

Influence of anti-TNF- α treatment on liver and kidney functions in patients with ankylosing spondylitis: A retrospective longitudinal study

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Abstract

Objective: To retrospectively evaluate the effect of anti-tumor necrosis factor-alpha (TNF- α) drugs on hepatic and renal functions in patients with ankylosing spondylitis (AS).

Methods: A total of 148 patients (89 male, 59 female) who were followed up for a minimum duration of 1 year on newly started anti TNF- α therapy were included. Patients were divided into 5 groups based on the TNF- α treatment received. Initially, pre-treatment BASDAI (Bath Ankylosing Spondylitis Disease Activity) scores and laboratory results were compared between the groups before the treatment. Also, ESR (erythrocyte sedimentation rate), C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, and creatinine values were compared before treatment and at 3, 6, and 12 months after treatment. Also presence of hematuria and proteinuria was examined.

Results: Of the overall group, 68 (45%), 33 (22%), 23 (15%), 18 (12%), and 6 (4%) received golimumab, certolizumab, etanercept, adalimumab, and infliximab. Baseline demographic characteristics, disease activity scores, and laboratory parameters were comparable between the groups ($P > .05$). There was a significant decline in BASDAI scores from baseline at 12 months (pre-treatment 5.24 ± 0.5 , 3.01 ± 0.48 post-treatment at 12 months, $P < .001$). Although there was an increase in AST and ALT from baseline to 3, 6, and 12 months of treatment, the values remained within normal range ($P > .05$). Also, there were no significant changes in mean creatinine levels ($P > .05$). There were no correlations between disease activity parameters (ESR, CRP, and BASDAI) and hepatic and renal functions ($P > .05$).

Conclusion: No hepatotoxicity or nephrotoxicity were found in association with the use of anti-TNF- α agents over a 1 year period. However, hepatotoxicity and nephrotoxicity are among known adverse effects of these agents. Based on the existing literature data, routine monitoring of patients in terms of potential hepatic and renal toxicity before and after treatment remains a valid recommendation in clinical practice.

Keywords: Ankylosing spondylitis, anti-TNF- α treatment, hepatotoxicity, nephrotoxicity, disease activity

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Introduction

Systemic rheumatologic disorders may lead to hepatotoxic or nephrotoxic effects as a result of the disease process itself or due to treatments administered.^{1,2} Hepatotoxic or nephrotoxic effects have been previously described for nonsteroidal anti-inflammatory drugs (NSAIDs), disease modifying antirheumatic drugs (DMARD), immunosuppressive agents (glucocorticoids, methotrexate, azathioprine, and sulfasalazine), and antitumor necrosis factor-alpha (anti-TNF- α) drugs.³⁻⁵ TNF- α is the major proinflammatory cytokine involved in many chronic inflammatory disorders, and particularly in ankylosing spondylitis (AS), playing roles in the regulation of the immune responses, T-cell-related cellular injury, as well as in hepatic regeneration.^{6,7} Anti-TNF- α drugs have been effectively utilized for the treatment of spondyloarthritis since 2002.⁸ Adalimumab (ADA), infliximab (IFX), certolizumab (CZP), and golimumab (GOL) are monoclonal antibodies, while etanercept (ETA) is a receptor fusion protein. Well known and frequent side effects of these agents include infections, allergic reactions, pruritus, injection site reactions, and fever.⁹ Despite some evidence suggesting hepatotoxic effects associated with agents,^{10,11} contradictory data are also available.¹² Similarly, case reports of nephrotoxicity have been published, despite being very rare.⁴

This study was undertaken to retrospectively evaluate the effect of anti-TNF- α agents, which are very commonly used in AS treatment, on hepatic and renal functions.

