Hepatic Safety of Febuxostat Compared with Allopurinol in Gout Patients with Fatty Liver Disease

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ABSTRACT. ***Objective.*** Febuxostat has superior renal safety to allopurinol, but data on its hepatic safety are limited. Thus we compared the hepatotoxicity of febuxostat and allopurinol, and the clinical factors associated with hepatotoxicity, in patients with gout and fatty liver disease (FLD).

Methods. We included gout patients treated with allopurinol or febuxostat who were diagnosed with fatty liver based on ultrasonography or computed tomography. Hepatotoxicity was defined as follows: (1) elevation of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) at least 3× the upper limit of normal, when the baseline AST/ALT was normal; or (2) doubling of the baseline AST/ALT, when the baseline AST/ALT was elevated. The factors associated with hepatotoxicity were evaluated by Cox regression analysis.

Results. Of 134 patients identified with gout and FLD, 32 (23.9%) received febuxostat and 102 (76.1%) received allopurinol. There were no significant differences in age, body mass index, comorbidity, or disease severity between the groups; however, the incidence of hepatotoxicity was significantly lower in the febuxostat group (3/32, 9.4%) than in the allopurinol group (36/102, 35.3%, p = 0.005). Diabetes (HR 3.549, 95% CI 1.374–9.165, p = 0.009) and colchicine use (HR 11.518, 95% CI 5.515–24.054, p < 0.001) were associated with a higher risk of hepatotoxicity, whereas febuxostat use was associated with a lower risk of hepatotoxicity (HR 0.282, 95% CI 0.086–0.926, p = 0.037).

Conclusion. In the 32 patients studied, febuxostat was well tolerated in patients with gout and FLD. However, the presence of diabetes and colchicine use may increase the risk of hepatotoxicity.
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Longterm urate-lowering therapy is necessary for the effective treatment of chronic gout. Allopurinol is metabolized to the active metabolite, oxypurinol, which is primarily cleared by the kidney[1]; thus, dose adjustment or avoidance are required to minimize toxicity in patients with renal impairment. A potent new selective xanthine oxidase inhibitor, febuxostat, has become available that is metabolized mainly by glucuronide formation and oxidation in the liver, but not in the kidney[2], making it suitable for use in patients with impaired renal function[3]. Regarding hepatic safety, the incidence of abnormal liver function tests (LFT) for allopurinol and febuxostat has been reported at 2–6% and 2–13%, respectively[4,5]. In a previous phase III study, drug discontinuation because of LFT elevation was slightly higher in a group taking 120 mg febuxostat than in a group taking allopurinol[6]. Moreover, a case of severe hepatitis has been reported after treatment with febuxostat[7,8].

Gout is frequently associated with an increased risk of metabolic syndrome, including the nonalcoholic fatty liver disease (NAFLD), with 23.1% of patients with gout also having NAFLD; elevated uric acid levels are an independent risk factor for NAFLD, which in turn increases the risk of drug-induced liver injury[9,10,11,12]. Despite this, there is only limited research about febuxostat hepatotoxicity in patients with gout and fatty liver disease (FLD).

Thus we aimed to compare the hepatotoxicity of febuxostat and allopurinol in patients with FLD, and to clarify the clinical factors associated with any hepatotoxicity.

MATERIALS AND METHODS

Study population. In our retrospective cohort study, we reviewed the electronic medical records of patients with FLD treated with allopurinol or febuxostat for gout if they had comorbid FLD between January 1997 and December 2017 at a tertiary referral hospital in Seoul, South Korea. We included all the patients who were administered allopurinol or febuxostat during the study period. Among these, we identified the patients with FLD

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from the results of abdominal ultrasound or computed tomography (CT). Patients who were taking a urate-lowering agent other than allopurinol or febuxostat were excluded, as were patients who had a history of hepatitis B or C, drug-induced hepatitis, or autoimmune hepatitis. The study protocol was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea (No. 2017-1009). The requirement for informed consent was waived because of the retrospective design.

The following data were collected from medical records: demographic information including age, sex, and body mass index (kg/m^2); comorbid medical conditions such as hypertension, diabetes mellitus (DM), hyperlipidemia, and renal insufficiency; alcohol intake; severity of the FLD; drug exposure, including allopurinol, febuxostat, colchicine, statins, and nonsteroidal antiinflammatory drugs; and laboratory data, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin, creatinine, and serum uric acid levels.

