Improvement in hepatic fibrosis estimated by Fibrosis-4 index in pegloticase treated chronic refractory gout patients

N. Schlesinger[1], V.K. Rustgi[2], A.E. Yeo[3], P.E. Lipsky[4]

[1]Division of Rheumatology and Gout Center, [2]Hepatology, Center for Liver Diseases and Liver Masses, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA; [3]Yeo Analytics, LLC, Jersey City, NJ, USA; [4]AMPEL BioSolutions, LLC, Charlottesville, VA, USA.

Abstract

Objective

To determine whether lowering serum urate (SU) affects the course of non-alcoholic fatty liver disease (NAFLD).

Methods

Retrospective data analysis from chronic refractory gout patients who participated in two 6-month pegloticase randomised clinical trials compared patients who received pegloticase biweekly to those who received placebo. Patients with persistent urate-lowering to <1 mg/dL in response to biweekly pegloticase (responders, n=36) were compared to those who received placebo (n=43). NAFLD was assessed using the Fibrosis-4 (Fib-4) index. Comparisons between groups were carried out using 2 sample Wilcoxon tests or regression analysis.

Results

At baseline the mean (standard deviation [SD]) Fib-4 values were 1.40 (0.86) in pegloticase responders, and 1.04 (0.53) in patients receiving placebo. Patients receiving placebo exhibited a change of 0.26 (0.41) in Fib-4 score over 6 months vs 0.13 (0.62) for pegloticase responders (p=0.048). When only patients with a Fib-4 value >1.3 were considered (n=27), a significant difference in the change in the Fib-4 values between pegloticase responders vs. placebo was observed (-0.15 [0.67] vs. 0.7 [0.42], p=0.04). The correlation between the SU area under the curve (AUC) over the 6-month trial period and the change in Fib-4 value was R=0.33 (p=0.0004). Multivariable analysis indicated SU AUC was the only significant contributor to the change in Fib-4 values (p=0.018).

Conclusion

Persistent lowering of SU significantly reduced Fib-4 scores, implying a possible effect on NAFLD progression. These results support the consideration of a complete analysis of the impact of profound urate-lowering on NAFLD as measured by the Fib-4 index.

Key words

hyperuricaemia, urate, therapy, Fibrosis-4 index, non-alcoholic fatty liver disease

Naomi Schlesinger, MD
Vinod K. Rustgi, MD, MBA
Anthony E. Yeo, MBBS, PhD, MPH
Peter E. Lipsky, MD

Please address correspondence to:
Naomi Schlesinger,
Division of Rheumatology,
Rutgers Robert Wood Johnson
Medical School - Gout Center,
Department of Medicine,
Medical Education Building, Room 468,
New Brunswick, NJ 08903-0019, USA.
E-mail: schlesna@rutgers.edu

Received on November 29, 2021; accepted in revised form on February 21, 2022.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2023.

Funding: this independent data analysis was supported by funding from Horizon Therapeutics. The funder of this study had no role in study design, data analysis, data interpretation or writing of the results.

Competing interests: N. Schlesinger has received consulting fees from Novartis and Horizon Therapeutics.
V.K. Rustgi has received research support from Genfitand and participated in Speaker's bureaus for Gilead and Abbvie.
A.E. Yeo has received contractor fees from Horizon Therapeutics, USA.
P.E. Lipsky has received consultant fees from Horizon Therapeutics, USA.

Introduction

Gout, a common chronic inflammatory metabolic disease manifested by persistently elevated serum urate (SU) levels, is associated with multiple comorbidities including, type 2 diabetes mellitus, hypertension, hyperlipidaemia, cardiovascular disease, chronic kidney disease, metabolic syndrome, and obesity (1-4). Although it has not received as much attention as other comorbidities, gout and elevated SU (hyperuricaemia) have both been shown to be associated with increased risk for non-alcoholic fatty liver disease (NAFLD). A large-scale study in China included 54,325 subjects (1930 with gout and 6169 with NAFLD). It showed that the prevalence of NAFLD was significantly higher in patients with gout (23.1%) *versus* those without gout (10.9%) even after adjustment for age, sex, presence of metabolic syndrome, and low estimated glomerular filtration rate (eGFR) (4). This study and several other cross-sectional epidemiologic analyses have shown that elevated SU is significantly associated with the frequency of NAFLD in patients with or without gout (5-12). In a cohort of 166 patients with biopsy-proven NAFLD, approximately 20% of patients had hyperuricaemia. Moreover, hyperuricaemia (OR 4.906) was linked to the NAFLD activity score by multiple logistic regression analysis and was found to be independently associated with the severity of histological liver damage suggesting, that SU was a serum marker for liver damage (13).

