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Comparison of topiroxostat and allopurinol in Japanese hyperuricemic patients with or without gout: a phase 3, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group study

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SUMMARY

What is known and objective: **There are no clinical reports that have compared topiroxostat, a selective xanthine oxidase inhibitor, with allopurinol in serum urate-lowering efficacy. The aim of this study was to compare the efficacy and safety of topiroxostat and allopurinol in Japanese hyperuricemic patients with or without gout.**

Methods: **A phase 3, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group study conducted in Japan. Patients who had inadequate serum urate levels (a gout patient: serum urate level ≥416·4 μmol/L; an asymptomatic hyperuricemic patient with specific complications (urinary lithiasis, hypertension, hyperlipidemia and/or diabetes): serum urate level ≥475·8 μmol/L; and an asymptomatic hyperuricemic patient with no specific complications: serum urate level ≥535·3 μmol/L) were randomized to topiroxostat 120 mg/day or allopurinol 200 mg/day, with an equal allocation ratio, for 16 weeks. To prevent the onset of gouty arthritis by rapid serum urate reduction, these doses were increased in a stepwise manner. The primary efficacy endpoint was the per cent change in serum urate level from baseline to the final visit.**

Results and discussion: **Overall, 206 patients were randomly assigned to topiroxostat and allopurinol. Two hundred and three patients (allopurinol: n = 105, topiroxostat: n = 98) received at least one dose of the study drug and had their serum urate level assessed at least once. The baseline characteristics were comparable between groups. The mean age of patients was 53·0 ± 11·4 years and 99% of patients were male. The primary efficacy endpoint was −34·3 ± 11·1% in the allopurinol group (n = 105) and −36·3 ± 12·7% in the topiroxostat group (n = 98). Non-inferiority of the serum urate-lowering efficacy of topiroxostat to allopurinol was proved by the predefined non-inferiority margin (95% confidence interval, −5·3 to 1·3%). The overall incidences of adverse events and adverse drug reactions were similar between both groups.**

What is new and conclusion: **Topiroxostat 120 mg/day provides non-inferior serum urate reduction compared with allopurinol 200 mg/day and is well tolerated in Japanese hyperuricemic patients with or without gout.**

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WHAT IS KNOWN AND OBJECTIVE

Gout is a common disease in adult males, and its acute symptom, the so-called gout attack, causes impaired quality of life.[1] Because gout is related to monosodium urate crystal deposition, a causative disease of gout is hyperuricemia, which is defined as a serum urate level >416·4 μmol/L in Japan.[2] Therefore, it is essential to control hyperuricemia in order to treat gout and its related disorders such as gouty arthritis. Surprisingly, the prevalence of hyperuricemia in male was approximately 20% in United States and 15–20% in Japan.[3,4]

Recent clinical reports have suggested a link between high serum urate levels and life-threatening diseases such as cardiovascular disease, chronic kidney disease (CKD) and hypertension.[5–10] Therefore, the management of hyperuricemia has become increasingly import. In Japan, in consideration of the results of these observational studies and some interventional studies, asymptomatic hyperuricemia (serum urate level ≥475·8 μmol/L) with lifestyle-related disease such as CKD, urinary lithiasis, hypertension, hyperlipidemia or diabetes can be treated with urate-lowering drugs according to the individual patient's clinical condition.[2,11,12] This therapeutic policy is significantly different compared with that of other countries.

Topiroxostat, formerly known as FYX-051, is a selective xanthine oxidoreductase (XOR) inhibitor recently approved in Japan for the treatment of hyperuricemia with or without gout and has been developed for the treatment of diabetic nephropathy (UPWARD; NCT02327754).[13,14] In contrast to allopurinol, the pharmacokinetics of topiroxostat was not affected by renal function.[15,16] Compared with febuxostat, whereas a part of the metabolites of febuxostat consists of active oxidative metabolites, the major metabolites of topiroxostat (*N*-glucuronide and *N*-oxide form) were generally inactive to XOR (IC_{50} ≥10 μmol/L), and the urinary excretion rate of topiroxostat is <0·1% in patients with moderate renal impairment.[16–18] In view of the fact that hyperuricemic patients have CKD with relatively high frequency, these pharmacokinetic profiles are useful.[19]

We previously reported that topiroxostat significantly reduced serum urate levels and urinary albumin creatinine ratios in Japanese hyperuricemic stage 3 CKD patients without dose adjustment in a 22-week clinical trial.[20] However, no clinical trial has reported that compared the serum urate-lowering efficacy of topiroxostat with other XOR inhibitors. This study was designed

to test the serum urate-lowering efficacy and safety of topiroxostat compared with allopurinol in Japanese hyperuricemic patients with or without gout.

