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PATIENT OPINION

Evaluation of the performance of extreme patient-reported outcomes as surrogate markers for fibromyalgia in axial spondyloarthritis

Daniela Santos-Faria[1,2] · Maxime Dougados[2,3] · Laure Gossec[4] · Serge Perrot[5] · Anna Moltó[2,3]

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Abstract

Objectives The aim of the study is to evaluate the performance of extreme patient-reported outcomes (PRO) against definitions of fibromyalgia (FM) in patients with axial spondyloarthritis (axSpA).

Methods Ancillary analysis of the Predict-SpA trial, an observational study of axSpA patients receiving TNF-α inhibitor, was performed. 'Extreme PRO' was defined as a score ≥ 8 on three out of the first five Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) questions (scored 0–10). FM was defined by the American College of Rheumatology (ACR) 1990 criteria and the Fibromyalgia Rapid Screening Test (FiRST). Performances of 'extreme PRO' for FM were evaluated by the sensitivity, specificity and positive likelihood ratio using the 1990 ACR criteria as gold standard. As secondary analysis, the FiRST was used as the external standard.

Results The prevalence of 'extreme PRO' in this population was 28.8% at baseline and decreased to 9.9% at 12 weeks. 'Extreme PRO' had low sensitivity 12 weeks after TNF initiation (0.18, 95% confidence interval [CI] 0.10–0.27 vs 0.60, 95% CI 0.50–0.71, at baseline), but high specificity (0.92, 95% CI 0.89–0.94 vs 0.78, 95% 0.74–0.82, at baseline), using ACR 1990 criteria as gold standard. Performances when tested against FiRST at 12 weeks showed higher sensitivity (0.27, 95% CI 0.20–0.35) and specificity (0.96, 95% CI 0.94–0.98).

Conclusion The proposed extreme PRO definition showed great specificity for FM recognition in patients with axSpA, suggesting it could be used in observational studies when specific items for FM classification are not available.

Keywords Patient-reported outcomes · BASDAI · Fibromyalgia · Spondyloarthritis

Introduction

Fibromyalgia (FM) is an idiopathic diffuse pain syndrome leading to significant functional disability and the chronic widespread musculoskeletal pain is its hallmark symptom, and it is often accompanied by symptoms such as fatigue, stiffness and depression [1]. In the general population, its prevalence has been estimated around 2–7%, predominantly women [1, 2]. However, FM has been reported to be more frequent in patients with inflammatory rheumatic diseases such as rheumatoid arthritis, Sjögren disease or spondyloarthritis (SpA) [3, 4].

The American College of Rheumatology (ACR) criteria, namely ACR 1990 criteria, ACR 2010 and modified ACR 2010 criteria, are applied for FM diagnosis [5, 6]. The ACR 1990 criteria may be considered as the 'gold standard' for FM recognition. However, they were mostly developed for research purposes and are difficult to implement in clinical practice. Therefore, the self-reported Fibromyalgia Rapid

✉ Daniela Santos-Faria
danielasantosfaria@gmail.com

1 Rheumatology Department, Unidade Local de Saúde do Alto Minho (ULSAM), Hospital Conde de Bertiandos, Largo Conde de Bertiandos, 4990-078 Ponte de Lima, Portugal

2 Rheumatology Department, Cochin Hospital, Paris Descartes University, AP-HP, Paris, France

3 INSERM (U1153), Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France

4 Department of Rheumatology, Pitié-Salpêtrière Hospital, Sorbonne Universités, UPMC Université, AP-HP, Paris, France

5 Pain Center and INSERM U987, Cochin Hospital, Paris Descartes University, AP-HP, Paris, France

Screening Tool (FiRST) was developed as an easy-to-use screening tool with high performances [7]. This brief and simple questionnaire was validated reporting a sensitivity of 90.5% and a specificity of 85.7% for the detection of FM [7].

Axial SpA (axSpA) is a chronic inflammatory rheumatic disease involving the axial skeleton, but also peripherical joints and enthesis, [8] and in this population, prevalence of concomitant FM has been reported to range 4–21% [3, 9–16].

