Different drug survival of first line tumour necrosis factor inhibitors in radiographic and non-radiographic axial spondyloarthritis: a multicentre retrospective survey

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Abstract

Objective

Good drug survival of tumour necrosis factor inhibitors (TNFi) has been shown in axial spondyloarthritis (axSpA) patients treated in real-life setting. However, few studies have compared drug survival of the first TNF inhibitor between radiographic axSpA (r-axSpA) and non-radiographic axSpA (nr-axSpA) patients in real-world clinical practice. The aim of this work was to evaluate the effectiveness by assessing the retention rate of first-line TNFi in r-axSpA and nr-axSpA patients. Baseline predictive factors for TNFi discontinuation were also evaluated.

Methods

We retrospectively assessed axSpA patients, who underwent first line therapy with TNFi. Demographic and clinical data was obtained through structured interview, review of medical records and physical examination. Disease activity indices such as the Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Disease Activity Score evaluating C Reactive Protein (ASDAS-CRP), Leeds Enthesitis Index (LEI) were assessed at baseline. Moreover Health Assessment Questionnaire-Disability Index (HAQ), erythrocyte sedimentation rate (ESR, mm/h), CRP (mg/dl) and HLA-B27 were recorded as well. Data on x-ray and magnetic resonance imaging of the sacroiliac joints were also collected. Drug retention rates were analysed using Kaplan-Meier curves; log-rank test was performed to demonstrate differences in the survival functions. Cox regression models were used to estimate the inference of several disease and clinical characteristics on drug discontinuation.

Results

Drug survival of first-line TNFi was significantly lower in patients who had nr-axSpA than in those with r-axSpA (p=0.005). HLA-B27 frequency was higher in patients with x-ray sacroiliitis than in those with nr-axSpA (p=0.01) as well as mean CRP serum level (p=0.0001), whereas both mean BASDAI and LEI score were higher in patients with nr-axSpA than in those with r-axSpA (p=0.018 and p=0.007, respectively). Global retention rate in our cohort was 60.34% with mean survival time (MST) of 58.68 months (95% CI 47.93–69.42). MST for patients diagnosed with r-axSpA was 66.79 months (95% CI 53.54–80.04) and 39.05 months (95% CI 24.12–53.99) for those with nr-axSpA. Moreover, nr-axSpA (HR 1.620), higher BMI (HR 1.093) and BASFI, (HR 1.192) had an impact on drug discontinuation, whereas HLA-B27 presence (HR. 0.523) had protective effect.

Conclusion

Effectiveness of TNFi, seems to be lower in nr-axSpA patients than in those with r-axSpA. In addition obesity and functional disability negatively impact the persistence on first line TNFi in axSpA patients in real life setting.

Key words

axial spondyloarthritis, TNF inhibitors, drug survival, sacroiliitis, x-ray

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Introduction

Spondyloarthritis (SpA) is a group of inflammatory rheumatic diseases sharing common clinical features such as involvement of axial skeleton and peripheral joints, the presence of enthesitis, dactylitis, typical extra-articular manifestations, and a genetic association with the type I major histocompatibility complex HLA-B27 (1, 2). The classical form of axial SpA (axSpA), is marked by structural damage of the sacroiliac joints on conventional radiographs (3), however the advance in magnetic resonance imaging (MRI) has allowed to disclose early abnormalities in the sacroiliac joints without radiographic changes (4, 5). Recently, according to the Assessment of Spondyloarthritis International Society (ASAS) criteria, patients have been classified into two groups depending on the presence of sacroiliitis on x-ray: 1) radiographic ax-SpA (r-axSpA) including patients with radiographic sacroiliitis, whose prototype is represented by the classical ankylosing spondylitis (AS), and 2) non-radiographic axSpA (nr-axSpA) including patients with or without sacroiliitis on MRI (6). Growing evidence has shown that nr-axSpA and r-axSpA have comparable, but not the same clinical manifestations and burden of disease, however the main difference seems to be associated with the lack of ossification in nr-axSpA (7). On one hand, randomised controlled trials have suggested that treatment with anti-TNF agents is effective in reducing disease activity, pain, and signs of inflammation, improving function and spinal mobility in patients with AS (8-12). On the other hand, convincing results support the employment of anti-TNF agents in nr-axSpA (13-16), albeit their use in these patients still remains topic of debate. A good drug survival of TNF inhibitors (TNFi) has been shown in axSpA patients treated in real-life setting, irrespective of the specific administered agent. To date, few studies have compared drug survival of the first TNF inhibitor treatment between patients with r-axSpA and nr-axSpA in real-world clinical practice, although it has been demonstrated that TNFi response rates were higher in patients with r-axSpA than in those with nr-axSpA (17). Therefore, the aim of this work was to evaluate the effectiveness by assessing the retention rate of first-line TNFi in r-axSpA and nr-axSpA patients. Baseline predictive factors for TNFi discontinuation were also evaluated.