METHODS

Study design

The study design was a phase 3, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group study. We conducted the study at 21 hospitals in Japan. The institutional review board at each centre approved the study protocol, including the informed consent form, related documents and the implementation of the study. The study was conducted in compliance with the Declaration of Helsinki, the Pharmaceutical Affairs Law of Japan, Good Clinical Practice guidelines (GCP) and other applicable regulatory requirements. Written informed consent was obtained from all of the participating patients prior to the initiation of any study-related procedures. The clinical trial information of the study was registered with the Japan Pharmaceutical Information Center on April 2010 (Registration number: JapicCTI-101108).

Inclusion and exclusion criteria

Patients who met all of the inclusion criteria and did not meet any exclusion criteria were enrolled the study. The inclusion criteria of the study were as follows: age 20–74 years at the day of submission of written informed consent; the serum urate level at the run-in period was ≥416·4 μmol/L (in gout or gouty tophus patients), ≥475·8 μmol/L (in patients with asymptomatic hyperuricemia who are being diagnosed as or treated for urinary lithiasis, hypertension, hyperlipidemia and/or diabetes) or ≥535·3 μmol/L (in asymptomatic hyperuricemic patients who are not being diagnosed as or treated for these complications described above); outpatient (included no plan of hospital admission); and patients who can provide voluntary informed consent. The exclusion criteria were as follows: an attack of gouty arthritis within 2 weeks prior to the first day of the study drug administration; hyperuricemia secondary to certain disorders; HbA1c (NGSP) ≥8·4%; hepatic function impairment [serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥100 IU/L]; impaired renal function [estimated glomerular filtration rate (eGFR) <50 mL/min/1·73 m^2]; severe hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg); hypersensitivity to allopurinol; or the presence of any other clinically significant medical condition that could potentially preclude participation in this study. Patients who had used urate-lowering agents (probenecid, bucolome, benzbromarone or allopurinol), colchicine, agents potentially affecting the serum urate level (pyrazinamide, ethambutol, mizoribine or cyclosporine) and/or agents that could potentially cause adverse drug interaction with the study drug (6-mercaptopurine, azathioprine, vidarabine,warfarin potassium, chlorpropamide, cyclophosphamide, phenytoin, theophylline, pentostatin, captopril, hydrochlorothiazide or ampicillin) entered a washout period of ≥14 days before the run-in period after providing informed consent. The above-mentioned drugs were prohibited during the study period.

In the run-in period, we classified the type of hyperuricemia into the following four types: (i) patients with urinary excretion of urate [E_{UA} (mg/kg/h)] >0·51 and urate clearance [C_{UA} (mL/min)] ≥7·3 were defined as 'urate overproduction type'; (ii) patients with E_{UA} <0·48 or C_{UA} <7·3 were defined as 'urate underexcretion type'; (iii) patients with E_{UA} >0·51 and C_{UA} <7·3 were defined as 'combined type'; and (iv) patients with 0·48 ≤ E_{UA} ≤0·51 and C_{UA} ≥7·3 were defined as 'normal type'.[21] The 24-h urine collection is normally used for the classification.[22] However, we used a 60-min urine collection method in view of difficulties for the 24-h urine collection in outpatient settings.

Randomization, blinding, intervention and follow-up

A randomized block allocation of the study drug was conducted by an independent organization. Patients, study investigators and local sponsor personnel were masked to treatment assignment until the final database lock. At the end of the run-in period, eligible patients received allopurinol or topiroxostat (ratio 1 : 1) for 16 weeks. To maintain an appropriate double-blinding condition, the serum urate levels after randomization were concealed and a double-dummy design was adopted.

We chose the dose of topiroxostat on the basis of previous results from a dose-ranging phase 2a study, in which topiroxostat 120 mg/day demonstrated a significant reduction in serum urate levels. On the other hand, although the approved dosage of allopurinol is defined as 200–300 mg/day in Japan, the frequently prescribed dose of allopurinol is 100 mg/day, and the highest dosage is considered to be 200 mg/day in clinical practice.[23] Therefore, we compared topiroxostat 120 mg/day with allopurinol 200 mg/day, which is the substantive highest dose of allopurinol. In this study, we used the dose up-titration method to minimize the risk of gouty arthritis arising in association with rapid serum urate reduction.[24] Specifically, the dosage of allopurinol in the study was set as 100 mg/day for the first 2 weeks and then 200 mg/day for 14 weeks. The dosage of topiroxostat in the study was set as 40 mg/day for the first 2 weeks and then 80 mg/day for 4 weeks, and 120 mg/day for 10 weeks. The study scheme, including follow-up visit, is shown in Fig. 1.