Patient-reported outcome (PRO) measures are used in daily clinical practice to assess disease activity [17] and in axSpA, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is the most used PRO [18].

AxSpA patients with FM have been reported to present higher BASDAI scores [3, 9–12, 15, 16] and a definition based on 'extreme PRO' has been proposed to be used as a surrogate marker of FM in axSpA patients in which the FM criteria were not available [19, 20]. Indeed, patients fulfilling the 'extreme PRO' definition were more frequently females, older and with a history of depression/antidepressant intake [12, 19], i.e. similar clinical characteristics as FM patients. Nevertheless, to date, the performance of such definition against gold standard criteria for FM has not been evaluated.

In this context, we performed this analysis aiming to evaluate the performance of an 'extreme PRO' definition for FM recognition according to (a) the 1990 ACR criteria and (b) the FiRST questionnaire, in an axSpA population.

Methods

Study design and population

This is an ancillary analysis of the Predict-SpA study, which has been presented elsewhere [16]. Briefly, the Predict-SpA study was a prospective, multicentric and observational study (clinicaltrials.gov: NCT03039088) of patients suffering from axSpA (according to the treating rheumatologist), in whom a tumour necrosis factor blocker (TNFb) was initiated because of axial symptoms of axSpA. The study included two visits: baseline and 12 weeks after TNFb initiation.

Study groups

Extreme PRO were defined as a score ≥ 8 (0–10 scale) on three out of the first five BASDAI questions (morning stiffness duration was not included) based on previous reports [19, 20]: fatigue, spinal pain, peripheral arthritis, enthesitis and intensity of morning stiffness. Patients with more than three out of the first five BASDAI questions missing were excluded. For this analysis, it was considered the 'extreme PRO' collected at baseline and in the second visit, 12 weeks after TNFb initiation.

FM definition

FM was defined according to: (a) the 1990 ACR criteria, applied by the treating rheumatologist; (b) the FiRST criteria according to a score ≥ 5/6 on the FiRST questionnaire completed at baseline and 12 weeks after TNFb therapy initiation.

Data collection

At baseline, demographic data (age, gender, educational level, smoking status, body weight and height), disease characteristics (disease duration, radiographic/MRI sacroiliitis, presence of peripheral and extra-articular features, HLA B27 status, past or present presence of an abnormal C-reactive protein [CRP], family history of SpA and non-steroid anti-inflammatory drugs [NSAID] good response) and items included in 1990 ACR FM criteria were collected. Disease activity scores (BASDAI, Ankylosing Spondylitis Disease Activity Score [ASDAS]), Bath Ankylosing Spondylitis Functional Index (BASFI) and the FiRST questionnaire were completed at baseline and at 12 weeks.

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Statistical analysis

Descriptive analysis of the 'extreme PRO' in this axSpA population

The number of patients fulfilling the 'extreme PRO' definition was calculated, and patient and disease characteristics were compared between the groups with or without 'extreme PRO'. Chi-squared test and fisher exact test were used, as appropriate, for categorical variables. For continuous variables, according to the variable normality, it was used parametric (t-test) or non-parametric (Mann–Whitney test) tests.

Evaluation of the performances of the 'extreme PRO' definition for FM recognition against the 1990 ACR criteria

Sensitivity (Se) (true positives/all positives), specificity (Spe) (true negatives/all negatives) and positive likelihood ratio (LR+) (Se/1-Spe) of the 'extreme PRO' definition and their 95% confidence intervals (CI) were estimated at baseline and 12 weeks after TNFb initiation.

Evaluation of the performances of the 'extreme PRO' definition for FM recognition against the FiRST

As a secondary analysis, the performances (Se, Spe and LR+) of the 'extreme PRO' definition for FM recognition against the FiRST were estimated.

The analysis was performed with the statistical software Statistical Package for the Social Sciences (SPSS) version 23.

