Evaluation of extreme patient-reported outcome in early spondyloarthritis and its impact on the effect of TNF-α blockers treatment

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Abstract

Objective

To describe the prevalence of extreme patient-reported outcomes (PRO) in an early axial spondyloarthritis setting, to compare the phenotype of patients with/without extreme PRO and to evaluate the impact of extreme PRO on the effectiveness of TNF-α blockers (TNFb).

Methods

This analysis was performed in the DESIR cohort. Extreme PRO were measured at baseline and were defined as a score ≥8 on at least three of first five BASDAI items. Phenotype of patient's with/without extreme PRO was compared. Impact of extreme PRO on TNFb effectiveness was evaluated by comparing the retention rate of the first TNFb in both groups by survival curves analysis (log-rank and Cox analysis).

Results

Extreme PRO were present in 95 out of the 708 patients (13.4%). Patients with extreme PRO were older (mean (SD) age of 35.4(8.6) years vs. 33.5(8.7) years), more frequently females (65.3% vs. 51.9%), had higher BASDAI (7.1 vs. 4.1), reported more frequently history of depression (25.3% vs. 10.2%) and use of anti-depressive drugs (19.0% vs. 7.2%). TNFb treatment was more frequently initiated in the extreme PRO group (48.4% vs. 25.5%), while the proportion of patients still on TNFb at 2 years was significantly lower in the extreme PRO group 18.6% (n=8) vs. 39.5% (n=60). Presence of extreme PRO was independently associated with first TNFb discontinuation (HR 1.8, [95% CI 1.2;2.9], p=0.01).

Conclusion

Although presence of extreme PRO in this early axSpA setting was not very frequent, patients with extreme PRO were more likely to receive a TNFb and less likely to maintain the treatment at 2 years. Further studies evaluating the specific impact of extreme PRO on TNFb treatment in axSpA are warranted.

Key words

patient-reported outcomes, BASDAI, spondyloarthritis, TNF-α blockers, fibromyalgia

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Introduction

Spondyloarthritis (SpA) is a disease with different clinical features. The most distinctive musculoskeletal characteristics are axial pain, peripheral arthritis, dactylitis and enthesitis (1-3).

Fibromyalgia (FM) is a chronic widespread pain condition of unknown aetiology. It is considered to be a pain amplification syndrome associated with a central nervous system sensitisation mechanism (4). Its prevalence has been estimated to be around 2–7% of the general global population and is observed predominantly in women (5-7). Moreover, FM is often accompanied by symptoms such as fatigue, depression and stiffness (8-10). Recently, 2016 revisions to the 2010/2011-FM diagnostic criteria were published (11). In this revision, the authors have specified that diagnosis of FM does not exclude the presence of other clinically important illnesses (11), referring for the first time to the potential presence of FM as a "comorbidity" accompanying another chronic disease. Indeed, FM has been reported to be more frequent in patients with inflammatory rheumatic diseases such as Sjögren's syndrome, rheumatoid arthritis or SpA (9, 12-15) compared to the general population. For example, prevalence of coexisting FM with SpA is reported to be between 4% and 21% (10, 12, 16-19).

In clinical practice, Patient Reported Outcomes (PRO) are very often used (20) and in the field of axSpA, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is the most used PRO to assess disease activity (21-22). Since FM patients are known to report high level of pain and disability and are often refractory to NSAID therapy (23), in case of a concomitant FM in patients with axial SpA (axSpA), a risk exists of overestimating disease activity if only assessed by PROs. Indeed, this may result in therapeutic escalation (*i.e.* initiating TNF-α blocker (TNFb)) in axSpA patients with concomitant FM, with the resulting difficulties of evaluating treatment response in these patients who tend to always report high pain scores. A recent study (24) suggested that extreme PRO (*i.e.* three out of the first five BASDAI questions ≥8/10) could be used as surrogate marker for FM in an axSpA setting in case the items to calculate the FM criteria are not available. Further, extreme PRO and more precisely higher BASDAI scores have been observed in SpA patients with concomitant FM (25), and in this group of patients, depression, use of antidepressants and females were more frequent (25).

