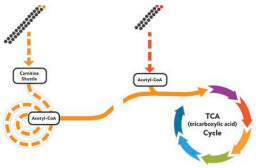
EXPERT PERSPECTIVES:

BRIDGING GAPS, OPTIMIZING TREATMENT IN ADULTS WITH LC-FAODS



Editor's Note: This is a transcript of a presentation on October 18, 2024. It has been edited and condensed for clarity.
To obtain credit for participation CLICK HERE

Module 1: Understanding Long-Chain Fatty Acid Oxidation Disorders

Jerry Vockley, MD, PhD: Let's start off with some introduction on long-chain fatty acid oxidation disorders (LC-FAODs). These are rare metabolic conditions. They're caused by genetic defects or variants in the genes that encode the enzymes required for fatty acid oxidation and these defects lead to a hindrance of the conversion of stored fats into energy during times of fasting or high-energy demands, such as exercise or illness. The end result is both an energy deficit and the accumulation of toxic intermediates that can lead to organ dysfunction.

I mentioned that these are genetic disorders, and they are all inherited in an autosomal recessive fashion. So, in other words, both parents have to be a carrier of the disease and one quarter of the time, they will pass the disorder on to a child.

This figure demonstrates the important energy interactions that you'll need to know about to understand disorders of long-chain fatty acid oxidation. Long-chain fatty acid oxidation occurs in the mitochondria and there are 3 interacting pathways that are necessary for this energy generation to be efficient. First of all, the long-chain fats, when they're mobilized from our fat stores during fasting or stress, are transported from the bloodstream into the cell. Once they are in the cell, they're activated to a form that is called an acyl-coA. Acyl-coA, at least the long-chain ones, can't get directly into mitochondria and so they use something called the carnitine shuttle. Carnitine binds to the acyl-coA, it's imported into the mitochondria using 3 enzymatic steps, abbreviated CPT I, CACT, and CPT II. And that releases the carnitine to go back out in the cytoplasm and do another cycle of import and the acyl-coA, the activated fat, is now inside the mitochondria.

Once in the mitochondria, acyl-coA undergoes 4 steps that lead to the release of 2 energy molecules, called reducing equivalents, as well as an acetyl-coA, a fat that's been chain-shortened by 2 carbons. That's what an acetyl-coA is. The reducing equivalents are the fuel for oxidative phosphorylation, that's the cycle in the cell that makes adenosine triphosphate (ATP) while the acetyl-coA can enter a third metabolic pathway, called the TCA cycle, tricarboxylic acid cycle. That cycle, in turn, generates more reducing equivalents for oxidative phosphorylation and the generation of ATP. So, when this cycle doesn't work, you get a deficit of ATP production, the metabolic fuel of the cell.

What are the consequences of this reduction in ATP? Well, you need ATP for all of your cellular functions, and so all of them can be affected, and the high energy organs are the ones that are affected the most. The end result is a decrease in the production of ketones, that's the end product of fatty acid oxidation, the acetyl-coA goes to make ketones, and it's that alternative fuel that you can use to glucose when you're fasting. You have a decrease in some of the intra-TCA cycle substrates and this can lead to further problems in energy generation, and without ATP, you can't make glucose. Gluconeogenesis is the process that the body uses when you're fasting to keep your glucose levels normal and, without ATP, you can drop glucose production.

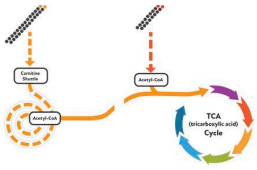
Historically, these disorders were identified in critically ill children or adults and, in the adult population, this can still be true. Fortunately, we now identify all of these disorders by newborn screening and so it's becoming increasingly rare, at least in developed countries, with expanded newborn screening, to identify these individuals symptomatically. Rather, we get them in the newborn screening before they become symptomatic. That screening typically happens at about 24 to 48 hours of age, and this is before all the most serious or severe forms of the disease occur. The follow-up testing can be accomplished before the baby goes home or after the baby goes home if the newborn screen hasn't come back yet or the baby's home quickly and the definitive diagnosis typically requires additional evaluation and testing. That's done through a metabolic physician. In the United States, that is a geneticist with specific training in metabolic disease. And once that diagnosis is confirmed, the patient can be treated.

