Predictors of drug retention and treatment response in axial spondyloarthritis patients treated with certolizumab: real-life results from the HURBIO registry

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Abstract

Objective

To assess the real-life retention rate of certolizumab and factors related to retention of certolizumab.

Method

We analysed all patients who received at least 1 dose of certolizumab and were registered in the HURBIO database. Patients with at least 1 control visit were included in efficacy analysis. Drug retention rates were calculated using the Kaplan-Meier method and predictors of drug retention was determined by Cox proportional hazard model. Factors predicting BASDAI50 response at first visit were analysed by the logistic regression analysis. Reasons of switching and discontinuation were also determined.

Results

A total of 325 (AS (76%), female 55%) patients were recruited. Median follow-up while receiving certolizumab was 13 (4.7–22.7) months. At 1 year, overall certolizumab retention rate was 72.5%. Predictors of poor certolizumab retention were: Current or ex-smoker [HR 1.11 (0.70–1.76), p=0.65], high CRP levels [HR 0.72 (0.45–1.16), p=0.18], biologic-naïve [HR 0.81 (0.49–1.32), p=0.39] and good BASDAI50 response at first control visit [HR 0.54 (0.30–0.96), p=0.04]. Mean duration from starting certolizumab to the first control visit was 3 (3-6) months. Predictors of poor BASDAI50 response: Presence of nr-axSpa [RR 2.12 (1.01–4.51), p=0.05], female gender [RR 2.14 (1.20–3.82), p=0.01] and history of biologic therapy [RR 3.52 (1.95–6.33), p<0.001]. The most common causes of drug switch were primary failure and drug side-effects.

Conclusion

In this study, good BASDAI50 response at first visit seems to be a strong predictor of higher retention of certolizumab in patients with axial spondyloarthritis.

Key words

certolizumab, BASDAI50, axSpA

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Introductıon

Axial spondyloarthritis (axSpA) is an inflammatory arthropathy of the spine which typically affects sacroiliac joints and usually presenting as chronic back pain, typically before the age of 45 (1). Patients with axSpA can be classified as having either of two subtypes of axSpA: ankylosing spondylitis (AS) or non-radiographic axSpA (nr-axSpA) (1). Patients with AS exhibit radiographic abnormalities consistent with sacroiliitis, but such findings are absent or minimal on plain radiography in nr-axSpA (1).

In recent two decades, our understanding of axSpA was largely changed with the exploration of tumour necrosis factor (TNF) molecules in sacroiliac joints (2). Today, there are five anti-TNF molecules available for axSpA treatment: infliximab (IFX), adalimumab (ADA), etanercept (ETN), certolizumab (CZP), and golimumab (GOL). The efficacy of these agents is approved by numerous clinical trials (3).

Drug retention rates and possible factors related to drug retention have been questioned by several long-term analyses of clinical trials and real-life data provided by biologic registries. Young age, male sex, smoking, high inflammatory markers, concomitant DMARD use have been found as predictive factors for drug retention in several studies (4-8). However, in most of these studies, most of the patients were prescribed any of the 3 earlier drugs: IFX, ADA, ETN (9). In current literature, real-life data regarding drug retention of CZP is scant.

In this study, our main aim was to determine the real-life retention rate of CZP and factors related to retention of CZP. Secondary objectives of this study were to determine treatment response at the first control visit and factors predicting this response, the former anti-TNF exposure, causes and rate of switching to another anti-TNF and adverse events related to CZP.

Methods

Study population

We conducted this study with AS and nr-AxSpA patients who received at least 1 dose of CZP in our clinic and were registered in the Hacettepe University biological database (HUR-BIO) which was set up in 2005 (10). Plain radiographs of all patients were re-evaluated and all patients met the Assessment in Ankylosing Spondylitis International Working Group criteria, which defines ankylosing spondylitis as the prototype of SpA with predominantly axial involvement typically bilateral grade 2 or at least unilateral grade 3 sacroiliitis on plain radiography and defines nr-AxSpA as axial SpA without plain radiographic changes of sacroiliitis (11). Patients with at least 1 control visit were included in the efficacy analysis.

