Original article

Quantifying and predicting the effect of anti-TNF therapy on axSpA-related fatigue: results from the BSRBR-AS registry and meta-analysis

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Abstract

Objectives. Effective management of axial spondyloarthritis (axSpA)-related fatigue is a major unmet clinical need. Anti-TNF therapy may reduce fatigue levels, although any effect has yet to be definitively quantified and predictors of any such improvements are unknown.

Methods. The British Society of Rheumatology Register in Axial Spondyloarthritis (BSRBR-AS) prospectively recruited axSpA patients across the UK. Changes in fatigue levels (measured using the Chalder Fatigue Scale) >1 year were compared between those starting anti-TNF therapy at the time of recruitment and those not. Differences between treatment groups were adjusted using propensity score matching. Results were meta-analysed with the extant literature to calculate pooled estimates. Then, among those BSRBR-AS anti-TNF commencers with clinically relevant fatigue, baseline predictors of response were investigated.

Results. Of the 998 BSRBR-AS recruits with complete fatigue data, 310 were anti-TNF commencers. At 1-year follow-up, the former group reported a mean fatigue change of −2.6 (95% CI −4.1, −1.9) points while the latter reported a mean worsening of fatigue by 0.2 points. Following propensity score adjustment, those commencing anti-TNF therapy reduced fatigue by 3.0 points compared with those not. Of those with significant fatigue and commencing anti-TNF, poor sleep quality at baseline predicted fatigue improvement. In the meta-analysis, including 1109 subjects, treatment with anti-TNF therapy resulted in a significant improvement in fatigue [Standardized mean difference (SMD) = 0.36, 95% CI 0.15, 1.56].

Conclusion. Anti-TNF therapy results in a significant but modest reduction in fatigue amongst axSpA patients, with those reporting poor sleep quality most likely to report improvement. Effective management will likely require additional approaches.

Key words: fatigue, anti-tumour necrosis factor, axial spondylarthritis, sleep, registry, meta-analysis

> **Rheumatology key messages**
> - Anti-TNF therapy significantly reduces axSpA related fatigue although the size of effect is small.
> - Anti-TNF therapy mostly likely reduces fatigue in AxSpA patients with high fatigue and sleep disturbance.

Introduction

Fatigue represents a critical priority among patients with axial spondyloarthritis (axSpA) [1]. This pervasive symptom, reported by 50–65% of patients [2, 3], is a principal determinant of impaired quality of life [3]. Although the EULAR 2016 guidelines state that the primary focus of axSpA management is to improve quality of life [4], no specific interventions are currently recommended for axSpA-related fatigue.

Anecdotally there are patients who report substantial improvements in their fatigue following anti-TNF therapy. Certainly, there are randomized controlled trials (RCT) where fatigue has been recorded as a secondary

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outcome that have reported clinically significant fatigue reductions in comparison to placebo [5]. However, there appears to be considerable variability between studies; for example, Dougados *et al*. [6] failed to identify a significant fatigue benefit in their trial of etanercept. Given the heterogeneous nature of this symptom, it may be that only specific sub-groups of patients experience meaningful reductions in fatigue, although the characteristics of any such groupings have yet to be elucidated.

Using the real-world British Society of Rheumatology Register in Axial Spondyloarthritis (BSRBR-AS) registry, we aimed to quantify the effect of anti-TNF therapy on fatigue among axSpA patients and to then synthesize these findings with existing studies in a meta-analysis. We then sought to characterize those axSpA patients who experienced a meaningful improvement in fatigue following anti-TNF therapy.

Methods

BSRBR-AS analysis

Data were obtained from a UK-wide prospective cohort study, the BSRBR-AS. The BSRBR-AS study recruited approximately 2500 patients who met the Assessment of SpondyloArthritis International Society for radiographic or non-radiographic axSpA from 83 centres across the UK between 2012 and 2017. Eligible patients commencing anti-TNF therapy were assigned to the 'biologics' sub-cohort, the remainder to the 'non-biologics' sub-cohort. Detailed methodology of the BSRBR-AS study can be found in the study protocol, which has been published previously [7].

Clinical data were entered into electronic Case Report Forms collected at recruitment, routine clinical visits and at 12-month follow-up. Patients were also invited to complete survey questionnaires that included demographic information, Bath disease assessment indices [8], sleep quality [9], anxiety/depression [10] and quality of life [11].

