

Concise report

Similar biologic drug response regardless of radiographic status in axial spondyloarthritis: data from the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis registry

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Abstract

Objective. To describe the baseline characteristics, biologic DMARD (bDMARD) response and drug survival of axial SpA (axSpA) patients in the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS) according to radiographic status.

Methods. The BSRBR-AS is a national prospective cohort including axSpA participants classified according to the Assessment of SpondyloArthritis international Society criteria. In this analysis, baseline data of patients starting bDMARDs were compared. Ankylosing Spondylitis Disease Activity Scores (ASDAS) for low disease status, clinically important improvement (CII) and major improvement (MI) at 1 year were used to assess treatment response. Cox proportional hazards analysis was performed after adjusting for clinically relevant confounders.

Results. A total of 1145 axSpA patients were included. Higher male prevalence, older age and longer disease duration were seen in the radiographic axSpA (r-axSpA) subgroup. Based on a complete case analysis (290 patients), two-thirds of patients achieved an ASDAS low disease state at 1 year regardless of radiographic status [non-radiographic axSpA (nr-axSpA) 64.2% vs r-axSpA 66.1]. No statistically significant differences were seen between the subgroups in attaining ASDAS CII (nr-axSpA 50.7% vs r-axSpA 44.7%) or MI (nr-axSpA 20% vs r-axSpA 18.7%). Drug survival probability curves were similar for both subgroups and the hazard ratio for nr-axSpA/axSpA was 0.94 (95% CI 0.69, 1.28) when adjusted for sex, age, baseline ASDAS with CRP, smoking status, disease duration, HLA-B27 and prescribed biologic.

Conclusions. Although there appeared to be some differences in the baseline characteristics when exploring this cohort according to radiographic status, which are likely related to the natural history of the disease, the level of biologic response and drug survival was comparable between nr-axSpA and r-axSpA.

Key words: ankylosing spondylitis, axial spondyloarthritis, drug survival, biological therapy, epidemiology

Rheumatology key messages

- This is the largest prospective study comparing nr-axSpA and r-axSpA showing similar baseline characteristics.
- Drug response evaluated by ASDAS and drug survival was comparable between nr-axSpA and r-axSpA.
- These results add evidence that similar treatment strategies should be followed in nr-axSpA and r-axSpA.

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Introduction

AS is the established phenotype of axial SpA (axSpA), an inflammatory condition affecting primarily the entheses and axial skeleton, with a usually earlier, more heterogeneous phenotype classified as non-radiographic axSpA (nr-axSpA) [1]. Nr-axSpA has caused much controversy in recent years, with some arguing that it represents an

earlier disease stage that might progress to AS, called radiographic axSpA (r-axSpA), while others believe that it represents a separate entity that should be treated distinctively. Following the introduction of the Assessment of Spondyloarthritis international Society (ASAS) classification criteria [2], the rheumatology community has an increased awareness of the diagnostic issues in axSpA if such criteria are misused, particularly in the non-radiographic patient subgroup. Yet, despite growing evidence that nr-axSpA and r-axSpA show a comparable burden of disease [3], different treatment strategies are still suggested [4].

Biologic DMARDs (bDMARDs) have completely changed the outlook for patients with axSpA, with significant numbers achieving long-term remission or low disease activity over time. There are ample data on the efficacy of TNF inhibitors (TNFis) in nr-axSpA coming from phase III trials [5–8]. However, only a handful of trials (RAPID-axSpA and ESTHER trial) [5, 6] and a post-hoc analysis of the INFAST study looked at the whole axSpA spectrum [9], including patients with both non-radiographic and radiographic disease and showing comparable results across both subgroups. Real-life data are even more scarce, with only a couple of small studies [10, 11] and two larger cohorts, the DANBIO register and the Swiss Clinical Quality Management (SCQM) Cohort [12, 13] published to date.

The British Society for Rheumatology Biologics Registry for Ankylosing Spondylitis (BSRBR-AS) [14] holds a large volume of data comprising both patient subgroups (AS and nr-axSpA), with significant numbers exposed to biologic agents. Based on the hypothesis that both subgroups are part of the same disease continuum and hence have a comparable response to treatment, the aims of this study were to explore the baseline characteristics of the two populations in the BSRBR-AS cohort and to evaluate the level of disease control according to the Ankylosing Spondylitis Disease Activity Score (ASDAS) and the drug survival of the first bDMARD at 1 year.

