Tumor Necrosis Factor-α Inhibition in Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis: Treatment Response, Drug Survival, and Patient Outcome

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ABSTRACT. ***Objective.*** The purpose of this study was to (1) evaluate baseline characteristics of nonradiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS) treated with tumor necrosis factor-α inhibitors (TNFi), (2) assess the response to first TNFi treatment, and (3) compare drug-survival duration and rates.

Methods. Inclusion criteria were patients with axSpA who initiated first TNFi treatment between April 2001 and July 2014 and were followed up for at least 3 months. Efficacy criteria were an improvement of at least 2 points (on a 0–10 scale) or a 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Baseline characteristics, responses at 12 months, and drug survival were compared between AS and nr-axSpA.

Results. A total of 361 patients were included in the study (AS, n = 263 and nr-axSpA, n = 98). Patients with AS were more often men (65.02% vs 45.92%, p = 0.001) and had longer symptom duration (11.71 ± 9.52 vs 7.34 ± 9.30 yrs, p < 0.001). Median levels of acute-phase reactants (C-reactive protein and erythrocyte sedimentation rate) were significantly higher in patients with AS (p < 0.001 for both). Median BASDAI scores at first TNFi initiation were not higher in patients with nr-axSpA than in patients with AS (59, 49–70 vs 60, 50–70, p = 0.73). BASDAI 20 and BASDAI 50 response rates at 12 months were not statistically different between patients with AS and patients with nr-axSpA (74.58% vs 64.58%, p = 0.19 and 61.02% vs 50.00%, p = 0.19, respectively). No statistically significant difference in terms of survival was observed between patients with AS and nr-axSpA (p = 1.00).

Conclusion. Treatment response and drug survival were similar in patients with AS and nr-axSpA after first TNFi initiation. (First Release November 15 2015; J Rheumatol 2015;42:2376–82; doi:10.3899/jrheum.150372)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS | NONRADIOGRAPHIC AXIAL SPONDYLOARTHRITIS
TNF-α INHIBITION | TREATMENT RESPONSE | DRUG SURVIVAL

The Assessment in Spondyloarthritis International Society (ASAS) has adapted the classification of spondyloarthritis (SpA) with the aim of achieving earlier diagnosis and has introduced the concept of predominantly axial versus peripheral disease[1,2]. Patients presenting with persisting back pain > 3 months and an age of onset < 45 years are classified as having axial SpA (axSpA) in the presence of either sacroiliitis [on radiographs or magnetic resonance imaging (MRI)] and at least 1 additional typical SpA feature (imaging arm), or HLA-B27 positivity and 2 additional SpA characteristics (clinical arm)[1]. Depending on radiographic evidence indicating the presence or absence of definitive structural sacroiliac joint (SIJ) changes, patients are further classified as having either ankylosing spondylitis (AS) or nonradiographic axSpA (nr-axSpA)[3].

It has been confirmed in a Swiss cohort that patients with nr-axSpA have the same level of perceived disease activity and pain as patients with AS, but lower objective signs of inflammation, such as elevated C-reactive protein (CRP) levels[4]. Patients with nr-axSpA were included in the latest update of the international ASAS recommendations for the use of tumor necrosis factor-α inhibitors (TNFi)[5]. However, in the licensing guidance by the European Medicines Agency,

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TNFi is indicated for the treatment of adults with severe SpA without radiographic evidence of AS, but with objective signs of inflammation by MRI or elevated CRP, who have had an inadequate response to or are intolerant of nonsteroidal antiinflammatory drugs (NSAID). Further, there is still an ongoing debate about the preliminary decision by the US Food and Drug Administration[6].

Several studies have demonstrated that TNFi are efficient in nr-axSpA[7,8,9]. Intriguingly, few investigations have directly compared patients with AS with patients with nr-axSpA[4,10,11], and fewer still have compared rates of response to first TNFi treatment. In real-world clinical practice, TNFi response rates were higher in patients with AS than in patients with nr-axSpA[4]. However, similar response rates were found after treatment with etanercept (ETN) or certolizumab pegol (CZP) in 2 clinical trials[12,13].

