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# Triheptanoin in patients with long-chain fatty acid oxidation disorders: clinical experience in Italy

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## Abstract

**Background** Long-chain fatty acid oxidation disorders (LC-FAOD) are rare and potentially life-threatening diseases that cause deficient energy production and accumulation of toxic metabolites. Despite dietary management, adherence to maximum fasting guidelines, restricted long-chain triglyceride intake and supplementation with medium-chain triglyceride (MCT) oil (current standard of care), most patients experience recurrent decompensation episodes that can require hospitalisation. Herein, we analysed the effectiveness and safety of triheptanoin (a highly purified, synthetic medium odd-chain triglyceride) treatment in a cohort of Italian patients with LC-FAOD.

**Methods** This retrospective, nationwide study included nine patients with LC-FAOD who switched from standard therapy with MCT oil to triheptanoin oral liquid. Data were collected between 2018 and 2022. Clinical outcome measures were the number and duration of intercurrent catabolic episodes and number and duration of metabolic decompensation episodes requiring hospitalisation. Creatine kinase (CK) levels and treatment-related adverse effects were also reported.

**Results** Patients were provided a mean  $\pm$  standard deviation (SD) triheptanoin dose of  $1.5 \pm 0.9$  g/kg/day in four divided administrations, which accounted for  $23.9 \pm 8.9\%$  of patients' total daily caloric intake. Triheptanoin treatment was started between 2.7 and 16 years of age and was continued for  $2.2 \pm 0.9$  years. The number of intercurrent catabolic episodes during triheptanoin treatment was significantly lower than during MCT therapy ( $4.3 \pm 5.3$  vs  $22.0 \pm 22.2$ ;  $p = 0.034$ ), as were the number of metabolic decompensations requiring hospitalisation (mean  $\pm$  SD:  $2.0 \pm 2.5$  vs  $18.3 \pm 17.7$ ;  $p = 0.014$ ), and annualised hospitalisation rates and duration. Mean CK levels (outside metabolic decompensation episodes) were lower with triheptanoin treatment versus MCT oil for seven patients. No intensive care unit admissions were required during triheptanoin treatment. Epigastric pain and diarrhoea were recorded as adverse effects during both MCT and triheptanoin treatment.

**Conclusions** The significant improvement in clinical outcome measures after the administration of triheptanoin highlights that this treatment approach can be more effective than MCT supplementation in patients with LC-FAOD. Triheptanoin was well tolerated and decreased the number of intercurrent catabolic episodes, metabolic decompensation episodes requiring hospitalisation, and the annualised rate and duration of hospitalisations.

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**Keywords** Inherited metabolic disorders, Long-chain fatty acid oxidation disorders, Medium-chain triglyceride oil, Triheptanoin

## Background

Long-chain fatty acid oxidation disorders (LC-FAOD) are rare, autosomal recessive, potentially life-threatening disorders leading to deficient energy production and accumulation of toxic metabolites [1, 2]. Deficiencies in any of the long-chain fatty acid  $\beta$ -oxidation enzymes can cause metabolic disorders, such as very long-chain acyl-coenzyme A dehydrogenase deficiency (VLCADD), long-chain hydroxyacyl-coenzyme-A dehydrogenase deficiency (LCHADD) and mitochondrial trifunctional protein deficiency (MTPD), or as disorders of carnitine transport, such as carnitine palmitoyltransferase type 1 deficiency (CPT1D), carnitine palmitoyltransferase type 2 deficiency (CPT2D) and carnitine-acylcarnitine translocase deficiency (CACTD) [2].

Common signs and symptoms in LC-FAOD in the first weeks of life include cardiac arrhythmias, hypoglycaemia and sudden death; later in infancy and early childhood, the disease presents as liver- or cardiac-related symptoms or skeletal muscle dysfunction, including fasting or stress-related hypoketotic hypoglycaemia, hyperammonaemia (or Reye-like syndrome), conduction abnormalities, arrhythmias, dilated or hypertrophic cardiomyopathy and muscle weakness or fasting- and exercise-induced rhabdomyolysis [3]. Patients with adolescent or adult-onset LC-FAOD predominantly experience muscular symptoms, including rhabdomyolysis and cardiomyopathy. Episodes of metabolic decompensation are usually triggered by fasting, intercurrent febrile illnesses or prolonged exercise [4]. Different from other LC-FAOD, most patients with LCHADD and MTPD also present with peripheral sensory-motor polyneuropathy and pigmentary retinopathy during the course of the disease [3], and more rarely with hypoparathyroidism [1].

