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ORIGINAL ARTICLE

Efficacy of Tumor Necrosis Factor Inhibitors in Patients With Ankylosing Spondylitis

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Objectives: This study aims to investigate the efficacy of tumor necrosis factor-alpha blockers such as infliximab, etanercept, and adalimumab in the treatment of ankylosing spondylitis.

Patients and methods: The outcome of tumor necrosis factor-alpha blocker treatment was analyzed retrospectively in 59 patients with ankylosing spondylitis who were being treated in our clinic during last nine years. The patients' Assessment of SpondyloArthritis International Society (ASAS) 20 and ASAS 40 response rates, adverse drugs effects, and treatment compliance were evaluated.

Results: ASAS 20 response was achieved by 89.8% of the patients in the third month, and by 93.2% in the sixth month. ASAS 40 response was achieved by 61% of the patients in the third and sixth month. No statistically significant difference was detected between the three tumor necrosis factor-alpha blockers with regards to the ASAS 40 response rates. Mild infections, observed in 31 of the patients, were the most common side effects. Serious side effect was observed in only one patient. The number of patients who withdrew from the treatment for various reasons was six.

Conclusion: Treatment with infliximab, etanercept, or adalimumab is clinically effective and safe.

Keywords: Ankylosing spondylitis; treatment; tumor necrosis factors-α blockers.

Ankylosing spondylitis (AS) is a systemic and chronic inflammatory rheumatic disease of the axial skeleton including the spine and sacroiliac joints. Extra-spinal features include peripheral arthritis, uveitis, enteritis, and psoriasis.[1] The prevalence of AS, which is the prototype of the spondyloarthritis, is 0.1-1.1% and it affects men at a higher rate than women, and usually starts in the third decade of life.[2] Traditional disease modifying anti-rheumatic drugs (DMARDs) are usually ineffective for the spinal component of the disease. Exercise therapy and non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of the treatment.[1,3,4]

Over the last decade, dramatic improvements in the therapeutic field of AS have been achieved. Tumor necrosis factor-alpha (TNF-α) blockers have been introduced in many studies as a novel and effective alternative for the treatment of AS patients who are refractory to NSAIDs and DMARDs.[5-7] An optimal treatment for AS should target both symptomatic relief of pain, stiffness and fatigue, offering biological benefits for the reduction or prevention of joint damages and ankylosis.[3] Recent randomized controlled studies conducted with TNF blockers have demonstrated that these drugs are effective in the treatment of spinal pain, limited mobility and function, and also extra-spinal involvement.[5,8,9] In clinical practice, however, the optimal duration for use of these agents and the safety profile of TNF blockers have not been elucidated yet. In the update version of the literature review on the treatment with biologics, Baraliakos et al.[10] showed strong evidences on the long-term efficacy and safety of TNF blockers in AS patients. In another study,

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Baraliakos et al.[9] provided treatment outcomes of TNF blockers at eight years of treatment.

Despite reduced vertebral inflammation and improved sacroiliac joint as assessed by magnetic resonance imaging, there is currently no evidence regarding the prevention and decrease of structural damage by TNF blockers.[11-13] In the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy, the authors reported no statistically significant difference in radiological damage among patients on infliximab (INF) and non-receiving patients at the end of two years, and that INF did not inhibit structural damage.[14] In a two-year study including 41 AS patients on INF and 41 AS patients on conventional agents, Baraliakos et al.[15] re-assessed the patients at baseline and at two years of the study. The authors identified decreased modified Stoke Ankylosing Spondylitis Spinal Scores in the group treated with INF.[15] On the other hand, van der Heijde et al.[16] assessed the radiographs of patients with AS who received adalimumab (ADA) (n=37) and those who did not receive any TNF blocker at baseline and at two years. The authors found no statistically significant difference in the modified Stoke Ankylosing Spondylitis Spinal Scores. In 2009, the SpondyloArthritis International Society (ASAS) and the European League Against Rheumatism agreed for a second update of the recommendations for the management of AS, and the use of anti-TNF agents.[10]

In this article, we aimed to present our clinical experience over the last decade regarding the use of anti-TNF-α drugs in the management of AS.