The purpose of our observational study, which involved a tertiary care cohort, was to (1) evaluate baseline characteristics of nr-axSpA and AS treated by TNFi, (2) assess the response to TNFi treatment in nr-axSpA versus AS, and (3) compare drug-survival duration and rates.

MATERIALS AND METHODS

Patients. This single-center, retrospective observational study was conducted from April 2001 to July 2014. The charts of all patients with axSpA who had undergone treatment with at least 1 TNFi for more than 3 months were reviewed. Patient charts were retrieved from the Department of Health Informatics. The ASAS criteria were used to establish the diagnosis of axSpA[1]. The patients' demographic and clinical characteristics were collected according to a standardized procedure (age, sex, duration of symptoms, and HLA-B27 status). Current or past uveitis, psoriasis, and inflammatory bowel disease (IBD) were investigated. Positive SpA family history was also investigated. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), erythrocyte sedimentation rate (ESR), and CRP at initiation of first TNFi were recorded. Radiographs and MRI of SIJ (past or present) and/or MRI detection of spinal inflammation (past or present) were also recorded. Depending on radiographic evidence indicating the presence or absence of definitive structural SIJ changes, patients were further classified as having either AS or nr-axSpA.

Treatments. The number of conventional synthetic disease-modifying antirheumatic drugs (DMARD) prescribed prior to initiation of first TNFi was recorded. Longterm systemic corticosteroid therapy (oral, for more than 3 mos) prior to or at initiation of first TNFi was also investigated. The TNFi drugs used were ETN (25 mg twice weekly or 50 mg once weekly, available in France since 2002 for patients with AS only), infliximab (IFX; 3 to 5 mg/kg every 6 to 8 weeks, available since 2003 for patients with AS only), adalimumab (ADA; 40 mg every 14 days, available since 2006 for patients with AS and since 2012 for patients with nr-axSpA), and golimumab (50 mg per mo, available since 2009 for patients with AS only)[14,15,16]. The Société Française de Rhumatologie (SFR) guidelines were usually used to validate initiation of TNFi[17]. These drugs are indicated for AS (and for nr-axSpA in the case of ADA) in the event of inadequate response to NSAID, which is defined either as persistence of symptoms despite maximum-dose NSAID therapy, or as persistent disease activity with a BASDAI > 4/10 or an Ankylosis Spondylitis Disease Activity Score (ASDAS) > 2.1 during NSAID therapy[17].

Evaluation of efficacy and drug survival. Because of the retrospective characteristic of this observational study (inevitably consisting of missing data), we expected that it would be difficult to achieve response criteria, such as ASDAS, ASAS20, ASAS40, ASAS 5/6, and ASAS partial remission. We therefore pragmatically evaluated responding patients at 3 and 12 months (± 3 mos) according to the ASAS[5] and SFR[17] guidelines, i.e., BASDAI 50 (50% improvement of BASDAI) and/or at least a 2-point improvement of the BASDAI on a scale of 0–10 for predominantly axial forms. Clinically relevant responses (BASDAI < 20 and < 40) were also examined at 12 months. The reasons for discontinuation of treatment at 12 months (± 3 mos) were also recorded. These included (1) development of adverse effects, (2) primary inefficacy, (3) escape (progressive loss of efficacy after a satisfactory initial response), or (4) other (patient's personal decision, pregnancy, loss to followup).

At the end of our study, in patients who continued treatment for more than 3 months, we evaluated the outcome according to continuation of treatment or discontinuation of treatment for (1) adverse effects, (2) primary inefficacy, (3) escape, or (4) other (patient's personal decision, pregnancy, lost to followup). Possible switching to another TNFi was also studied. The decision to discontinue first TNFi treatment was based on the prescribing physician's opinion. The median duration of treatment was analyzed for the whole group of axSpA, and drug survival for first TNFi was compared between AS and nr-axSpA.

Statistical analysis. Statistical analyses were performed using STATA version 13.1. Descriptive data analysis was initially performed. Descriptive statistics for continuous variables were expressed as mean and SD or median and range. Categorical variables were expressed as frequency and percentage. Differences in continuous variables between AS and nr-axSpA were assessed using Student t tests, and in categorical variables using Pearson chi-square tests. Drug survival was analyzed by means of Kaplan-Meier curves and log-rank tests. Predictive factors of BASDAI 50 of first TNFi were examined at 3 and 12 months for the whole population and for AS and nr-axSpA separately (according to age, sex, disease duration, CRP, and HLA-B27 status). Finally, for all results, $p \leq 0.05$ was considered to be statistically significant.