Hence we hypothesised that in a subset of patients presenting with extreme PRO (*i.e.* very high BASDAI) in axSpA might indeed be considered as a surrogate marker for FM and that such extreme PRO may have an impact on TNFb treatment effect. Hence, we performed this study with 3 objectives: a) to describe the prevalence of extreme PRO in an early axSpA setting; b) to compare the phenotype of patients with/without extreme PRO and c) to evaluate the impact of extreme PROs on TNFb treatment effect.

Methods

Study population

DESIR (French acronym for "devenir des spondyloarthropathies indifférenciées récentes") is a French early axSpA cohort (clinicaltrials.gov NCT01648907) (26). Detailed study design of the cohort has been reported previously (26). In brief, it is a longitudinal cohort of adults with inflammatory back pain (IBP) for >3 months and <3 years duration and suggestive of axSpA, according to the rheumatologist. Follow-up is still ongoing and planned over 20 years, but the data used for this present analysis includes only the first 2 years of follow-up. This study is fulfilling the current Good Clinical Practice Guidelines and has obtained the approval of the appropriate ethical committee. All patients from DESIR were included in our analysis and provided informed consent.

Data collection

The following information was collected at baseline: age, gender, date of symptoms onset, date of SpA diagnosis, smoking status (if ever smoked), body weight and height, HLA B27 status, past or present presence of an abnormal C-reactive protein (CRP), radiographic/

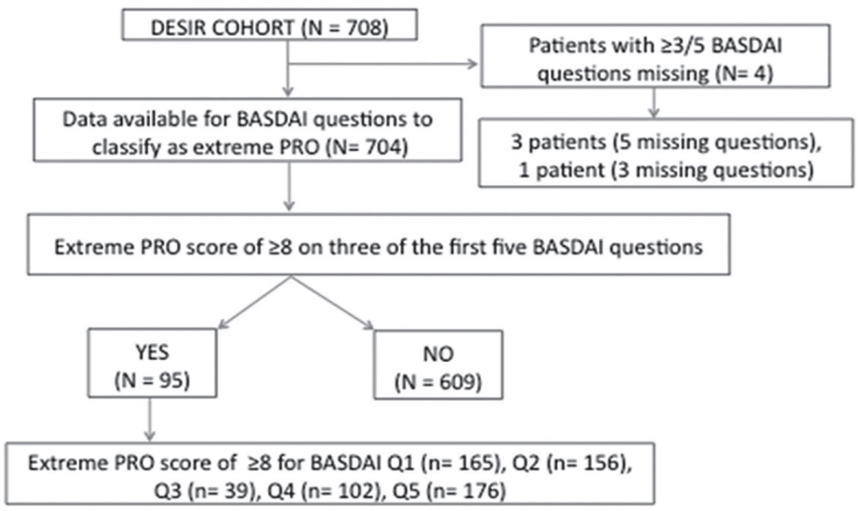

Fig. 1. Distribution of extreme PRO scores in DESIR study population.

Table I. Description of extreme PRO scores in DESIR cohort.

	Total population (n=708)	With extreme PRO (n=95)	Without extreme PRO (n=609)	*p*-value	NA
BASDAI Q1- Fatigue (0-10)	5.7 (2.3)	8.3 (1.1)	5.3 (2.2)	<0.0001	3
BASDAI Q2- Spinal Pain (0-10)	5.3 (2.5)	8.1 (1.3)	4.9 (2.3)	<0.0001	4
BASDAI Q3- Peripheral Pain (0-10)	2.7 (2.7)	4.8 (3.1)	2.4 (2.5)	<0.0001	5
BASDAI Q4- Enthesitis Pain (0-10)	4.0 (3.0)	7.3 (2.4)	3.5 (2.7)	<0.0001	4
BASDAI Q5- Morning stiffness intensity (0-10)	5.2 (2.7)	8.2 (1.4)	4.8 (2.6)	<0.0001	4
BASDAI Total	4.5 (2.0)	7.1 (1.1)	4.1 (1.8)	<0.0001	4

All results presented as mean (SD) for continuous variables
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; NA: data not available; SD: standard deviation.

