Major Clinical Manifestation Events and Healthcare Resource Use Among Patients With Long-chain Fatty Acid Oxidation Disorders (LC-FAOD) Pre- and Post-triheptanoin Initiation: A Retrospective Claims Database Analysis in the US

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BACKGROUND

- Long-chain fatty acid oxidation disorders (LC-FAOD) are a group of rare inborn errors of metabolism that lead to energy depletion and major clinical events (MCEs), including rhabdomyolysis, hypoglycemia, and cardiomyopathy
- Current LC-FAOD management strategies include diet and exercise restrictions, avoidance of fasting, and treatment with triheptanoin
- Triheptanoin is the first and only FDA-approved treatment for children and adults with LC-FAOD
- This retrospective cohort study assessed MCEs and healthcare resource use (HRU) among commercially insured US patients with LC-FAOD treated with triheptanoin

METHODS

- The IQVIA PharMetrics® Plus database was searched for patients who initiated triheptanoin after FDA approval (30 June 2020) to the end of September 2023
- Patients with LC-FAOD treated with triheptanoin were selected using the following criteria:
  - Confirmed diagnosis of LC-FAOD defined as at least one ICD-10-CM Diagnosis Code E71.310 in any billing position of a claim in the database
  - Evidence of a triheptanoin prescription starting from 01 July 2020, identified using NDC code 69794005050. The first date of a triheptanoin claim was defined as the index date
  - At least 12 months of medical and pharmacy continuous enrollment before the index date
  - At least 6 months of medical and pharmacy continuous enrollment after the index date
- Patients with LC-FAOD not treated with triheptanoin were selected using the following criteria:
  - Confirmed diagnosis of LC-FAOD defined as at least one ICD-10-CM Diagnosis Code E71.310 in any billing position of a claim in the database
  - No evidence of a triheptanoin prescription identified using NDC code 69794005050
  - An index date randomly assigned based on the distribution of index dates from the triheptanoin-treated cohort
  - At least 12 months of medical and pharmacy continuous enrollment before the index date
  - At least 6 months of medical and pharmacy continuous enrollment after the index date
- Patients were excluded from the study if there was any evidence of participation in clinical trial with ICD-10-CM Diagnosis Code Z00.6, any evidence of pregnancy, or any evidence of long-term hospitalization
- Complications and medical history were assessed during all time periods available before the index date and were identified using ICD-10-CM Diagnosis Codes in any care setting
- MCEs were defined as rhabdomyolysis, hypoglycemia, and/or cardiomyopathy in an inpatient and/or emergency room setting identified using ICD-10 Diagnosis Codes
- MCEs and HRU of all disease related diagnoses were assessed up to 18 months before the baseline period and at least 6 months after triheptanoin initiation
- Annualized event rates and durations were calculated

RESULTS

- 34 triheptanoin-treated patients and 179 patients with LC-FAOD not treated with triheptanoin were included in the study
- Among triheptanoin-treated patients:
  - 23 (67.6%) were pediatric
  - 11 (32.4%) were female
  - Median age at triheptanoin initiation was 7 years for pediatric patients and 29 years for adult patients
  - All triheptanoin-treated patients were commercially insured
- Among patients with LC-FAOD not treated with triheptanoin:
  - 134 (76.5%) were pediatric
  - 92 (51.4%) were female
  - Median age was 7 years for pediatric patients and 35 years for adult patients
  - Most patients not treated with triheptanoin were commercially insured

Table 1. Baseline Demographics for Patients Treated With Triheptanoin vs Patients Not Treated With Triheptanoin