RESULTS

Demographics, disease characteristics, and disease activity. From April 2001 to July 2014, a total of 387 patients diagnosed with axSpA were treated with at least 1 TNFi for more than 3 months. A total of 263 patients fulfilling the modified New York criteria were classified with AS and 98 patients were classified with nr-axSpA (67 patients were HLA-B27–positive and 39 had sacroiliitis on MRI), while the remaining patients (n = 26) had an unknown modified New York criteria status.

The demographic characteristics of the patients with AS and nr-axSpA at first TNFi initiation are summarized in Table 1. Patients with AS were more often men than patients with nr-axSpA (65.02% vs 45.92%, p = 0.001). The proportion of HLA-B27–positive patients was similar in the AS and nr-axSpA groups (78.13% vs 72.83%, p = 0.31). Patients with nr-axSpA had an earlier age at first TNFi initiation compared with patients with AS (40.97 ± 12.94 yrs vs 43.93 ± 11.99 yrs, p = 0.04). Symptom duration was longer in patients with AS than in patients with nr-axSpA (11.71 ± 9.52 yrs vs 7.34 ± 9.30 yrs, p < 0.001). The frequencies of positive SpA family history and nonskeletal manifestations (uveitis, psoriasis, IBD) were similar in the 2 groups, except for psoriasis, which was more frequent in nr-axSpA than in AS (18.37% vs 9.51%, p = 0.02).

MRI scanning of the SIJ, or the SIJ and the spine, was more often used in patients with nr-axSpA than in patients

Table 1. Demographic, clinical, and MRI characteristics of patients at first line TNFi initiation. Values are n (%) unless otherwise specified.

Characteristic	No. Patients Assessed	Radiographic axSpA, n = 263	nr-axSpA, n = 98	p
Male*	361	171 (65.02)	45 (45.92)	**0.001**
Age, yrs, mean ± SD	360	43.93 ± 11.99	40.97 ± 12.94	**0.04**
Symptom duration, yrs, mean ± SD	326	11.71 ± 9.52	7.34 ± 9.30	**< 0.001**
Symptom duration ≤ 5 yrs*	326	77 (32.91)	51 (55.43)	**< 0.001**
HLA-B27–positive*	316	175 (78.13)	67 (72.83)	0.31
Current or past uveitis*	361	47 (17.87)	12 (12.24)	0.19
Current or past IBD*	361	36 (13.69)	12 (12.24)	0.72
Current or past psoriasis*	361	25 (9.51)	18 (18.37)	**0.02**
Positive SpA family history*	361	41 (15.59)	20 (20.41)	0.28
MRI of sacroiliac*	119	49 (18.6)	70 (71.4)	**< 0.001**
Sacroiliitis on MRI, past or present*	119	40 (81.6)	39 (59.7)	**0.003**
MRI of spine*	81	43 (16.3)	38 (38.8)	**< 0.001**
MRI detection of spinal inflammation, past or present*	81	20 (46.5)	15 (39.5)	0.52

* Percentage values refer to the number of patients with available information. Significant data are in bold face. MRI: magnetic resonance imaging; TNFi: tumor necrosis factor inhibitor; SpA: spondyloarthritis; axSpA: axial SpA; nr-axSpA; nonradiographic axSpA; IBD: inflammatory bowel disease.

with AS (Table 1). However, the frequency of inflammation on MRI of the SIJ was higher in the AS group (81.6% vs 59.7%, p = 0.003). Frequency of MRI detection of spinal inflammation did not differ between the 2 groups.

Details on NSAID and immunosuppressive drug treatment are shown in Table 2. The frequencies of NSAID and immunosuppressive drug treatment use (DMARD and glucocorticoids) at first TNFi initiation were similar in the 2 groups.