The diagnosis of gout was made based on the American College of Rheumatology/European League Against Rheumatism collaborative initiative criteria[13]. The diagnosis of fatty liver was based on ultrasound or CT findings that were reviewed and graded by independent radiologists[14]. The primary outcome of interest was hepatotoxicity. Hepatotoxicity was defined as follows: (1) elevation of AST/ALT to at least 3× the upper normal of limit when the baseline AST/ALT was normal; or (2) doubling of the baseline AST/ALT when the baseline AST/ALT was elevated[15,16]. Renal insufficiency was defined as an estimated glomerular filtration rate of < 60 ml/min/1.73 m^2, using the Chronic Kidney Disease Epidemiology Collaboration equation.

Statistical analysis. The chi-square and Fisher's exact tests were used to compare categorical data. Continuous values are expressed as means (SD) or as median [interquartile range (IQR)] and were calculated using the Student t test for parametric data or the Mann–Whitney U test for nonparametric data. Cox regression analysis with backward elimination was performed to identify risk factors for hepatotoxicity, reporting the HR and 95% CI. Variables that had a p value of < 0.2 on univariate analysis were selected for multivariate analysis, but a p value of < 0.05 was otherwise considered statically significant in all analyses. We used IBM SPSS Version 20.0 (IBM Corp.) for all statistical analyses.

RESULTS

Comparison of clinical features in the allopurinol and febuxostat groups. Of the 134 included patients, 102 were taking allopurinol and 32 were taking febuxostat; 20 patients from the febuxostat group had previously been treated with allopurinol. The reason for the discontinuation of allopurinol was either inefficacy (18/20, 90%) or an adverse event (gastrointestinal discomfort or mild LFT elevation; 2/22, 10%). The median allopurinol dose was 192 mg (IQR 131.8–217.3 mg) and the median febuxostat dose was 41 mg (IQR 39.3–72.8 mg). Table 1 shows the baseline clinical characteristics and laboratory data for patients by exposure to allopurinol or febuxostat. There were no significant differences in the main clinical features between the 2 groups, including disease severity, LFT elevation, and serum uric acid levels.

The median followup durations were 56 weeks (IQR 15.8–167.3 weeks) and 84 weeks (IQR 28–126.8 weeks) for patients treated with allopurinol and febuxostat, respectively (p = 0.607; Table 2). Hepatotoxicity developed in 36 patients (35.3%) receiving allopurinol and in 3 patients (9.4%) receiving febuxostat, and the difference between groups was significant (p = 0.005). The times to development of hepatotoxicity were 17.5 weeks (IQR 5.5–41.5 weeks) and 21 weeks (IQR, 21–53.5 weeks) in patients receiving allopurinol and febuxostat, respectively (p = 0.464).

Clinical factors associated with hepatotoxicity in patients with gout and FLD. Cox regression analysis was performed to evaluate the clinical factors associated with hepatotoxicity. Univariate analysis indicated that age and colchicine use were significantly associated with hepatotoxicity, but that febuxostat exposure was associated with a lower risk of hepatotoxicity (Table 3). Multivariate analysis showed that diabetes (HR 3.549, 95% CI 1.374–9.165, p = 0.009) and colchicine use (HR 11.518, 95% CI 5.515–24.054, p < 0.001) were significantly associated with an increasing risk of hepatotoxicity, and that febuxostat was significantly associated with a lower risk of hepatotoxicity (HR 0.282, 95% CI 0.086–0.926, p = 0.037), compared with allopurinol (Table 4).

DISCUSSION

In our present study, we showed that febuxostat use was not significantly associated with an increased risk of hepatotoxicity in patients with gout and FLD. Instead, those exposed to allopurinol had a significantly higher incidence of hepatotoxicity, and multivariate analysis showed that the risk of hepatoxicity was significantly increased by the presence of diabetes and the use of colchicine.

