Ankylosing Spondylitis versus Nonradiographic Axial Spondyloarthritis: Comparison of Tumor Necrosis Factor Inhibitor Effectiveness and Effect of HLA-B27 Status. An Observational Cohort Study from the Nationwide DANBIO Registry

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ABSTRACT. ***Objective.*** To compare baseline disease activity and treatment effectiveness in biologic-naive patients with nonradiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS) who initiate tumor necrosis factor inhibitor (TNFi) treatment and to study the role of potential confounders (e.g., HLA-B27 status).

Methods. Observational cohort study based on prospectively registered data in the nationwide DANBIO registry. We used Kaplan-Meier plots, Cox, and logistic regression analyses to study the effect of diagnosis (nr-axSpA vs AS) and potential confounders (sex/age/start yr/HLA-B27/disease duration/TNFi-type/smoking/baseline disease activity) on TNFi adherence and response [e.g., Bath Ankylosing Spondylitis Activity Index (BASDAI) 50%/20 mm].

Results. The study included 1250 TNFi-naive patients with axSpA (29% nr-axSpA, 50% AS, 21% lacked radiographs of sacroiliac joints). Patients with nr-axSpA were more frequently women (50%/27%) and HLA-B27–negative (85/338 = 25%), compared to AS (81/476 = 17%; $p < 0.01$). At TNFi start patients with nr-axSpA had higher visual analog scale scores [median (quartiles)] for pain: 72 mm (55–84)/65 mm (48–77); global: 76 mm (62–88)/68 mm (50–80); fatigue: 74 mm (55–85)/67 mm (50–80); and BASDAI: 64 (54–77)/59 (46–71); all $p < 0.01$. However, patients with nr-axSpA had lower C-reactive protein: 7 mg/l (3–17)/11 mg/l (5–22); and BAS Metrology Index: 20 (10–40)/40 (20–50); all $p < 0.01$. Median (95% CI) treatment adherence was poorer in nr-axSpA than in AS: 1.59 years (1.15–2.02) versus 3.67 years (2.86–4.49), $p < 0.0001$; but only in univariate and not confounder-adjusted analyses ($p > 0.05$). Response rates were similar in AS and nr-axSpA ($p > 0.05$). HLA-B27 negativity was associated with poorer treatment adherence [HLA-B27 negative/positive, nr-axSpA: HR 1.74 (1.29–2.36), AS: HR 2.04 (1.53–2.71), both $p < 0.0001$]; and lower response rates (nr-axSpA: 18/61 = 30% vs 93/168 = 55%; AS: 17/59 = 29% vs 157/291 = 54%, both $p < 0.05$).

Conclusion. In this nationwide cohort, patients with nr-axSpA had higher subjective disease activity at start of first TNFi treatment, but similar outcomes to patients with AS after confounder adjustment. HLA-B27 positivity was associated with better outcomes irrespective of axSpA subdiagnosis. (J Rheumatol First Release December 1 2016; doi:10.3899/jrheum.160958)

Key Indexing Terms:
AXIAL SPONDYLOARTHRITIS
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The disease spectrum of axial spondyloarthritis (axSpA) includes patients with radiographic axSpA (ankylosing spondylitis, AS), who fulfill the modified New York criteria, and patients with nonradiographic axSpA (nr-axSpA)[1,2,3].

Since the introduction of the Assessment of Spondyloarthritis international Society (ASAS) classification criteria aiming to identify patients with axSpA at earlier disease stages, it has been discussed how patients with nr-axSpA differ from patients with AS[4,5]. Only a minority of patients with nr-axSpA develops radiographic changes and AS within 10 years of followup[6,7]. Further, patients with nr-axSpA are more frequently women with a lower grade of spinal inflammation on spinal and sacroiliac magnetic resonance imaging (MRI)[8,9], and other studies have demonstrated similar levels of pain and disability among patients with nr-axSpA and AS[9,10,11].

The beneficial effect of tumor necrosis factor inhibitors (TNFi) on treatment outcomes is well established in AS[10,12,13]. In nr-axSpA, the effect of TNFi seems to depend on objective signs of inflammation, e.g., increased C-reactive protein (CRP) level and/or active inflammation on MRI[5,14,15,16,17].

Few previous observational studies have compared TNFi treatment outcomes among patients with nr-axSpA versus AS[9,18,19]. These studies included < 100 patients with nr-axSpA[18,19], were not nationwide[18,19], did not include data on longterm outcomes or treatment duration[9], reported results only from univariate analyses[19], or did not include in multivariate analyses data on relevant potential confounders, e.g., HLA-B27 status, smoking status, or year of starting TNFi[9,18].

The primary aim of our present study was to compare baseline disease activity and treatment effectiveness by univariate and confounder-adjusted analyses in a large cohort of biologic-naive patients with AS versus nr-axSpA, who initiated TNFi treatment in clinical practice. Secondarily, our aim was to explore the effect of potential confounders, e.g., HLA-B27 status and CRP.

MATERIALS AND METHODS

The DANBIO quality registry was initiated in 2000 and covers > 90% of Danish adults with rheumatic diseases treated in routine care with biologic disease-modifying antirheumatic drugs (DMARD)[20]. In accordance with national treatment guidelines and quality indicators, patients are monitored prospectively by online registrations (www.danbio-online.dk) of disease activity and outcomes at least biannually and when medication is changed[20,21]. According to Danish legislation, registration and publication of data from clinical registries do not require patient consent or approval by ethics committees.