Median levels of acute-phase reactants (CRP and ESR) were significantly higher in patients with AS, as was the proportion of patients with elevated CRP levels (> 5 mg/l) and ESR (> 20 mm/h; Table 2). Median BASDAI scores at first TNFi initiation were not higher in patients with nr-axSpA (59, 49–70 vs 60, 50–70, p = 0.73), nor was the proportion of patients with elevated BASDAI levels (> 40/100).

Treatment response, drug survival, and patient outcome. Regarding the first TNFi used, there was no statistical difference between the AS and nr-axSpA groups (p = 0.86). IFX was the TNFi most commonly used as first treatment (nearly 41% of cases for both groups), followed by ETN (28% in patients with AS) and ADA (27% in patients with nr-axSpA). Followup visit information with complete datasets for the calculation of response rates was available at 3 months for 52.85% of the patients with AS (139 out of 263

Table 2. Medication use and disease activity of patients at first TNFi initiation. Values are n (%) unless otherwise specified.

Characteristic	No. Patients Assessed	Radiographic axSpA, n = 263	nr-axSpA, n = 98	p
Ever DMARD use*	361	103 (39.2)	29 (29.6)	0.09
Current DMARD use*	361	32 (12.2)	12 (12.2)	0.98
Current NSAID*	361	144 (61.2)	60 (54.7)	0.27
Current GC*	361	17 (6.5)	3 (3.1)	0.21
BASDAI, median (IQR)	309	60 (50–70)	59 (49–70)	0.73
BASDAI ≥ 40*	309	91.3	89.7	0.68
CRP level, mg/l, median (IQR)	234	11 (5–23)	5 (2–12)	**< 0.001**
Elevated CRP level*	234	134 (79.8)	36 (54.5)	**< 0.001**
ESR, mm/h, median (IQR)	227	20 (10–32)	10 (4–20)	**< 0.001**
ESR ≥ 20 mm/h*	227	86 (51.8)	17 (27.9)	**0.001**

* Percentage values refer to the number of patients with available information. Significant data are in bold face. TNFi: tumor necrosis factor inhibitor; axSpA: axial spondyloarthritis; nr-axSpA; nonradiographic axSpA; DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug; GC: glucocorticoid; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; IQR: interquartile range; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

patients) and 43.88% of the patients with nr-axSpA (43 out of 98 patients). The baseline disease characteristics of patients without or with incomplete followup were similar to those included in the analysis (results not shown). BASDAI 20 and BASDAI 50 response rates at 3 months were not statistically different between patients with AS and patients with nr-axSpA (64.03% vs 62.79%, p = 0.88 and 45.32% vs 39.53%, p = 0.50, respectively).

Twenty-two patients still receiving their first TNFi at the end of our study were treated for less than 12 months. At 12 months, 255 out of 339 patients (75.22%) were still receiving first TNFi. Followup visit information with complete datasets for the calculation of response rates was available for 63.78% of the patients with AS (118 out of 185 patients) and 68.57% of the patients with nr-axSpA (48 out of 70 patients; Table 3). The baseline disease characteristics of patients without or with incomplete followup were similar to those included in the analysis (results not shown). BASDAI 20 and BASDAI 50 response rates were not statistically different between patients with AS and nr-axSpA (74.58% vs 64.58%, p = 0.19 and 61.02% vs 50.00%, p = 0.19, respectively). Clinically relevant responses (BASDAI < 20 and < 40) were quite similar in both groups. In a subgroup analysis of patients with elevated CRP levels at baseline, no significant differences in the response to first TNFi were observed in both the AS and nr-axSpA groups (Table 3). We studied predictors of BASDAI 50 response for the entire population and for the AS and nr-axSpA groups (Supplementary Table 1 available from the authors on request). BASDAI 50 responders at 12 months were younger (all patients, p = 0.03), more often men (all patients and AS, p = 0.02 for both), had longer disease duration (all patients, p = 0.03 and AS, p = 0.01), and had a higher proportion of patients with elevated CRP levels (> 5 mg/l) at baseline (all patients, p = 0.01 and nr-axSpA, p = 0.04).

At 12 months, 255 patients were still receiving first TNFi whereas 84 had stopped for several reasons: 10.53% of patients for adverse effects (n = 38), 8.59% of patients for primary inefficacy (n = 31), 2.49% of patients for escape (n = 9), and 1.66% of patients for other reasons (n = 6).

