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SCHOLARENA

Journal of Rheumatology and Arthritis Research

RESEARCH ARTICLE

Hepatotoxicity of Anti-Inflammatory Drugs Used to Treat Gout Attacks

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Citation: Mikhnevich E.A, Lemiasheuskaya S.S, Ruban A.A (2026) Hepatotoxicity of Anti-Inflammatory Drugs Used to Treat Gout Attacks. J Rhemat & Arth Res 3: 101

Abstract

Introduction: Gouty arthritis (GA) is characterized by acute joint inflammation and an intense pain syndrome. The following anti-inflammatory drugs (AIDs) are used to reduce pain and inflammation: non-steroidal anti-inflammatory drugs (NSAIDs), Colchicine, and Glucocorticosteroids (GCS). In gout, pathological liver changes may be associated with metabolic changes (obesity, dyslipidemia) as well as the toxic effects of alcohol and medication.

Objective: To evaluate the hepatotoxicity of AIDs used to treat GA.

Materials and Methods: The study included 663 patients with GA, who met the ACR classification criteria (1977), consecutively admitted to the Rheumatology Department of Municipal Clinical Hospital No.11 from January 2013 to January 2023. Patients without treatment, those who used topical agents, those with chronic liver disease and biochemical markers altered before treatment were excluded. The final examination included 532 patients. Hepatotoxicity (HTX) consisted of patients with an increase in blood ALT concentration of >2 times the upper limit of normal (ULN) during AIDs treatment, drug-induced liver injury (DILI) was defined according to EASL (2019) and ACR (2021) recommendations. The updated RUCAM (Roussel Uclaf Causality Assessment Method) scale was used to evaluate cause-and-effect relationships.

Results: Among 532 patients, monotherapy was prescribed to 394 patients: NSAIDs in 368 cases (93.4%), Colchicine in 19 (4.8%), and GCS in 7 (1.8%) cases. The prescription of Colchicine 1 to 4 mg per day, as well as GCS (Prednisolone and Methylprednisolone per os, Diprospan i/m and i/a, Dexamethasone i/m) showed no effect on ALT/AST levels. NSAIDs were hepatotoxic in 60 cases (15.2%): Diclofenac in 36 cases of 173 (20.8%), Nimesulide in 12 of 82 (14.3%), Etoricoxib in 6 of 22 (27.3%), Meloxicam in 1 of 39 (2.6%), other NSAIDs (Etodolac, Xefocam, Dexketoprofen, Ketorolac and Dexalgin) were led to HTX in 1 case each. Among 60 patients with HTX, 56 took NSAIDs in higher than average doses for a short period 13 (8-17) days. When comparing the proportion of HTX, it was less frequent with Meloxicam than with Diclofenac ($F = 0.035$, $p = 0.004$) and Etoricoxib ($F = 0.139$, $p = 0.007$).

An increase of blood ALT concentration > 3 ULN was observed in 17 cases, > 5 ULN was observed in 4 patients taking Diclofenac and in 2 taking Nimesulide. DILI was considered in 7 patients: 5 - on Diclofenac, 2- on Nimesulide.

Combined administration of two NSAIDs at moderate therapeutic doses during 3-5 days was practiced in 81 cases, with HTX observed in 11 cases. When NSAID was prescribed with Colchicine, HTX developed in 3 of 36 patients taking Diclofenac in higher than average doses. In 21 patients, when combination of one NSAID and GCS (diprospan i/m or i/a) was prescribed no case of HTX was registered.

The risk of developing HTX was associated only with doses of NSAIDs above the average therapeutic ($p < 0.001$; OR -13.1 95% CI 3.59-25.2).

Conclusions: Colchicine and GCS in monotherapy of GA did not cause HTX. Exclusively NSAIDs caused HTX, with Meloxicam showing lower hepatotoxicity as compared to Diclofenac and Etoricoxib. DILI was identified in 7 cases. The combination of NSAIDs with GCS did not result in HTX, while Diclofenac combined to Colchicine can led to the HTX. The risk of developing HTX was associated only with doses of NSAIDs above the average therapeutic.

