Reumatismo, 2024; 76 (4): 260-265

Assessment of liver and kidney function in patients with ankylosing spondylitis on long-term non-steroidal anti-inflammatory drug therapy

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SUMMARY

Objective. This study aimed to analyze the status of liver [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] and kidney (serum creatinine) function in ankylosing spondylitis (AS) patients assuming continuously non-steroidal anti-inflammatory drugs (NSAIDs) alone over a long period.

Methods. Between 2013 and 2022, there were records of 385 AS patients. Of them, 56 were receiving only NSAIDs, and the files of these patients were retrospectively analyzed. Demographic and clinical characteristics were collected. Blood tests, including serum creatinine, AST, and ALT, were assessed at each visit.

Results. Of the 56 patients, 39 were male. The mean age was 45.30 years, and the follow-up period was 9.80 years. Of them, 44.6% used indomethacin, 26.8% naproxen, 17.9% diclofenac, 5.4% acemetacin, 3.6% meloxicam, and 1.8% celecoxib. The mean baseline serum creatinine was 0.71 mg/dL. The mean baseline serum AST and ALT were 19.6 u/L and 22.9 u/L, respectively. Baseline creatinine, AST, and ALT were not statistically significantly different between sexes. There was a statistically significant difference between mean creatinine concentrations at baseline and at year 3. One patient on naproxen discontinued treatment due to elevated creatinine. The creatinine level decreased during the patient's follow-up. Liver enzymes above 3 times the normal value were not seen in any patient.

Conclusions. Based on real-world data, long-term use of NSAIDs has generally not led to acute liver and kidney injury or progressive impairment of hepatorenal function requiring discontinuation of treatment.

Key words: *Ankylosing spondylitis, AST, ALT, serum creatinine, NSAIDs.*

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INTRODUCTION

The current goal of treatment in ankylosing spondylitis (AS) is to achieve remission or low disease activity and to increase the life expectancy of patients to a level comparable to that of the general population (1). Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line drug therapy for patients with AS. Continued use is preferred in patients who respond well to NSAIDs if symptoms need to be controlled (2). Given the persistent nature of inflammation in AS, it is recommended that NSAIDs are prescribed on a fixed regimen at the highest possible dose, as continuous control of low disease activity may prevent the progression of structural changes in the spine (3, 4). However, long-term use of NSAIDs raises issues of gastrointestinal, renal, and cardiovascular safety (5, 6). NSAIDs are frequently used to treat musculoskeletal and rheumatic diseases by reducing pain and inflammation. NSAIDs decrease inflammation by blocking cyclooxygenase, which lowers the synthesis of prostaglandins (PGs). However, PGs play a role in renal hemodynamics to maintain renal blood flow. NSAIDs that inhibit PGs have the potential to affect renal function by constricting afferent arterioles. Blood pressure and systemic blood volume management are other functions of PGs. NSAIDs may inhibit natriuresis and diuresis, leading to sodium and water retention and increased blood pressure (7).

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Hepatotoxicity is another serious complication associated with NSAIDs; however, its incidence is less frequent compared with gastrointestinal damage, cardiovascular diseases, and renal failure (8, 9). Most NSAID-induced liver damage is likely idiosyncratic, and there are only a few occurrences of clinically severe liver impairment (1-10 cases per 100,000 prescriptions). Although two NSAIDs, sulindac and diclofenac, are most commonly associated with hepatotoxicity, almost all commonly used NSAIDs have been associated with clinically significant drug-induced liver injury, at least in rare cases (10, 11). Ibuprofen was confirmed to be safe in terms of hepatotoxicity by a fairly recent comprehensive evaluation, in spite of several published reports that suggested otherwise (12).

Data on the safety of long-term NSAID use are limited and variable. When analyzing cases of drug-induced liver and kidney injury, acute injury is the main focus of researchers, but liver and kidney dysfunction with long-term NSAID use in patients who have not experienced acute episodes has not been adequately studied in heterogeneous samples. The aim of this study was to analyze the status of liver and kidney function in patients with AS on long-term NSAID treatment.

MATERIALS AND METHODS

Patient population and data collection

In this retrospective observational single-center study, we reviewed the electronic medical records of patients with AS diagnosed according to the modified New York criteria and followed for more than 5 years at our tertiary care hospital between January 2013 and December 2022. Patients with suppressed disease activity on continuous NSAID treatment and without renal or hepatic comorbidities, malignancies, or alcohol use were included in the study. Demographic and clinical characteristics were recorded. Age, gender, human leukocyte antigen B27 (HLA-B27) status, and treatment strategies (NSAIDs) were evaluated. Blood tests, such as serum creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), were evaluated at baseline and at subsequent intervals of 1, 2, 3, 4 and 5 years following treatment initiation.

