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Long-term major clinical outcomes in patients with long chain fatty acid oxidation disorders before and after transition to triheptanoin treatment—A retrospective chart review

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ABSTRACT

Background: Long chain fatty acid oxidation disorders (LC-FAODs) are caused by defects in the metabolic pathway that converts stored long-chain fatty acids into energy, leading to a deficiency in mitochondrial energy production during times of physiologic stress and fasting. Severe and potentially life threatening clinical manifestations include rhabdomyolysis, hypoglycemia, hypotonia/weakness, cardiomyopathy and sudden death. We present the largest cohort of patients to date treated with triheptanoin, a specialized medium odd chain (C7) triglyceride, as a novel energy source for the treatment of LC-FAOD.

Methods: This was a retrospective, comprehensive medical record review study of data from 20 of a total 24 patients with LC-FAOD who were treated for up to 12.5 years with triheptanoin, as part of a compassionate use protocol. Clinical outcomes including hospitalization event rates, number of hospitalization days/year, and abnormal laboratory values were determined for the total period of the study before and after triheptanoin treatment, as well as for specified periods before and after initiation of triheptanoin treatment. Other events of interest were documented including rhabdomyolysis, hypoglycemia, and cardiomyopathy.

Results: LC-FAOD in these 20 subjects was associated with 320 hospitalizations from birth to the end date of study. The mean hospitalization days/year decreased significantly by 67% during the period after triheptanoin initiation ($n = 15$; 5.76 vs 17.55 vs; $P = 0.0242$) and a trend toward a 35% lower hospitalization event rate was observed in the period after triheptanoin initiation compared with the before-treatment period ($n = 16$ subjects >6 months of age; 1.26 vs 1.94; $P = 0.1126$). The hypoglycemia event rate per year in 9 subjects with hypoglycemia problems declined significantly by 96% (0.04 vs 0.92; $P = 0.0091$) and related hospitalization days/year were also significantly reduced ($n = 9$; 0.18 vs 8.42; $P = 0.0257$). The rhabdomyolysis hospital event rate in 11 affected subjects was similar before and after treatment but the number of hospitalization days/year trended lower in the period after triheptanoin initiation ($n = 9$; 2.36 vs 5.94; $P = 0.1224$) and peak CK levels trended toward a 68% decrease from 85,855 to 27,597 units in 7 subjects with reported peak CK values before and after treatment ($P = 0.1279$). Triheptanoin was generally well tolerated. Gastrointestinal symptoms were the most commonly reported side effects.

Conclusions: This retrospective study represents the largest analysis reported to date of treatment of LC-FAOD with triheptanoin. The data suggest that triheptanoin improves the course of disease by decreasing the incidence and duration of major clinical manifestations and should be the focus of prospective investigations. Significant heterogeneity in the routine clinical care provided to subjects during the periods studied and the natural variation of clinical course of LC-FAODs with time emphasize the need of additional study of the use of triheptanoin.

Abbreviations: CACT, carnitine acylcarnitine translocase; CM, cardiomyopathy; CRF, case report forms; ECHO, echocardiography; ER, emergency room; LC-FAOD, long chain fatty acid oxidation disorder; MCT, Medium Chain Triglyceride; TFP, trifunctional protein; CK, creatine kinase; CPT, carnitine palmitoyltransferase deficiencies; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; LCHAD, long-chain 3-hydroxy-acyl-CoA dehydrogenase; VLCAD, very long chain acyl-CoA dehydrogenase.

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1. Introduction

Inherited autosomal recessive defects in the mitochondrial long-chain fatty acid oxidation pathways are collectively referred to as long-chain fatty acid oxidation disorders (LC-FAOD). LC-FAODs are caused by enzyme deficiencies of the carnitine cycle or the mitochondrial β-oxidation pathway that converts fatty acids into energy, leading to deficiencies in mitochondrial energy metabolism [1]. Partial or incomplete oxidation of fatty acids leads to accumulation of high concentrations of metabolic intermediates in blood and organs and potentially devastating systemic effects such as hypoglycemia and acidosis [2].

LC-FAODs are characterized clinically by episodic crises of energy metabolism, particularly during periods of physiologic stress, infection, or fasting. Symptoms vary by age of onset and the clinical phenotype evolves over time. Neonates and young children may exhibit hypoglycemia, hepatic dysfunction, rhabdomyolysis, and cardiomyopathy while adolescents and adults primarily experience exercise or stress-induced rhabdomyolysis, which may be severe [3].