For this study, our outcome of interest was fatigue, measured using the Chalder Fatigue Scale (CFS) [12]. This 11-item questionnaire is one of the most commonly employed measures of fatigue. Validated in both general and clinical populations [13], it examines physical and mental fatigue dimensions. Items are rated on a four-point (0–3) Likert scale (0 ='better than usual', 1 ='no worse than usual', 2 ='worse than usual' and 3 ='much worse than usual'). The scores are totalled (0–33), with higher scores indicating greater fatigue. A reduction of ≥ 2 is considered clinically important when used to evaluate treatment response [14]. In addition, by dichotomizing individual question responses at the median, a bimodal fatigue score can be generated ranging from 0 to 11 to classify fatigue where >3 is considered to be clinically important [12].

Participants who had completed the fatigue scale at baseline and 12 (3) month follow-up were eligible for this analysis. Analysis was conducted on the June 2017 download of data.

The study complies with the Declaration of Helsinki. Ethical approval was granted by the National Research Ethics Service Committee North East – County Durham and Tees Valley (Research Ethics Committee reference – 11/NE/0374). Appropriate National Health Service (NHS) Research and Development approvals were obtained for each site and inform consent obtained.

In order to quantify the effect of anti-TNF therapy on fatigue in the BSRBR-AS, we examined the change in fatigue between baseline and 12 months for the 'biologic' and 'non-biologic' cohorts using the Likert CFS scale. In observational studies, treatment assignment is not random and large differences in observed covariates are likely to exist between patients who received biologic therapy and patients who did not. This decision to commence biologic therapy is often influenced by patient factors and clinical characteristics such as disease activity. Therefore, a direct comparison of the two clinical cohorts can lead to confounding by indication. To reduce this bias, we carried out propensity score matching, introduced by Rosenbaum and Rubin [15]. A logistic regression model was used to estimate a propensity score modelled by covariates that represented subject characteristics at recruitment (baseline): age, gender, smoking status, disease duration and serum CRP. Therefore, the propensity score is the probability of receiving a treatment conditional on a vector of observed covariates [15]. After adjusting for observed differences between the biologic and non-biologic sub-cohorts, an independent *t* test was used to compare the mean changes in fatigue.

We next examined the mean changes in fatigue between treatment groups among selected patients with clinically significant baseline fatigue ($CFS_{bimodal} > 3$). Regression models were then employed to explore univariate predictors of clinically important fatigue response (change in score ≥ 2 on CFS_{likert}) among this subgroup of patients. All data analyses were performed using STATA version 14.0 (StataCorp, College Station, TX, USA).

Systematic review and meta-analysis

Electronic databases: Ovid MEDLINE, EMBASE, Evidence Based Medicine, and Cochrane Library, were searched up to October 2018. A detailed search strategy can be found in Supplementary material, available at *Rheumatology* online. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used to guide the conduct and reporting of this systematic review and meta-analysis [16].

Inclusion criteria were based on the following:

- population: adults with axSpA or AS by recognized criteria/clinical diagnosis;
- study design: observational studies (longitudinal prospective and retrospective studies with follow-up), RCTs and quasi RCTs were included. RCTs compared a biologic with or without a conventional DMARD (csDMARD) against a placebo with or without the same csDMARD; and
- outcomes: there must be a measure of fatigue reported either before or at the time of commencing biologic

treatment and after, that is, quantitative results to allow change in fatigue to be measured.

Potentially eligible abstracts were independently screened by two reviewers (M.K., J.S.) and any disagreements were resolved by discussion. Relevant data from included studies were extracted by M.K. and cross-checked by a second reviewer (J.S.). Where studies were potentially eligible but data presented in the manuscript did not allow for inclusion in the meta-analysis, authors of the study were contacted to request for data.

For continuous outcome variables, the mean difference of change in fatigue parameters was calculated with 95% CIs. Heterogeneity was assessed using the Chi-square statistic. Where there was evidence of moderate-to-high heterogeneity ($I^2 > 40\%$), results were analysed using a random-effects model.