The relationship between gout, hyperuricaemia, and NAFLD raises the question of whether administration of urate-lowering therapy in patients with either gout or asymptomatic hyperuricaemia might influence the severity of the liver disease. While this issue has not been addressed in clinical trials, the correlations noted above have prompted the suggestion that urate-lowering might be a treatment target for the prevention and treatment of NAFLD (14-15).

In species other than humans and some non-human primates, the enzyme uricase (urate oxidase) converts urate to allantoin, which is more soluble and readily excreted. The uricase gene has been inactivated by mutation and is non-functional in humans and some other primates (16). The direct consequence is that humans have higher SU levels than other animals. To reduce the elevated SU levels, a PEGylated recombinant mammalian uricase, pegloticase, was developed to catalyse urate oxidation to allantoin, thereby profoundly lowering SU levels (Fig. 1A).

There are several methods available to clinicians to diagnose liver disease. Invasive approaches include liver biopsy; however, this is expensive and not routinely performed (17). Therefore, various imaging methods and biomarkers have been tested over the years to diagnose fatty liver and liver fibrosis (18). Among the most used biomarkers is the four-factor fibrosis (FIB-4) index, a validated non-invasive estimate of liver fibrosis in a variety of liver diseases, which is increasingly used as a measure to help determine NAFLD status (19-20). The score is easy to use and inexpensive because it uses a combination of routine blood tests to indicate whether a patient has a high or low probability of advanced fibrosis. The FIB-4 index formula combines the patient age with measurements of 3 biomarkers: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count, parameters that are routinely included in the investigation of liver disease (18).

The availability of data from two randomised controlled trials (RCTs) of pegloticase allowed testing the hypothesis that lowering SU might improve the Fib-4 index. (21)

Methods

Studies providing data

Pegloticase was assessed in two identical 6-month RCTs (NCT00325195; NCT01356498), with methods that have been described in detail previously (21). The trials received institutional review board approval at each site. Written informed consent and Health Insurance Portability and Accountability Act assurances were completed for each participant before enrollment. The design and conduct of the studies complied with the Declaration of Helsinki. Ethics review was waived because this is a *post hoc* analysis of anonymised data.

Participants
Patients were ≥18 years of age with baseline SU ≥8.0 mg/dL and met one or more of the following entry criteria: ≥3 self-reported gout flares during the previous 18 months; ≥1 tophi; and, gouty arthropathy.
Patients enrolled in the two RCTs also had a contraindication to allopurinol or failure to normalise plasma urate (PU) after ≥3 months of treatment with the maximum medically appropriate dose (21).

Treatment
Patients received 12 biweekly intravenous infusions that contained pegloticase 8 mg at each infusion (q2w group) or placebo infusions.

Assessments
Plasma urate was determined at baseline, at approximately 2 and 24 hours after the first infusion, preceding each biweekly infusion, and at 5 additional prespecified time points in both months 3 and 6: 2 hours, 1 day, and 7 days after the week-9 and week-21 infusions and 2 hours and 7 days after the week-11 and week-23 infusions. Responders were defined as patients with PU <6.0 mg/dL for ≥80% of the time during both months 3 and 6, the periods extending respectively from the week-9 infusion to just prior to the week-13 infusion, and from the week-21 infusion to the week-25 final study visit (21).

Assessment of fibrosis
Since liver biopsy information was not available for these patients, the NAFLD activity score, which is based on histological grading and staging for NAFLD, could not be performed, and we relied on the Fib-4 index, calculated from measurements of aspartate aminotransferase (AST), alanine amino transferase (ALT), platelet count, and age (age x AST/platelets x √ALT). A Fib-4 value of 1.3 is an indication that further evaluation of NAFLD is warranted (17-18). The Fib-4 scores in our study were calculated using clinical laboratory values from samples collected at screening and after 6, 8, 12, and 24 weeks of pegloticase treatment.

Table I. Baseline demographic and clinical characteristics of patients included in the analysis.

Characteristic	q2w Responders (n=36)	Placebo (n=43)
Age, years (mean [SD])	61·2 (14·2)	55·4 (12·2)
Gender (n [%] male)	26 (72·2%)	36 (83·7%)
Disease duration, years (mean [SD])	17 (14·4)	13·3 (9·7)
Patients with >1 flare in the past 18 months	33 (91·7%)	37 (86·1%)
Acute flares in prior 18 months (mean [SD])	12·4 (11·6)	10·2 (16·4)
Tophus present (n [%])	25 (69·4%)	29 (67·4%)
Mean serum urate, mg/dL (mean [SD])	10·1 (2·9)	9·2 (2·8)
Serum urate >6 mg/dL	33 (91·7%)	35 (83·3%)
Fib-4 score (mean [SD])	1·40 (0·86)	1·04 (0·53)
Comorbidities (n [%])		
Hypertension	25 (69·4%)	31 (72·1%)
Dyslipidaemia	21 (58·3%)	19 (44·2%)
Diabetes mellitus	13 (37·1%)	8 (18·6%)
Coronary artery disease	5 (14·3%)	6 (14·0%)
Cardiac failure	7 (20·0%)	6 (14·0%)
Weight (kg, mean (SD)	93·0 (21·8)	99·8 (27·3)
BMI (mean (SD)	32·0 (7·0)	32·3 (7·4)

Fib-4: Fibrosis-4 index; SD: standard deviation.

