Comparison of Clinical Advantage between Topiroxostat and Febuxostat in Hemodialysis Patients

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To determine the response of hemodialysis (HD) patients to topiroxostat after a switch from febuxostat, we evaluated the efficacy, tolerability, and serum concentration of topiroxostat in HD patients after the switch. In this 16-month prospective observational study, we assessed the serum uric acid (UA) levels, other laboratory data, and serum topiroxostat concentrations of 10 HD patients who had been receiving febuxostat at a dose of 10 mg/d for over 1 year. No statistical difference was observed between the tolerability index at baseline and 16 months after the switch to topiroxostat. Serum UA after the switch in all patients (attained serum UA levels of ≤6 mg/dL) was 5.6±1.7 mg/dL (60%) at baseline, 4.9±0.5 mg/dL (100%) at 6 months and 5.7±0.4 mg/dL (50%) at 16 months (p=0.25), respectively. In patients with baseline serum UA levels >6 mg/dL, serum UA was significantly reduced at 6 and 16 months compared with baseline. Minimum serum concentrations of serum topiroxostat were lower than the limit of quantification (<25 mg/mL). Our results indicate that a switch from febuxostat 10 mg/d to topiroxostat 40 mg/d might reduce serum UA levels, with no change in other clinical laboratory data over the long term. These effects were more frequent in patients with high serum UA levels. Furthermore, topiroxostat therapy was more cost effective than febuxostat therapy. Thus, topiroxostat therapy could be a better treatment option for HD patients who develop high serum UA levels after febuxostat 10 mg/d administration.

Key words topiroxostat; febuxostat; hemodialysis; serum uric acid level; serum concentration

Elevated serum uric acid (UA) levels (hyperuricemia) are known to be associated with comorbid conditions such as cardiovascular disease (CVD), chronic kidney disease (CKD) and hypertension.3) CVD is associated with risks of morbidity and mortality in hemodialysis (HD) patients,2) and CKD patients receive urate-lowering therapy, mainly in the form of xanthine oxidase (XO) inhibitors.4) One of these XO inhibitors is topiroxostat, whose primary metabolite is topiroxostat N-glucuronide.4) In a multicenter, double-blind randomized controlled trial comparing the XO inhibitors topiroxostat 120 mg/d and allopurinol 200 mg/d in Japanese hyperuricemic patients with or without gout, topiroxostat showed a non-inferior decrease in serum UA levels compared with allopurinol and was well tolerated (change in serum urate levels of −36.3 vs. −34.3%, respectively).5) In another study involving hyperuricemic stage 3 CKD patients with or without gout, topiroxostat 160 mg reduced serum UA levels (−45.3%) and urinary albumin-to-creatinine ratio (−33.0%) over 22 weeks.9) Also, in HD patients receiving topiroxostat therapy, serum UA levels were reduced from 9 to 5 mg/dL and the serum concentrations of topiroxostat were 25 ng/mL before HD sessions.7

Febuxostat is another XO inhibitor, with febuxostat acyl-glucuronide as its primary metabolite.8) Population pharmacokinetics and therapeutic analysis of febuxostat have revealed that severe renal dysfunction had no influence on the pharmacokinetic parameters of febuxostat.9) In HD patients, we reported that a switch from allopurinol to febuxostat reduced serum UA levels, with no effect on other clinical laboratory data.10) However, Mayer et al.11) reported a significant linear relationship between creatinine clearance and the production of febuxostat metabolites, based on Cmax and 24-h area under the curve indices, suggesting that febuxostat metabolites can accumulate in HD patients.

In our hospital, HD patients who had been receiving febuxostat 10 mg/d tended to show increased serum UA levels over a 6-month period. When serum UA levels remained elevated by febuxostat 10 mg/d therapy, we considered two management options for urate-lowering therapy: an increase in the dose of febuxostat to 20 mg/d or a switch to topiroxostat 40 mg/d. We opted for the switch to topiroxostat 40 mg/d therapy to avoid the potential for febuxostat metabolites to accumulate. Thus, in this study, we evaluate the efficacy, tolerability, and serum concentration of topiroxostat in HD patients after the switch from febuxostat.