Results

Among the 527 patients from the main study, 21 patients did not attend the follow-up visit or did not complete all questionnaires, yielding a total of 526 patients for the evaluation of extreme PRO at baseline and a total of 507 patients at 12 weeks.

Descriptive analysis

Table 1 summarizes the patient and disease characteristics of the patients included. 149 (29.4%) at baseline and 50 (9.9%) 12 weeks after TNFb initiation fulfilled the 'extreme PRO' definition. Among the 149 patients with 'extreme PRO' at baseline, 32 maintained an extreme PRO at 12 weeks. Patients fulfilling the definition at baseline or/and 12 weeks after TNFb initiation were more frequently female, had more frequently a history of antidepressant intake and less a university degree. Patients with an 'extreme PRO' at follow-up had a higher body mass index (BMI) (27.7 Kg/cm^2 vs 25.9 Kg/cm^2, $p = 0.002$).

Performance of the 'extreme PRO' definition against 1990 ACR FM criteria

Prevalence of FM according to 1990 ACR criteria was 16.3% (86/526) in this population (supplementary table 1 and 2). Sensitivity, specificity and LR + of the 'extreme PRO' at baseline for the recognition of FM were 0.60 (95% CI 0.50–0.71), 0.78 (95% CI 0.74–0.82) and 2.74 (95% CI 2.15–3.50), respectively. The presence of an 'extreme PRO' after 12 weeks showed an increased specificity (0.92, 95% CI 0.89–0.94), but a lower sensitivity (0.18, 95% CI 0.10–0.27) and a similar LR+ (2.22, 95% CI 1.27–3.88).

Performance of the 'extreme PRO' definition against FiRST

At baseline, 202 (38.4%) patients fulfilled the FiRST definition (supplementary table 3). On the other hand, 128 (25.2%) out of 507 patients fulfilled the FiRST definition at 12 weeks (supplementary table 4).

The sensitivity, specificity and LR + of the baseline 'extreme PRO' for FM recognition by FiRST were 0.41 (95% CI 0.34–0.48), 0.80 (95% CI 0.75–0.84) and 2.02 (95% CI 1.54–2.65), respectively. The specificity and LR + increased when tested 'extreme PRO' at 12 weeks for FM recognition by FiRST (0.96 [95% CI 0.94–0.98] and 6.91 [95% CI 3.90–12.22]), respectively; while sensitivity decreased (0.27 [95% CI 0.20–0.35)].

Discussion

In this study, 23.4% of patients eligible to initiate a TNFi treatment reported an 'extreme PRO', a higher prevalence than previously assessed in axSpA [19, 20]. The prevalence at follow-up visit after 12 weeks of treatment was 9.9%, which is in line with data reported in previous studies (e.g. 13.4% in DESIR cohort [20]).

Patients fulfilling this definition were more frequently female, a lower level of studies and a higher antidepressant intake, also in agreement with previously reported data [19, 20]. Our findings confirm a prevalence and characteristics of the axSpA patients fulfilling the 'extreme PRO' comparable to those with axSpA with concomitant FM [3, 10–16].

Patients with an 'extreme PRO' at baseline were more frequently HLB27 positive with a higher CRP. Notably, the patients reporting an 'extreme PRO' 12 weeks after TNFb initiation presented a higher ASDAS score at baseline, but associated with a lower CRP, as well as a higher BMI, showing a greater weight for the PRO and probably for a concomitant FM. The 'extreme PRO' reported only at baseline could be more related to the axSpA, in patients eligible to initiate a TNFi treatment.