Data collection

We collected these following demographic data: age, gender, education level, body mass index (BMI), the prevalence of comorbidities, history of orthopedic surgery, smoking history, disease duration, family history of SpA, the rate of HLA-B27 positivity, history of uveitis. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), pain-visual Analogue Scale (VAS), patient global assessment of disease activity (PGA)-VAS, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores were used to assess disease activity. BASDAI50 response which was defined as 50% improvement of the initial BASDAI (BASDAI 50) at the first control visit was used to assess the early response of patients to certolizumab. Prior anti-TNF therapy, rate and causes of treatment switch or discontinuation and adverse events were also recorded. As the rate of missing data about concomitant or preceding synthetic disease-modifying anti-rheumatic drug were high, we did not include these data to further analysis.

Our study is compliant with the Helsinki Declaration and approved by Hacettepe University ethical committee (approval no. KA-17058).

Statistical analyses

Statistical analysis was performed using the Statistical Package for the Social Sciences software (v. 25 .0; IBM Corporation, Armonk, NY, USA). The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov,

skewness and curtosis) to determine whether or not they are normally distributed. The data of descriptive analysis were expressed as either mean ± standard deviation (SD) or the median, interquartile range (IQR). Categorical variables were compared with the Chi-square test or Fisher's exact test where appropriate. The Student *t*-test and Mann-Whitney U-test was used to compare the normally and non-normally distributed continuous data between two groups, respectively.

The univariate effects of age, gender, BMI, educational level, history of anti-TNF treatment, disease duration, type of axial disease, baseline ESR-CRP levels, achievement of BASDAI50 response criteria on certolizumab retention were investigated using the log-rank test. The Kaplan-Meier survival estimates were calculated. The possible factors identified with univariate analyses ($p<0.20$) were further entered into the Cox regression analysis, with the backward selection, to determine independent predictors of certolizumab retention. Among correlated factors with similar effects on certolizumab retention, only those with clinical significance were included. The proportional hazards assumption and model fit was assessed by means of residual (Schonfeld and Martingale) analysis.

Possible factors (same factors tested for Cox regression analysis) identified with univariate analyses ($p<0.20$), were further entered into the logistic regression analysis to determine independent predictors of BASDAI50 response. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit.

A 5% Type-I error level was used to infer statistical significance.

Results

Patients' characteristics

A total of 325 patients [AS: 248 (76%) or nr-AxSpA: 77 (24)] were recruited. Mean age was 40.0±10.7 years and 180 (55%) of patients were female. Mean disease duration was 7.7±5.9 years. Approximately two-thirds of all patients were graduated from high school or university. Smoking (ex- or current) ratio was 56%. Hypertension, diabetes and obesity (BMI>30) were prevalent in 12%, 6.5%, 27.5% of patients, respectively. History of the knee, hip or disc herniation (lumber or cervical) surgery were recorded in 5 (1.5%), 5 (1.5%) and 11 (3.4%) patients, respectively. Disease duration, HLA-B27 positivity, baseline ESR and CRP levels were higher in AS group compared to nr-AxSpA group. Details of demographic and baseline disease characteristics are given in Table I.

Table I. Demographic and baseline disease characteristics of all patients who ever received certolizumab.

	All (n=325)	Ankylosing spondylitis (n=248)	Non-radiographic axial SpA (n=77)	*p*-value
Female*	180 (55)	136 (54.8)	44 (57.1)	0.72
Age, mean SD	40 ± 10.7	40.6 ± 10.9	38 ± 9.6	0.10
Disease duration (years), mean (SD)	7.7 ± 5.9	8.2 ± 6.2	6.1 ± 4.8	**0.003**
HLA-B27 (+) °*	91 (41.7)	75 (47.5)	16 (26.7)	**0.005**
Family history of SpA*	59 (18.2)	45 (18.2)	14 (18.2)	1.00
Uveitis*	26 (8.0)	22 (8.9)	4 (5.2)	0.21
Disease activity before starting certolizumab**	(n=305)	(n=229)	(n=76)	
- ESR (mm/h)	16 (7-33)	19 (8-36)	10.5 (4-23.5)	**<0.001**
- CRP (mg/l)	9.1 (3.8-20.5)	10.2 (4.5-27.5)	5.7 (3.0-10.4)	**<0.001**
- PGA VAS (0-100 mm)	60 (50-80)	60 (50-80)	60 (50-80)	0.76
- Pain VAS (0-100 mm)	70 (50-80)	70 (50-80)	60 (50-80)	0.73
- BASFI (0-10)	4.6 (2.2-6.7)	4.4 (2.1-6.8)	4.7 (2.5-6.5)	0.57
- BASDAI (0-10)	5.8 (4.3-7.3)	5.9 (4.4-7.6)	5.8 (4.3-7.2)	0.61

* n (%), **Median (IQR). °Calculated over 218 patients with HLA-B27 testing.
BASFI: Bath Ankylosing Spondylitis Functional Index, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, IQR: interquartile range, VAS: visual analogue scale.