Methods

A total of 148 (89 male and 59 female) AS patients who met the Assessment of Spondyloarthritis International Society (ASAS) criteria were included in the study. The data of patients who received anti-TNF- α treatment for at least 1 year were retrospectively scanned from the electronic database of the hospital. Patients receiving anti-TNF- α agents due to other rheumatologic disorders (rheumatoid arthritis, psoriatic arthritis, etc.) were excluded, as intensive course of DMARD therapy could have an impact on study parameters. Prior to the study, BASDAI (Bath Ankylosing Spondylitis Disease Activity) scores, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were recorded. Patients were inquired, particularly with respect to the regular use of NSAIDs or isoniazid prophylaxis. Since many patients receive isoniazid prophylaxis at the initiation of anti-TNF- α drugs, only patients with such prophylaxis were included to rule out possible enzyme elevations due to isoniazid use and to perform an unconfounded analysis. Also hepatitis carriers, patients receiving regular NSAIDs or other agents possibly associated with hepatotoxic effects, and those switching between anti-TNF- α treatments were excluded. Five patient groups were defined on the basis of the anti-TNF- α agent administered. Initially, pre-treatment BASDAI scores and laboratory parameters were compared between the groups before the treatment and at 3, 6, and 12 months of treatment: ESR, CRP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, uric acid, creatinine kinase (CK), leukocyte (WBC), neutrophil, lymphocyte, platelet, eosinophil, hemoglobin (Hb), hematocrit, mean erythrocyte volume (MCV), mean erythrocyte hemoglobin concentration (MCHC), mean erythrocyte distribution width (RDW), and mean platelet volume (MPV). The study protocol was approved by the Ethics Committee for Clinical Research (September 11, 2020, No. 540).

Main Points

- Anti-TNF- α agents are used in the treatment of AS.
- Liver and renal functions are rarely affected in AS patients receiving anti-TNF- α therapy.
- In AS patients receiving anti-TNF- α treatment, no adverse effects on liver and kidney functions have been detected at least 1 year of follow-up.

Statistical analysis

SPSS V21.0 (IBM Corp.; Armonk, NY, USA) software was used for statistical analyses. Categorical data were compared with chi-square or Fisher's exact test as required. Mean values between two or more independent groups were compared with one-way ANOVA test. The correlation between enzyme levels and BASDAI scores was tested using Pearson's correlation analysis for data with normal distribution and using Spearman's correlation analysis for data without normal distribution. A *P* value of less than .05 was considered statistically significant.

Results

In the overall group of 148 AS patients, the mean age was 37.1 ± 9.1 . The mean age in male and female patients was 36.6 ± 8.8 and 37.7 ± 9.4 years, respectively ($P > .05$). At baseline, prior to the initiation of anti-TNF- α treatment, the mean BASDAI score was 5.24 ± 0.55 , ESR was 14.3 ± 12.7 mm/h, and CRP was 9.2 ± 14.4 mg/L. Of all patients, 68 (45%), 33 (22%), 23 (15%), 18 (12%), and 6 (4%) received GOL, CZP, ETA, ADA, and IFX, respectively. At baseline, study groups were comparable with respect to demographic data, disease activity score, and laboratory parameters ($P > .05$) (Table 1). There was a significant decline in BASDAI scores from baseline to month 12 (from 5.24 ± 0.5 to 3.01 ± 0.48 , $P < .001$). A comparison of mean change in AST, ALT, urea, and creatinine from baseline to months 3, 6, and 12 showed an increase in AST and ALT values that remained within the normal range. Also, mean AST and ALT did not differ significantly at 3 months ($P = .0195$ and $P = .425$, respectively), 6 months ($P = .5$ and $P = .267$, respectively), and 12 months ($P = .184$ and $P = .424$, respectively) (Figures 1 and 2). Mean creatinine values were also similar across these assessment time-points ($P = .501$, $P = .092$, and $P = .904$ at 3, 6, and 12 months, respectively) (Figure 3). Two patients had proteinuria (less than 300 mg/day) and hematuria. Of these two patients, the first received ADA and had an established diagnosis of chronic cystitis, while the other had multiple nephrolithiasis causing pelvicalyceal ectasia on the right and received GOL. A glomerular renal pathology was not considered in both patients. Additionally, 10 other patients with mild and isolated hematuria did not undergo renal biopsy, due to the absence of other renal findings. Follow-up of the hematological parameters over the 1 year course of the study did not show cytopenia or anemia in any patients (Table 2).