The median duration of prescription of first TNFi therapy was 26 months (interquartile range 9–62). In terms of drug survival, no statistically significant difference was observed between AS and nr-axSpA (p = 1.00; Figure 1) and between patients with low (< 5 mg/l) or elevated CRP levels (p = 0.09; Supplementary Figure 1 available from the authors on request).

Patient outcome is presented in Figure 2. At the end of our study, 156 out of 361 patients (43.2%) had switched to second TNFi therapy and 178 out of 361 patients (49.3%) were still taking first TNFi therapy. The main reason for switching to second TNFi therapy was adverse effects in 38.9% of cases (56/156), mostly allergies, repeated infections, hepatic cytolysis, or various intolerances (fatigue, injection site erythema). Other reasons were escape, followed by primary inefficacy, and miscellaneous (pregnancy, patient's choice). The most commonly used second TNFi drug was ADA (44.2%).

DISCUSSION

We have described a cohort of patients with AS and nr-axSpA enrolled in a longitudinal retrospective study at first TNFi initiation. The unique study design of this cohort revealed a number of interesting findings: (1) Our data support previous findings regarding predominant male distribution and longer disease duration in patients with AS; (2) the frequency of extraarticular manifestations (including IBD and uveitis) and the frequency of HLA-B27 positivity were similar between the 2 groups; (3) the level of disease activity as measured by the BASDAI at first TNFi initiation was also highly comparable between patients with AS and those with nr-axSpA; (4) patients with nr-axSpA were also shown to have lower levels of acute-phase reactants such as CRP and ESR; and (5) rates of response to TNFi, survival analysis, and outcome

Table 3. Response rates after 12 months of treatment with the first TNFi. The percentage figures refer to the number of patients with available information. Values are n (%) unless otherwise specified.

Characteristic	No. Patients Assessed	Radiographic axSpA, n = 185	nr-axSpA, n = 70	p
All patients				
BASDAI 20	166	88 (74.58)	31 (64.58)	0.19
BASDAI 50	166	72 (61.02)	24 (50.00)	0.19
BASDAI ≤ 40	179	100 (80.00)	37 (68.52)	0.09
BASDAI ≤ 20	179	58 (46.30)	25 (46.40)	0.99
Patients with elevated CRP level at baseline				
BASDAI 20	89	54 (79.41)	16 (76.19)	0.75
BASDAI 50	89	45 (66.18)	13 (61.90)	0.72
BASDAI ≤ 40	95	61 (85.92)	20 (83.33)	0.76
BASDAI ≤ 20	95	35 (62.50)	15 (49.30)	0.26

TNFi: tumor necrosis factor inhibitor; axSpA: axial spondyloarthritis; nr-axSpA: nonradiographic axSpA; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein.

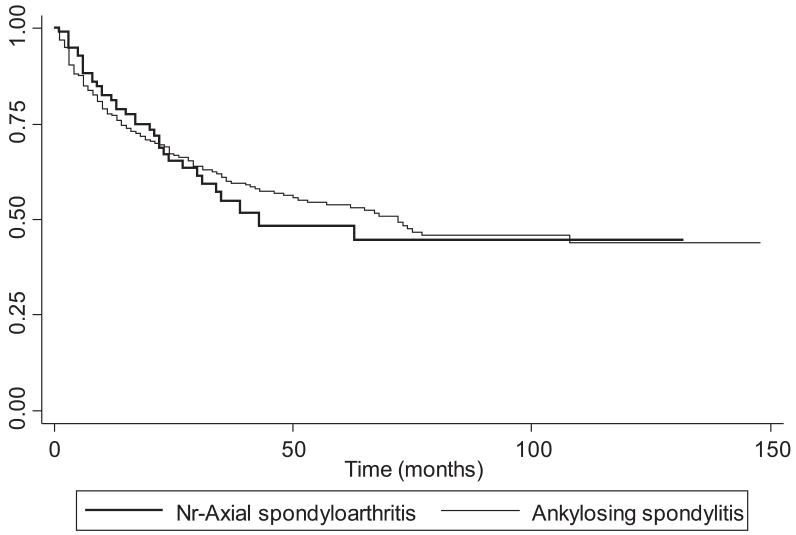

Figure 1. Kaplan-Meier survival analysis of persistence. Nr-axial spondyloarthritis: nonradiographic spondyloarthritis.

