Acute severe liver dysfunction induced by febuxostat in a patient undergoing hemodialysis

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Abstract A 58-year-old man with chronic kidney disease (CKD) was admitted to our hospital for hemodialysis (HD) therapy. He had been administered allopurinol (100 mg/day) before hospitalization, and we replaced it with febuxostat (10 mg/day), a new xanthine oxidase inhibitor. Levels of aspartate aminotransferase, alanine transaminase (ALT), and lactate dehydrogenase were within the normal ranges in the morning before febuxostat administration, but 6 h after administration, these parameters increased markedly to approximately 10 times the levels before administration. Although we stopped administering febuxostat, his serum potassium levels increased at a rate of 1 mmol/L every 12 h, and he had to undergo HD daily to lower the serum potassium levels. The levels of liver function test parameters peaked on the fourth hospital day (ALT, 1134 IU/L; AST, 1485 IU/L; and LDH, 1869 IU/L) and recovered to normal ranges on the 13th hospital day. In this case, febuxostat appeared to have a relationship with acute liver dysfunction in the clinical course. Therefore, it would be important to check liver function test parameters frequently after febuxostat initiation and also to initiate a lower than usual dose of febuxostat, especially in patients with CKD and those who are undergoing HD.

Keywords Adverse effect · Febuxostat · Hyperuricemia · Hemodialysis · Liver dysfunction

Introduction

It is important to manage hyperuricemia by preventing coronary vascular disease and chronic kidney disease (CKD). Febuxostat, a nonpurine xanthine oxidase (XO) inhibitor, is a new oral medicine for the treatment of hyperuricemia. This drug is metabolized by the liver [1]; therefore, it is easy to use the drug in patients with CKD, including those undergoing hemodialysis (HD). However, different drug types can cause adverse effects in varying degrees.

We describe a rare case of acute severe liver dysfunction induced by febuxostat in a patient undergoing HD. When severe adverse effects occur, appropriate management is necessary.

Case report

A 58-year-old man with stage 5 CKD caused by diabetes mellitus was brought to our hospital by ambulance and was diagnosed with congestive heart failure. He had a medical history of diabetes mellitus, hypertension, and duodenal ulcer. He had no hepatitis B or hepatitis C virus infection. For 6 months before admission, he had been administered losartan (100 mg/day), cilnidipine (20 mg/day), hydrochlorothiazide (12.5 mg/day), azosemide (15 mg/day), calcium carbonate (1000 mg/day), calcitriol (0.5 µg/day), dipyridamole (300 mg/day), shakuyaku-kanzo-to (2.5 g/day), insulin aspart (6 U/day), and allopurinol (100 mg/day). He had a family history of diabetes mellitus but no allergic history. His physical examination on admission revealed a body height of 167 cm; body weight, 57 kg; body temperature, 36.4 °C; blood pressure, 129/83 mmHg; and heart rate, 95 beats per minute. The palpebral

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Fig. 1 Changes in liver function test parameters. *Pre* pre-hemodialysis laboratory data; *Post* post-hemodialysis laboratory data; *1st day* the first hospital day; *2nd day* the second hospital day; *3rd day* the third hospital day; *4th day* the fourth hospital day

conjunctiva was slightly pale but not icteric. No remarkable findings were observed in heart sounds, respiratory sounds, the abdomen, or the skin. There was bilateral pitting edema on his legs.

The main laboratory findings on admission were as follows: total bilirubin, 0.34 mg/dL; direct bilirubin, 0.12 mg/dL; aspartate aminotransferase (AST), 15 IU/L; alanine transaminase (ALT), 13 IU/L; lactate dehydrogenase (LDH), 228 IU/L; alkaline phosphatase, 273 IU/L; γ -glutamyl transpeptidase (γ -GTP), 33 IU/L; creatine kinase (CK), 244 IU/L; CK-MB, 14 IU/L; sodium, 131 mmol/L; potassium, 5.9 mmol/L; chloride, 102 mmol/L; calcium, 7.0 mg/dL; phosphate, 7.4 mg/dL; blood urea nitrogen, 111 mg/dL; Cre, 13.8 mg/dL; UA, 9.2 mg/dL; glycated hemoglobin, 5.5 % (NGSP); white blood cell count, 8620/ μ L; hemoglobin, 9.1 g/dL; platelet count, 44.8 $\times$ 104/ μ L; lactic acid, 11.7 mg/dL; bicarbonate, 10.7 mmol/L; and troponin T, negative. A chest X-ray showed pulmonary vascular congestion, and an electrocardiogram showed complete right bundle branch block.

We started intermittent HD using a vascular catheter, and all oral medications were discontinued, except losartan, azosemide, calcium carbonate, and calcitriol because of the necessity to manage blood pressure, body fluid balance, and calcium–phosphate balance.