Characteristic, n (%)	Triheptanoin-treated			Not Treated With Triheptanoin		
	Total	Pediatric	Adult	Total	Pediatric	Adult
Total Number of Patients	**34**	**23**	**11**	**179**	**134**	**45**
Sex						
Female	11 (32.4)	5 (21.7)	6 (54.6)	92 (51.4)	69 (51.5)	23 (51.1)
Age (years)						
Mean (SD)	16.8 (16.9)	7.9 (3.8)	35.6 (18.4)	16.8 (20.1)	7.5 (4.1)	44.3 (23.2)
Median (IQR)	10 (6, 22)	7 (5, 11)	29 (22, 39)	9 (4, 18)	7 (4, 11)	35 (23, 59)
Min, Max	1, 76	1, 16	18, 76	1, 85	1, 17	18, 85
Payer Type						
Commercial fully insured	26 (76.5)	18 (78.3)	8 (72.7)	55 (30.7)	37 (27.6)	18 (40.0)
Commercial self-Insured (employer sponsored)	8 (23.5)	5 (21.7)	3 (27.3)	116 (64.8)	95 (70.9)	21 (46.7)
Medicaid	0 (0)	0 (0)	0 (0)	2 (1.1)	2 (1.5)	0 (0)
Medicare	0 (0)	0 (0)	0 (0)	6 (3.35)	0 (0)	6 (13.33)
Geographic Region						
Midwest	10 (29.4)	4 (17.4)	6 (54.6)	61 (34.1)	49 (36.6)	12 (26.7)
Northeast	6 (17.7)	4 (17.4)	2 (18.2)	26 (14.5)	19 (14.2)	7 (15.6)
South,	15 (44.1)	13 (56.5)	2 (18.2)	68 (38.0)	47 (35.1)	21 (46.7)
West	3 (8.8)	2 (8.7)	1 (9.1)	24 (13.4)	19 (14.2)	5 (11.1)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Follow-up Time (months)						
Mean (SD)	21.8 (11.6)	21.4 (10.9)	22.6 (13.6)	25.6 (10.8)	25.6 (11.1)	26.1 (10.8)
Median (IQR)	21 (12,33)	21 (12,29)	17 (7,37)	27 (15, 36)	27 (14, 36)	26 (16,36)
Min, Max	6, 39	6, 39	6, 38	6, 39	6, 39	6, 39

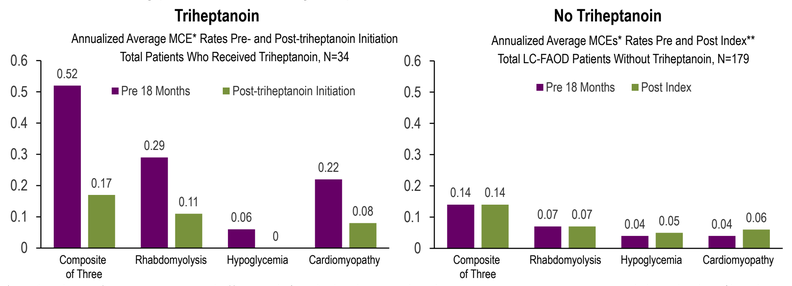
- Among patients treated with triheptanoin, 65.2% of pediatrics and 72.7% of adults had a diagnosis history of rhabdomyolysis, hypoglycemia, and/or cardiomyopathy
- Medical history was different between patients with LC-FAOD treated and not treated with triheptanoin; patients treated with triheptanoin had increased incidence rates of rhabdomyolysis and cardiomyopathy

Table 2. Manifestation and Complication History (All Settings of Care)