Efficacy endpoints

The primary efficacy endpoint was the per cent change in serum urate level from baseline to the final visit. The secondary efficacy endpoints were the proportion of patients with serum urate levels ≤356·9 μmol/L at the final visit, and the per cent change and change in serum urate levels from baseline to the each visit.

Safety evaluations

During the study, vital signs, 12-lead electrocardiography, clinical laboratory tests and clinical examination were recorded at each visit. The clinical investigators assessed any adverse events (AEs), their severity and the causal relationship with the study drug. AEs were classified according to system organ class and preferred term (MEDDRA/J, version 13.0; Japanese Maintenance Organization, Tokyo, Japan). The incidence of AEs, serious AEs and AEs leading to discontinuation of the study were summarized as number of patients and percentage in each study group.

Statistical analyses

The sample size calculation was based on the result of a phase 2a study of topiroxostat and on the result of the clinical study of allopurinol.[25] We assumed that the per cent change in serum urate

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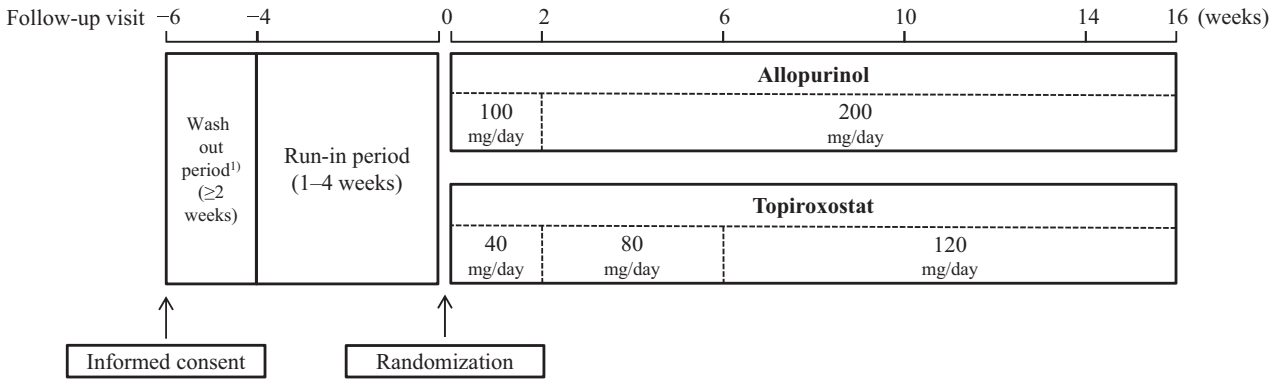

Fig. 1. Study schema. [1)]In the event, patients had been prescribed urate-lowering agents or agents affecting the serum urate level.

level from baseline in topiroxostat was −38·8% and −33·9% in allopurinol, with an assumed standard deviation (SD) of 10·0% in each group. The non-inferiority margin was predefined as 8·0%, which was less than a quarter of the difference between allopurinol (−33·9%) and placebo (0·0%). An estimated 89 patients per group would be needed to provide approximately 90% power to show both non-inferiority of topiroxostat to allopurinol for the per cent change in serum urate levels with a one-sided significance level of 0·025 and the superiority of topiroxostat to allopurinol for the per cent change in serum urate levels with a two-sided significance level of 0·05. Assuming that some patients would discontinue from the study, we allocated 100 patients per group.