Methods

Patients from four rheumatology centres, all affected with axSpA according to ASAS criteria (18), who underwent first line therapy with TNFi from January 1st 2012 to September 30th 2016 were retrospectively assessed. Demographic and clinical data including age, gender, disease duration and presence of extra-articular manifestations (*i.e.*, uveitis, inflammatory bowel diseases, psoriasis) was obtained through structured interview, review of medical records, physical examination. Moreover a course of non-steroidal anti-inflammatory drugs, at full dosage for four weeks, was given to all axSpA patients before starting TNFi. Disease activity indices such as the Bath AS Metrology Index (BASMI), Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), AS Disease Activity Score evaluating C Reactive Protein (ASDAS-CRP), Leeds Enthesitis Index (LEI) were evaluated at baseline. Moreover Health Assessment Questionnaire-Disability Index (HAQ), erythrocyte sedimentation rate (ESR, mm/h), CRP (mg/dl) and HLA-B27 were recorded as well (the main demographic characteristics and clinical features are depicted in Table I). Time to discontinuation was defined as the time between drug initiation and last administration plus one dispensation interval. All observations were censored at the last registered visit before September 30th 2016. The reasons of discontinuation were classified as 1) primary failure (defined as lack of clinical response within 6 months after starting anti-TNF therapy), 2) secondary failure (loss of efficacy on subsequent clinic visit following an initial response, 3) adverse events, or 4) other reasons. Data on x-ray examination and MRI of the sacroiliac joints were also collected. Furthermore, patients were classified as affected with nr-axSpa if no evidence of

radiographic sacroiliitis, according to modified New York criteria was noticed (3). Written informed consent was obtained from all patients.

Mean ± standard deviation (SD) or median and interquantile range (IQR) were used when appropriate for continuous variables. Welch's *t*-test or Mann-Whitney U-test were carried out when appropriate to compare means while either χ^2 test or Fisher's exact test were used when appropriate to identify differences in proportions. Drug retention rates were analysed using Kaplan-Meier curves; log-rank test was performed to demonstrate differences in the survival function. Constancy over time of ratio of hazards for stratified data was also assessed. Gender, disease duration, the presence of extra-articular manifestations, eventual peripheral joint involvement, concomitant therapy with conventional synthetic disease modifying drugs, HLA-B27 positivity, the diagnosis of nr-axSpA, BASMI, BASDAI, BASFI, ASDAS-CRP, LEI, HAQ, ESR and CRP were screened by univariate Cox regression (α=0.05) to select factors affecting drug discontinuation. Multivariate Cox regression model were then fitted including all the predictors found significant and then performing backward selection (α=0.20). Goodness of fit of the final model was assessed comparing Cox-Snell residuals to Nelson-Aalen cumulative hazard function. Statistical analyses were carried out using STATA 14.2 (StataCorp, TX, USA) and SAS 9.4 (SAS, Cary, NC, USA).

Results

We retrospectively assessed 179 patients, (96 female, 55.63%), with mean age at symptoms onset (± SD) 42.9±13.6 and mean disease duration at the baseline of 4.89±5.50 years. Eighty-seven out of 179 patients (48.6%) were treated with Adalimumab (ADA), 43/179 (24.02%) with Etanercept (ETN), 21/179 (11.73%) with Infliximab (IFX), 20/179 (11.17%) with Golimumab (GOL), whereas 8/179 (4.47%) with Certolizumab Pegol (CZP). HLA-B27 frequency was higher in patients with x-ray sacroiliitis than in those with nr-axSpA (*p*=0.01) as well as mean CRP serum level (*p*=0.0001), whereas both mean BASDAI and LEI score were higher in patients with nr-axSpA than in those with r-axSpA (*p*=0.018 and *p*=0.007, respectively). Similarly, psoriasis was more frequent in patients with nr-axSpA (*p*=0.02). Global retention rate in our cohort was 60.34% with mean survival time (MST) of 58.68 months (95% CI 47.93–69.42). MST for patients diagnosed with r-axSpA was 66.79 months (95% CI 53.54–80.04) and 39.05 months (95% CI 24.12–53.99) for those with nr-axSpA. Retention rates for r-axSpA patients and nr-axSpA ones were 64.88% and 47.92%, respectively. At α=0.05 we had good statistical power (β=0.1) to estimate effect size in term of Δ hazard ratio