Manifestation/Complication, n (%)	Pediatric		Adult	
	Triheptanoin (n=23)	No Triheptanoin (n=134)	Triheptanoin (n=11)	No Triheptanoin (n=45)
Major Clinical Manifestations	15 (65.2)	30 (22.4)	8 (72.7)	17 (37.8)
Rhabdomyolysis	7 (30.4)	13 (9.7)	8 (72.7)	8 (17.8)
Hypoglycemia	4 (17.4)	15 (11.2)	1 (9.1)	8 (17.8)
Cardiomyopathy	10 (43.5)	11 (8.2)	2 (18.2)	4 (8.9)
Other Muscular Disorders	5 (21.7)	16 (11.9)	6 (54.6)	19 (42.2)
Myopathy	0 (0)	2 (1.5)	2 (18.2)	6 (13.3)
Mitochondrial myopathy	0 (0)	1 (0.8)	0 (0)	3 (6.7)
Other myopathy	0 (0)	2 (1.5)	2 (18.2)	6 (13.3)
Muscle weakness	3 (13.0)	7 (5.2)	0 (0)	11 (24.4)
Myalgia	2 (8.7)	10 (7.5)	6 (54.6)	9 (20.0)
Myoglobinuria	0 (0)	1 (0.8)	1 (9.1)	1 (2.2)
Overall Hepatic	2 (8.7)	5 (3.7)	2 (18.2)	9 (20.0)
Fatty liver	0 (0)	1 (0.8)	0 (0)	5 (11.1)
Hepatomegaly	0 (0)	0 (0)	0 (0)	2 (4.4)
Other liver disorder	1 (4.4)	1 (0.8)	1 (9.1)	4 (8.9)
Abnormal liver	1 (4.4)	4 (3.0)	1 (9.1)	6 (13.3)
Overall Renal	2 (8.7)	5 (3.7)	3 (27.3)	15 (33.3)
Acute kidney failure	2 (8.7)	5 (3.7)	1 (9.1)	9 (20.0)
Chronic kidney disease	0 (0)	0 (0)	2 (18.2)	8 (17.8)
Other	13 (56.5)	67 (50.0)	10 (90.9)	36 (80.0)
Retinopathy	0 (0)	5 (3.7)	2 (18.2)	1 (2.2)
Retinal disorder	0 (0)	0 (0)	0 (0)	1 (2.2)
Neuropathy	3 (13.0)	3 (2.2)	2 (18.2)	4 (8.9)
Fatigue	7 (30.4)	23 (17.2)	2 (18.2)	26 (57.8)
Pain	11 (47.8)	53 (39.6)	9 (81.8)	36 (80.0)
Abnormal Serum Enzyme Levels	6 (26.1)	19 (14.2)	5 (45.5)	11 (24.4)
Acidosis	6 (26.1)	11 (8.2)	2 (18.2)	8 (17.8)
Digestive System	14 (60.9)	75 (56.0)	6 (54.6)	33 (73.3)
Pancreatitis	0 (0)	0 (0)	0 (0)	3 (6.7)
Intestinal gas	0 (0)	3 (2.2)	0 (0)	8 (17.8)
Nausea and/or vomiting	13 (56.5)	54 (40.3)	3 (27.3)	18 (40.0)
Gallstones	0 (0)	0 (0)	1 (9.1)	1 (2.2)
Diarrhea	5 (21.7)	24 (17.9)	1 (9.1)	12 (26.7)
Abdominal pain	3 (13.0)	21 (15.7)	3 (27.3)	21 (46.7)
GERD	3 (13.0)	18 (13.4)	1 (9.1)	19 (42.2)
Cardiovascular/Cardiopulmonary	5 (21.7)	9 (6.7)	2 (18.2)	24 (53.3)
Pulmonary hypertension	1 (4.4)	0 (0)	0 (0)	3 (6.7)
Hypertension	1 (4.4)	1 (0.8)	1 (9.1)	16 (35.6)
Atherosclerotic heart disease	0 (0)	1 (0.8)	1 (9.1)	5 (11.1)
Psychiatric/Neurologic	2 (8.7)	17 (12.7)	6 (54.6)	18 (40.0)
Seizure	0 (0)	0 (0)	0 (0)	2 (4.4)
Depression	0 (0)	6 (4.5)	3 (27.3)	9 (20.0)
Insomnia	1 (4.4)	3 (2.2)	0 (0)	7 (15.6)
Anxiety	1 (4.4)	15 (11.2)	5 (45.5)	14 (31.1)

Figure 1. Annualized MCE Rates Among All Patients

- Before receiving triheptanoin, the annualized average total MCE rate was 0.52 versus 0.17 after triheptanoin initiation. Reductions were observed in all three MCEs: rhabdomyolysis decreased from 0.29 to 0.11, hypoglycemia from 0.06 to 0.00, and cardiomyopathy from 0.22 to 0.10 (**Figure 1**)
- MCE rates among patients not receiving triheptanoin remained the same



*Hospitalization and/or emergency room visits. **Index date for patients not receiving triheptanoin were randomly assigned according to the distribution of triheptanoin initiation dates from the cohort of patients who received triheptanoin.

