Response to Compressive 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 highest, with severe life-threatening cardiomyopathy, arrhythmia, heart failure, hypoglycemia, hepatic dysfunction and myopathy.

Medium chain triglycerides are transported directly into the mitochondria, 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 chain triglycerides (MCT), which are readily converted to ketones for energy production via the Tricarboxylic Acid Cycle (TCA). Mortality and morbidity remain high despite standard treatment1. 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 pathogenesis2. Triheptanoin (Udoxid) is an investigational, specially designed synthetic medium odd chain (C7) triglyceride that is carboxylated to ketones, and also provides propionic acid, an anaplerotic molecule that replaces the deficient TCA cycle intermediates, resulting in an increase in ketogenesis 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.

METHODS

Clinical data were provided by the treating physicians for patients with Long Chain Acyl CoA Dehydrogenase Deficiency (LC-ACD) (n=3), Camptome-Camptome Transverse Disacia (CACT) (n=1), Triheptanoin Proton Deficiency (TFP) (n=1) and Long Chain-Hydratase Acyl CoA Dehydrogenase Deficiency (LCHAD) (n=1).

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 3 previously unreported mutations; c.1678+3_1678+6delATG, c.1978A>T and c.1980C>T. The patient was noted to have moderate left ventricular hypokinesis (LHV); at 7 months she was hospitalized with severe LHV, peripheral edema, cardiomegaly, shock, and acidosis. The initial 24-hour ECHO was limited and did 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 15%. 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 LHV. After 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 adverse events have been reported.

Case 2: VLCAD

A male patient presented in the neonatal 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 that showed a novel c.828delA mutation. The patient was noted to have severe dextrocardia 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 impaired cardiac function and the potential for continued deterioration, at age 9 months, the patient was started on triheptanoin (4g/kg/day) on day 16 of hospitalization. Three days later the patient was weaned off MCT, the patient was started on triheptanoin at 4g/kg/day. The pre-treatment EF was 21% and within 2-3 days the EF was 55%. There have been no adverse drug reactions.

Case 3: TFP

A male patient presented in the neonatal 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 that showed a novel c.828delA mutation. The patient was noted to have severe dextrocardia 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 impaired cardiac function and the potential for continued deterioration, at age 9 months, the patient was started on triheptanoin (4g/kg/day) on day 16 of hospitalization. Three days later the patient was weaned off MCT, the patient was started on triheptanoin at 4g/kg/day. The pre-treatment EF was 21% and within 2-3 days the EF was 55%. There have been no adverse drug reactions.

Case 4: LCHAD

A male 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 homozygous 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 cardiopulmonary resuscitation. 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 CR 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 a c.845C>T (a previously reported deleterious mutation) in C32.1. 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 3-3.5 days improved to 71%. The patient was weaned from all pressor support and discharged after 3 weeks. A subsequent hospitalization was necessary for c.845C>T, with very frequent obtunds and mild fever, secondary to pulmonary embolism, treated with heparin. She had mild elevation of ammonia (109 uM/L, normal < 30 uM/L), 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 4g/kg/day without significant side-effects.

CONCLUSION

Infants with LC-FAODs and cardiomyopathy continue to suffer significant morbidity and mortality despite management with current standard of care, including medium odd 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.

REFERENCES


Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Mutations</th>
<th>Age (months)</th>
<th>VLCAD (EF)</th>
<th>TFP (EF)</th>
<th>LCHAD (EF)</th>
<th>CACT (EF)</th>
<th>Time on Triheptanoin</th>
<th>Time on Triheptanoin</th>
<th>Time on Triheptanoin</th>
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<tbody>
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<td>1</td>
<td>VLCAD</td>
<td>c.1678+3_1678+6delATG, c.1978A&gt;T, c.1980C&gt;T</td>
<td>3</td>
<td>69%</td>
<td>63%</td>
<td>63%</td>
<td>71%</td>
<td>33 months</td>
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<td>25 months</td>
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<td>2</td>
<td>VLCAD</td>
<td>Homozygous 1528G&gt;C mutation</td>
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<td>TFP</td>
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<td>68%</td>
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*at time of data collection, July 2015