Response to Compassionate Use of Triheptanoin in Infants With Cardiomyopathy Due to Long Chain Fatty Acid Oxidation Defects (LC-FAODs)

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INTRODUCTION

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. The most severe LC-FAOD phenotypes may present in early infancy, when energy needs are higher, with severe life-threatening cardiomyopathy, arrhythmia, heart failure, hypoglycemia, hepatic dysfunction and rhabdomyolysis[1].

Medium chain triglycerides are transported directly into the mitochondrion, thus bypassing the carnitine cycle and long chain beta-oxidation pathways. Standard treatment for LC-FAODs has been a low-fat, high carbohydrate diet, supplemented with medium even chain triglycerides (MCT), which are ultimately catabolized to ketones for energy production via the Tricarboxylic Acid Cycle (TCA)[2]. Morbidity and mortality remain high despite standard treatment[3]. Animal studies have shown that the heart especially has a high energy requirement, much of which is provided by ketones, and depletion of the TCA cycle (cataplerosis) may contribute to the pathogenesis[4]. Triheptanoin (UX007) is an investigational, specially designed synthetic medium odd chain (C7) triglyceride that is catabolized to ketones, and also provides propionyl CoA, an anaplerotic molecule that replaces the deficient TCA cycle intermediates, resulting in glycogen sparing and net production of glucose, and which may provide a novel energy source for the treatment of LC-FAOD.

Five compassionate use cases are described demonstrating the potential efficacy of triheptanoin for the treatment of severe cardiomyopathy due to LC-FAODs presenting in the first year of life.

Key clinical features are shown in Table 1.

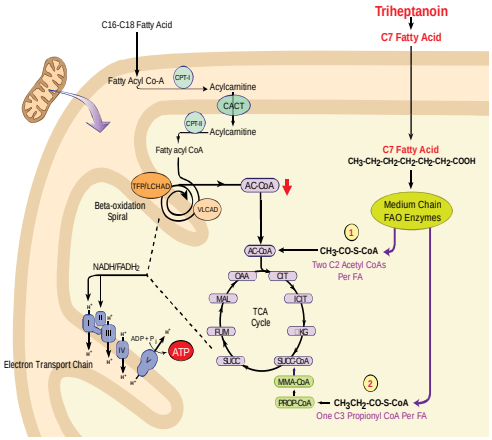

Table 1

Patient	Diagnosis	Mutations	Age / Symptoms at First Presentation	Prior Treatment with MCT	Age at Treatment with Triheptanoin	Ejection Fraction Pre Triheptanoin	Ejection Fraction Post Triheptanoin	Time on Treatment *
1	VLCAD	c.1678+3_1678+6 del AAGT c.1878G>A	Neonatal hypoglycemia 3 months cardiac dysfunction	Yes	7 months	N/A	63%	36 months ongoing
2	VLCAD	Homozygous truncating mutation	Neonatal hypoglycemia Cardiac dysfunction	Yes	6 months	39%	69%	10 weeks stopped
3	TFP	c.1165A>G c.1289T>C	Neonatal hypoglycemia	Yes	8 months	44%	52%	25 months ongoing
4	LCHAD	1528G>C 1528G>C	10 months Acute cardiomyopathy	Yes	10 months	22%	33%	11 months ongoing
5	CACT	c.84delT del+3p21.31	Neonatal hypoglycemia Cardiac dysfunction	Yes	10 months	21%	71%	9 months ongoing

*at time of data collection, July 2015

METHODS

Clinical data were provided by the treating physicians for patients with Very Long Chain Acyl CoA Dehydrogenase Deficiency (VLCAD) (n=2), Carnitine-Acyl Carnitine Translocase Deficiency (CACT) (n=1), Trifunctional Protein Deficiency (TFP) (n=1) and Long Chain Hydroxy Acyl CoA Dehydrogenase Deficiency (LCHAD) (n=1).