Results

The effect of anti-TNF on fatigue in the BSRBR-AS

Of the 2420 BSRBR-AS subjects, 998 had completed the fatigue questionnaire at both baseline and 12-month follow-up. There were no clinically significant differences between those analyses and those excluded (Supplementary Table 1, available at *Rheumatology* online>). Of these, 310 were recruited to the 'biologic cohort' (28% etanercept, 68% adalimumab, 4% certolizumab) and 688 to the 'non-biologic cohort'. Many baseline characteristics of the cohorts were similar (Table 1), although subjects starting anti-TNF therapy were significantly younger (47 *vs* 54 years) with lower disease duration (9 *vs* 16 years). They were also more likely to be smokers (21% *vs* 11%). Average

fatigue levels at study entry were similar between cohorts (3.4 *vs* 2.7 points). Over the 12-month follow-up period, 82% of the biologic cohort remained on anti-TNF.

Subjects starting anti-TNF for axSpA reported a 2.6-point reduction of fatigue after 1 year (95% CI −4.1, −1.9) with no significant differences between agents. In contrast, the non-biologic cohort reported a 0.4-point increase in fatigue. Following propensity score adjustment, the difference (−3.0 points, 95% CI −4.1, −1.9) was statistically significant (Table 2).

Meta-analysis of anti-TNF effect on axSpA fatigue

The search strategy initially identified 443 manuscripts of which only four (involving 805 participants) met eligibility criteria for inclusion in the meta-analysis (see Fig. 1). Of these, three were multicentre RCTs and one an observational study, with follow-up ranging between four and 32 weeks (see Supplementary Table 2, available at *Rheumatology* online).

Due to a variation in fatigue measures between studies, standardized mean differences were computed. Overall, anti-TNF treated axSpA subjects experienced a small but significant improvement in fatigue in comparison to non-biologically treated axSpA subjects (SMD = 0.36, 95% CI 0.15, 1.56) (Fig. 2). A high level of heterogeneity was observed ($I^2 = 64.5\%$).

Characteristics of fatigue responders in the BSRBR-AS

Within the BSRBR-AS biologics cohort, 205 (66%) subjects reported clinically significant fatigue at baseline. Of these, 139 (68%) experienced a clinically relevant improvement in their fatigue at 1 year. These
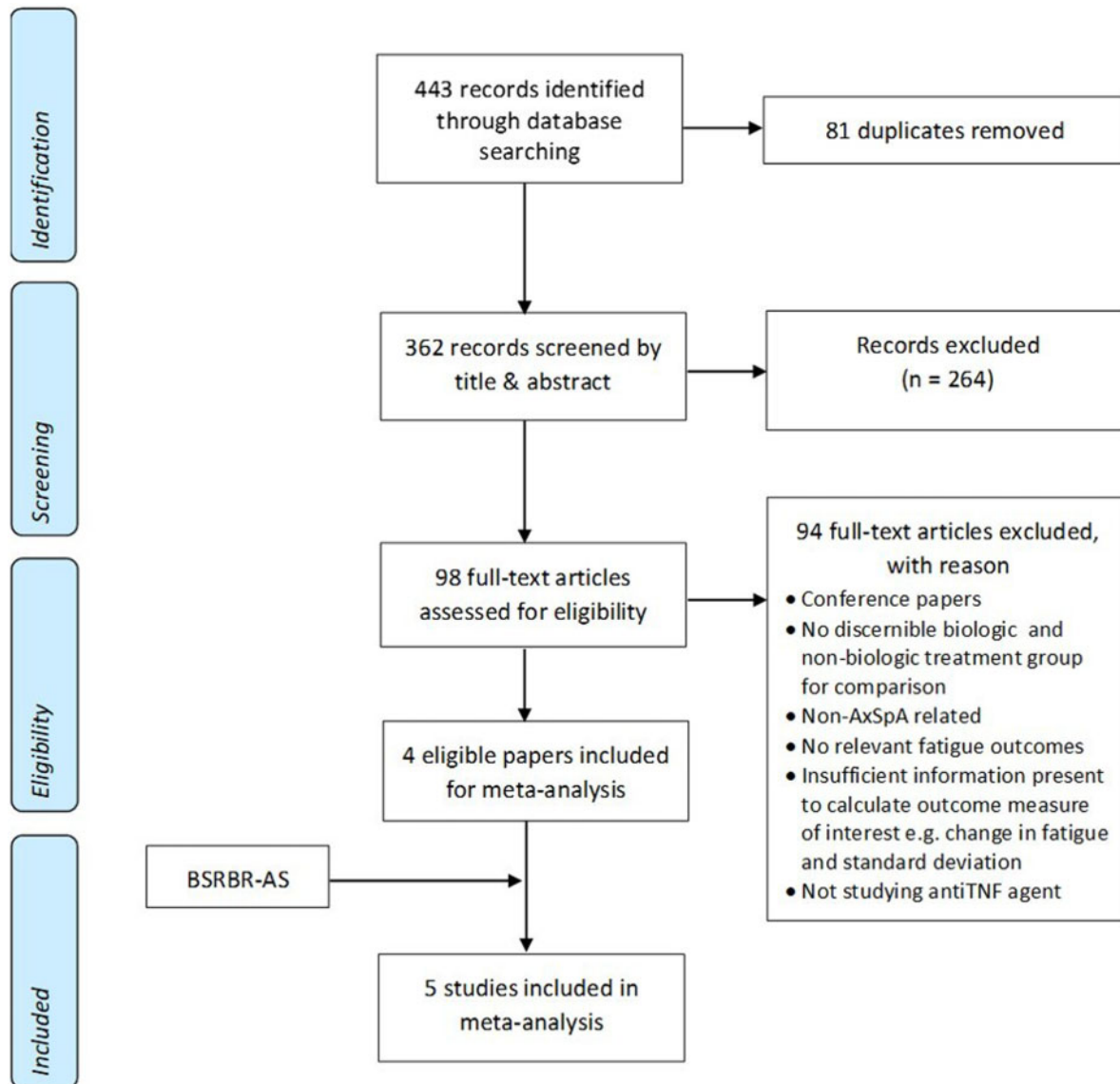
TABLE 1 BSRBR-AS study: baseline characteristics of biologic and non-biologic cohorts