Now, keep in mind that while newborn screening identifies most cases of fatty acid oxidation disorders there are mild versions that can be missed, and so never assume that a patient who has symptoms consistent with a fatty acid oxidation disorder doesn't have it because they've had newborn screening. Further testing is always necessary when symptoms arise and especially in adults because newborn screening for these disorders has only been in place about 20 or 25 years in most states. And so, the adults might not have been screened.

Just a few facts about LC-FAODs. About 100 newborns a year born in the United States and that's based on an incidence of somewhere around 1 to 15 cases per 100,000 births worldwide. In the US, it's closer to that more frequent number. This accounts in the United States to about 2 hospitalizations a year at a mean of 17.5 days. A significant morbidity.

The acute and chronic symptoms are important to understand here because both can be problematic. Acutely, they're related to the loss of energy and you don't always understand what is causing them to happen. Sometimes it's an illness, but sometimes you can't identify it. They're very difficult to predict. You just don't know when they're going to happen. Over the age of an individual, we have very severe newborns, but there are milder forms, as I said, that don't evolve until adulthood and the symptoms evolve over time, and we'll see that in a second. But importantly, these are episodic diseases. There may be some chronic, consistent findings, but they manifest during times of high energy need.

I mentioned that these are symptoms that develop over time and change over time. Low blood sugar, hypoglycemia with or without



high ammonia, and some liver dysfunction is most common in the newborn period. In adults, it's much more common to see muscle weakness and there's a period between about 6 years and early adolescence when they transition from one form to the other. Cardiomyopathy with heart muscle damage can occur at any age.

There are some additional signs to keep in mind with some of these disorders. Retinopathy and peripheral neuropathy are specific to 1 of the disorders in this pathway, called trifunctional protein deficiency (TPP) or 1 of the individual activities of the trifunctional protein, long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHAD). Those individuals can also have some gastrointestinal (GI) symptoms. Cognitive issues fortunately are not common, and if they occur, they're usually the result of secondary neurologic damage that occurs during an episode of hypoglycemia, hypoxia, or hyperammonemia.

Module 2: Historical Treatment & Introduction of Triheptanoin

Sandy van Calcar, PhD, RD, LD: I will start with some historical treatment that we typically use for patients with LC-FAODs. We primarily focus on both nutritional and symptomatic management and, for dietary modifications, one of the things we want to do is to prevent prolonged fasting to reduce the risk of metabolic crises.

When patients are fasting, they will increase the need to use their fatty acid stores in adipose tissue which will increase the risk for developing symptoms associated with these disorders. We typically want to limit long-chain fat to 10% to 35% of total energy intake. Long-chain fats are the fats that are found in foods. How strict we need to be with limiting these long-chain fats depends on the disease severity. Those with more severe forms will limit the fat intake from their diet to a stricter degree than those with milder forms of these disorders.

We also use medium-chain triglycerides, abbreviated here as MCT, and again, it depends on the severity of the disorders how much MCT we will add to their diet. Those with mild or moderate forms of these disorders, we often have a 50/50 split between dietary fat and MCT sources. With severe forms of these disorders, we will give more MCT, typically a 2:1 ratio with MCT to long-chain fat intake.

Some additional information about medium-chain triglyceride supplementation. The reason we use MCT is that medium-chain triglycerides are able to bypass the defective enzymes in long-chain fatty acid-beta oxidation. Medium-chain triglycerides can diffuse across the mitochondrial membrane without needing carnitine transport. They will enter beta-oxidation after the long-chain fatty acid enzymes and will be metabolized using medium-chain and short-chain acyl-coA dehydrogenase enzymes which are unaffected in these disorders. MCT doses and long-chain fat rarely exceed 35% of total energy intake for adults, given their often inability to tolerate really high doses of medium-chain triglycerides.

Triheptanoin is FDA-approved for the treatment of patients with LC-FAODs. Triheptanoin itself is a medium-chain triglyceride and it's indicated as a source of calories and fatty acids for the treatment of adults and pediatric patients with molecularly-confirmed LC-FAODs.