Urate exposure
Areas under the curve (AUC) of SU were calculated according to the equation:

$$AUC = \int_a^b F(X)\, dX$$

where *a* and *b* are points on the X axis and F(X) is the integral of function using SAS. Because the curves were not always continuous functions, the trapezoidal rule was employed to approximate the definitive integral.

Data analysis
All comparisons between groups were carried out using 2 sample Wilcoxon tests or regression analysis. The 2 sample Wilcoxon test was used for analysis of continuous variables, whereas regression analysis was used to predict the value of a variance based on the value of another variable We performed a regression model with variables including diabetes mellitus (DM), total cholesterol, estimated glomerular filtration rate (eGFR), cumulative AUC, age, sex and race, and body mass index (BMI). Spearman rank-order correlations were carried out and linear and multiple regression were employed to determine variables associated with Fib-4 scores. Statistical significance was defined as $p<0.05$. All calculations were carried out with SAS v. 9.4 (Cary, NC).

Analysis of populations
Results from two groups were evaluated: 1) patients who maintained persistent low levels of PU in response to treatment with biweekly pegloticase; and 2) patients who received placebo.

Results

The demographic and clinical characteristics for the two groups of patients evaluated are summarised in Table I and are typical of patients with advanced gout.

Changes from baseline in liver functions
There were no significant changes in liver functions from their values at screening compared to 14 (±days) post-dose (*p*-value between q2 and placebo cohorts).
The mean ALT at screening was 30.17 and 29.4 14 days post-dose ($p=0.7499$); the mean AST at screening was 25.2 and 26 14 days post-dose ($p=0.7377$); the mean total bilirubin- at screening was 0.478 and 0.462 14 days post-dose ($p=0.7636$); the mean alkaline phosphatase at screening was 96.47 and 92.5 14 days post-dose. ($p=0.2579$).

Changes from baseline in Fib-4 scores
The effects of pegloticase and placebo on Fib-4 scores are shown in Figure 1A-B. Patients receiving placebo exhibited a mean reduction (standard deviation) of 0.26 (0.41) in the Fib-4

score over the 6 months of the RCTs compared with 0.13 (0.62) for the pegloticase responders (p=0.048, by linear regression) (Fig. 1A). When only the patients with a Fib-4 value >1.3 at baseline were considered (n=27), a significant difference in the change in the Fib-4 values over the 6-month trials between pegloticase responders and those receiving placebo was also observed (-0.15 [0.67] *vs*. 0.37 [0.42], p=0.04, 2-sample Wilcoxon test) (Fig. 1B).

Relationship between SU exposure and change from baseline in Fib-4 score

The effects of pegloticase treatment on the AUC for SU over the courses of the two RCTs are shown in Figure 2A for all patients, and for patients with a Fib-4 score >1.3. For both analyses, there were significant between-group differences in urate exposure (p=0.032 and p=0.0021, respectively). The correlation between SU AUC over the 6 months of the trial and the change in Fib-4 value for all patients was R=0.33, p=0.0004 (Fig. 2B).

Regression analysis

Multiple regression analysis was used to assess the effects of treatment group (pegloticase responders or placebo), random serum glucose levels, cumulative AUC for SU, DM, total cholesterol, eGFR, age, sex and race, and BMI on changes from baseline in Fib-4 scores. This analysis indicated that cumulative SU AUC was the only variable significantly associated with change from baseline in Fib-4 scores (p=0.0394) (Table II).

