**Comparison of comorbidities and treatment between ankylosing spondylitis and non-radiographic axial spondyloarthritis in the United States**

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**Abstract**

**Objectives**. To compare comorbidities and biologic DMARD (bDMARD) use between ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) patients, using a large cohort of patients from routine clinical practice in the United States (US).

**Methods**. We performed a cross-sectional study using electronic medical records from two academic hospitals in the US. Data were extracted using automated searches (≥3 ICD codes combined with text-searches) and supplemented with manual chart review. Patients were categorised into AS or nr-axSpA according to classification criteria. Disease features, comorbidities (from a list of 39 chronic conditions) and history of bDMARD prescription were compared using descriptive statistics.

**Results**. Among 965 patients identified, 775 (80%) were classified as having axSpA. The cohort was predominantly male (74%) with a mean age of 52.5 years (SD 16.8). AS patients were significantly older (54 vs 46 years), more frequently male (77% vs 64%) and had higher serum inflammatory markers than those with nr-axSpA (median CRP 3.4 vs 2.2mg/dl). Half of all patients had at least one comorbidity. The mean number of comorbidities was 1.5 (SD 2.2) and similar between AS and nr-axSpA groups. A history of bDMARD-use was seen in 55% of patients with no difference between groups. The most commonly prescribed bDMARDs were adalimumab (31%) and etanercept (29%). Ever-prescriptions of individual bDMARDs were similar between AS and nr-axSpA.

**Conclusion**. Despite age differences, nr-axSpA patients had similar comorbidity burdens as those with AS. Both groups received comparable bDMARD treatment in this US clinic-based cohort.

**Keywords**: ankylosing spondylitis, non-radiographic axial spondyloarthritis, comorbidity, biologic DMARDs, United States

**Key messages**

* Despite their younger age, non-radiographic axSpA patients had similar comorbidity burden as those with AS.
* There were no differences in biologic DMARD use between AS and nr-axSpA in this US cohort.

**Introduction**

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease predominantly affecting the spine. It can be classified into ankylosing spondylitis (AS), where sacroiliac joint damage is evident on plain-film radiographs, or non-radiographic axSpA (nr-axSpA) with no damage on plain-films [1]. They have similar symptom burdens and clinical features, for example disease activity and prevalence of HLA-B27 positivity [2,3]. AS patients differ from their nr-axSpA counterparts in being older, more frequently male and having higher levels of CRP [2,3]. Age and gender are both associated with comorbidities in the general population [4]. Systemic inflammation is also a risk factor for several diseases, including cardiovascular disease [5]. Whether comorbidities differ between nr-axSpA and AS groups has not been examined. Indeed, literature on comorbidities in general are limited for axSpA. Characterising comorbidity burden is important since it is associated with several adverse disease outcomes [6].

Another similarity between AS and nr-axSpA is their response to TNF inhibitors (TNFi) in clinical trials [7,8]. However, no biologic DMARDs (bDMARDs) are currently licenced for nr-axSpA in the United States (US). The Corrona psoriatic arthritis and SpA registry recently reported that bDMARD-use between AS and nr-axSpA patients were similar [9]. These findings have yet to be reproduced using routine clinical data and prescription of individual biologics has not been described. Prescription of some bDMARDs may be directly influenced by the presence of certain comorbidities (e.g. cancer) and indirectly through inability to use NSAIDs (e.g. renal disease). Whether comorbidities are associated with bDMARD prescribing has not been examined.

We compared clinical characteristics, comorbidities and prescribing patterns between AS and nr-axSpA patients in the US, using a large cohort of patients from routine clinical practice.