PATIENTS AND METHODS

Between March 2003 and December 2012, medical files of 59 patients (43 males; mean age 38.76±1.38 years; range 18 to 60 years and 16 females; mean age 43.00±1.36 years; range 32 to 50 years) at the age of ≥18 who were diagnosed with AS according to the modified New York criteria[17] and treated with TNF blockers at Ankara Diskapi Yildirim Beyazit Education and Research Hospital, Physical Medicine and Rehabilitation Outpatient Clinic were retrospectively analyzed. Patients were divided into three groups according to the treatment they received including INF, etanercept (ETA), or ADA. Based on the recommendations of ASAS,[18] treatment with one of the TNF blockers was initiated in patients with a high disease activity [defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 U on a 0-10 scale],[19] despite treatment with at least two different NSAIDs for three months. For patients who had an induration of ≥5 mm in the purified protein derivative (PPD) test, tuberculosis (TB) prophylaxis with isoniazid 300 mg daily was administered for nine months, followed by TNF blockers after a month. The standard doses of TNF blockers used were as follows: INF at a dose of 5 mg/kg on week 0 and 2, and then given every six weeks; ETA at a dose of 25 mg twice weekly or 50 mg weekly; and ADA at a dose of 40 mg given once every two weeks.

Demographic characteristics of the patients, disease duration, human leukocyte antigen B-27 (HLA-B27) status, hip involvement, the number of peripheral arthritis, extra-articular involvement, the presence of joint prosthesis, PPD test results and prophylaxis for TB were recorded. Concomitant use of DMARDs and NSAIDs as well as any interruption for DMARDs and NSAIDs use during the treatment with TNF blockers were noted. Drug-related adverse events (AEs) which occurred during treatment and any reason for treatment discontinuation were also documented. We also provided the treatment outcomes of TNF blockers at eight and nine years as well as the remission rates of patients on INF, ETA and ADA. The rate of treatment switch due to AEs, unresponsiveness and side effects of TNF blockers were also reported.

Clinical assessment of the patients during the follow-up period was performed by using a numeric rating scale scoring system between 0 and 10 in terms of disease activity (Bath Ankylosing Spondylitis Disease Activity Index; BASDAI), metrology (Bath Ankylosing Spondylitis Metrology Index; BASMI) and function (Bath Ankylosing Spondylitis Functional Index; BASFI).[20] The Turkish versions of BASDAI and BASFI which underwent validity and reliability test were used.[21,22] The enthesitis score was determined by examining 13 enthesitic localizations with Maastricht Ankylosing Spondylitis Enthesitis Score. Peripheral joint involvement was assessed based on the number of swollen joints (a total of 64 joints). Laboratory parameters for inflammation during the first three months of

the treatment [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], and the patient global assessment (PGA) and the enthesis responses were recorded. The efficacy of TNF blockers were assessed by using the ASAS group core set of criteria for symptomatic improvement in AS defined as 20 and 40% response.[23] Data are expressed in percentages. Clinical outcome assessments were performed at screening, baseline, and on week 3, 6, 12, 24, 48, 60, 72, 84, 96, and 108.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA) software program. The Shapiro-Wilk test was used to determine if the continuous variables were normally distributed. The Levene test was used to examine the homogeneity of variances. Data were expressed in mean ± standard deviation (SD) or median (min. - max.), where applicable. One-way ANOVA was used to compare mean values between the groups, whereas the Kruskal-Wallis test was performed to compare median values. When the *p* value in the Kruskal-Wallis test was statistically significant, the Conover's non-parametric multiple comparison test was used to determine the differences between the groups. Categorical data were analyzed by Pearson's Chi-square, Fisher's exact or Likelihood ratio tests. The Wilcoxon signed-rank test was used to compare measurement times for continuous data between the groups, while the McNemar's test was used for nominal variables. A p value of <0.05 was considered statistically significant. However, in all possible multiple comparisons, The Bonferroni correction was applied to check type I errors.