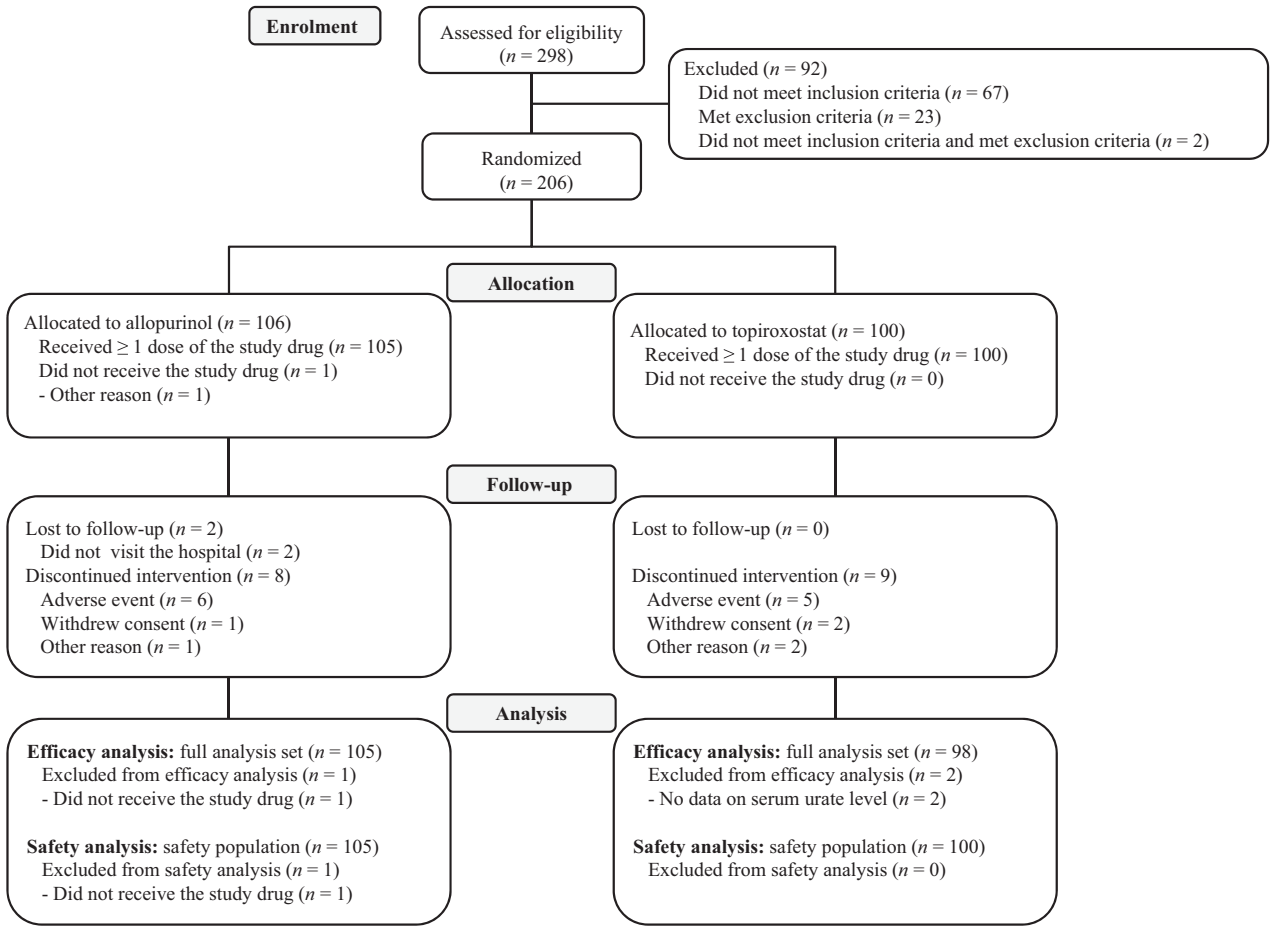

Fig. 2. Flow diagram of the study.

Table 1. Baseline characteristics (full analysis set)

	Allopurinol 200 mg/day (n = 105)	Topiroxostat 120 mg/day (n = 98)	P-Value*
Age (year)	53·7 ± 11·9	52·3 ± 10·9	0·3736
Male, n (%)	104 (99·0)	97 (99·0)	1·0000
Female, n (%)	1 (1·0)	1 (1·0)	
BMI (kg/m^2)	25·8 ± 4·2	26·7 ± 4·7	0·1683
Duration of hyperuricemia (year)	8·5 ± 7·0	9·0 ± 7·4	0·6458
Have treatment history of hyperuricemia, n (%)	88 (83·8)	78 (79·6)	0·4366
Serum urate (μmol/L)	505·4 ± 56·9	512·5 ± 64·5	0·4064
Estimated glomerular filtration rate (mL/min/1·73 m^2)	73·8 ± 14·6	73·3 ± 13·8	0·7750
Classification of hyperuricemia, n (%)			
Urate overproduction type	11 (10·5)	11 (11·2)	0·9715
Urate underexcretion type	84 (80·0)	79 (80·6)	
Combined type	8 (7·6)	6 (6·1)	
Normal type	2 (1·9)	2 (2·0)	
Have history of gouty arthritis, n (%)	75 (71·4)	72 (73·5)	0·7451
Existence of gouty tophus, n (%)	1 (1·0)	7 (7·1)	0·0303
Family history of gout, n (%)	22 (21·0)	14 (14·3)	0·2139
Entered washout period, n (%)	67 (63·8)	64 (65·3)	0·8237

*t-test for continuous variables; Fisher's exact test for sex, classification of hyperuricemia and existence of gouty tophus; chi-square test for the other categorical variables.
To convert serum urate levels from μmol/L to mg/dL, divide by 59·48.

Primary analyses were performed on the full analysis set, consisting of all randomized patients who received at least one dose of the study drug, were measured for the efficacy variable (serum urate level) at least once after randomization and had no critical GCP violation. For the efficacy analyses, if patients dropped out of the study before completion, the missing data were input based on the last observation carried forward (LOCF) method.