A very good specificity of the 'extreme PRO' definition was assessed when tested against the "gold standard criteria" (1990 ACR criteria), but more interestingly, an even better specificity when tested against the FiRST questionnaire. The 'extreme PRO' after 12 weeks of treatment was less prevalent, but with a better agreement with FM diagnosis and a higher specificity. The higher sensitivity and lower specificity of 'extreme PRO' at baseline leave to the inclusion of more FM patients despite capturing some "false" FM, which reported high levels of pain and fatigue, probably related to the axSpA symptoms in patients with a high activity disease and eligible to begin a TNFb. Nevertheless, 12 weeks after the treatment initiation, the sensitivity of extreme PRO for FM diagnosis was lower and its specificity was better, leading to the inclusion of fewer FM patients but capturing fewer "false" FM despite missing some "true" diagnosis. At this point, the 'extreme PRO' seems more associated with the symptoms related to FM and not to the axial symptoms. Although not all FM diagnoses were captured, when an 'extreme PRO' was found in patients with the disease more

Table 1 Patient and disease characteristics of patients with/without extreme PROs

	Extreme PRO at baseline[a]				Extreme PRO at 12 weeks[a]			
	All patients $N=526$	Yes $n=149$	No $n=377$	P	All patients $N=507$	Yes $n=50$	No $n=457$	P
Age (years)	41.27 ± 11.57	42.48 ± 11.09	40.87 ± 11.71	NS	41.38 ± 11.58	43.75 ± 11.77	41.12 ± 11.54	NS
Gender (Female)	245/526 (46.6%)	86/149 (57.7%)	159/377 (42.2%)	0.001	236/507 (46.5%)	30/50 (60.0%)	206/457 (45.1%)	0.045
Disease duration (years)	6.26 ± 8.59	6.07 ± 7.57	6.36 ± 8.98	NS	6.20 ± 8.47	5.87 ± 9.11	6.24 ± 8.41	NS
Education (University)	236/524 (45.0%)	51/148 (34.5%)	185/376 (49.2%)	0.002	228/506 (45.1%)	12/50 (24.0%)	216/456 (47.4%)	0.002
BMI (kg/cm^2)	25.95 ± 5.21	25.95 ± 5.26	25.95 ± 5.20	NS	26.04 ± 5.19	27.73 ± 6.48	25.86 ± 5.00	0.002
Smoking status (Ever)	331/523 (63.3%)	92/148 (62.2%)	239/375 (63.7%)	NS	316/504 (62.7%)	31/50 (62.0%)	285/454 (62.8%)	NS
Inflammatory back pain	494/526 (93.9%)	149/149 (94.0%)	354/377 (93.9%)	NS	505/507 (99.6%)	50/50 (100.0%)	455/457 (99.6%)	NS
History of peripheral synovitis	143/520 (27.5%)	44/147 (29.9%)	99/373 (26.5%)	NS	139/501 (27.7%)	15/50 (30.0%)	124/451 (27.5%)	NS
History of peripheral enthesitis	280/522 (53.6%)	89/148 (60.1%)	191/374 (51.1%)	NS	274/503 (54.5%)	31/50 (62.0%)	243/453 (53.6%)	NS
History of dactylitis	58/522 (11.1%)	17/146 (11.6%)	41/376 (10.9%)	NS	57/503 (11.3%)	2/50 (4.0%)	55/453 (12.1%)	NS
History of IBD	29/523 (5.5%)	14/147 (9.5%)	15/377 (4.0%)	0.013	28/504 (5.6%)	4/50 (8.0%)	24/454 (5.3%)	NS
History of psoriasis	101/524 (19.3%)	22/147 (15.0%)	79/377 (21.0%)	0.018	100/505 (19.8%)	6/49 (12.2%)	94/456 (20.6%)	NS
History of uveitis	84/523 (17.0%)	22/148 (14.9%)	67/375 (17.9%)	NS	86/507 (17.1%)	10/50 (20.0%)	76/454 (16.7%)	NS
Family history of SpA	211/526 (40.1%)	59/149 (39.6%)	152/377 (40.3%)	NS	201/507 (39.7%)	15/50 (30.0%)	186/457 (40.7%)	NS
HLA B27 positive	303/468 (64.7%)	51/119 (47.9%)	246/349 (70.5%)	< 0.001	292/451 (64.7%)	22/42 (52.4%)	270/409 (66.0%)	NS
Good NSAID response	385/510 (75.5%)	114/143 (79.7%)	271/367 (73.8%)	NS	373/491 (76.0%)	36/48 (75.0%)	337/443 (76.1%)	NS
X-ray sacroiliitis	279/502 (55.6%)	82/143 (57.3%)	197/359 (54.9%)	NS	270/485 (55.7%)	24/47 (51.1%)	246/438 (56.2%)	NS
MRI sacroiliitis	276/403 (68.5%)	71/112 (63.4%)	205/291 (70.4%)	NS	262/387(67.7%)	23/40 (57.5%)	239/347 (68.9%)	NS
Elevated CRP at baseline[b]	311/512 (60.7%)	83/145 (57.2%)	228/367(62.1%)	NS	305/493 (61.9%)	20/49 (40.8%)	285/444 (64.2%)	0.001
History of antidepressant intake	103/518 (19.9%)	45/145 (31.0%)	58/373 (15.5%)	< 0.001	100/501 (20.0%)	20/49 (40.8%)	80/452 (17.7%)	< 0.001
Baseline CRP (mg/L)	15.27 ± 25.42	20.20 ± 31.79	13.38 ± 22.24	< 0.001	15.59 ± 25.79	12.18 ± 27.38	15.96 ± 25.62	0.003
Baseline BASDAI	5.68 ± 11.82	7.55 ± 1.05	4.96 ± 1.51	< 0.001	5.67 ± 1.84	7.18 ± 1.46	5.51 ± 1.80	0.040
Baseline ASDAS	3.33 ± 0.92	4.00 ± 0.87	3.07 ± 0.80	< 0.001	3.34 ± 0.93	3.60 ± 0.90	3.31 ± 0.93	0.016