The current standard of care for LC-FAOD is dietary management, including maximum fasting guidelines (under healthy steady-state conditions and according to age), restricted long-chain triglyceride (LCT) intake and supplementation with medium-chain triglyceride (MCT) oil [5]. Despite this management approach, most patients will experience recurrent, sometimes life-threatening, decompensation episodes that can often require hospitalisation [6]. Triheptanoin is a highly purified, synthetic medium odd-chain (C7) triglyceride that can bypass long-chain oxidation [7]. It is approved in the United States (US) as a source of calories and fatty acids in patients with LC-FAOD [8], but is only available as a part of compassionate use programs in other countries [9, 10].

A randomised clinical study demonstrated improved cardiac structure and function (at rest and during exercise) with triheptanoin versus an even-chain triglyceride (trioctanoin) for 4 months [11]; other studies showed a reduction in the annual rate and duration of major clinical events (i.e. rhabdomyolysis, hypoglycaemia and cardiomyopathy) compared with the pre-treatment period [7, 9]. Similarly, retrospective observational studies have reported a decreased incidence of major clinical events and lower hospitalisation rates with triheptanoin compared with MCT oil [12, 13], as well as stabilisation of cardiac function in patients with paediatric cardiomyopathy [14].

In this study, we retrospectively examined the effectiveness and safety of triheptanoin treatment compared with MCT oil in a cohort of patients with LC-FAOD in Italy.

## Methods

### Study design and patients

In this retrospective nationwide study, data were collected from patients who were diagnosed with LC-FAOD (the molecular variants detected in the different genes were: HDBHA: Glu510Gln; HDBHB: Thr69Ile, Gly427Glu, and Gly301Ser; CPT2: Tyr628Ser, His555Gln, and Ser113Leu; ACADVL: Gly185Ser, Val283Ala, His335Pro). Patients were treated with oral triheptanoin (provided at a mean dose of  $1.5 \pm 0.9$  g/kg/day in four divided administrations) as part of an Agenzia Italiana del Farmaco (AIFA)-funded programme at five centres in Italy between 2018 and 2022. Patients were observed for a maximum of 4 years of triheptanoin treatment.

Ethics approval for this study was obtained from the ethics committee of AOU Citta della Salute e della Scienza di Torino, Italy (0069665–109/2023).

### Outcome measures

The following data were retrospectively collected from medical records: LC-FAOD diagnosis, age at diagnosis, method of diagnosis, age at the time of study enrolment, weight, height, body mass index (BMI) and details of treatment with MCT oil and subsequent triheptanoin treatment (i.e. duration, daily dose and percentage of total daily calories). Clinical outcome measures were the number of intercurrent catabolic episodes, the number of metabolic decompensation episodes requiring hospitalisation or intensive care unit (ICU) admissions, the number of hospitalisations per year (annualised hospitalisation rate) and days per hospitalisation, both during

standard MCT therapy and during subsequent triheptanoin treatment. Creatine kinase (CK) levels (during and outside of metabolic decompensation episodes) and adverse effects during treatment were also assessed.

### Statistical analysis

Descriptive statistics were used for all analyses, and data are reported as mean  $\pm$  standard deviation (SD). The Shapiro–Wilk test was used to check normal distribution of data. Differences between groups were established with the Student's *t*-test or Wilcoxon–Mann–Whitney *U* test for parametric and non-parametric variables, respectively. The level of statistical significance for all calculations was taken as a two-tailed *p*-value less than 0.05.

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY, USA).

## Results

### Patient characteristics

Nine patients (four males and five females) with LC-FAOD were treated with triheptanoin between 2018 and 2022 and were included in this analysis. Four patients had a diagnosis of MTPD, three had CPT2D and two had VLCADD (Table 1). The diagnosis was established by clinical symptoms alone in six patients, clinical symptoms plus newborn screening (NBS) by tandem mass spectrometry in two patients and NBS alone in one patient. In all patients, diagnosis of LC-FAOD was genetically confirmed. The mean age at diagnosis was  $1.5 \pm 1.8$  years. At the time of study enrolment, patients had a mean age of  $11.1 \pm 4.5$  years and a mean BMI *z*-score of  $0.09 \pm 1.00$ .