PATIENTS AND METHODS

Subjects This 16-month prospective observational study involved HD patients who had been receiving once daily oral doses of febuxostat 10 mg/d for over 1 year in Kaetsu Hospital. All enrolled patients were switched to twice daily oral doses of topiroxostat 40 mg/d in January 2015. Clinical laboratory data were collected from July 2014 to May 2016. Blood samples were obtained via vascular access before HD sessions: 1 h after topiroxostat administration in patients who had morning HD sessions and just before topiroxostat administration in those remaining patients who had evening HD sessions.

Levels of the following clinical parameters were considered as an overall tolerability index and were measured at baseline and 3, 12, and 16 months after the switch to topiroxostat therapy: hemoglobin, hematocrit, platelet count, blood urea nitrogen, serum creatinine, serum sodium, serum potassium, serum chloride, serum calcium, serum inorganic phospho-

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rus, aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total protein. Serum UA levels representing the efficacy index were assessed at baseline and at 6 and 16 months after the switch.

Mean serum UA levels were determined and target levels were ≤6 mg/dL. We assessed serum UA levels for patient background factors according to whether baseline serum UA levels were ≤6 and >6 mg/dL at 6 and 16 months after the switch to topiroxostat therapy. Baseline was set as December 2014 and the end of study as 16 months after the switch to topiroxostat therapy or discontinuation of topiroxostat therapy. Hepatotoxicity was defined as a 3-fold increase in AST or ALT levels from the upper limit of baseline. To determine serum topiroxostat concentrations, we obtained blood samples just before HD sessions 3 months after the switch to topiroxostat 40 mg/d therapy (April 2015).

All data are expressed as means±standard deviation (S.D.). Statistical analysis was performed using one-way ANOVA followed by Wilcoxon’s signed rank test. Significance was set at p<0.05. The software package JMP 9 (SAS Institute Inc., Cary, NC, U.S.A.) was used for all statistical analysis.

This study was performed in accordance with the principles found in the Declaration of Helsinki and was approved by the Ethics Committee of Kaetsu Hospital. Written informed consent was obtained from all patients before enrollment in the study.

Assay Topiroxostat was provided by Sanwa Kagaku Kenkyusho Co., Ltd. (Aichi, Japan). Oasis hydrophilic lipophilic balance (HLB) 1-cc (30-mg) extraction cartridges were purchased from Waters Corporation (Milford, MA, U.S.A.). All other chemicals were of analytical grade and commercially available.

Serum topiroxostat concentrations were determined by HPLC using ofloxacin (3 µg/mL) as the internal standard (IS). Briefly, sample processing was performed using a solid phase extraction cartridge. A 200-µL sample (100 µL serum sample +40 µL IS +500 µL 0.044 M phosphate buffer solution; pH 2.6) was loaded and the cartridge washed with 270 µL of 5% methanol in water. The sample was further eluted with 200 µL of 100% methanol, and 50 µL was injected onto the HPLC column for analysis. The HPLC system consisted of a reverse-phase column (Shim-Pack, CLC-ODS, Shimadzu Corp., Kyoto, Japan), and mobile phase fluorescence was monitored (excitation wavelength, 282 nm; emission wavelength, 429 nm). The mobile phase consisted of a mixture of acetonitrile and 0.5% triethylamine in 0.044 M sodium dihydrogenphosphate (1:7 by volume), and the flow rate was 1.0 mL/min. Retention times of the IS and topiroxostat were 13 and 27 min, respectively. The lower limit of quantification of this system is 25 ng/mL in 100 µL of serum. Inter- and intra-day variations were <5%.

RESULTS

Eleven HD patients receiving febuxostat 10 mg/d were considered candidate subjects. However, data from 10 patients were analyzed in this study because 1 patient was excluded from the study due to cessation of topiroxostat therapy 5 months after the switch to topiroxostat therapy because his serum UA levels had decreased to <4 mg/dL.

All 10 patients had oliguria or anuria, and there were no changes in diuretic therapy during the study period. None took any steroid or non-steroidal anti-inflammatory drugs during the study period. After the study commenced, because serum UA levels of topiroxostat were <5 mg/dL in all patients, the twice daily oral doses of 40 mg/d were reduced to 20 mg/d in all patients 7 to 8 months after the switch to topiroxostat therapy. Two of the 10 patients were subsequently withdrawn from topiroxostat therapy by the study investigators 10 to 13 months after the switch to topiroxostat therapy because their levels had dropped to <5 mg/dL. Thus, data were analyzed for 8 patients after their withdrawal.