On the second hospital day, we replaced allopurinol (100 mg/day) with febuxostat (10 mg/day after breakfast) and began administering sodium polystyrene sulfonate for hyperkalemia. In the morning, AST, ALT, and LDH levels were within normal ranges, but laboratory data obtained after hemodialysis revealed marked elevation in the levels of these parameters (Fig. 1). On the third hospital day, these levels were approximately 10 times higher than the levels recorded on the previous day. Therefore, we stopped administering febuxostat on the fourth hospital day. Thus,

febuxostat was administered only twice, whereas sodium polystyrene sulfonate was continued.

Moreover, serum potassium levels increased at a rate of 1 mmol/L every 12 h and finally reached >6 mmol/L. Therefore, the patient had to undergo HD daily to lower these levels for 6 consecutive days. The levels of liver function test parameters peaked on the fourth hospital day at the following levels: ALT, 1134 IU/L; AST, 1485 IU/L; and LDH, 1869 IU/L. Skin and mucosal membrane symptoms suggestive of an allergic process were not present, and the patient had no eosinophilia. Thereafter, these parameters were restored to normal ranges on the 13th hospital day. The patient underwent an operation to create a dialysis shunt. He was discharged from the hospital 3 weeks after admission.

Discussion

Here, we have reported a case of acute severe liver dysfunction that was most likely caused by febuxostat. Comprehensive laboratory testing to search for causes other than febuxostat demonstrated that suspected virus titers were within normal ranges (Table 1). We considered the possibility of a drug allergy caused by febuxostat and liver damage caused by the excessive elevated circulating levels of febuxostat. Therefore, we measured febuxostat concentrations in the serum (Fig. 2) and performed a drug-induced lymphocyte stimulation test (DLST) to febuxostat approximately 2 months after the liver dysfunction occurred (Table 2). However, the DLST results were negative and the serum concentrations of febuxostat did not appear to be higher than those in clinical trials. He had been taking 9 medications orally before admission, and was continued only losartan, azosemide, calcium carbonate, and calcitriol

Table 1 Additional laboratory data for liver dysfunction

IgM-HA antibody	<0.40
HBs antigen	(–)
HCV antibody	(–)
EBV-VCA IgG (IFA)	1:40
EBV-VCA IgM (IFA)	1:<10
CMV IgM (EIA)	0.43(–)
HIV antibody	(–)

with febuxostat after admission. Thus, we cannot exclude the possibility that liver dysfunction is induced by drugs themselves, in particular shakuyaku-kanzo-to, and the interaction between febuxostat and other medications taking after admission. However, severe liver dysfunction improved by only febuxostat discontinuation and therefore, we considered that acute liver dysfunction is caused by febuxostat initiation.

Febuxostat, a new XO inhibitor developed by Teijin Pharma Ltd. (Tokyo, Japan), has been approved as a therapeutic product in many countries including in Japan [2]. Unlike allopurinol, febuxostat is metabolized primarily by hepatic glucuronide formation and oxidation [1]. Grabowski et al. [3] reported that the mean cumulative recovery of febuxostat in excreta was 94 % in 6 healthy male subjects; 49 % was excreted through urine, and 45 % was excreted through feces. Among patients with different levels of renal impairment, Mayer et al. [4] reported that an 80-mg dose of febuxostat administered once daily appeared to be safe and well tolerated and that dose adjustment did not seem to be necessary on the basis of differences in renal function. Moreover, Khosravan et al. [5] administered an 80-mg dose of febuxostat once daily to subjects with mild

or moderate hepatic impairment and concluded that dose adjustment of febuxostat would not be required with or without hepatic impairment. In Japan, a between-group comparative study did not report any clinically significant adverse events associated with febuxostat administration in patients with impaired renal function [6]. Another study reported no apparent adverse events in 5 patients undergoing long-term HD whose hyperuricemia was successfully treated [7]. However, thus far, febuxostat therapy has not been thoroughly evaluated in patients with severe CKD or in those undergoing HD.

Our patient had been administered oral allopurinol until starting febuxostat. Hung et al. [8] published the first report of a strong association between allopurinol-induced severe cutaneous adverse reactions [including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)] and human leukocyte antigen (HLA)-B*58:01 in Han Chinese patients. A strong association between HLA-B*58:01 and allopurinol-induced SJS and TEN has been reported in Japanese patients [9]. Furthermore, drug-induced liver injury (DILI) is the most frequently reported adverse drug event in Japan [10]. DILI associated with most drugs is considered to be idiosyncratic, immune-mediated (i.e., allergic), and mediated through mechanisms associated with metabolism. Associations between HLA alleles and DILI have been found for several drugs [10]. Therefore, we examined the patient's HLA alleles and found that they did not include HLA-B*58:01; his profile was HLA-A*24:02, HLA-B*52:01, and HLA-DRB1*15:02. As no studies have reported an association between our patient's HLA and DILI, the association between this patient's HLA alleles and his reaction to febuxostat remains unclear.

