Research Article

Does Late Axial Spondyloarthropathy Diagnosis Cause Extra Anti-TNF Therapy?

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Abstract: Introduction: Ankylosing Spondylitis (AS) is a chronic inflammatory rheumatic disease that mainly characterized by sacroiliac joint and spine involvement. Although there is no clear evidence that any of these agent prevent the radiologic progression, anti-TNF drugs provide significant improvements in the disease activity score, functional index and quality of life.

In AS patients, knowledge of the factors that determine the need for anti-TNF treatment will be associated with fewer complication sand better treatment. The purpose of this study is to investigate the possible factors which willmark the transition to the anti-TNF therapy in AS patients.

Materials and Methods: This study was conducted in the Rheumatology division of the Internal medicine department of the Ondokuz Mayis University of Medicine hospital between January 2012- June 2015. The study protocol was approved by the Ethics Committee of Ondokuz Mayis University. A total of 165 patients, who were diagnosed as AS according to the ASAS classification criteria, were enrolled in this study. There were 85 women (51.5%) and 80 men (48.5%), aged between 15-69. Patients were divided into two groups according to their use of anti-TNF drug.

Results: A total of 165 Ax-SpA patients (85 women and 80 men) were included in the study. The mean age was 37.82±11.24 years. The mean duration of the disease was 4.59±5.35 years. male gender, uveitis, delay in diagnosis, elevations in sedimentation CRP levels, increase in disease activity and functional indexes such as BASDAI and BASFI scores shows the more frequent need for anti-TNF drug use.

Conclusion: In our study, patients who needed anti-TNF treatment had a longer time between symptom onset and diagnosis than patients who did not hear. The delay in diagnosing these patients leads to a delay in treatment so that the focus of inflammation increases and these patients need more anti-TNF as this window of opportunity escapes.

Keywords: Ankylosing spondylitis, Low back pain, Anti-TNF treatments, NSAİD treatments, Sociodemographic characteristics, Treatment protocols.

INTRODUCTION

Axial Spondyloarthropathy (Ax-SpA) is classified under Spondyloarthropathy (SpA). Other group members of this disease group are reactive arthritis, psoriatic arthritis, juvenile Spondyloarthropathy, and Enteropathic Spondyloarthropathy related to inflammatory bowel disease [1, 2]. Ax-SpA is a chronic inflammatory rheumatic disease, which involves the sacroiliac joints and spine [3].

Different values were reported regarding its prevalence. However, it is one of the most common rheumatic inflammatory diseases. Low back and spine pain, prominence in axial movements, and kyphosis can be seen in later stages due to the involvement of the vertebral and paravertebral ligaments with sacroiliitis. Furthermore, these complaints and symptoms are the main morbidities of the disease [2, 4, 5]. It causes functional losses, mainly affecting spinal movement. Inflammation and pain in the spine and joints cause diminished physical activity, fatigue, sleep disturbance, depression, anxiety, and stress [6].

Factors such as male sex, early onset of the disease, peripheral arthritis, hip joint involvement, smoking, low education, and socioeconomic level negatively affect the condition [7]. Kyphosis due to axial Spondyloarthropathy develops in the advanced stage and is seen only in 30% of patients [2]. Although this is the worst part of the clinical spectrum, it should be kept in mind that the quality of life can be relatively improved with the intermittent use of non-steroidal anti-inflammatory drugs (NSAIDs) to reduce pain in people with a very remote possibility of developing kyphosis [8].

There is new evidence that initiating early treatment in axial Spondyloarthropathy may change this outcome. Initial studies show that radiographic progression of Ax-SpA is not retarded by anti-tumor necrosis factor (anti-TNF) therapy, while two observational studies show reduced radiographic progression with these agents [9,10]. One of these studies showed that a delay in the initiation of anti-TNF drugs was associated with

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greater radiographic progression [10]. Additionally, magnetic resonance imaging (MRI) studies have supported the relationship between inflammation and the advancement of ankylosis. The progression of acute inflammatory lesions to chronic fatty lesions is higher than in non-inflammatory sites [11].

Anti-TNF treatment of patients with active Ax-SpA using infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab strongly affects the disease activity [12-16]. There is evidence that anti-TNF drugs reduce inflammatory lesions detected by MRI. Anti-TNF therapy can rapidly relieve low back pain during the first two weeks in Ax-SpA, reduce disease activity, increase spine function and mobility, and ultimately achieve improvements in nearly all clinical pictures of Ax-SpA. Therefore, this study aimed to investigate factors that may lead to the transition to anti-TNF drugs and the effect of delayed diagnosis in Ax-SpA patients.