The baseline characteristics are summarized by study group using appropriate descriptive statistics. χ^2 test or Fisher's exact test for categorical variables and two-sample t-tests for continuous variables were implemented to test for homogeneity between study groups at baseline.

In the analyses of the primary efficacy endpoint, comparisons of the mean values between study groups were performed using two-sample t-test. Assessment of non-inferiority of topiroxostat to allopurinol was based on a prespecified non-inferiority margin of 8%. If non-inferiority was demonstrated, superiority of topiroxostat to allopurinol was assessed. In this case, the problem of multiple testing is avoided by a simple closed testing procedure.[26]

In the analyses of the secondary efficacy endpoints, two-sample t-tests were used for the continuous outcomes, and χ^2 test was used for binary outcomes.

Safety analyses were performed on the safety population, consisting of all randomized patients who receive at least one dose of the study drug and who had no critical GCP violation. χ^2 test or Fisher's exact test was used for the comparison of incidences between study groups.

We performed prespecified subgroup analyses to the per cent change in serum urate levels and the proportion of patients with serum urate level ≤356·9 μmol/L. The subgroups were as follows: age (≥65 or <65), with or without treatment history of hyperuricemia; baseline serum urate levels; and classification of hyperuricemia. Two-sample t-tests, χ^2 test or Fisher's exact test was used to make comparisons between study groups.

The significance level of all efficacy and safety analyses was set at 0·05 (two-sided) and all confidence intervals (CI) at a two-sided confidence level of 95%. For assessing the homogeneity of baseline characteristics, the significance level was set at 0·15 (two-sided). The continuous data were summarized as mean ± SD if not otherwise specified. These statistical analytical approaches were prespecified before the final database lock. No interim analyses were performed during the study period.

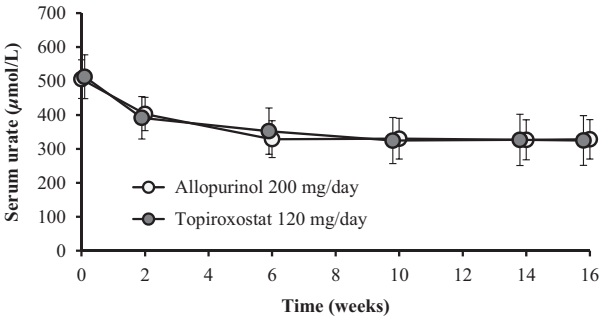

Fig. 3. Time course of serum urate levels (Full analysis set). Error bars indicate standard deviation. To convert serum urate levels from μmol/L to mg/dL, divide by 59·48.

RESULTS AND DISCUSSION

Patient flow

As far as we know, this is the first reported comparative clinical study of the serum urate-lowering effect of topiroxostat and allopurinol. The flow diagram of the study is summarized in Fig. 2. From April 2010 to January 2011, 298 patients were assessed for eligibility, and 206 patients were randomized to the study. Of note, one patient in the allopurinol group did not take the study drug at all; therefore, 205 patients were included in the safety population. Of 205 patients, two patients in the topiroxostat group discontinued the study without their serum urate levels being measured after randomization. As a result, 203 patients were included in the full analysis set. One hundred and eighty-six patients (95 patients in the allopurinol group and 91 patients in the topiroxostat group) completed the study. The baseline characteristics of the full analysis set were similar between groups except for existence of gouty tophus (Table 1). Overall, mean age was 53·0 ± 11·4 years, 99% of patients were male, mean serum urate level was 508·8 ± 60·6 μmol/L, mean body mass index was 26·3 ± 4·4 kg/m^2, mean duration of hyperuricemia was 8·8 ± 7·2 years, 80·3% of patients were considered to be the urate underexcretion type, and all patients were Japanese. 64·5% of patients had received serum urate-lowering agents just before entry into the study, and all of these patients entered a washout period of ≥2 weeks after providing informed consent.

Table 2. Prespecified subgroup analyses of per cent change in serum urate levels from baseline to the final visit (full analysis set)