Compliance with ethical standards

Before commencing the study, ethical approval was obtained from the local ethics committee. All participating individuals provided signed informed consent, ensuring compliance with ethical standards and respect for the rights and well-being of the study participants.

Statistical analysis

SPSS 25.0 (IBM Corporation, Armonk, NY, USA) was used for data analysis. Quantitative variables were expressed as mean ± standard deviation and categorical variables were expressed as n (%). The Wilcoxon signed-rank test was used to compare the measurement scores of a group at different times. Variables were analyzed at a 95% confidence level and a p-value less than 0.05 was considered significant.

RESULTS

A total of 385 patients with follow-up data spanning 5 years were analyzed. Of these, 56 (14.5%) were continuous NSAID users. The mean age of the patients was 45.3±11.0 years. HLA-B27 was positive in 60.7% of the patients. There was a history of anterior uveitis in 7.1% of the patients. Peripheral joint involvement occurred in 26.8% of them. The NSAIDs used were as follows: 44.6% indomethacin (mean age: 46.0±9.3, F/M:9/16), 26.8% naproxen (mean age: 48.5±13.8, F/M:5/10), 17.9% diclofenac (mean age: 40.3±10.9, F/M:3/7), 5.4% acemetacin (mean age: 45.3±12.4, F/M:0/3), 3.6% meloxicam (mean age: 44.0±4.2, F/M:0/2), 1.8% celecoxib (age:34, F/M:0/1). Mean baseline ALT level in the patients included in the study was 22.9±10.1 u/L, AST level was 19.6±6.14 u/L, and serum creatinine level was 0.71±0.14 mg/dL. Baseline creatinine, AST, and ALT levels were not statistically significantly different between

Table I - Multiple time point liver and kidney function in non-steroidal anti-inflammatory drug-treated ankylosing spondylitis patients.

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Serum creatinine, mg/dL	0.71±0.14	0.71±0.16*	0.73±0.18*	0.87±1.00***	0.77±0.35*	0.70±0.17*
AST, u/L	19.6±6.14	22±6.52**	24±6.59***	24.9±8.11***	25.8±7.29***	24.17±7.06***
ALT, u/L	22.9±10.1	24.9±2.5**	27.3±2.3***	30.9±17.2***	30.5±13.8***	30.4±15.9***

AST, aspartate aminotransferase; ALT, alanine aminotransferase. Continuous variables were presented as mean (standard deviation). Normal values for serum creatinine, AST, and ALT are <0.95 mg/dL, <35 u/L, and <35 u/L respectively. The p-values between baseline value and 1st-2nd-3rd-4th-5th years: *p>0.05; **p<0.05; ***p<0.001.

the sexes. The mean values of the renal and liver function tests according to the follow-up period are shown in Table I. There was a statistically significant difference between the mean creatinine levels at baseline and at year 3. There was a statistically significant effect between baseline and 1, 2, 3, 4 and 5 year liver function test mean levels. However, no patient reached a 3-fold increase in liver function tests from the normal value, which would require discontinuation of treatment. In a 44-year-old male patient who was not a regular outpatient, the creatinine level was 1.4 mg/dL during the first year of naproxen use. Four years later, an examination revealed a serum creatinine level of 5.85 mg/dL, prompting the discontinuation of NSAID treatment and the diagnosis of chronic kidney disease (CKD).

DISCUSSION

This study used long-term data from individuals with AS who were taking NSAIDs continuously to examine the association between NSAIDs and liver and renal function. There was a statistically significant effect between baseline AST/ALT levels and year 1, 2, 3, 4 and 5 means. There was a statistically significant difference between baseline and 3-year mean serum creatinine levels. Our findings support the safety of long-term NSAID usage in AS patients who do not have significant renal or hepatic impairment. However, the results should be interpreted considering the characteristics of AS, which is more common in young people. Patients with better renal function, fewer comorbidities, and a lower severity of AS may have been prescribed more NSAIDs than patients with worse renal function and more comorbidities, which could explain the why there was no clinically significant decline in renal function. In our study, the mean age was 45.3 years, and the lack of significant increase in creatinine value in long-term follow-up may be due to the low severity of chronic disease and comorbidity in the patients we selected.

AS patients may have more renal dysfunction than the general population due to several factors, including the presence of comorbidities such as hypertension and the use of nephrotoxic medications. In a Canadian population-based study, hypertensive kidney disease, acute kidney injury, CKD, and amyloidosis were among the renal problems that affected 2.1% of women and 3.4% of men with AS (13).