### Treatment regimens

Prior to starting triheptanoin treatment, the patients received MCT oil for a mean of  $7.0 \pm 4.5$  years. The

mean dose of MCT oil was  $1.7 \pm 0.8$  g/kg/day in four divided administrations, accounting for  $21 \pm 9\%$  of the total daily caloric intake (Table 2). Triheptanoin treatment was started at between 2.7 and 16 years of age and was continued for a mean of  $2.2 \pm 0.9$  years. Triheptanoin was provided at a mean dose of  $1.5 \pm 0.9$  g/kg/day in four divided administrations, accounting for  $24 \pm 9\%$  of the total daily caloric intake.

### Clinical events

As shown in Fig. 1a, each patient had a significant reduction in the total number of intercurrent catabolic episodes during triheptanoin therapy compared with prior MCT oil (triheptanoin  $4.3 \pm 5.3$  vs MCT  $22.0 \pm 22.2$ ;  $p = 0.034$ ). Similarly, all nine patients had a significant reduction in the number of metabolic decompensation episodes requiring hospitalisation after switching from MCT oil to triheptanoin treatment (triheptanoin  $2.0 \pm 2.5$  vs MCT  $18.3 \pm 17.7$ ;  $p = 0.014$ ; Fig. 1b). During treatment with MCT oil, three patients required four ICU admissions for metabolic decompensation (i.e. rhabdomyolysis without hypoglycaemia or cardiomyopathy), while no ICU admissions were required during triheptanoin treatment.

Eight of nine patients had a reduction in the annualised hospitalisation rate after switching from MCT oil to triheptanoin treatment (triheptanoin  $0.7 \pm 0.8$  vs MCT  $3.1 \pm 3.0$  per year;  $p = 0.03$ ; Fig. 2a), and seven had a reduction in the number of days per hospitalisation (triheptanoin  $3.6 \pm 3.4$  vs MCT  $10.5 \pm 5.0$ ;  $p = 0.004$ ; Fig. 2b). There were significant improvements in the number and duration of clinical events after triheptanoin therapy (Fig. 3).

**Table 1** Characteristics of nine patients with long-chain fatty acid oxidation disorders

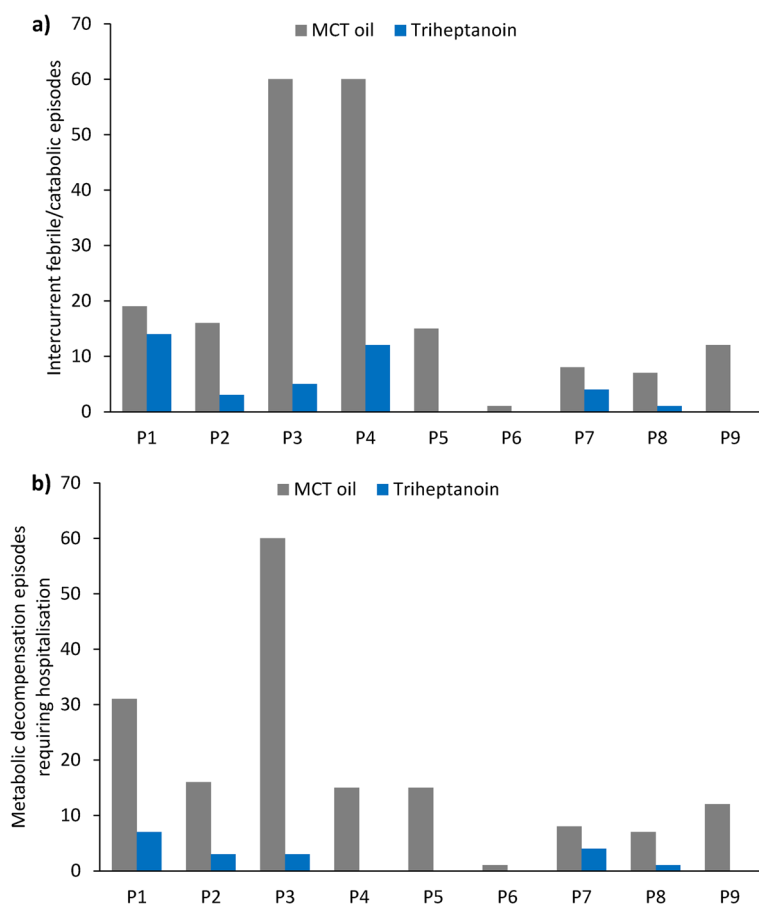
Patient	LC-FAOD diagnosis	Age at diagnosis (years)	Diagnosis method	Current age (years)	Current weight (kg)	Current height (cm)	Current BMI <i>z</i> -score
1	MTPD	0.1	NBS + clinical symptoms	7.4	24	118	1
2	MTPD	1.0	Clinical symptoms	5.0	17	112	-1.2
3	CPT2D	0.6	Clinical symptoms	18.2	66	185	-1.1
4	MTPD	0.5	Clinical symptoms	12.0	41	155	-0.6
5	CPT2D	4.0	Clinical symptoms	16.0	71	178	0.6
6	CPT2D	5.0	Clinical symptoms	8.0	25	124	0.3
7	VLCADD	2.0	Clinical symptoms	15.0	63	164	1.2
8	MTPD	0.01	NBS + clinical symptoms	9.0	32	146	-0.7
9	VLCADD	0.3	NBS	8.9	31	128	1.3

