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BRIEF COMMUNICATION

Treatment of two mitochondrial disease patients with a combination of febuxostat and inosine that enhances cellular ATP

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Abstract

Since mitochondria are energy-generating micro-organisms, most of the disorders in patients with mitochondrial diseases (mt-disease) are considered secondary to defects in ATP synthesis, although some other factors such as reactive oxygen species may be involved. A simultaneous oral administration of febuxostat and inosine was reported to elevate both hypoxanthine and ATP levels in peripheral blood. Based on those results, we attempted co-administration of febuxostat and inosine in two patients with mitochondrial disease: one patient with mitochondrial cardiomyopathy and the other patient with mitochondrial diabetes. In the former case, brain natriuretic peptide (BNP), which is a specific marker for heart failure, was decreased by 31%, and in the latter case, the insulinogenic index increased 3.1 times, suggesting the favorable action of the treatment. Considering that there is no effective treatment available for this disorder, the present therapy may be quite useful for the management of patients with mitochondrial diseases.

Mitochondrial disease (mt-disease) is a general term for genetic diseases caused by mutations of genes related to mitochondrial functions [1]. Clinical symptoms are widespread and involve the central nervous system, skeletal muscles, cardiovascular system, hearing loss and/or diabetes. Most of these disorders are secondary to defects in ATP synthesis [1], although some other factors such as reactive oxygen species may be involved. Various treatments have been attempted, but no therapy that is clearly effective has been available [2].

In healthy subjects, Kamatani et al. showed that a simultaneous oral administration of febuxostat, a drug for gout and hyperuricemia, and inosine elevates both hypoxanthine and ATP levels in peripheral blood [3]. Inosine is rapidly converted to hypoxanthine by purine nucleoside phosphorylase (PNP) and then metabolized via two steps to urate by xanthine oxidoreductase (XOR). When febuxostat, an inhibitor of XOR, is given together with inosine, serum hypoxanthine increases and is salvaged to IMP, and ATP levels are elevated [3]. If hypoxanthine is converted to xanthine, and finally to urate by XOR, it causes a lot of energy waste since de novo biosynthesis of one purine molecule requires seven ATP equivalents [4]. In an in vitro experiment, when human erythrocytes were incubated in saline with inosine without XOR inhibitor, because XOR is absent in human blood, decrease of ATP was suppressed [5].

Based on those results, we attempted co-administration of febuxostat and inosine in two patients with mt-disease: one patient with mt-cardiomyopathy and another with mt-diabetes.

Case 1 was an 80-year-old man with mt-cardiomyopathy. Severe heart failure and multiple premature ventricular contractions (PVC) were detected at 60 years of age. Direct sequencing of his mtDNA from the blood revealed a homoplasmic mutation (m.12192G > A) in the mitochondrial tRNA for histidine (*MT-TH*). Medications prescribed before the study, including $\alpha_1\beta$-adrenoreceptor blocker (Carvedilol®) and an anti-coagulant, were continued without changing the doses.

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Table 1 Data before and after treatment of a patient with mt-cardiomyopathy with febuxostat and inosine

	Before treatment	After treatment	Unit	Standard range
EKG	Atrial fibrillation, sporadic ventricular premature beats	Atrial fibrillation		
Echo-cardiogram	Normal	Normal		
Serum urate	3.04	1.29	mg/dL	3.7–7.0
BNP	295.1	204.4	pg/mL	<18.4
SBP	104	79	mmHg	
DBP	62	51	mmHg	
Pulse rate	76	66	per min	
ATP[a]	175.0	224.7	μM	
Hx[a]	2.6	16.8	μM	
X[a]	0.8	15.3	μM	

Hx: hypoxanthine, *X*: xanthine, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

[a]Values are those in the final solution [3]

Table 2 Results of 75 g OGTT before and after the treatment with febuxostat and inosine