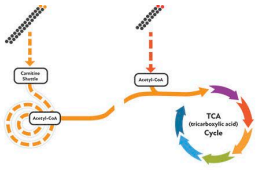
Triheptanoin provides an alternative energy source that bypasses the metabolic block in LC-FAODs. The traditional medium-chain triglycerides, which are indicated here as C8, traditional MCT is typically fatty acids of 8 carbons or 10 carbons long. This traditional MCT will be broken down through beta oxidation to produce acetyl-coA. Acetyl-coA is a 2-carbon fatty acid which will enter the TCA cycle to produce energy and be used in other pathways. The difference with triheptanoin is that it is a fatty acid with only 7 carbons and, as triheptanoin goes through beta oxidation, it will be broken down to produce 2 acetyl-coA, but leave a 3 carbon propionyl-coA. That 3 carbon propionyl-coA will go through a few other additional enzymes, producing methylmalonyl-coA. Methylmalonyl-coA will be converted to succinyl-coA and enter the TCA cycle at a later point in the TCA cycle. This allows production of fatty acids that can enter the TCA cycle at different points and has an anaplerotic effect, meaning that the TCA cycle will produce energy more efficiently, allowing for improved ATP production and gluconeogenesis, protein synthesis, and more efficient rate than the traditional 8-carbon medium-chain triglyceride.

Module 3: Optimizing Triheptanoin Therapy

Jerry Vockley, MD, PhD: We're going to spend some time now talking about the clinical use of triheptanoin, the trade name for that is Dojolvi, so you'll hear it referred to as that as well. Let's talk a little bit about some of thestudies that helped get triheptanoin approved. First of all, there was a head-to-head, double-blind comparison of triheptanoin and C8 trioctanoin in patients with LC-FAODs. These were all adults. It was a double-blind, randomized, controlled trial with 32 subjects with a variety of long-chain defects and it was a 4-month diet intervention containing 20% of total daily energy from either C7 or C8. These patients were well at the time and so there was not a lot of clinical information to collect. These patients were admitted to the hospital and then they had some sophisticated physiologic testing to look at muscle and heart function.

What was demonstrated was that the left ventricular ejection fraction increased by 7.4% in the C7 group compared to the C8 group. C7 is another shorthand for triheptanoin. The left ventricular wall mass also decreased in that group by about 8% and it increased by 15% in the trioctanoin group. This was a significant change between the 2 groups. The maximum heart rate, as an indicator of work, was almost 7 beats per minute lower in the C7 group during exercise testing. There was no significant difference in total energy expenditure. Overall, these patients had better heart function after 4 weeks on triheptanoin vs trioctanoin. And keep in mind that these patients were well, so there were no ill patients in the study.

There were, however, the anticipated hospitalizations due to intercurrent illnesses and there were 7 hospitalizations for acute rhabdomyolysis in both of these groups, indicating that they were about the same. Most of the adverse events that were reported



were mild with no real clinical significance or significant difference between the 2 groups. And these included intermittent muscle pain, fatigue, mildly elevated creatine kinase levels, things that we see in this patient population all along. And while both of these preparations can cause some GI upset, there was no significant difference between the incidence in the 2 groups.

Moving to the pivotal trial that was performed for approval of the drug, this was a single-arm, open-label, phase 2 study that enrolled patients with CPT-II, VLCAD, LCHAD and TFP deficiencies who had significant symptoms despite stable treatment. This trial was looking at a group of affected individuals who were having problems, unlike the previous study. After 4 weeks, all of these patients who were on MCT oil were switched to triheptanoin and they were titrated to get their calories between 25% and 35% from the triheptanoin. These patients exhibited a 28% improvement in distance walked in 12 minutes at week 18. They showed an exercise tolerance of 60% increase in watts generated at week 24 and, in an outcome study, they showed significant improvement in adult physical and mental scores with no change in the pediatric population patients who were in here.

From the standpoint of safety, adverse events were seen in 62% of these. These were mild to moderate, mostly they were GI related, however there was 1 gastroenteritis that was designated as serious and 1 patient who discontinued the study due to moderate diarrhea.

Now, that was a phase 2 trial and it was for a relatively short period of time, less than a half a year. The longer-term safety and efficacy were evaluated in another open-label, long-term, single-arm extension study with patients from all of the LC-FAODs. This included patients aged 6 months and up, including probably half of them who were in the adult age range. They were, as in the previous study, switched from their MCT oil to triheptanoin, titrated to that same 25% to 35% of daily calorie intake. And now here, because of the long-term extension study, these patients were followed up to 7 years with analysis at both 24 months and 48 months.

