

Co-Occurrence and Characteristics of Patients With Axial Spondyloarthritis Who Meet Criteria for Fibromyalgia

Results From a UK National Register

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Objective. To estimate the proportion of patients with axial spondyloarthritis (SpA) in a UK national biologics registry who met criteria for fibromyalgia (FM), and to delineate the characteristics of these patients.

Methods. Two cohorts of patients are prospectively recruited from across 83 centers in the UK for the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS). All patients are required to meet Assessment of SpondyloArthritis international Society (ASAS) criteria for axial SpA. Patients are either newly starting biologic therapy (biologics cohort) or are naive to treatment with biologic agents (non-biologics cohort) at the time of recruitment, and all patients are followed up prospectively. At recruitment and follow-up, clinical information and measurements are recorded while patients complete the 2011 research criteria for FM and assessments of the level of disease activity and work impact.

Results. Of the patients registered in the BSRBR-AS, 1,504 (68% male) were eligible for the current analysis, of whom 311 (20.7%) met the 2011 research criteria for FM. Prevalence of FM was similar between patients who fulfilled the modified New York

criteria for AS (19.7%) and those who fulfilled ASAS imaging criteria but not the modified New York criteria (25.2%); however, among those who fulfilled only the ASAS clinical criteria, the prevalence of FM was lower (9.5%). Patients who met FM criteria reported significantly worse disease activity, function, global severity scores, and quality of life, and were more likely to have moderate or severe levels of mood disorder and clinically important fatigue. Patients who met FM criteria reported experiencing work impairment around half their working time. Meeting FM criteria was not related to elevated C-reactive protein levels or most extraspinal manifestations, but was associated with a higher likelihood of having received biologic therapy.

Conclusion. Developing management approaches that would address the significant unmet clinical needs of the 1 in 5 patients with axial SpA who meet criteria for FM should be a research priority.

Fibromyalgia (FM) may be more common in patients with axial spondyloarthritis (SpA) than in the general population. In comparison to a population prevalence of 2–4% based on the American College of Rheumatology (ACR) 1990 criteria for FM (1), studies in patients with ankylosing spondylitis (AS) from Turkey (prevalence 12.6%; n = 119), Italy (prevalence 12.7%; n = 211), and Brazil (prevalence 15%; n = 71) have all shown a similar excess prevalence of FM (2–4). This is consistent with the observation of a high prevalence of FM in inflammatory rheumatic diseases in general (5).

However, distinguishing axial SpA from FM is problematic, given that the ACR 1990 criteria for FM require the report of axial skeleton pain, which is the key clinical feature of axial SpA, whereas enthesitis may result in multisite pain, which is the cardinal feature of

Supported in part by Arthritis Research UK (grant 21378).

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Submitted for publication March 8, 2017; accepted in revised form June 15, 2017.

FM and is included in all established or proposed sets of FM criteria (6–8). A pooled analysis of data from clinical trials assessing treatment of patients with AS with etanercept, sulfasalazine, or placebo has shown higher disease burden and poorer response to treatment in women (9,10). The trial investigators proposed that these findings may be due to the concomitant presence of FM, and identified comorbid FM as a priority for future research.

FM may distort responses to some of the key patient-reported measures used in axial SpA, such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) (11,12). In the above-mentioned study from Turkey in which AS patients with FM and those without FM were compared, there was no difference in the C-reactive protein (CRP) level or erythrocyte sedimentation rate, but those with FM had higher BASDAI scores (3). In July 2013, the US Food and Drug Administration (FDA) met to consider whether patients who had nonradiographic axial SpA, based on the Assessment of SpondyloArthritis international Society (ASAS) criteria (13), should be eligible for new therapies. The FDA committee recognized the unmet need for effective pharmacologic therapy for patients who had either positive changes only on magnetic resonance imaging (MRI) or positivity for HLA-B27 in conjunction with other clinical and laboratory features characteristic of SpA. The FDA was, however, concerned about the possibility that those with highly prevalent conditions such as mechanical back pain or FM, especially patients without evidence of changes on MRI, might be incorrectly diagnosed as having inflammatory spondylitis and could be inappropriately treated with expensive and potentially toxic biologic therapies. These observations highlight the need to better understand the characteristics of patients who have overlapping axial SpA and FM, to assess and distinguish the 2 conditions, and to develop treatment strategies that can effectively work in parallel.