Keywords: Gout, Drug-Induced Liver Injury, Nsads, Colchicine, Glucocorticosteroids, Hepatotoxity

Introduction

Gouty arthritis (GA) is a type of arthritis characterized by significant pain and inflammation, the first and important approach in its treatment is considered to be the rational management of GA. Nonsteroidal anti-inflammatory drugs (NSAIDs), Colchicine, and Glucocorticosteroids (GCS) have been recommended for the management of GA. To select the appropriate therapy, it is necessary to assess the severity of GA, the effectiveness of previously used anti-inflammatory drugs (AIDs) and their tolerability, to identify comorbidities and the medications for its treatment [1]. The latest recommendations for the management of GA were proposed by EULAR (European Alliance of Associations for Rheumatology) in 2016 and ACR (American College of Rheumatology) in 2020 [1,2].

Drug safety in modern medicine is given paramount importance. In patients with gout, AIDs are prescribed for a relatively short period, but considering the pain intensity, patients take high and maximum daily doses. Among the AIDs used to relieve acute gout, NSAIDs in particular are on the list of drugs most frequently contributing to the development of Drug-Induced Liver Injury (DILI) [3,4]. In addition, most patients with gout develop metabolic syndrome at a young age, one of the components of which is metabolically associated fatty liver disease (MAFLD), making the liver vulnerable when using hepatotoxic drugs [5]. Alcohol consumption also can play a role in liver damage in gout.

Traditionally, DILI includes both direct (intrinsic) and idiosyncratic injuries. Intrinsic DILI is dose-dependent, occurs in a majority of patients receiving drugs with inherent hepatotoxicity, typically within a short timeframe (hours to days) [6]. Idiosyncratic DILI is usually not dose-dependent, appears in a small number of patients after varying periods of drug use (days to weeks), and is associated with the development of genetically determined drug sensitivity. The 2019 European Association for the Study of Liver (EASL) 2019 and the 2021 American College of Gastroenterology guidelines provided a comprehensive analysis of current knowledge regarding DILI [6,7]. These documents reflect the etiological and risk factors, clinical and laboratory characteristics as well as approaches to treating DILI.

It can be assumed that in patients with gout on an initially unfavorable background and with the presence of many risk factors for liver damage, the prescription of hepatotoxic drugs may provoke the development of DILI to a greater extent than in the general population. In this regard, we found interesting to study the features of AIDs use in the management of GA at the outpatient stage of treatment and to assess their impact on the development of hepatotoxicity (HTX) in this group of patients.

Patients and Methods

Study Design and Population

The study was based on an analysis of data obtained from a retrospective, single-center study of patients with gout who were prescribed AIDs. The study was conducted in the Rheumatology Department of the 11th City Clinical Hospital of Minsk from January 2013 to January 2023.

During this period, clinical data and medical records of 663 patients with gout, consecutively hospitalized in the Rheumatology Department, were analyzed. The final analysis included 532 patients who fully met the study's inclusion criteria: the presence of GA (ACR, 1977) [8], initially normal blood alanine aminotransferase (ALT) levels (35 U/L for women, 40 U/L for men), use of AIDs throughout the observation period for at least 3 days, the group with HTX consisted of patients with an increase in blood ALT concentration of >2 times ULN during AIDs treatment and its normalization or a tendency towards it after discontinuation or correction of treatment.

All patients underwent outpatient blood sampling for analysis at the beginning of the GA, followed by repeat blood testing upon admission to the hospital and subsequent follow-up if changes were detected. The following data were recorded in detail: date of arthritis onset, the day of initiation of AIDs during the outpatient period of treatment, the AIDs doses, duration of treatment prior to admission, newly prescribing medication, herbs or dietary supplements, comorbid conditions and their treatment, and the day of detection of liver test abnormalities. When liver parameters increased, control testing was repeated in 5, 8 or 10 days depending on the degree of ALT elevation and its normalization. Discharge from the hospital was carried out after ALT blood level returned to normal or decreased to less than 2 ULN for cases with maximal ALT level ≥ 3.

