Evaluating patient-reported fatigue and serum biomarkers in axial spondyloarthritis[AQ4]

Letter to the Editor

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Elizabeth Reilly[1,2], [AQ3] Anita McGrogan[2] and Raj Sengupta[1]

[1]. Department of Rheumatology, Royal National Hospital for Rheumatic Diseases, Royal United Hospital NHS Trust and
[2]. Department of Pharmacy and Pharmacology, University of Bath, Bath, UK

Correspondence to: Elizabeth Reilly, Clinical Research Fellow in Rheumatology, Royal National Hospital for Rheumatic Diseases, Royal United Hospital NHS Trust, Bath, BA1 3NG, UK. E-mail: elizabethreilly2@nhs.net

DEAR EDITOR, fatigue is a common symptom in patients with axial spondyloarthritis (axSpA), having been described by 67.2% of patients with AS, and a similar rate in non-radiographic axial spondyloarthritis (nr-axSpA, 68.2%) [1].

Fatigue impacts upon quality of life [2], work productivity [3] and is associated with anxiety and depression [4].

We evaluated a broad selection of serum biomarkers (Supplementary Fig. S1, available at *Rheumatology* online), in a large cross-sectional mixed cohort of axSpA patients. The objective was to identify biomarker signals related to patient reported fatigue, defined by responses to Question 1 of the BASDAI [5], and explore the relationship with disease activity.

The Bath Spondyloarthritis Biobank (Research Ethics Council reference 13/SW/0096) at the Royal National Hospital for Rheumatic Diseases (Bath) is a longitudinal database of patients over the age of 18 years, being referred with a suspected or confirmed diagnosis of axSpA, following written patient consent. At the time of this study, the Biobank comprised 1176 patients with confirmed diagnoses, 77% with AS. The study was conducted in line with the principles of the declaration of Helsinki.

Demographic and clinical information, patient-reported outcome measures (BASDAI, BASFI, patient global and pain visual analogue scales) and BASMI are collected during routine clinical visits. Questionnaire and metrology data completed closest to the date of biobank enrolment was used for analysis.

Patients included in the study were drawn from the database based upon the completeness of their data (clinical data and serology) and had a confirmed diagnosis of AS (modified New York criteria), nr-axSpA (ASAS[AQ1] criteria) or mechanical back pain (MBP). A single 50 ml blood sample (serum and DNA) was collected at the time of enrolment into the Biobank, and all samples were analysed centrally by Myriad RBM (Austin, TX, USA) using the 47-protein Lumina Panel (Human Inflammation Multi Analyte Profile v 1.0 multiplex and Ultra-High Sensitive MCP-1 ELISA assays).

For each biomarker, lowest limit of quantitation (LLOQ, lowest amount of an analyte quantitatively determined with acceptable precision, where the coefficient of variation after serial dilutions is 30%) and serum low to high range (based upon 95% of the sample results from 100 healthy individuals) were reported.

Descriptive statistics were applied, using IBM SPSS Statistics version 24.0. All data were tested for normality using the Shapiro–Wilks test and QQ plots. Where biomarker results were below the LLOQ, these were recoded as 0. Data were described using means (s.d.) or median (interquartile range) as suitable. Where appropriate, Pearson Chi-squared, Mann–Whitney U or Kruskal–Wallis tests were employed to evaluate distributions between independent samples, and Spearman rank correlation coefficients were used to assess associations between non-parametric continuous independent samples.

Characteristics of the 273 patients are shown in Table 1: 195 (71.4%) were AS, 27 (9.9%) nr-axSpA and 51 (18.6%) MBP. A total of 88.8% of the AS cohort were HLA-B27 [AQ5]positive, compared with 77.8% in the nr-

axSpA cohort and only 13.7% of MBP. AS patients were older (mean age 53.8 years, *vs* 34.0 and 29.9 years in the nr-axSpA and MBP, $P < 0.01$), and had a higher proportion of males (74.4%, *vs* 44.4 and 43.1%, respectively, $P < 0.01$). Fifty-eight (29.7%) AS patients and only one nr-axSpA were currently on anti-TNF medications. Mean (s.d.) disease duration for AS was 22.5 years (13.6) and 1.8 years (4.2) in non-radiographic patients ($P < 0.01$).

