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Effect of Topiroxostat on Brain Natriuretic Peptide Level in Patients with Heart Failure with Preserved Ejection Fraction: A Pilot Study

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Background: Various optimal medical therapies have been established to treat heart failure (HF) with reduced ejection fraction (HFrEF). Both HFrEF and HF with preserved ejection fraction (HFpEF) are associated with poor outcomes. We investigated the effect of topiroxostat, an oral xanthine oxidoreductase inhibitor, for HFpEF patients with hyperuricemia or gout.

Methods: In this nonrandomized, open-label, single-arm trial, we administered topiroxostat 40-160 mg/day to HFpEF patients with hyperuricemia or gout to achieve a target uric acid level of 6.0 mg/dL. The primary outcome was rate of change in log-transformed brain natriuretic peptide (BNP) level from baseline to 24 weeks after topiroxostat treatment. The secondary outcomes included amount of change in BNP level, uric acid evaluation values, and oxidative stress marker levels after 24 weeks of topiroxostat treatment. Thirty-six patients were enrolled; three were excluded before study initiation.

Results: Change in log-transformed BNP level was −3.4 ± 8.9% ($p = 0.043$) after 24 weeks of topiroxostat treatment. The rate of change for the decrease in BNP level was −18.0 (−57.7, 4.0 pg/mL; $p = 0.041$). Levels of uric acid and 8-hydroxy-2′-deoxyguanosine/creatinine, an oxidative stress marker, also significantly decreased (−2.8 ± 1.6 mg/dL, $p < 0.001$, and −2.3 ± 3.7 ng/mgCr, $p = 0.009$, respectively).

Conclusions: BNP level was significantly lower in HFpEF patients with hyperuricemia or gout after topiroxostat administration; however, the rate of decrease was low. Further trials are needed to confirm our findings. (J Nippon Med Sch 2021; 88: 423–431)

Key words: topiroxostat, ejection fraction, heart failure, brain natriuretic peptide

Introduction

Accumulating evidence indicates that heart failure (HF) with hyperuricemia is associated with a poor prognosis[1–4], and recent studies of the relationship between hyperuricemia and cardiovascular disease suggest that impaired vascular endothelial function is a contributing factor for HF[5]. Xanthine oxidoreductase (XOR), an enzyme that mediates uric acid (UA) production, promotes arteriosclerosis by modulating vascular endothelial cells through production of UA[6]. In addition, XOR promotes cardiac remodeling by generating reactive oxygen species (ROS)[7,8]. Notably, topiroxostat, a novel non-purine selective XOR inhibitor, suppresses XOR activity and subsequent UA production. Although outcomes are worse for HF with hyperuricemia than for HF without hyperuricemia[9], it is unclear whether they are improved by administration of UA-lowering drugs such as topiroxostat.

HF with preserved ejection fraction (HFpEF) is characterized by HF symptoms that result from diastolic dysfunction and has attracted considerable recent attention[10]. Pathologically, HFpEF is classified on the basis of systemic inflammation, reduced nitric oxide bioavailability, and presence of interstitial fibrosis, which promotes diastolic left ventricular dysfunction[8]. HFpEF patients and HF patients with reduced ejection fraction (HFrEF) have the same mortality rate[11], and no effective treatment op-

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tions are available for HFpEF. Therefore, establishment of appropriate treatment modalities is an urgent concern in medical practice.

Brain natriuretic peptide (BNP) is an established surrogate marker for HF prognosis. Studies reported that for each 100-pg/mL increase in BNP level there was a 35% increase in the risk of death[12], and that topiroxostat effectively lowered levels of BNP and high-sensitivity C-reactive protein in patients with multiple cardiovascular risks[13]. Additionally, topiroxostat lowers UA levels in patients with hyperuricemia, who are at high risk of developing cardiovascular disease[13], and more strongly inhibits XOR activity than does allopurinol, which is a purine analog XOR inhibitor[14,15]. However, no studies have clarified the effects of topiroxostat in HFpEF patients. Therefore, this study examined if topiroxostat affects cardiac function in HFpEF patients with hyperuricemia, and if a decrease in plasma BNP level is a surrogate marker for HF.