Baseline demographics include smoking habits, age, sex, body mass index, disease duration, and current treatment with conventional synthetic DMARD. Disease activity and functional status are monitored by serum CRP level (normal range ≤ 10 mg/l); visual analog scales (VAS) for patient's global assessment (PtGA), pain, fatigue, and physician's global assessment (PGA); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Bath Ankylosing Spondylitis Function Index (BASFI); and Bath Ankylosing Spondylitis Metrology Index (BASMI). Registration of classification criteria (ASAS classification criteria, modified New York criteria) is optional and only available in a subset of patients.

All TNFi-naive patients were identified in DANBIO if they had initiated treatment with a biological drug between January 1 2005, and July 1, 2014, and had one of the International Classification of Diseases–10 diagnoses of AS (M45.9), sacroiliitis (M46.1), or inflammatory spondylopathy (M46.8, M46.9). All Danish departments of rheumatology were invited to participate in the study and to enter data regarding which classification criteria individual patients fulfilled upon start of their first biological drug. The additional data were collected from patient files [laboratory results (CRP, HLA-B27), patient history, objective examinations] and radiographic data. No second reading of radiographs or MRI was performed and no additional prospective laboratory testing or examinations were made. Thus, patients were classified as having axSpA if they fulfilled the ASAS criteria upon TNFi start[2]. According to available radiology descriptions of radiographs of the sacroiliac (SI) joints (sacroiliitis grade, uni- or bilaterally)[3], patients were classified as having AS or nr-axSpA. Patients with no available SI joint radiographs at treatment start were classified as "unspecified axSpA" (Figure 1).

Treatment adherence. Treatment adherence was calculated as the number of days each patient maintained treatment. Start date was the date of the first given dose and stop date was the date of the first missed dose. Temporary treatment interruptions (e.g., infections, surgery) of ≤ 3 months were allowed. All observations were censored by August 15, 2015.

Reasons for drug discontinuation are registered in DANBIO in prespec-

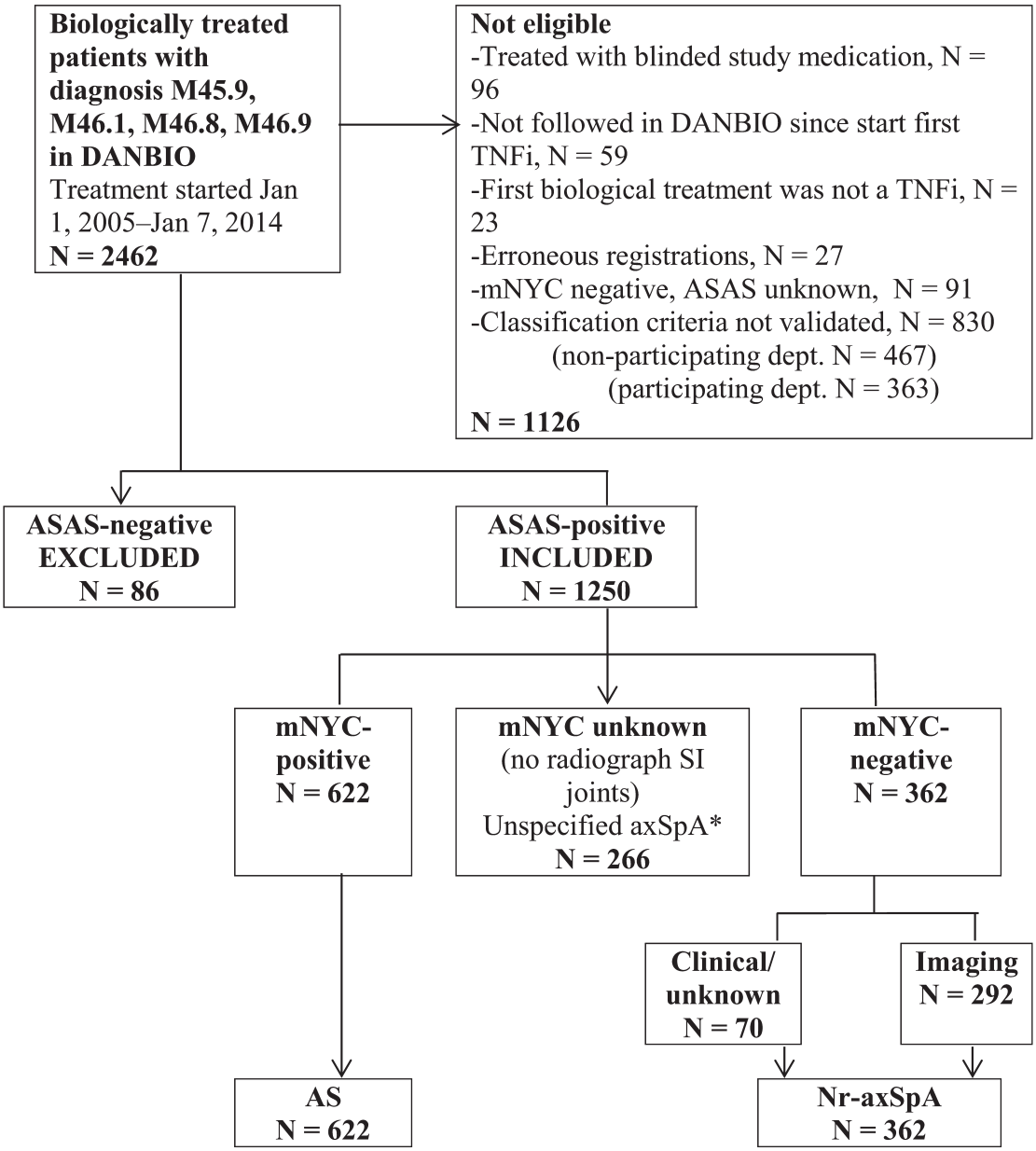

Figure 1. Patient disposition, inclusion and exclusion. * 238/266 patients (89%) with unspecified axSpA had inflammation on magnetic resonance images of the SI joints. DANBIO: DANBIO registry of rheumatic diseases; TNFi: tumor necrosis factor inhibitor; mNYC: modified New York criteria; ASAS: Assessment of Spondyloarthritis international Society; SI: sacroiliac; axSpA: axial spondyloarthritis; AS: ankylosing spondylitis; nr-axSpA: nonradiographic axSpA.