RESULTS

The baseline demographic and clinical characteristics of the patients with AS who were prescribed TNF blockers are shown in Table 1. The median duration of the disease was 16 years. There was no significant difference in age, sex, disease duration, the number of peripheral arthritis, hip involvement, PPD test results and prophylaxis for TB. The mean PPD test value was 10.66 mm (range, 0-22 mm) and TB prophylaxis was administered in 41 patients (69.49%). The difference in the duration of drug use between the INF and ADA group and also between the ETA and ADA group were statistically significant (p<0.001 and p=0.002, respectively). The mean PPD test value was higher in the ETA group (13 mm).

The HLA-B27 test was performed on only 16 patients and 15 were positive. Based on the extra-articular involvement assessment on admission, there was osteoporosis in five patients (8.47%), pulmonary involvement in four (6.77%), uveitis in seven (11.86%), psoriasis in two (3.38%) and inflammatory bowel disease in two (3.38%). The most frequent AS-related extra-articular condition was uveitis. Three patients (5.08%) had undergone bilateral hip replacement surgery, while two (3.38%) had undergone unilateral hip replacement surgery. Two patients (3.38%) had a

Table 1. Demographic and clinical features of patients according to tumor necrosis factors blockers

Parameters	Infliximab (n=21; 35.6%)					Etanercept (n=21; 35.6%)					Adalimumab (n=17; 28.8%)					
	n	%	Mean±SD	Med.	Min.-Max.	n	%	Mean±SD	Med.	Min.-Max.	n	%	Mean±SD	Med.	Min.-Max.	*p*
Age (year)			38.6±8.0					42.8±6.1					38.1±10.6			0.152†
Sex																0.548‡
Male	14	66.7				15	71.4				14	82.4				
Female	7	33.3				6	28.6				3	17.6				
Duration of disease (year)				14	5-30				17	4-36				15	4-30	0.260¶
Hip involvement	13	61.9				9	42.9				6	35.3				0.229‡
Associated peripheral arthritis	10	47.6				12	57.1				10	58.8				0.746‡
Duration of drugs (months)				48	12-101[a]				48	12-108[b]				23	6-60[a,b]	0.009¶
PPD (mm)				8	0-22				13	0-21				11	2-18	0.119¶
Prophylaxis	12	57.1				17	81.0				12	70.6				0.244‡

SD: Standard deviation; Med.: Median; Min.: Minimum; Max.: Maximum; † One way analysis of variance (One-Way ANOVA); ‡ Pearson's Chi-Square test; ¶ Kruskal Wallis test; a: The difference between the Infliximab group and Adalimumab group was statistically significant (p<0.001); b: The difference between the Etanercept group and Adalimumab group was statistically significant (p=0.002); PPD: Purified protein derivative test.

Table 2. Distribution of the enthesitis scores and the patient global assessment, erythrocyte sedimentation rate and C-reactive protein values according to the groups at baseline and third month

Variables	Baseline		Third month			Change		
	Mean	Min.-Max.	Mean	Min.-Max.	p†	Mean	Min.-Max.	p‡
Enthesitis score								0.294
Infliximab	0	0-8	0	0-19	0.371	0	-8-17	
Etanercept	1	0-9	0	0-3	0.003	-1	-6-0	
Adalimumab	0	0-9	0	0-9	0.041	0	-4-0	
Patient global assessment								0.765
Infliximab	7	1-10	3	0-5	<0.001	-4	-8-0.5	
Etanercept	7	3-9	2.5	1-5.5	<0.001	-4	-7-0.5	
Adalimumab	5	4-8	1	0-30	0.007	-4	-7-26	
Erythrocyte sedimentation rate								0.562
Infliximab	24	6-88	8	1-37	<0.001	-11.3	-70-3	
Etanercept	34	3-92	14	3-63	<0.001	-19	-76-13	
Adalimumab	20	1-87	14	3-26	0.005	-7	-66-6	
C-reactive protein								0.839
Infliximab	13	3-114	3	0.4-32	0.002	-7	-109-8	
Etanercept	12	2-189	4	0.8-56	0.002	-6	-99-35	
Adalimumab	11.5	1-61.6	3	1-25.5	0.002	-8.5	-52.6-0	