Methods

Longitudinal data from the prospective BSRBR-AS cohort study were used for this analysis. The BSRBR-AS cohort has been previously described [14]. Briefly, it includes axSpA patients meeting the ASAS criteria or the modified New York criteria for AS from 83 rheumatology centres across the UK recruited between December 2012 and December 2017. To enter the registry, patients with axSpA were required to be biologic naïve and were subsequently included in the ‘biologic cohort’ if starting a bDMARD (comprised only of TNFis at the time, mainly originator adalimumab, etanercept, infliximab or certolizumab pegol) or remained in the ‘non-biologic cohort’ otherwise. Clinical data and patient-reported questionnaires were retrieved at 3, 6 and 12 months and annually thereafter in the biologic cohort.

For this analysis, we included all axSpA patients starting a bDMARD who were categorized in the r-axSpA (participants with documented X-ray evidence of sacroiliitis as per the modified New York criteria in their medical notes) or the nr-axSpA subgroup (no such evidence). The primary outcome of our study was response to bDMARDs at 1 year follow-up defined as 12 months (s.d. 4) from the baseline visit and drug survival of the first initiated bDMARD. Treatment response was assessed with the ASDAS-CRP (calculated using collected CRP values and relevant patient-reported outcomes items). Where CRP was normal or <0.2 mg/dl, the value of 0.2 was used in the formula as recommended by Machado *et al.* [15]. Different scenarios were explored: patients achieving a low disease state (ASDAS <2.1), an ASDAS reduction of ≥ 2.0 [major improvement (MI)] or an ASDAS reduction of ≥ 1.1 [clinically important improvement (CII)]. Analysis was restricted to patients with an ASDAS available at baseline. We performed an additional analysis classifying patients as responders if they achieved an ASDAS low disease state or showed an ASDAS MI or CII. Where the 12 month assessment was missing but individuals remained on a drug, they were considered as responders if they demonstrated a response at 6 months.

Statistical analysis

Baseline characteristics were compared between both subgroups (nr- vs r-axSpA). Student’s *t*- or Mann–Whitney U test for continuous variables and chi-squared test for categorical variables were used. The proportion of patients attaining an ASDAS low disease state, MI or CII were compared when the ASDAS was available for both the baseline and 1 year time point (complete case analysis).

Drug survival was defined as the time from initiation to the end of the first bDMARD (switches to biosimilars were not considered a treatment discontinuation) or to the last available follow-up date (censoring) and were explored using Kaplan–Meier plots and the log-rank test. Cox proportional hazards analysis was performed after adjusting for clinically relevant confounders (sex, age, baseline ASDAS, smoking status, disease duration, HLA-B27 and prescribed biologic) to assess the possible impact of radiographic status on response to bDMARD therapy. The proportional hazards assumption was not violated after analytical and graphical testing. All analysis was conducted using Stata version 16.1 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics were available in 1145 patients (Table 1), of whom 727 (63.5%) had radiographic sacroiliitis and were classified as r-axSpA. Regarding the nr-axSpA population, 90% ($n=378$) had a positive SIJ MRI, as per the standardized ASAS definition, while only 40 patients were classified according to the clinical arm

TABLE 1 Baseline characteristics of patients of the BSRBR-AS cohort according to radiographic status

Variables	Level	nr-axSpA (n = 418)	r-axSpA (n = 727)	P-value
Age, mean (s.d.), years		39.7 (12.3)	46.1 (13.4)	<0.001
Sex, n (%)	Male	239 (57)	529 (73)	<0.001
Symptom duration, mean (s.d.), years		11.3 (10.9)	16.7 (12.9)	<0.001
Diagnostic delay, median (IQR), years		3.0 (1.0–10.0)	3.0 (0.0–11.0)	0.83
HLA-B27 (missing = 325)		227 (73)	387 (76)	0.40
Inflammatory back pain, n (%)		405 (97)	697 (97)	0.40
Uveitis, n (%)		92 (22)	205 (30)	0.003
Crohn's/colitis, n (%)		55 (13)	113 (17)	0.11
Psoriasis, n (%)		79 (19)	115 (17)	0.43
BMI, mean (s.d.)		27.5 (5.6)	28.2 (5.8)	0.10
Comorbidity count, mean (s.d.)		0.6 (0.9)	0.7 (1.0)	0.016
Smoking status, n (%)	Never smoked	148 (43)	218 (38)	0.040
	Ex-smoker	96 (28)	207 (36)	
	Current smoker	100 (29)	154 (27)	
CRP, median (IQR), mg/dL		0.5 (0.1–1.3)	0.9 (0.3–2.5)	<0.001
BASDAI, median (IQR)		6.7 (5.3–7.8)	6.5 (5.0–7.7)	0.12
BASFI, median (IQR)		5.9 (4.2–7.8)	6.5 (4.4–8.3)	0.043
BAS-G, mean (s.d.)		7.0 (2.0)	6.8 (2.0)	0.056
ASDAS-CRP, mean (s.d.)		2.8 (0.8)	2.8 (0.9)	0.32
ASQOL, median (IQR)		13.0 (9.0–16.0)	13.0 (9.0–15.5)	0.29
Concomitant NSAID use, n (%)		311 (75)	560 (77)	0.43
Biologic (to start), n (%)	Adalimumab	238 (57)	436 (60)	0.20
	Etanercept	131 (31)	220 (30)	
	Certolizumab	35 (8)	47 (6)	
	Golimumab	5 (1)	12 (2)	
	Secukinumab	7 (2)	10 (1)	
	Infliximab	2 (<1)	2 (<1)	

ASQOL: Ankylosing Spondylitis Quality of Life questionnaire.