Fig. 2 Changes in the serum concentration of febuxostat. Febuxostat concentrations were determined using blood serum proteins; however, in clinical trials, febuxostat concentrations were determined using plasma proteins. Therefore, our data may not necessarily reflect the clinical trial data that are used as reference values

Table 2 Drug-induced lymphocyte stimulation test

Allopurinol	101 % (SI)
Febuxostat	92 % (SI)

Judgment criteria: positive, >180 %; negative, ≤180 %

SI stimulation index

Recently, management of uric acid levels has been considered very important in animal experiment [11] and in humans [12]. Also, febuxostat can be easily prescribed for patients with CKD and those undergoing HD, considering the metabolic mechanism of this drug. Febuxostat at a daily dose of 80 mg or 120 mg is more effective in lowering serum uric acid levels than allopurinol at the commonly administered daily dose of 300 mg [13]. Furthermore, in the clinical setting, we have encountered serious adverse effects with allopurinol therapy, including drug-induced hypersensitivity syndrome. Therefore, febuxostat is a potential alternative to allopurinol for patients with CKD and those undergoing HD.

We are unable to clarify the precise mechanism underlying the hyperkalemia with severe liver dysfunction in the present case. However, severe hyperkalemia may have been caused by potassium leakage from damaged liver cells even without potassium ingestion. For the early detection and prevention of serious adverse effects induced by febuxostat, it would be important to check liver function test parameters frequently after febuxostat initiation. Furthermore, it might also be important to initiate a lower than usual dose of febuxostat, if possible, in patients with CKD or those undergoing HD.

Conclusion

We reported the case of a patient undergoing HD who experienced acute liver dysfunction caused by febuxostat therapy. Previous reports on acute severe liver dysfunction induced by febuxostat are scarce. However, according to our experience, to avoid the progression of febuxostat-induced liver damage, liver function test parameters should be considered, especially in patients with CKD and those undergoing HD.

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Conflict of interest The authors have declared that no conflict of interest exists.

References

1. El-Zawawy H, Mandell BF. Managing gout: how is it different in patients with chronic kidney disease? *Cleve Clin J Med*. 2010;77:919–28.
2. Okamoto K. A new-generation uric acid production inhibitor febuxostat. *Jpn Pharmacol Ther*. 2010;38:955–62.
3. Grabowski BA, Khosravan R, Vernillet L, Mulford DJ. Metabolism and excretion of [14C] febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase, in healthy male subjects. *J Clin Pharmacol*. 2011;51:189–201.
4. Mayer MD, Khosravan R, Vernillet L, Wu JT, Joseph-Ridge N, Mulford DJ. Pharmacokinetics and pharmacodynamics of febuxostat, a new non-purine selective inhibitor of xanthine oxidase in subjects with renal impairment. *Am J Ther*. 2005;12:22–34.
5. Khosravan R, Grabowski BA, Mayer MD, Wu JT, Joseph-Ridge N, Vernillet L. The effect of mild and moderate hepatic impairment on pharmacokinetics, pharmacodynamics, and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. *J Clin Pharmacol*. 2006;46:88–102.
6. Tatsuo H, Iwao O. A repeated oral administration study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with impaired renal function in Japan: pharmacokinetic and pharmacodynamic study. *J Clin Rheumatol*. 2011;17:S27–34.
7. Horikoshi R, Akimoto T, Inoue M, Morishita Y, Kusano E. Febuxostat for hyperuricemia: experience with patients on chronic hemodialysis treatment. *Clin Exp Nephrol*. 2013;17:149–50.
8. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, Lin JL, Yang LC, Hong HS, Chen MJ, Lai PC, Wu, Chu CY, Wang KH, Chen CH, Fann CS, Wu JY, ChenYT, Chen YT. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA*. 2005;102:4134–9.
9. Tohkin M, Kaniwa N, Saito Y, Sugiyama E, Kurose K, Nishikawa J, Hasegawa R, Aihara M, Matsunaga K, Abe M, Furuya H, Takahashi Y, Ikeda H, Muramatsu M, Ueta M, Sotozono C, Kinoshita S, Ikezawa Z. Japan Pharmacogenomics Data Science Consortium. A whole-genome association study of major determinants for allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. *Pharmacogenomics J*. 2013;13:60–9.
10. Koniwa N, Saito Y. Pharmacogenomics of severe cutaneous adverse reactions and drug-induced liver injury. *J Hum Genet*. 2013;58:317–26.
11. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, Kang DH, Gordon KL, Watanabe S, Nakagawa T, Lan HY, Johnson RJ. Hyperuricemia induces a primary renal arteriopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol*. 2002;282:F991–7.
12. Højeggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, De Faire U, Fyhrquist F, Ibsen H, Kristianson K, Ledeballe-Pedersen O, Lindholm LH, Nieminen, Omvik P, Oparil S, Wedel H, Chen C, Dahlöf B, LIFE Study Group. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. *Kidney Int*. 2004;65:1041–9.
13. Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, Streit J, Joseph-Ridge N. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005;353:2450–61.