Min.: Minimum; Max.: Maximum; † Comparisons between the baseline and the third month within the groups were considered as statistically significant for results that were p<0.017 according to the Wilcoxon Rank Test, the Bonferroni Correction; ‡ Comparisons between the groups regarding the changes that occurred at the end of third month compared to the baseline were considered as significant for results that were p<0.05 according to the Kruskal Wallis test; ESR ≤20 mm/h and CRP ≤8 mg/dL were considered as normal values.

history of TB and had been treated with anti-TB medications.

The enthesitis scores and changes from baseline in PGA, ESR and CRP values at three months of TNF blocker treatment are shown in Table 2. A statistically significant improvement in PGA, ESR and CRP was observed with each of the three TNF blockers. A statistically significant decrease in the enthesitis score at the end of the third month was observed only in patients on ETA (p=0.003).

Regardless of the TNF blockers used, changes from baseline in the measurements of BASDAI, BASFI and BASMI at various follow-up periods are shown in Table 3. According to these changes, a statistically significant decrease in the BASDAI, BASFI and BASMI scores of 59 patients was observed at three and six months. This decrease continued up to 72 months for the BASDAI and BASFI, and up to 48 months for the BASMI. A total of 59 patients were under follow-up at six months, while 31 patients were under follow-up at

Table 3. Amount of change in the Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index and Bath Ankylosing Spondylitis Metrology Index values in all patients from the third month of follow-up until the end of the follow-up, and the evaluation of these changes compared to baseline

	BASDAI			BASFI			BASMI		
Variables	n	Mean±SD	p†	n	Mean±SD	p†	n	Mean±SD	p†
Month									
3rd	59	-3.56±1.75	<0.0001	59	-2.39±1.90	<0.0001	59	-0.86±1.27	<0.0001
6th	59	-4.04±1.84	<0.0001	59	-3.02±1.95	<0.0001	59	-1.07±1.48	<0.0001
12th	56	-4.20±1.96	<0.0001	56	-3.27±2.00	<0.0001	56	-1.09±1.21	<0.0001
24th	43	-4.07±2.05	<0.0001	43	-3.60±2.19	<0.0001	43	-1.12±1.43	<0.0001
36th	40	-4.12±1.89	<0.0001	40	-3.75±1.80	<0.0001	40	-1.03±1.44	0.0002
48th	31	-4.46±1.81	<0.0001	31	-3.79±1.72	<0.0001	31	-1.16±1.44	0.0005
60th	24	-4.79±1.80	<0.0001	24	-4.42±1.61	<0.0001	24	-1.04±1.57	0.0047
72nd	15	-5.31±1.86	0.0006	15	-4.49±1.82	0.0006	15	-1.07±1.62	0.0304
84th	21	-5.60±2.11	0.0022	12	-3.79±1.54	0.0022	12	-0.67±1.07	0.0537
96th	5	-4.94±2.51	0.0431	6	-3.41±1.43	0.0277	6	-1.33±1.37	0.0707
108th	1	-2.50±0	–	1	-3.50±0	–	1	-2.00±0	–

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; SD: Standard deviation; † p<0.0008 was accepted as statistically significant for the Wilcoxon rank test, the Bonferroni correction.

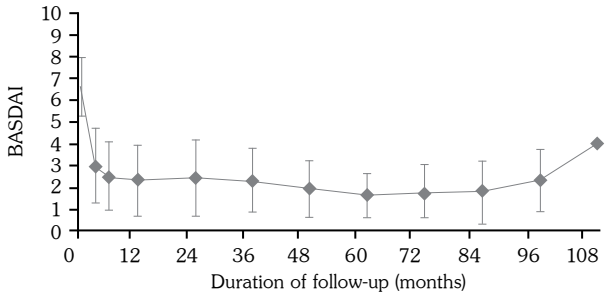

Figure 1. Bath Ankylosing Spondylitis Disease Activity Index with respect to the follow-up periods.

