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Triheptanoin treatment in patients with pediatric cardiomyopathy associated with long chain-fatty acid oxidation disorders

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ABSTRACT

Long-chain fatty acid oxidation disorders (LC-FAOD) can cause cardiac hypertrophy and cardiomyopathy, often presenting in infancy, typically leading to death or heart transplant despite ongoing treatment. Previous data on triheptanoin treatment of cardiomyopathy in LC-FAOD suggested a clinical benefit on heart function during acute failure. An additional series of LC-FAOD patients with critical emergencies associated with cardiomyopathy was treated with triheptanoin under emergency treatment or compassionate use protocols. Case reports from 10 patients (8 infants) with moderate or severe cardiomyopathy associated with LC-FAOD are summarized. The majority of these patients were detected by newborn screening, with follow up confirmatory testing, including mutation analysis; all patients were managed with standard treatment, including medium chain triglyceride (MCT) oil. While on this regimen, they presented with acute heart failure requiring hospitalization and cardiac support (ventilation, ECMO, vasopressors) and, in some cases, resuscitation. The patients discontinued MCT oil and began treatment with triheptanoin, an investigational drug. Triheptanoin is expected to provide anaplerotic metabolites, to replace deficient TCA cycle intermediates and improve effective energy metabolism. Cardiac function was measured by echocardiography and ejection fraction (EF) was assessed. EF was moderately to severely impaired prior to triheptanoin treatment, ranging from 12–45%. Improvements in EF began between 2 and 21 days following initiation of triheptanoin, and peaked at 33–71%, with 9 of 10 patients achieving EF in the normal range. Continued treatment was associated with longer-term stabilization of clinical signs of cardiomyopathy. The most common adverse event observed was gastrointestinal distress. Of the 10 patients, 7 have continued on treatment, 1 elected to discontinue due to tolerability issues, and 2 patients died from other causes. Two of the case histories illustrate that cardiomyopathy may also develop later in childhood and/or persist into adulthood. Overall, the presented cases suggest a therapeutic effect of triheptanoin in the management of acute cardiomyopathy associated with LC-FAOD.

1. Introduction

Long-chain fatty acid oxidation disorders (LC-FAODs) represent a group of autosomal recessive inborn errors of metabolism with an estimated prevalence of ~1:17,000 in the US, based on newborn screening data. LC-FAOD are caused by defects in nuclear genes that encode six mitochondrial enzymes involved in the oxidation of long chain fats for energy during times of fasting and physiologic stress. The genes and their associated diseases include carnitine palmitoyl transferase 1 (CPT-I), carnitine palmitoyl transferase 2 (CPT-II), carnitine/acylcarnitine translocase (CACT), very long-chain acyl-CoA dehydrogenase (VLCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and mitochondrial trifunctional protein (TFP) deficiencies. As a result of the enzymatic block, partial or incomplete oxidation of fatty acids occurs, leading to accumulation of high concentrations of potentially toxic fatty acid intermediates and an energy deficit state in

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many organ systems. Management of LC-FAODs includes diligent avoidance of fasting combined with the use of low fat/high carbohydrate diets, carnitine supplementation in some cases, medium chain triglyceride (MCT) oil supplementation [1,2]. A comprehensive clinical survey over 30 years of experience and 187 cases at one center suggests LC-FAODs as a group have a mortality rate of 50% or higher when diagnosed symptomatically, despite increased awareness of the disorders and management over the last 2 decades [3]. Newborn screening and early treatment have reduced mortality, but carefully followed cohorts indicate major medical events continue to occur despite newborn screening diagnosis and management [1,2].

Patients with LC-FAOD present at any age with acute crises of energy metabolism and severe energy deficiency, even with treatment compliance rates of >80% [1,3]. The main presentations are characterized by involvement of the liver, skeletal muscle, or heart associated with hypoglycemia/liver dysfunction early in life, muscle weakness/rhabdomyolysis later in life, and episodic cardiomyopathy with or without arrhythmias at any age. The pattern and severity of organ involvement are generally not predictable based on the inherited defect [4–8] [9].

1.1. Cardiomyopathy in LC-FAOD

LC-FAODs display a varying degree of cardiac manifestation that likely reflects the heart's particular reliance on fatty acid oxidation for up to 90% of its energy. Studies in mouse models support the importance of fatty acid oxidation to cardiac function; VLCAD-deficient mice develop progressive cardiac dysfunction even without the trigger of catabolic situations [10]. Cardiomyopathy secondary to LC-FAOD is more likely to present in the first year of life than in older pediatric ages [11, 12] and can present as hypertrophic or dilated cardiomyopathy (DCM); arrhythmias are also common. In a study of 18 symptomatic VLCAD patients prior to newborn screening, infantile CM was the most common presenting phenotype [8]. In general, hypertrophic cardiomyopathy carries a higher risk of death and the rate of heart transplantation is greater for those who present as infants or with inborn errors of metabolism or with mixed hypertrophic and dilated or restrictive cardiomyopathy [13]. DCM is the most common form of cardiomyopathy in LC-FAOD [14], and is characterized by dilatation and impaired systolic contractile function. Patients with DCM may be asymptomatic or demonstrate physical examination findings of congestive heart failure depending on the degree of ventricular dysfunction. A 2-dimensional echocardiogram (2D ECHO) is the primary imaging modality to establish cardiac anatomy and function. Treatment may include diuretics, angiotensin-converting enzyme (ACE) inhibition, and beta-blockers; if these fail, treatment may be escalated to intravenous inotropic therapy, respiratory ventilation, and mechanical cardiac support, including extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VAD). Patients with refractory symptomatic heart failure are candidates for transplant.