Table I. Main clinical and demographic features of our cohort

	r-axSpA (131) (73.18%)	nr-axSpA (48) (26.82%)	*p*-value
Symptoms onset, years, mean ± SD*	41.33 ± 13.27	46.65 ± 13.99	0.0029
BMI, mean ± SD	25.31 ± 4.26	25.82 ± 2.51	>0.05
Disease duration, months, median (IQR)*	48 (20 -120)	11 (5 - 25)	<0.0001
LEI, median (IQR) *	0 (0 - 0)	1.71 ± 1.93	0.007
HAQ, median (IQR)	0.625 (0.125-1.325)	0.925 (0.500-1.325)	>0.05
BASDAI, mean ± SD *	5.02 ± 2.14	5.95 ± 2.03	0.0180
BASMI, mean ± SD	3.55 ± 1.66	3.57 ± 0.75	>0.05
BASFI, mean ± SD	3.86 ± 2.70	4.89 ± 2.77	>0.05
ASDAS-CRP, mean ± SD	3.06 ± 1.03	3.29 ± 0.75	>0.05
ESR, mm/h, mean ± SD	23.79 ± 19.53	21.53 ± 14.59	>0.05
CRP, mg/L, mean ± SD *	11.76 ± 23.75	2.30 ± 3.09	0.0001
HLA-B27, n (%)*	58 (56.86)	9 (31.03)	0.014
Female, n (%)	71 (54.20)	25 (52.08)	>0.05
Uveitis, n (%)	25 (19.08)	9 (18.75)	>0.05
IBD, n (%)	10 (7.69)	7 (14.58)	>0.05
Dactylitis, n (%)	7 (5.38)	4 (8.33)	>0.05
Psoriasis, n (%)*	3 (2.29)	5 (10.42)	0.020
Peripheral joint involvement, n (%)	65 (50.00)	21 (43.75)	>0.05.

r-axSpA: radiographic axial spondyloarthritis; nr-axSpA: non-radiographic axial spondyloarthritis; BMI: Body Mass Index; LEI: Leeds Enthesitis Index; HAQ: Health Assessment Questionnaire-Disability Index; BASDAI: Bath AS Disease Activity Index; BASMI: Bath AS Metrology Index; BASFI: Bath AS Functional Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score evaluating CRP; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table II. Causes of therapy discontinuation for patients with r-axSpA and nr-axSpa.

Causes of discontinuation of 1st TNFi	number (%)	r-axSpA	nr-axSpA
Adverse events	16 (22.54)	11 (23.91)	5 (20)
Primary failure	34 (47.89)	21 (45.65)	13 (52.00)
Secondary failure	13 (18.31)	9 (19.57)	4 (16.00)
Other reasons	8 (11.26)	5 (10.87)	3 (12)
Total	71 (39.66)	46 (25.69)	25 (13.97)

r-axSpA: radiographic axial spondyloarthritis; nr-axSpA: non-radiographic axial spondyloarthritis; TNFi: tumour necrosis factor inhibitors.

Table III. Hazard ratios for final Multivariate Cox Regression model with 95% CI. Patients without radiographic signs of sacroiliitis show a trend towards a 60% higher risk of discontinuing therapy than those with r-axSpA (overall significance of the model *p*<0.001).

Parameter	*p*-value	HR	95% Confidence Limits	
nr-axSpA	0.160	1.620	0.816	3.230
BMI	0.059	1.093	0.997	1.199
BASFI	0.008	1.192	1.045	1.358
HLA-B27	0.050	0.523	0.273	1.002

nr-axSpA: non-radiographic axial Spondyloarthritis; BMI: Body Mass Index; BASFI: Bath AS Functional Index.

(HR) of 0.50 between drug persistence of the latter groups. With this premise Log-Rank test showed a significant difference between survival function of r-axSpA patients and nr-axSpA ones (p=0.005).