Materials and Methods

Study Design and Ethical Considerations

The *Suggestion of using topiroxostat for a group of hyperuricemic congestive heart failure patients with preserved ejection fraction for better treatment outcomes* (SOUGHT) study was a prospective, single-center, open-label, single-arm pilot study that included patients recruited between March 2017 and April 2018. The trial was registered with the University Hospital Medical Information Network (registration number, UMIN000024981). The study protocol was approved by the institutional ethics committee of the Nippon Medical School Hospital (ID: 228005). On the basis of previous findings[13], this trial was designed to have 80% power to detect a reduction of 39% in log-transformed BNP levels at 24 weeks, with a type I error of 0.05 (two-sided). Therefore, we determined that the appropriate sample size was 32 patients[13]. Assuming a 10% drop-out rate, we registered 36 patients in this trial. The investigation conformed with the principles outlined in the Declaration of Helsinki. All enrolled patients provided written informed consent before the beginning of the study.

Patients

In this trial, we enrolled HFpEF patients with hyperuricemia or gout. The diagnostic criteria for HFpEF were based on European Society of Cardiology guidelines[16]. Hyperuricemia was defined as a UA level $\geq$7.0 mg/dL. Patients who met all the following inclusion criteria were included in this trial: age between 20 and 90 years, presence of hyperuricemia or gout, no medication for hyperuricemia or gout during the 4 weeks before the trial, diagnosis of HFpEF, clinically stable HF, and ability to provide written consent. The exclusion criteria were allergy to topiroxostat, febuxostat, or allopurinol; intake of mercaptopurine or azathioprine; coronary artery bypass grafting surgery or percutaneous coronary intervention during the previous 6 months; malignancy; high alanine aminotransferase and aspartate aminotransferase levels; chronic hepatitis B or C; liver cirrhosis; severe renal dysfunction; or any other condition that would make trial participation inappropriate.

Study Protocol

Eligible patients began taking oral topiroxostat within 8 weeks after providing written informed consent. We followed-up patients every 6 weeks for 24 weeks. We set the therapeutic level of UA at <6.0 mg/dL, as suggested by American College of Rheumatology guidelines[17]. Patients started taking topiroxostat 20 mg every morning and evening, after meals. The dose was increased by 40 mg/day every 6 weeks until the target dose of 120 mg/day was reached, unless serum UA level was <3.0 mg/dL. Patients with a UA level of 6.0 mg/dL or lower were continuously monitored while taking topiroxostat 120 mg/day. The dose was increased from 120 mg/day to 160 mg/day only when patients were unable to achieve a serum UA level <6.0 mg/dL. If a patient exhibited gouty arthritis on the day of topiroxostat treatment initiation or a planned dose increase, we did not increase the dose or start topiroxostat treatment. If serum UA level was below 3.0 mg/dL after initiating, or increasing the dose of, topiroxostat, the dosage was lowered.

Study Outcomes

The primary outcome was rate of change in plasma BNP level, as a surrogate marker for HF, from baseline to 24 weeks after topiroxostat treatment. We evaluated change in log-transformed BNP level because plasma BNP levels are not normally distributed[18]. The secondary outcomes were values and changes in the following variables at each observation: (1) UA evaluation, including serum UA level, plasma XOR activity, and hypoxanthine and xanthine levels; blood samples were collected with a blood collection tube coated with ethylenediaminetetraacetic acid-2K and were centrifuged at 2,000 g for 10 min at 4°C for plasma separation; plasma XOR activity was measured with liquid chromatography-triple quadrupole mass spectrometry (Nexera HLC, SHIMADZU, Japan/QTRAP 4500, SCIEX) to detect [^{13}C2, ^{15}N2] UA, with [^{13}C2, ^{15}N2] xanthine as a substrate, as pre-