Figure 2. Annualized MCE Duration Among All Patients in Days

- Reduction in annualized MCE duration was consistent with reduction of MCE rates in the triheptanoin-treated group (**Figure 2**)
- This trend was consistent among pediatrics and adults (data not shown)

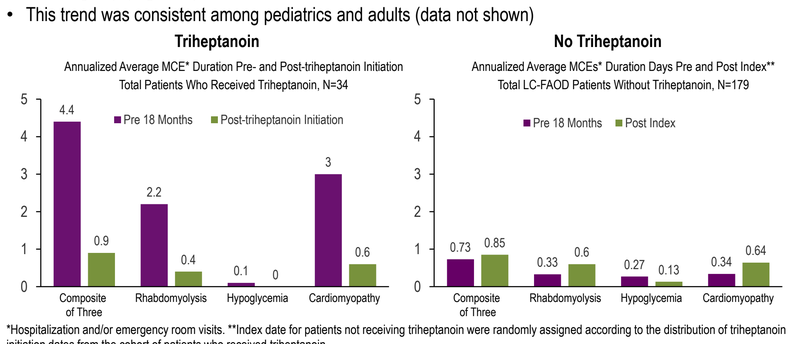


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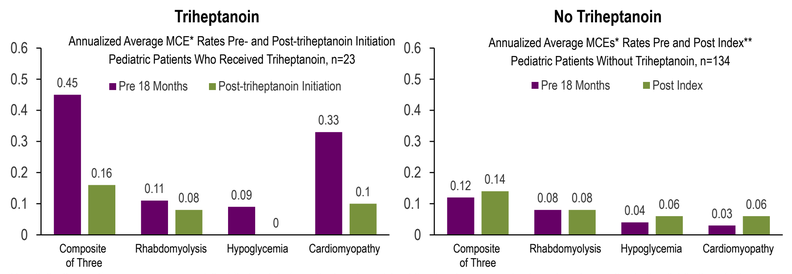
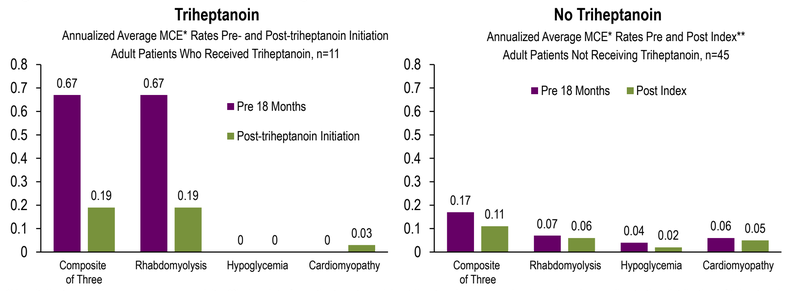
Figure 3. Annualized MCE Rates Among Pediatric Patients Only

- MCE rate reductions were observed in both pediatric and adult patients treated with triheptanoin while the trend was not observed among patients not treated with triheptanoin (**Figures 3** and **4**)



*Hospitalization and/or emergency room visits. **Index date for patients not receiving triheptanoin were randomly assigned according to the distribution of triheptanoin initiation dates from the cohort of patients who received triheptanoin.

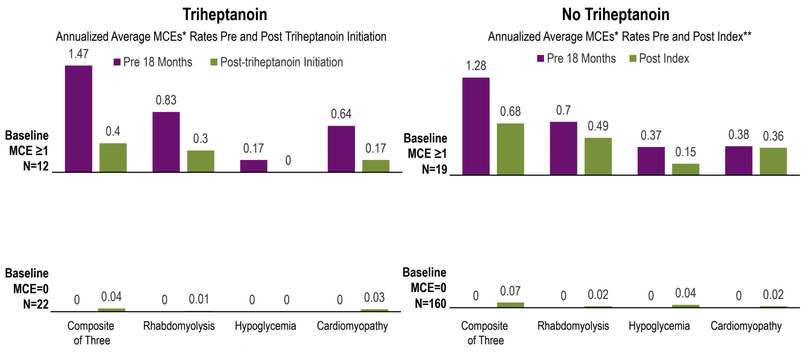
Figure 4. Annualized MCE Rates Among Adult Patients



*Hospitalization and/or emergency room visits. **Index date for patients not receiving triheptanoin were randomly assigned according to the distribution of triheptanoin initiation dates from the cohort of patients who received triheptanoin.