In a biologic-experienced group, distribution of former anti-TNF therapies as follows: 95 (66%) patients adalimumab, 70 (49%) patients etanercept, 54 (38%) patients infliximab and 38 (27%) patients golimumab.

Treatment response and predictors of response

Patients with at least one visit after starting certolizumab (271, 83.4%) were included to further analyses to compare the effectiveness of the drug (see Fig. 1). Median follow-up of these patients when they were receiving certolizumab was 13 (4.7–22.7) months. To test the overall effectiveness of certolizumab, we compared the ESR (mm/h), CRP (mg/dl), PGA VAS (0–100mm), pain VAS (0–100 mm) and BASFI (0–10mm) values at the visit just before starting certolizumab and the last visit of the patient under certolizumab therapy. Baseline *versus* last visit values for these parameters as follows: ESR: 16 (7-33) *vs*. 10 (4–21); CRP: 0.91 (0.38–2.05) *vs*. 0.43 (0.25–0.76); PGA VAS: 60 (50–80) *vs*. 40 (20–60); pain VAS 70 (50–80) *vs*. 40 (20–70); BASFI 4.6 (2.2–6.7) *vs*. 2.6 (0.7–5.1); $p<0.001$ for all parameters.

Mean duration from starting certolizumab to the first control visit was 3 (3–6) months. We had both initial and the first control visit BASDAI values of 237 (87.5%) out of 271 patients. 78 (33%) of these patients achieved the BASDAI50 response criteria. Logistic regression analysis revealed these factors as possible predictors of poor BASDAI50 response: *Presence of nr-axSpa* [RR 2.12 (1.01–4.51), $p=0.05$], *female gender* [RR 2.14 (1.20–3.82), $p=0.01$] and *history of biologic therapy* [RR 3.52 (1.95–6.33), $p<0.001$]. Although a high rate of BASDAI50 response was seen in HLA-B27 positive patients (43% *vs*. 27%, $p=0.03$), the rate of missing data was high that we could not include this parameter into the final regression model.

Certolizumab retention and predictive factors

At 1 year, overall certolizumab retention rate was 72.5% (Fig. 2A). Median certolizumab retention was 30 (24-36) months. Certolizumab retention was similar in AS and nr-AxSpA patients (log-rank, $p=0.24$, Fig. 2B) Unadjusted certolizumab retention was found sig-