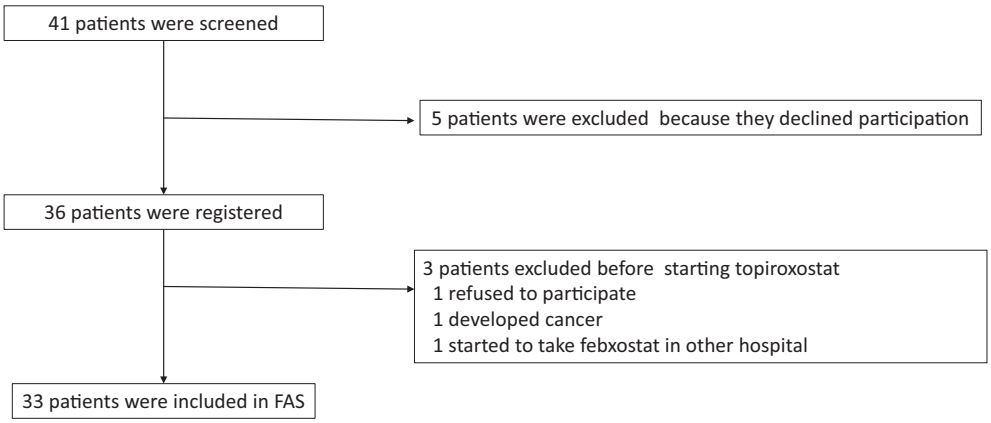

Fig. 1 Flow chart of patient enrollment in the SOUGHT study. The flow chart shows the number of patients screened, excluded, and registered.
FAS, full analysis set.

viously described[19–21]; (2) cardiac function (amount of change in BNP and log-transformed BNP levels, troponin T, high-sensitivity C-reactive protein, and left ventricular ejection fraction [LVEF], as assessed with the Teichholz or Modified Simpson method); (3) left ventricular mass index; (4) mitral E/E′ ratio; (5) mitral E/A ratio; (6) left atrial dimension; (7) tricuspid annular plane systolic excursion; (8) tricuspid regurgitation peak gradient; and (9) peripheral vascular endothelial function, as assessed by the reactive hyperemia index (RHI), which was evaluated by reactive hyperemia peripheral arterial tonometry with an Endo-PAT2000 device (Itamar Medical, Caesarea, Israel). Measurement of RHI with reactive hyperemia peripheral arterial tonometry is described in detail elsewhere[22]. In addition, oxidative stress markers (urinary 8-hydroxy-2′-deoxyguanosine [8-OHdG]), blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), as evaluated by the modified Modification of Diet in Renal Disease method with a new Japanese coefficient according to a three-variable Japanese equation ($eGFR[mL/min/1.73\ m^2] = 194\times[Scr]^{-1.094}\times[Age]^{-0.287}\times[0.739$ if female]), cystatin C, urinary liver type-fatty acid protein, and general health-related items (body weight, body mass index, blood pressure, and pulse) were considered secondary outcomes. All safety analyses were performed in the safety population. We defined adverse events (AEs) as cerebral infarction, myocardial infarction, and HF exacerbation. Topiroxostat administration was continued in patients who had mild AEs. We also evaluated incidence rates of liver dysfunction and gouty arthritis.

Statistical Analyses

The endpoints were primarily analyzed by using the full analysis set, which included 33 patients. Safety analysis sets were evaluated by using the safety population, which comprised all or some of the enrolled patients. Categorical variables are expressed as prevalence rates (%). Continuous variables are presented as means and standard deviations or medians and interquartile ranges, as appropriate. The paired t-test was used to compare change in log-transformed BNP level from baseline to 24 weeks after topiroxostat treatment. The Wilcoxon signed-rank test was used to analyze variables that were not normally distributed, such as plasma BNP level. For data requiring multiple observations at multiple points after the start of the study, the paired t-test for within-group comparisons and longitudinal data analysis using a mixed-effects model for repeated measures were conducted. A two-sided p-value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient Details

A total of 41 patients were eligible for this study. Five patients declined to participate; thus, 36 patients were registered. Three patients withdrew from the study before taking the first dose of topiroxostat. Therefore, 33 patients were included in the final analysis (**Fig. 1**).