		Allopurinol		Topiroxostat			
		Mean per cent change (95% CI) (number of patients)				Difference (95% CI) vs. allopurinol	*P*-value*
Age	<65 years	−33·5 (−35·7 to −31·2)	(84)	−35·2 (−38·0 to −32·4)	(82)	−1·7 (−5·3 to 1·8)	0·3399
	≥65 years	−37·4 (−43·4 to −31·4)	(21)	−41·8 (−48·0 to −35·7)	(16)	−4·4 (−12·9 to 4·0)	0·2906
Treatment history of hyperuricemia	No	−32·2 (−37·5 to −26·8)	(17)	−32·7 (−39·0 to −26·3)	(20)	−0·5 (−8·7 to 7·7)	0·9012
	Yes	−34·7 (−37·0 to −32·3)	(88)	−37·2 (−40·0 to −34·4)	(78)	−2·5 (−6·2 to 1·1)	0·1659
Serum urate level at baseline	≤416·4 > 475·8 μmol/L	−28·9 (−33·0 to −24·8)	(29)	−34·6 (−39·6 to −29·5)	(27)	−5·7 (−12·0 to 0·7)	0·0793
	≤475·8 > 535·3 μmol/L	−36·9 (−40·0 to −33·9)	(51)	−36·7 (−41·0 to −32·4)	(42)	0·2 (−4·9 to 5·3)	0·9251
	≤535·3 > 594·8 μmol/L	−33·6 (−38·5 to −28·7)	(19)	−38·4 (−44·7 to −32·2)	(14)	−4·8 (−12·3 to 2·6)	0·1955
	≥594·8 μmol/L	−39·5 (−48·1 to −31·0)	(6)	−36·2 (−42·3 to −30·1)	(15)	3·3 (−7·1 to 13·8)	0·5110
Classification of hyperuricemia	Overproduction type	−35·0 (−41·4 to −28·5)	(11)	−45·8 (−52·7 to −39·0)	(11)	−10·9 (−19·7 to −2·0)	0·0182
	Underexcretion type	−34·0 (−36·3 to −31·6)	(84)	−34·9 (−37·6 to −32·1)	(79)	−0·9 (−4·5 to 2·7)	0·6231
	Combined type	−38·1 (−51·8 to −24·4)	(8)	−34·8 (−52·5 to −17·2)	(6)	3·2 (−16·3 to 22·7)	0·7249
	Normal type	−27·2 (−42·3 to −12·1)	(2)	−44·1 (−102·9 to 14·6)	(2)	−16·9 (−37·4 to 3·6)	0·0712

*Two-sample *t*-tests.
To convert serum urate levels from μmol/L to mg/dL, divide by 59·48.

Efficacy

The primary efficacy endpoint – the per cent change in serum urate level from baseline to the final visit – was −34·3 ± 11·1% in allopurinol group (n = 105) and −36·3 ± 12·7% in topiroxostat group (n = 98) with between-group difference −2·0% (95% CI: −5·3 to 1·3%) (P = 0·2264; two-sample *t*-test). Because the upper limit of 95% CI of the between-group difference was lower than the prespecified non-inferiority margin, the non-inferiority of the serum urate-lowering efficacy of topiroxostat to allopurinol was proved.

The per cent changes in serum urate levels in the allopurinol group after 6 weeks of treatment in this study were generally same with the per cent change of serum urate in the other clinical study of allopurinol.[27] In addition, the effect was constant until week 16 in the allopurinol group in this study (Fig. 3). Therefore, we believe that the results obtained in this study are reasonable and practical. The robustness was supported by the result from per-protocol analysis (Appendix S1). In addition, the results of the prespecified subgroup analyses demonstrated that the per cent change in serum urate level of topiroxostat was numerically similar except for the result of the overproduction type (Table 2). The reason for that may have been the small sample size; however, this remains unclear and warrants further studies.

The proportion of patients with a serum urate level ≤356·9 μmol/L was not significant with topiroxostat [72·4% (95% CI: 62·5 to 81·0)] compared with allopurinol [73·3% (95% CI: 63·8 to 81·5)], with a between-group difference of −0·9% (95% CI: −13·1 to 11·4) (P = 0·8873, χ^2 test) (Fig. 4). For each prespecified subgroup analysis, the percentage was similar between groups (Table 3). The per cent change and change in serum urate levels from baseline at each visit are shown in Appendix S2 and S3.

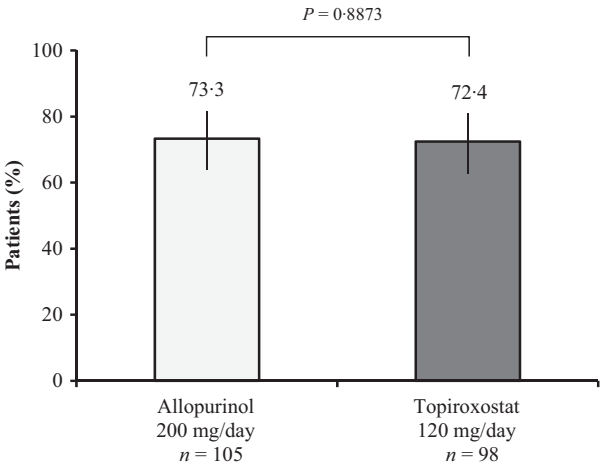

Fig. 4. Proportion of patients with a serum urate level ≤356·9 μmol/L (full analysis set). Error bars indicate 95% confidence interval.