Febuxostat is mainly metabolized by the liver, not by the kidney, so it is considered safer than allopurinol for use in patients with reduced renal function. However, the safety of febuxostat compared with allopurinol in patients with FLD has not been established. A previous study showed that there were no significant differences in the pharmacokinetic variables of febuxostat or in the serum uric acid levels of patients with impaired hepatic function compared with those with normal hepatic function. In addition, a recent study reported that febuxostat showed a hepatoprotective effect by attenuating lipid accumulation and the inflammatory response in HEp-G2 cells exposed to a mixture of free fatty acids[17]. However, that study provided no data about hepatic safety, and in particular did not perform a comparison with allopurinol. In our present study, among the 32 patients with FLD who were treated with febuxostat, 3 (9.4%) developed hepatotoxicity, which was significantly lower than the incidence among patients taking allopurinol (36/102, 35.3%). These findings indicate that febuxostat was well tolerated in patients with FLD, being associated with fewer cases of hepatotoxicity when compared with allopurinol.

Drug-induced liver injury has been associated with high mortality in patients with preexisting liver disease compared with patients who have no preexisting disease[18]. In addition, the presence of NAFLD has been associated to about a 4-fold increased risk of drug-induced liver injury[12]. Previous studies have shown that gout is an independent risk factor for NAFLD, and that the severity of NAFLD is higher in patients with gout than in those without[9]. According to the Roussel Uclaf Causality Assessment Method (RUCAM), an estab-

Table 1. Comparison of baseline variables for allopurinol and febuxostat.

Variables	Allopurinol, n = 102	Febuxostat, n = 32	p
Age, yrs	47.9 (11.9)	51.5 (14.1)	0.157
Male	100 (98)	32 (100)	1.00
BMI, kg/m², median (IQR)*	27 (25–29), n = 88	28 (26–32), n = 31	0.202
Referred for gout	65 (63.7)	18 (56.2)	0.447
Comorbidity	18 (19.1)	16 (22.9)	0.562
Hypertension	42 (41.2)	16 (50)	0.379
Diabetes mellitus	14 (13.7)	2 (6.2)	0.356
Renal insufficiency	12 (11.8)	1 (3.1)	0.189
Hyperlipidemia	25 (25)	9 (28.1)	0.725
Alcohol intake			0.556
None	25 (24.5)	9 (28.1)	
< 50 g/week	72 (70.6)	20 (62.5)	
> 50 g/week	5 (4.9)	3 (9.4)	
FLD severity			0.853
Mild	42 (41.2)	12 (37.5)	
Moderate	42 (41.2)	13 (40.6)	
Severe	18 (17.6)	7 (21.9)	
Laboratory data			
AST, IU/l, median (IQR)	34 (27–44)	41.5 (26.5.3–51)	0.257
ALT, IU/l, median (IQR)	45 (31–63.3)	64.5 (27–78.8)	0.411
ALP, IU/l, median (IQR)	71 (59–89.5)	67.5 (55.3–83.3)	0.321
Bilirubin, IU/l, median (IQR)	0.8 (0.7–1.1)	0.8 (0.6–0.9)	0.151
GFR, ml/min/1.73 m²	83.8 (20.9)	88.1 (16.8)	0.294
Uric acid, mg/dl*	8.3 (1.8), n = 99	8.6 (1.4)	0.299

Values are mean (SD) unless otherwise specified. *Missing values were excluded from analysis. BMI: body mass index; IQR: interquartile range; FLD: fatty liver disease; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GFR, glomerular filtration rate.

Table 2. Outcomes data for allopurinol and febuxostat.

Variables	Allopurinol, n = 102	Febuxostat, n = 32	p
Followup duration, weeks, median (IQR)	56 (15.8–167.3)	84 (28–126.8)	0.607
Dose, mg/day, median (IQR)	192 (131.8–217.3)	41 (39.3–72.8)	
Hepatotoxicity, n %	36 (35.3)	3 (9.4)	0.005
Time to event, weeks, median (IQR)	17.5 (5.5–41.5)	21 (21–53.5)	0.464

IQR: interquartile range.

lished tool for assessing causality in drug-induced liver injury[19], of the 102 patients taking allopurinol in our study, 2 patients likely had drug-induced liver injury [1 = RUCAM score 9 (highly probable), 1 = RUCAM score 6 (probable)]. By contrast, there were no cases of drug-induced liver injury in the febuxostat group when using this method. These results suggest that febuxostat remained safer than allopurinol, even when applying a stricter method for assessing the causality of drug-induced toxicity. Indeed, in the multivariate analysis, febuxostat was associated with lower risk of hepatotoxicity compared with allopurinol (HR 0.282, 95% CI 0.086–0.926, p = 0.037).