The exclusion criteria included: the presence of a known liver disease with cytolytic syndrome, viral or chronic hepatitis, excess of aspartate aminotransferase (AST) level over ALT or positive de Ritis index, lithiasis of common biliary tract, chronic heart failure, newly prescribed drugs with known hepatotoxicity, absence of AIDs intake, or local drug application, malignancies.

Methods

The examination of patients at the outpatient and inpatient stages included general clinical examination methods, measurement of weight and waist circumference, biochemical blood analysis to determine the concentration of ALT, AST, alkaline phosphatase, gamma-glutamyl transpeptidase, bilirubin, albumin, uric acid, C-reactive protein, lipid profile, glucose, creatinine, urea. Acute liver injury is detected generally by ALT, ALP, and bilirubin.

The severity of cytolysis was based on increasing blood ALT concentrations: > 1 the upper limit of normal (ULN) but < 2 ULN was defined as minimal hypertrasaminasemia, > 2 ULN was interpreted as minimal severity, > 3 ULN as mild and > 5 ULN as moderate. HTX was considered based on the ALT level > 2 ULN. The cases of DILI were defined according to guidelines by EASL and AGA by one of the following thresholds: ALT level ≥ 5 ULN, or ALP ≥ 2 ULN, or ALT ≥ 3 ULN and bilirubin > 2 ULN [6,7]. Liver injury is defined as hepatocellular when ALT level rises ≥ 5 ULN alone or when the ratio (R) of ALT to ALP is ≥ 5. Cholestatic pattern is designated when ALP level ≥ 2 ULN alone or R ≤ 2, in mixed pattern R is between 2 and 5.

The severity of liver injury was assessed according to the American scheme: Grade I – AST/ALT elevated ≤ 3 ULN, bilirubin - ≤ 1.5 ULN; Grade II – AST/ALT elevated ≥ 3-5 ULN, bilirubin - ≥ 1.5-3 ULN; Grade III-IV – AST/ALT elevated > 5 ULN, bilirubin - > 3 ULN [7].

To assess the causal relationships between drug intake and the development of DILI, the updated RUCAM scale (Roussel Uclaf

Causality Assessment Method), 2016 was applied [6,9]. Scores were grouped into likelihood levels of excluded (score ≤ 0), unlikely (1-2), possibly (3-5), probably (6-8), and highly probably (> 8). Score points are based on timing of medication exposure and the onset of liver test abnormalities and its disappearance/decrease, risk factors for DILI, competing medication, competing diagnosis. All score points were determined and then summed, reflecting the overall score for the likelihood of developing the DILI. Based on R value at presentation DILI was categorized into hepatocellular and mixed/cholestatic patterns.

Pain assessment was performed using a visual analog scale (VAS). The severity of GA was assessed according to the recommendations of the ACR 2012 [10]. Hyperuricemia was defined as a blood uric acid concentration above 360 μmol/L.

In patients with ALT level ≥ 5 ULN, autoimmune (presence of antinuclear antibodies, smooth muscles antibodies, liver and kidney microsomal microsomal antibodies, and immunoglobulin G level) and infectious causes of liver damage (presence of hepatitis B and C) were excluded. All patients underwent the following instrumental examinations: electrocardiogram, radiography and/or ultrasound of the joints, abdominal organs, and esophagogastroduodenoscopy.

Table 1: Characteristics of patients in the groups

Parameters	HTX n=74	Control n=356	P
Men, % (n)	93.2 (69)	86.0 (306)	Ns
Age (years), Me	52 (42-60)	58 (52-65)	p < 0.001
Age of onset of gout (years), Me	43.5 (34-54)	50 (45-57)	p < 0.001
Duration of gout (days), Me	7 (2-12)	7 (3-13)	Ns
Protracted course of arthritis, % (n)	37.8 (28)	48.6 (173)	Ns
Polyarthritis, % (n)	36.5 (27)	39.9 (142)	Ns
Tophis, % (n)	45.9 (34)	42.4 (151)	Ns
Urolithiasis, % (n)	23.0 (17)	24.4 (87)	Ns
Uric acid >360 μmol/l, % (n)	93.2 (69)	98.3 (350)	Ns
GUT, % (n)	20.3 (15)	18.3 (65)	Ns
Alcohol prior the attack, % (n)	62.2 (46)	46.1 (164)	p = 0.012
NSAIDs, ↑ doses % (n)	94.6 (70)	68.5 (244)	p < 0.001
HT, % (n)	83.8 (62)	89.3 (318)	Ns
Dyslipidemia, % (n)	89.2 (66)	80.3 (286)	Ns
DM, % (n)	10.8 (8)	16.9 (60)	Ns
CC, % (n)	6.8 (5)	16.3 (58)	p = 0.035
BMI ≥ 30 кг/м² % (n)	52.7 (39)	57.0 (203)	Ns
Blood creatinine concentration ↑ % (n)	39.2 (29)	53.9 (192)	p = 0.021

