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Original Article

Anti-TNF treatment in ankylosing spondylitis patients with chronic kidney disease: Is it effective and safe?

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Abstract

Objective: This study aims to examine the efficacy and safety of the antitumor necrosis factor (TNF) drugs in ankylosing spondylitis (AS) patients with chronic kidney disease.

Methods: In this study, 24 male patients with a glomerular filtration rate (GFR) of <60 mL min^{-1} 1.73 m^{-2} were included among 863 patients who were followed-up once in 3 months regularly from 2010 to 2018 years. Twenty-four patients were chosen for the control group among 420 male patients whose renal functions were normal using random sampling. We examined C-reactive protein, erythrocyte sedimentation rate, serum creatinine, and GFR values, and also the measurements of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were recorded at the beginning of the treatment with anti-TNF agents and in the 3rd, 6th, 9th, 12th, and final visit months.

Results: Eleven (45.9%) of the patients included in the study were in the routine dialysis program. The initial anti-TNF treatments were etanercept (62.5%), infliximab (16.7%), adalimumab (16.7%), and golimumab (4.1%). Treatment was effective in 22 (91.7%) of the patients. When the values of the two groups' patients were compared at the beginning of the treatment, there was a substantial reduction regarding BASDAI ($P < .001$). Pleural effusion, infective endocarditis, septic arthritis, and prosthesis infection were major side effects (n = 4). The mortality rate of the 24 patients was 29.2% (n = 7).

Conclusion: This study demonstrated that anti-TNF drug treatment is effective and safe in patients with AS who have chronic kidney disease.

Keywords: Ankylosing spondylitis, anti-TNF drugs, chronic kidney disease, efficacy, safe

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the axial skeleton that frequently causes inflammatory back pain and progressive spine stiffness.[1] AS patients are frequently treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs). Antitumor necrosis factor-α (anti-TNF-α) drugs have been shown to be effective and safe in patients who have developed resistance to conventional treatment.[2,3]

Inflammatory bowel disease, acute anterior uveitis, and psoriasis are the most common extra-articular manifestations of AS.[3,4] AS may also affect other organs, including the heart, lung, bone, and kidney.[5] Even though the renal involvement in AS is rare, the renal involvement may cause NSAID nephropathy, glomerulonephritis, and secondary renal amyloidosis (AA type).[6,7] When we reviewed the relevant literature, very few DMARDs can be used while treating AS patients with chronic renal failure, which is under-researched.[8] Renal toxicity related to the use of NSAIDs was well described. The use of NSAIDs may lead to acute renal failure in older patients in particular, who may be hypovolemic and have comorbidities. NSAIDs can, moreover, act in an additive or synergistic fashion with DMARDs for renal toxicity production.[9]

Anti-TNF-α is another effective treatment for RA and SpA.[2] There have been few studies on the efficacy and safety of anti-TNF-α in patients with chronic kidney disease, most especially end-stage renal disease (ESRD).[6,10–12] Therefore, we aimed to determine the safety and efficacy profile of these agents in this group of patients.

Methods

In this study, we reviewed the medical records using the modified New York criteria from 2010 to 2018 at the state university hospital where this study was carried out. In this hospital, patients are registered in the