Figure 5. Annualized MCE Rate by Baseline MCE Occurrence

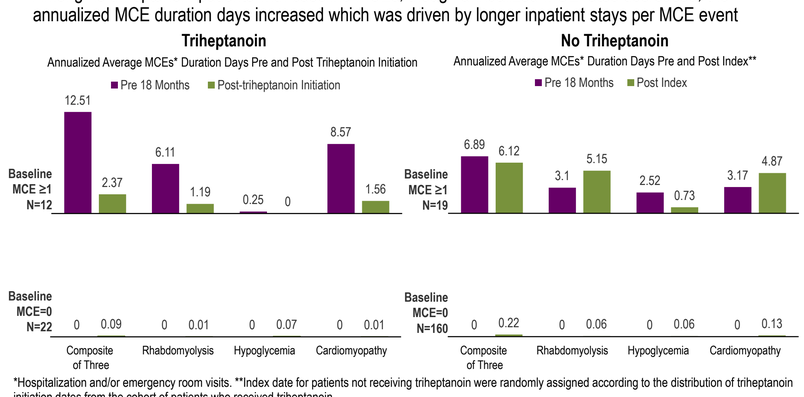
- Patients with baseline MCEs treated with triheptanoin had greater reduction in annualized number of MCEs compared with patients not receiving triheptanoin
- Among patients without MCEs up to 18 months prior to triheptanoin, post treatment MCEs were rare and similar to patients not treated with triheptanoin



*Hospitalization and/or emergency room visits. **Index date for patients not receiving triheptanoin were randomly assigned according to the distribution of triheptanoin initiation dates from the cohort of patients who received triheptanoin.

Figure 6. Annualized MCE Duration Stratified by Baseline MCE Occurrence

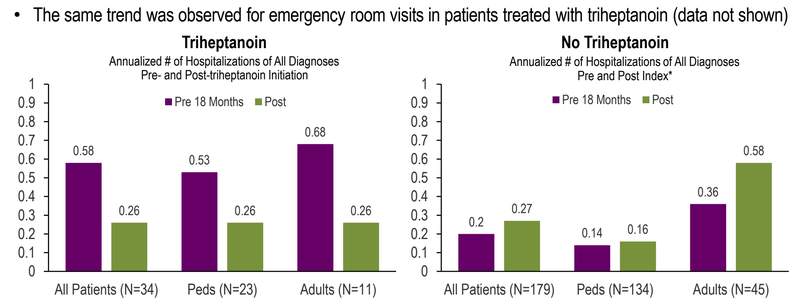
- Patients with baseline MCEs treated with triheptanoin had decreased duration post treatment; this trend was consistent with MCE rates
- Among no triheptanoin patients with baseline MCEs, though annualized MCE rates decreased, the annualized MCE duration days increased which was driven by longer inpatient stays per MCE event



*Hospitalization and/or emergency room visits. **Index date for patients not receiving triheptanoin were randomly assigned according to the distribution of triheptanoin initiation dates from the cohort of patients who received triheptanoin.

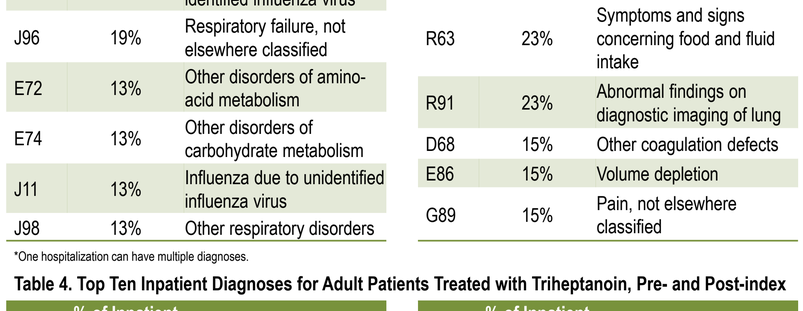
Figure 7. Annualized Hospital Admission Rate – All Diagnoses

- Overall hospitalization numbers and durations showed large reductions after triheptanoin initiation for both pediatric and adult patients (**Figures 7** and **8**)
- Among patients not receiving triheptanoin, hospitalization rates increased over time, especially among adults
- The same trend was observed for emergency room visits in patients treated with triheptanoin (data not shown)



*Index date for patients not receiving triheptanoin were randomly assigned according to the distribution of triheptanoin initiation dates from the cohort of patients who received triheptanoin.