Me-median (25%-75%), GUT – hypouricemic therapy, HT- hypertension, DM- diabete mellitus, CC – catastrophes cardiovasculares, ↑doses – doses above the average therapeutic doses.

Patient characteristics are presented in Table 1, including gout characteristics and the following comorbid conditions: hypertension (HT), ischemic heart disease (IHD), cardiovascular catastrophes (CC), including stroke and myocardial infarction, diabetes mellitus (DM), body mass index (BMI), calculated as weight (kg) divided by height squared (m^2) and categorised as ≥ 30

kg/m² for obesity, dyslipidemia, blood creatinine concentration, regular alcohol consumption, and alcohol consumption before a gout attack .

Methods of Statistical Data Processing

The obtained data were subjected to statistical analysis using the applied software package STATISTICA 10.0. To compare parameters in two independent groups, the non-parametric Mann-Whitney test was used. Differences between independent samples in the frequency of the studied characteristics were assessed using Fisher's exact and the chi-squared (χ^2) tests. Statistical significance of differences was accepted at a probability of error-free prediction of at least 95.5% ($p<0.05$). Odds ratios were calculated with ± 95% confidence interval (OR, ± 95% CI).

Table 2: Patients distribution depending on the AID used, % (n)

Drugs	All patients n=532	Patients with HTX n=74
Monotherapy	74.6 (394)	81.1 (60)
NSAIDs	93.4 (368)	100 (60)
Colchicine	4.8 (19)	0 (0)
GCS	1.8 (7)	0 (0)
Combination of AIDs	25.4 (138)	18.9 (14)
2 NSAIDs	58.7 (81)	78.6 (11)
NSAIDs + Colchicine	26.1 (36)	21.4 (3)
NSAIDs + GCS	15.2 (21)	0 (0)

AIDs – anti-inflammatory drugs, HTX-hepatotoxicity

Results

Monotherapie of AIDs. Among 532 patients with GA monotherapy was prescribed to the majority of patients - 74.6% (Table 2). The prescription of NSAIDs was dominated - 93.4%, Colchicine and GCS were used in a small number of patients, in 4.8% and 1.8%, respectively. The administration of two

AIDs simultaneously was practiced in almost a quarter of all patients - in 25.4%, among which cases two NSAIDs simultaneously prevailed – in 58.7%, NSAIDs in combination with Colchicine – in 26.1%, and with GCS – in 15.2% of cases.

HTX during GA monotherapy was caused exclusively by NSAIDs. Colchicine, administered in doses from 1 mg to 4 mg per day, did not cause cytolytic syndrome in any patient, nor did GCS used as monotherapy, which were prescribed in various ways: Diprospan intramuscularly (IM) – 2 patients or intra-articularly (IA) – 1 patient, Prednisolone 15 mg/day and Methylprednisolone 8 mg/day and 24 mg/day per os – 3 patients, Dexamethasone 8 mg IM, for 3 consecutive days – 1 patient.

Among 368 cases of treatment with NSAIDs, the leading positions were occupied by: Diclofenac (47.0%), Nimesulide (22.8%), Meloxicam (10.6%), together accounting for 80.4%. When analyzing HTX, the highest percentage was observed with Etoricoxib – 27.3%, Diclofenac slightly less – 20.9%, Nimesulide – 14.3%, and the lowest percentage of liver injury was observed with Meloxicam – only 2.6% (Table 3). When comparing the percentage of HTX cases among the most commonly used NSAIDs, liver injury occurred less frequently with Meloxicam compared to Diclofenac ($F = 0.035$, $p = 0.004$) and Etoricoxib ($F = 0.139$, $p = 0.007$); in other cases, no difference was observed.