Causes of discontinuation, classified as primary failure, secondary failure, adverse events, and other reasons (Table II), occurred without significant difference between patients affected with r-axSpA and nr-axSpA (p>0.05).

As a result of the initial screening, nr-axSpA, (HR 1.95, 95% CI 1.19-3.18), female gender (HR 1.66, 95% CI 1.02-2.70) as well as BMI (HR 1.08, 95% CI 1.01-1.15), HLA-B27 (HR 0.42, 95% CI 0.24-0.74), BASDAI (HR 1.28, 95% CI 1.11-1.48) and BASFI (HR 1.26, 95% CI 1.13-1.41), all determined at baseline, were fitted in saturated multivariate Cox model. BMI, HLA-B27 and BASFI were retained in the final model along with the diagnosis of nr-axSpA (overall significance p<0.001). For patients with nr-axSpA, there was a trend towards a 60% higher risk of discontinuing anti-TNF therapy than for those with x-ray sacroiliitis. Similarly, higher BASFI and BMI were found to have an impact on drug discontinuation. Conversely HLA-B27 had a protective effect (Table III). Nelson–Aalen hazard function following very closely Cox-Snell residuals over time showed that the final model fitted well the data in predicting drug discontinuation, except for large values of time (Fig. 2).

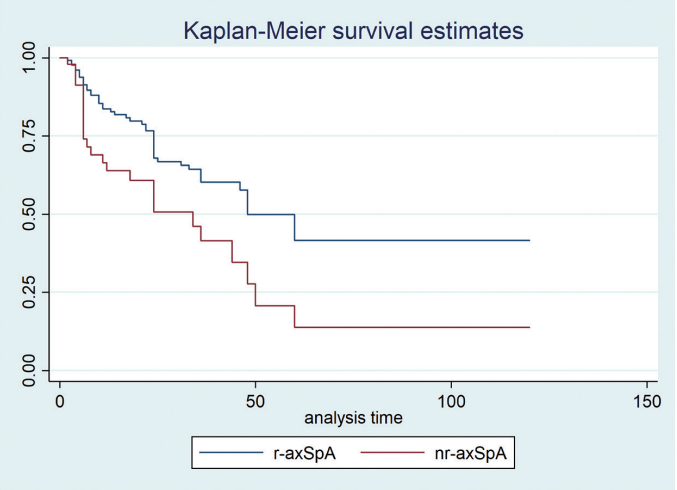

Fig. 1. Kaplan-Meier curves. Patients were stratified according the presence of radiographic sacroiliitis. r-axSpA: radiographic axial spondyloarthritis; nr-axSpA: non-radiographic axial spondyloarthritis

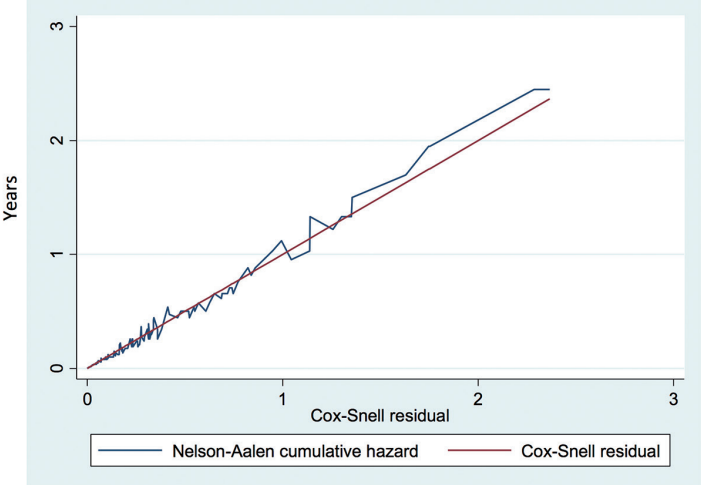

Fig. 2. Cox-Snell residuals following closely Nelson-Aalen cumulative Hazard function over time demonstrate that our model fitted well the data, except for large value of time.