As an initial step in such endeavors, the current study, within a cohort from a UK national registry of patients with axial SpA, aimed to 1) determine the prevalence of FM among patients meeting the ASAS criteria for axial SpA, and 2) identify clinical and patient-reported measures that might distinguish axial SpA patients with comorbid FM.

PATIENTS AND METHODS

The British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS) is a prospective

cohort study in which patients who meet the ASAS definition of axial SpA have been recruited from 83 secondary care centers in the UK, with the first centers recruiting from December 2012. Patients meeting only the ASAS clinical criteria for axial SpA have been eligible to be recruited from November 2014. At the time of recruitment into the register, all patients are naive to anti-tumor necrosis factor (anti-TNF) biologic therapy but may be either starting such therapy (adalimumab, etanercept, or certulizumab pegol) or continuing on their current therapy. The study protocol has previously been published (14).

For patients starting on biologic therapy, clinical and patient-reported information is collected at the time of recruitment and at 3, 6, and 12 months of follow-up. For patients not taking biologic agents, information is collected at the time of recruitment and annually thereafter, but these patients may transfer to the follow-up schedule of patients receiving biologic therapy if they commence such therapy at a later date. From September 2015 onward, the patient-reported data have included the 2011 research criteria for FM (8). Satisfying the FM research criteria depends on the presence of widespread pain and somatic symptoms.

Patients in the register were included in the current analysis if they had completed the 2011 FM research criteria either at recruitment or at follow-up. We used data from the time of the first completion of the items in the criteria set. Information on clinical status at the time of recruitment allowed us to determine whether patients were known to meet imaging criteria for axial SpA (the modified New York criteria for AS [15] and/or the ASAS imaging criteria [13]) or to not meet such criteria (only meeting the ASAS clinical criteria). Data collected from or measured in each patient included the BASDAI, the BASFI, the Bath Ankylosing Spondylitis Metrology Index (16), and the Bath Ankylosing Spondylitis Global Assessment (17), each scored to provide a scale from 0 (best) to 10 (worst).

In addition, extraspinal manifestations were assessed, including uveitis, psoriasis, inflammatory bowel disease, and swollen and tender joint counts (of 44 joints assessed), in accordance with the ASAS recommendations for studies of SpA (18). Quality of life was measured using the 18-item Ankylosing Spondylitis Quality of Life (ASQoL) scale (17), providing a score from 0 (good quality of life) to 18 (poor quality of life). The EuroQol 5-domain (EQ-5D) questionnaire, a 5-item generic scale, was used to assess health-related quality of life, with scores ranging from 0 (equivalent to death) to 1 (best possible health), although scores lower than 0 (worse than death) are also possible (19). Other patient-reported measures collected were a sleep disturbance score that consisted of 4 items (each scored 0–5; total score 0–20), with higher scores indicating worse problems with sleep disturbance (20).

Furthermore, the 11-item Chalder fatigue scale was used to measure the extent and severity of fatigue. Each item was scored as 0 or 1, providing a total score of 0–11, with higher scores indicating worse fatigue. A score of ≥ 4 is taken to indicate significant fatigue (21). For assessment of mental health status, the Hospital Anxiety and Depression Scale (HADS) (22), a measure of emotional distress, anxiety disorders, and depression in patients with somatic or psychiatric disorders, primary care patients, and the general population, was used. The HADS has been shown to have a 2-factor structure

corresponding to the anxiety and depression subscales (23). Each subscale has 7 items, scored 0–3, providing a total score for anxiety and for depression of 0–21, with higher scores indicating higher levels of anxiety or depression. Scale scores are categorized as 0–7 (normal), 8–10 (mild), 11–14 (moderate), and 15–21 (severe). Patients also completed the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem, a validated instrument to measure impairments in work, including both absenteeism and impaired performance while at work (presenteeism) (24).

Height and weight (for the calculation of the body mass index [BMI]) and the CRP level were measured in each patient. Furthermore, we constructed a comorbidity index based on the number of comorbidities reported by the clinician to be present in each patient (including myocardial infarction, angina, congestive cardiac failure, stroke, hypertension, diabetes, asthma, chronic bronchitis or emphysema, peptic ulcer, liver disease, renal disease, tuberculosis, demyelination, depression, or cancer).