ified categories: lack of effect, adverse events, disease remission, pregnancy, surgery, cancer, death, infection, loss to followup, and other reasons. In our study, reasons for discontinuation were categorized into adverse events (including infection, death, or cancer), lack of effect, and other (pregnancy, surgery, loss to followup, remission, other, several reasons for discontinuation).

Treatment response. Disease activity was evaluated at baseline and after 3 and 6 months of therapy. The baseline visit was defined as a visit within the time frame that ranged from 60 days before until 6 days after initiation of TNFi treatment. For the 3-month visit, the time frame was between 10 and 17 weeks, and for the 6-month visit, 18–32 weeks after treatment start. If more than 1 registration occurred within a given time frame for an individual patient, the registration closest to the given timepoint was selected for analysis. If a patient had no registrations within a given time window, data were registered as missing for that visit. Clinical and laboratory outcome measures included BASDAI, BASFI, BASMI, PtGA, fatigue, pain, PGA, and CRP.

Clinical response was defined as achievement of either a 50% or a 20-mm reduction in BASDAI (BASDAI 50%/20-mm response)[22,23]. Arbitrarily, we classified patients as responders if they achieved clinical response (yes/no) at both the 3- and 6-month visits compared with baseline. In the case of missing data at either of those visits, 1 registration of clinical response was sufficient to classify the patient as a responder. Patients who stopped treatment within the first 3 months of therapy were considered nonresponders (n = 74). Response rates were calculated as the proportion of

patients who achieved BASDAI 50%/20-mm response. As secondary outcomes, ASAS response criteria for 40% improvement in disease activity (ASAS 40) and ASAS criteria for partial remission were calculated[23,24].

Since November 2010, the ASAS Disease Activity Score (ASDAS) has been registered in DANBIO. Among patients with available data, we calculated the proportion of patients who achieved inactive disease (ASDAS < 1.3) at the 3- or 6-month visit (similar to the algorithm described for BASDAI 50%/20 mm response). Similarly, the proportion of patients with clinically important improvement in ASDAS (change of ≥ 1.1 between baseline and 3- or 6-month visit) was calculated[25].

Statistics. Statistical analyses were performed by SPSS (version 20.0, SPSS Inc.). Demographic and descriptive data are presented by medians [interquartile ranges (IQR)]. Groups were compared by nonparametric tests (chi-square, Kruskal-Wallis, and Mann-Whitney U tests). P values < 0.05 were considered statistically significant.

Kaplan-Meier plots and log rank tests were performed for analyses of treatment adherence stratified by diagnosis (nr-axSpA/AS/unspecified axSpA). We performed univariate and multivariate Cox regression analyses to study the effect of diagnosis on treatment adherence and calculated HR for treatment discontinuation. The following baseline factors were included as potential confounders *a priori*: age, sex, disease duration (since diagnosis of axSpA), calendar year of starting TNFi (2005–2008/2009–2011/2012–2014), TNFi drug [adalimumab/etanercept/infliximab (IFX)/golimumab/certolizumab pegol], methotrexate use (yes/no), HLA-B27 status (positive/ negative), CRP (≤ 10 mg/l/> 10 mg/l), smoking status (current/previous/never), BASDAI, and BASMI. Because PtGA, fatigue, pain and BASFI strongly correlated with BASDAI (Spearman's ρ = 0.69–0.73, p < 0.01), only BASDAI was included. The variables that by univariate analysis gained p < 0.1 were included in the multivariate model and stepwise backward selection was conducted, leaving only statistically significant variables in the model. Age, sex, and the interaction terms HLA-B27*sex and diagnosis*sex remained in the model irrespective of p value.

Response rates were reported by percentages. The numbers needed to treat (NNT) to achieve response were calculated as the reciprocal values of the response rates.

All primary analyses were based on observed data without imputation of missing data. For the multivariate analysis, the following sensitivity analyses were performed: (1) multiple imputation of missing data (SPSS, 5 imputation steps)[26]; (2) exclusion of patients with nr-axSpA diagnosed according to the clinical arm of the classification criteria (n = 70; Figure 1); and (3) classification of all patients with unspecified axSpA as either AS or nr-axSpA.

RESULTS

Study population. Among 2462 biologic-naive patients with axSpA registered in DANBIO with a relevant diagnosis who initiated TNFi treatment between January 1, 2005, and July 1, 2014 (Figure 1), the diagnosis was validated retrospectively in 1336. Most of the patients who did not have the diagnosis validated came from departments that did not participate in the study. A total of 1250 patients (93%) fulfilled the ASAS criteria for axSpA and were included (Figure 1). Of these, 622 patients fulfilled the classification criteria for AS, 362 for nr-axSpA, and 266 patients had unspecified axSpA. Withdrawal analysis showed that the included and excluded patients had similar sex and age distribution (p > 0.05, not shown).