Patient Characteristics

The patients' baseline characteristics are summarized in **Table 1**. Twelve patients (36%) were female and 21 (64%) were male. Mean patient age and body mass index were 72 ± 10 years and 24.3 ± 5.2 kg/m^2, respectively. Mean serum UA level at baseline was 8.0 ± 1.8 mg/dL. Only one patient had a prior history of gout. At baseline,

Table 1 Baseline characteristics of HFpEF patients (N = 33)

Demographics	
Age, years, mean ± SD	72 ± 10
Sex, female, n (%)	12 (36)
Male, n (%)	21 (64)
BMI, kg/m², mean ± SD	24.3 ± 5.2
NYHA class, n (%)	
I	10 (30)
II	23 (70)
Underlying disease (duplicated), n (%)	
Hypertension	13 (39)
Atrial fibrillation/Atrial flutter	20 (61)
Ischemic heart disease	6 (18)
Valvular disease	8 (24)
Cardiomyopathy	5 (15)
Vital signs, mean ± SD	
SBP, mmHg	131.8 ± 20.9
DBP, mmHg	69.7 ± 9.8
HR, beats per min	69.9 ± 12.5
Comorbidity, n (%)	
CKD	27 (82)
Hypertension	11 (33)
Dyslipidemia	22 (67)
Diabetes mellitus	10 (30)
Gout	1 (3)
Laboratory values, echocardiography data	
BNP, pg/mL, median (IQR)	195.0 (93.2-316.0)
Cre, mg/dL, mean ± SD	1.2 ± 0.4
UA, mg/dL, mean ± SD	8.0 ± 1.8
LVEF (%), mean ± SD	67.8 ± 7.3
Medication, n (%)	
ACE-i	10 (30)
ARB	13 (39)
β-blocker	15 (46)
Diuretics	24 (73)
Ca^{2+} blocker	13 (39)
Anticoagulation	20 (61)
Antiplatelet	4 (12)
Statins	19 (58)
Diabetes drugs	10 (30)

ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CKD, chronic kidney disease; Cre, creatinine; DBP, diastolic blood pressure; HR, heart rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association classification; SBP, systolic blood pressure; SD, standard deviation; UA, uric acid

mean LVEF was 67.8 ± 7.3% and creatinine level was 1.2 ± 0.4 mg/dL. Median BNP level was 195.0 (93.2-316.0) pg/mL. Some patients had multiple underlying cardiovascular diseases, namely, hypertension (39%), arrhythmia (55%), ischemic heart disease (18%), valvular disease (24%), and cardiomyopathy (15%).

Outcomes

Average topiroxostat dose was 104.0 ± 32.5 mg at 12 weeks and 110.7 ± 25.0 mg at 24 weeks. The results for the primary outcomes are shown in **Figure 2**. The rate of

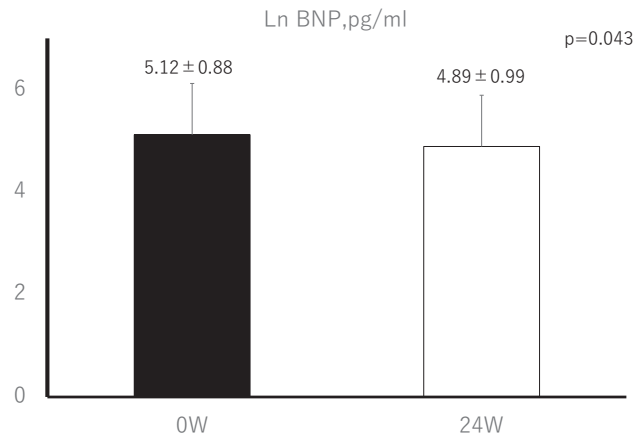

Fig. 2 Change in log-transformed brain natriuretic peptide level. Change in brain natriuretic peptide (BNP) levels from baseline to 24 weeks after topiroxostat treatment.

change in log-transformed BNP level, a surrogate marker of HF, was significantly lower at week 24 than at week 0 (−3.4 ± 8.9%, p = 0.043; **Fig. 2**). The results for secondary outcomes are presented in **Table 2** and **Figure 3**. There was a significant difference in the amount of change in the plasma BNP and log-transformed BNP levels between weeks 24 and 0 (−18.0 [−57.7, 4.0] pg/mL, p = 0.041, and −0.16 ± 0.41 ln(pg/mL), p = 0.040, respectively). Topiroxostat significantly lowered serum UA level (p < 0.001) and plasma XOR activity (p < 0.001), and increased hypoxanthine (p < 0.001) and xanthine (p < 0.001) levels, as compared with values at baseline. At week 24, BUN (p = 0.004), creatinine (p = 0.009), and cystatin C (p = 0.01) levels were slightly but significantly higher. Regarding oxidative stress markers, urinary 8-OHdG/creatinine levels were significantly lower (p = 0.009) than at baseline. RHI values at baseline and 24 weeks were not significantly different (p = 0.13). Correlation analysis showed that no test variable was correlated with BNP level. The most frequently reported AE was HF exacerbation (4 patients), which resulted in discontinuation of topiroxostat in two patients. Gouty arthritis was reported in two patients in the safety population.