Patient profiles are shown in Table 1 and drug treatments in Table 2. During the study period, HD background did not change. In terms of anti-hypertensive agents taken during the study period, 3 patients started taking them and 2 patients stopped taking them: 3 patients started taking a calcium channel blocker, alpha adrenergic blocker, or beta blocker; 1 patient stopped taking an angiotensin receptor blocker; and 1 patient stopped taking an angiotensin receptor blocker and calcium channel blocker. Patients were administered azilsartan, candesartan, or olmesartan as an angiotensin receptor blocker. As for hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, 1 patient started taking pravastatin. For phosphate binders, none of the patients changed to another phosphate binder, but 3 patients receiving lanthanium carbonate had their dosage increased and 3 other patients started taking lanthanium carbonate. In the study period, hematinics (iron and other

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>N</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.5±12.2</td>
</tr>
<tr>
<td>Sex (female / male)</td>
<td>1/9</td>
</tr>
<tr>
<td>Dry weight</td>
<td>61.0±17.1</td>
</tr>
<tr>
<td>Hemodialysis duration (years)</td>
<td>13.7±6.1</td>
</tr>
<tr>
<td>Etiology of renal disease (n)</td>
<td>Glomerulonephritis: 5, Polycystic kidney disease: 3, Other: 2</td>
</tr>
<tr>
<td>Cardiovascular disease (n)</td>
<td>Diabetes: 2, Hyperlipidemia: 1, Cerebral infarction: 1</td>
</tr>
</tbody>
</table>

Values are means±standard deviation.

Table 2. Drug Treatments Administered to Patients at Baseline and at the End of the Study Period

<table>
<thead>
<tr>
<th>Medication</th>
<th>Baseline</th>
<th>End of the study</th>
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</thead>
<tbody>
<tr>
<td>Antihypertensive agents</td>
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<td></td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Alpha adrenergic blocker</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Phosphate binders</td>
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<td></td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Sevelamer hydrochloride</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Bixalomer</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are number of medications taken.
Average serum UA levels in patients with baseline UA >6 mg/dL.

None withdrew from the study due to side effects or allergic reactions.

Changes in serum UA levels during the observation period are shown in Fig. 1. Serum UA levels tended to increase during febuxostat 10 mg/d therapy, but tended to decrease after changing to topiroxostat 40 mg/d therapy. The subsequent reduction in topiroxostat therapy from 40 to 20 mg/d stabilized serum UA levels to below the target level of ≤6 mg/dL. Serum UA levels in all patients after the switch to topiroxostat were 5.6±1.7 (60%) at baseline, 4.9±0.5 (100%) at 6 months, and 5.7±0.4 (50%) at 16 months (p=0.25).

Patients characteristics and changes in serum UA levels at 6 and 16 months in the two groups according to baseline serum UA levels are shown in Table 4. Serum UA levels at 6 and 16 months in the two groups according to baseline serum UA levels were not significantly different in the ≤6 mg/dL group but were not significantly different in the >6 mg/dL group. Two patients were withdrawn between 10 and 13 months from topiroxostat therapy due to serum UA levels >5 mg/dL in the ≤6 mg/dL group.

Serum topiroxostat concentrations were 41.4, 205.4, and 261.5 ng/mL in 3 patients who had morning HD sessions and were lower than the limit of quantification (<25 ng/mL) in 5 patients who had evening HD sessions. Serum topiroxostat concentrations were not obtained for the remaining 2 patients who had evening HD sessions, resulting in interference peaks in HPLC measurements.

**DISCUSSION**

In this study, we switch HD patients who had been re-
ceiving febuxostat therapy at our hospital from febuxostat 10 mg/d to topiroxostat 40 mg/d because their serum UA levels had shown a tendency to increase over a 6-month period. As a result, the topiroxostat 40 mg/d therapy tended to reduce serum UA levels (5.6±1.7 vs. 4.9±0.5 mg/dL) from 6 months onwards. In addition, attainment of serum UA levels of ≤6 mg/dL tended to be higher at 6 months (100%) than at baseline (60%).