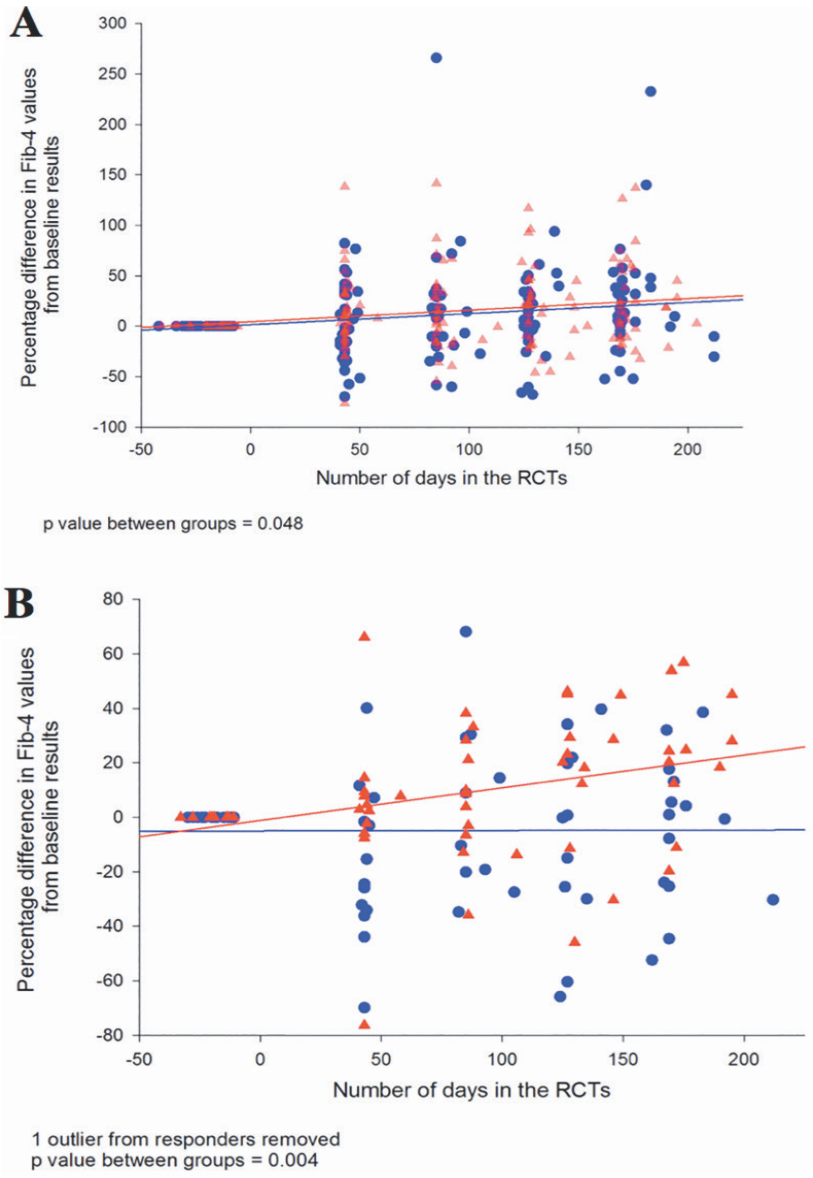

Fig. 1. Effects of pegloticase and placebo on Fib-4 scores for all patients (**A**) and on Fib-4 scores for patients with Fib-4 scores >1.3 at baseline (**B**).

Table II. Relationships between variables included in multiple regression model and change from baseline in Fib-4 score.

Variable	Parameter estimate	p-value
Group (q2w responders and placebo patients)	0.0118	0.4731
Diabetes mellitus	-0.08191	0.1694
Total cholesterol (mg/dL)	-0.00044929	0.4637
eGFR (mL/min/1·73 m^2)	-0.00179	0.1399
Cumulative AUC of serum urate (mg/dL• hours)	0.0000046	**0.0453**
Age	0.00098018	0.7036
Sex	0.15554	0.0291
Race	-0.03751	0.5011
BMI	0.0057	0.1276

AUC: area under the curve; eGFR: estimated glomerular filtration rate; Fib-4: Fibrosis 4 index.

Discussion

The data from the present analysis are consistent with the conclusion that persistent lowering of SU had a significant impact on the Fib-4 index, implying a possible effect on the course of NAFLD. For patients with a Fib-4 score >1.3 at baseline, urate-lowering not only stabilised Fib-4 scores but also decreased Fib-4 scores in some patients implying an improvement in hepatic fibrosis. The positive effect of urate-lowering on the severity of NAFLD is consistent with results in murine models in which administration of urate-lowering therapy decreased lipid peroxidation and M1 macrophage accumulation in the liver and improved alanine aminotransferase and aspartate aminotransferase levels in treated gout patients (22).