Characteristics at baseline. Patients with AS had longer disease duration, were older, more frequently men, and HLA-B27–positive compared to patients with nr-axSpA, and they more frequently had a history of uveitis but less frequently of dactylitis (Table 1). Patients with AS more often started treatment before 2008 and were more frequently treated with IFX, had higher CRP and BASMI but lower global, fatigue, and pain scores and lower BASDAI compared to patients with nr-axSpA (Table 1). Patients with unspecified axSpA more frequently started treatment after 2008 compared to patients with AS or nr-axSpA, and fewer were HLA-B27–positive (both p < 0.05).

Treatment adherence, AS versus nr-axSpA. The cumulated followup time was 3359 patient-years (median followup time: 2.5 yrs; 95% CI 2.01–3.00). Patients with nr-axSpA had poorer treatment adherence than patients with AS [median treatment duration, AS: 3.67 (2.86–4.49), nr-axSpA: 1.59 (1.15–2.02); p < 0.0001]. However, this was found only in univariate (Figure 2A) but not in multivariate analysis (Table 2). Men had longer treatment adherence than women in both AS and nr-axSpA (not shown). The treatment adherence was similar among patients with nr-axSpA who fulfilled the imaging classification criteria versus the clinical criteria [1.59 yrs (1.16–2.01) vs 1.33 yrs (0.0–3.27), p = 0.5].

Patients with nr-axSpA more often stopped treatment because of lack of effect compared to AS (Supplementary Table 1, available with the online version of this article).

Response rates, AS versus nr-axSpA. Changes in disease activity at the 3-month followup were similar among patients with nr-axSpA and AS for most scores but not for BASMI (Supplementary Table 2, available with the online version of this article). Treatment responses were similar among patients with AS and nr-axSpA (Figure 3A).

Treatment adherence and response rates, effect of HLA-B27. HLA-B27–positive patients stayed on treatment longer than HLA-B27–negative patients (Table 2). The same was true when stratified according to axSpA subgroup (univariate comparisons; log rank, Mantel-Cox test, both p < 0.0001; Figure 2B). Similar results were found in the sensitivity analyses.

HLA-B27–positive patients, regardless of diagnosis, had significantly higher response rates compared to HLA-B27–negative patients (Figure 3B). NNT to achieve BASDAI 50%/20 mm response was 2 for patients with AS who were HLA-B27–positive versus NNT = 4 for patients with AS who were HLA-B27–negative; similar values were found in nr-axSpA.

Treatment adherence and response rates, effect of increased CRP at baseline. At baseline, 51% (238/469) of patients with AS and 39% (113/290) of patients with nr-axSpA had increased CRP (> 10 mg/l). Treatment adherence lasted longer among patients with increased CRP (Table 2), but mainly in AS (Supplementary Figure, available online at jrheum.org). In contrast, BASDAI 50%/20 mm response rates were higher among patients with CRP > 10 mg/l in both AS and nr-axSpA [AS: 58% (118/204) vs 39% (76/196); nr-axSpA: 60% (52/87) vs 41% (55/134), both p < 0.005].

Table 1. Baseline demographics according to classification criteria at baseline (start of the first TNFi treatment course) for nr-axSpA, AS, and unspecified axSpA. Data are medians (interquartile ranges) unless otherwise stated.

	No. Pts. with Available Data, n	All Pts.	Nr-axSpA	AS	Unspecified AxSpA[#]	p*
N		1250	362	622	266	
Age, yrs	1250	40 (31–49)	38 (30–46)	42 (33–52)	38 (29–46)	< 0.001
Male, n (%)	1250	792 (63)	183 (51)	455 (73)	154 (58)	< 0.0001
HLA-B27–positive, n (%)	1045	811 (65)	253 (70)	395 (83)	163 (61)	0.005
BMI, kg/cm^2	728	25 (23–29)	25 (22–30)	26 (23–29)	24 (23–28)	0.4
MTX, yes, n (%)	1250	222 (18)	59 (16)	129 (21)	34 (13)	0.09
Manifestations ever, n (%)						
Inflammatory back pain	1177	1131 (91)	326 (90)	562 (90)	243 (91)	0.07
Family disposition	885	199 (16)	67 (19)	98 (16)	34 (13)	0.9
Peripheral arthritis	1119	441 (35)	146 (40)	190 (31)	105 (39)	0.05
Enthesitis	909	218 (17)	72 (20)	95 (15)	51 (19)	0.5
Uveitis	1042	249 (20)	67 (19)	145 (23)	37 (14)	0.02
Psoriasis	1018	75 (6)	31 (9)	35 (6)	9 (3)	0.2
Dactylitis	871	40 (3)	21 (6)	9 (1)	10 (4)	< 0.0001
IBD	1031	104 (8)	31 (9)	42 (7)	31 (12)	0.5
NSAID response	876	614 (49)	179 (49)	310 (49)	125 (47)	0.9
Elevated CRP	1093	575 (46)	164 (45)	307 (49)	104 (39)	0.003
Symptom duration, yrs	1040	9 (3–18)	6 (3–13)	13 (6–23)	5 (2–11)	< 0.0001
Disease duration, yrs	1155	1 (0–6)	1 (0–3)	3 (1–12)	1 (0–3)	< 0.0001
Smoking status, n (%)	976					
Current		377(30)	97 (27)	216 (41)	64 (24)	
Previous		177 (14)	42 (12)	103 (20)	32 (12)	0.2
Never		422 (33)	119 (33)	204 (39)	99 (37)	
First TNFi drug, n (%)	1250					
Adalimumab		519 (41)	151 (42)	258 (41)	110 (41)	< 0.0001
Certolizumab pegol		8 (1)	5 (1)	2 (0)	1 (0)	
Etanercept		183 (15)	53 (14)	100 (16)	30 (11)	
Golimumab		246 (20)	85 (23)	88 (14)	73 (27)	
Infliximab		294 (24)	68 (19)	174 (28)	52 (20)	
First TNFi start yr, n (%)	1250					
2005–2008		376 (30)	79 (21)	259 (41)	38 (14)	< 0.0001
2009–2011		442 (35)	132 (36)	194 (31)	116 (45)	
2012–2014		432 (34)	151 (41)	169 (27)	112 (42)	
CRP, mg/l	964	9 (3–20)	7 (3–17)	11 (5–22)	6 (2–16)	< 0.0001
BASDAI, mm	1012	61 (49–73)	64 (54–77)	59 (46–71	63 (51–74)	< 0.0001
BASDAI, question 5, mm	783	73 (52–86)	75 (55–91)	71 (51–84)	74 (54–86)	0.02
BASDAI, question 6, mm	785	60 (36–86)	68 (39–90)	56 (32–83)	59 (39–86)	0.02
BASFI, mm	980	50 (34–68)	52 (33–69)	49 (34–67)	51 (31–67)	0.7
PGA, mm	676	37 (22–51)	38 (22–53)	38 (22–53)	35 (22–45)	0.6
BASMI	848	30 (10–40)	20 (10–40)	40 (20–50)	20 (10–40)	< 0.0001
PtGA, mm	938	72 (53–85)	76 (62–88)	68 (50–80)	74 (59–88)	< 0.0001
Pain, mm	937	67 (50–80)	72 (55–84)	65 (48–77)	68 (50–81)	< 0.0001
Fatigue, mm	846	70 (52–83)	74 (55–85)	67 (50–80)	72 (54–85)	0.001