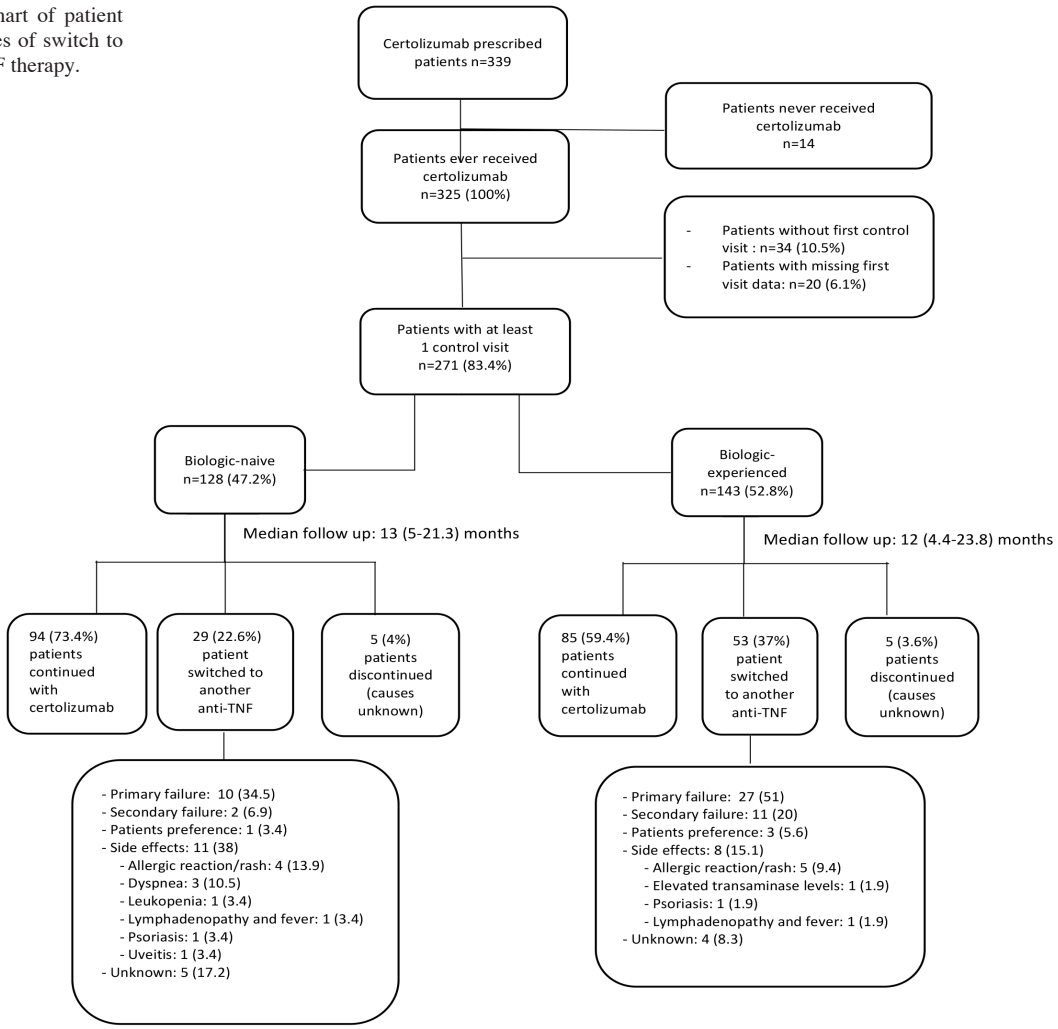

Fig. 1. Flow chart of patient enrolment, causes of switch to another anti-TNF therapy.

nificantly higher in biologic-naïve and patients with good BASDAI50 response at the first visit by univariate analyses (log-rank, p=0.03 and p=0.007, Fig. 2C and D, respectively). Possible predictors related to poor certolizumab retention were analyzed by Cox proportional hazard model and revealed these factors: *Current or ex-smoker* [HR 1.11 (0.70–1.76), p=0.65], *high CRP levels* [HR 0.72 (0.45–1.16), p=0.18], *biologic-naïve* [HR 0.81 (0.49–1.32), p=0.39] and *good BASDAI50 response at first control visit* [HR 0.54 (0.30–0.96), p=0.04].

Treatment discontinuation and switches

Certolizumab was discontinued in 92 (34%) of 271 patients; 34 (26.5%) of them were biologic-naïve and 58 (40.5%) of them were biologic-experienced. In both groups, 5 patients discontinued their therapies and lost to follow-up, so, their certolizumab-exposure time was calculated according to their last visit. Switch to another biologic treatment was made in 29 (22.6%) biologic-naïve and 53 (37%) the biologic-experienced patients.Switch rate was significantly higher in biologic experienced group (p=0.021, log-rank). As the cause of the treatment switch, treatment failure rate (primary and secondary) was higher in biologic-experienced patients (41.5% *vs*. 71%); however, side effects were occurred more frequent in biologic-naïve group (38% *vs*. 15.1%). The most common side effect was allergic reactions in both groups. Details of therapy switch and side effects are given in Figure 1.

Discussion

In this study, presenting the real-life experience of certolizumab in axial SpA patients, the certolizumab retention rate was 72.5% at 1 year and median drug survival was 30 months. Presence of nr-AxSpA, female gender, and former anti-TNF usage were found as predictors of poor treatment response at the first visit. Good treatment response at the first visit defined by BASDAI50 response was found as the only factor predicting better certolizumab retention. To our knowledge, our study has the longest real-life follow-up duration of patients on certolizumab.