Discussion

In this study, log-transformed BNP and urinary 8-OHdG/creatinine levels (oxidative stress markers) significantly improved during 24 weeks of topiroxostat treatment in HFpEF patients with hyperuricemia or gout. Increased oxidative stress and impaired vascular endothelial function are known causes of HF in HFpEF patients[5]. Our findings suggest that topiroxostat might decrease oxidative stress, reduce intracellular UA levels, and improve vascular endothelial cell function, which are three possible mechanisms by which improved BNP level, a surrogate marker for HF, affects chronic HF.

ROS are produced via activation of xanthine oxidase, and XOR inhibitors reduce oxidative stress[5]. Accumulating evidence indicates that increased oxidative stress promotes left ventricular remodeling, and topiroxostat may decrease ROS and inhibit left ventricular remodeling. Previous small-scale studies suggested that purine analog XOR inhibitors reduce plasma BNP level and improve vascular endothelial dysfunction[23–25]. Improved peripheral vascular endothelial function decreases left ventricular afterload in the short term and ameliorates LV remodeling in the long term. Moreover, improved coronary artery endothelial function improves myocardial blood flow and decreases ischemia, which, in turn, improves left ventricular function. In the present study we noted a significant difference in improvement of BNP levels, a surrogate marker of HF, but no significant difference in the improvement of vascular endothelial function. Vascular endothelial dysfunction might not be reversible in elderly adults with a long history of HF[26]. Large-scale, randomized, placebo-controlled studies have not yet shown that purine analog XOR inhibitors improve outcomes in chronic HF patients with hyperuricemia[27,28]. Notably, topiroxostat has a stronger inhibitory effect than purine analog XOR inhibitors on XOR activity[14,15]. High XOR activity in HF leads to onset of cardiovascular events[29]; thus, the strong XOR inhibitory effect of topiroxostat might help lower BNP levels, as demonstrated in the present study.

Some evidence suggests that febuxostat use increases the risk of cardiovascular events[30,31]. As compared with febuxostat, topiroxostat is a hybrid XOR inhibitor and has a different mechanism of action[32]. It is unclear whether the greater mortality observed after febuxostat treatment would also be seen with topiroxostat. In addition, because the mechanism by which febuxostat increases cardiovascular events is unknown, it cannot be concluded that the increase in cardiovascular events caused by febuxostat would also be seen after treatment with topiroxostat.

Topiroxostat improved renal function and urinary albumin/creatinine ratio in previous studies[33,34]. However, no improvement in albumin/creatinine ratio was noted in the present study, probably because of the small sample size. Furthermore, deterioration of BUN, creatinine, and cystatin C levels was observed. Although increased diuretic use was unavoidable in two patients, it is un-

Table 2 Changes in secondary endpoints from baseline to 24 weeks after topiroxostat treatment