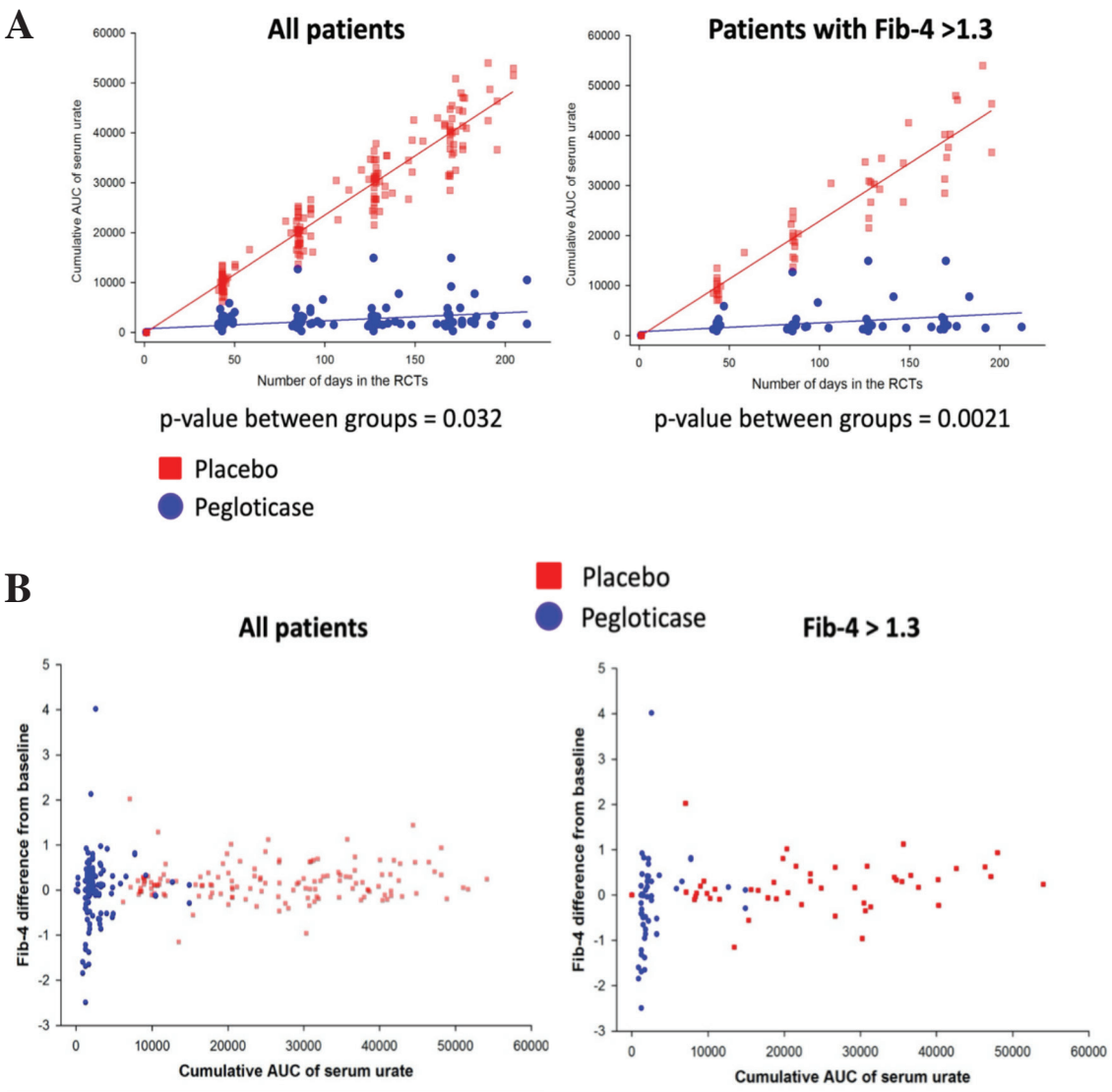

Fig. 2A. Cumulative AUCs for serum urate for all patients and for patients with Fib-4 scores >1.3 at baseline. **B**. Relationship between serum urate AUC over the 6 months of the trial and the change in Fib-4 score for all patients and patients with Fib-4 value >1.3 at baseline.

The regression analysis conducted as a part of this study indicated that SU over the 6 months of the RCTs was the only variable among those evaluated significantly associated with a change from baseline in Fib-4 scores. The present observation that lower SU was significantly correlated with the Fib4 index, and presumably the severity of fibrosis, is consistent with results from earlier association studies. Results from the analysis carried out by Kuo and colleagues showed that the odds ratios for NAFLD in subjects without gout, after adjustment for age, sex, presence of metabolic syndrome, and low eGFR, were 2.16, 3.98, and 5.99, respectively, for SU levels 5.0–6.9 mg/dL, 7.0–8.9 mg/dL, and ≥9.0 mg/dL. The respective odds ratios for NAFLD in those with gout were 2.61, 2.87, 4.53, and 6.31 (5). Another more recent multivariate analysis adjusted for age, gender, arterial hypertension, and serum creatinine showed that subjects in the top tertile for SU (≥6.8 mg/dL for men and ≥5.6 mg/dL for women) more frequently had hepatocellular steatosis than those in the lower two tertiles (8). Serum urate levels have also been associated with more severe hepatic fibrosis in patients with one or more components of the metabolic syndrome (23). In contrast, results from a study of 130 patients with biopsy-proven non-alcoholic steatohepatitis indicated that severity of fibrosis demonstrated by biopsy was inversely correlated with SU level (24). Two meta-analyses of results from observational studies carried out by the same group have indicated that hyperuricaemia is associated with increased risk for NAFLD (25), but not with severity of fibrosis in patients who have been diagnosed with NAFLD (26).