Continuous factors	Biologic cohort (*n* = 310)	Non-biologic cohort (*n* = 688)	Difference[a] (95% CI)
Male, %	67.4	70.6	−3.2 (−9.4, 3.1)
Age (mean), years	46.9	53.6	−6.7 (−7.2, −6.2)
Disease duration (mean), years	9.2	15.7	−6.4 (−6.9, −6.0)
Current smokers, %	20.9	10.8	10.1 (5.0, 15.2)
Employed, %	63.1	59.0	4.1 (−2.4, 10.6)
CRP, mg/dL	25.3	22.8	2.5 (1.4, 3.6)
Disease activity—BASDAI [scored 0 (best) to 10 (worst)]	6.2	3.7	2.6 (2.4, 2.8)
Disease activity—ASDAS (higher score = worst disease activity)	3.6	2.5	1.0 (0.9, 1.2)
BASFI [scored 0 (best) to 10 (worst)]	6.1	3.7	2.4 (2.2, 2.6)
BAS-G [scored 0 (best) to 10 (worst)]	7.0	3.7	3.3 (3.1, 3.4)
Spinal pain [scored 0 (best) to 10 (worst)]	6.1	3.2	2.9 (2.7, 3.1)
ASQoL [scored 0 (best) to 18 (worst)]	11.6	6.0	5.6 (5.3, 5.9)
Sleep disturbance [scored 0 (best) to 20 (worst)]	12.8	8.6	4.2 (3.9, 4.6)
Fatigue [scored 0 (best) to 11 (worst)]	3.4	2.7	0.7 (0.4, 1.0)
Anxiety (HADS) [scored 0 (best) to 21 (worst)]	8.7	6.2	2.5 (2.2, 2.8)
Depression (HADS) [scored 0 (best) to 21 (worst)]	7.2	4.6	2.7 (2.4, 2.9)

[a]Difference = biologic–non-biologic cohort. ASDAS: assessment of spondyloarthritis disease activity score; ASQoL: AS quality of life index; VAS: visual analogue scale; HADS: hospital anxiety and depression scales.