**Methods**

Study population

We conducted a descriptive study using data from electronic medical records (EMR). The Partners HealthCare EMR is used by two large tertiary care centres, Brigham and Women’s Hospital and Massachusetts General Hospital. These hospitals provide care for approximately 4.6 million patients in the Greater Boston area, Massachusetts. Both hospitals have been using EMRs for at least two decades. We searched for and extracted records from the earliest available date through August 2018. Preliminary searches using published criteria [10] performed poorly in our EMR; therefore, we combined the use of ICD codes with a simple text-search of radiology reports. The search criteria were ≥3 ICD-9 or 10 codes for AS (720.x or M45.x) and string-text mention of “sacroiliitis”, “ankylosis” or “syndesmophyte” (whether present or absent) in radiology reports, including plain X-rays, MRIs or CT scans. No codes exist for axSpA in ICD-9 or 10. Each patient’s clinical records were manually reviewed. For variables that required an index date, it was defined as the date of the latest clinical record for each patient. The Partners HealthCare Institutional Review Board approved all aspects of this study.

Disease definition

Patients with a clinical diagnosis of AS were classified for this study as AS if they fulfilled the modified New York criteria [11], and as nr-axSpA if they fulfilled the Assessment of Spondyloarthritis international Society (ASAS) imaging or clinical criteria for axSpA [12] but not the modified New York criteria. Since this was primarily a clinical rather than research cohort, investigations required for classification might be omitted when patients attend with a previously established diagnosis. We categorised patients with incomplete data for classification criteria as “Probable” AS if they had imaging pathology consistent with AS (e.g. ankylosis of the vertebrae or sacroiliac joint fusion) on plain-film radiographs, CT or MRI; patients with less definitive changes on CT/MRI (e.g. sacroiliac joint sclerosis/irregularity) were categorised as “Probable” nr-axSpA. Both Definite and Probable cases of AS and nr-axSpA were included in the primary analyses. Patients with a clinical diagnosis of AS upon manual medical record review but no supportive evidence from radiology reports or medical notes, and those with ICD codes but no formal clinical diagnosis of axSpA, were excluded. A flow-chart of the classification process is shown in Supplementary figure 1.

Patient characteristics, comorbidity and medications

We recorded historical presence of the following SpA features through manual chart review: uveitis, psoriasis, inflammatory bowel disease (IBD), peripheral arthritis, enthesitis, dactylitis, HLA-B27 status and family history (of AS, psoriasis, uveitis, reactive arthritis or IBD) [12].

Codified EMR data was extracted from within one year prior to the index date including: age, sex, body mass index (BMI), smoking status, comorbidities, pain visual analogue scale (VAS), ESR and CRP. For comorbidities, a list of 39 chronic conditions adapted from the Radner multimorbidity index [13] were identified using ICD-9 and 10 codes within one year prior to the index date.

Medication history was obtained using codified EMR medication lists for ever-use of bDMARDs (infliximab, adalimumab, etanercept, golimumab, certolizumab pegol, secukinumab, ustekinumab), conventional synthetic DMARDs (csDMARDs: sulfasalazine, methotrexate, leflunomide), NSAIDs (ibuprofen, naproxen, celecoxib, diclofenac, indomethacin, meloxicam) and prednisone. Etoricoxib is not licensed in the US [14].

Statistical analyses

The above described variables were compared according to diagnosis, AS vs nr-axSpA, using Student’s t- or Mann-Whitney U tests for continuous variables and Chi-squared or Fisher’s exact test for categorical variables. To examine associations between comorbidities and bDMARD-prescription, we used age-adjusted logistic regression models with ever-prescription of bDMARD as the dependent variable and each comorbidity in turn as the independent variable. This model was repeated using the number of comorbidities as the independent variable. Sensitivity analyses were conducted using only definite AS and nr-axSpA cases. All analyses were performed using Stata version 13.

**Results**

Among 965 patients who fulfilled the initial inclusion criteria from the Partners’ EMR, 775 patients (80%) were classified as axSpA and the remainder were excluded. 641 (83%) patients were classified as AS (553 definite, 88 probable) and 134 (17%) as nr-axSpA (93 definite, 41 probable). The cohort was predominantly male (74%) with a mean age of 52.5 years (SD 16.8). HLA-B27 was tested in 58% of patients and among them 80% were positive. 91% of index-date-records for each patient were from 2012 to 2018, 63% from 2018.