Overall, the long-term effects of triheptanoin are reported here. For triheptanoin-naive patients, these are individuals who were not on triheptanoin going into the long-term extension study. They had 2 major clinical events defined as either hypoglycemia development or worsening of cardiomyopathy or rhabdomyolysis per patient per year. At the end of the treatment, and going into the long-term extension study, this was reduced to 0.28 events per patient per year for a reduction of 86%. This translated into reduced hospitalizations at about 85% and the mean duration you can see here was almost 28 months. There was a rollover from other studies that were ongoing, particularly that initial study that I just mentioned, and these patients had a reduction in clinical events. It reduced to 1 event per patient per year for a reduction of 43% and a hospitalizations reduction of 47%. This was at almost 47 months of treatment. And then there was a whole group of patients who came in, started triheptanoin for a variety of individual studies or extended access patients and there was no baseline on these patients, but they had an end-of-treatment clinical event rate of about 1.4 and this was for almost 50 months of treatment.

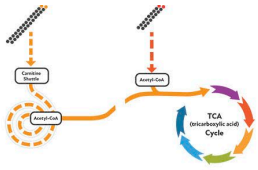
Overall, the patients who started from a naive standpoint did the best and had a significant reduction in their pretreatment symptoms. Adverse events reported during this study were similar to the last one. Adverse events were largely disease-related and of mild to moderate severity. There were 7 which were deemed treatment-related and serious and these were in 5 patients. All of these resolved and those patients remained on the study.

Sandy van Calcar, PhD, RD, LD: I would like to discuss how we recommend dosage for triheptanoin or Dojolvi. The doses are dependent on the patient's energy needs. We calculate what we call DCI, patient's daily caloric intake. For patients who are already on MCT, we will stop MCT products and substitute triheptanoin as the triheptanoin is added to their treatment regimen. The target dose is up to 35% of their daily caloric intake. Oftentimes, this may be lower for older patients, again, who seem to have lower tolerance for the very high doses of triheptanoin, as well as the traditional MCT. This dose is divided into at least 4 doses during the day, typically given with meals or snacks.

To initiate and titrate triheptanoin, it depends on if the patient is new to triheptanoin and not treated with traditional MCT. For these patients, we will start at a dose of 10% of that daily caloric intake and increase to a goal of up to 35% of total energy requirement over 2 to 3 weeks. The dose is often increased by 5% increments every 2 to 3 days. For those who are on the traditional MCT and are changing to triheptanoin, the dose of triheptanoin will start at the last tolerated dose of MCT. Once the patient is known to tolerate that dose of triheptanoin, the dose will gradually be increased by 5% increments every 2 to 3 days with, again, the goal of reaching up to 35% of total calorie intake.

To improve tolerability, patients need to use smaller, frequent doses and these doses can be adjusted for the patient's GI symptoms. Often 4 doses are recommended; some patients will need more doses than that during the day. We are shooting, again, for a maximum dose of 35% of total calories, but we do want to maintain the triheptanoin dose at the highest tolerated dose if that 35% DCI goal is not achieved.

Triheptanoin can be mixed with soft foods or liquids. These are some examples of foods that can be used. Plain or sweetened fat-free yogurt, fat-free milk or cottage cheese, whole grain hot cereal, fat-free pudding, smoothies can be made with fruit and juice and add the triheptanoin to that. Applesauce or similarly semi-liquid foods also work, as well. Some patients will have a higher tolerance to dietary fat and for those patients using low-fat versions of these different foods is appropriate. Those with more severe forms oftentimes do need to use the fat-free versions of the foods that are listed.



To determine the estimated energy requirements for the patient, these are calculated based on their individual needs. If the patient is known to the clinic, oftentimes we do know their typical energy intake and can start with that as their DCI. Oftentimes, though, patients with LC-FAODs have lower resting and total energy expenditures and so using the traditional energy calculations may end up overestimating their caloric needs. This is an estimate, a place to start, but monitoring a patient and working with them to find a dose that works best for each patient is definitely recommended.