TABLE 2 BSRBS-AS study: changes in fatigue between biologic and non-biologic cohort (matched by propensity score)

	Biologic cohort	Non-biologic cohort	Mean difference in change (95% CI)
Change in fatigue (whole cohort)	−2.6	0.4	−3.0 (−4.1, −1.9)
Change in fatigue (clinically significant fatigue at baseline)	−4.1	−1.2	−2.8 (−4.3, −1.3)

FIG. 1 PRISMA flowchart of study selection and inclusion

Identification

443 records identified through database searching → 81 duplicates removed

Screening

362 records screened by title & abstract → Records excluded (n = 264)

Eligibility

98 full-text articles assessed for eligibility → 94 full-text articles excluded, with reason
- Conference papers
- No discernible biologic and non-biologic treatment group for comparison
- Non-AxSpA related
- No relevant fatigue outcomes
- Insufficient information present to calculate outcome measure of interest e.g. change in fatigue and standard deviation
- Not studying antiTNF agent

4 eligible papers included for meta-analysis

BSRBR-AS →

Included

5 studies included in meta-analysis

subjects were significantly more likely to report poor sleep and high fatigue levels at baseline. Baseline CRP was not significantly related to fatigue response (Table 3).

Discussion

Anti-TNF therapy is associated with a significant, albeit small, improvement in fatigue among patients with axSpA. Patients with sleep difficulties appear marginally

more likely to experience a clinically relevant reduction in fatigue following this intervention.

The precise mechanisms of axSpA-related fatigue are unknown. Biologically, pro-inflammatory cytokines such as TNFα are implicated in the generation of sickness behaviours – a constellation of body responses to inflammation of which fatigue is salient [17]. However, observational studies have identified multiple associations, implying a multi-factorial origin, with systemic inflammation not consistently relating to fatigue [18, 19]. Thus, the observed improvements following anti-TNF therapy may be partly derived indirectly from improvements in pain, sleep disturbance and mental health [18–20].

FIG. 2 Forest plot of fatigue change differences between patients receiving biologics and non-biologics
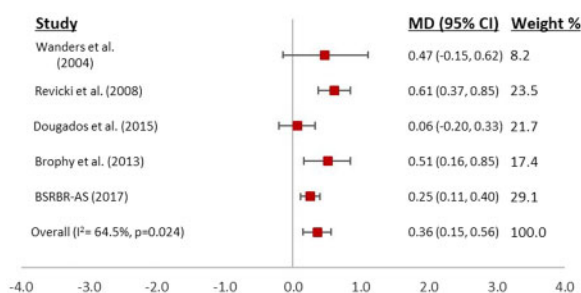
The modest effect of anti-TNFα on axSpA-related fatigue aligns with a recent uncontrolled observational study that reported general improvements in fatigue scores following treatment with this therapy; however, 80% of patients still experienced severe fatigue at 3 months follow-up [21]. Therefore, if such a pharmacological approach is to ever be usefully clinically applied for axSpA fatigue, it will have to be directed towards select sub-populations.

In the BSRBR-AS cohort reported here, poor sleep appears to predict fatigue response to anti-TNFα. We speculate that those patients with a combination of fatigue and sleep disturbance identify themselves as maintaining a sickness behaviour-like endotype. Both subjective [18, 20] and objective polysomnographic measures of sleep quality [22] have previously been related to fatigue in this clinical population. Moreover, there is also accumulating evidence that TNFα is a key sleep regulatory molecule that mediates both sleep-promoting and inhibitory neural circuits [23]; indeed, axSpA patients consistently report improvements in their sleep following prescription of anti-TNFα therapy [24, 25]. While affording some putative biological insights, the prediction effect is modest and so any endotype will likely represent a small, clinically less useful, subgroup.

The similarities in prevalence and impact of fatigue across inflammatory rheumatic diseases have led to the plausible suggestion that pathophysiology is shared. In line with this, the fatigue effect size reported here is comparable to that observed following cytokine targeted

TABLE 3 BSRBR-AS: Univariate factors associated with improvement in fatigue amongst those with clinically significant fatigue at baseline