Patient characteristics according to diagnosis are shown in Table 1. AS patients were significantly older (54 vs 46 years) and more frequently male (77% vs 64%). HLA-B27 was more frequently tested in nr-axSpA patients, although the proportion of positive results were similar between the two groups. There were no differences in extra-axial manifestations except psoriasis, which was more frequently recorded in AS patients (13% vs 6%, P=0.035). AS patients also had higher median ESR (13.0 vs 9.5mm/hr) and CRP (3.4 vs 2.2mg/dl) levels, but pain VAS was similar to the nr-axSpA group.

Half of all patients had at least one comorbidity (histogram in Supplementary figure 2). The mean number of comorbidities in this cohort was 1.5 (SD 2.2), and similar between AS and nr-axSpA groups. The common comorbidities were anxiety (11%), coronary heart disease (11%), cancer (11%), hypertension (9%), depression (8%) and diabetes (7%). There were no differences in prevalence of the 39 chronic conditions between the two diagnoses, except chronic kidney disease which was higher in AS patients (3% vs 0%) (Supplementary table 1).

A history of bDMARD-use was seen in 55% of all patients, csDMARDs in 25%, NSAIDs in 76%, and prednisone in 35% of patients. The most commonly prescribed bDMARDs were adalimumab (31%) and etanercept (29%). Ever-prescriptions of each bDMARD was similar between AS and nr-axSpA groups (Table 2). The most commonly prescribed csDMARDs were sulfasalazine (13%) and methotrexate (16%). NSAID prescription was also similar between the two groups, except meloxicam which was more frequently prescribed in patients with nr-axSpA.

We did not find any evidence that the number of comorbidities, or the presence of individual comorbidities, were associated with bDMARD-use (supplementary table 2).

Sensitivity analysis comparing only those with definite diagnoses of AS and nr-axSpA did not significantly change results (see supplementary tables 3 and 4).

**Discussion**

In this large US cohort of patients with axSpA, previously reported differences in characteristics between AS and nr-axSpA were confirmed: AS patients were more frequently male and had higher levels of inflammatory markers. Despite their younger age, nr-axSpA patients had similar comorbidity burdens as those with AS. We also found that AS and nr-axSpA patients received comparable treatment using bDMARDs, and that bDMARD-use was not associated with comorbidities.

This study contributes one of the most detailed descriptions of comorbidities in axSpA. The high comorbidity burden, even among younger nr-axSpA patients, highlights the importance of identifying and managing co-existing conditions in these patients. We found no significant differences in prevalence of individual morbidities between the two groups except CKD which was present in 3% of AS but none of nr-axSpA patients. This may be related to the age difference or longer use of NSAIDs, but should not be over-interpreted in the context of multiple comparisons.

The mean number of comorbidities in our axSpA cohort was similar to the 1.6 conditions reported among rheumatoid arthritis patients, using the same index in the Brigham and Women’s Hospital Rheumatoid Arthritis Sequential Study (BRASS) cohort [13]. The BRASS cohort was older (mean age 58 years) than this axSpA group (mean age 53 years). Notably, axSpA subjects had a higher prevalence of anxiety (11% vs 4%); this adds to an increasing body of literature highlighting the importance of mental health in these patients [15]. The age of our cohort may also explain the higher prevalence of uveitis at 26% (the risk of which increases with disease duration [16]) than reported in the Corrona SpA registry at 17%. We found a much lower prevalence of enthesitis than Corrona (4% vs 33%), which likely reflects more systematic screening and reporting in research registries than routine clinical practice. There was no difference in the prevalence of enthesitis between AS and nr-axSpA groups, which is consistent with existing literature [2,3]. The difference in prevalence of psoriasis from chart review (13% in AS and 6% in nr-axSpA) was unexpected and may be an issue of documentation; there was no difference in psoriasis prevalence based on ICD codes (data not shown).