The macronutrient distribution, that would be the distribution of carbohydrate, fat, and protein. We're not restricting carbohydrate. We want to assure adequate intake to prevent hypoglycemia and support their glucose energy needs. Typically, we are not restricting total fat, but rather we are dividing it between long-chain fat dietary sources and the medium-chain triglycerides, whether that be the traditional MCT or triheptanoin. And for proteins, we want to provide sufficient protein to support growth and maintain protein status, while helping to maintain lean body mass.

Individualized dosing and nutrition planning is necessary. For dosing, we want to adjust the triheptanoin dose based on the patient's response and tolerability. As I've said before, often adults may not be able to reach that 35% goal of total energy. In that case, we may consider using lower doses. And this is based on clinical judgment and patient-specific factors. Again, we're using a tailored approach. We want to customize the macronutrient ratios based on the patient's specific needs and their response. And we will also use regular monitoring. This will include labs that are frequently measured for patients with LC-FAODs and also assess their metabolic stability and clinical outcome. Again, we can modify doses of triheptanoin, modify their nutrition plans based on their ongoing evaluations and feedback.

This shows you some differences between treating with triheptanoin vs the traditional medium-chain triglyceride sources. As discussed before, MCT oil with 8- carbon fatty acids supplies acetyl-coA only, lacking that additional propionyl coA provided by the triheptanoin. There are some dosing differences between the 2. With traditional MCT oil, we often reach 15% to 25% of daily calorie needs. With triheptanoin, our goal is 25% to 35% daily calorie intake. It should be noted that triheptanoin studies determining this range of intake were completed mostly on patients with severe forms of these disorders. Those with milder forms of the LC-FAODs may not need to reach a dose of 35% of daily caloric needs to achieve the response and the benefit that we are trying to achieve. Triheptanoin and MCT have been shown to have similar side effects. Most commonly, this is GI distress causing diarrhea, abdominal pain/discomfort, and vomiting.

Module 4: Clinical Case Vignettes

Jerry Vockley, MD, PhD: Let's look at a couple of example cases. Dr. van Calcar and I will present them and discuss some of the issues around them. The first case is a 28-year-old woman. She was diagnosed with very long-chain acyl-CoA dehydrogenase at age 12 years. She had a milder form of the disease and she'd been stable, treated with MCT oil at 35 mL per day since then. However, she says she's now experiencing increased fatigue, some weakness with mild exertion and she's had a couple of episodes of rhabdomyolysis over the years, once at age 16 years and one at 22 years. Overall, some chronic symptoms with an occasional acute exacerbation.

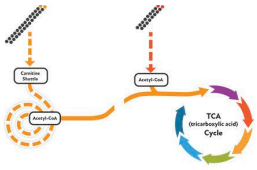
Our laboratory evaluation reveals elevated creatine kinase at 8,000 U/L. No problems with renal function. She is having chronic symptoms with laboratory evidence of rhabdomyolysis. As a result of this, we're going to go ahead and start her on triheptanoin. Her weight is 60 kg, her total daily caloric intake calculated to be 2300 calories. Dr. van Calcar, what would be the appropriate initial daily dose for this patient and how would you calculate that and get it started?

Sandy van Calcar, PhD, RD, LD: Okay, first of all, the website available for Dojolvi does have calculators that can be used to determine the triheptanoin dosage based on that daily caloric intake. This simplifies the calculation process, but the steps that we would follow for this patient is that since she is taking 35 mL of the traditional MCT oil, we would go ahead and switch her to an equivalent amount of triheptanoin. Start her on a dose of 35 mL triheptanoin and divide this into 4 or more doses throughout the day.

We want to determine the calories that she is getting from that 35 mL triheptanoin, so triheptanoin provides 8.3 kcal/mL, so we multiple 35 mL times that number and she was receiving about 290 calories from that triheptanoin dose. We then want to determine our goal intake using that 25% to 35% of total daily caloric intake or that 2300 kcal intake. We would come up with a lower end using 25% of daily caloric intake and determine the calories at the higher end at 35% of daily caloric intake. And you can see that the range is from 575 to 805 calories per day. We can then convert those calories to milliliters (mL). Triheptanoin provides approximately 8.3 kcal/mL, so her dose range of triheptanoin is 70 to 97 mL per day. We'll want to gradually increase the amount of triheptanoin that she is taking, typically increasing in 5% to 10% increments and we'll be adding about 3 to 4 mL to that initial 35 mL per day dose. Our goal is to reach that target range of 69 to 97 mL per day, but we will need to consider the patient's clinical tolerance and response to determine the actual requirement for that patient.