		Before treatment	After treatment
Insulin (IRI) (μU/mL)	Before	0.55	0.62
	30 min	3.06	6.42
	60 min	4.94	7.25
	90 min	9.67	11.4
	120 min	8.29	16.1
Plasma glucose (PG) (mg/dL)	Before	80	85
	30 min	195	170
	60 min	311	262
	90 min	392	329
	120 min	434	395
Urine glucose (mg/dL)	Before	6	3
	60 min	208	4
	120 min	4050	1880
30 min ΔIRI/ΔPG (insulinogenic index)		0.022	0.068

We administered 20 mg febuxostat and 0.5 g inosine twice a day for 14 days. Throughout this study, the patient developed no symptoms. Both serum urate and BNP levels declined from 3.04 to 1.29 mg/dL and from 295.1 to 204.4 pg/mL (a 31% decrease), respectively (Table 1). Electrocardiogram showed that PVC disappeared, but atrial fibrillation remained. Systolic blood pressure and diastolic blood pressure declined without adverse events (Table 1). ATP, hypoxanthine and xanthine in the blood, determined by the methods previously described [3], increased by 1.3, 6.5 and 19.1 folds, respectively (Table 1).

Case 2 was a 48-year-old woman with mt-diabetes. She was diagnosed with gestational diabetes at 31 years of age and with type 2 diabetes at 33 years of age. She was revealed to have a heteroplasmic mutation (m.3243A > G) of the mt gene (*MT-TL1*) from the blood and started insulin injection therapy at 38 years of age. Medications prescribed before the study were continued with the same doses, and study treatment was given using the same protocol as case 1 without adverse event. The levels of serum urate and HbA_1c decreased from 7.7 to 2.4 mg/dL and from 8.2 to 8.0 %, respectively, and other data remained unchanged including serum creatinine level (0.83 mg/dL). A 75 g OGTT (Oral Glucose Tolerance Test) was performed on the first day, before the administration of the test drugs, and the last day of the trial. The OGTT revealed a decline of plasma glucose level from 311 to 262 mg/dL and from 434 to 395 mg/dL at 1 h and 2 h, respectively (Table 2), and an increase of plasma insulin level from 3.06 to 6.42, 4.94 to 7.25, and from 8.29 to 16.1 μU/mL at 30 min, 1 h, and 2 h, respectively. Insulinogenic index (ratio of insulin concentration at 30 min minus fasting insulin to the difference of glucose at the same times) improved from 0.022 to 0.068 (3.1 fold).

Our preliminary study suggests that simultaneous administration of febuxostat and inosine or a mixed drug containing both the compounds effectively and safely treat mt-diseases. XOR inhibitor other than febuxostat, such as allopurinol or topiroxostat, may substitute for febuxostat, and inosine may be replaced by inosinic acid or hypoxanthine.

Based on the June 2018 Integrated Mitochondrial Protein Index from MitoMiner [6], over 1600 proteins coded by chromosomal genes are known to be associated with mitochondria. Since humans have about 20,000 genes [7], that means that about 8% of all genes are associated with mitochondria and with energy. This suggests that many genetic diseases other than those defined as "mitochondrial disease" may be associated with mitochondrial dysfunction. Furthermore, there are many reports suggesting that common diseases, such as Alzheimer's disease [8–10] and Parkinson's disease [11], have mitochondrial dysfunction. Thus, the present treatment may be useful for many disease categories in which cellular-energy deficiency or mitochondrial dysfunction is involved. It is of interest that mitochondrial function was reported to decrease by 8% per 10 years of age [12], and aging is related to mitochondrial dysfunction [13].

Our therapy combining an XOR inhibitor and inosine, a purine nucleoside, is similar to the treatment for genetic deficiency of carbamoyl-phosphate synthetase 2 (CAD) that causes a deficiency of pyrimidine nucleotides [14]. Through treatment with oral uridine, a pyrimidine nucleoside, CNS

symptoms were dramatically improved in patients with CAD deficiency [14].

The limitations of our study are that only a very small number of the patients were treated, improvement of clinical manifestations was not confirmed and the effects on biomarkers may not be caused by the enhancement of ATP.

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Compliance with ethical standards

Conflict of interest NK is employed by and owns stock of StaGen Co. Ltd. The remaining authors declare that they have no conflict of interest.

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