[#] No baseline radiograph of sacroiliac joints available. * Nr-axSpA versus AS. Chi square or nonparametric testing (Mann-Whitney U test) for continuous data. TNFi: tumor necrosis factor inhibitor; AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Function Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMI: body mass index; MTX: methotrexate; CRP: C-reactive protein; IBD: inflammatory bowel disease; NSAID: nonsteroidal antiinflammatory response; nr-axSpA: nonradiographic axSpA; VAS: visual analog scale; PGA: physician's global assessment; PtGA: patient's global assessment.

DISCUSSION

In this nationwide study of patients with nr-axSpA and AS initiating TNFi treatment in routine care, we found differences in baseline demographics and disease activity at treatment start, but similar response rates after 6 months of treatment. Treatment adherence was independent of diagnosis in adjusted analyses, while poorer adherence for patients with nr-axSpA was observed in univariate analyses. HLA-B27 status was strongly associated with outcomes irrespective of axSpA subtype.

Since the implementation of the ASAS criteria and the expansion of the axSpA disease spectrum with the nr-axSpA patient group, it has been discussed whether nr-axSpA and AS represent a continuum or 2 different disease entities.

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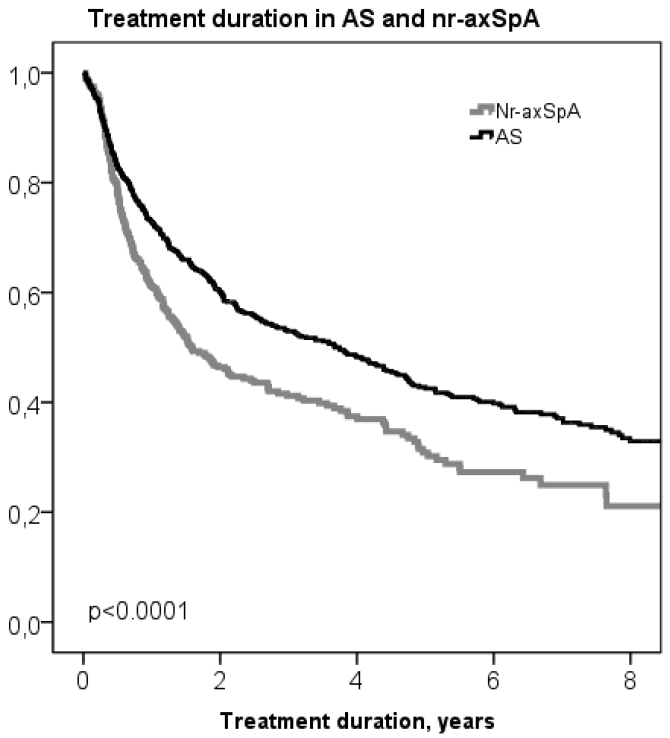

	Withdrawn (0–8 yrs)	Patients still treated, yr								
		0	1	2	3	4	5	6	7	8
AS	**354**	622	445	338	267	215	168	131	97	55
Nr-axSpA	**232**	362	219	138	98	74	47	31	16	9

Figure 2A. Treatment duration of first tumor necrosis factor inhibitor. A. Results stratified by diagnosis (AS/nr-axSpA).