MRI sacroiliitis according to local reading, presence of extra-articular features, BASDAI (and its separate questions) (21), patient and physician global assessment, Bath Ankylosing Spondylitis Functional Index (BASFI) (27), SpA treatments since disease onset including information on non-steroidal anti-inflammatory drugs (NSAIDs), and start/end date of discontinuation for each TNFb.

Information on past or current use of psychotropic medications (*i.e.* muscle relaxants, antidepressants, or anxiolytics), 3rd ladder analgesics (*i.e.* opioids) (28, 29), and history of depression were collected.

It should be noted that no specific FM criteria sets (neither 1990 nor 2010/11 ACR FM criteria) were collected in DESIR. However, the treating rheumatologist could report FM as a comorbidity in the case report form at each visit.

Definition of extreme PRO

For this study we chose BASDAI as our PRO, as it is one of the most widely used PRO in clinical practice. Extreme PRO based on BASDAI score is scarcely reported. Based on one recent article (24), extreme PRO was defined as 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 stiffness, collected at baseline.

Patients missing more than 3 out of the first 5 BASDAI questions were excluded from this analysis.

Statistical analysis

• *Prevalence of extreme PRO*

Extreme PRO prevalence was estimated by calculating the n (%) of patients fulfilling the extreme PRO definition.

• *Comparison of phenotype among patients with/without extreme PRO*

Patients with extreme PRO scores were compared to the rest of the cohort in terms of demographics, disease characteristics, activity and severity by *t*-test or Chi-square as appropriate.

• *Evaluation of the impact of extreme PRO on TNFb effectiveness*

Retention rate of the first TNFb treatment over the first 2 years of follow-up (length of 2 years of TNFb treatment) in patients with/without extreme PROs was estimated by survival analysis (Kaplan-Meier curves) and compared by the log-rank test (bivariate analysis). A multivariable Cox analysis was performed, including in the model the presence of extreme PRO, but also other parameters frequently reported to influence treatment effectiveness (*i.e.* MRI (30) and x-ray sacroiliitis (19), presence of elevated CRP (31), HLA B27 (32), female gender (33)), to evaluate the impact of an extreme PRO on the retention rate, adjusting for other confounders.

Statistical significance was set at $p<0.05$. The analysis was performed with the statistical software SAS 9.4 and R 3.2.3.

Results

Prevalence of extreme PRO scores in DESIR

Out of the 708 patients from the DESIR cohort, answers to more than 3 questions of the BASDAI were missing in 4 patients; thus, 704 patients were included in our analysis. Of them, 95 met the definition of extreme PRO, (*i.e.* scored ≥8 in at least 3 of the first 5 BASDAI questions), yielding a prevalence of extreme PRO of 13.4%. (Fig. 1, Table I)

Comparison of the phenotype characteristics of patients with/without extreme PROs

Patients with extreme PRO were older (mean (SD) age of 35.4 (8.6) vs. 33.5 (8.7) years, $p=0.03$), with disease onset at an older age (34.0 (8.3) *vs.* 31.9 (8.7) years, $p=0.03$) and more frequently females (65.3% *vs.* 51.9%, $p=0.02$); however, it should be noted that no differences were found with regard to the

Table II. Comparison of phenotype in patients with/ without extreme PRO scores in DESIR cohort.