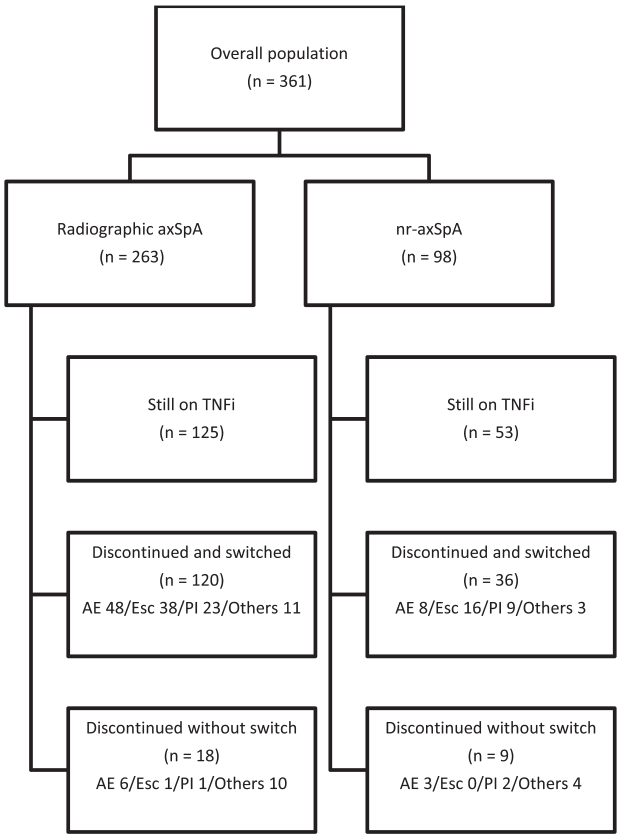

Figure 2. Outcome of patients who continued treatment for more than 3 months according to the first sequence and to continuation (still receiving anti-TNF-α) or discontinuation of treatment for (1) AE, (2) Esc (progressive loss of efficacy after a satisfactory initial response), (3) PI, or (4) other causes. SpA: spondyloarthritis; axSpA: axial SpA; nr-axSpA: nonradiographic axSpA; anti-TNF-α: anti-tumor necrosis factor-α; AE: adverse effects; Esc: escape; PI: primary inefficacy.

were not statistically different between patients with AS and patients with nr-axSpA.

The 2 groups differed mainly in sex distribution[4,10,11,18]. Indeed, patients with nr-axSpA, in contrast to those with AS, were predominantly women, as was observed in the GErman SPondyloarthritis Inception Cohort (GESPIC; 57.1%)[11] and in a Canadian cohort (52.1%)[18]. Disease duration at first TNFi initiation was longer in patients with AS than nr-axSpA, as observed[10,11,18].

Similarities in frequency of extraarticular manifestations (uveitis and IBD) among patients with nr-axSpA AS and nr-axSpA were comparable in our study, except for psoriasis, as observed[4,10,11,18]. The proportions of HLA-B27–positive patients were also similar[4,10,11,18]. We confirmed a similar burden of perceived disease activity (BASDAI) in AS and nr-axSpA[10,11,18], whereas for Ciurea, *et al*[4] BASDAI was higher in patients with AS.

Our data support previous findings regarding objective markers of inflammation in patients with axSpA. Indeed, the levels of acute-phase reactants were higher in patients with AS (a higher proportion of patients with an elevated CRP level and ESR, and higher levels of both markers in patients with AS)[4,10,11,18]. Moreover, patients with nr-axSpA were also shown to have fewer inflammatory lesions on MRI of the SIJ in our study. Patients with nr-axSpA were also shown to have fewer inflammatory lesions on MRI of the spine in a previous study[10], whereas the opposite was found on MRI of the SIJ in another study[4]. However, our finding should be interpreted with caution because of the small number of patients assessed for MRI in both groups, particularly for MRI of the spine.

