Summary - Fatty Acid Oxidation Disorders - Emerging Therapies

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Today's presentation focuses on emerging therapies is Fatty Acid Oxidation Disorders (FAOD). FAODs have a close working relationship with the mitochondrial respiratory chain. International Network for Fatty Acid Oxidation Research and Management (INFORM) has been formed to promote and spread research, education, and therapies for FAOD (slide 2). INFORM provides a collaborative working network for ongoing communication and research between members. Dr. Vockley noted conflicts of interest (slide 3), including research funding and consultation. Past international meetings have been successful, and the next INFORM symposium is scheduled for this May in Boston, MA (slides 4-6), focusing on:

- basic science of FAOD
- clinical research
- identifying what patients feel is important to study
- how best to inform patients of clinical trials and help them participate in the trials

The organizing committee and clinical trials are international (slide 7) with the intention of making INFORM a collaborative effort around the globe.

As previously stated, FAODs have a close working relationship with the mitochondrial respiratory chain. Taking care with the nomenclature is key so not to misuse terminology as to what is FAOD and what is primary mitochondrial disease. Three interrelated and interdependent cycles all impact energy production, but not all are primary mitochondrial disease.

Mitochondrial energy metabolism includes (slide 10):

- **Respiratory or Electron Transport Chain (ETC)** – energy- or ATP-creating process within the mitochondria. The ETC needs electrons for this process, creating an interdependence upon other cycles to function properly.
- **FAOD** -- another energy cycle within the mitochondria that provides electrons or "fuel" to the respiratory chain by taking fats stored in the body, typically long chain fats, and, when fasting or under stress, catalyzes enzymatic or chemical reactions by chopping off 2 carbon units at a time and feeding those carbon units into the TCA cycle. The enzymatic reactions of the FAOD cycle generate reducing equivalents, which are chemicals that can feed into the ETC and provide the fuel to generate ATP. If a body does not have the ability to oxidize fatty acids, the lack of electrons or "fuel" produced affects energy production in the ETC of the mitochondria, causing symptoms and problems for the body. Patients with FAOD have evidence of *secondary* respiratory chain dysfunction. Some respiratory chain issues are related to FAOD, therefore, many of the same therapies that help with

respiratory chain deficiencies are now believed to also benefit those with FAOD. FAODs are easy to diagnosis with the acylcarnitine profile, and most FAODs are identified with newborn screening and then confirmed by gene sequencing. Mitochondrial respiratory chain defects are much more difficult to diagnosis.

- **Krebs, TCA, or Citric Acid Cycle** -- also provides electrons or "fuel" to the respiratory chain. The enzymatic reactions of the TCA cycle generate reducing equivalents, which are chemicals that can feed into the ETC, providing the fuel to generate ATP.

Current treatments for FAOD focus on diet. Fatty Acid Oxidation is broken down into two groups: long and medium chain, or medium and short chain, plus long chain. Medium chain defects can bypass all of the enzymes that are necessary for metabolizing the longer chain, natural fats found in the diet and, instead, use a different system. In long chain FAOD, feeding medium chain triglyceride oil (8-carbon chain, or C8) was an early therapy as the medium chain fats bypass metabolism, but patients still developed hypoglycemia, a primary symptom of FAOD, and still had problems with muscle breakdown, called rhabdomyolysis. Dr. Charles Roe in Dallas, TX, originated the idea of using a 7-carbon chain (C7) for fuel. The TCA cycle needs both 2- and 3-carbon units to function. Only 2-carbon units are generated by the breakdown of the 8-carbon chain and eventually, the unit runs out of the needed 3-carbon units and stops working. C7 oils (7 carbon chain) naturally break down into both C2 and C3 units (2- and 3-carbon units), which provides a more balance fuel for the TCA cycle.

FAODs Clinical Trials (slide 11)

1. **Triheptanoin** -- triglyceride composed of three C7 fatty acids.

- FDA clinical trial with Phase 2, primarily completed at University of Oregon and University of Pittsburgh.
- Publication on compassionate use
- Clinical trials are very expensive (millions of dollars), especially for rare diseases
- Phase 3 to begin soon

- **Retroactive Triheptanoin Study** -- Drug has been use for 15-17 years, therefore, the first study was retrospective (slide 12) with an exhaustive record review of 20 charts. Some patients were on the drug long term as patients of Dr. Roe who then transitioned to Dr. Vockley. Study outcomes included episodes of hypoglycemia, incidence of rhabdomyolysis, and hospitalizations during the 2 years before and 2 years after patients started triheptanoin. Outcomes:
  - Fewer hospitalization days (67%) per year were statically significant among study patients (slide 13), graphed in color by disease type. Both number of admissions and length of stay were decreased significantly.
  - Hypoglycemic events dropped to no events in nearly all patients (slide 14).
  - Rhabdomyolysis hospitalizations showed some reduction in episodes as noted by shorter hospitalizations (by 60%) and milder symptoms, although number of hospitalizations did not decrease overall (slide 15).
  - Additional studies are needed!