A longitudinal study of patients with NAFLD has provided information about the mechanisms that may underlie the relationship between elevated SU and this hepatic disease. A 7-year prospective analysis of 5549 subjects (281 with NAFLD at baseline and all without hyperuricaemia) indicated that the presence of NAFLD was associated with increased risk for incident hyperuricaemia (HR=1.609). Results from *in vitro* and rodent models of NAFLD showed that this condition significantly increased the expression of xanthine oxidase (27). The increased risk for incident hyperuricaemia in patients with NAFLD has been demonstrated in a second longitudinal study (28). All

these results suggest that hyperuricaemia may occur secondary to NAFLD and may be related to the upregulation of hepatic xanthine oxidase in individuals with this disease.

There is also evidence from longitudinal studies that the elevated SU increases the risk for incident NAFLD. Results from an 8-year prospective study indicated that the incidence of new NAFLD was increased in patients with hyperuricaemia, but the relative timing for the two diagnoses was not stated (29). A 7-year study that included 5741 Korean men with no evidence of NAFLD on liver ultrasound and with no major risk factors for liver disease at baseline indicated that those in the highest baseline quartile for SU had an HR of 1.84 for the development of fatty liver detected by ultrasound *versus* those in the lowest quartile (30). A 5-year longitudinal retrospective study included 4954 subjects without risk factors for liver disease. Incidence rates for NAFLD were compared in four groups of patients with baseline SU levels of 0.6–3.9, 3.9–4.8, 4.8–5.9, and 5.9–12.6 mg/dL. The respective incidences of NAFLD in the four groups by the end of the study were 5.6%, 9.8%, 16.2%, and 20.9%. Multiple logistic regression analysis demonstrated that hyperuricaemia was associated with the development of NAFLD (31).

The mechanism by which urate damages the liver is not fully delineated, although specific transporters, including SLC2A9, are known to actively transport urate into hepatocytes (32-33). Results from studies in experimental animals have shown further that inhibition of xanthine oxidase, an enzyme involved in purine metabolism leading to a reduction in urate production, can prevent the development of non-alcoholic steatohepatitis in rodents fed a high-fat diet (34). Additionally, intracellular urate can generate superoxide ions (O2-), leading to oxidative stress and decreased nitric oxide generation with a resultant increase in inflammation and cell injury (35). Finally, the NOD-like receptor protein 3 (NLRP3) inflammasome important in gouty inflammation has been suggested to induce liver inflammation in NAFLD (36). Activation of the NLRP3 inflammasome, which is highly expressed in the liver, can be stimulated by urate crystals (37) and soluble urate (38). Pegloticase, by profoundly reducing urate levels, may lessen both NLRP3-mediated inflammation as well as the direct pro-oxidant activity of intracytoplasmic urate (39).

Conclusion

Although numerous studies have shown the association of hyperuricaemia and NAFLD, this is the first to show that profoundly decreasing SU can slow the progression of NAFLD and hepatic fibrosis as measured by the Fib-4 index.

The shortcomings of this study include the absence of biopsy verification of the underlying liver disease and the study's relatively short duration. Despite this, the data clearly show that progression of the Fib-4 index is prevented and reversed in some subjects with persistent urate-lowering. Since pegloticase directly metabolises urate and has no effect on xanthine oxidase, the clinical benefit can be assigned directly to the decrease in SU, thereby implicating urate in the progression of NAFLD and hepatic fibrosis as measured by the Fib-4 index.