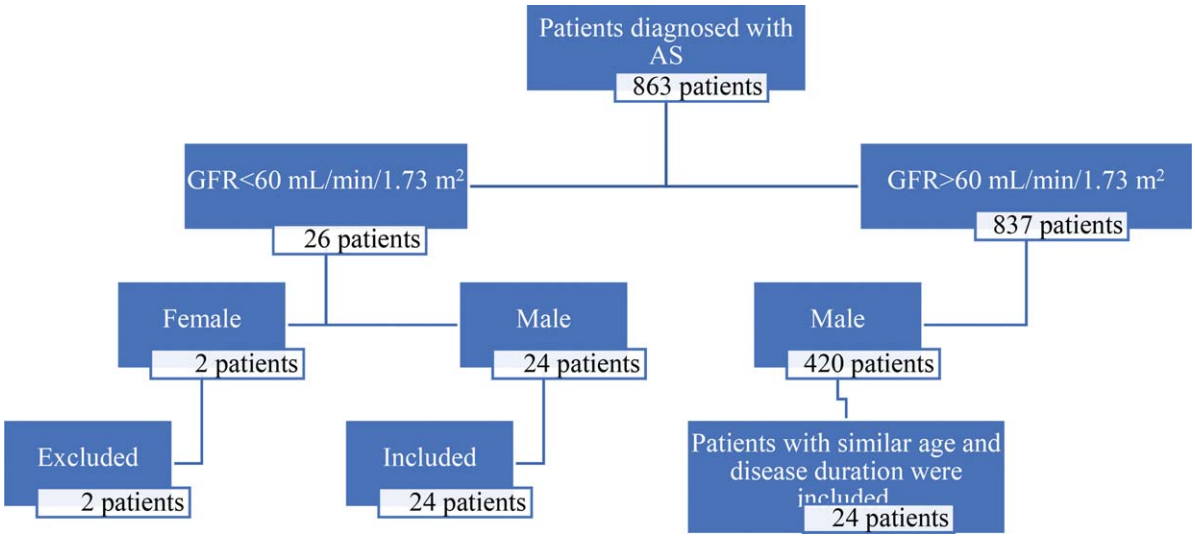

Figure 1. Flowchart of patient selection strategy.

database system called TURKBIO, where disease activities, laboratory parameters, and developing side effects are recorded at each visit from the beginning of the treatment. We determined 26 patients who had chronic kidney disease. The patients whose estimated glomerular filtration rate (GFR) were <60 mL min^{-1} 1.73 m^{-2} for more than 3 months were considered patients with chronic kidney disease. Two female patients were excluded from this study, and 24 male patients were included. Major exclusion criteria were acute renal failure. Patient selection is presented in the flow chart (Figure 1). Twenty-four patients whose renal functions were normal and had similar age distribution and disease durations were chosen as a control group among the male patients diagnosed with 420 AS using random sampling. We examined 48 patients (24 with chronic kidney disease and 24 without chronic kidney disease as a control group) for age, duration of illness, the presence of HLA B27, extra-articular manifestations, and laboratory and urinalysis results. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum creatinine, and GFR values, and the measurement of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were recorded at the beginning of the treatment with anti-TNF agents and in the 3rd, 6th, 9th, 12th, and final visit months. Infections that required hospitalization were recorded as serious infections, and infections with outpatient treatment were recorded as minor infections.

Main Points

- Anti-TNF drugs are effective in patients with ankylosing spondylitis who have chronic kidney disease.
- Anti-TNF drugs can be used safely in ankylosing spondylitis patients with chronic kidney disease.
- Anti-TNF drugs are a good treatment option for ankylosing spondylitis with chronic kidney disease.

Statistical analysis

The Shapiro–Wilk test was used to determine whether or not the variables had a normal distribution. The values of variables were reported as mean, standard deviation, or median (minimum – maximum). For group comparisons, the independent samples t-test or Mann–Whitney U test were used based on normality test results. Percent change values were computed based on the initial measurement for measurements obtained at different times (initial, 3rd, 6th, 9th, 12th, and final visit month), and between-group comparisons were performed using the Mann–Whitney U test. Categorical variables were compared by the Chi-square test and Fisher's exact test. Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM SPSS Corp.; Armonk, NY, USA) software was used for statistical analyses, and $P < .05$ was considered statistical significance.

Results

The mean age of the patients was 54.66 ± 10.78 years. The median disease duration of AS was 19 years (Table 1). HLA-B27 value was positive in 15 (62.5%) patients. Seven (29.2%) patients had peripheral involvement, three (12%) patients had uveitis, and two patients (8.3%) had inflammatory bowel disease. Five (20.8%) patients underwent renal biopsy, and one (4.17%) patient rectal biopsy. Pathological diagnoses were IgA nephropathy (one patient), renal cell carcinoma (one patient), and amyloidosis (four patients). During the follow-up, 11 patients (45.9%) were in the routine dialysis program (Table 2). Except for two patients, all patients used NSAIDs. Fifteen patients (62.5%) used one, seven patients (29.2%) used two, and two patients (8.3%) used three anti-TNF drugs. The initial anti-TNF treatments were etanercept (54.2%), infliximab (25%), and adalimumab (20.8%). In four patients with CKD who were on dialysis, etanercept was administered once weekly at a dose of 25 mg. No dose reduction was applied in our other patients.