Table 1 Cohort characteristics of patients evaluated for fatigue and serum biomarkers by diagnostic group

Characteristic	AS	nr-axSpA	MBP	*P*-value
n (%)	195 (71.4)	27 (9.9)	51 (18.6)	—
Age, mean (s.d.), years	53.8 (13.4)	34.0 (9.0)	29.9 (9.4)	<0.01
HLA-B27 positive	173 (88.7)	21 (77.8)	7 (13.7)	<0.01
Male	145 (74.4)	12 (44.4)	22 (43.1)	<0.01
Family history of SpA	50 (25.6)	10 (37.0)	7 (13.7)	<0.01
Current smokers	40 (20.5)	5 (18.5)	12 (23.5)	0.08
Previous extraarticular manifestations	129 (66.2)	17 (63.0)	15 (29.4)	<0.01
Current biologic therapy	58 (29.7)	1 (3.7)	—	<0.01
Disease duration, mean (s.d.), years	22.5 (13.6)	1.8 (4.2)	0.0 (0.1)	<0.01
Total BASDAI, mean (s.d.)	3.8 (2.1)	4.8 (2.0)	5.3 (1.9)	<0.01
BASDAI Q1, mean (s.d.)	4.7 (2.4)	5.2 (2.5)	5.5 (2.5)	0.08
Total BASDAI without Q1, mean (s.d.)	2.8 (1.7)	3.8 (1.7)	4.2 (1.7)	<0.01
ASDAS, mean (s.d.)	2.7 (1.2)	2.4 (0.8)	2.7 (0.8)	0.41
BASFI, mean (s.d.)	4.0 (2.4)	2.6 (2.1)	3.6 (2.4)	<0.01
BASMI, mean (s.d.)	4.1 (2.0)	1.6 (1.4)	—	<0.01

Number of patients with characteristic, *n* and percentage of group, %, unless stated. *P*-value using Kruskal–Wallis or ANOVA as appropriate. nr-axSpA: non-radiographic axial spondyloarthritis.

Mean (s.d.) BASDAI Q1 score (which pertains specifically to fatigue) was highest in MBP [5.5 (2.5); nr-axSpA 5.2 (2.5), AS 4.7 (2.4), $P = 0.08$] but not significant.

Using Spearman rank, significant correlations ($P \leq 0.01$) were found in patients with AS and nr-axSpA between self-reported levels of fatigue (Q1) and their total BASDAI, BASDAI calculated excluding Q1, ASDAS, BASFI and back pain scores.

Significant correlations ($P \leq 0.01$) in the AS cohort were also found between fatigue and levels of serum biomarkers macrophage inflammatory protein 1β (MIP1β) and VEGF, but this association was not seen in either the nr-axSpA or MBP groups.

Patients on TNFi demonstrated lower MIP1β (mean 506.8 pg/ml *vs* 625.0 pg/ml, $P = 0.001$), and reported lower fatigue (mean BASDAI Q1 score 3.7 *vs* 5.2, $P < 0.001$).

This work has identified an association between fatigue and serum biomarkers MIP1β and VEGF in AS patients, while those on anti-TNF treatment were found to have both lower fatigue and MIP1β. The larger AS sample size and relative low proportion of patients on TNFi must be appreciated, and hence these results require further validation in another cohort. MIP1-α has previously been shown to decline with TNF inhibition in AS [6], with no similar previous findings for MIP1β. A previous study, however, has linked MIP1β to fatigue in SLE [7], but this is the first work of its type to raise a possible role in SpA.

Rheumatology key messages

- Fatigued AS patients demonstrate higher MIP1β and VEGF, but patients on TNFi have lower MIP1β.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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