Hyperuricemia Resistant to a Xanthine Oxidase Inhibitor, Topiroxostat: a Case Report

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Abstract

Hyperuricemia is a common complication of chronic kidney disease. Gout is a clinical symptom of hyperuricemia, and lowering serum uric acid concentration has been recommended to prevent its recurrence. We present a case whose hyperuricemia was resistant to a xanthine oxidase inhibitor, febuxostat, but not another inhibitor, topiroxostat, while both are presumed to inhibit the same enzymatic center of this rate-limiting enzyme for uric acid production. The different efficacy indicates that xanthine oxidase inhibitors are not interchangeable even among those acting on the same site of the enzyme.

Introduction

Hyperuricemia is a common complication of chronic kidney disease (CKD), because the kidney normally excretes around two-thirds of urate load [1, 2]. Gout is a clinical symptom of hyperuricemia, which typically presents acute onset monoarthritis at the first metatarsophalangeal joint in the foot [3]. Lowering serum uric acid concentration (sUA) has been recommended to prevent the recurrence of gout, and pharmacological sUA-lowering therapy is generally required, because dietary and lifestyle optimization can reduce sUA only slightly [2, 3]. Because of renal impairment, which weakens the efficacy of uricosuric agents, the agents that inhibit xanthine oxidase (XO), the rate-limiting enzyme for uric acid production, are generally used to lower sUA in hyperuricemic CKD patients [1, 2]. In this report, we present a case whose hyperuricemia was resistant to a XO inhibitor, febuxostat, but not another inhibitor, topiroxostat, while both are presumed to inhibit the same enzymatic center of XO.

Case Report

An 80-year-old man with chronic kidney disease (CKD) stage G4 had a gout attack, when his serum uric acid concentration (sUA) and creatinine concentration were 12.2 and 3.2 mg/dL, respectively (Table 1). After the symptom of gouty arthritis was relieved by glucocorticoid therapy, sUA-lowering therapy by oral administration of topiroxostat was started. However, even 2 months after the dose of topiroxostat had been increased to 60 mg/day, sUA did not decrease (Fig. 1); it was 10.8 mg/dL while it had been around 10.5 mg/dL before the gout attack. Then, febuxostat 40 mg/day was substituted for topiroxostat 60 mg/day. The substitution lowered sUA to 7.0 mg/dL by 1 month and further to 6.2 mg/dL by 2 months. During the treatment his serum creatinine concentration increased to 4.4 mg/dL, but renal replacement therapy was not started.

Table 1
Laboratory measurements at the gout attack

Blood cells	Serum chemistry
WBC ($10^3/\mu\text{L}$)5.8 (3.6 – 8.0)	Total protein (g/dL)7.5 (6.5 – 8.0)
RBC ($10^6/\mu\text{L}$)3.43 (4.1 – 5.6)	Albumin (g/dL)4.3 (3.8 – 4.6)
Hb (g/dL)11.1 (13.0 – 18.0)	BUN (mg/dL)79.9 (8.0 – 20.0)
Plt ($10^5/\mu\text{L}$)1.25 (1.2 – 4.0)	Creatinine (mg/dL)3.2 (0.6 – 1.2)
	Uric acid (mg/dL)12.2 (3.0 – 7.0)
	Sodium (mM/L)140 (136 – 146)
	Potassium (mM/l)4.5 (3.7 – 4.8)
	Chloride (mM/l)106 (98 – 108)
	Calcium (mg/dl)9.0 (8.2 – 10.8)
	Phosphate (mg/dl)4.2 (2.5 – 4.3)
Normal ranges are shown in parentheses.	
BUN, blood urea nitrogen; Hb, hemoglobin; Plt, platelet; RBC, red blood cell; WBC, white blood cell.	

Discussion

This report presented a case of hyperuricemia, which was resistant to a XO inhibitor, topiroxostat, but not another inhibitor, febuxostat. The different efficacy indicates that XO inhibitors are not interchangeable even among those acting on the same site of XO and that it is worth to try other inhibitors when one inhibitor is ineffective.

Topiroxostat is presumed to inhibit XO by forming a tight complex with molybdenum at the enzymatic center [4, 5]. Febuxostat is also presumed to inhibit the same enzymatic center [6]. It was reported that topiroxostat 60 mg/day provided sUA-lowering efficacy as well as febuxostat 40 mg/day in CKD patients [7]. It was also reported that topiroxostat 20 mg/day lowered sUA in most of the patients even with advanced CKD [8]. Thus, irrespective the stage of CKD, topiroxostat 60 mg/day is expected to lower sUA. However, while febuxostat 40 mg/day lowered the sUA of the present case, topiroxostat 60 mg/day did not lower the sUA; the level of sUA 2 months after the therapy by topiroxostat 60 mg/day did not differ from that before the gout attack.

The clinical course indicated that topiroxostat did not inhibit the XO of the present case while febuxostat did. We did not measure the blood concentration of topiroxostat and could not clarify whether topiroxostat was delivered to the XO. The topiroxostat resistance, however, is presumed to be attributable to either (i) topiroxostat was not delivered to the XO or (ii) the delivered topiroxostat did not inhibit the XO.

Some genetic mutation in either the topiroxostat transporters or the XO of the present case would have made the XO not inhibitable by topiroxostat.

In summary, XO inhibitors are not interchangeable even among those blocking the same site of XO. Their efficacy will differ between individuals depending on their delivery system and affinity for XO in each individual. Thus, it is worth to try other inhibitors when one inhibitor is ineffective.

Declarations

Authors' Contributions

T.K.: data acquisition and manuscript writing. S.Y.: data acquisition. M.T.: concept and manuscript writing.

Compliance with Ethical Standards

Conflict of interest: The authors declared that they have no conflict of interests.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

Informed consent: Informed consent was obtained from the patient reported.

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Figures

Figure 1

Levels of sUA. The horizontal axis indicates months after the gout attack. sUA, serum uric acid concentration.