Treatment was effective in 22 patients (91.7%). When the results of ESR, CRP, and BASDAI were evaluated at the beginning of treatment with anti-TNF agents and the 3rd, 6th, 9th, 12th, and final visit months of AS patients with chronic kidney disease and without renal failure, there was a substantial reduction in both groups compared to the baseline ($P < .001$). When the ESR, CRP, and BASDAI results were evaluated with the paired T-test, all visits showed a statistically significant decrease compared to baseline (respectively, $P < .001$, <.003, and <.001) (Figure 2 and Table 3).

When biological therapy was initiated, 17 of the patients had a GFR level of <60 mL min^{-1} 1.73 m^{-2}. The total duration of exposure to anti-TNF drugs was 46.5 months. There was no statistically significant increase in the patients' creatinine levels at the 3rd, 6th, 9th, and 12th months compared to the beginning. However, there was a significant increase in the final visit compared to base values ($P = .002$). There was no statistically significant increase in the patients' GFR levels at the 3rd, 6th, 9th, and 12th months compared to the

Table 1. Comparison of the Baseline Characteristics and Clinical Features of the AS Patients with and without Chronic Kidney Disease

Characteristics	AS and Chronic Kidney Disease (n = 24)	AS Only (n = 24)	Total (n = 48)	P-Value
Age	54.66 ± 10.78	54.08 ± 10.91	54.37 ± 10.74	.853[a]
Disease duration (year)	19.5 ± 12.6	15.54 ± 9.16	17.52 ± 11.08	.22[a]
The total duration of exposure to the anti-TNF drug (month)	46.5 (8-108)	63.5 (18-144)	60 (8-144)	.107[b]
Positive HLA B27	15 (62.5%)	19 (79.2%)	34 (70.8%)	.204[c]
Peripheral joint involvement	7 (29.2%)	8 (33.3%)	15 (31.3%)	.755[c]
Uveitis	3 (12%)	1 (4.2%)	4 (8.3%)	.609[d]
Inflammatory bowel disease	2 (8.3%)	1 (4.2%)	3 (6.3%)	>.999[d]
Diabetes mellitus	7 (29.2%)	5 (20.8%)	12 (25%)	.505[c]
Hypertension	22 (91.6%)	4 (16.6%)	26 (54.1%)	.000[d]
Smoking	12 (50%)	10 (41.7%)	22 (45.8%)	.264[c]
Alcohol consumption	3 (12.5%)	5 (20.8%)	8 (16.7%)	.701[d]
NSAIDs	22 (91.7%)	18 (75%)	40 (83.7%)	.245[d]
ESR	42.5 (16-120)	48.5 (12-83)	48 (12-120)	.643[b]
CRP	19.5 (2.9-77)	25.5 (3-65)	22 (2.9-77)	.397[b]
BASDAI	6.2 (3.10-8)	5.4 (3.7-7.6)	6 (3.1-8)	**.01**[b]
GFR	48 (8-115)	94.5 (84-136)	86 (8-136)	**.000**[b]

Data were presented as mean ± SD, median (minimum: maximum), and n (%) values.
[a]Independent samples t-test.
[b]Mann–Whitney U test.
[c]Chi-square test.
[d]Fisher's exact test.

Table 2. The Characteristics of Dialysis-Dependent Chronic Kidney Disease Patients

Pt	Age	AS Duration (Years)	CKD Etiology	CKD Duration (Years)	Total Biologic Treatment Time (Months)	Biologic Treatment Duration (Months) (GFR < 60)	Biologic Treatment Duration (Months) (Dialysis)	Biologic Treatment (Months)	Dose Reduction	Serious Infection	Malignancy
1*	45	7	Nephrolithiasis	5	27	27	–	Inflix (27)	No	Diarrhea	
2	54	22	Idiopathic	12	105	105	36	Eta (27) Inflix (78)	No		Renal cell carsinoma
3	59	33	DM	7	36	36	18	Inflix (36)	No		
4*	57	8	Idiopathic	5	8	8	8	Eta (8)	No	Infective endocarditis	
5	60	14	Amyloidosis	6	96	52	28	Ada (44) Eta (52)	Eta 25 mg/ weekly		Lung cancer
6	51	31	Amyloidosis	6	72	72	72	Eta (72)	No		
7	57	23	Amyloidosis	9	24	24	24	Inflix (12) Eta (12)	No		
8*	61	35	Idiopathic	5	108	108	72	Eta (108)	Eta 25 mg/ weekly		
9*	47	19	Idiopathic	12	78	78	78	Inflix (28) Ada (20) Eta (30)	Eta 25 mg/ weekly	Sepsis secondary to gallbladder perforation	
10	64	26	IgA-related nephropathy	6	39	27	18	Eta (18) Ada (3) Eta (18)	Eta 25 mg/ weekly	Pneumonia	Lung cancer
11	68	46	Idiopathic	10	106	106	96	Ada (6) Eta (36) Goli (64)	No		

Pt, patient; AS, ankylosing spondylitis; CKD, chronic kidney disease; Ex, exitus; DM, diabetes mellitus; inflix, infliximab; Eta, etanercept; Ada, adalimumab; Goli, golimumab.
*Deceased patients.