The current standard of care for LC-FAOD is dietary management. Treatment may vary according to the specific disorder and the severity of the underlying enzyme deficiency, but may include a low fat, high carbohydrate diet, the avoidance of fasting, and supplementation with carnitine and/or medium even chain triglyceride (MCT) oil, along with aggressive treatment of co-morbid illness [4,5]. The effectiveness of therapies has largely been reported on a case-by-case basis with little information available from well-controlled clinical studies. A retrospective analysis of 187 clinically diagnosed patients with LC-FAOD concluded that mortality rates have not changed overall for patients during the past 30 years, even with an evolving standard of care, and overall there is greater than 50% mortality in each decade, with some indications having mortality in the 60–95% range during their period of review [2]. However, newborn screening and early treatment may reduce mortality and improve outcomes [6], although long-term experience has not yet been published. Despite diagnosis and treatment from the newborn period, one study demonstrated that FAOD subjects still had a major decompensation rate of ~25% in the two years after birth [7]. Thus, patients require better treatment options, particularly to prevent the major decompensation events that lead to hospitalization and major morbidity and mortality.

The primary objective of this study was to evaluate the impact of triheptanoin treatment on the major clinical manifestations of LC-FAOD by performing a comprehensive and systematic medical chart review of patients treated for up to 12.5 years with triheptanoin through a compassionate use program.

2. Patients and methods

2.1. Study population

Twenty patients with LC-FAOD (11 males, 9 females) of 24 total patients that were treated with triheptanoin long-term as part of a compassionate use program were included in a retrospective medical chart review (Table 1). Patients were treated at Children's Hospital of Pittsburgh of UPMC (University of Pittsburgh Medical Center, Pittsburgh, PA) with a majority of patients having transferred from Baylor Research Institute (Dallas, TX), but the subjects were originally identified by referrals for compassionate use from throughout the US. Patients with acute metabolic symptoms were treated emergently by the local metabolic specialist. All patients had a confirmed diagnosis of one of the LC-FAOD disorders: mitochondrial trifunctional protein (TFP) deficiency, carnitine palmitoyltransferase deficiencies (CPT II), very long chain acyl-CoA dehydrogenase (VLCAD) deficiency, isolated long-chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD) deficiency, or carnitine acylcarnitine translocase (CACT) deficiency. Written informed consent was obtained from participants or from a legally authorized representative for participants who were under the age of 18. The study was reviewed and approved by the Institutional Review Board at the University of Pittsburgh.

Table 1
Patient demographics and disease history.

Characteristic	N = 20
Age, years, median (range)[a]	12.7 (1.6 to 60.9)
Sex, female, n (%)	9 (45%)
Ethnicity/race	
White/non-Hispanic	19 (95%)
Other/Hispanic	1 (5%)
LC-FAOD diagnosis type, n (%)	
MTFP	2 (10%)
CPT1	0
CPT2	3 (15%)
VLCAD	9 (45%)
LCHAD	5 (25%)
CACT	1 (5%)
Family history of LC-FAOD, n (%)	9 (45%)
Age at symptom onset, median (range)	0 (0 to 9.75)
<1 year	16 (80%)
10 years	1 (5%)
Unknown	3 (15%)
Age at diagnosis	
≤1 year	14 (70%)
>1 year to ≤ 5 years	3 (15%)
>5 years to ≤ 10 years	1 (5%)
>10 years	2 (10%)
Method of diagnosis[b]	
Prenatal screening	2 (10%)
Newborn screening	9 (45%)
Acylcarnitine profile	15 (75%)
Skin biopsy	12 (60%)
Other	4 (20%)
MCT use	17 (85%)

[a] Age at time of chart review.
[b] Some patients were diagnosed by more than one method.

2.2. Data extraction and analysis

A systematic, protocol-driven, comprehensive medical chart review of patients' records was used to establish a clinical baseline on standard of care treatment and then document the clinical outcomes after initiating triheptanoin treatment. Data from 120 individual patient medical charts were extracted to approximately 1600 case report forms covering 330 patient-years of time. The median pretreatment period was 3.7 years (range 0.05–51.39) and the median triheptanoin treatment time was 8.7 years (range 0.5–12.5). Seventeen of the 20 subjects had 5 years or longer duration of treatment using triheptanoin.

Data collection and analysis focused on major clinical events including hospitalizations and emergency room admissions related to FAOD disease and related complications, including: 1) rhabdomyolysis, 2) hypoglycemia and 3) cardiomyopathy. Events that included documented *verbatim* terms from medical staff such as “rhabdomyolysis” or “hypoglycemia” were included even when a correlated lab result was not available. Number of hospitalizations (including emergency department visits), days of hospitalization, and laboratory values were abstracted. The number and severity of events [defined as creatine kinase (CK) levels > 5000 U/L] associated with rhabdomyolysis events occurring pre- and post-triheptanoin treatment initiation were compared. Hypoglycemia was not plausibly analyzed by glucose levels due to emergency interventions that affect glycemia during these medical events, however, when available, blood glucose levels < 60 mg/dL were recorded. For infants who received triheptanoin in the first six months of life (n = 4), the time period prior to initiation of triheptanoin treatment was not sufficient to enable an accurate comparison of events pre and post treatment, so analyses of infants were conducted separately for events of interest. Hospitalization event rates were calculated as the number of events occurring during the risk duration/length of risk duration in years. Pre-triheptanoin risk duration was calculated as

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