Safety

Summary of AEs in this study is shown in Table 4. Sixteen-week treatment with topiroxostat 120 mg/day was well tolerated, in which the incidence of overall AEs was similar to that of allopurinol 200 mg/day (P = 0·3329, χ^2 test). The incidence of adverse drug reaction was numerically higher in topiroxostat group than in the allopurinol group (P = 0·1974, χ^2 test), but the incidences of AEs that necessitated withdrawal from the study were similar between groups. One death in the allopurinol group and two serious AEs (one prostate cancer and one colon polyp) in the topiroxostat group occurred in the study. No causalities between study drugs and these serious AEs were reported. Five patients in the topiroxostat group discontinued from the study due to AEs. These AEs were drug eruption, urinary β2-microglobulin increased, upper abdominal pain in one patient each and rash in two patients. In the allopurinol group, six patients (cardiac hypertrophy leading to death, rhabdomyolysis, ALT and AST increased, urticaria in one patient each and gouty arthritis in two patients) discontinued from the study due to AEs. Clinical

Table 3. Prespecified subgroup analyses of the proportion of patients with a serum urate level ≤356·9 μmol/L at the final visit (full analysis set)

		Allopurinol	Topiroxostat	Difference (95% CI) vs. allopurinol	*P*-value
		no./total no. (%) (95% CI)			
Age	<65 years	59/84 (70·2) (59·3 to 79·7)	55/82 (67·1) (55·8 to 77·1)	−3·2 (−17·3 to 10·9)	0·6602*
	≥65 years	18/21 (85·7) (63·7 to 97·0)	16/16 (100·0) (79·4 to 100·0)	14·3 (−0·7 to 29·3)	0·2432†
Treatment history of hyperuricemia	No	14/17 (82·4) (56·6 to 96·2)	15/20 (75·0) (50·9 to 91·3)	−7·4 (−33·6 to 18·9)	0·7013†
	Yes	63/88 (71·6) (61·0 to 80·7)	56/78 (71·8) (60·5 to 81·4)	0·2 (−13·5 to 13·9)	0·9767*
Serum urate level at baseline	≤416·4 > 475·8 μmol/L	25/29 (86·2) (68·3 to 96·1)	26/27 (96·3) (81·0 to 99·9)	10·1 (−4·3 to 24·5)	0·3533†
	≤475·8 > 535·3 μmol/L	38/51 (74·5) (60·4 to 85·7)	31/42 (73·8) (58·0 to 86·1)	−0·7 (−18·6 to 17·2)	0·9387*
	≤535·3 > 594·8 μmol/L	11/19 (57·9) (33·5 to 79·7)	8/14 (57·1) (28·9 to 82·3)	−0·8 (−34·9 to 33·4)	0·9655*
	≥594·8 μmol/L	3/6 (50·0) (11·8 to 88·2)	6/15 (40·0) (16·3 to 67·7)	−10·0 (−57·1 to 37·1)	1·0000†
Classification of hyperuricemia	Overproduction type	9/11 (81·8) (48·2 to 97·7)	11/11 (100·0) (71·5 to 100·0)	18·2 (−4·6 to 41·0)	0·4761†
	Underexcretion type	63/84 (75·0) (64·4 to 83·8)	56/79 (70·9) (59·6 to 80·6)	−4·1 (−17·8 to 9·5)	0·5543*
	Combined type	4/8 (50·0) (15·7 to 84·3)	2/6 (33·3) (4·3 to 77·7)	−16·7 (−67·9 to 34·6)	0·6270†
	Normal type	1/2 (50·0) (1·3 to 98·7)	2/2 (100·0) (15·8 to 100·0)	50·0 (−19·3 to 100·0)	1·0000†

*χ^2 test, †Fisher's exact test.
To convert serum urate levels from μmol/L to mg/dL, divide by 59·48.

Table 4. Summary of AEs (safety population)

	Allopurinol (*n* = 105)	Topiroxostat (*n* = 100)
Any AE, *n* (%)	98 (93·3)	97 (97·0)
Any serious AE, *n* (%)	1 (1·0)	2 (2·0)
Any adverse drug reaction, *n* (%)	29 (27·6)	36 (36·0)
AEs necessitated withdrawal of the patient from the study, *n* (%)	6 (5·7)	5 (5·0)
Frequent AEs (incidence ≥10%), *n* (%)		
Nasopharyngitis	10 (9·5)	10 (10·0)
Gouty arthritis	8 (7·6)	12 (12·0)
ALT increased	8 (7·6)	24 (24·0)
AST increased	12 (11·4)	24 (24·0)
β2-microglobulin increased	16 (15·2)	16 (16·0)
Urinary β2-microglobulin increased	24 (22·9)	16 (16·0)
Urinary NAG increased	21 (20·0)	25 (25·0)
Blood amylase increased	11 (10·5)	6 (6·0)
Blood CPK increased	16 (15·2)	17 (17·0)
Blood triglycerides increased	40 (38·1)	42 (42·0)
γGTP increased	5 (4·8)	15 (15·0)
WBC count increased	11 (10·5)	5 (5·0)
Urinary α1-microglobulin increased	33 (31·4)	34 (34·0)