Consistent with prior studies from the US and Europe, we found no differences in the prevalence of HLA-B27 positivity between AS and nr-axSpA groups, but higher inflammatory markers and proportion of males in AS. These results support the hypothesis that both diagnoses belong to the same disease spectrum, and that males and those with higher inflammatory markers are more likely to progress to radiographic damage [17]. Although we had limited data on disease severity measures, our finding that symptom burden (i.e., pain) was similar between the diagnoses is consistent with more detailed outcome measures from the Corrona SpA registry, where the two groups had similar disease activity, functional impairment and quality of life [9]. These results are supportive of guidelines that recommend a unified treatment approach for all axSpA patients [18].

Our results confirm those from the Corrona SpA registry that bDMARDs are widely used for nr-axSpA in clinical practice. This is consistent with the ACR/SAA/SPARTAN treatment recommendations for AS and ax-SpA [19] even though bDMARDs are not yet licensed (in 2018) for this indication in the US. Clinicians are likely relying on a clinical diagnosis rather than classification criteria for making treatment decisions. The proportions of patients prescribed bDMARDs and csDMARDs were similar to that reported in Corrona.

Identifying cases from historical EMR data is challenging in the context of evolving terminology and classification criteria. There are no ICD-9 or -10 codes for axSpA, and using ICD code alone to classify AS has limited accuracy [10]. The high positive predictive value (80%) of our search strategy likely came at the cost of reduced sensitivity, in particular for the detection of nr-axSpA cases. Requiring three or more ICD codes and radiological keywords may have selected individuals with more advanced disease, which may explain the older age of our cohort. Nevertheless, our ratio of AS:nr-axSpA cases was similar to that of the Corrona SpA registry. Automated phenotyping, employing natural language processing [20], of axSpA in EMR data is an area that needs further research to take full advantage of these large cohorts.

A key strength of this study is the large number of patients from routine clinical practice of two academic hospitals. However, there were limitations. In the US, patients can, and do, change their hospitals and care-providers such that diagnoses are often made at prior institutions and by different providers; therefore, data were not consistently available for variables such as disease or symptom duration. Since this was not a research cohort, disease severity measures were not systematically collected to allow comparison. Treatment decisions in the US are made by the provider together with the patient; insurance companies do not require documentation of BASDAI in order to prescribe biologics. The pain data available to us was consistent with more detailed outcome measures from the Corrona SpA registry.

Using ICD codes to derive comorbidities may have limited accuracy for some diseases and may explain the low prevalence of hypertension in our study [21]; any inaccuracies are likely to be the same for both AS and nr-axSpA groups and would not result in directional bias. Codified EMR medication data could not be used to determine current-use of individual drugs. Furthermore, NSAIDs may be bought over the counter, and infliximab can be prescribed on infusion charts and not coded. It is also possible for patients to consult and receive treatment from rheumatologists outside of Partners HealthCare, which would not be coded. The proportion of patients who had ever used prednisone was high. This could be due to several reasons: short courses prescribed for symptom flares would be counted; our data extended back to a time when other treatment options were limited; we did not have data to distinguish prednisone prescribed for other co-existing conditions. We also did not have data on cumulative NSAID exposure as they are widely available over-the-counter in the US. While the comorbidities consequent of glucocorticoids and NSAIDs are well recognised, how they affect the number and type of comorbidities in axSpA would be an interesting area for future study, but one that we cannot adequately study in the current dataset.

In conclusion, nr-axSpA patients had similar comorbidity burdens as those with AS. These findings highlight the importance of identifying and managing comorbidities in these patients and support a unified management approach for the full spectrum of axSpA. In this large US cohort, AS and nr-axSpA patients received comparable bDMARD treatment.