	With extreme PRO (n=95)[+]	Without extreme PRO (n=609)[+]	*p*-value
Age	35.4 (8.6)	33.5 (8.7)	0.031
Gender (Female)	62 (65.3%)	316 (51.9%)	0.022
Age at disease onset (Years)	34.0 (8.3)	31.9 (8.7)	0.025
Disease duration (Years)	1.5 (0.8)	1.52 (0.9) [n=608]	NS
Smoking status (ever)	39 (41.1%)	217 (35.7%) [n=608]	NS
HLA B27 positive	52 (54.7%)	357 (58.7%) [n=608]	NS
Radiographic sacroiliitis	11 (12.0%) [n=92]	100 (16.7%) [n=599]	NS
MRI sacroilliitis	26 (28.3%) [n=92]	204 (34.2%) [n=597]	NS
CRP ≥6 mg/L	29 (31.2%) [n=93]	175 (29.8%) [n=588]	NS
Past history or current arthritis	60 (63.2%)	342 (56.2%)	NS
Past history or current enthesitis	50 (52.6%)	298 (48.9%)	NS
ASAS criteria at baseline	52 (57.8%) [n=90]	393 (65.5%) [n=600]	NS
NSAIDs [++] (baseline)	61 (64.2%)	498 (82.3%)	<0.0001
Synthetic DMARDs (yes/no) [+++] (baseline)	13 (13.7%)	82 (13.5%)	NS
BASDAI TOTAL (0-10)	7.1 (1.1)	4.1 (1.8)	<0.0001
Patient Global Assessment of Disease (BASG week) (0–10)	8.0 (1.6) [n=94]	4.7 (2.4) [n=606]	<0.0001
Bath Ankylosing Spondylitis Functional Index (0–10)	5.1 (2.4)	2.7 (2.1) [n=604]	<0.0001
SF36 Mental Component Summary*	31.1 (9.8) [n=94]	41.6 (10.8) [n=600]	<0.0001
SF36 Physical Component Summary*	33.8 (6.9) [n=94]	40.9 (9.2) [n=600]	<0.0001
History of depression	24 (25.3%)	62 (10.2%)	<0.0001
Anti-depressive treatment	18 (19.0%)	44 (7.2%)	0.0004
Muscle relaxant treatment	40 (42.1%)	136 (22.3%)	<0.0001
Fibromyalgia**	3 (3.2%)	5 (0.8%)	-

All results presented as mean (SD) for continuous variables or number (%) for categorical variables. Extreme PRO group was defined as score of ≥8 on three of the first 5 BASDAI questions. [+]A total of 4 patients had too many missing values to be classified in either group, [++]NSAIDs, non-steroidal anti-inflammatory drugs; [+++]DMARDs: disease-modifying anti-rheumatic drugs; *SF36: 36-Item Short Form Health Survey; **Fibromyalgia reported as comborbidity by the rheumatologist.

disease phenotype (*i.e.* HLA B27 positive status, radiographic sacroiliitis, MRI evidence of sacroiliitis, CRP values, past or current history of arthritis/ enthesitis) (Table II)

Patients fulfilling the extreme PRO definition reported significantly higher BASDAI scores (7.1 (1.1) *vs.* 4.1 (1.8), $p<0.01$), and also significantly higher values for other PRO such as patient global assessment of disease activity, BASFI, Short Form-36 (SF-36) Physical Component Summary (PCS) and Mental Component summary (MCS) (Table II). History of depression, use of antidepressant and muscle relaxant treatment was significantly higher amongst patients with extreme PRO scores (Table II).

Evaluation of the impact of extreme PRO on TNFb effectiveness

Among the 704 patients included in the analysis 201 (28.6%) received a TNFb over the first 2 years of follow-up. The proportion of patients initiating a TNFb treatment was significantly higher in the extreme PRO group 48.4% (n=46 out of 95) *vs.* 25.5% (n=155 out of 609), $p<0.01$, respectively.

Table III. Cox multivariable analysis for the prediction of the anti-TNF treatment discontinuation.

	Hazard ratio (95%CI)	*p*-value
MRI sacroiliitis	0.84 (0.50 – 1.41)	0.51
X-ray sacroiliitis	0.52 (0.30 – 0.91)	0.02
CRP	1.01 (0.99 – 1.02)	0.31
HLAB27	0.66 (0.43 – 1.02)	0.06
Gender (female)	1.37 (0.86 – 2.21)	0.19
Extreme PRO	1.82 (1.16 – 2.85)	<0.01
Type of first anti-TNF		
Etanercept *vs.* Adalimumab	1.30 (0.84 – 1.99)	0.24
Infliximab *vs.* Adalimumab	0.51 (0.20 – 1.33)	0.17

Retention rate of the first TNFb at 2 years (median [95% CI]) in patients with/without extreme PRO scores was 9.4 [5.1–15.6] months and 20.5 [13.2–29.2] months respectively, *i.e.* significantly shorter in patients with extreme PRO ($p=0.01$).