Continuous factors	Likelihood of improvement Coefficient (95% CI)
Age	0.01 (−0.02, 0.02)
CRP, mg/l	0.002 (−0.004, 0.01)
Disease Activity—BASDAI (no fatigue) [scored 0 (best) to 10 (worst)]	0.01 (−0.14, 0.16)
Disease Activity—ASDAS (higher score = worst disease activity)	0.12 (−0.19, 0.43)
BASFI [scored 0 (best) to 10 (worst)]	0.02 (−0.11, 0.15)
BAS-G [scored 0 (best) to 10 (worst)]	0.03 (−0.16, 0.22)
Spinal pain [scored 0 (best) to 10 (worst)]	−0.09 (−0.23, 0.04)
ASQoL [scored 0 (best) to 18 (worst)]	−0.02 (−0.09, 0.06)
Fatigue [scored 0 (best) to 11 (worst)]	0.16 (0.03, 0.30*)
Sleep disturbance [scored 0 (best) to 20 (worst)]	0.07 (0.02, 0.12*)
Anxiety (HADS) [scored 0 (best) to 21 (worst)]	−0.05 (−0.12, 0.02)
Depression (HADS) [scored 0 (best) to 21 (worst)]	−0.01 (−0.09, 0.07)
WPAI_absenteeism (scored as percentage of previous week)	0.01 (−0.01, 0.02)
WPAI_presenteeism (scored as percentage of previous week)	−0.01 (−0.03, 0.01)
WPAI_work impairment (scored as percentage of previous week)	−0.01 (−0.02, 0.01)
WPAI_activity impairment (scored as percentage of previous week)	0.001 (−0.01, 0.01)
Dichotomous factors	Odds ratio (95% CI)
Gender (female *vs* male)	0.70 (0.37, 1.27)
Work status (yes *vs* no)	1.42 (0.78, 2.59)
Job type (mainly physical *vs* mainly sedentary)	0.48 (0.22, 1.06)
Concurrent FM (2011 mod. of ACR2010 criteria: yes *vs* no)	0.75 (0.22, 2.52)

ASQoL: ankylosing spondylitis quality of life index; HADS: hospital anxiety and depression scales; WPAI: work productivity and activity impairment scale. *P <0.05.

biological therapy in RA [26] and PsA [27]. In practical terms, this further supports the future pragmatic delivery of generic rather than disease-specific management approaches.

These data should be interpreted in the context of a number of limitations. First, significant heterogeneity existed between the studies identified within the systematic review. All studies, however, evidenced a positive effect on fatigue and no studies reported a substantial benefit. Secondly, the fatigue outcome measure varied between studies that required the computation of standardized mean differences. Thirdly, assessing outcomes at multiple time points would have been ideal. BSRBR-AS fatigue outcomes were restricted to the 1-year follow-up visit due to inadequate available data at other time points, while follow-up across the other studies ranged between 1 and 24 months. The overall effect is unlikely to be greatly influenced by such variation because anti-TNFα response is generally stable after 3 months [28] and only the small Wanders study restricted follow-up to less than 3 months. A sensitivity analysis excluding this study recorded a similar overall estimate (SMD = 0.35, 95% CI 0.12, 0.58). Fourthly, none of the selected studies were primarily designed to evaluate fatigue response in the target population; that is, axSpA patients experiencing important fatigue. Instead only patients with high disease activity were recruited, regardless of fatigue status. We have identified high baseline fatigue as a predictor of response and by corollary would anticipate enhanced anti-TNF effects within this clinically relevant subgroup. Moreover, because it is unlikely that a RCT testing anti-TNF with the primary aim of alleviating fatigue will ever be conducted, the present evidence is likely the best achievable. Fifthly, the high numbers of excluded patients relate to high levels of missing fatigue data in the registry. This may introduce issues of external validity, although no major clinical differences were observed between those included and excluded. Finally, propensity scoring cannot entirely remove concerns regarding confounding by indication. It is, however, reassuring that the BSRBR-AS estimates are positioned in between those extracted from randomized controlled trials.

In summary, although many axSpA patients with active disease appear to experience a clinically meaningful fatigue response following anti-TNF therapy, the size of benefit is modest. These data further emphasize the multi-factorial basis of fatigue in axSpA. TNFα pathways may primarily support the maintenance of fatigue in a specific subgroup of patients. The combination of poor sleep quality and fatigue may distinguish such patients. Future research, primarily designed to investigate fatigue, should seek to better classify this strata. Such an approach will inform a truly personalized medical approach to managing this patient priority.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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