Retrospective Chart Review
Triheptanoin in FAOD patients
ICIEM Presentation

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Conflicts of Interest

Funding from:
- NIH and FDA on FODs
- Ultragenyx Pharmaceutical for Triheptanoin
- Hyperion for an MCAD trial
- Alexion Pharmaceutical
- BioMarin Pharmaceutical
- Consultant PerkinElmer Genetics
Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD)

- Six proteins affected
- Block in transport or β-oxidation
- Substantial morbidity
- >50% mortality despite SOC (Baruteaux et al 2012)
Treatment of LC-FAOD with Triheptanoin

C16-C18 Fatty Acid

Fatty Acyl Co-A

CPT-I

Acylcarnitine

CACT

CPT-II

Acylcarnitine

Fatty acyl Co-A

Triheptanoin

C7 Fatty Acid

Medium Chain FAO Enzymes

1  CH3-CO-S-CoA
   Two C2 Acetyl CoAs Per FA

2  CH3CH2-CO-S-CoA
   One C3 Propionyl CoA Per FA

Electron Transport Chain

TPP/LCHAD

Beta-oxidation Spiral

NADH/FADH2

H+ ADP + P1

ATP

TCA Cycle

OAA

CIT

MAL

FUM

αKG

SUCC

SUCC-CoA

MMA-CoA

PROP-CoA
Triheptanoin Compassionate Use

- Combined experience of Baylor Research Institute (Dallas) and University of Pittsburgh
- Resolution of hypoglycemic episodes
- Reduced hospitalizations
- Fewer/less severe episodes of rhabdomyolysis
- Improved cardiomyopathy
Cardiomyopathy in LC-FAOD

Previous retrospective data, including from Barone et al 2012

- 12 patients with cardiomyopathy prior to triheptanoin
  - 8 resolved completely
  - 4 with continued cardiomyopathy
    - 3 improved
    - 1 stable
Title: A retrospective medical record review study to assess the clinical outcome of triheptanoin treatment on patients affected by LC-FAOD

Study Design: Comprehensive protocol-driven medical record review study

Subjects: 20 patients consented and evaluated of 24 patients treated with triheptanoin for up to 13 years in a compassionate use protocol

Site: Children’s Hospital of Pittsburgh of UPMC
- The majority of patients transferred from Baylor Research Institute

Objective: Evaluate the impact of triheptanoin on hospitalizations (events) for:
- Rhabdomyolysis
- Hypoglycemia
- Cardiomyopathy
- CK and glucose levels

Methods/Analysis: Calculation of event rates prior to and after triheptanoin treatment
Scope and Limitations

- Intensive record collection and review process
  - 1581 Case Report Forms generated
  - 241 years of patient records
  - 319 hospitalizations
  - 120 individual charts

- Due to the nature of a retrospective chart review study, some incomplete data remains
  - Only major events (hospitalizations) can be reliably captured
  - Non-major events are difficult to characterize
  - Degree of dosing compliance or metabolic control difficult to quantify with chart review
Baseline Disease Characterizations

**Pre-Treatment FAOD History**

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>N = 20 (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyolysis</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Poor feeding/weight gain</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Altered mental status/coma</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>7 (35%)</td>
</tr>
</tbody>
</table>
### Triheptanoin Treatment History

<table>
<thead>
<tr>
<th>Age at Start of Treatment*</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1 year</td>
</tr>
<tr>
<td>0-1 month (Neonates)</td>
<td>-</td>
</tr>
<tr>
<td>1 month-2 years (Infants)</td>
<td>1</td>
</tr>
<tr>
<td>2-12 years (Children)</td>
<td>-</td>
</tr>
<tr>
<td>12-16 years (Adolescents)</td>
<td>-</td>
</tr>
<tr>
<td>&gt;16 years (Other)</td>
<td>-</td>
</tr>
<tr>
<td>Total N (%)</td>
<td>1</td>
</tr>
</tbody>
</table>

*Dose levels varied over time and per subject. Target dose levels were initially 2-4 g/kg and later 1-2 g/kg Triheptanoin.*
Hospitalizations/Year

Decreased 30% Following Triheptanoin Treatment*

*Excludes data for 4 infants dosed within first 6 months of life
Infant Hospitalizations/Year

Decreased 89% Following Triheptanoin Treatment*

*Includes 4 infants dosed within first 6 months of life

*CACT n = 1
*VLCAD n = 2
*LCHAD n = 1
Total Hospital Days/Year

Decreased 67% Following Triheptanoin Treatment*

*Excludes data for 4 infants dosed within first 6 months of life
*Excludes hospitalizations with unknown discharge dates
*Excludes patients without any pre-treatment hospitalization days

VLCAD n = 7
LCHAD n = 4
CPT2 n = 1
TFP n = 2

p = 0.048
Hypoglycemia Events/Year

Decreased 96% Following Triheptanoin Treatment*

*Includes only those patients with hypoglycemia events prior to treatment

*Excludes data for 4 infants dosed within first 6 months of life

Number of Events Per Year

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLCAD</td>
<td>5</td>
</tr>
<tr>
<td>LCHAD</td>
<td>2</td>
</tr>
<tr>
<td>TFP</td>
<td>1</td>
</tr>
<tr>
<td>CPT2</td>
<td>1</td>
</tr>
</tbody>
</table>

p = 0.009

*Includes only those patients with hypoglycemia events prior to treatment

*Excludes data for 4 infants dosed within first 6 months of life
Mean Total Hospital Days/Year Hypoglycemia