Further, it is debated whether the TNFi treatment effects in AS can be extrapolated to nr-axSpA[15,27]. In Denmark, patients with nr-axSpA and AS are approached similarly in daily practice: a clinical evaluation must ensure that the correct diagnosis has been made (based on ASAS or modified New York classification criteria), and ≥ 2 measurements of high disease activity (BASDAI ≥ 40 mm) and failure of 2 nonsteroidal anti-inflammatory drugs (NSAID) must be documented in DANBIO before TNFi treatment starts[28,29,30]. The TNFi treatment is tax-paid and provided free of charge to individual patients. Thus, treatment with TNFi in nr-axSpA does not require elevated CRP or active inflammation on MRI at baseline, in contrast to the guidelines applied in some countries[5,14].

In accordance with previous studies, patients with nr-axSpA were more frequently women[8,9,11,19,31,32] and had shorter disease duration[9,11,19,33]. Further, they were more often HLA-B27–negative compared to patients with AS[33]. In a Swiss cohort of nr-axSpA and AS patients, HLA-B27 positivity was present in 70% (nr-axSpA) and 84% (AS)[9], nearly identical to the rates found in our study. However, the frequency of HLA-B27 positivity among patients with axSpA seems to vary among different cohorts[8,11,19].

In the early years (2005–2008), patients with AS dominated, in contrast to the later years (2012–2014), mirroring the gradual implementation of the ASAS classification criteria from 2009[1,2] and explaining why patients with AS more frequently received IFX (the first TNFi available).

Patients with AS had higher CRP[18,19] and BASMI at TNFi treatment start, which may reflect more active inflammation and structural damage, respectively[9,31,32]. In contrast, patients with nr-axSpA had higher subjective measures of disease activity compared to patients with AS. A similar tendency was observed in the Swiss cohort[9]. However, 2 previous observational studies[18,19] and several randomized trials[8,9,11,34,35] found similar baseline BASDAI and VAS scores in nr-axSpA and AS. These differences between cohorts are difficult to account for, but may reflect national differences in the management of these patient groups and the selection of patients for biological treatment. The higher prevalence of women in the nr-axSpA group might also

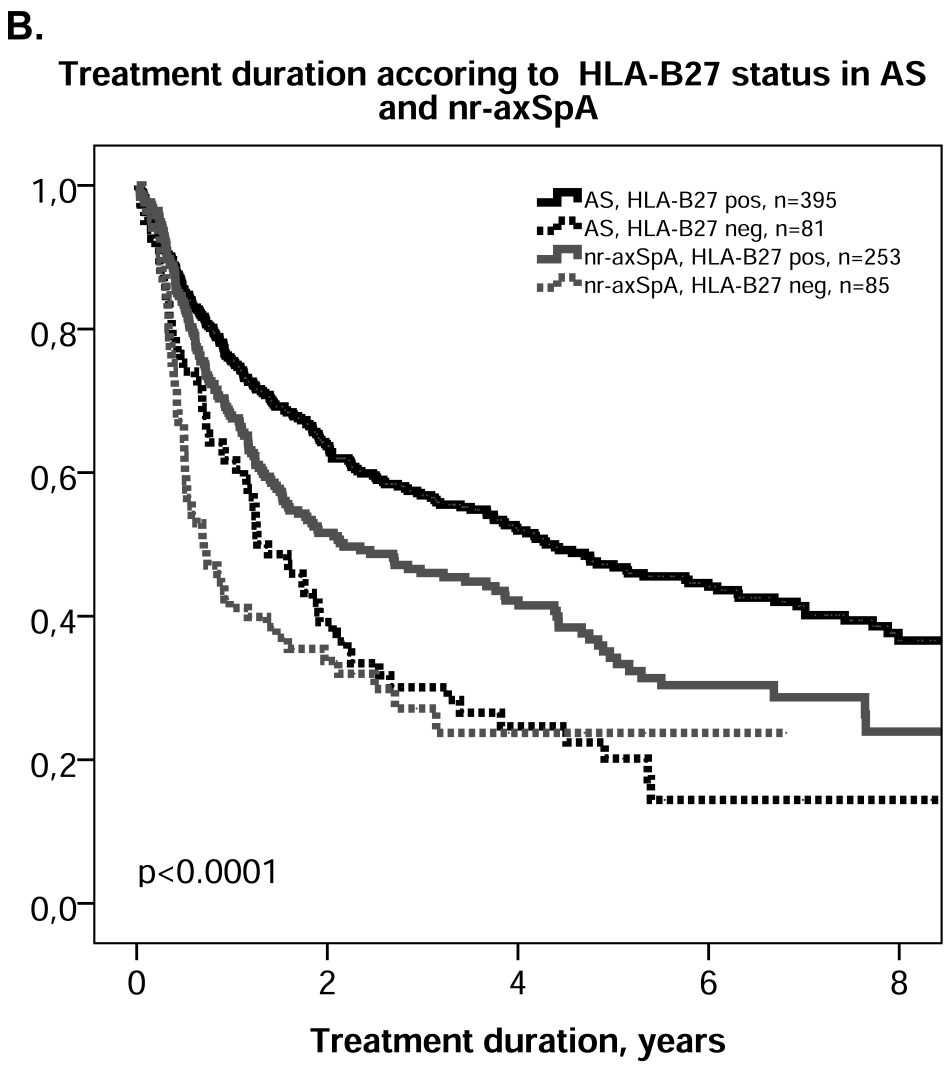

Figure 2B. Results stratified by diagnosis (AS/nr-axSpA) and HLA-B27 status (positive/negative). Median treatment duration (95% CI): AS and HLA-B27–positive: 4.3 years (3.1–5.5); AS and HLA-B27–negative: 1.3 years [0.7–1.8; HR 2.04 (1.53–2.71)]; nr-axSpA and HLA-B27–positive: 2.2 years (1.0–3.3); nr-axSpA and HLA-B27–negative: 0.7 years [1.9–3.2; HR 1.74 (1.29–2.36)]. In a subanalysis including only HLA-B27–positive patients, patients with AS had significantly better treatment adherence than patients with nr-axSpA (p = 0.002). AS: ankylosing spondylitis; nr-axSpA: nonradiographic axial spondyloarthritis.

contribute to higher scores in patient-reported outcomes[36,37].