48 months. Only one patient was under follow-up at 108 months. Changes from baseline in the BASDAI score during the follow-up period are shown in Figure 1.

A total of 89.8% and 93.2% patients achieved ASAS 20 response at three months and at six months, respectively. There was no statistically significant difference in the ASAS 20 response rates among the three TNF blockers. The number of patients who achieved ASAS 40 response was 61.0% at three and six months. There was no statistically significant difference in the ASAS 40 response rates among the three TNF blockers. The ASAS 40 response rates with INF, ETA and ADA treatment during the follow-up period are shown in Figure 2.

Although 54 patients (77.14%) (11 methotrexate, 43 sulphasalazine) were using concomitant DMARDs at the initial TNF blocker treatment, 14 patients (20%) (3 methotrexate, 11 sulphasalazine) discontinued DMARDs. While 32 patients (54.23%) were using NSAIDs concomitantly at the initial of the treatment, six patients (10.16%) discontinued NSAIDs. Twelve patients (20.33%) were switched to a second TNF blocker drug, while one patient (1.69%) used all three drugs. Of three patients who had INF-related infusion reactions, two were switched to ETA and one to ADA. Three patients who were unresponsive to the treatment were also switched to ETA. Two patients who were on INF treatment were switched to ETA due to increased liver transaminase level in one and psoriasis in the other. One of two patients on ETA treatment was prescribed ADA, while one was prescribed INF due to the unresponsiveness to ETA treatment. One patient who was on ETA treatment was switched to ADA due to psoriasis. One patient was also switched from ETA to INF due to uveitis. One patient who had INF-related infusion reactions and switched to ETA was prescribed ADA as a third-line biologic.

One patient on a TNF blocker discontinued treatment due to skin TB, one female patient due to the willingness to become pregnant, one male patient due to the willingness to be father, two patients due to non-compliance with treatment, and one patient due to the lack of response.

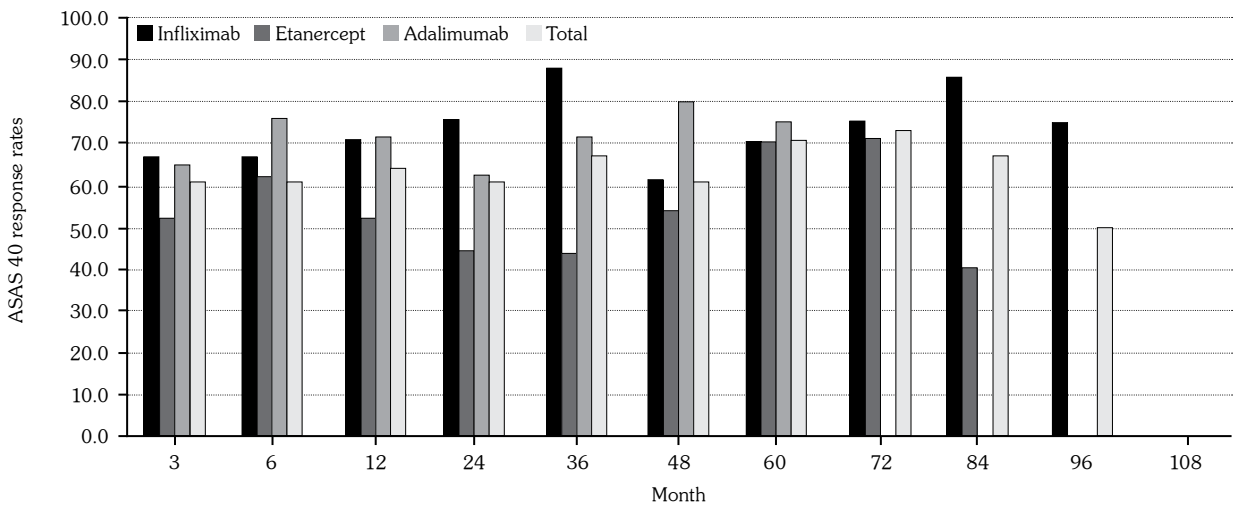

Figure 2. The SpondyloArthritis International Society 40 response rates.