BMI body mass index, CPT2D carnitine palmitoyl transferase 2 deficiency, LC-FAOD long-chain fatty acid oxidation disorders, MTPD mitochondrial trifunctional protein deficiency, NBS newborn screening, VLCADD very long-chain acyl-CoA dehydrogenase deficiency

**Table 2** Comparison of MCT oil versus triheptanoin in nine patients with long-chain fatty acid oxidation disorders

Patient	MCT oil treatment					Triheptanoin				
	Treatment duration (years)	Age during treatment (years)	Hypolipidic diet, mean fat (g/kg/day)	Mean MCT dose (g/kg/day)	Calories from MCT (%)	Treatment duration (years)	Age during treatment (years)	Hypolipidic diet, mean fat (g/kg/day)	Mean triheptanoin dose (g/kg/day)	Calories from triheptanoin (%)
1	3.2	0.1–3.3	2.6	2.6	22	4.0	3.3–7.3	2.8	2.4	30
2	1.7	1.0–2.7	2.5	2.5	30	2.3	2.7–5.0	3.2	2.9	32
3	15.4	0.6–16.0	0.9	0.5	10	2.5	16.0–18.5	1.0	0.7	23
4	10.0	0.5–11.0	–	1.0	13	1.0	11.0–12.0	–	0.5	10
5	6.0	7.0–13.0	–	0.5	8	3.0	13.0–16.0	1.6	1.1	29
6	1.0	5.0–6.0	–	2.0	24	2.0	6.0–8.0	2.1	0.8	10
7	11.0	2.0–13.0	–	2.0	26	2.0	13.0–15.0	1.7	1.0	34
8	7.0	0–7.0	–	1.7	20	2.0	7.0–9.0	–	2.5	26
9	7.0	1.0–8.0	2.3	2.3	36	1.0	8.0–9.0	2.6	1.3	21

MCT Medium-chain triglycerides



**Fig. 1** The number of **a** intercurrent febrile/catabolic episodes and **b** metabolic decompensation episodes requiring hospitalisation during medium-chain triglyceride (MCT) oil and subsequent triheptanoin treatment in each patient (P)

**Creatine kinase levels**

Each patient showed a reduction in mean CK levels during metabolic decompensation after switching from MCT oil to triheptanoin treatment (Fig. 4a). Overall, mean CK levels during decompensation decreased from  $66,178 \pm 57,565$  IU/L to  $30,550 \pm 24,958$  IU/L during triheptanoin treatment, although this difference was not statistically significant ( $p=0.218$ ). One patient experienced two severe episodes of rhabdomyolysis (with concomitant high transaminases) during treatment with MCT oil that required continuous veno-venous haemodialysis. There were no occurrences of hypoketotic hypoglycaemia, cardiomyopathy, muscle weakness, hyperammonaemia (or Reye-like syndrome) or hepatomegaly during triheptanoin treatment.