MATERIALS AND METHODS

Patient Selection

A total of 165 Ax-SpA patients, aged between18-68, 85 women (51.5%) and 80 men (48.5%), were included in the study. Patients applied to the Department of Internal Medicine, Faculty of Medicine, Ondokuz Mayıs University (Turkey) between January 2012 and June 2015 and were diagnosed with Ax-SpA or followed up with the diagnosis of Ax-SpA according to the ASAS (Assessment of Spondyloarthritis International Society) classification criteria [17] were included in the study. Before the study, participants in the patient and control groups were informed about the study, and written informed consent was obtained. The study was conducted according to the Declaration of Helsinki. Ethics board approval was taken from the Ondokuz Mayıs University Ethics Committee (OMÜ KAEK 2015/362 on 10.09.2015).

Clinical and Laboratory Evaluations

The ASAS classification criteria for axial Spondyloarthropathy include two different measures: genetic (HLA-B27 positivity and ≥2SpA findings) and imaging (sacroiliitis and ≥ 1 SpA findings). Since HLA-B27 could not be evaluated, 217 patients diagnosed with the imaging method (age ≥18) were assessed, and 52 patients not accepting to join or not appearing in their appointments were excluded from the study. Of the 165 participants who agreed to join and were followed up regularly, in addition to demographic characteristics (e.g., age, sex, and education), the history of Ax-SpA diagnosis, previous uveitis attacks, and family members diagnosed with Ax-SpA was queried.

Patients who accepted to participate were divided into two groups: those who received anti-TNF therapy (n=48) and those who did not (n=117). Before anti-TNF treatment, hepatitis indicators were checked, chest X-rays were taken, PPD tests were performed, and patients were examined for signs of infection. Anti-TNF therapy was initiated in patients with typical test results. NSAID use, its duration, and sulfasalazine (SSZ) use were questioned in 117 patients who were not receiving anti-TNF therapy. The group receiving anti-TNF (not responding to treatment with two different and sequential NSAIDs before) consisted of 48 patients who started anti-TNF treatment and continued to use anti-TNF actively. Also, the NSAID needs of the patients were questioned.

In the follow-up, disease activity, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Functional Index (BASFI) scores were measured [18, 19]. ESR levels, CRP levels, BASDAI scores, and BASFI scores of the patients at the last follow-up and the patients who applied were compared. Additionally, labor loss in the last three months and one year was evaluated retrospectively.

STATISTICAL ANALYSIS

Data were entered into the computer and analyzed using the SPSS for Windows 22.0 (SPSS Inc., Chicago, IL) software. Descriptive statistics were presented as means ± standard deviations (min.-max.), frequencies, and proportions. Categorical variables were analyzed with the Yates' corrected Chi-square test (or Fisher's exact test). The conformity of the variables to the normal distribution was assessed visually (histogram and probability graphs) and Shapiro-Wilk test. The student's t-test was applied to determine the significance between two independent groups regarding symmetrically-distributed numerical variables, whereas the Mann-Whitney U test was used to analyze skewed variables. Finally, Bonferroni-corrected pairwise comparisons were applied to check the significances between subgroups. $p<0.05$ was accepted as statistically significant.

RESULTS

A total of 165 Ax-SpA patients (85 women and 80 men) were included in the study. The mean age was 37.82±11.24 years. The mean duration of the disease was 4.59±5.35 years. Of the patients, 12.5% (n=21) had family members diagnosed with Ax-SpA. The frequency of uveitis was 14.3% (n=24). The average number of applications of the patients within the last year was 3.96±3.37 times. The time interval between the onset of symptoms and the diagnosis of Ax-SpA was 26.97±36.44 months (Table **1**). Of the patients, 18 were using NSAIDs, 2 were using sulfasalazine, and 97 were using NSAIDs and sulfasalazine together, whereas 48 were using anti-TNF.

Table 1. Sociodemographics and Clinical Characteristics of the Patients.