In accordance with previous observational[9,18,19,38] and randomized studies[33,34,35], we found that patients with nr-axSpA and AS had similar response rates after 6 months. Patients with nr-axSpA, however, had poorer treatment adherence and more often stopped owing to lack of effect in crude analyses, but not after adjustment for differences in baseline characteristics, which may be considered confounders (CRP, sex, BASFI, HLA-B27 positivity). Previous studies have shown conflicting results[18,19]. Poorer treatment adherence has been demonstrated in female TNFi-treated patients with axSpA[36,39]. Further, patients with nr-axSpA more often started treatment during recent years where more different TNFi were available, enabling more frequent drug switching[40]. The association between HLA-B27 status and TNFi treatment outcomes has not been reported previously, to our knowledge. In early axSpA, HLA-B27 positivity is associated with younger age at disease onset[11], spinal inflammation, and radiographic changes[41]. Thus, HLA-B27 may be linked to disease severity and outcomes potentially modifiable to TNFi treatment. It cannot be excluded that inconsistencies in the interpretation of radiographs and MRI[16,42] may have resulted in misclassification of patients. Because no such misclassification is possible for HLA-B27, this might have had an effect on the statistical analyses. It was beyond the scope of our present study to explore this issue further, and our results reflect clinical routine, where images are read by local radiologists.

Table 2. HR for stopping treatment. Univariate and multivariate Cox regression analyses (backwards selection) included *a priori* confounders.

	Univariate Analyses		Final Multivariate Model, Backward Selection	
	HR (95% CI)	p	HR (95% CI)	p
Diagnosis				
AS	1	< 0.0001	—	—
Nr-axSpA	1.41 (1.20–1.67)			
Sex				
Men	1	< 0.0001	1	0.002
Women	1.72 (1.46–2.03)		1.52 (1.16–1.97)	
Disease duration, yrs	0.99 (0.98–0.99)	0.02	—	—
Age				
< 45 yrs	0.91 (0.77–1.07)	0.2	1.05 (0.83–1.33)	0.6
≥ 45 yrs	1		1	
TNFi start year				
2005–2008	0.58 (0.47–0.72)	< 0.0001	—	—
2009–2011	0.82 (0.67–1.01)			
2012–2014	1			
HLA-B27+	1	< 0.0001	1	< 0.0001
HLA-B27–negative	1.93 (1.61–2.32)		2.15 (1.51–3.06)	
TNFi drug type				
Adalimumab	1	0.10		
Etanercept	1.01 (0.79–1.28)		—	—
Infliximab	1.01 (0.82–1.23)			
Golimumab	1.35 (1.05–1.73)			
Smoking				
Current	1.52 (1.25–1.86)	< 0.0001		
Previous	1.34 (1.04–1.72)		—	—
Never	1			
Baseline BASDAI, mm	1.01 (1.01–1.02)	< 0.0001	1.01 (1.00–1.02)	0.002
Baseline BASMI, mm	0.99 (0.99–1.00)	0.6	—	—
Baseline CRP				
≤ 10 mg/l	1.52 (1.26–1.84)	< 0.0001	1.36 (1.08–1.71)	0.01
> 10 mg/l	1		1	

Similar results regarding effects of HLA-B27 and axSpA subdiagnosis were found when (1) applying multiple imputation of missing data; and (2) patients with nr-axSpA diagnosed according to the clinical arm were excluded. AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; TNFi: tumor necrosis factor inhibitor; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; nr-axSpA: nonradiographic axSpA.

In the general population, the ratio of nr-axSpA to AS is about 1:1[5,43]. In contrast, more patients in our study had AS than nr-axSpA. This difference may be explained, at least in part, by the selection of patients for biological therapy in routine care: Rheumatologists more often assign TNFi treatment to patients with AS[9]. Further, the study included patients initiating TNFi before the ASAS criteria were implemented (2005–2009). One in 5 patients had unspecified axSpA (i.e., lacked radiographs of the SI joints at TNFi treatment start), and most of these started TNFi after 2009. This indicates that the clinicians seem to put more emphasis on MRI findings than on radiographic results after the introduction of the ASAS classification criteria.

In our present study, the majority of patients with nr-axSpA fulfilled the "imaging arm" of the ASAS criteria. Concerns have been raised regarding the "clinical arm" and the risk of erroneously diagnosing chronic mechanical back pain as nr-axSpA[27]. Reassuringly, sensitivity analyses in which the clinical arm was excluded showed similar results for axSpA subgroups.

It has previously been shown that fibromyalgia (FM) occurs in 15%–20% of patients with axSpA[44] and that FM is associated with poorer TNFi adherence rates and higher disease activity scores[45]. In a recent study, HLA-B27 positivity rates and imaging results were, however, similar in a cross-sectional cohort of axSpA patients with/without FM[45]. It is possible that uneven distribution of FM among patients with nr-axSpA and AS in the present study affected the results, but we had no data to explore this further.