BMI Body mass index, *NSAID* Non-steroidal anti-inflammatory drugs, *IBD* Inflammatory bowel disease, *CRP* C-reactive protein, *BASDAI* Bath Ankylosing Spondylitis

[a]Defined according to the scores ≥ 8 on three of the first five BASDAI questions (i.e. morning stiffness duration was not included): (1) fatigue, (2) spinal pain, (3) peripheral arthritis, (4) enthesitis and (5) intensity of morning

[b]Defined as > 6 mg/L

controlled 12 weeks after TNFb initiation, it corresponded to a "true" FM diagnosis.

An extreme PRO evaluated at baseline can be associated with concomitant FM or axial symptoms in SpA context. However, when reported after treatment, an 'extreme PRO' is more specific for FM association.

As previously described for concomitant FM and SpA [12, 16], patients with 'extreme PRO' also receive more frequently TNFb [20], with slightly lower response rates [19, 20]. The recognition of a concomitant FM is important for the optimal management of axSpA patients to avoid the risk of overestimating disease activity and therapeutic escalation, if only assessed by PRO.

This study has the limitation of being a post hoc analysis of the Predict-SpA trial, in which all patients were candidates to a TNFb treatment. This analysis was focused on PRO reported at baseline, as well as after 12 weeks of treatment with TNFb, i.e. in patients with controlled disease.

Furthermore, the opportunity of a unique study collecting both the classic axSpA PROs and the specific items used to classify and screen fibromyalgia, to evaluate the performances of a definition that has been used in trials or observational studies, represents the strength of the study.

The results of this analysis confirm the high specificity of such definition, regardless of the instrument used as gold standard. Based on our results, we confirm the good performance of the proposed axSpA 'extreme PRO' definition, as a surrogate for FM and suggests that this definition could be used in studies in which specific instruments for FM recognition are not available. Because of the impact of this comorbidity on the evaluation of the treatment effect of anti-rheumatic drugs [12, 16, 19], one might consider these 'extreme PRO' as potential exclusion criteria in phase II or III trials evaluating anti-rheumatic drugs.

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Compliance with ethical standards

Conflict of interest None of the authors has any conflicts of interest to declare for the present study.

Ethics committee CPP Île de France 3 - date 24/10/2014. The manuscript has been read and approved by all the authors and we confirm that each individual named as an author meets the journal's criteria for authorship.

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