Data regarding real-life results of CZP is scant in current literature. In a study from Spain including 336 patients with axSpA, certolizumab retention rate was 76%, similar to our study(12). In this study, BASDAI50 response rate, according to the last visit, was 41% and BASFI score was lower in the last visit compared to the first visit (12). BASDAI50 response was slightly lower in our study, this may be due to different application of BASDAI50 response criteria in this study and our study. Another multicentre real-life data regarding certolizumab including 666 axSpA patients, certolizumab was found ef-

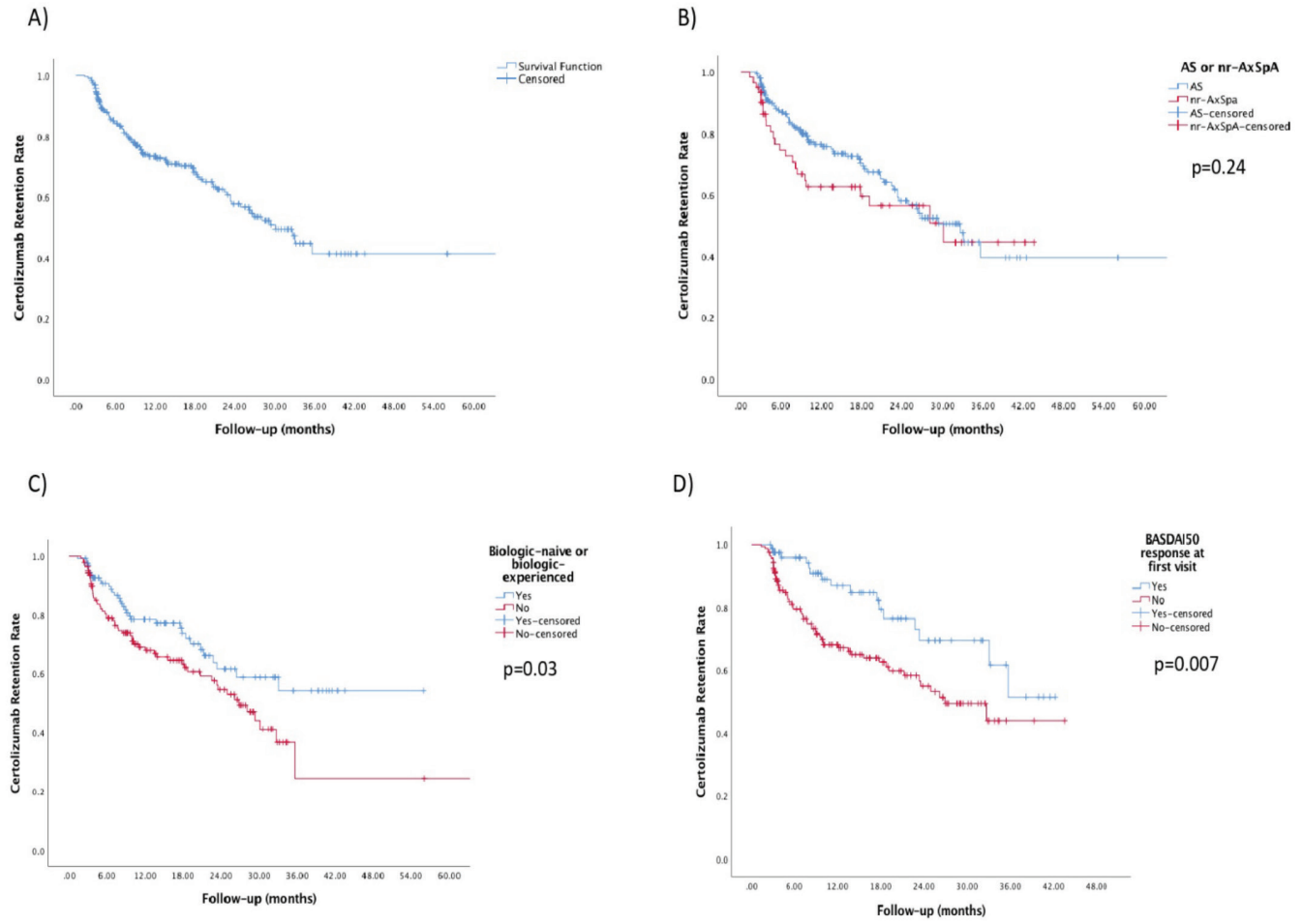

Fig. 2. **A**: Unadjusted certolizumab retention; **B**: Unadjusted certolizumab retention in AS and nr-AxSpA patients; **C**: Unadjusted certolizumab retention in biologic-naive or biologic-experienced AS and nr-AxSpA patients; **D**: Unadjusted certolizumab retention in BASDAI50-responder or non-responder AS and nr-AxSpA patients.