The strength of our study is that it includes a large nationwide cohort of patients treated in routine care with valid data from a clinical registry collected independently of treatment and subdiagnosis. Further, comprehensive data regarding several potential confounders were available, e.g.,

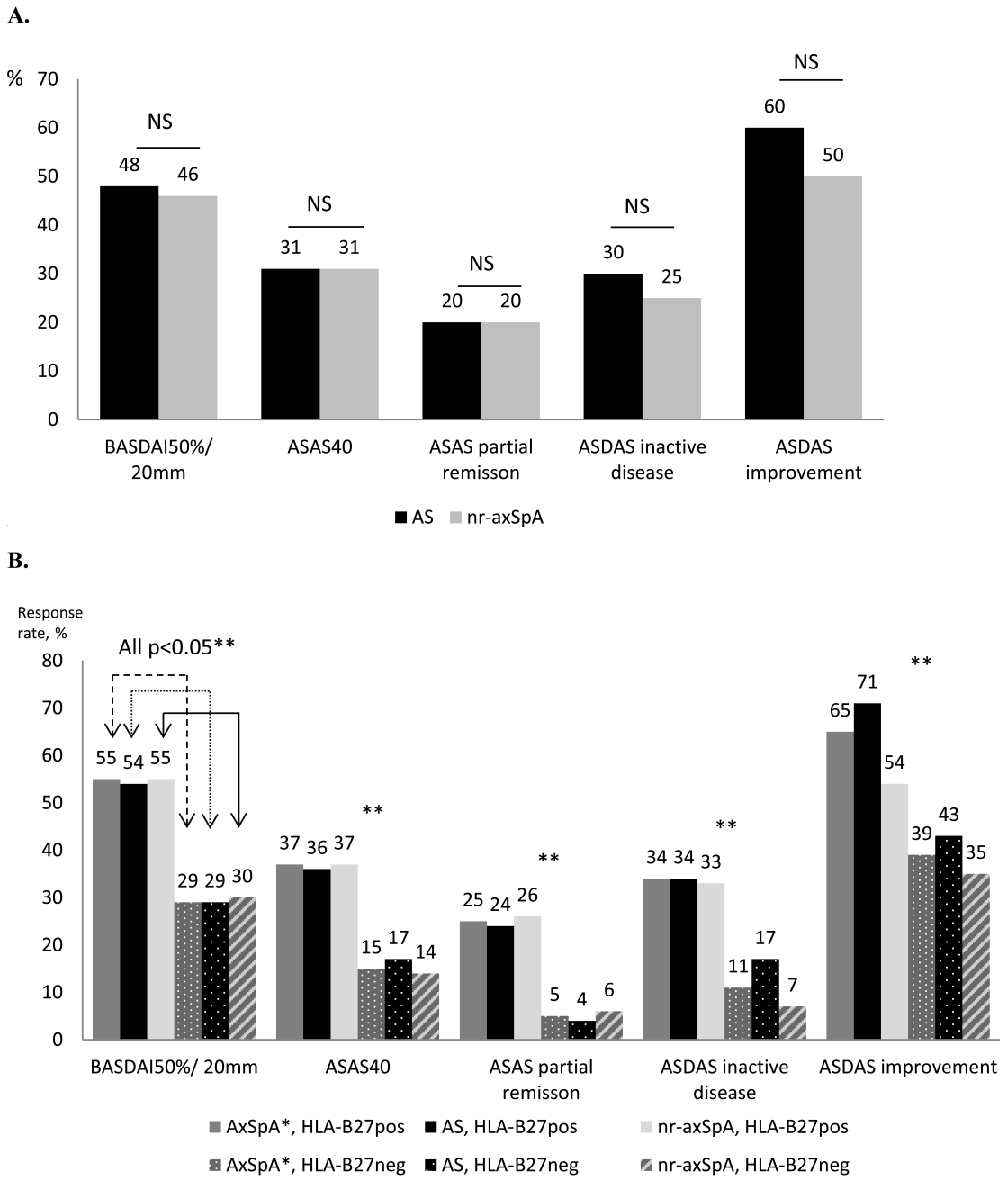

Figure 3. Response rates (3–6 mos). A. Stratified by diagnosis (AS vs nr-axSpA). Percentage of patients with available response rates: BASDAI 50%/20-mm response rates 690/984 = 70%; ASAS 40 451/984 = 46%; ASAS partial remission 307/984 = 57%; ASDAS inactive disease 307/984 = 31%; ASDAS improvement 211/984 = 21%. B. Stratified by HLA-B27 status and axSpA subdiagnosis. * Patients with unspecified axSpA not included. ** For all comparisons of response rates (AS HLA-B27–positive vs AS HLA-B27–negative, etc.), $p < 0.05$. NS: non-significant; AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; nr-axSpA: nonradiographic axSpA; ASAS: Assessment of Spondyloarthritis international Society classification criteria; BASDAI: Bath Ankylosing Spondylitis Activity Index; ASDAS: ASAS Disease Activity Score.

smoking status, disease duration, HLA-B27 status, and baseline disease activity.

Current NSAID use is not registered routinely in DANBIO. Concomitant use of NSAID is known to have an effect on inflammation and outcomes[46,47], so this might have affected our results. We were able to validate the diagnosis in about half of the Danish biologically treated patients with axSpA by a retrospective, voluntary review of the patient

files. The withdrawal analysis revealed similar age and sex distribution among included and excluded patients, which indicate that selection bias was minimal and we therefore consider the results to be generalizable.

Patients with nr-axSpA had higher subjective disease activity at the start of first TNFi treatment, but had outcomes similar to patients with AS after adjustment for confounders. HLA-B27 positivity was associated with better outcomes irrespective of axSpA subdiagnosis.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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