All patients were detected by newborn screening and managed with standard treatment, including MCT. Triheptanoin was provided on a compassionate use basis upon request by the treating physicians, approval of the local institutional review board, and emergency Investigational New Drug (eIND) approval by the US Food and Drug Agency.

RESULTS

Case 1: VLCAD

A female patient presented with neonatal hypoglycemia (blood glucose level of 5 mg/dL; 0.3 mmol/L) and metabolic acidosis that improved with intravenous dextrose. Newborn screening results were positive for VLCAD, later confirmed by mutation analysis that showed 2 previously unreported mutations, c.1678+3_1678+6 del AAGT/ c.1878>A, predicted to be deleterious. The patient was managed with MCT enriched formula.

Biventricular hypertrophy was observed at age 3 weeks. At age 3 months, the patient was noted to have moderate left ventricular hypertrophy (LVH); at 7 months she was hospitalized with severe LVH, pericardial effusion, cardiogenic shock, and ascites. The initial 2D ECHO study was limited and does not provide an Ejection Fraction (EF) value. At this time heart transplant was considered but not pursued. A subsequent 2D ECHO assessment revealed poor LV function and Shortening Fraction (SF) of 35%. Due to the limited response to standard IV dextrose and pressor treatment, the potential of triheptanoin therapy was explored. The patient was started on triheptanoin resulting in a rapid clinical response of cardiac function over 2-3 days; the next available 2D ECHO report, 3 weeks after starting triheptanoin, showed an improved EF of 63% and mild LVH.

A subsequent 2D ECHO assessment, 3 months after starting triheptanoin, was normal. At the time of this report, the patient continues on triheptanoin treatment and cardiac function remains normal. No significant tolerance issues have been reported.

Case 2: VLCAD

A male patient presented in the newborn period with hypoglycemia and cardiac dysfunction, which gradually improved on MCT-containing formula. The newborn screening result was positive for VLCAD confirmed by mutation analysis for a homozygous truncating mutation, predicted to be severe. At age 6 months he presented with acute viral symptoms (adenovirus and rhinovirus positive) to the Emergency Department and suffered cardiac arrest requiring approximately 45 minutes of resuscitation.

The patient was noted to have severe dilated cardiomyopathy and was placed on Extracorporeal Membrane Oxygenation (ECMO) for 20 days, as well as standard cardiac pressors. MCT was given intermittently because of concern for gastrointestinal absorption. Following evaluation, the patient was not considered suitable for a heart transplant. The only available 2D ECHO report showed an EF of 39%. On Day 18 of the hospitalization the patient was started on triheptanoin with the dose ranging from 2.6-3.3 g/kg/day, and was weaned from ECMO 2 days later. The patient continued to make clinical improvement despite concerns for absorption of enteral feeds with triheptanoin and intermittent cessation of feeds due to vomiting and fasting for procedures (e.g. IV line placement).The patient experienced another acute infection (rotavirus) and a reaction to routine immunizations, with rhabdomyolysis, but stable cardiac function.

Eight weeks after starting triheptanoin the patient was discharged and sent home. He was hospitalized again 3 days later with rhabdomyolysis secondary to rhinovirus infection. Cardiac status remained stable, with 2D ECHO report of mild LV dysfunction and mild-moderate cardiomyopathy. Two weeks later, triheptanoin was discontinued at the request of the parents because of ongoing gastrointestinal symptoms. A follow up 2D ECHO 1 month later showed an EF of 69%.

Case 3: TFP

A female patient presented in the neonatal period with hypoglycemia (37 mg/dL, 2.1 mmol/L) that responded to treatment with high dextrose IV infusion and MCT formula. Newborn screening was positive and mutation analysis confirmed the diagnosis of TFP deficiency with heterozygous HADHB mutations: c.1165A>G/c.1289T>C. The second mutation has been previously associated with lethal cardiomyopathy.