Table 4. Adverse events occurred during the follow-up period

All adverse events	Infliximab	Etanercept	Adalimumab	Total (% of all AEs)	
	n	n	n	n	%
Infusion reaction	3			3	4.28
Headache		1	1	2	2.85
Skin allergic reactions					
Itching/eruption	4	5	2	11	15.71
Hair loss	1			1	1.42
Oral ulcers			1	1	1.42
Elevation of liver enzymes	2	3	1	6	8.57
Elevation of creatinine	1			1	1.42
Elevation of bilirubin	1			1	1.42
Mild infections					
Skin infection	3	1		4	5.71
Upper respiratory infection	4	2	3	9	12.85
Influenza	2	3		5	7.14
Pulmonary infection	5	2	1	8	11.42
Urinary tract infection	3	2		5	7.14
Severe/opportunistic infections					
Skin tuberculosis		1		1	1.42
Uveitis	4	3	2	9	12.85
Psoriasis	1	1		2	2.85
Kidney stone	3			3	4.28

AEs: Adverse events.

The AEs which occurred during the follow-up period are summarized for an individual drug in Table 4. A total of 70 AEs were identified in all patients, of which 31 were mild infections. The most frequent infections were upper respiratory infections (URIs) (12.85%) and pulmonary infections (11.42%). Nine patients had uveitis and two patients had psoriasis. Patients with uveitis were switched from a TNF blocker to another. Among all drugs used, only ETA was interrupted, due to the development of skin TB.

The study included patients who were diagnosed earlier and newly, and under follow-up for nine years receiving biological agents. The number of earlier patients who were under follow-up for nine, eight and seven years was low. Some of them withdrew from the study due to side effects or unresponsiveness to the treatment over time. The higher number of newly patients who were under follow-up for three, six and 12 months may be explained by a higher prescription rate of biological agents in recent years.

DISCUSSION

In our study, we report the treatment outcomes of three TNF blockers which were used in the management of AS in 59 patients who were under follow-up for nine years. The duration of follow-up ranged between three months at the early stage and 108 months at the late stage. A total of 59 patients and 43 patients (72.88%) completed a three-month and 24-month follow-up, while 31 patients (52.54%) were under follow-up up to 48 months. Six patients completed a 96-month follow-up, whereas one patient completed a 108-month follow-up. We observed that compliance to the treatment was overall good, except in six patients who discontinued TNF blocker use.

In a study including 69 patients with AS on INF treatment (n=30) or placebo (n=35), Baraliakos et al.[9] reported that 65 patients (94%), 38 patients (55%) and 33 patients (48%) continued treatment for three months, five years and eight years respectively. Patients who completed eight-year treatment had a lower disease activity and good functional capacity.

In another study including 201 AS patients who were treated with INF for two years, van der Heijde et al.[24] reported that 61% of the patients had ASAS 20 response on week 24, compared to 19% of the patients on placebo. In addition, Haibel et al.[25] administered ADA 40 mg to 14 AS patients on alternate weeks over 52 weeks. A total of 70% of the patients had improved function, nocturnal pain and PGA, with 50% reporting a substantial ASAS 50 response. The authors also

reported that 86% of the patients achieved ASAS 20 response at week 20. The number of patients achieving ASAS 20 response in our study was highest for six months. Fifty-five patients (93.2%) achieved ASAS 20 responses. No difference in the ASAS 20 response rate was observed among the three TNF blockers. Based on the ASAS 40 response rates, 36 patients (61%) achieved remission at three, six and 12 months, indicating no differences in the effectiveness of the drugs.