fective at 12 weeks, ASAS20 response was achieved in 57.4% patients(13). Also the effectivity continued over 24 weeks, represented as 63.8% achievement of ASAS20 criteria (13). Because of the methodological issues, we could not calculate the ASAS20 response in our study. Although we used different response criteria, certolizumab found as an effective treatment option. Four-year outcome analysis of the randomised clinical trial of certolizumab (RAPID-axSpA) revealed sustained efficacy of certolizumab, ASAS20 response rate was 54.1% (14, 15). In another long-term analysis of RAPID-axSpA, achievement of a good response at 12 weeks was found as a strong predictor of low disease activity at 48 weeks, similar to our results (14, 16).

Several studies from different countries and databases revealed different retention rates of INF, ADA, and ETA in axSpA patients so fort. In a recent study from France, overall retention of these agents were similar and 78% at 1 year, 72% at 2 years, 62% at 3 years, 52% at 5 years and 38% at 10 years (17). However, in DANBIO registry, same agents had a lower retention rate as 74% and 63%, at 1 and 2 years, respectively, similar first year retention to our study (18). Another multicentre study from Italy by Scire *et al*., reported that the 1-year retention rates of these agents are over 80% and the overall survival off ETA and ADA were significantly higher than INF in AS patients (19). Similar to the study by Scire *et al*., in a early study conducted in 2015 from the HURBIO database, 1-year retention rates of INF, ADA and ETA were 84%, 81% and 85%, respectively, relatively higher retention rates from the current study (20). In that study, rate of anti-TNF-experienced patients were 29.7%, much lower than the current study (52.8% in the current study); this may explain the lower retention rate of certolizumab in current study (18). Data regarding the golimumab retention rate is relatively scant and in one of the major studies regarding this perspective, the overall 2-year retention rate of golimumab was 62.8% in 120 AS patients (21).

Male gender, high inflammatory response and presence of AS were suggested by several studies for the predictors of better drug retention (4, 5, 18, 20, 22). Similar to current study, overall drug retention rates were found similar between patients with AS and nr-AxSpA in earlier studies (20). However, in a recent study by Lopalco and colleagues, survival of first-line anti-TNF agents were significantly higher in nr-AxSpA patients (23). According to DANBIO registry, clinical response defined by BASDAI50 response was found as a

predictor of continued treatment, similar to our study (18, 24). Another study evaluating effects of persistently high patient-reported outcomes (PRO) including the at least three of the first five BASDAI items on anti-TNF treatment, authors concluded that the patients with higher PRO were less likely to maintain the treatment at 2 years, in other words, non-responding patients were less to maintain the treatment (25). Predictive factors of good treatment-response differ from one study to another. Young age at the start of treatment, being nonsmoker, high baseline CRP levels were found as predictors of response, in a recent study including patients receiving INF, ADA or ETA (17). Also, similar factors were found in DANBIO registry (18). We could not observe these factors as a predictor of response in our study. However, having nr-axSpA was found as a risk factor for poor response in several studies, similar to ours (17, 26).

Treatment discontinuation was mostly due to the inefficacy of certolizumab (primary or secondary) in our study, consistent with the studies related with other anti-TNF therapies (4, 17, 18). However, the rate of inefficacy was higher in biologic-experienced group in our study. This data needs to be evaluated in other studies and reasons should be elucidated.

The main limitation of our study was its one-centre design. Our results should be validated in larger and multicentre studies. Also, the high missing data rate for several parameters must be counted as another limitation of our study.

In conclusion, good BASDAI50 response at the first visit was found as a strong predictor of longer certolizumab retention. Also, the presence of AS, male gender and absence of previous anti-TNF history were found as predictors of a better response to certolizumab.

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