An area-level deprivation score was calculated (the Index of Multiple Deprivation [IMD]) using comparable official government indices from the relevant individual countries within the UK. These were the English IMD (EIMD), Scottish IMD (SIMD), and Welsh IMD (WIMD). Each IMD was based on lower-level census areas, which represent neighborhoods. All indices include income, employment, health, education, housing, and crime/community safety. Both the SIMD and the WIMD include access to services, while in the EIMD, this is combined with the housing domain. Additionally, the EIMD adds living environment, and the WIMD adds physical environment. The IMDs were categorized into quintiles and standardized to be presented on a scale of 1–5, ranging from the most deprived (IMD score of 1) to least deprived (IMD score of 5), in accordance with the practices of the SIMD.

We compared the range of clinical and patient-reported measures collected from patients with axial SpA according to whether they met the 2011 research criteria for FM. Comparisons were carried out using *t*-tests (continuous outcomes), 2-sample proportion tests (binary outcomes), chi-square tests (categorical nonordered outcomes), and nonparametric tests for trend (ordinal outcomes) or for comparison of distributions (Mann-Whitney U test) as appropriate. The 95% confidence intervals (95% CIs) are given for effect estimates. This analysis used data from the January 2017 version of the study database.

RESULTS

Participants and prevalence of FM. Among the 2,449 participants in the BSRBR-AS, 1,504 (68% male) were eligible for the current study, of whom 553 (35.4%) were in the biologics-exposed cohort. The study population is described in Table 1. Patients had a median age of 51.2 years, and reported a median time since symptom onset of 19 years. Among the cohort of eligible patients, 82.2% of those who had been tested were HLA-B27 positive, and ~1 in 6 were current smokers. Most participants (69.2%) met the modified New York criteria for AS, an additional 26.5% fulfilled

Table 1. Characteristics of the study population of 1,504 patients with axial spondyloarthritis*

Age, median (IQR) years	51.2 (40.1–63.1)
Sex, no. (%) male	1,025 (68.2)
Time since symptom onset, median (IQR) years	19 (9–33)
HLA-B27 status	
No. not tested	574
No. positive (% of tested)	765 (82.2)
No. negative (% of tested)	165 (17.8)
CRP, median (IQR) mg/dl	0.55 (0.10–2.00)
Smoking status, no. (%)†	
Current smoker	247 (16.7)
Former smoker	578 (39.2)
Never smoker	651 (44.1)
Diagnostic criteria fulfilled, no. (%)	
Modified New York criteria	1,041 (69.2)
ASAS imaging criteria but not modified New York criteria	398 (26.5)
ASAS clinical criteria only	65 (4.3)

* IQR = interquartile range; CRP = C-reactive protein; ASAS = Assessment of SpondyloArthritis international Society.

† The total number of patients with available data on smoking status was 1,476.

the ASAS imaging criteria but not the modified New York criteria, and 4.3% fulfilled only the ASAS clinical criteria. Among the patients, 311 (20.7%) met the 2011 research criteria for FM. The proportion of patients meeting the FM criteria in each of the respective axial SpA criteria groups (modified New York criteria, ASAS imaging criteria but not modified New York criteria, and ASAS clinical criteria only) was 19.7%, 25.2%, and 9.5% ($P = 0.006$).

The proportion meeting the FM criteria was higher among female patients (26.1%, versus 18.2% of male patients; $P < 0.001$), but there was no difference by age group ($P = 0.56$). HLA-B27-positive patients were less likely than HLA-B27-negative patients or untested patients to meet the FM criteria (17.0%, versus 32.1% and 21.7%, respectively; each $P < 0.001$). The prevalence of FM did vary by level of area deprivation: those with IMD scores in the most deprived quintile had an FM prevalence of 38.0%, those in the least deprived quintile had an FM prevalence of 13.8%, and in the intermediate quintiles of IMD, the prevalence of FM varied from 17.5% to 20.3% (all $P < 0.001$).

