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Open-label clinical trial of bezafibrate treatment in patients with fatty acid oxidation disorders in Japan

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ABSTRACT

Introduction: Fatty acid oxidation disorders (FAODs) are rare diseases caused by defects in mitochondrial fatty acid oxidation (FAO) enzymes. While the efficacy of bezafibrate, a peroxisome proliferator-activated receptor agonist, on the *in vitro* FAO capacity has been reported, the *in vivo* efficacy remains controversial. Therefore, we conducted a clinical trial of bezafibrate in Japanese patients with FAODs.

Materials and methods: This trial was an open-label, non-randomized, and multicenter study of bezafibrate treatment in 6 patients with very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency and 2 patients with carnitine palmitoyltransferase-II (CPT-2) deficiency (median age, 8.2 years; ranging from 5.8 to 26.4 years). Bezafibrate was administered for 6 months following a 6-month observation period. The primary endpoint was the frequency of myopathic attacks, and the secondary endpoints were serum acylcarnitines (ACs, C14:1 or C16 + C18:1), creatine kinase (CK) levels, degree of muscle pain (VAS; visual analog scale) during myopathic attacks, and quality of life (QOL; evaluated using validated questionnaires).

Results: The frequency of myopathic attacks after bezafibrate administration decreased in 3 patients, increased in 3, and did not change in 2. The CK, AC, and VAS values during attacks could be estimated in only three or four patients, but a half of the patients did not experience attacks before or after treatment. Changes in CK, AC, and VAS values varied across individuals. In contrast, three components of QOL, namely, physical functioning, role

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limitation due to physical problems (role physical), and social functioning, were significantly elevated. No adverse drug reactions were observed.

Conclusion: In this study, the frequency of myopathic attacks and CK, AC, and VAS values during the attacks could not be evaluated due to several limitations, such as a small trial population. Our findings indicate that bezafibrate improves the QOL of patients with FAODs, but its efficacy must be examined in future investigations.

1. Introduction

Mitochondrial fatty acid oxidation disorders (FAODs) are caused by defects in mitochondrial enzymes involved in fatty acid β-oxidation (FAO), which play an important role in energy production during periods when energy production from carbohydrates is reduced [1]. FAO enzymes include very long-, medium-, and short-chain acyl-CoA dehydrogenases (VLCAD, MCAD, and SCAD, respectively), trifunctional protein (TFP), carnitine-acylcarnitine translocase (CACT), carnitine palmitoyltransferase-II (CPT-2), electron transfer flavoprotein, and electron transfer flavoprotein dehydrogenase. Patients with FAODs exhibit various symptoms triggered by infection, diarrhea, long fasting, or muscular exertion [2]. FAODs are clinically classified into 3 types: (1) neonatal onset type, which develops during the neonatal period or early infancy with profound hypoglycemia, hepatic dysfunction, or cardiac failure and is often fatal; (2) infantile onset type (intermediate type), which exhibits intermittent attacks of lethargy, hepatic dysfunction, hypoglycemia, and occasionally encephalopathy or even sudden infant death; and (3) adult onset myopathic type, which involves episodic attacks of muscle weakness, myalgia, myoglobinuria, or rhabdomyolysis after school age [3]. Although no drug treatments are currently available for FAODs, avoiding long fasting, minimizing exercise, maintaining a low fat and high carbohydrate diet, and using medium-chain triglyceride oil for long-chain FAODs in the stable condition are used for prophylaxis against metabolic attacks. Further, early glucose infusion is recommended in acute phases such as pyrexia, diarrhea, or lethargy [4].