Table 3: Patients distribution with cytolysis to NSAIDs, % (n)

NSAIDs N=368	ALT>1 ULN	ALT>2 ULN	ALT>3 ULN	ALT>5 ULN	Total
Diclofenac n=173	12.1 (21)	11.6 (20)	6.9 (12)	2.3 (4)	32.9 (57)
Nimesulide n=84	14.3 (12)	9.5 (8)	2.4 (2)	2.4 (2)	28.6 (24)
Meloxicam n=39	20.5 (8)	2.6 (1)	0 (0)	0 (0)	23.1 (9)
Etoricoxib n=22	9.1 (2)	18.2 (4)	9.1 (2)	0 (0)	36.4 (8)
Ketorol n=11	36.4 (4)	9.1 (1)	0 (0)	0 (0)	45.5 (5)
Etodine n=9	22.2 (2)	11.1 (1)	0 (0)	0 (0)	33.3 (3)
Xefocam n=5	40.0 (2)	20.0 (1)	0 (0)	0 (0)	60.0 (3)
Dexalgin n=2	0 (0)	0 (0)	50.0 (1)	0 (0)	50.0 (1)
Dexketoprofen n=2	0 (0)	50.0 (1)	0 (0)	0(0)	50.0 (1)

ULN- the upper limit of normal

Ketorol, Ethodine, Xefocam, Dexketoprofen and Dexalgin were the cause of liver injury in 1 case each from a small number of patients. An increase of blood ALT concentration more than 3 ULN was observed in 17 cases: 12 cases with Diclofenac, 2 cases each with Nimesulide and Etoricoxib, and 1 case with Dexalgin. Of these, an elevation in blood ALT level more than 5 ULN was observed in 4 patients taking Diclofenac and in 2 taking Nimesulide. In all other cases, ALT values increased less significantly - more than 2 ULN. The doses of NSAIDs used by the patients exceeded the average daily doses: Diclofenac 100-400 mg, Nimesulide 300-400 mg, in one case 600 mg, Etoricoxib 120 mg, Etodolac 800 mg. Exceptions were 4 cases when average daily NSAIDs doses were used.

Considering the total cytolytic syndrome, it manifested to a lesser extent when taking Meloxicam - 23.1% of cases, and to the greatest extent with Etoricoxib - 36.4% of cases. Among the rarely used NSAIDs, high percentages of cytolysis are noteworthy when taking Ketorolac - 45.5%, and in 3 patients out of 5 patients with Xefocam.

Combination of AIDs. When two NSAIDs were co-administered, HTX was observed in 14 out of 138 cases (10.1%), which did not differ from the percentage of liver injury cases with NSAIDs monotherapy ($p > 0.05$). HTX developed in 11 cases out of 81 (13.6%) when 2 NSAIDs were prescribed at average therapeutic doses - one per os, the other IM from 3 to 5 days, one - 7 days. An increase in the blood ALT concentration more than 3 ULN was registered in 4 patients and more than 5 ULN was observed in one case of a combination of Diclofenac IM at a dose of 75 mg and Meloxicam 15 mg per day during 7 days.

With the concomitant use of NSAIDs and Colchicine at a dose of 1 mg per day, 3 out of 36 patients developed HTX with an ALT level greater than 2 ULN, while Diclofenac being taken in doses ranging from 100 to 200 mg per day. In case of the combination of NSAIDs and GCS in 21 patients, no cases of liver injury were detected. No difference was found in the proportions of HTX cases between NSAIDs monotherapy and combination ($p > 0.05$).