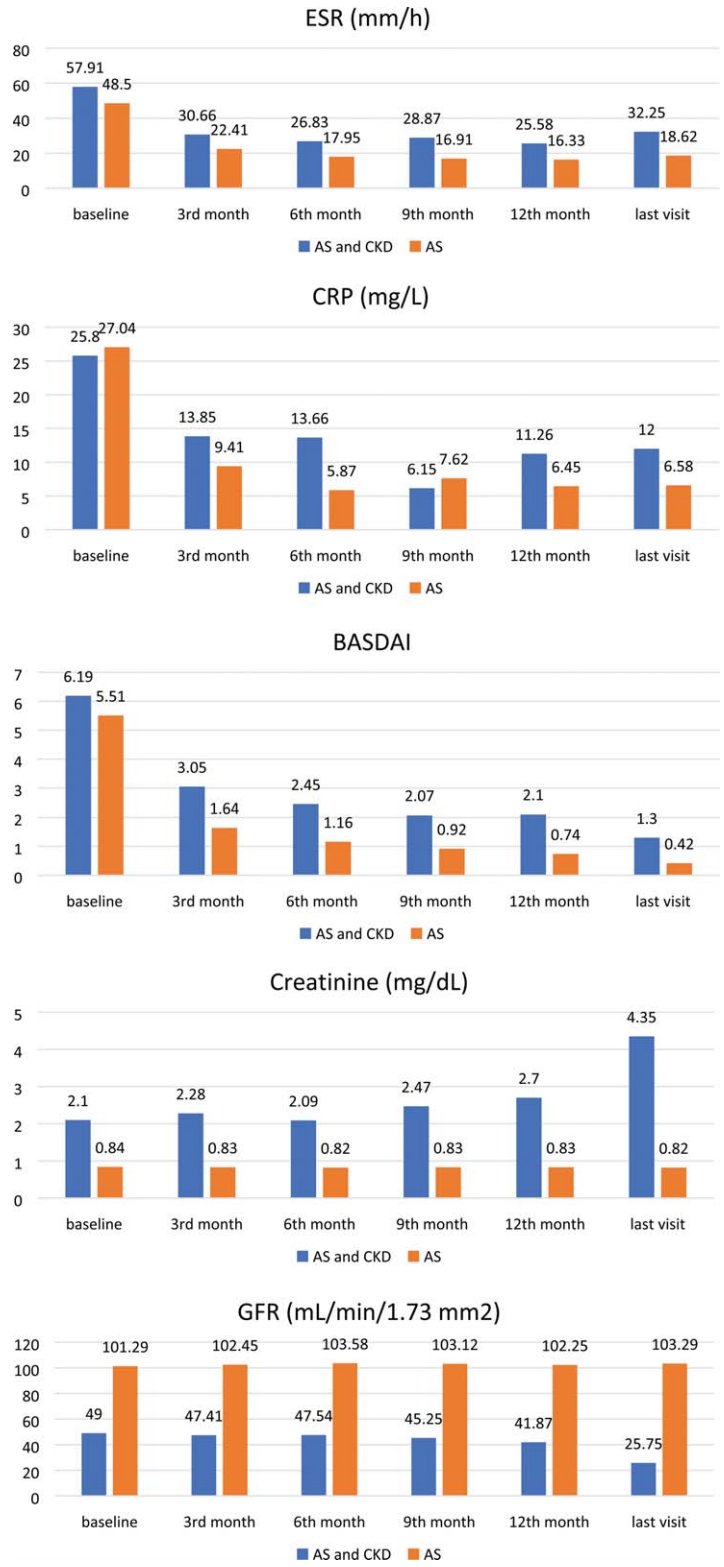

Figure 2. Comparison of laboratory values and disease activity scores of AS patients with and without chronic kidney disease at the beginning of treatment, 3rd, 6th, 9th, 12th month, and final visit. AS: ankylosing spondylitis; CKD: chronic kidney disease; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; GFR: glomerular filtration rate.

beginning. Although there was no significant change in GFR levels in the first year, a significant decrease was observed in GFR levels over the years ($P = .001$) (Figure 2 and Table 3).