No previous study has examined the effect of switching from febuxostat to topiroxostat therapy in HD patients. However, Oyama et al.7 reported a reduction in serum UA levels from febuxostat to topiroxostat therapy, which is similar to our result. Moreover, because patients with serum UA levels reduced to <4.5 mg/dL were either withdrawn from the study or had their topiroxostat dosage reduced, serum UA levels at 16 months were 5.7±0.4 mg/dL by topiroxostat 20 mg/d therapy, equivalent to baseline levels. Therefore, topiroxostat 40 mg therapy decreased serum UA levels compared with febuxostat 10 mg/d therapy.

In the group with baseline serum UA levels >6 mg/dL, serum UA concentration at 6 and 16 months was significantly reduced compared with baseline (Table 4). This suggests that topiroxostat 20 or 40 mg/d therapy might better reduce serum UA levels than febuxostat 10 mg/d therapy in patients with high serum UA levels due to the febuxostat 10 mg/d therapy. With regards to drug cost for such patients, twice daily oral doses of topiroxostat 40 mg/d are cheaper than once daily oral doses of febuxostat 20 mg/d (42 vs. 58 yen/d, respectively) in Japan. The drug cost is an important consideration because urate-lowering therapies are routinely administered on a long-term basis. Therefore, compared to febuxostat, topiroxostat 40 mg/d therapy would be more cost-effective.

The clinical laboratory data (i.e., the tolerability index) showed no significant changes from the baseline to 16 months after the switch to topiroxostat therapy. Hosoya et al.5 reported similar overall incidence of adverse events and drug reactions between topiroxostat and allopurinol groups from baseline to 4 months. Topiroxostat was well tolerated in our study and was continued over 16 months. However, febuxostat therapy for hyperuricemia in CKD patients has been reported to cause liver dysfunction3) and acute neutropenia4); therefore, it is important to monitor for these side effects in CKD patients receiving topiroxostat therapy.

Our results showed large variation in the concentration of serum topiroxostat (40 mg/d twice daily orally) before the morning and evening HD sessions (41.4 to 261.5 mg/mL), and the evening measurements were below the limit of quantification. It is likely that these values represent minimum and maximum serum concentrations. Oyama et al.7 reported serum topiroxostat concentrations of 25 ng/mL at 4 weeks before HD, similar to those observed in our study. Therefore, it is possible that there is no serum topiroxostat accumulation in HD patients.

Angiotensin receptor blockers have not been shown to lower serum UA levels, except for losartan, which increased urinary UA excretion leading to lower serum UA levels.3) None of the patients in this study received losartan. Sevelamer hydrochloride, a phosphate binder, was found to be associated with a significant reduction in serum UA levels,10 but among the patients taking sevelamer hydrochloride in this study, none had to stop taking it and none started taking it. Therefore, it is likely that angiotensin receptor blockers and sevelamer did not affect serum UA levels in this study. In addition, changes in dosages of hematinics and erythropoiesis-stimulating agents during the study period had no significant effect on patients’ hemoglobin levels.

Blood pressure readings were not collected in this study; however, 3 patients started taking antihypertensive agents and 2 patients stopped taking them. A few studies have reported no significant differences in the degree of reduction of systolic blood pressure levels between patients receiving topiroxostat and those receiving placebo.5) In line with our results, topiroxostat therapy may have little effect on blood pressure in HD patients.

Our study has certain limitations. These include the small sample size, lack of a control group, and few female patients, which could limit the generalizability of results. Also, the mechanism underlying the elevation of serum urate during administration of 10 mg febuxostat was unclear. Dietary changes might have caused elevated serum urate level because the HD patients in this study are about 60 years old, and still lead active lives. Therefore, more robust studies are needed to confirm these findings.

Taken together, our results indicate that a switch from febuxostat 10 mg/d to topiroxostat 40 mg/d in HD patients—especially those with high serum UA levels—might sufficiently reduce serum UA, with no long-term changes in other clinical laboratory parameters. In addition, topiroxostat therapy was more cost-effective than febuxostat therapy. Therefore, topiroxostat might be a better treatment option for HD patients who develop high serum UA levels on febuxostat 10 mg/d.

Acknowledgments The authors thank the hospital staff and patients who participated in this study.

Conflict of Interest The authors declare no conflict of interest.

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