In our study, DM was associated with hepatotoxicity in gout patients with FLD (HR 3.549, 95% CI 1.374–9.165). DM is considered a risk factor for idiosyncratic drug-induced liver injury[20]. In a previous study of patients with rheumatoid arthritis who received methotrexate, patients with diabetes showed a higher prevalence of drug-induced liver injury[21]. In addition, patients with diabetes had a reduced drug metabolic capacity[22]. Together, these may explain the increased risk of hepatotoxicity among patients with diabetes.

Colchicine is generally thought of as being unlikely to cause hepatotoxicity[23]. However, several cases of colchicine-induced acute hepatitis have been reported during treatment with standard doses[24,25]. In our study, the regimen of colchicine was 0.6 mg/day or 1.2 mg/day and was mostly administered prophylactically. The median exposure duration was 110 days (IQR 47.5–264.5) and the median dose was 1.2 mg/day (IQR 0.9–1.2 mg/day). The median exposure dose of colchicine did not differ between the 2 groups. However, colchicine use was also identified as being significantly associated with a higher risk of hepatotoxicity in patients with

Table 3. Univariate analysis of variables associated with hepatotoxicity.

Variables	HR	95% CI	p
Age, yrs	0.970	0.945–0.996	0.024
Female	0.048	0.343–7.230	0.595
BMI, > 30 kg/m²*	0.758	0.331–1.737	0.513
Diabetes mellitus	1.861	0.779–4.449	0.162
Hypertension	0.669	0.366–1.336	0.279
Renal insufficiency	1.095	0.389–3.085	0.864
Colchicine	9.330	4.695–18.541	< 0.001
Statin	0.544	0.265–1.116	0.097
Alcohol intake			0.494
None, ref			
< 50 g/week	0.858	0.413–1.779	0.680
> 50 g/week	1.758	0.480–6.439	0.394
FLD severity			0.891
Mild, ref			
Moderate	1.101	0.554–2.187	0.783
Severe	0.882	0.344–2.260	0.794
Allopurinol, ref			
Febuxostat	0.247	0.076–0.802	0.020
NSAID	1.566	0.686–3.575	0.287

*Missing value was excluded from analysis. BMI: body mass index; FLD: fatty liver disease; NSAID: nonsteroidal antiinflammatory drugs.

Table 4. Multivariate analysis of variables associated with hepatotoxicity.

Variables	HR	95% CI	p
Allopurinol, ref			
Febuxostat	0.282	0.086–0.926	0.037
Diabetes mellitus	3.549	1.374–9.165	0.009
Colchicine	11.518	5.515–24.054	< 0.001

gout and FLD (HR 11.518, 95% CI 5.515–24.054, p < 0.001). Although the mechanism of this increased risk of hepatotoxicity was unclear, it could be because colchicine being primarily metabolized and excreted by the liver[26]. Indeed, an increased risk of adverse events (including leukopenia) has been reported in patients with liver cirrhosis[27].

Our present study has some limitations. First, it was not clear whether hepatotoxicity was directly related to drug use. It is possible, for example, that the LFT elevations were caused by a worsening of the underlying FLD. Second, because the study design was retrospective and at a single center, we cannot exclude the possibility of selection bias, and it was difficult to know whether subjects had been exposed to alcohol during the study period and the amount of alcohol they had consumed. Third, the number of patients taking febuxostat was small, which may have affected the power to detect a clinically meaningful difference, and the selection of allopurinol or febuxostat was based on diverse clinical circumstances, including the preference of individual physicians. Thus, the baseline clinical characteristics, including the frequency of renal insufficiency, could not be completely matched between the allopurinol and febuxostat groups. Despite these limitations, and to the best of our knowledge, ours is the first study to have compared the hepatic safety of febuxostat with allopurinol in patients with gout and FLD.

Our results suggest that febuxostat is safe regarding hepatotoxicity compared with allopurinol in patients with FLD. Instead, the presence of diabetes and the use of colchicine may increase the risk of hepatotoxicity. Given the increasing worldwide occurrence of FLD, our results provide preliminary evidence of the safety of febuxostat in patients with gout and comorbid FLD. Further studies are required to confirm these findings.

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