Pleural effusion, infective endocarditis, septic arthritis, and prosthesis infection occurred as major side effects (n = 4). The death rate of the 24 patients was 29.2% (n = 7), and the causes of death were Crohn activation, sepsis secondary to pneumonia, sepsis secondary to gallbladder perforation, diabetic ketoacidosis, myocardial infarction, and traffic accident.

While six of the AS patients with chronic kidney disease (25%) had a serious infection, six had a minor infection (25%), and 12 patients (50%) had no infection. In the AS control group without renal failure, a serious infection developed in only one patient (4.2%) and a minor infection in 13 patients (54.2%). While there was no significant difference in the rate of total infection occurrence between the two groups ($P = .56$), serious infections were more frequent in the group with chronic kidney disease ($P < .05$). When the patients using etanercept were examined, there was no significant difference between the other drugs in terms of infection development risk ($P = .673$). Three cases had lung cancer in the patient group, and lung cancer occurred in one patient and basal cell carcinoma in one patient in the control group (Table 4).

Discussion

The fact that anti-TNF drugs were used in the treatment of AS almost led to advancements in the treatment of the disease and improved the quality of life of patients. Although these drugs' efficacy and safety in the general population have been demonstrated in many studies, data in specific patient groups, such as patients with renal failure, are limited.[6,10–13] Renal dysfunctions are critical in the course of AS, both because they occur for other reasons and because they can present as extra-articular involvement of AS. In this study, we aimed to evaluate the efficacy and safety of anti-TNF drugs in patients with AS with chronic kidney disease.

With their efficacy and safety, anti-TNF agents are considered crucial in treating spondyloarthritis (SPA). TNF inhibitors are hydrolyzed at lysosomes and appear to be unaffected by renal function.[13] As a result, these agents seem to be an appropriate form of treatment for hemodialysis patients with ESRD (HD). However, there is a scarcity of data on the effectiveness, safety, and long-term efficacy of TNF blockers in ESRD.[14] In this study, we sought to investigate anti-TNF agents' use on SPA patients with chronic kidney disease to contribute to the literature. Among the 420 male SPA patients, chronic kidney disease was present in 24 of them. ESRD brings about cytokine disturbances and hypercytokinemia because of the reduced removal rate and also increased cytokine generation.[15] Cure et al.'s[16] findings indicated that because of the potential effects of TNF-α, including anti-inflammatory and antioxidant characteristics,

Table 3. Comparison of Laboratory Values and Disease Activity Scores of AS Patients with and without Chronic Kidney Disease at the Beginning of Treatment, 3rd, 6th, 9th, 12th Month, and Final Visit

		Baseline	3rd Month	6th Month	9th Month	12th Month	Last Visit	*P*-Value
AS and CKD	ESR	57.91 ± 29.97	**30.66 ± 20.0***	**26.83 ± 16.31***	**28.87 ± 23.16***	**25.58 ± 19.37***	**32.25 ± 22.89***	**<.001***
	CRP	25.8 ± 19.45	**13.85 ± 14.1****	**13.66 ± 19.56****	**6.15 ± 5.48***	**11.26 ± 18.56***	**12 ± 13.05‡**	**<.05****
	BASDAI	6.19 ± 1.15	**3.05 ± 2.21***	**2.45 ± 1.96***	**2.07 ± 1.91***	**2.1 ± 2.01***	**1.3 ± 1.07***	**<.003‡**
	Creatinine	2.10 ± 1.55	2.28 ± 1.95	2.09 ± 1.47	2.47 ± 2.14	2.7 ± 2.23	4.35 ± 2.83†	**<.002†**
	GFR	49 ± 26.1	47.41 ± 22.63	47.54 ± 21.04	45.25 ± 22.44	41.87 ± 21.83	25.75 ± 21.3*	
AS	ESR	48.5 ± 17.82	**22.41 ± 16.07***	**17.95 ± 10.48***	**16.91 ± 11.47***	**16.33 ± 8.26***	**18.62 ± 12.23***	
	CRP	27.04 ± 15.38	**9.41 ± 10.37***	**5.87 ± 6.81***	**7.62 ± 12.56***	**6.45 ± 9.4***	**6.58 ± 10.18***	
	BASDAI	5.51 ± 0.94	**1.64 ± 1.1***	**1.16 ± 1.04***	**0.92 ± 0.67***	**0.74 ± 0.99***	**0.42 ± 0.5***	
	Creatinine	0.84 ± 0.14	0.83 ± 0.12	0.82 ± 0.13	0.83 ± 0.1	0.83 ± 0.89	0.82 ± 0.08	
	GFR	101.29 ± 16.1	102.45 ± 14	103.58 ± 14.83	103.12 ± 12.58	102.25 ± 11.17	103.29 ± 9.1	