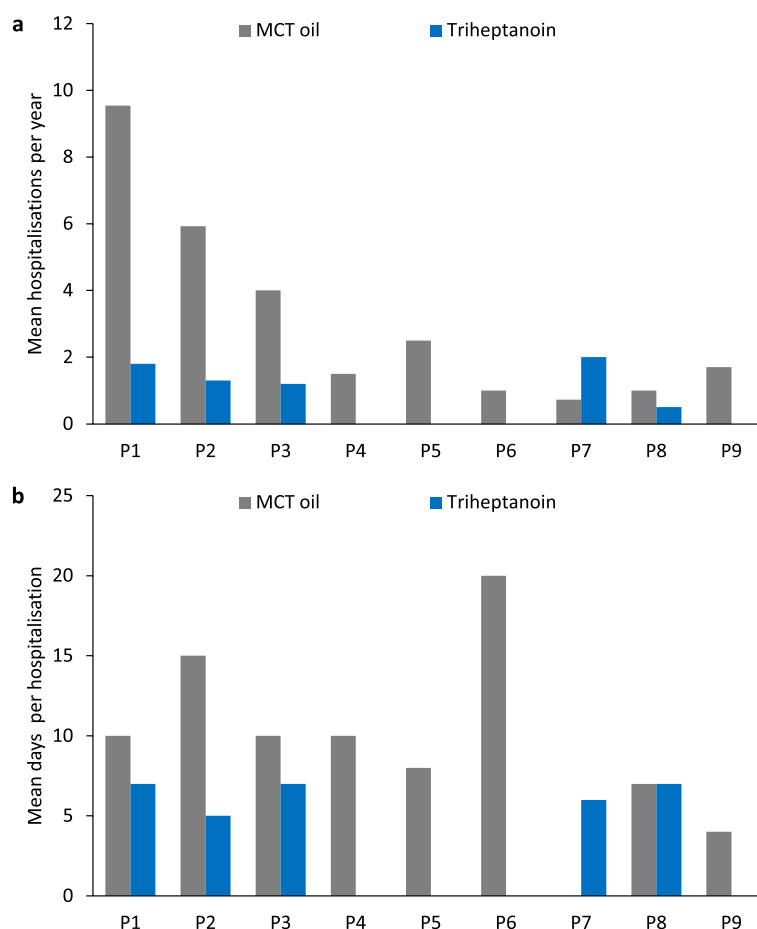
Mean well-being CK levels (i.e. outside metabolic decompensation episodes) were lower with triheptanoin treatment versus MCT oil for seven patients (Fig. 4b), with a mean CK level for all patients of  $828 \pm 1238$  UI/L during MCT oil treatment vs  $274 \pm 242$  UI/L during triheptanoin treatment ( $p=0.207$ ).

**Safety**

Two patients reported adverse effects during MCT oil treatment: diarrhoea in Patient 3 and epigastric pain in Patient 7, which resolved after the administration of a proton pump inhibitor. One patient (Patient 3) had adverse effects during triheptanoin treatment (epigastric pain and diarrhoea).

**Discussion**

In this study, nine patients with LC-FAOD received triheptanoin treatment (accounting for 10–34% of the total daily caloric intake) for a mean of 2.2 years after switching from standard therapy with MCT oil (accounting for 8–36% of the total daily caloric intake) for a mean of 7.0 years. The focus of long-term nutritional management in LC-FAOD is to use an energy source other than long-chain fatty acids to provide sufficient daily calories [15]. Dietary management usually involves avoiding prolonged fasting, restriction of LCTs, a modest increase in carbohydrates and MCT supplementation as an alternative form of energy to LCTs [5, 6, 15].