No significant correlations were observed between disease activity markers (ESR, CRP, and BASDAI) and hepatic or renal functions ($P > .05$).

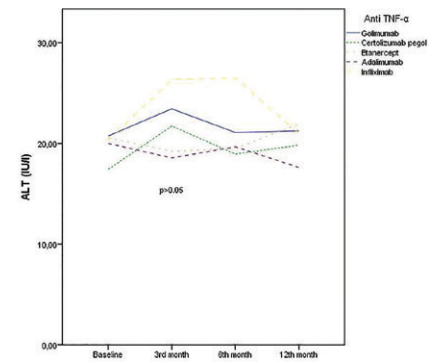


Figure 1. Comparison of ALT levels of groups. ALT: alanine aminotransferase.

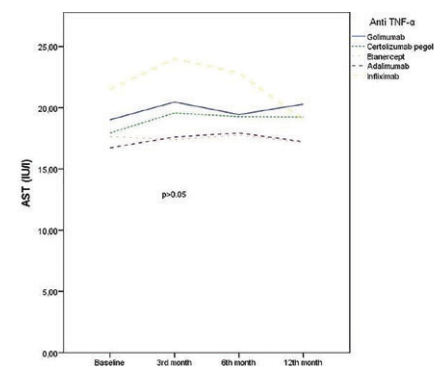


Figure 2. Comparison of AST levels of groups. AST: aspartate aminotransferase.

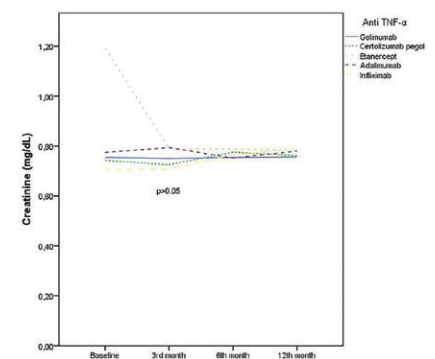


Figure 3. Comparison of creatinine levels of groups.

Discussion

In this study, we retrospectively analyzed the effect of different anti-TNF- α drugs on hepatic and renal functions in a group of AS patients. Minimal changes have been observed in hepatic and renal functions over several months of the study that remained within the normal range. Different anti-TNF- α drugs had similar effects on hepatic and renal functions. For many years, these agents have been used effectively and safely for the treatment of AS. Studies on these five biological agents found significant improvements in disease activity score and clinical

Table 1. Comparison of demographic, clinical, and biochemical parameters of groups.