Paired samples t-test.
Significant values compared to baseline are given in bold.

Table 4. Comparison of Infection and Malignancy of AS Patients with and without Chronic Kidney Disease

	AS and Chronic Kidney Disease (n = 24)	AS Only (n = 24)	Total (n = 48)	*P*-Value
Infection	12 (50%)	14 (58.3%)	26 (54.2%)	.562
Serious infection	6 (25%)	1 (4.2%)	7 (14.6%)	**.04**
Minor infection	6 (25%)	13 (54.2%)	19 (39.6%)	**.03**
Malignancy	3 (12.5%)	2 (8.3%)	5 (10.4%)	1.0

Chi-square test.

adalimumab was found to be protective against kidney injury. The findings obtained in these studies suggest that anti-TNF blockers are highly likely to be safe in patients with chronic kidney disease, consistent with our findings.

When the relevant published studies are reviewed, the number of SPA patients included is 12, 6, and 5.[6,13,17] To the best of our knowledge, in the relevant literature to date, the present study explored the largest number of patients who had a SPA using TNF blocker with renal involvement.

Patients with AS and patients with RA are often under the risk of renal failure than healthy individuals given the potential toxicity of drugs used and complications, such as amyloidosis, nonspecific glomerulopathy, immunoglobulin A (IgA) nephropathy, and analgesic nephropathy.[6,18] Because most drugs used in the treatment of AS and RA have an increased risk of renal toxicity (e.g., methotrexate, DMARDs, and NSAIDs), the dose should be modified.[8,19]

El Maghraoui reported in his review article in 2011 that the incidence of renal disorders ranged from 10% to 30% in SPA patients.[20] Singh et al.[21] discovered that amyloidosis was more common in aggressive and active AS, as well as in older patients with the long-term disease. Secondary amyloidosis is one of the most significant culprits of ESRD in patients with RA and SpA.[22] Our findings were consistent with Singh et al.'s study. The AA type was also found in our patient with renal amyloidosis. Two of our four patients diagnosed with amyloidosis received etanercept treatment: one had infliximab and the other had adalimumab. Proteinuria and hematuria were found in one patient with IgA glomerulonephritis, according to our findings.

Fernández-Nebro et al.[23] used infliximab and etanercept to treat 25 RA, AS, and PsA patients with amyloidosis. The results revealed that anti-TNF treatment could be effective and safe. In Senel's study, anti-TNF treatment reduced acute-phase reactants and proteinuria in the majority of patients, while renal function remained stable or improved in 83% of renal amyloidosis patients.[13] Hueber et al.'s[14] study reported management with renal failure of the 11 patients (nine patients with RA, one patient with psoriatic arthritis, and one patient with juvenile rheumatoid arthritis) treated with infliximab, etanercept, or adalimumab. Their findings revealed that TNF blockers did not worsen renal function even in the patients who underwent HD.[14,24]

Autoimmune renal disease triggered by biologic drugs has been reported in the literature, although rarely. Biologics-induced autoimmune diseases of the kidneys are rare but can be life-threatening, leading to renal failure and death. The clinical presentation is usually skin lesions, especially purpura and lower extremity edema. There is little or no systemic involvement. Reasons that might explain renal failure, such as infectious diseases, diabetes, hypertension, or other medications, have been ruled out. Cases of autoimmune renal disease have been reported with etanercept, adalimumab, and infliximab.[25] In our study, 17 patients had a GFR of <60 mL min^{-1} 1.73 m^{-2} at baseline. Two of the other seven patients were renal transplant recipients, two patients had hypertension, one patient had diabetes mellitus, one patient had amyloidosis, and another patient had IgA nephropathy.