References

1. ROBINSON PC: Gout - an update of aetiology, genetics, co-morbidities and management. *Maturitas* 2018; 118: 67-73. https://doi.org/10.1016/j.maturitas.2018.10.012
2. THOTTAM GE, KRASNOKUTSKY S, PILLINGER MH: Gout and metabolic syndrome: a tangled web. *Curr Rheumatol Rep* 2017;19: 60. https://doi.org/10.1007/s11926-017-0688-y
3. WÄNDELL P, CARLSSON AC, LJUNGGREN G: Gout and its comorbidities in the total population of Stockholm. *Prev Med* 2015; 81: 387-91. https://doi.org/10.1016/j.ypmed.2015.10.003
4. PUNZI L, SCANU A, GALOZZI P, LUISETTO R, SPINELLA P, SCIRÈ CA, OLIVIERO F: One year in review 2020: gout. *Clin Exp Rheumatol* 2020; 38(5): 807-21.
5. KUO CF, YU KH, LUO SF *et al*.: Gout and risk of non-alcoholic fatty liver disease. *Scand J Rheumatol* 2010; 39(6): 466-71. https://doi.org/10.3109/03009741003742797
6. ABBASI S, HALEEM N, JADOON S, FAROOQ A: Association of non-alcoholic fatty liver disease with serum uric acid. *J Ayub Med Coll Abbottabad* 2019; 31(1): 64-66.
7. ORAL A, SAHIN T, TURKER F, KOCAK E: Relationship between serum uric acid levels and nonalcoholic fatty liver disease in non-obese patients. *Medicina* (Kaunas) 2019; 55(9): E600. https://doi.org/10.3390/medicina55090600
8. FERNÁNDEZ RODRÍGUEZ CM, ALLER R, GUTIÉRREZ GARCÍA ML *et al*.: Higher levels of serum uric acid influences hepatic damage in patients with non-alcoholic fatty liver disease (NAFLD). *Rev Esp Enferm Dig* 2019; 111(4): 264-9. https://doi.org/10.17235/reed.2019.5965/2018
9. SANDRA S, LESMANA CRA, PURNAMASARI D *et al*.: Hyperuricemia as an independent risk factor for non-alcoholic fatty liver disease (NAFLD) progression evaluated using controlled attenuation parameter-transient elastography: Lesson learnt from tertiary referral center. *Diabetes Metab Syndr* 2019; 13(1): 424-8. https://doi.org/10.1016/j.dsx.2018.10.001
10. ZHENG X, GONG L, LUO R *et al*.: Serum uric acid and non-alcoholic fatty liver disease in non-obesity Chinese adults. *Lipids Health Dis* 2017; 1681): 202. https://doi.org/10.1186/s12944-017-0531-5
11. XU C: Hyperuricemia and nonalcoholic fatty liver disease: from bedside to bench and back. *Hepatol Int* 2016; 10(2): 286-93. https://doi.org/10.1007/s12072-015-9682-5
12. WAH-KHEONG C, KHEAN-LEE G: Epidemiology of a fast emerging disease in the Asia-Pacific region: non-alcoholic fatty liver disease. *Hepatol Int* 2013; 7(1): 65-71. https://doi.org/10.1007/s12072-012-9384-1
13. PETTA S, CAMMÁ C, CABIBI D *et al*.: Hyperuricemia is associated with histological liver damage in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2011; 34(7): 757-66. https://doi.org/10.1111/j.1365-2036.2011.04788.x
14. SUN DQ, WU SJ, LIU WY *et al*.: Serum uric acid: a new therapeutic target for nonalcoholic fatty liver disease. *Expert Opin Ther Targets* 2016; 20(3): 375-87. https://doi.org/10.1517/14728222.2016.1096930
15. PASCHOS P, ATHYROS VG, TSIMPERIDIS A *et al*.: Can serum uric acid lowering therapy contribute to the prevention or treatment of nonalcoholic fatty liver disease? *Curr Vasc Pharmacol* 2018; 16(3): 269-75. https://doi.org/10.2174/1570161115666170621082237
16. ÁLVAREZ-LANO B, MACARRÓN-VICENTE J: Uric acid and evolution. *Rheumatology* 2010; 49(11): 2010-15. https://doi.org/10.1093/rheumatology/keq204
17. GUDOWSKA M, WRONA A, GRUSZEWSKA E *et al*.*:* Simple non-invasive markers for early diagnosis and determination of the severity of liver diseases. *Clin Exp Hepatol* 2016; 2(4): 149-54. https://doi.org/10.5114/ceh.2016.63872
18. AGBIM U, ASRANI SK: Non-invasive assessment of liver fibrosis and prognosis: an update on serum and elastography markers. *Expert Rev Gastroenterol Hepatol* 2019; 13(4): 361-74. https://doi.org/10.1080/17474124.2019.1579641
19. SHAH AG, LYDECKER A, MURRAY K *et al*.: Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2009; 7(10): 1104-12. https://doi.org/10.1016/j.cgh.2009.05.033