A study by Ciurea, *et al*[4] was, to our knowledge, the first to analyze the response to TNFi in patients with nr-axSpA

and AS in real-world clinical practice. They found that, with the exception of patients with elevated CRP levels at baseline, higher rates of response to TNFi were achieved in patients with AS. Indeed, response rates at 1 year were higher in patients with AS when measured by ASAS40, but did not reach statistical significance when measured by BASDAI 50[4]. However, similar response rates were found after treatment with ETN or CZP in 2 clinical trials[12,13]. Indeed, Song, *et al*[12] found similar response rates in patients with AS and nr-axSpA after 1 year of treatment with ETN (ESTHER trial). It is interesting to note that there was only a small, albeit nonsignificant, advantage in favor of the nr-axSpA group in some of the outcome variables, such as BASDAI 50 (75% vs 50%), in these patients with early axSpA. Landewé, *et al*[13] found that a significant treatment effect (ASAS40, ASDAS, BASDAI) was seen for both subpopulations through Week 24 in a Phase III study with CZP. Patients had to have elevated CRP levels and/or sacroiliitis on MRI at baseline. Regarding the response rates, these results are in accordance with our results. Indeed, for BASDAI 20 and BASDAI 50 responses at 3 and 12 months, as well as for clinically relevant responses (BASDAI < 20 and < 40) at 12 months, there was no statistically significant difference between patients with AS and patients with nr-axSpA. Younger age, male sex, longer disease duration, and higher proportion of patients with elevated CRP levels (> 5 mg/l) at baseline were associated with a better BASDAI 50 response at 12 months in our cohort. If longer disease duration is not known to be a predictive factor of good response, our results should be interpreted with caution because of the retrospective characteristic of our study.

Moreover, to our knowledge, this is the first study providing data on drug survival and outcome in patients with AS compared with patients with nr-axSpA. Interestingly, we observed a similar survival analysis between the 2 groups, providing additional data to strengthen the validity of the concept of axSpA as a single disease with different stages[19]. It has been demonstrated that short symptom duration, elevated CRP, and MRI-positivity are the best predictors of a good response to TNFi, both in patients with AS[20,21] and patients with nr-axSpA[7,22]. It might partially explain the discrepancy between the results obtained by Ciurea, *et al*[4] and those obtained in clinical trials[12,13] because of the inclusion criteria differences observed. Another argument to strengthen the validity of the concept of axSpA as a single disease with different stages is the progression from nr-axSpA to AS. Indeed, the rate of progression from nr-axSpA to AS was 11.6% over 2 years in a cohort of 210 patients with axSpA (GESPIC)[23]. It is remarkable that elevated CRP and active sacroiliitis on MRI are also the strongest predictors of structural damage development in the SIJ and, therefore, of progression from nonradiographic to radiographic stages[23,24].

Our study is limited because the data represent a tertiary SpA center and may not be generalizable to the SpA population as a whole. However, our cohort may represent a population of more severe SpA compared with general rheumatology practice. A major limitation of this type of study, which is inherent to the observational character of the cohort, is missing followup data. Data on treatment response at 12 months were available in 63.78% of the patients with AS and in 68.57% of the patients with nr-axSpA. Moreover, response criteria such as BASFI, ASDAS, ASAS20, ASAS40, ASAS 5/6, and ASAS partial remission have not been assessed. There is also a selection bias by virtue of the retrospective cohort study design. Indeed, patients with nr-axSpA and AS without TNFi treatment were not retrieved, but they might affect the baseline characteristics of an overall nr-axSpA and AS cohort. Finally, information is missing regarding imaging assessments. It is unknown which modules served to evaluate pelvic radiographs, sacroiliac, and spinal MRI; how many readers assessed the images, the previous experience of readers; or the reliability of both radiographic and MRI readings.

The results of our study provide additional data to strengthen the idea of axSpA as a single disease, and there is a spectrum from nonradiographic to radiographic disease with or without HLA-B27–positive status, just like "rheumatoid arthritis" first, and then ACPA-positive or -negative, or erosive or nonerosive. Indeed, treatment response, drug survival, and patient outcome in our study were similar in patients with AS and nr-axSpA after first TNFi initiation. For rheumatologists in daily practice, our results emphasize the fact that all active SpA should be treated in the same way, according to the ASAS recommendations, disregarding the preexistence or not of structural damage.

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