Etanercept pharmacokinetics in patients with ESRD on HD were comparable to healthy people with normal renal function. It is important to note that the dose of etanercept should not be revised for patients with HD.[26] Don et al.[27] noted that the etanercept administration appeared safe in their selected population, although increased infection risk was observed in the patients with dialysis. For patients with chronic kidney disease and without chronic kidney disease, there was a statistically significant decrease in the 3rd, 6th, 9th, 12th, and final visit months compared to the beginning of the treatment regarding ESR and CRP values. Besides, as expected, there was a statistically significant decrease in the BASDAI score in both groups compared to the baseline. This finding suggests that the

efficacy of the treatment was sufficient in the patient with chronic kidney disease. The increase in the creatinine value and the decrease in the GFR value were statistically significant, but this finding may arise from the chronic kidney disease prognosis. 83.3% of the patients had hypertension, and approximately 30% had diabetes mellitus. Also, all patients, except two patients, had regular and intensive use of NSAIDs. Moreover, two-thirds of the patients had a GFR <60 mL min^{-1} 1.73 m^{-2} at the onset of treatment. We think that there may be an increase in renal functions due to all these reasons.

In light of the relevant literature, we have reported our data regarding the TNF blockers' efficiency and safety so far. Because of the nature of the disease and also the immunosuppressive effects of the TNF blockers, we think that the infection risk should take attention. Although anti-TNFs have various benefits, they also have side effects, such as infections.[28] Many registry studies and meta-analyzes of TNF-α inhibitor treatment have found that the incidence of bacterial, fungal, opportunistic, or severe infections is higher with the use of these drugs than in the general population and with the use of conventional synthetic DMARDs.[29] Infections are a major cause of morbidity and mortality in patients with CKD at all stages. They are the second leading cause of death, increase the risk of cardiovascular events, and require frequent hospitalizations.[30] According to American data, the risk of dying from sepsis is about 250 times higher in hemodialysis patients than in the general population.[31] In a meta-analysis of 25 randomized, double-blind, controlled trials involving 4,527 patients with ankylosing spondylitis, the risk of severe infection in AS and nonradiographic patients with axial spondyloarthropathy treated with biologics did not differ from the control group.[32] In line with Esatoğlu's findings, in our study, two patients suffered from infections that may lead to sepsis.[17] When our AS patients with chronic kidney disease and our control group were compared, there was no difference in the number of infections, but serious infections requiring hospitalization were more in the group with chronic kidney disease. However, disease duration and activity, as well as previous and concurrent treatments other than biologics and concomitant diseases, may alter our estimates of the risk of severe infection.[32] For this reason, patients should be evaluated in a multidisciplinary manner. Most of our patients had been diagnosed with chronic renal failure for a long time and almost half of them received dialysis treatment. This could be an explanation for the increased risk of infection. The number of patients with malignancy was also similar. Studies have shown that the risk of malignancy increases in CKD patients both in the predialysis period and while receiving dialysis treatment.[33,34] Most meta-analyses showed no increased risk of cancer in patients using TNF inhibitors.[35,36] However, specific forms of cancer, such as malignant melanoma, nonmelanoma skin cancer, and lymphoma, have been linked to anti-TNF medication.[37] In our study, lung cancer was diagnosed in three smokers, CKD, and AS patients.

The main limitation of this study is that our data were not prospective. Only two of our patients were female, while the other 24 were male. We considered excluding these two female patients from the study. The fact that only the male sex was studied is another limitation of our study. In order to show the chronic kidney disease etiology, a biopsy was not performed for each patient. Besides, our findings were limited to patients with chronic kidney disease with SPA. However, our patients were followed-up every 3 months for 8 years. The sample size is fairly small to draw conclusions, but the long follow-up time is the strength of our study.

Conclusion

In light of real-life data, the findings showed that the decrease in BASDAI, indicating kidney failure disease activity, resulted in a significant reduction, as in the control group. While infection rates were similar, infections that require hospitalization might be more common in patients with renal failure. Patients should be closely monitored due to the immunosuppressive state that arose from both anti-TNF drugs and renal failure and should be alerted to the possible side effects, such as infections. Prospective studies with more patients may help develop management strategies for biological use in patients with renal failure.

Ethics Committee Approval: Ethical committee approval was received from the Local Clinical Research Ethics Committee of Uludağ University (decision number: 2019-8/16).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.N.C.; Design - Y.P.; Data Collection and/or Processing - Y.P., S.G.Ç.; Writing - B.N.C., B.Y.; Critical Review - E.D.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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