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| Table 1. Characteristics of 775 axSpA patients, compared according to diagnosis. |
|  | Ankylosing spondylitis (n=641) | Non-radiographic axial spondyloarthritis (n=134) | P-value |
| Age, years | 53.8 (16.6) | 46.3 (16.5) | <0.001 |
| Male | 490 (77%) | 85 (64%) | 0.002 |
| BMI (kg/m2) | 28.0 (6.2) | 28.0 (5.9) | 0.950 |
| Smoking | 71 (11%) | 17 (13%) | 0.590 |
| HLA-B27 tested | 359 (56%) | 88 (66%) | 0.039 |
| HLA-B27 positive | 287 (80%) | 69 (78%) | 0.750 |
| Family history\* | 81 (13%) | 22 (17%) | 0.170 |
| Uveitis | 165 (26%) | 36 (29%) | 0.570 |
| Psoriasis | 82 (13%) | 8 (6%) | 0.035 |
| IBD | 70 (11%) | 10 (8%) | 0.290 |
| Peripheral arthritis | 114 (18%) | 22 (17%) | 0.870 |
| Enthesitis | 24 (4%) | 7 (6%) | 0.360 |
| Dactylitis | 16 (3%) | 1 (1%) | 0.230 |
| ESR tested | 255 (40%) | 50 (37%) | 0.590 |
| ESR result (mm/hr) median (IQR) | 13.0 (6.0 to 27.0) | 9.5 (5.0 to 21.0) | 0.042 |
| CRP tested | 323 (50%) | 63 (47%) | 0.480 |
| CRP result (mg/dl), median (IQR) | 3.4 (1.2 to 11.0) | 2.2 (0.7 to 5.3) | 0.007 |
| Pain VAS available | 227 (35%) | 53 (40%) | 0.360 |
| Pain VAS | 2.2 (3.0) | 3.0 (3.3) | 0.120 |
| Comorbidity count\*\*, mean (SD) | 1.5 (2.2) | 1.3 (2.2) | 0.290 |
| Data collected at the latest clinical visit (the index date) for each patient and are shown as mean (SD) and n (%) unless otherwise specified. ESR, CRP and pain VAS within one year prior to the index date were included.BMI, body mass index; VAS, visual analogue scale; IQR, interquartile range; SD, standard deviation; IBD, inflammatory bowel disease.\*family history of axial spondyloarthritis, psoriasis, uveitis, reactive arthritis or IBD.\*\*number of comorbidities among a list of 39 chronic conditions |

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| Table 2. Comparing medications used in 775 axSpA patients according to diagnosis.  |
|  | Ankylosing spondylitis (n=641) | Non-radiographic axial spondyloarthritis (n=134) | P-value |
| bDMARDs | 353 (55%) | 70 (52%) | 0.550 |
| Adalimumab | 205 (32%) | 39 (29%) | 0.510 |
| Etanercept | 190 (30%) | 36 (27%) | 0.520 |
| Infliximab | 85 (13%) | 17 (13%) | 0.860 |
| Golimumab | 26 (4%) | 7 (5%) | 0.540 |
| Certolizumab pegol | 20 (3%) | 3 (2%) | 0.782 |
| Secukinumab | 21 (3%) | 4 (3%) | 1.000 |
| Ustekinumab | 12 (2%) | 0 | 0.238 |
| csDMARDs | 158 (25%) | 35 (26%) | 0.720 |
| Sulfasalazine | 81 (13%) | 18 (13%) | 0.800 |
| Methotrexate | 101 (16%) | 23 (17%) | 0.690 |
| Leflunomide | 4 (1%) | 3 (2%) | 0.104 |
| NSAIDs | 480 (75%) | 106 (79%) | 0.300 |
| Ibuprofen | 234 (37%) | 61 (46%) | 0.051 |
| Naproxen | 204 (32%) | 49 (37%) | 0.290 |
| Indomethacin | 157 (24%) | 28 (21%) | 0.370 |
| Celecoxib | 116 (18%) | 19 (14%) | 0.280 |
| Diclofenac | 86 (13%) | 23 (17%) | 0.260 |
| Meloxicam | 58 (9%) | 20 (15%) | 0.040 |
| Prednisone | 223 (35%) | 51 (38%) | 0.470 |
| bDMARD, biologic disease modifying anti-rheumatic drugs; csDMARD, conventional synthetic DMARD; NSAID, non-steroidal anti-inflammatory drugs. |