In a multi-center trial, van der Heijde et al.[26] administered 40 mg ADA on alternate weeks to 208 AS patients who were refractory to second-line agents such as NSAIDs and methotrexate. A total of 30% of the patients completed the study and a significantly greater ASAS 20 response was observed on week 12 in 58.2% of the patients on ADA, compared to those receiving placebo. Significant improvement in spinal mobility was observed based on the BASMI and enthesis score on week 12 and 24. No serious side effects were observed.[26]

Coates et al.[5] conducted a study including 113 patients using either INF, ETA or ADA. The mean duration for use of TNF blockers was 21 (range 1 to 88) months. A relatively high proportion of patients (35%) were receiving concomitant DMARDs. A total of 8.0% of the patients (n=9) had serious side effects or allergy requiring the interruption or switching of the therapy. The mean BASDAI decreased from 6.57 to 3.12, while the mean BASFI decreased from 6.45 to 4.16. The mean CRP decreased from 31 to 7 g/dL. Thirty three patients were treated with a single medication for 24 months and decreased BASDAI, BASFI and CRP values more than >20 g/dL were achieved.[5] In our study, the initial rate of concomitant DMARDs and NSAIDs at baseline was 91.52% and 54.23%, respectively. During treatment with any one of these three drugs, 23.72% of the patients discontinued DMARDs, while 10.16% discontinued NSAIDs. On the other hand, the mean decrease in BASDAI, BASFI and BASMI values were 4.46, 3.79 and 1.16, respectively in 31 patients who completed a 48-month follow-up period. Pain relief and improved function with a significant decrease in ESR and CRP values, the indicators of inflammation, were observed in these patients.

Martin-Mola et al.[27] treated 59 AS patients with ETA, and 37 patients (62.7%) completed a three-year study. Of 14 patients, the reasons for discontinuation were AEs for seven patients (23.7%), unresponsiveness in one patient (1.7%), and other causes in six patients (10.2%). One patient with a history of heart disease developed myocardial infarction (MI) and cholelithiasis, leading to death. Another patient died due to MI at five months following the discontinuation of ETA. One patient died at one month due to MI and multiple organ failure. Four patients were excluded due to serious infections including acute infection of the sigmoid colon in one patient, pneumonia leading to sepsis in one patient, and human immunodeficiency virus seropositivity in another patient. The authors also reported three cancer cases who were diagnosed during the study, including metastatic prostate carcinoma, squamous cell carcinoma of the skin, and chronic lymphoid leukemia.[27] In our study, we assessed TNF blocker-related AEs and found INF-related infusion reactions in three patients. However, these patients received outpatient treatment. Two of them were switched to ETA, while one was switched to ADA. Allergic skin reactions were also observed in 11 patients with a higher rate in patients on ETA. A total of 12.85% of the patients had URIs which were the most frequently seen mild infections in our study, indicating a lower incidence compared to the literature data. Upper respiratory infection is the most common AE in the literature.[26,28-30] Braun et al.[6] reported that 51% of the patients who were on INF treatment and 35% of the patients in the placebo group had URIs. Baraliakos et al.[10] reported that the incidence of mild infection was 84.5(58.4)/100 per subject year in three TNF blocker groups, while it was 63.6(63.0)/100 per subject year in the placebo group. The authors also suggested that the incidence of infection decreased with a long-term treatment, indicating no significant difference among INF, ETA, and ADA treatment. Martin-Mola et al.[27] also reported that 44 patients (96%) who were on INF treatment had an AE at least and the most common AE was URI (37%). In our study, one male patient developed a skin TB requiring treatment discontinuation. The ETA treatment was interrupted and the patient was given anti-TB treatment. At baseline, he was not initiated TB prophylaxis, as the PDD test result was 1 mm. Skin TB developed at eight years of

treatment. Turkey is one of the endemic areas for TB in the world with a higher incidence than the Western countries.[31] Two patients (3.38%) were previously diagnosed with TB and treated with a full dose of anti-TB medications. The mean PDD test value was 10.66 mm (range 0 to 22 mm) in our study, and 41 patients (69.49%) underwent TB prophylaxis.[6,9]