Only absence of x-ray sacroiliitis (HR =0.5 [95% CI 0.3; 0.9], $p=0.02$) and the presence of extreme PRO (HR 1.8, [95% CI 1.2; 2.9], $p=0.01$) were selected by the Cox multivariable analysis as factors independently associated with discontinuation of the first TNFb treatment (Table III).

Discussion

Our study reports and confirms several findings. First, we report a 13.4% prevalence of such extreme PRO scores in DESIR cohort, which is comparable to the prevalence reported for concomitant FM in spondyloarthritis (10, 12, 17, 18, 25) and the percentage (14.6%) of patients fulfilling this definition in another nr-axSpA study (24). Secondly patients with extreme PRO scores were more frequently female, older, presented with later onset of axSpA and had more frequently a history of depression and antidepressant intake (25); how-

Fig. 2. First TNFb retention rate over 2 years of follow-up.

ever no significant difference with regard to axSpA disease phenotype was observed.

Thirdly, patients with extreme PRO received more frequently a TNFb. This is not surprising, since a BASDAI ≥4/10 is required prior to TNFb initiation (34). However, retention rate of the first TNFb was significantly lower in patients with extreme PRO, and the extreme PRO was independently associated with first TNFb discontinuation in the multivariate analysis. All these results suggest that indeed presence of extreme PRO in early axSpA have an impact on the assessment of disease activity and treatment response, potentially leading to an impact also on management decisions.

Our study has some limitations but also some strengths. First, we did not collect FM information according to specific validated FM criteria (*e.g.* 1990 ACR criteria for FM), so we could not evaluate the performance of the extreme PRO for the FM diagnosis. However, we used a definition of extreme PRO that was previously used in an axSpA population (24). In this trial, patients fulfilling this definition of extreme PRO had higher depression scores. Similarly, in our study, axSpA patients with extreme PRO were more frequently females and taking antidepressant drugs, two characteristics that have been reported to be more frequent in axSpA patients with concomitant FM (19). However, axSpA disease phenotype (*e.g.* presence of HLAB27, MRI and x-ray sacroiilits, etc.) of patients with/without extreme PRO in our study was comparable, suggesting that these patients were not FM patients misclassified as axSpA but rather true axSpA with concomitant FM.

Secondly, we could not evaluate treatment effect at short term (*e.g.* after 12 weeks of treatment) since TNFb treatment was initiated at any time during the follow-up, according to the treating rheumatologists choice. Nevertheless we could evaluate the long-term (*i.e.* 2 years) retention rate of the drug, which is a widely validated effectiveness measure. Also extra-articular manifestations were not considered and it might be possible that in few cases the presence of such manifestations might have played a role in initiating TNFb despite possible presence of FM.

Furthermore one could argue that the number of patients treated with TNFb on the extreme PRO group was not very large (n=48) and that might influence the results of our survival analysis. However our multivariable analysis selected the presence of extreme PRO as an independent factor associated with TNFb discontinuation, but also radiographic sacroiliitis (which has been largely reported as a predictive factor for good treatment response) as independently associated to TNFb continuation, reinforcing the external validity of our results.

One other difference that should be noted is that in this study based on the DESIR cohort, adult patients with IBP, suspected to have early axSpA (>3 months and <3 years disease duration) were recruited. A total of 64.5% of patients at baseline fulfilled the ASAS criteria at baseline, in contrast in the study by Dougados M *et al.* (24), where all patients fulfilled the ASAS axSpA criteria without fulfilling the modified New York criteria for radiographic axSpA.

Finally our study was performed on one of the largest early axSpA cohort. In this cohort all patients were biologically naïve and were treated with NSAIDs at baseline, which replicates the daily clinical practice scenario. Another strength of this study is that, to the best of the author's knowledge, this is the first time that the impact of extreme PRO on long-term TNFb effectiveness is assessed.

Our results suggest that a subset of patients with extreme PRO might be considered, in some cases, particularly in the absence of objective signs of inflammation, as a surrogate marker for FM in early axSpA, and that such presence appears to have a negative impact on TNFb retention rate. Further studies evaluating the performances of extreme PRO in FM screening but also the prospective ones evaluating the impact of extreme PRO and FM on treatment effectiveness should confirm (or not) our findings.

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