	0 W	24 W	p
Vital signs, mean ± SD			
Body weight, kg	63.4 ± 17.5	63.5 ± 17.1	0.90
BMI, kg/m^2	24.3 ± 5.2	24.3 ± 5.0	0.85
SBP, mmHg	131.8 ± 20.9	125.1 ± 19.0	0.10
DBP, mmHg	69.7 ± 9.8	66.7 ± 9.5	0.12
HR, beats per min	69.9 ± 12.5	71.9 ± 17.7	0.73
Blood test values, mean ± SD			
WBC, count/μL	5,809.1 ± 2,005.4	6,172.7 ± 2,307.5	0.18
Hb, g/dL	12.8 ± 2.0	12.5 ± 1.9	0.19
AST, IU/L	22.6 ± 6.6	24.8 ± 11.9	0.17
ALT, IU/L	18.5 ± 8.4	20.3 ± 11.7	0.22
T-Bil, mg/dL	0.7 ± 0.3	0.7 ± 0.3	0.58
LDL-C, mg/dL	99.3 ± 31.8	94.5 ± 28.7	0.07
TG, mg/dL	133.8 ± 102.9	148.7 ± 99.3	0.38
UA, mg/dL	8.0 ± 1.8	5.2 ± 2.0	<0.001
XOR, pmol/h/mL	57.4 ± 62.0	8.9 ± 5.2	<0.001
Hypoxanthine, μM	2.1 ± 0.8	4.4 ± 2.4	<0.001
Xanthine, μM	0.7 ± 0.3	12.1 ± 7.0	<0.001
Troponin T, ng/mL	0.02 ± 0.02	0.02 ± 0.02	0.74
hs-CRP, ng/mL	1,754.7 ± 3,045.1	2,849.6 ± 6,714.2	0.49
BNP, pg/mL, median (IQR)	195.0 (93.2-316.0)	158.5 (70.3-258.0)	0.041
Renal function, mean ± SD			
BUN, mg/dL	22.4 ± 8.1	25.2 ± 9.9	0.004
Cre, mg/dL	1.2 ± 0.4	1.3 ± 0.5	0.009
eGFR, mL/min/1.73 m^2	46.1 ± 15.6	44.4 ± 17.5	0.27
Cystatin C, mg/dL	1.5 ± 0.5	1.6 ± 0.6	0.01
Urinary albumin/Cre, mg/gCr	441.6 ± 1,103	342.6 ± 1,118	0.17
Urinary L-FABP/Cre, μg/gCr	13.5 ± 31.9	12.2 ± 37.4	0.93
Oxidative stress markers, mean ± SD			
Urinary 8OHdG/Cre, ng/mgCr	8.2 ± 8.2	6.2 ± 6.8	0.009
Echocardiography, mean ± SD			
LVEF (%)	67.8 ± 7.3	64.7 ± 8.8	0.06
LVMI, g/m^2	102.3 ± 55.4	92.2 ± 26.9	0.16
E/E′	16.0 ± 10.0	14.7 ± 7.2	0.12
E/A	1.1 ± 1.1	1.0 ± 0.7	0.62
LAD, mm	44.5 ± 8.5	43.7 ± 7.5	0.10
TAPSE, mm	17.1 ± 4.0	17.3 ± 4.0	0.45
TRPG, mmHg	27.3 ± 10.2	27.9 ± 8.2	0.55
Vascular endothelial function			
Endo-PAT RHI	2.0 ± 0.6	1.8 ± 0.5	0.13

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cre, creatinine; DBP, diastolic blood pressure; E/A, mitral E/A ratio; E/E′, mitral E/E′ ratio; eGFR, estimated glomerular filtration rate; Endo-PAT, endothelial peripheral arterial tonometry; Hb, hemoglobin, HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LAD, left atrial diameter; LDL-C, low-density lipoprotein-cholesterol; L-FABP, L-type fatty acid-binding protein; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; RHI, reactive hyperemia index; SD, standard deviation; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; T-bil, total bilirubin; TG, triglyceride; TRPG, tricuspid regurgitation peak gradient; UA, uric acid; W, weeks; WBC, white blood cell; XOR, xanthine oxidoreductase; 8-OHdG, 8-hydroxy-2-deoxyguanosine