Figure 8. Annualized Inpatient Duration – All Diagnoses



*Index date for patients not receiving triheptanoin were randomly assigned according to the distribution of triheptanoin initiation dates from the cohort of patients who received triheptanoin.

- Among patients treated with triheptanoin, there were 27 hospital admissions (16 for pediatrics, 11 for adults) up to 18 months before baseline, and 20 hospital admissions (13 for pediatrics and 7 for adults) during an average of 21.8 months (median of 21 months) of follow-up
- The most common hospitalization diagnoses pre- and post-treatment are listed in **Table 3** for pediatric patients and **Table 4** for adult patients

Table 3. Top Ten Inpatient Diagnoses for Pediatric Patients Treated with Triheptanoin, Pre- and Post-index

ICD-10	% of Inpatient Events With Diagnosis*	Disease Description Before Using Triheptanoin
E86	31%	Volume depletion
R11	25%	Nausea and vomiting
E87	19%	Other disorders of fluid, electrolyte and acid-base balance
I42	19%	Cardiomyopathy
J10	19%	Influenza due to other identified influenza virus
J96	19%	Respiratory failure, not elsewhere classified
E72	13%	Other disorders of amino-acid metabolism
E74	13%	Other disorders of carbohydrate metabolism
J11	13%	Influenza due to unidentified influenza virus
J98	13%	Other respiratory disorders
E88	31%	Other and unspecified metabolic disorders
M62	31%	Other disorders of muscle
A08	23%	Viral and other specified intestinal infections
I42	23%	Cardiomyopathy
R11	23%	Nausea and vomiting
R63	23%	Symptoms and signs concerning food and fluid intake
R91	23%	Abnormal findings on diagnostic imaging of lung
D68	15%	Other coagulation defects
E86	15%	Volume depletion
G89	15%	Pain, not elsewhere classified

*One hospitalization can have multiple diagnoses.

Table 4. Top Ten Inpatient Diagnoses for Adult Patients Treated with Triheptanoin, Pre- and Post-index

ICD-10	% of Inpatient Events With Diagnosis*	Disease Description Before Using Triheptanoin
M62	45%	Other disorders of muscle
E86	18%	Volume depletion
J96	18%	Respiratory failure, not elsewhere classified
R10	18%	Abdominal and pelvic pain
R11	18%	Nausea and vomiting
A08	10%	Viral and other specified intestinal infections
G72	10%	Other and unspecified myopathies
H66	10%	Suppurative and unspecified otitis media
I31	10%	Other diseases of pericardium
J18	1	Pneumonia, unspecified organism
R11	43%	Nausea and vomiting
A08	29%	Viral and other specified intestinal infections
E86	29%	Volume depletion
E88	29%	Other and unspecified metabolic disorders
I42	29%	Cardiomyopathy
I51	29%	Complications and ill-defined descriptions of heart disease
J96	29%	Respiratory failure, not elsewhere classified
K52	29%	Other and unspecified noninfective gastroenteritis and colitis
R10	29%	Abdominal and pelvic pain
R63	29%	Symptoms and signs concerning food and fluid intake

*One hospitalization can have multiple diagnoses.

LIMITATIONS

- In claims data, payment records are based on diagnostic coding that may be driven by reimbursement concerns and may or may not accurately reflect the true medical condition
- Our analysis only used ICD-10 codes to identify LC-FAOD and subtype information was not available
  - The LC-FAOD population may be broader than clinical trial patients; therefore, asymptomatic or patients with mild LC-FAOD may have been included
- Due to the small sample size, study results might be biased and skewed by outliers. Though outliers with long-term hospitalizations were excluded from this analysis
- The treated versus not treated populations were not matched by baseline characteristics and had differences in medical history; outcomes comparisons between the cohorts were not controlled for baseline differences and were not statistically powered to detect differences between groups

CONCLUSIONS

- **This study demonstrated that patients with LC-FAOD experienced fewer MCEs and fewer inpatient visits after receiving triheptanoin**
- **Future studies comparing a no-treatment disease cohort are needed to better understand the triheptanoin treatment effect**

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