Disease indices for axial SpA. Patients who met the 2011 FM research criteria had markedly worse indices of disease (Table 2). They had significantly worse disease activity, function, metrology, and global status. Of the 1,034 participants who had a CRP measurement available, there was no significant difference between those who did meet FM criteria and those who did not meet FM criteria in the proportion having a CRP level that exceeded 1 mg/dl (39.3% versus 38.7%; $P = 0.86$). There was no difference in the overall distribution of

Table 2. Disease measures in patients with axial spondyloarthritis according to their meeting or not meeting the 2011 research criteria for FM*

Disease index	Mean score (95% CI)		Difference (95% CI) in mean score
	Meeting 2011 criteria for FM	Not meeting 2011 criteria for FM	
BASDAI disease activity	6.7 (6.5, 6.9)	3.6 (3.5, 3.8)	3.1 (2.8, 3.3)
BASFI function	6.6 (6.4, 6.9)	3.7 (3.6, 3.9)	2.9 (2.6, 3.3)
BASMI metrology	4.2 (4.0, 4.5)	3.6 (3.5, 3.8)	0.6 (0.3, 0.9)
BASG global health	6.9 (6.7, 7.2)	3.7 (3.6, 3.8)	3.2 (2.9, 3.6)

* FM = fibromyalgia; 95% CI = 95% confidence interval; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index (scale 0–10); BASFI = Bath Ankylosing Spondylitis Functional Index (scale 0–10); BASMI = Bath Ankylosing Spondylitis Metrology Index (scale 0–10); BASG = Bath Ankylosing Spondylitis Global Score (scale 0–10).

CRP level ($P = 0.82$ by Mann-Whitney U test) nor was there any difference in CRP level within either the biologics cohort ($P = 0.53$) or the non-biologics cohort ($P = 0.76$).

Patient-reported measures. Quality of life was significantly worse in those patients who met the FM research criteria, regardless of whether quality of life was measured by a disease-specific measure or a generic measure (Table 3). Patients meeting the FM criteria had significantly higher scores on the HADS anxiety and depression subscales compared to those who did not meet the FM criteria. Of those who met the FM criteria, 39.9% were classified as having moderate or severe depression, in comparison to 7.0% of patients who did not meet the FM criteria ($P < 0.001$). The comparable proportions of patients reporting moderate or severe anxiety were 55.3% among those meeting the FM criteria and 17.9% among those not meeting the FM criteria ($P < 0.001$). Patients who met the FM criteria also had higher scores for the extent of

sleep disturbance and levels of fatigue, with the score exceeding the cutoff value for clinically important fatigue in 79.2% of patients in the FM group compared to 34.2% in the non-FM group ($P < 0.001$).

Clinical status and therapy. Patients who satisfied the FM research criteria had a higher BMI than those who did not meet the FM criteria (mean 28.7 kg/m² versus 27.6 kg/m², difference of 1.2 kg/m² [95% CI 0.3, 2.0]). In addition, those in the FM criteria group, as compared to those in the non-FM criteria group, had a greater swollen joint count (mean 0.47 versus 0.21, difference of 0.26 [95% CI 0.03, 0.49]) and greater tender joint count (mean 1.3 versus 0.5, difference of 0.8 [95% CI 0.4, 1.2]) and were more likely to report at least 1 comorbidity (36.9% versus 19.9%; $P < 0.001$). In contrast, there was only a small, and not statistically significant, excess in the proportion of patients reporting extraspinal manifestations among patients positive for the FM criteria compared to those not meeting the FM criteria (for uveitis, 19.0% versus 18.0%; for psoriasis, 9.2% versus 6.4%; for inflammatory bowel disease, 8.5% versus 7.0%). Patients meeting the FM research criteria were more likely to be receiving biologic therapy compared to those not meeting the FM research criteria (50.5% versus 31.5%).

Work-related factors. Patients meeting the criteria for FM reported a significantly greater percentage of work time missed compared to patients not meeting the FM criteria (15.1% of work time missed versus 2.5% of work time missed, difference of 12.7% [95% CI 9.7, 15.4%]). Moreover, patients in the FM group reported that when present at work, their work was impaired for around one-half (50.8%) of their working time, in comparison to that reported by the non-FM group, who reported interference of work around one-quarter (22.8%) of their working time (difference of 28.1% [95% CI 23.8, 32.3%]).