Jerry Vockley, MD, PhD: Great, thanks. And I'll only note that, while we have target doses, sometimes in the real world, patients don't always tolerate as much as we'd like them to take and we would be happy to get her anywhere between her existing 35 mL of MCT oil up to that lower level of 70 mL that Dr. van Calcar calculated. Getting somewhere in the middle of that range is better than nothing at all, although we will, of course, shoot for the calculated dose.

Sandy van Calcar, PhD, RD, LD: Our second case is a 35-year-old male who was diagnosed with late-onset CPT-II deficiency at age 22 years, after recurrent episodes of rhabdomyolysis. He presents with



persistent abdominal pain and diarrhea. He was recently started on 70 mL of triheptanoin. At this appointment, he shows no significant findings on physical exam. He weighs 70 kg. Laboratory tests reveal that he has normal blood glucose and creatine kinase levels, but mild electrolyte imbalances consistent with diarrhea are noted. At this time, what are the most appropriate next steps in his management?

Jerry Vockley, MD, PhD: Well, this is a somewhat common occurrence. The patients who are having some GI intolerance to the drug. A lot of that depends on the total dose, but also how quickly it's ramped up. Since this is someone who was not on chronic MCT oil treatment, they often need a lower starting dose and a slower increase. And we don't have that data, but I wouldn't be surprised if this patient was pushed a little bit too far a little bit too fast and, as a result, developed some diarrhea.

To treat this patient, we were already told that there are some minor electrolyte imbalances and so we would address that. Typically, what that means is just providing some additional oral electrolyte solution to try to get that back up. If the imbalance was severe, you might admit them to the hospital to try to correct it. But it very rarely gets to the point where that's a significant problem. However, ongoing diarrhea is a problem and we really will need to correct the dosing or adjust the dosing of triheptanoin to accommodate that. I'll ask Dr. van Calcar to comment here. Typically, what we will end up doing is adjust the dose downward a little bit, increase back up slowly as tolerated, mix it with some food to try to reduce the gastrointestinal issues, and get this patient a little bit closer to target with less side effects. Dr. van Calcar, please describe some of the things you try to do when you have a patient that's not tolerating their triheptanoin very well.

Sandy van Calcar, PhD, RD, LD: Yes, so for this patient, I would want to make sure that he is taking the triheptanoin correctly, making sure he's mixing it with food to reduce GI discomfort, most likely dividing it into smaller, more frequent doses during the day. And as Dr. Vockley commented, reducing the dose and actually restarting at a much lower dose. Titration can often help improve tolerance to the triheptanoin. For some patients, we will need to stop lower than our target dose, but often doing these steps will allow us to improve tolerance of the triheptanoin for these patients.

Jerry Vockley, MD, PhD: Thanks, and I'll just note that the vast majority of our patients that we start on triheptanoin are able to tolerate some of it. Sometimes, the dose is less than we want, but usually we're okay. We will see more problems in individuals who you're starting as adults as opposed to the pediatric patients who are transitioning over to an adult care provider because of their age.

Module 5: Point-of-Care Resource

Jerry Vockley, MD, PhD: We're going to finish up by helping you with some additional resources to review both some of the points around those cases as well as the earlier information that we discussed. This will be a downloadable resource for you if you're participating in this activity and hopefully it will help you care for your patients with LC-FAODs.

The resource is divided into 4 broad categories. The first provides some additional information on the definition and the characteristics of LC-FAODs, as well as their impact on the patient's quality of life. The second section reviews triheptanoin therapy, the role in long-chain fatty acid oxidation treatment and why you would use it and when, review the dosing and administration and then some additional pointers on monitoring the therapy and safety considerations. The third part points you to some patient education and counseling resources. These include some tips on lifestyle modification and dietary considerations and then talk a little bit more about the relationship of the patient's lifestyle with symptoms and the ongoing complications of LC-FAODs. And then finally, the fourth section provides some additional resources for support for your patients, including references for patient advocacy groups and some educational materials and online communities that will be available to them. I hope you find this useful. Go ahead and download it, take a look at it, and apply it to your clinical practice.

This activity is supported by an educational grant from Ultragenyx Pharmaceutical, Inc.