[2]. Compared with nr-axSpA, those with r-axSpA were more likely to be male, older and had longer disease duration. Uveitis was more frequently reported in the r-axSpA population, who also were more likely to be ever-smokers. Baseline BASFI and CRP levels were higher in the r-axSpA subgroup. When exploring comorbidities, these were statistically more frequent in the r-axSpA subgroup, with the main difference seen in the prevalence of hypertension (see [supplementary material 1](#), available at *Rheumatology* online).

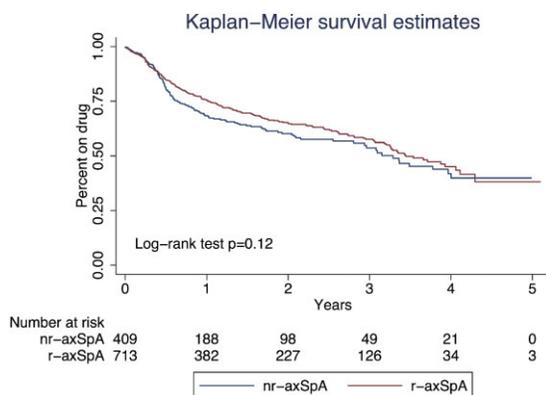
Disease activity and treatment response

Disease activity measures and functional index at baseline and the 1 year time point are presented in [supplementary material 2](#), available at *Rheumatology* online. Follow-up ASDAS was available in only 290 patients, so we explored the baseline characteristics of patients with missing values and found no significant differences in baseline ASDAS-CRP, concomitant NSAID or TNF drug used ([supplementary material 3](#), available at *Rheumatology* online). Of note, patients with missing values were significantly younger and had a shorter disease duration. Overall, two-thirds of the patients with available follow-up ASDAS data achieved a low disease state (ASDAS <2.1) at 1 year regardless of radiographic status [nr-axSpA 64.2% vs r-axSpA 66.1%; difference -1.9% (95% CI -13.7, 9.8)]. Further, no significant differences

were seen between the subgroups in attaining ASDAS CII [nr-axSpA 50.7% vs r-axSpA 44.7%; difference 6.0% (95% CI -7.8, 19.8)] or MI [nr-axSpA 20% vs r-axSpA 18.7%; difference 1.3% (95% CI -9.7, 12.3)]. Additionally, no differences were seen between the r- and nr-axSpA subgroups when patients were classified as responders (ASDAS low disease state, CII or MI) or non-responders [nr-axSpA 76.2% vs r-axSpA 72.6 responders; difference 3.6% (95% CI -5.2, 12.3)].

Drug survival

The median follow-up was 24 months (IQR 12–39). The first bDMARD stop time was available for 1122 patients. A total of 387 patients (33.8%) stopped their first bDMARD due to adverse events (nr-axSpA 34%, r-axSpA 37%) and lack of efficacy (nr-axSpA 35%, r-axSpA 30%) as the most frequent reasons for discontinuation, with no statistically significant differences found between both subgroups. Kaplan–Meier curves were similar for both subgroups (log-rank test $P=0.12$), with a median survival time of 39.5 months (95% CI 33.7, 48.1) in the nr-axSpA subgroup vs 41.4 months (95% CI 38.5, 49.4) in the r-axSpA subgroup ([Fig. 1](#)). In the multivariable analysis, the hazard ratio for nr-axSpA/axSpA was 0.94 (95% CI 0.69, 1.28) when adjusted for sex, age, baseline ASDAS-CRP, smoking status, disease duration, HLA-B27 status and prescribed biologic.

Fig. 1 Kaplan–Meier survival curves of nr-axSpA vs r-axSpA

Interaction terms with gender and HLA-B27 were added into the model and did not show significant differences. When subdividing the nr-axSpA population into those fulfilling the ASAS imaging or clinical criteria, survival curves were similar for the three subgroups ([supplementary material 4](#), available at *Rheumatology* online).