Events Decreased 98% Following Triheptanoin*

*Includes only those patients with hypoglycemia events prior to treatment
*Excludes data for 4 infants dosed within first 6 months of life
*Excludes hospitalizations with unknown discharge dates

![Graph showing hospital days per year pre and post treatment with Triheptanoin for various genetic conditions.](image)

- VLCAD n = 5
- LCHAD n = 2
- TFP n = 1
- CPT2 n = 1

p = 0.025
Rhabdomyolysis Events/Year

Similar Before and After Triheptanoin Treatment*

- Includes only those patients with rhabdomyolysis events prior to treatment
- Excludes data for 4 infants dosed within first 6 months of life

Number of Events Per Year

- VLCAD n = 4
- LCHAD n = 3
- CPT2 n = 2
- TFP n = 2

p = 0.423

*Includes only those patients with rhabdomyolysis events prior to treatment
*Excludes data for 4 infants dosed within first 6 months of life
Mean Total RH Hospital Days/Year

Decreased 60% for Rhabdomyolysis Events*

*Includes only those patients with rhabdomyolysis events prior to treatment
*Excludes data for 4 infants dosed within first 6 months of life

VLCAD n = 3
LCHAD n = 3
CPT2 n = 1
TFP n = 2

p = 0.124
Peak CK for RH Events

Decreased 60% Following Triheptanoin*

*Includes only those patients with rhabdomyolysis events prior to treatment
*Excludes data for 4 infants dosed within first 6 months of life

Peak CK Levels

Pre-Trihep  Post-Trihep

VLCAD n = 3  LCHAD n = 3  CPT2 n = 1  TFP n = 2

p = 0.201

*Includes only those patients with rhabdomyolysis events prior to treatment
*Excludes data for 4 infants dosed within first 6 months of life
Conclusions

- LC-FAOD lead to frequent complications/hospitalizations
- Treatment with triheptanoin appears to reduce the hospitalizations and hospital days
- Hypoglycemic hospitalizations were nearly eliminated
- Rhabdomyolysis hospitalization # not changed but hospital days decreased

<table>
<thead>
<tr>
<th></th>
<th>Decrease in Event Rate</th>
<th>Decrease in # of Hospitalization Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Events</td>
<td>30%</td>
<td>67%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>96%</td>
<td>98%</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>No Change</td>
<td>60%</td>
</tr>
</tbody>
</table>
Triheptanoin (UX007) Next Steps

- Continue Compassionate Use Program (Vockley)
- Complete the ongoing Phase 2 Orphan Product Trial (Vockley/Gillingham)
- Open-label Phase 2 Study to Assess Safety and Clinical Effects of UX007 in Subjects with Severe LC-FAOD (Ultragenyx)
- Confirmatory Phase 3 Trial (Ultragenyx)
Acknowledgements

- FAOD Patients and Families
- University of Pittsburgh
  - Elizabeth McCracken, MS, CGC
  - Stephanie DeWard, MS, CGC
  - Jennifer Baker, MA
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- Ultragenyx Pharmaceutical Inc.
  - Kristen Hsu
  - Deborah Marsden, MD
  - Alison Skrinar, PhD
  - Emil Kakkis, MD, PhD
Thank You!
Back-up
Total Hospital Days/Year

Decreased 69% Following Triheptanoin Treatment*

*Excludes data for 4 infants dosed within first 6 months of life
*Excludes hospitalizations with unknown discharge dates
Median Total Hospital Days/Year

Decreased 79% for Rhabdomyolysis Events

*Includes only those patients with rhabdomyolysis events prior to treatment
*Excludes data for 4 infants dosed within first 6 months of life
*Excludes hospitalizations with unknown discharge dates
“Severe” Rhabdomyolysis Events (>5000 u/l)

Declined 45% Following Triheptanoin *

*Includes only those patients with rhabdomyolysis events (CK >5,000 U/L) prior to treatment
*Excludes data for 4 infants dosed within first 6 months of life

*Includes only those patients with rhabdomyolysis events (CK >5,000 U/L) prior to treatment

*Excludes data for 4 infants dosed within first 6 months of life

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Number of Events Per Year

- VLCAD n = 4
- LCHAD n = 3
- TFP n = 2
- CPT2 n = 1

p = 0.217
Total Hospital Days/Year for “Severe” Rhabdomyolysis Events (>5000 u/l)
Decreased 67% Following Triheptanoin Treatment*

*Includes only those patients with rhabdomyolysis events (CK >5,000 U/L) prior to treatment
*Excludes data for 4 infants dosed within first 6 months of life
*Excludes hospitalizations with unknown discharge dates

![Graph showing hospital days per year with pre-Trihep and post-Trihep data for VLCAD (n=3), LCHAD (n=2), and TFP (n=2). The graph demonstrates a decrease in hospital days post-Trihep treatment. The p-value is 0.109.](image_url)