Table 3. Patient-reported measures in patients with axial spondyloarthritis according to their meeting or not meeting the 2011 research criteria for FM*

Patient-reported measure	Mean score (95% CI)		Difference (95% CI) in mean score
	Meeting 2011 criteria for FM	Not meeting 2011 criteria for FM	
ASQoL quality of life score	13.1 (12.7, 13.6)	6.1 (5.8, 6.4)	7.1 (6.4, 7.7)
EQ-5D quality of life score	0.45 (0.42, 0.48)	0.76 (0.74, 0.77)	-0.31 (-0.33, -0.28)
HADS depression score	9.4 (8.9, 9.8)	4.6 (4.4, 4.8)	4.8 (4.3, 5.2)
HADS anxiety score	11.0 (10.5, 11.5)	6.4 (6.2, 6.6)	4.7 (4.1, 5.2)
SDS sleep	13.4 (12.7, 14.0)	8.1 (7.8, 8.4)	5.3 (4.5, 6.0)
CFS fatigue	6.8 (6.4, 7.2)	2.8 (2.6, 3.0)	4.0 (3.5, 4.4)

* FM = fibromyalgia; 95% CI = 95% confidence interval; ASQoL = Ankylosing Spondylitis Quality of Life (scale 0–18); EQ-5D = EuroQol 5-domain (scale 0–1 or <1); HADS = Hospital Anxiety and Depression Scale (scale 0–21); SDS = sleep disturbance score (scale 0–20); CFS = Chalder fatigue scale (scale 0–11).

DISCUSSION

This UK national study, the largest to have been conducted to date on the co-occurrence of axial SpA and FM, demonstrated that ~1 in 5 patients with axial SpA met the current research criteria for FM. The proportion who met the FM criteria was not higher among those meeting only the ASAS clinical criteria. Patients who met the FM criteria had considerably worse disease indices, had a significantly greater number of physical and psychological comorbidities, had markedly poorer quality of life (as measured by generic and disease-specific scales), and reported a much greater impact on work than those who did not fulfill the FM criteria. In contrast, there were no differences in measurements of inflammation and no differences in the prevalence of most extraspinal disease manifestations.

This multicenter study involved a relatively unselected patient population from secondary care centers, with recruitment taking place across both specialist and nonspecialist centers. Moreover, this analysis involved data from patients who were naive to treatment with anti-TNF biologic agents, including those who were newly starting on biologic therapy and those who had previously started (although all patients, at the time of recruitment to the register, are naive to biologic therapy). Therefore, the results are likely to represent the prevalence of those who meet FM criteria in a typical secondary care population of axial SpA patients.

The key methodologic issue in the current study is that the 2011 FM research criteria used in this study have not been validated specifically for use in patients with axial SpA. Indeed, neither these criteria nor any other criteria set (nor screening instrument) for FM have been validated for use in patients with any type of inflammatory arthritis. The 2010 preliminary diagnostic criteria for FM (for clinician completion) and the 2011 research criteria for FM (for patient completion) both require that the patient “does not have a disorder that would otherwise explain the pain” (7,8). However, this is challenging for the clinician to determine and almost impossible for the patient to assess, and it is noteworthy that most studies in which the 2010 or 2011 FM research criteria have been implemented have ignored this specific requirement, as we have done in the current study. Nevertheless, applying these criteria can identify patients with significant unmet clinical needs.

In a study by Almodóvar et al (25), conducted in Spain, AS patients with an elevated BASDAI/Bath Ankylosing Spondylitis Radiological Index (BASRI) or elevated BASFI:BASRI ratio had a high probability of having a diagnosis of FM. In the same study, there was

also some evidence that patients with AS and FM (in comparison to those with AS only) responded less well to management strategies such as nonsteroidal antiinflammatory drug therapy. Because of the potential for distortion of the patient-reported measures that influence management decisions (such as the BASDAI, which includes items on both pain and fatigue), it has been hypothesized that some patients with AS and FM may inappropriately receive biologic therapy.