	GOL	CZP	ETA	ADA	IFX	P
Female/male	21/47	19/14	7/16	7/11	5/1	> .05
Age (years)	37.1 \pm 8.7	35.8 \pm 9.1	39.7 \pm 10.1	34 \pm 8.6	43.2 \pm 3.9	> .05
BASDAI (pretreatment)	5.25 \pm 0.6	5.26 \pm 0.44	5.11 \pm 0.5	5.32 \pm 0.36	5.42 \pm 0.38	> .05
WBC (μ L)	8.39 \pm 0.2	8.53 \pm 0.43	9.20 \pm 0.39	8.67 \pm 0.52	10.28 \pm 1.7	> .05
Neutrophil (μ L)	4.91 \pm 1.4	5.07 \pm 1.92	5.86 \pm 1.73	5.08 \pm 2.07	6.55 \pm 3.45	> .05
Lymphocyte (μ L)	2.67 \pm 0.9	2.65 \pm 1.01	2.55 \pm 0.72	2.65 \pm 0.77	2.83 \pm 0.81	> .05
Eosinophil (μ L)	0.18 \pm 0.1	0.19 \pm 0.12	0.26 \pm 0.23	0.195 \pm 0.12	0.26 \pm 0.15	> .05
Hb (g/dL)	14.5 \pm 1.8	14.0 \pm 1.8	14.7 \pm 1.7	14.8 \pm 1.5	13.3 \pm 2.1	> .05
Hct (%)	44.0 \pm 4.9	42.8 \pm 5.0	45.0 \pm 4.9	45.40 \pm 4.0	41.5 \pm 5.3	> .05
MCV (fL)	85.3 \pm 6.4	85.0 \pm 6.7	91.5 \pm 22.8	87.7 \pm 4.6	82.7 \pm 9.3	> .05
MCHC (g/dL)	32.6 \pm 1.6	32.6 \pm 1.2	32.5 \pm 0.7	50.4 \pm 75.7	31.9 \pm 1.9	> .05
RDW (%)	13.7 \pm 1.3	13.8 \pm 1.0	69.6 \pm 268.4	13.1 \pm 1.1	33.6 \pm 48.6	> .05
MPV (fL)	9.6 \pm 1.0	9.8 \pm 1.1	9.6 \pm 0.9	9.5 \pm 1.0	10.6 \pm 0.6	> .05
Platelet (μ L)	293 \pm 79	290 \pm 65	290 \pm 86	280 \pm 49	304 \pm 79	> .05
AST (IU/L)	19.0 \pm 5.9	17.9 \pm 4.1	17.6 \pm 4.6	16.7 \pm 4.2	21.5 \pm 12.5	> .05
ALT (IU/L)	20.7 \pm 11	17.4 \pm 6.9	20.5 \pm 12.6	20.0 \pm 11.6	20.3 \pm 12.3	> .05
Urea (mg/dL)	28.0 \pm 9.0	28.2 \pm 6.3	25.4 \pm 6.1	25.6 \pm 7.8	27.0 \pm 7.4	> .05
Creatinine (mg/dL)	0.7 \pm 0.1	0.7 \pm 0.1	1.1 \pm 2.0	0.7 \pm 0.1	0.7 \pm 0.1	> .05
Uric acid (mg/dL)	4.9 \pm 1.1	4.6 \pm 1.4	4.9 \pm 1.1	5.2 \pm 1.4	5.0 \pm 2.2	> .05
ESR (mm/h)	14.3 \pm 12	12.6 \pm 10.7	15.5 \pm 15.7	14.1 \pm 18.0	16.6 \pm 11.7	> .05
CRP (mg/L)	9.2 \pm 14.4	8.4 \pm 15.6	11.8 \pm 15.1	12.0 \pm 20.8	5.4 \pm 4.3	> .05
CK (IU/L)	98.4 \pm 48	113.8 \pm 73.4	81.1 \pm 34.4	93.1 \pm 48.2	72.6 \pm 19.3	> .05
Hematuria (n)	6 (8.8%)	4 (12.1%)	0 (0%)	2 (11.1%)	0 (0%)	> .05
Proteinuria (n)	1 (1.5%)	0 (0%)	0 (0%)	1 (1.5%)	0 (0%)	> .05

GOL, golimumab; CZP, certolizumab pegol; ETA, etanercept; ADA, adalimumab; IFX, infliximab; BASDAI, Bath Ankylosing Spondylitis Disease Activity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CK, creatine kinase; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; MPV, mean platelet volume; RDW, red cell distribution width; WBC, white blood cell.