NSAID usage may have a negative impact on renal function, according to previous cohort studies. In community-based elderly populations, there have been documented dose-response associations between changes in renal function and cumulative NSAID dosage (14). Among US Army troops in a retrospective longitudinal cohort analysis, the highest level of NSAID exposure was associated with a small but significant increase in acute kidney injury and CKD (15). These results raised concerns regarding renal damage linked to NSAID treatment over an extended period of time in AS patients. A recent study by Koo *et al.* used the electronic medical records of 1.280 AS patients to examine the connection between long-term NSAID usage and renal function (16). The authors of the study concluded that there was no significant clinical association between the NSAID intake score and changes in estimated glomerular filtration rate in AS patients. Nevertheless, this score evaluates the "intensity" of NSAID

use as opposed to the total amount of NSAIDs taken; hence, it is invalid when considering NSAID usage over an extended period of time.

The relative risk of renal failure was higher in the group not exposed to NSAIDs compared with the group exposed to non-selective NSAIDs in a Swedish national population-based cohort study of patients with spondyloarthritis that examined the cardiovascular and renal safety of non-selective NSAIDs and selective COX-2 inhibitors (17). Celecoxib had fewer renal events and more favorable cardiorenal safety outcomes, according to a recent publication comparing the cardiorenal risk of celecoxib with naproxen or ibuprofen in a secondary analysis of the PRECISION (Prospective Randomized Evaluation of the Integrated Safety of Celecoxib *versus* Ibuprofen or Naproxen) study (18). In a study on elderly patients, an increased risk of ibuprofen-induced renal impairment was reported in patients with coronary artery disease. Based on the starting renal function and the existence of risk factors, it implies that different NSAIDs may have different effects on renal function (19).

Liver dysfunction is a serious problem in patients taking long-term NSAIDs and it is necessary to ensure the safety of the treatment (20, 21). NSAIDs are the most frequently used medications, both as prescription and as over-the-counter drugs. They can cause mild elevation of liver enzymes in up to 15% of patients, which normalizes after discontinuation (22). The decision to withhold or discontinue NSAIDs is usually made based on clinical judgment, patient safety, and the overall risk-benefit ratio. However, levels greater than three times the upper limit of normal are often used for drug withdrawal (23-25). As our study is one of the few pilot studies involving patients with AS who are long-term and regular users of NSAIDs, it is important to investigate the possibility of NSAID hepatotoxicity in real clinical practice. In this study, no significant increases in transaminase levels were generally observed, and NSAID treatment was continued in the case of elevation less than three times the normal level.

In a multicenter controlled study, the hepatotoxicity risks of nimesulide, ibuprofen, and diclofenac sodium were compared. Considering the relationship between acute and severe liver injury and NSAID use, it was shown that nimesulide and ibuprofen were associated with a higher risk among other NSAIDs (4). Diclofenac exposure was linked to increased liver damage according to another population-based investigation. Nonetheless, this study's risk of fatalities, hospitalizations, and major liver adverse events was minimal (26).

It is necessary to pay attention to the presence of risk factors for liver damage in patients using NSAIDs. The severity of comorbidities including obesity should be considered as one of these risk factors. In our study, it is not possible to ascertain the frequency of transaminase elevation according to the specific NSAID, due to the small number of patients. However, we feel that the data obtained on liver function in patients taking NSAIDs continuously for 5 years are clinically important.

The limitations of the study include the lack of a control group, the limited number of patients in a single center, the lack of evaluation of disease activity and of radiographic progression. In addition, the type of medication administered does not reflect NSAIDs used in other countries, and none of the patients in the study used ibuprofen.

CONCLUSIONS

In conclusion, people with AS, especially those who are younger, have a very low incidence of impaired renal function. When used in people with pre-existing risk factors such as advanced age, reduced renal function, and comorbidities, NSAIDs may have adverse effects on renal function and should be used with caution. More long-term, multi-center trials are needed to find out how long-term use of NSAIDs affects liver and kidney function in people with AS.

Contributions

Both authors contributed to the conceptualization of the study, data curation, interpretation of the data. They wrote and adjusted

the concept and the draft of the original manuscript.

Conflict of interest
The authors have declared no conflicts of interest.

Ethics approval and consent to participate
Local Ethics Committee approval was given by the local medical ethics committee (Decision No: 2104) of the Celal Bayar University before starting this study.

Informed consent
A signed, informed consent was taken from all participants.

Funding
None.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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