The average duration of NSAIDs use before the development of liver injury was 13 (8-17) days. Hyperbilirubinemia was observed in 8 patients in the HTX group, exceeding 2 ULN in only 3 cases. By discharge, the blood bilirubin concentration normalized in two patients; in the third it was close to normal. Upon discharge from the hospital, the cytolytic syndrome in patients with HTX was completely resolved in more than half of the patients - 52.7% (n=39), in the rest, there was a tendency toward normalization - the ALT blood level was less than 2 ULN, in cases where the ALT level had increased to ≥ 3-5 ULN. No clinically significant manifestations of HTX were noted, except for icteric sclera observed by the physician.

According to the guidelines by EASL and AGA, the HTX during monotherapy with NSAIDs was considered as cases of DILI in 7 patients (5 on Diclofenac, 2 on Nimesulide), 6 of them had a hepatocellular pattern and 1 had a mixed pattern. The severity of liver injury was assessed as Grade I – 37 cases, Grade II – 17, Grade III-IV – 6.

When comparing patients with and without HTX, no gender difference was observed ($p > 0.05$) (Table 1). At the same time, patients with HTX were younger ($p < 0.001$), and characterized by earlier onset of gout than the control group ($p < 0.001$). There was no difference in the duration of AIDs use ($p=0.061$) as well as in parameters of the gout severity ($p > 0.05$). However, during the attack, an increase in blood creatinine concentration above normal was more common in the comparison group ($p=0.021$), as for comorbidity, there were statistically more patients with cardiovascular catastrophes in the same group (32 miocardial infarction and 26 strokes) ($p=0.035$). The development of HTX was significantly more frequent when taking NSAIDs in doses higher than the average daily dose ($p < 0.001$) and with an alcohol consumption prior to the attack ($p=0.012$). Noteworthy is the high percentage of uncontrolled hyperuricemia and the low use of hypouricemic therapy among our patients.

After adjusting for the gender and age to comparable parameters across groups with NSAIDs monotherapy, the risk of developing HTX remained associated with NSAIDs doses exceeding the average daily doses ($p < 0.001$; OR -9.52, 95% CI 3.59-25.2) (Table 4).

Table 4: Characteristics of patients in the compared groups with monotherapy of NSAIDs

Parameters	DILI n=60	Control n=168	P
Men, % (n)	95.0 (57)	93.5 (157)	Ns
Urolithiasis, % (n)	21.7 (13)	30.4 (51)	Ns
Polyarthritis, % (n)	36.5 (27)	39.9 (142)	Ns
Uric acid > 360 μmol/l, % (n)	98.3 (59)	94.6 (159)	Ns
Alcohol before the attack, % (n)	56.7 (34)	48.2 (81)	Ns
CRP ↑ % (n)	63.3 (38)	66.7 (112)	Ns
HT, % (n)	83.3 (50)	80.4 (135)	Ns
DM, % (n)	8.3 (5)	13.7 (23)	Ns
AF	6.7 (4)	11.9 (20)	Ns
CC, % (n)	6.7 (4)	13.1 (22)	Ns
Dyslipidemia, % (n)	83.3 (50)	81.5 (137)	Ns
BMI ≥ 30 кг/м² % (n)	51.7 (31)	60,1 (101)	Ns
Blood creatinine concentration ↑ % (n)	31.7 (19)	32.7 (55)	Ns
GFR60 ml/min, % (n)	23.3 (14)	35.7 (60)	Ns
NSAIDs, ↑ doses % (n)	93.3 (56)	59.5(100)	p < 0.000
GUT, % (n)	15.0 (9)	10.1 (17)	Ns
Regular ethanol use, % (n)	93.3 (56)	83.8 (141)	Ns

Me-median (25%-75%), GFR - Glomerular Filtration Rate, NSAIDs - Nonsteroidal anti-inflammatory drugs, ESR -erythrocyte sedimentation rate, CRP- C-reactive protein, GUT – hypouricemic therapy, HT- hypertension, DM- diabete mellitus, AF -Atrial Fibrillation, CC – catastrophes cardiovasculares, ↑doses – doses above the average therapeutic doses.