Discussion

In the present study, we assessed the retention rate of TNFi in biologic-naive r-axSpA and nr-axSpA patients. Previous data demonstrated that drug survival on first line TNFi was significantly higher in patients marked by structural damage of the sacroiliac joints on conventional radiographs (18). Unlike prior studies have reported nr-axSpA male patients as better survivors in anti-TNF therapy (19), in our study, gender did not impact on drug discontinuation in multivariate analysis. As expected, the presence of HLA-B27 allele was observed more frequently in r-axSpA compared to patients with nr-axSpA (20). In this regard, HLA-B27 haplotype appears to contribute to sacroiliac joints inflammation that may lead to the development of radiographic signs (21). The protective effect of HLA-B27 on drug discontinuation seems to confirm previous evidence identifying patients whose outcomes were potentially modifiable to TNFi treatment (22). In our study, patients with r-axSpA had increased CRP compared to nr-axSpA ones, and this finding may explain a longer treatment adherence on anti-TNF in r-axSpA, as higher CRP serum levels often reflect a more active inflammation and might represent a strong predictor of damage progression from non-radiographic to radiographic stages (23). Similarly to our results, data from a French observational study aimed at evaluating the retention rates of first line anti-TNF treatments in axSpA, have shown that the presence of high CRP levels, sacroiliitis on x-ray as well as low BASDAI were associated with a better drug retention. Interestingly, concomitant or prior employment of disease-modifying anti-rheumatic drugs in patients with extra-spinal symptoms allowed a better management of their disease, thus increasing drug survival (24). Yet, results from a recent cohort study based on the nationwide DANBIO registry suggest that axSpA patients with high baseline BASDAI, more often women, HLA-B27 negative, and obese display lower treatment response and persistence on drug with the first TNFi. Similar results have been found for patients with high

BASFI, pain score and patient global score. On this basis, other possible causes of pain should be taken into account when the lack of treatment response is present (25). The possible association between disease activity measures and clinical outcomes is not univocal. On one hand previous studies have shown a similar burden of disease evaluated by the patient reported BASDAI and impaired function (BASFI) between r-axSpA and nr-axSpA (26, 27), suggesting that higher BASDAI and BASFI seem to be associated with a better clinical response to TNF-α blockers (28). On the other hand, BASDAI and BASFI are not specific for axSpA, as high scores might be detected in patients with other conditions such as fibromyalgia (FM). Although the ASAS criteria are classification and not diagnostic criteria, they have become widely used as a guide to diagnosis in clinical practice. However caution should be used to apply them as a diagnostic tool when objective signs of structural damage or inflammation are absent, since approximately 20–30% of patients with FM suffer from inflammatory back pain, making it more difficult to differentiate from nr-axSpA (29). In this regard, a recent French study has reported a proportion of 21.4% of nr-axSpA patients, without sacroiliitis on MRI nor elevated CRP, also diagnosed with fibromyalgia. In particular, axSpA patients with coexisting FM presented significantly with more enthesitis, higher BASDAI and VAS-pain and poorer BASFI, furthermore the 2-years retention rate of the first TNFi was lower in the group of patients with concomitant FM (30). Based on this evidence, in our cohort, it is conceivable that concomitant FM might have been responsible for therapy discontinuation in nr-axSpA group, albeit its presence was not assessed in such patients, thus representing the main limitation of our study.

Moreover, our study confirmed the negative influence of obesity on treatment outcome in patients with axSpA. Consistently, a recent meta-analysis showed that the odds of reaching a good response or achieving remission were lower in obese than in non-obese patients who were treated with anti-TNF agents (31). Another limitation of our study may be found in its retrospective observational design, therefore some data were missing and this might have affected our results. Furthermore, diagnosing sacroiliitis on MRI may vary according to the expertise of the physician (32). In daily practice, awareness of clinical history may influence resident radiologists in reading sacroiliac-joints MRIs and represent a pitfall, leading clinicians to classify patients as affected with axSpA. On the other hand, in clinical trials more than one reader, often blinded for clinical information, view the images providing more objective judgments on MRI abnormalities in the sacroiliac joints (13, 33). Therefore, it cannot be excluded that inconsistencies in the interpretation of MRI may have resulted in misclassification of patients and biased therapeutic approach. In this regards, a recent report has demonstrated that positive findings on MRI of the sacro-iliac joints that are highly suggestive, but not reflective of axSpA may be seen frequently in unaffected individuals such as runners and chronic back pain affected patients (34). In conclusion, effectiveness of TNFi seems to be lower in patients with nr-axSpA than in those affected with r-axSpA. Functional disability along with obesity may account for these findings. Accordingly clinicians should be aware of those factors in managing nr-axSpA patients in real life setting.

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