cal manifestations. However, their effect on structural damage is more controversial. Side effects such as the increased risk of latent infections (particularly tuberculosis) and malignancy are well known.^{13,14} On the other hand, their effect on hepatic functions has been less well demarcated. In some placebo-controlled studies, elevation in hepatic enzymes has been reported during treatment with anti-TNF- α agents. For instance, in a double-blind, placebo-controlled, 24-week study by Van der Heijde et al.¹⁵ examining the efficacy and safety of ADA in AS patients, there was a significant increase in AST, ALT, and total bilirubin concentrations as compared to placebo. In six patients receiving ADA and one patient receiving placebo, a \geq 3-fold increase in ALT was noted. During their follow-up, ALT was renormalized in four cases. On the other hand, AST elevations have been less frequently reported.¹⁵ In a randomized-controlled study

of the efficacy and safety of GOL, Inman et al.¹⁶ reported significant AST and ALT elevations from baseline among eight patients in the GOL arm, and in one patient in the placebo arm. To summarize, in both studies, ADA and GOL treatments were associated with significantly more marked hepatic enzyme elevations. Whether anti-TNF- α agents used in the treatment of AS are different in terms of this side effect is not clear. In one study involving RA patients, IFX was the agent that was most frequently associated with hepatic enzyme elevations in comparison with DMARDs, followed by ADA, while ETA had no such effects.¹¹ Conversely, van Denderen et al.¹⁰ observed hepatic enzyme elevations in 9% of the AS patients receiving ETA. On the other hand, none of the anti-TNF- α agents in our study did not lead to hepatic enzyme elevations during the initial phase of the treatment as well as during the longer term follow-up. In our

country, in a study by Capkin et al.,¹² ETA, ADA, and IFX were not found to be associated with increased hepatic enzymes, although GOL and certolizumab were not studied.¹² In contrast, our study group also involved patients treated with these two agents, and our results were comparable with that study. Several mechanisms have been proposed to explain the hepatotoxic effects of TNF- α drugs. First hypothesis points out to potential concealed infections due to strong immunosuppressive effects of these agents, causing hepatic injury. This is more marked in viral infections, particularly in hepatitis B infections.³ In this study, no patients had positive markers for hepatitis. In some studies, increased auto-antibody levels have been detected among patients treated with anti-TNF- α drugs. The second proposed mechanism suggests that the concomitant autoimmune disorders (eg, systemic lupus erythematosus, multiple sclerosis, and

Table 2. Laboratory parameters at baseline, 3, 6, and 12-month patients.

	Baseline	Third month	Sixth month	Twelfth month	P
WBC (μ L)	8.65 \pm 2.30	8.49 \pm 2.14	8.62 \pm 2.11	8.41 \pm 2.00	> .05
Neutrophil (μ L)	5.18 \pm 1.82	4.89 \pm 1.53	5.02 \pm 1.70	4.88 \pm 1.68	> .05
Lymphocyte (μ L)	2.65 \pm 0.89	2.88 \pm 2.10	2.70 \pm 0.96	2.63 \pm 0.89	> .05
Eosinophil (μ L)	0.20 \pm 0.15	0.49 \pm 3.43	0.19 \pm 0.15	0.18 \pm 0.14	> .05
Hb (g/dL)	14.4 \pm 1.8	14.3 \pm 1.7	14.4 \pm 1.8	14.4 \pm 1.7	> .05
Hct (%)	43.9 \pm 4.9	44.0 \pm 4.6	44.4 \pm 4.8	44.2 \pm 5.0	> .05
MCV (fL)	86.4 \pm 10.8	86.0 \pm 6.1	86.6 \pm 5.9	86.5 \pm 6.0	> .05
MCHC (g/dL)	32.6 \pm 1.4	32.3 \pm 1.5	32.2 \pm 1.5	32.1 \pm 1.7	> .05
RDW (%)	13.6 \pm 1.2	13.6 \pm 1.3	13.4 \pm 1.2	13.5 \pm 1.5	> .05
MPV (fL)	9.7 \pm 1.0	9.9 \pm 1.1	9.9 \pm 1.0	9.9 \pm 1.0	> .05
Platelet (μ L)	291 \pm 73	284 \pm 71	285 \pm 68	285 \pm 67	> .05
AST (IU/L)	18.3 \pm 5.6	19.5 \pm 9.9	19.1 \pm 7.7	19.1 \pm 7.3	> .05
ALT (IU/L)	19.8 \pm 10.8	21.9 \pm 17.0	20.4 \pm 13.1	20.5 \pm 12.8	> .05
Urea (mg/dL)	27.3 \pm 7.8	27.8 \pm 12.9	25.7 \pm 7.0	25.6 \pm 7.3	> .05
Creatinine (mg/dL)	0.7 \pm 0.1	0.7 \pm 0.1	0.7 \pm 0.1	0.7 \pm 0.1	> .05
Uric acid (mg/dL)	4.8 \pm 1.2	4.8 \pm 1.1	4.9 \pm 1.1	4.8 \pm 1.1	> .05
ESR (mm/h)	14.2 \pm 13.3	12.5 \pm 11.3	11.3 \pm 9.1	10.6 \pm 9.1	> .05
CRP (mg/L)	9.6 \pm 15.3	7.7 \pm 10.7	6.6 \pm 11.5	5.0 \pm 8.2	> .05
CK (IU/L)	97.5 \pm 53.2	92.7 \pm 42.3	107.0 \pm 123.1	88.7 \pm 35.0	> .05
BASDAI	5.24 \pm 0.5	-	-	3.01 \pm 0.4	< .01