Discussion

Our study showed that NSAIDs traditionally remain the group of AIDs most frequently prescribed by outpatient physicians for relieving pain, whereas Colchicine and GCS were offered in a small percentage of cases (4.8% and 1.8%), apparently due to greater experience with NSAIDs, and doctors' knowledge of their high efficacy in gout, and their relatively low cost. More than 80% of NSAIDs prescriptions consisted of Diclofenac, Nimesulide, and Meloxicam, which is explainable in terms of the high anti-inflammatory efficacy of the first two in gout and the relative safety of Meloxicam in patients, especially those with comorbidities.

All cases of HTX were provoked by NSAIDs use, both as monotherapy and in combination with other AIDs, despite the relatively short duration of its use in GA. Among NSAIDs, Meloxicam showed lower hepatotoxicity compared to Diclofenac and Etoricoxib. The whole cytolytic syndrome occurred in very high proportion from one-quarter of patients taking Meloxicam and 36.4 of those taking Etoricoxib. Since in a previous study, patients with minimal hypertransaminasemia (> 1 ULN ALT < 2 ULN) during NSAIDs use were considered as a risk group for developing HTX, it can be assumed that with continued use at the same doses over 11 days, it will develop [11].

No difference in the proportion of HTX was found between NSAIDs monotherapy and simultaneous use of two NSAIDs, which allows the physician in case of severe pain to administer one NSAIDs parenterally and the other per os for a short period of up to 3-5 days, without exceeding the average therapeutic doses of each of them, although the advisability of such combined NSAIDs administration is criticized, and preference is given to NSAIDs monotherapy [1,2].

Table 5 presents LiverTox data for January 2026, which compiles all reports of drug-induced hepatotoxicity, including treatments for GA [12]. As can be seen, Diclofenac and Nimesulide account for the highest percentage of cytolysis, with the toxicity of Diclofenac and Nimesulide varying from elevated transaminase levels to hepatitis with jaundice, acute liver failure, and even death. Full recovery of liver function takes from 1 to 3 months after discontinuation of their use. For Nimesulide, more than 100 cases of hepatitis with jaundice have been reported, developing from 3-5 days to 6 months after initiation, with a mean latent period of 4 weeks. The mortality in these hepatitis cases reached 20%. As in our case, the use of Meloxicam proved to be the safest for the liver: no fatal outcomes or acute liver failure have been registered.

Table 5: NSAIDs hepatotoxicity by LiverTOX

NSAIDs	Cytolysis	ALT>3 ULN
Diclofenac	15%	2-4%
Nimesulide	15%	1%
Meloxicam	7%	1%
Ketorolac	1%	1%
Etodolac	2%	1%

The administration of Colchicine as monotherapy in our patients was safe for the liver, but in combination with Diclofenac, HTX can occur and is most likely associated with the intake of the latter indoses over 100 mg/day. The combination of Colchicine and NSAIDs is the most recommended and quite rational for the management of gout flares, provided that average therapeutic doses of NSAIDs are not exceeded. According to LiverTox, the use of Colchicine, including long-term use, does not cause cytolytic syndrome. Moreover, the drug is used off-label to treat certain liver diseases (alcoholic hepatitis, primary biliary cirrhosis). High doses of Colchicine are recommended to be avoided, as they are associated with high toxicity, affecting the liver, and manifested by vomiting, diarrhea, weakness, and metabolic acidosis, followed by rhabdomyolysis and multiple organ

failure. It is believed that the cytolysis in this situation is associated with rhabdomyolysis. Modern regimens of Colchicine use in GA allow achieving both clinical effects and avoiding adverse reactions [1,2]. When prescribing Colchicine to elderly people, it is recommended to monitor kidney and liver function, as well as to be aware of the potentiation of Colchicine's toxic effects when co-administered with macrolides, cyclosporine, calcium channel blockers, and lipid-lowering drugs.

Both monotherapy with GCS and also the addition of NSAIDs to their long-acting forms (IA or IM) did not result in any cases of HTX, indicating the safety and probable protective effect of GCS on the liver. The use of GCS for the treatment of GA is generally considered when NSAIDs and Colchicine are contraindicated or ineffective. During systemic administration of GCS in a short course at low to moderate doses, liver damage and cytolytic syndrome are not observed, although prolonged use may lead to the activation of viral hepatitis and the development of hepatic steatosis, the latter quickly resolving after GCS withdrawal. Only pulse therapy with Methylprednisolone may pose a danger to the liver, after which jaundice with cytolysis can appear within 1-6 weeks.