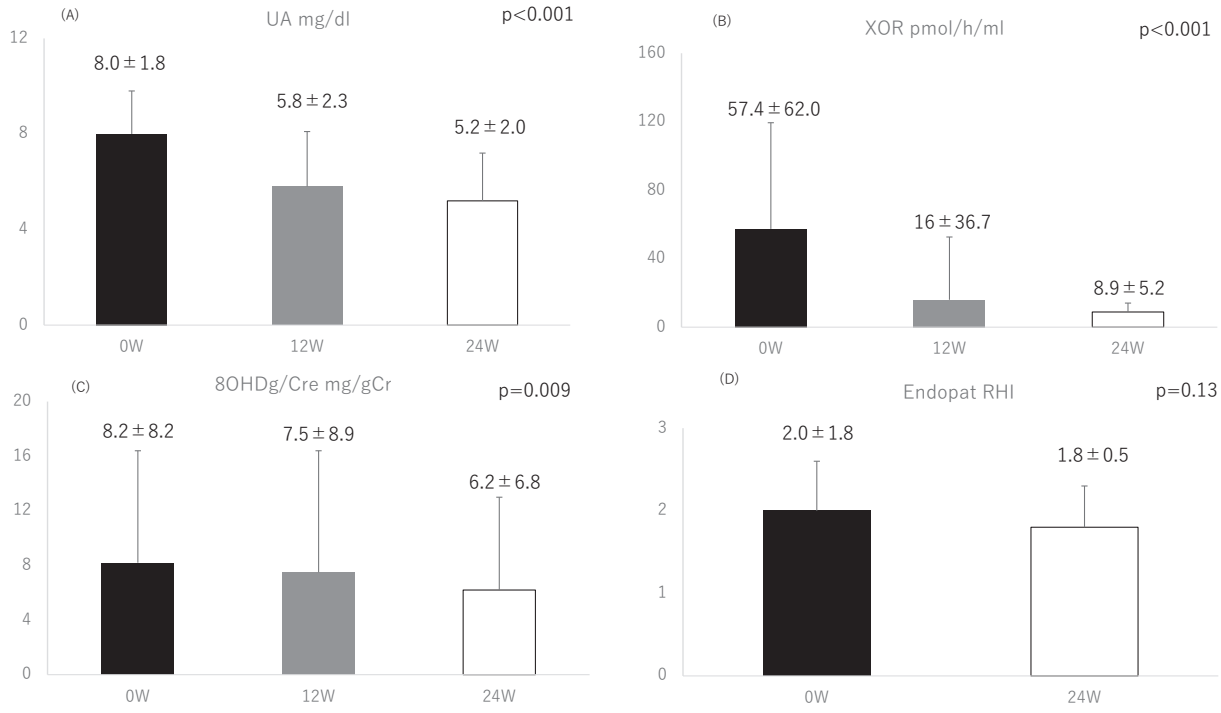

Fig. 3 Results for secondary study outcomes. (A) Change in uric acid (UA) levels from baseline to each observation point. (B) Xanthine oxidoreductase (XOR) activity from baseline to each observation point. (C) 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels from baseline to each observation point. (D) Endothelial peripheral arterial tonometry (Endo-PAT) reactive hyperemia index (RHI) from baseline to 24 weeks after topiroxostat treatment.

clear if volume depletion was important, because the mean body weight of the patients did not change during the study. Previous studies have indicated that the progression rate of eGFR is 1.0 mL/min/1.73 m^2 per year[35]. In the present study, most patients had overt albuminuria (>300 mg/gCr) and moderate-to-severe renal dysfunction (equivalent to stage 3 chronic kidney disease). Poor renal function at baseline is associated with earlier progression of renal function deterioration[35]. Therefore, it is possible that we observed the natural history of chronic kidney disease progression.

Limitations

This study has several limitations. First, it did not include a control group, and the authors were not blinded to the procedures. In addition, because of the open-label design, the possibility of inherent bias cannot be ruled out and it cannot be concluded that BNP level reductions were caused by topiroxostat. Second, while improvements in log-transformed BNP level and urinary 8-OHdG/creatinine level attributable to topiroxostat may be useful for HFpEF patients, the amount of change in BNP level was small. Therefore, the clinical effect of topiroxostat on BNP, a surrogate marker for HF, was limited. This pilot study was insufficient to confirm clinical benefits, owing to its small sample size. Correlation analysis showed no correlation between test variables and BNP levels. Third, the study included patients from a single center. This study was a single-arm pilot study and one hypothesis was tested. Future studies should examine whether topiroxostat improves outcomes for HFpEF patients.

Conclusion

In this study, log-transformed BNP level significantly improved in HFpEF patients with hyperuricemia or gout. There was a significant difference in the amount of change in plasma BNP and log-transformed BNP levels. However, the amount of change in plasma BNP level was small, and the clinical effect of topiroxostat on BNP, a surrogate marker for HF, was limited. Further randomized controlled trials with a control group, larger sample, and patients from multiple centers are needed in order to confirm our findings.

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Conflict of Interest: None.

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