Study Parameters		**Study Group (n=165)**
Demographic Features	Age (year)	37.82±11.24
	Sex (Female / Male)	85/80
Clinical Features	Ax-SpA duration (year)	4.59±5.35
	Time between symptoms and diagnosis (month)	26.97±36.44
	Uveitis	24 (14.3%)
	Number of applications in the last year	3.96±3.37
	Ax-SpA family history	21 (12.5%)
Treatment Protocols	NSAID	18 (10.7)
	Sulfasalazine	2 (1.1)
	NSAID+ sulfasalazine	97 (57.7)
	Anti-TNF	48 (28.5)

Of the 48 patients treated with anti-TNF, 15 (31%) were using adalimumab, 13 (27%) etanercept, 12 (25%) golimumab, 5 (10%) certolizumab, and 3 (6%) infliximab. Anti-TNF treatment was started 35.25±41.35 months after the diagnosis, and it was used for 20.60±21.27 months.

When the anti-TNF-treated group was compared with the disease-modifying Anti-Rheumatological Drugs (DMARDs) and NSAID-treated groups, no difference was found between age, family history of AS, educational level, and current status of ESR, CRP, BASDAI, and BASFI scores (Table **2**). On the other hand, male gender, duration of disease, delayed diagnosis, frequency of uveitis, the annual number of hospital visits, time gap between last admission and current admission, pre-treatment ESR, CRP, BASDAI, and BASFI values were significantly higher in the anti-TNF treatment group (Table **2**).

Table 2. Demographic, Clinical, and Laboratory Characteristics of Patients with/without Anti-TNF Therapy.

Study Parameters		**DMARD and NSAID Group (n=117)**	**Anti-TNF Group (n=48)**	**p**
Socio Demographic	Age (year)	37 (15-69)	38 (15-69)	0.873
	Sex (Male)	58.9%	70.8%	0.001
Clinical Features	Delay in diagnosis (months)	25.02±32.70	32.06±444.72	0.012
	Disease birge (year)	3.79±4.76	6.70±66.26	0.014
	Family History	13.6%	8.3%	0.489
	Uveitis	12/105	12/36	0.028
	Number of applications (last year)	2.96±2.63	6.42±3.81	<0.001
	Active at current applications (n)	19 (16%)	4 (8%)	0.278
	Duration until the last application (month)	6.7±6.8 (1-24)	2.4±3.9 (1-24)	<0.001
Laboratory Tests	ESR at admission (mm/hour)	40.1±26.0	54.4±26.7	0.001
	Current ESR (mm/hour)	24.9±19.8	20.8±19.6	0.096
	CRP at admission (mg/L)	29.2±52.0	50.8±51.1	<0.001
	Current CRP (mg/L)	7.2±12.5	5.6±11.3	0.238
Measurement	BASDAI at admission	5.2±1.7	6.2±1.60	<0.001
	Current BASDAI	2.0±1.4	1.9±1.5	0.508
	BASFI at admission	5.8±1.8 (2-10)	6.6±1.7 (1-10)	0.005
	Current BASFI	2.27±1.68	2.37±1.62 (0-5)	0.726

Note: Comparisons were made with the Student t-test. ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index.

When the anti-TNF treatment group was compared with the DMARD and NSAID groups, no difference was found regarding employment status and loss of labor in the last three months and one year (p> 0.05) (Table **3**).

Table 3. Evaluation of the Employment Status of Patients with/without Anti-TNF-Treatment and Workforce Loss in the Last Three Months and One Year.

Study Parameters		DMARD and NSAID Group Number (%*)	Anti-TNF Group Number (%*)	p
Job Status	Unemployed	66 (58.9)	22 (46.8)	0.219
	Employed	46 (41.1)	25 (53.2)	
Sick Leave in the Last Three Months	Not present	41 (89.1)	24 (96.0)	0.414
	Present	5 (10.9)	1 (4.0)	
Sick Leave in the Last Year	Not present	35 (76.1)	19 (76.0)	0.998
	Present	11 (23.9)	6 (24.0)	

DISCUSSION

There is evidence that effective early treatment of Ax-SpA inflammation can alter disease outcomes. In clinical practice, identifying high-risk persons and indications for rapid treatment have gained importance. Thus, in addition to the accurate diagnosis of high-risk individuals, early targeted therapy guidance tips were investigated in RA-affected Ax-SpA patients to assess the window of opportunity. One of the most prominent clinical features and mostly feared morbidities of axial Spondyloarthropathy is the development of structural spine injury over time. Various studies have reported 20-45% radiographic progression of Ax-SpA within two years [20-24].

