheum Dis* 2016;76:708-11.

3 Ørnbjerg LM, Brahe CH, Askling J, Ciurea A, Mann H, Fatos Onen, et al. Treatment response and drug retention rates in 24,195 biologic-naïve patients with axial spondyloarthritis initiating TNFi treatment – routine care data from 12 registries in the EuroSpA collaboration. *Ann Rheum Dis* Accepted for publication July 2019.

4 van Riel PL. The development of the disease activity score (DAS) and the disease activity score using 28 joint counts (DAS28). *Clin Exp Rheumatol* 2014;32:S-65-74.

5 Michelsen B, Sexton J, Smolen JS, Aletaha D, Krogh NS, van der Heijde D, et al. Can disease activity in patients with psoriatic arthritis be adequately assessed by a modified Disease Activity index for PSoriatic Arthritis (DAPSA) based on 28 joints? *Ann Rheum Dis* 2018;77:1736-41.

6 Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P and Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21:2286-91.

7 Lukas C, Landewe R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009;68:18-24.

8 van der Heijde D, Dougados M, Landewe R, Sieper J, Maksymowych WP, Rudwaleit M, et al. Sustained efficacy, safety and patient-reported outcomes of certolizumab pegol in axial spondyloarthritis: 4-year outcomes from RAPID-axSpA. *Rheumatology (Oxford)* 2017;56:1498-509.

9 Machado PM, Landewé R and van der Heijde D. Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. *Ann Rheum Dis* 2018;77:1539-40.

10 Saber TP, Ng CT, Renard G, Lynch BM, Pontifex E, Walsh CA, et al. Remission in psoriatic arthritis: is it possible and how can it be predicted? *Arthritis Res Ther* 2010;12:R94.

11 Challa DN, Kvrgic Z, Cheville AL, Crowson CS, Bongartz T, Mason TG, et al. Patient-provider discordance between global assessments of disease activity in rheumatoid arthritis: a comprehensive clinical evaluation. *Arthritis Res Ther* 2017;19:212.

12 Desthieux C, Granger B, Balanescu AR, Balint P, Braun J, Canete JD, et al. Determinants of Patient-Physician Discordance in Global Assessment in Psoriatic Arthritis: A Multicenter European Study. *Arthritis Care Res (Hoboken)* 2017;69:1606-11.

13 Howells L, Chisholm A, Cotterill S, Chinoy H, Warren RB and Bundy C. Impact of disease severity, illness beliefs, and coping strategies on outcomes in psoriatic arthritis. *Arthritis Care Res (Hoboken)* 2018;70:295-302.

14 Vander Cruyssen B, De Keyser F, Kruithof E, Mielants H and Van den Bosch F. Comparison of different outcome measures for psoriatic arthritis in patients treated with infliximab or placebo. *Ann Rheum Dis* 2007;66:138-40.

Figure 1 TNFi retention rates across ΔPEG 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