ALT, alanine aminotransferase; AE, adverse event; AST, aspartate aminotransferase; NAG, β-*N*-acetyl-D-glucosaminidase; CPK, creatine phosphokinase; γGTP, γ-glutamyltransferase; WBC, white blood cell.

investigators determined that all of these AEs (except for cardiac hypertrophy leading to death, ALT and AST increased, and urticaria) were adverse drug reactions.

In spite of the gradual dose up-titration method, the incidence of gouty arthritis was not statistically significant, but tended to have a higher incidence in the topiroxostat group than in the allopurinol group ($P = 0·2906$, χ^2 test) (Table 4). In detail, all patients had mild severity of gouty arthritis that occurred in the topiroxostat group except for one patient who had moderate severity, and none of the patients discontinued from the study because of gouty arthritis.

As for the results of liver function test, the incidences of 'ALT increased', 'AST increased' and 'γ-glutamyltransferase (γGTP) increased' were 2- to 3-fold higher in the topiroxostat group than in the allopurinol group (Table 4). The severity of all of these AEs was mild in the topiroxostat group, and these patients did not discontinue from the study.

No severe skin-related AE was observed, but some skin-related AEs including rash occurred in both groups [allopurinol group: 5·7% (6/105), topiroxostat group: 7·0% (7/100)]. Among these patients, one patient [urticaria (severity: mild)] in allopurinol group and three patients [drug eruption in one patient (severity: moderate) and rash in two patients (severity: mild)] in the topiroxostat group discontinued from the study. The severities of the other skin-related AEs were mild. Five of six patients in allopurinol group and all of seven patients in topiroxostat group were recovered from skin-related AEs, and one patient in allopurinol group was recovering from the skin-related AEs (pruritus and eczema).

It is clinically important to evaluate the safety profile in patients who took urate-lowering agents before enrolling in the study. Among washout patients in safety population, 6·0% (4/67) in allopurinol group and 6·2% (4/65) in topiroxostat group developed skin-related AEs. The incidences were numerically similar between groups, but various urate-lowering agents were prescribed before participation of the study, and these urate-lowering agents were not controlled. Therefore, the profile of the skin-related AE in patients who switched from other urate-lowering agents to topiroxostat is uncertain at this time. When prescribing topiroxostat, clinicians should assume that there may be an occurrence of gouty arthritis, abnormal liver function test results or skin diseases.

Limitations

Our study had several potential limitations. First, the mean baseline serum urate level of the study was relatively low compared with that of previous clinical studies conducted in countries other than Japan.[28] Therefore, no conclusion can be made in more severe

hyperuricemic patients. Second, all of the patients who participated in our study were Japanese, limiting generalizability to other ethnic populations. Third, to avoid the onset of allopurinol hypersensitivity, the inclusion of renal-impaired patients was limited; therefore, the serum urate-lowering efficacy of topiroxostat 120 mg/day in renal-impaired patients is uncertain. Finally, because of the difficulty of the 24-h urine collection, the classification method in our study was significantly different method in outside Japan. Therefore, the result of subgroup analysis by the classification of hyperuricemia in this study may have a different result from that by the classification of the 24-h urine collection.

WHAT IS NEW AND CONCLUSION

Topiroxostat 120 mg/day provides non-inferior serum urate reduction compared with allopurinol 200 mg/day and is well tolerated in Japanese hyperuricemic patients with or without gout.

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CONFLICT OF INTEREST

TH has received consultant fees and/or speaker's honoraria from Fuji Yakuhin Co., Ltd., and/or Sanwa Kagaku Kenkyusho Co., Ltd., the manufacturer of topiroxostat. YO, HH and RS were employees of Sanwa Kagaku Kenkyusho Co., Ltd., at the time of the study. TO was an employee of Fuji Yakuhin Co., Ltd., at the time of the study.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Summary of primary efficacy endpoint (Per-protocol set).

Appendix S2 Percent change in serum urate levels from baseline to each visit (Full analysis set).

Appendix S3 Change in serum urate level from baseline to each visit (Full analysis set).

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