Bezafibrate [2-(p-(2-(p-chlorobenzamido)ethyl)-phenoxy)-2-methyl propionic acid] is a peroxisome proliferator-activated receptor (PPAR) agonist [5] that decreases human serum lipid levels [6,7]. Recent reports demonstrated that bezafibrate may represent a promising drug for FAODs by enhancing the transcription of several β-oxidation enzymes *in vitro* [8–11]. Moreover, the clinical efficacy of bezafibrate for CPT-2 or multiple acyl-CoA dehydrogenase (MAD) deficiencies was recently reported by French and Japanese groups, respectively [12–14]. Conversely, a 3-month, randomized, double-blind, crossover study involving a bezafibrate clinical trial in patients with CPT-2 and VLCAD deficiencies failed to demonstrate improvement in clinical symptoms or in some physical abilities [15]. Hence, the clinical efficacy of bezafibrate for FAODs is still controversial [16–18].

In this study, we evaluated the efficacy and safety of bezafibrate for treating patients with FAODs by a clinical trial resembling the study design of a previously reported French clinical trial [12].

2. Materials and methods

2.1. Design

This study was a non-randomized, uncontrolled multicenter, open-label trial.

2.2. Standard protocol approvals, registrations, and patient consents

This study was approved by the Institutional Review Boards (IRBs)

Table 1
Clinical features and genotypes of the patients before enrollment.

	VLCADD-1	VLCADD-2	VLCADD-3	VLCADD-4	VLCADD-5	VLCADD-6	CPT2D-1	CPT2D-2
Age	26 y	7 y	25 y	6 y	6 y	22 y	9 y	5 y
Sex	F	F	M	F	M	F	F	F
Diagnosis	VLCADD	VLCADD	VLCADD	VLCADD	VLCADD	VLCADD	CPT-2D	CPT-2D
Mutation	F113* K382Q	A333fs R450H	Untested Untested	R229X K382Q	L243F V547 M	E285G V400 M	R51G E174K	F383Y R477W
Onset age	1.5 y	4.11 y	5 mo	Around 1 y	3 y	Around 13 y	1.3 y	3.7 y
Diagnosis age	5 y	5 y	13 y	0 mo	3 y	22 y	3 y	8 mo
Body weight (kg)	56	24	58	20	21	47	35	17
Clinical features	Myalgia or fatigue	Myalgia	Myalgia or fatigue	Myalgia or fatigue	Myalgia or rhabdomyolysis	Myalgia or rhabdomyolysis	Myalgia	Rhabdomyolysis or hyper CK
Frequency of								
Severe attacks	20/year	3/year	0	Several times/year	1–2/year	5/year	Several times/year	1/year
Moderate attacks	50–60/year	4/year	0	12/year	0	7/year	Uncountable	0
Mild attacks	Almost every day	6/year	2/year	Uncountable	0	12/year	Uncountable	0
Treatments								
Carnitine (mg/day)	750 mg	None	400–600 mg	almost none	None	1800 mg	1000 mg	900–1800 mg
MCT oil/milk	None	None	Yes	None	Yes	None	Yes	None
Restriction of activity	Prolonged walk and standing	PE, exercise, and excursion	Airing	Unclear	None	None	None	None
Responsiveness of bezafibrate *in vitro*	Good	Good	Untested	Good	Good	Good	Good	Untested
CK baseline (IU/L)	1933 ± 1220	180 ± 104	768 ± 612	1112 ± 1253	81 ± 13	590 ± 660	1201 ± 20	308 ± 169
C14:1 baseline (μM)	10.41 ± 4.64	1.18 ± 0.60	3.27 ± 4.05	2.98 ± 0.88	1.37 ± 1.77	1.36 ± 0.85		
C16 + C18:1 baseline (μM)							8.52 ± 5.40	6.94 ± 5.70

y, year; mo, month; M, male; F, female; VLCADD, very long-chain acyl-CoA dehydrogenase deficiency; CPT-2D, carnitine palmitoyltransferase-2 deficiency; PE, physical education. Frequency of attacks and treatments were provided in the year prior to enrolment. Responsiveness of bezafibrate *in vitro* was evaluated using the *in vitro* probe acylcarnitine assay [8].