- **FDA Triheptanoin Trial** -- prospective, randomized, double-blind study (slide 17). Patients agreeing to be part of the study were randomized to a diet with either standard MCT oil (C8) or Triheptanoin (C7). Neither patients, staff, nor investigators knew which the patient was receiving. Exercise testing, MRI scans, and tests to assess the body's ability to generate energy were performed both at baseline and again four months after the drug was initiated.
  - 30 patients enrolled in the study (slide 18).
  - Adverse events were events associated with the disease (i.e. hypoglycemia) and were evident in both groups. Both groups complained of mild GI symptoms when taking both the C8 and C7 oil (slide 19).
  - C7 is similarly tolerated as C8 (MCT) (slide 20).
  - Patients who received C7 had improved cardiac function as evidenced by a 7% left ventricular ejection fraction (slide 21) as compared to those on MCT oil.
  - Patients on C7 had a significantly lower heart rate (-7 beats per minute) for the same amount of work (slide 22), thus utilizing less cardiac energy. The heart was studied because FAODs cause heart symptoms as the heart depends on fatty acid oxidation for 80% of its energy!
  - Patients on C8 (MCT oil) had a decreased heart rate (-15 BPM) as compared to patients on carbohydrate diet.
  - No observable skeletal muscle effect (slide 25).
  - Similar CPK, acylcarnitines, and ketones.

- **Ultragenyx Phase 2 Study**-- Larger, open label clinical trials are now being carried out with Ultragenyx (slides 28 -29) in both acute and chronic disease.
  - Safety -- Safe and well tolerated with no new potential risks identified. Most common adverse event is GI upset (similar to MCT).
  - Exercise results (8 patients) -- 60% increase in exercise energy generated compared to baseline and a 28% increase in 12-minute walk distance compared to baseline.
  - General Outcomes -- decrease in overall major medical events. Timeframe to approval is difficult to predict

These studies not only impact FAODs, but may show benefit to patients with a primary mitochondrial defect by providing better substrates for the respiratory chain.

2. **Anti-inflammatories --** Rhabdomyolysis -- patients with FAOD have very high levels of cytokines, which are inflammation proteins that signal the body to have an inflammatory response. Also elevated are macrophage surfaces markers, which are found at the cellar level to make that inflammatory response. Anti-inflammatory treatment may help FAOD patients as FAOD patients are believed to sit at the edge of cliff of inflammation.

3. **Bendavia** (Stealth Biotherapeutics) -- Cardiolipin isa fat that lives in the mitochondrial membrane, which is important in keeping the shape and integrity of the mitochondria (slide 33-34). In primary mitochondrial respiratory chain defects,

this lipid becomes altered and causes the mitochondria to lose its integrity and fall apart. Bendavia basically knocks cardiolipin back into shape when it loses it shape. Bendavia has been tested in heart attack patients with positive results of reducing cardiomyocyte apoptosis (programmed cell death). Stealth is running a clinical trail now, studying patients with mitochondrial respiratory chain deficiencies to see if Bendavia works for those with an energy deficit relative to a genetic disorder. Bendavia may be studied in patients with FAODs in the near future.

4. **RTA 408** (Reata Pharm., Inc.) is in clinical trials for primary mitochondrial respiratory chain deficiencies and will likely also benefit FAOD patients by increasing the expression of genes involved with energy metabolism. Levels of proteins involved in the mitochondrial respiratory chain as well as proteins that aid fatty acid oxidation are increased, which improves energy metabolism (slides 35-37). RTA408 improves antioxidant gene response to oxidative stress in Friedrich's ataxia. INFORM is working with Reata to develop a clinical trail for the FAOD population.

5. **Mitobridge** --developed similar products as Reata.

6. **Uridine** (Wellstat Therapeutics) --molecule tested in patients with respiratory chain deficiencies (slide 37). Uridine helps to stabilize sick mitochondria by regulating Mito APT-sensitive potassium channel, activating Mito-KATP and increasing APT synthesis, and possibly decreasing inflammatory signaling. INFORM is working with Wellstat to bring Uridine to the FAOD community.

7. **Raviciti in MCAD (Horizon)** --previously approved for binding ammonia. By treating cells with Raviciti, the activity of the cells improves by stabilizing the MCAD (slides 38- 39). Horizon Pharma is sponsoring a study of Raviciti in patients with MCAD. This clinical trial is recruiting patients.

Conclusion -- Treatment of respiratory chain deficiencies and fatty acid oxidation disorders has entered a dynamic and exciting time! Simply treating symptoms has been replaced by to treating and improving the underlying bioenergetics. More compounds are becoming available with a promise of big changes in the field over the next 10 years. Individuals are needed to participate in these clinical trials to push these new drugs forward. Patients are encouraged to get involved to improve the future for all! More information about the above clinical trials, including contact information can be found at: **clinicaltrials.gov**.