In our study, the main risk for the development of HTX in patients with gout were NSAIDs in doses above the average therapeutic range, which is consistent with other studies [3,6]. Typically, high doses of NSAIDs are prescribed for GA, and moreover, patients exceed them on their own: daily doses of Diclofenac reached 400 mg per day, and Nimesulide - 600 mg. Upon reduction of NSAIDs doses to average therapeutic levels or their withdrawal, concentration of blood ALT quickly normalized, supporting dose-dependency among observed HTX patients.

In a large-scale study in which 17,289 patients who took Diclofenac for various reasons, an increase in blood ALT level of more than 3 ULN was observed in 3.1% of them within the first 6 months of treatment [13]. Diclofenac-induced HTX has most often been observed at doses of 150 mg per day and higher. Nimesulide, as well as Diclofenac, was frequently prescribed to patients with gout due to its high efficacy and good bioavailability. A study of 400,000 participants by G.Traversa et al. found that the incidence of serious liver complications with Nimesulide intake reached 35.3 per 100,000 patient-years; with Diclofenac – 39.2; with Ketorolac – 66.8; and Ibuprofen – 44.6. Therefore, it was concluded that the use of Nimesulide was associated with a slight increase in the risk of HTX [14].

As presumed, the higher percentage of HTX development with NSAIDs used among patients with gout may be explained by an unfavorable background, attributed both to comorbidities (HT, dyslipidemia, obesity, DM) and hyperuricemia, which contribute to the development of NAFLD, on the one hand, and regular ethanol consumption, on the other, which generally makes patients with gout a high-risk group for HTX if they are prescribed hepatotoxic drugs [15]. Regarding hyperuricemia, it is known that it can have toxic effect on hepatocytes and contribute to an increase in liver enzymes [16].

In this regard, when prescribing hepatotoxic drugs, especially NSAIDs, to patients with gout, it is advisable to monitor liver function, especially in the presence of multiple risk factors for HTX. Of particular interest is the possibility of assessing the risk of developing HTX in accordance with the chemical structure of the substance and the predicted protein target in the patient. Such a mechanistic model was built by Liu A. and al. [17].

In the case of a history of HTX and especially DILI episodes associated with NSAIDs use, a more rational approach should be considered the use of alternative medication. In these cases, Colchicine in monotherapy, or in combination with moderate or minimal doses of NSAIDs and GCS, will be the most optimal options both for coexisting cardiovascular pathology and in the prevention of HTX. A crucial factor in combating gout flares and chronic systemic inflammation caused by hyperuricemia remains rational urate-lowering therapy.

Conclusions

1. Colchicine and GCS as monotherapy of GA did not induce HTX.

2. Meloxicam demonstrated lower HTX compared to Diclofenac and Etoricoxib in patients with GA.

3. Combinations of NSAIDs with long-acting GCS (IA or IM) resulted in no HTX cases, whereas the combination of Diclofenac and Colchicine can lead to liver injury due to exceeding the average daily doses of Diclofenac.

4. Combinations of two NSAIDs at moderate doses lasting for 3-5 days were associated with the development of HTX in a comparable proportion to NSAIDs monotherapy.

5. Cases of HTX in patient with gout were characterized as asymptomatic, transient, and rather mild than moderate severity, 7 cases of DILI (5 on Diclofenac, 2 on Nimesulide) were registered with a favorable outcome.

6. The risk of developing HTX during GA management was associated with exceeding the average therapeutic doses of NSAIDs.

7. Patients with gout could be considered a high-risk group for HTX when prescribed hepatotoxic drugs.

Declarations

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Municipal Clinical University Hospital No. 11 of Minsk and registered (№32) and by the Scientific Council of the Medical University, Minsk. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its amendments or comparable ethical standards. All participant provided written informed consent to the processing of personal date in medical information systems.

Disclosure

Conflict of Interest

None.

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