20. STERLING RK, LISSEN E, CLUMECK N *et al*.: Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006; 43(6): 1317-25. https://doi.org/10.1002/hep.21178
21. SUNDY JS, BARAF HS, YOOD RA *et al*.: Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *JAMA* 2011; 306(7): 711-20. https://doi.org/10.1001/jama.2011.1169
22. NISHIKAWA T, NAGATA N, SHIMAKAMI T *et al*.: Xanthine oxidase inhibition attenuates insulin resistance and diet-induced steatohepatitis in mice. *Sci Rep* 2020; 10(1): 815. https://doi.org/10.1038/s41598-020-57784-3
23. MIKOLASEVIC I, MILIC S, ORLIC L *et al*.: Factors associated with significant liver steatosis and fibrosis as assessed by transient elastography in patients with one or more components of the metabolic syndrome. *J Diabetes Complications* 2016; 30(7): 1347-53. https://doi.org/10.1016/j.jdiacomp.2016.05.014
24. HUANG JF, YEH ML, YU ML *et al*.: Hyperuricemia inversely correlates with disease severity in Taiwanese nonalcoholic steatohepatitis patients. *PloS One* 2015; 10: e0139796. https://doi.org/10.1371/journal.pone.0139796
25. WIJARNPREECHA K, PANJAWATANAN P, LEKUTHAI N *et al*.: Hyperuricaemia and risk of nonalcoholic fatty liver disease: a meta-analysis. *Liver Int* 2017; 37(6): 906-18. https://doi.org/10.1111/liv.13329
26. JARUVONGVANICH V, AHUJA W, WIJARNPREECHA K, UNGPRASERT P: Hyperuricemia is not associated with severity of liver fibrosis in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2017; 29(9): 694-7. https://doi.org/10.1097/meg.0000000000000931
27. XU C, WAN X, XU L *et al:*. Xanthine oxidase in non-alcoholic fatty liver disease and hyperuricemia: One stone hits two birds. *J Hepatol* 2015; 62(6): 1412-9. https://doi.org/10.1016/j.jhep.2015.01.019
28. NI Q, LU X, CHEN C, DU H, ZHANG R: Risk factors for the development of hyperuricemia: A STROBE-compliant cross-sectional and longitudinal study. *Medicine* (Baltimore) 2019; 98(42): e17597. https://doi.org/10.1097/md.0000000000017597
29. LU ZY, SHAO Z, LI YL, WULASIHAN M, CHEN XH: Prevalence of and risk factors for nonalcoholic fatty liver disease in a Chinese population: an 8-year follow-up study. *World J Gastroenterol* 2016; 22(13): 3663-9. https://doi.org/10.3748/wjg.v22.i13.3663
30. RYU S, CHANG Y, KIM SG *et al*.:. Serum uric acid levels predict incident nonalcoholic fatty liver disease in healthy Korean men. *Metabolism* 2011; 60(6): 860-6. https://doi.org/10.1016/j.metabol.2010.08.005
31. LEE JW, CHO YK, RYAN M *et al*.: Serum uric acid as a predictor for the development of nonalcoholic fatty liver disease in apparently healthy subjects: a 5-year retrospective cohort study. *Gut Liver* 2010; 4(3): 378-83. https://doi.org/10.5009/gnl.2010.4.3.378
32. BANNASCH D, SAFRA N, YOUNG A *et al*.: Mutations in the SLC2A9 gene cause hyperuricosuria and hyperuricemia in the dog. *PLoS Genet* 2008; 4(11): e1000246. https://doi.org/10.1371/journal.pgen.1000246
33. PREITNER F, BONNY O, LAVERRIÈRE A *et al*.: Glut9 is a major regulator of urate homeostasis and its genetic inactivation induces hyperuricosuria and urate nephropathy. *Proc Natl Acad Sci USA* 2009; 106(36): 15501-6. https://doi.org/10.1073/pnas.0904411106
34. NAKATSU Y, SENO Y, KUSHIYAMA A *et al*.: The xanthine oxidase inhibitor febuxostat suppresses development of nonalcoholic steatohepatitis in a rodent model. *Am J Physiol Gastrointest Liver Physiol* 2015; 309(1): G42-51. https://doi.org/10.1152/ajpgi.00443.2014
35. LIN KM, LU CL, HUNG KC *et al*.: The paradoxical role of uric acid in osteoporosis. *Nutrients* 2019; 11(9): 2111. https://doi.org/10.3390/nu11092111
36. SZABO G, PETRASEK J: Inflammasome activation and function in liver disease. *Nat Rev Gastroenterol Hepatol* 2015; 12(7): 387-400. https://doi.org/10.1038/nrgastro.2015.94
37. SCHRODER K, TSCHOPP J: The inflammasomes. *Cell* 2010; 140(6): 821-32. https://doi.org/10.1016/j.cell.2010.01.040
38. BRAGA TT, FORNI ME, CORREA-COSTA M *et al*.: Soluble uric acid activates the NLRP3 inflammasome. *Sci Rep* 2017; 7: 39884. https://doi.org/10.1038/srep39884
39. SAUTIN YY, JOHNSON RJ: Uric acid: the oxidant-antioxidant paradox. *Nucleosides Nucleotides Nucleic Acids* 2008; 27(6): 608-19. https://doi.org/10.1080/15257770802138558