Before imaging the sacroiliac joint with MRI, advanced-stage Ax-SpA-patients with clinical and radiological progression can be diagnosed by direct radiography. Studies conducted during this period have reported that Ax-SpA is more common in men with severer symptoms [25]. However, there is no gender difference in the frequency of AS in studies performed after sacroiliac MRI imaging since patients with early-stage non-radiographic axial SpondyloArthritis [nr-Ax-SpA) are diagnosed by MRI [26]. In a meta-analysis of eight studies including 2236 patients with Ax-SpA and 1242 patients with nr-AxSpa, 70.4% of Ax-SpA patients were male, whereas only 46.5% of patients with nr-AxSpA were male [26]. Although this was not the main purpose of this study, similar female/male ratios were found with the existing studies. Similar to the available literature, the male gender was significantly higher in this study's patients treated with anti-TNF.

Clinical determinants of radiographic progression detected to date include high ESR and CRP, tobacco smoking, male sex, uveitis, presence of basal syndesmophytes, and increased disease activity scales in BASDAI and BASFI [24, 27, 28]. Similarly, it is not surprising that patients treated with anti-TNF in this study had more males and higher ESH, CRP, BASDAI, and BASFI values in the pre-anti-TNF period. Male gender and high ESR, CRP, BASDAI, and BASFI values were thought to require anti-TNF therapy.

The window of opportunity is very important in rheumatoid arthritis (RA). Early treatment with DMARDs has been shown to lower disease activity and joint erosion and provide better treatment responses [29]. In addition, it provides a greater rate of drug-free follow-up of patients in remission after treatment. These findings have led to changes in RA treatment methods by focusing on early diagnosis and treatment [29, 30]. As with RA, Ax-SpA is claimed to be a window of opportunity [31]. Fatty transformation of inflammatory lesions has been reported during the follow-up with MRI. Osteoblastic activity continues, and ossification occurs in areas of fatty change despite anti-inflammatory therapy. Therefore, initiating early treatment may prevent radiological progression in Ax-SpA, which prevents the development of inflammation in other regions after diagnosis.

In this study, symptom onset and diagnostic delays were longer in patients who needed or did not need anti-TNF therapy. This is thought to support the view that there may be a window of opportunity in Ax-SpA. Delayed diagnosis of these patients also leads to a delay in treatment, and failure to use this window of opportunity may result in the need for more anti-TNF therapy. Haroon *et al*. found that patients with delayed anti-TNF therapy in Ax-SpA for more than 10 years had higher spinal involvement progression than patients who started anti-TNF treatment earlier, and anti-TNF therapy (n = 334) has been shown to be associated with a 50% reduction in spinal progression rates [10]. In a study conducted in the Netherlands (n=210), spinal radiographic progression was reduced after more than 4 years of follow-up with anti-TNF [32].

It is stated that instead of conventional therapy, anti-TNF therapy should be preferred in patients with high disease activity. Comparing patients with high and low disease activity despite traditional management, patients with high disease activity respond better to anti-TNF treatment. In this study, 99 patients were using SSZ. Randomized trials comparing placebo with SSZ have shown efficacy in peripheral joint disease but little or no benefit for axial manifestations [33, 34]. A randomized study of patients with Ax-SpA significantly improved disease activity in patients treated with etanercept

compared to patients treated with SSZ, regardless of peripheral joint involvement. This study shows that anti-TNFs are more effective than SSZ [35]. The use of SSZ in patients with predominantly peripheral signs of involvement is also supported by current guidelines.

In this study, high BASDAI and BASFI scores and high ESR and CRP levels were observed in patients with high disease activity, and a significant response was observed with anti-TNF therapy. However, after anti-TNF treatment, a decrease in ESR and CRP values and the BASFI and BASDAI scores were observed. This finding supports the switch to anti-TNF therapy when high disease activity and inadequate response to NSAID is present.

Some of the limitations of this study are its retrospective design, lack of HLA-B27 testing, and the small number of the group receiving anti-TNF therapy.

CONCLUSION

In conclusion, male gender, uveitis, ESR and CRP elevation, disease activity, and functional index scales were known as risk factors for BASDAI and BASFI AX-SpA and were evaluated as risk factors for the need for anti-TNF therapy. In addition, this study showed that the delay in diagnosis increased the requirement for anti-TNF treatment. Therefore, studies should investigate whether the delay in diagnosis is a risk factor for structural damage in the long term. In other words, it should be examined whether there is a window of opportunity, and long-term structural damage should be assessed.

AUTHORS' CONTRIBUTION

Fatih TAY: Wrote the paper, performed the analysis.

Metin Özgen: Conceived and designed the analysis, wrote the paper.

Mustafa Buyukkor: Contributed for language.

CONFLICT OF INTEREST

Declared none.

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