On routine follow up 2D ECHO evaluation, at age 8 months, the patient had significant LVH and an EF of 44%. Due to concern for impaired cardiac function and the potential for continued deterioration, at age 9 months, the patient was started on triheptanoin at 1.5 g/kg/d. At follow up 3 weeks later, the EF was 52%. The patient has had intermittent mild decrease of EF associated with intercurrent viral infections, including one overnight hospitalization for elevated CK, with subsequent recovery.

At age 18 months the patient had normal motor function, speech and language development and the most recent EF was 67%. The triheptanoin dose is 2g/kg/d. No significant tolerance issues were reported.

Case 4: LCHAD

A female patient presented at age 10 months with severe cardiomyopathy and heart failure, with 2D ECHO EF 27%. Soon afterwards the patient developed a brady-arrhythmia and cardiac arrest.

Prior history was unremarkable. She was detected by newborn screening and mutation analysis showed homozygosity for the common LCHAD mutation, 1528G>C. She was managed on MCT formula.

Following resuscitation the patient was started on ECMO and continued for 19 days. Treatment included nasogastric tube MCT (with intermittent interruptions due to poor absorption), parenteral nutrition with 30% dextrose, an investigational intravenous MCT 10%/LCT 10% emulsion, and cardiac pressor drugs. The patient was evaluated and deemed unsuitable for heart transplant. Due to lack of improvement in cardiac status and a 2D ECHO EF of 22%, the patient was started on triheptanoin (4g/kg/day) on day 16 of hospitalization. Three days later the patient was weaned from ECMO and showed gradual improvement in cardiac function, with an EF of 33% at discharge. Triheptanoin treatment continues at age 11 months. There have been no further metabolic decompensations, and the most recent EF was 55%. There have been no adverse drug reactions.

Case 5: CACT

A female patient presented at age 10 months with severe cardiomyopathy with heart failure and ascites, due to an acute viral gastroenteritis and dehydration. The patient developed cardio-respiratory arrest and was managed with cardiac pressors, IV high concentration dextrose. ECMO was unable to be initiated because of her very poor clinical status and inadequate vascular access.

Prior history was significant for presentation at 23 hours of life, with severe hypoglycemia, hypothermia, hyperammonemia, increased CK and 2D ECHO evidence of right ventricular hypertrophy. Management consisted of standard treatment, including high dextrose infusion and MCT formula. Newborn screening was positive and mutation analysis confirmed CACT with c.84delT (a previously reported deleterious mutation)/del+3p21.31. At age 6 months, the patient had an acute decompensation with severe cardiomyopathy, managed with ECMO and MCT supplements, and gradually recovered.

Due to severe cardiac failure and lack of response to maximal pressor drug support and gastrostomy infusion of MCT, the patient was started on triheptanoin at 4g/kg/day. The pre-treatment EF was 21% and within 2-3 days improved to 71%. The patient was weaned from all pressor support and discharged after 3 weeks. A subsequent hospitalization was necessary for c. difficile colitis, with very frequent stools and mild fever, likely secondary to previous antibiotic treatment, treated with metronidazole. She had mild elevation of ammonia (109 uM/L, normal < 30 uM), which responded to IV dextrose fluids. Other metabolic parameters, including cardiac function were within normal limits. At the time of this report treatment with triheptanoin continues at a dose of 4 g/kg/d without significant intolerance.

CONCLUSION

Infants with LC-FAODs and cardiomyopathy continue to suffer significant morbidity and mortality despite management with current standard of care, including medium even chain triglycerides. Treatment with triheptanoin, a novel investigational medium odd chain fatty, acid may provide alternative substrate replacement due to its ketogenic, gluconeogenic and anaplerotic properties. The presented case histories demonstrate a potential therapeutic effect of triheptanoin in the management of cardiomyopathy associated with LC-FAODs. Three additional severe cases have been identified and treated successfully with triheptanoin. Further studies are warranted to confirm these initial promising findings.

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