Although patients who met the FM research criteria did not demonstrate any differences in the prevalence of most extraspinal manifestations of the disease, they did have a greater number of swollen and tender joints, which might imply that their disease activity is greater. The only other study, of which we are aware, that has used similar FM criteria (the 2010 preliminary diagnostic criteria for FM, which are the clinician version of the 2011 FM research criteria) evaluated 91 patients with axial SpA in clinics in Germany and showed that 34.1% of the patients met the 2010 criteria for FM (26). In contrast, a much lower proportion of patients (14.3%) met the ACR 1990 classification criteria for FM. A study by Bello et al (27) used the self-administered Fibromyalgia Rapid Screening Tool (FiRST) (28) to screen 196 patients with a clinical diagnosis of SpA who were attending a single tertiary care university hospital in France. They reported a prevalence of FM of 21%. There was no difference in the prevalence of FM between patients satisfying the ASAS imaging criteria and those satisfying the ASAS clinical criteria. Patients with coexisting FM also had higher BASDAI, spinal pain, and BASFI scores. There was no statistically significant difference in the proportion of patients with FM and those without FM receiving anti-TNF therapy. However, patients with FM who received anti-TNF therapy were much less likely to be receiving the same therapy 2 years later (28.1% versus 41.7%; $P = 0.01$).

The European League Against Rheumatism (EULAR) has recently revised its recommendations for the management of FM, and all specific recommendations are now based on either systematic review or meta-analysis (29). However, the EULAR working group noted that there were no trials informing clinicians as to how to treat FM when it occurs in conjunction with an inflammatory arthritis; this was therefore made a priority recommendation for future research. There are effective therapies for FM (albeit most have modest effect sizes), including both nonpharmacologic and pharmacologic approaches. Indeed, there is a consensus, reflected in recommendations produced at both the national and the international level, that nonpharmacologic treatments, principally cognitive behavior therapy and exercise,

should constitute first-line therapy (30). Whether such therapies are as effective in managing FM as a comorbidity alongside best care for an inflammatory condition, and whether long-term outcomes could be improved, remains to be determined.

Even in the absence of validated criteria for FM in patients with inflammatory arthritis, the 2011 FM research criteria identify a group of axial SpA patients who have markedly worse patient-reported disease activity scores, high levels of comorbidity, and clinically important differences in measures of quality of life. For example, the ASQoL score of patients who satisfied the FM criteria (mean 13.1) indicated worse quality of life than the level deemed acceptable by patients (ASQoL score of 8.0) (31). Moreover, according to reference centile charts of the BASDAI, patients who met the criteria for FM had a mean BASDAI score between the 75th and 90th centiles (32). Approximately 4 of 5 patients with axial SpA who met FM criteria had significant fatigue, and although there is some circularity in these observations (for example, fatigue is a single item in the 2011 FM research criteria), it nevertheless emphasizes that the items in the FM criteria set, when taken together, are identifying a group of patients with very significant unmet needs. This is particularly true in relation to work impact, since, among the patients meeting the criteria for FM, they reported ~15% of work time missed and impaired performance during more than one-half of their working time.

In summary, the findings from this study have shown that an important proportion of patients with axial SpA meet current research criteria for FM, but the proportion is no greater among those meeting only the ASAS clinical criteria. Patients meeting the FM research criteria have markedly worse disease indices, and this may therefore represent an unmet and unrecognized need among patients with axial SpA. A recent large-scale survey of a patient group conducted by the UK National Ankylosing Spondylitis Society identified “developing a greater understanding of the impact of dealing with other conditions associated with AS” as one of their top 10 research priorities (33). Future research should validate the use of FM research criteria sets in patients with inflammatory arthritis (including axial SpA) and investigate effective management strategies for patients in whom these rheumatic conditions co-occur.

ACKNOWLEDGMENTS

This work is part of the Fibromyalgia Optimal Management for Patients with Axial Spondyloarthritis (FOMAxS) Study, for which authors Macfarlane, Pathan, Martin,

Haywood, Siebert, Packham, and Atzeni are investigators or collaborators. Other investigators are Euthalia Roussou and Philip Mease. We are grateful to the staff at the BSRBR-AS recruiting centers (details available at <http://www.abdn.ac.uk/iahs/research/epidemiology/spondyloarthritis.php>) and to the BSRBR-AS administration team, which currently comprises Dr. Claudia Zabke, Dr. Elizabeth A. Ferguson-Jones, and Barry Morris, and previously Lindsay Grant, Jo Gibson, Louise Mitchell, Karen Meldrum, and Georgia Mannion-Krase.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Macfarlane had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Macfarlane, Martin, Haywood, Siebert, Atzeni.

Acquisition of data. Macfarlane, Pathan, Siebert, Packham, Jones.

Analysis and interpretation of data. Macfarlane, Barnish, Jones.

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