Uveitis was observed in nine patients (12.85%) during treatment, including one with frequent uveitis episodes prior to the initiation of the TNF blocker treatment. One patient was on ETA and switched to INF after an episode of uveitis. Due to another uveitis episode with INF, the patient was switched to ADA, which led to another uveitis episode.[5] Braun et al.[32] reported that the incidence of acute anterior uveitis per 100 patient years was 15.6 in the placebo group, and 6.8 per 100 patient year in the anti-TNF group. The INF treatment was also reported to inhibit the exacerbation of uveitis.[32] Baraliakos et al.[9] reported that 12 of 33 patients who were on INF treatment had acute anterior uveitis at baseline, and four patients had six exacerbation episodes at eight years of treatment. On the other hand, the authors did not observe any new-onset acute anterior uveitis. Martin-Mola et al.[27] reported that 10 of 20 patients who were on ETA had ≥1 exacerbation episode of uveitis and two patients had new-onset uveitis. None of the patients discontinued treatment. In a registry-based study conducted in 2007, there were 43 reported cases of uveitis associated with ETA, 14 associated with INF, and two associated with ADA.[33] The incidence of ETA-associated uveitis was higher compared to INF treatment among TNF blockers ($p<0.01$). This may be explained by its unique TNF-beta (β) inhibitory effect. On the other hand, TNF-β was associated with uveitis in animal studies. Therefore, ETA was expected to be effective in the treatment of uveitis. Compared to ETA, higher efficacy rate of INF in the treatment of extra-articular inflammatory diseases such as uveitis is another consideration.[33] As a result, it has been suggested that the beneficial effect of ETA is low, and INF is far more effective in the control of uveitis in patients with AS.[33,34]

In our study, we observed psoriasis in one patient on INF and one patient on ETA, which was consistent with the literature.[7,28,35] On the other hand, there is no case of kidney stones as an AE of INF treatment in the literature. However, kidney stones developed in three patients on INF in our study. This may be explained by regional and genetic differences.

In addition, the reason for the relatively lower incidence of AEs in patients on ADA can be attributed to the lower number of patients in this group and to the fact that this drug is newer. A total of 17 patients were on ADA, 21 on INF, and 21 on ETA treatments. The mean duration of ADA treatment was 23 months, while it was 48 months for INF and ETA treatment.

Baraliakos et al.[9] reported that a total of 36 AS patients were withdrawn from study due to treatment-related AEs. The most frequent AE was increased transaminase levels and anti-nuclear antibodies (n=8), followed by infusion site reactions (n=3) and unresponsiveness (n=3). In addition, one patient was also withdrawn from the study for one of the following diagnoses or conditions: TB (during the first three months of the study), positive testing for TB and refusing prophylaxis treatment, development of allergic granulomatosis of the lung, pancreatitis and worsening of overall condition after infusions.[9] Furthermore, six patients were excluded due to visiting other physicians, five due to expected pregnancy, two due to non-compliance and three due to unresponsiveness. Similarly, six patients discontinued treatment due to the following reasons in our study: the willingness to become pregnant in a female patient, the willingness to be father in a male patient, skin TB which was considered a serious side effect in one patient, non-compliance in two patients, and unresponsiveness in one patient.

There are some limitations in our study. These are particularly the lack of the HLA-B27 status in each patient, lack of antibody analysis in patients who were resistant to TNF blockers, and missing information on radiological damage of TNF blockers.

In conclusion, we did not observe serious infections, MI, cancer or neurodegenerative diseases such as multiple sclerosis with the TNF blocker treatment in our study. The number of patients who were lost to follow-up or who discontinued treatment was also low. Therefore, we conclude that the treatment of AS with any of the three TNF blockers may be safe with a high

rate of patient compliance. These medications may be successful in most cases in improving the clinical findings of AS.

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