Discussion

Publication of the ASAS classification criteria led to considerable debate over the last decade as to whether both nr-axSpA and r-axSpA should be considered the same entity. Incidentally, the ASAS criteria were never created to separate, but to encompass the whole axSpA continuum, facilitating the identification of homogeneous cohorts in clinical trials. In our analysis of real-world data from a prospective multicentre cohort, baseline demographic and clinical characteristics were broadly similar between nr-axSpA and r-axSpA (AS). Further, the level of bDMARD response according to the ASDAS was comparable at 1 year between subgroups, as was the survival time of the first bDMARD, even in the adjusted multivariable analysis. Baseline characteristics of our cohort were similar to previously published reports, although some particularities are worth mentioning. In our study, HLA-B27 prevalence was similar between nr- and r-axSpA, as shown in the SCQM cohort, while r-axSpA patients from the DANBIO study had a higher prevalence of positive HLA-B27 [12, 13]. There is a rationale to assuming that nr- and r-axSpA have the same genetic background as part of the whole axSpA continuum. The differences with the Danish registry might be explained by the heterogeneity of the included patients, as recruitment started in 2000, predating the publication of the ASAS criteria, which led to the cohort being classified retrospectively for the analysis. In the BSRBR-AS cohort, r-axSpA patients are more frequently male than nr-axSpA patients and this is in line with published literature [3]. In addition, CRP levels and smoking history were different between subgroups and might explain a

higher likelihood of progressing to r-axSpA, as these have been postulated as radiographic progression factors [16]. The higher radiographic damage of r-axSpA might relate to higher BASMI and BASFI scores found in this subgroup as part of the natural history of axSpA. Moreover, comorbidity count was statistically higher in patients with r-axSpA, mainly because of the prevalence of hypertension. Older age and longer disease duration in the r-axSpA subgroup might explain these findings [17].

We centred our analysis on the ASDAS response, as this has been shown to have good discriminatory power in both AS (r-axSpA) and nr-axSpA [18]. Similar to our real-world data, a recent clinical trial including patients with nr-axSpA and r-axSpA treated with certolizumab achieved the same treatment response at week 48 measured by ASDAS [19]. When exploring the available evidence in observational cohorts, the 1 year treatment response as per the ASDAS was higher in the r-axSpA subgroup in the SCQM cohort, although this was not statistically significant [13]. In the DANBIO study, the ASDAS response was similar between both subgroups, although this was evaluated at the 3 and 6 month time points. Differences in drug survival have been explored in a few cohorts [10, 12, 20]. Overall, all reports show similar treatment adherence in nr-axSpA and r-axSpA as outlined in our study. Interestingly, a small retrospective study from Italy did show lower drug survival in nr-axSpA [20] and poorer adherence in patients with nr-axSpA was seen in the DANBIO cohort [12], although this was not confirmed in the multivariate analysis. Most patients were classified as nr-axSpA due to a positive SIJ MRI (ASAS imaging arm), so conclusions on drug survival similarities between the clinical and imaging arms should be interpreted with caution.

To our knowledge, this is the largest prospective cohort study comparing drug response and baseline characteristics between nr-axSpA and r-axSpA. Another strength is the fact that the study inclusion criteria were based on fulfilment of the ASAS classification criteria as opposed to being retrospectively adjudicated, ensuring the homogeneity of the study population. A limitation of our study is mainly the amount of missing data at the 1 year time point. This issue was addressed by analysing excluded patients and finding that there were no differences in baseline disease activity or treatment used. The excluded patients were younger and had a shorter disease duration, suggesting that they were doing well, which might justify why they did not attend follow-up. An additional analysis using a 6 month assessment if they stayed on a bDMARD increased the sample to 407, showing the same proportion of responders. Also, statistical power was adequate (0.89) with this sample size at $\alpha=0.05$ to find a 20% difference between subgroups. In addition, we performed the drug survival analysis with most of the population (1122 patients), confirming the hypothesis that there are no differences between subgroups. Another limitation is the absence of regression analysis comparing the ASDAS response between

subgroups, as this overlapped with a similar study in this cohort looking at predictors of TNFi response in axSpA at the first follow-up (10 weeks–9 months) [21]. In that analysis, disease criteria were not associated with a lack of response, supporting our results. Moreover, it is well known that SIJ assessment has limited reliability, thus misclassification of nr/r-axSpA [22] may have occurred in some cases, although this cannot be confirmed in the absence of CT or MRI of all patients. However, this study reflects real-life practice whereby clinicians have to routinely consider this possibility.

In conclusion, nr-axSpA and r-axSpA present with similar baseline characteristics in a large multicentre cohort and achieve the same level of response to bDMARDs with analogous drug survival. These results support a unique treatment strategy for axSpA and encourage future clinical trial design to encompass the whole spectrum of axSpA rather than address nr-axSpA and r-axSpA as independent diseases.

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Data availability statement

The data underlying this article were provided by the BSRBR-AS register committee. Data will be shared on

request to the corresponding author with permission of the above institution.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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