BASDAI, Bath Ankylosing Spondylitis Disease Activity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CK, creatine kinase; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; MPV, mean platelet volume; RDW, red cell distribution width; WBC, white blood cell.

diabetes mellitus) and psoriasis may affect liver functions. In our study, no patients had such concomitant disorders. TNF- α is known to be involved in hepatic regeneration. Thus, another mechanism proposes that the antagonistic effect of anti-TNF- α agents may lead to dysfunctional hepatic repair as well as hepatic injury due to immune deregulation in association with TNF- α .¹⁷

To the best of our knowledge, although no previous studies have systematically examined the nephrotoxic potential of anti-TNF- α drugs, several case reports have been published in association with the use of ETA. These cases presented with minimal change disease, crescentic glomerulonephritis, or acute renal injury.^{4,18,19} TNF- α is an inflammatory cytokine with variable effects on glomeruli. In some experimental models of glomerulonephritis, TNF- α receptor deficient mice had less marked glomerular injury. Also, it has been proposed that TNF- α may lead to direct podocyte injury, hence its role in glomerular injury.^{20,21} In some other studies with contradictory findings, reduced expression of TNF- α was found to

be associated with other auto-immune diseases such as multiple sclerosis and diabetes mellitus.^{22,23} The immunoregulatory role of TNF- α may involve the downregulation of T cell apoptosis and T cell receptor signaling.²⁴ Two of our patients had coexistent proteinuria and hematuria. The first subject had a diagnosis of chronic cystitis and received ADA, with a proteinuria level of <300 mg/day and normal creatinine. The other patient had multiple renal stones causing right renal pelvicalyceal ectasia and received GOL. The clinical manifestations did not suggest glomerular pathology in both patients. In addition to these two cases, 10 other patients had mild and isolated hematuria. Renal biopsy was not performed in these 10 subjects, due to the lack of other renal findings. In the remaining participants, no significant changes in creatinine levels occurred over the 1 year follow-up period. Although cytopenia and anemia occurring in association with anti-TNF- α agents have been previously reported,^{25,26} none of our patients had such pathology.

In conclusion, minimal increases were seen in liver and kidney function tests in AS patients

who received anti-TNF- α treatment for at least 1 year, but these increases were within normal limits.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee for Clinical Research of Gazi Yaşargil Training and Research Hospital, Health Sciences University (Approval Date: September 11, 2020; Approval Number: 540).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - L.A.; Design - L.A.; Materials - L.A., M.A.B.; Data Collection and/or Processing - L.A., M.A.B.; Analysis and/or Interpretation - L.A., M.A.B.; Literature Search - L.A.; Writing Manuscript - L.A.; Critical Review - L.A.

Conflict of Interest: The authors have no conflict of interest to declare.

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