1.2. Rationale for triheptanoin in the treatment of cardiomyopathy associated with LC-FAOD

Traditional care for LC-FAOD includes supplementation with MCT oil, containing predominantly eight and ten carbon triglycerides. Since the long-chain fatty acid oxidation enzymes are not required to metabolize MCT, they can bypass the primary metabolic defect providing acetyl-CoA for the Krebs cycle. However, the Krebs cycle requires both even and odd chain intermediates to function, and thus may become secondarily impaired with this therapy, as observed directly in the heart of a murine FAOD model during heart failure [15]. The energy deficiency is accentuated by the need for aggressive gluconeogenesis with severe hypoglycemia and depletion of glycogen, which has the potential to further drain TCA cycle intermediates to feed the gluconeogenesis pathway.

Triheptanoin is an investigational drug comprised of a highly purified, pharmaceutical-grade, synthetic medium odd chain (C7) triglyceride. It has also previously been used in a less purified food grade [15]. It is initially catabolized in the gut to free heptanoate that can diffuse across membranes to enter cells. Heptanoyl-CoA is then metabolized by medium chain fatty acid oxidation enzymes to acetyl- and propionyl-CoA, as well as 4- and 5-carbon ketone bodies (Fig. 1). Propionyl-CoA is an anaplerotic molecule that restores the balance of the Krebs cycle intermediates pool via conversion to succinyl-CoA [15]. The restoration of Krebs cycle function improves flow of electrons to the mitochondrial respiratory chain recovering ATP production [16].

The potential for triheptanoin to provide both acetyl-CoA and anaplerotic substrates for the Krebs cycle as well as the known reliance of the heart on fatty acid oxidation for energy, provides a biochemical rationale to investigate treatment in pediatric cardiomyopathy including patients whose symptoms have progressed despite treatment with MCT. The first patient treated with triheptanoin, a young girl with VLCAD deficiency and chronic and recurrent cardiomyopathy (case 8 in this report), showed sustained cardiac improvement after transitioning to triheptanoin [17]. In a retrospective study, medical records from 14 patients ranging from 1.5–35 years of age with a history of cardiomyopathy who were treated with triheptanoin on a compassionate or emergency use basis were reviewed [5]. Following triheptanoin treatment, all improved or had stable ECHO parameters except one patient who required subsequent heart transplant. This manuscript reviews 10 cases (including the previously reported case 8) that further support the efficacy of triheptanoin for the treatment of severe cardiomyopathy due to LC-FAOD.

2. Materials and methods

2.1. Methodology

The reported case histories are from all patients treated with investigational triheptanoin for whom clinical data were provided by the treating physicians as of September 2015. The series includes patients with VLCAD (n = 4), CACT (n = 2), TFP (n = 2) and LCHAD (n = 2). Case 8 was previously reported after the original initiation of triheptanoin (at age 6 years) [17], and with case 10 in a retrospective chart review study [5]. The current case reports provide additional information on these patients.

Informed consent was obtained from the parent or legally authorized guardian prior to administration of triheptanoin. Triheptanoin was provided on a compassionate use basis upon request by the treating physicians, approval of the local institutional review board, and an emergency Investigational New Drug approval by the US Food and Drug Administration or enrollment in a compassionate use study. Of the 10 patients with cardiomyopathy presenting in childhood, 6 were treated under emergency INDs (US FDA) and 4 were enrolled in a compassionate use clinical program (JV).

Assessments such as ECHO were performed at multiple institutions with variable protocols according to local standards.

2.2. Treatment regimen(s)

Patients were provided with triheptanoin as a pharmaceutical-grade investigational product supplied by Ultragenyx Pharmaceutical, Inc. (Novato, CA USA), supplied as a clear and colorless to light yellow oil intended for oral administration. It is a purified, synthetic triglyceride compound manufactured by chemical synthesis from glycerol and heptanoic acid, and manufactured in accordance with Current Good Manufacturing Practice regulations, applicable International Conference on Harmonisation guidelines, and regional regulations. Historically, patients 8 and 10 were treated initially with a food-grade oil (Sasol, Germany) at the time of presentation, but were switched to pharmaceutical grade investigational product when it became available.