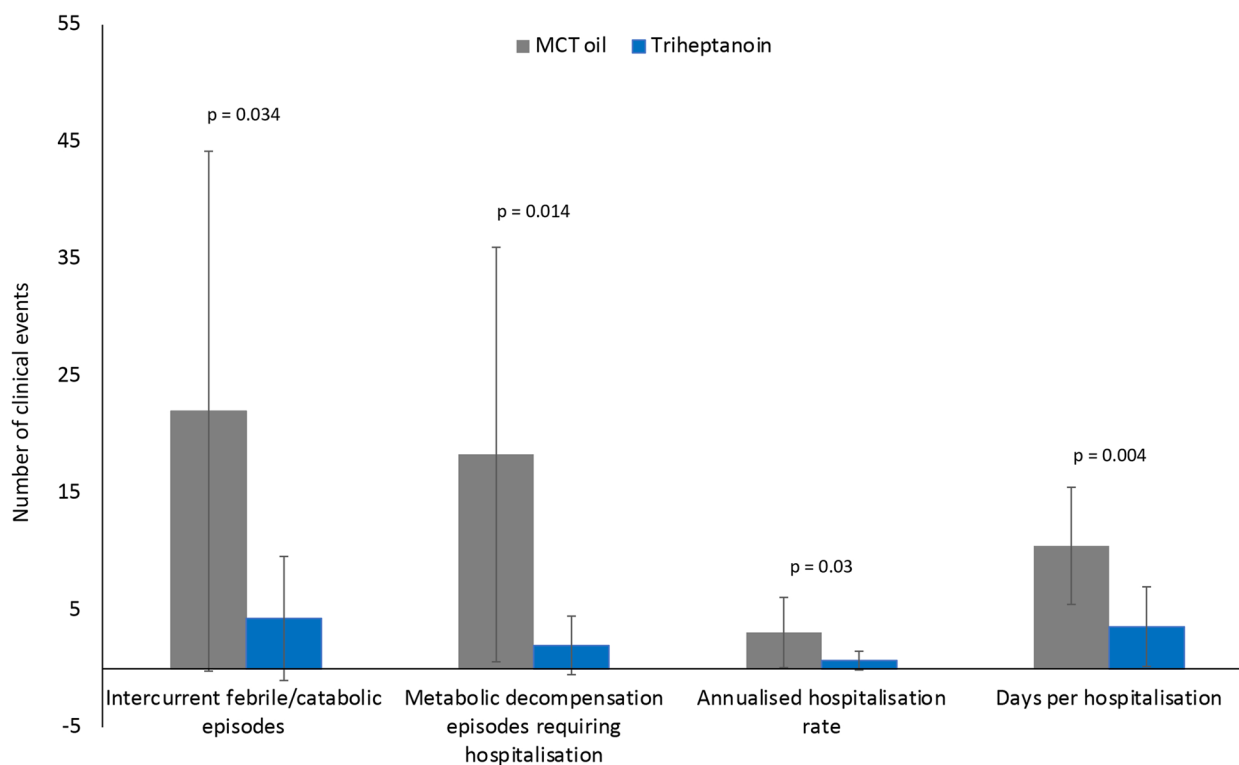
**Fig. 2** Mean number of **a** hospitalisations per year and **b** days per hospitalisation during medium-chain triglyceride (MCT) oil and subsequent triheptanoin treatment in each patient (P)

MCTs consist of even-chain fatty acids, are 6–12 carbons long, do not require L-carnitine for mitochondrial transport and do not require oxidation by long-chain acyl-coenzyme A (CoA) hydrogenase enzymes [15], thereby bypassing the metabolic defects in LC-FAOD [6]. The recommended limit for long-chain fatty acid intake ranges from 10% of total daily calories in patients with severe forms of LC-FAOD to 45% in infants with mild disease [15].

Triheptanoin represents an alternative to MCT that has been associated with improved clinical outcomes in patients with LC-FAOD [7, 9, 11, 16, 17]. Triheptanoin consists of odd-chain fatty acids (C7) with anaplerotic properties (different from even-chain variants), which are metabolised through  $\beta$ -oxidation to acetyl-CoA [15]. Since patients with LC-FAOD do not properly oxidise fat to acetyl-CoA, there is an impairment of the tricarboxylic cycle and consequent lack of ketone body formation. Triheptanoin is a source of acetyl-CoA and propionyl-CoA, resulting in increased substrate availability in the

tricarboxylic acid cycle [15]. The US prescribing information recommends providing up to 35% of total daily calories from triheptanoin, divided into at least four administrations per day [8]. A retrospective observational study conducted in the US reported that most patients survived the initial trigger event (e.g. severe infection) and demonstrated both short- and long-term improvements in manifestations of LC-FAOD following the initiation of triheptanoin therapy [17].

The current study found a significant reduction in the number of intercurrent catabolic episodes once patients switched from MCT oil to triheptanoin treatment. Enzyme deficiencies in the metabolic pathway that converts LCTs into energy can lead to depleted energy production, resulting in severe acute metabolic crises, such as rhabdomyolysis, hypoglycaemia and cardiomyopathy [18], which may lead to hospitalisation, ICU admission or premature death. In this study, metabolic decompensation episodes requiring hospitalisation were markedly reduced once triheptanoin treatment was started.



**Fig. 3** Comparison of the mean number of clinical events and hospitalisations during medium-chain triglyceride (MCT) oil and subsequent triheptanoin treatment in each patient (P)

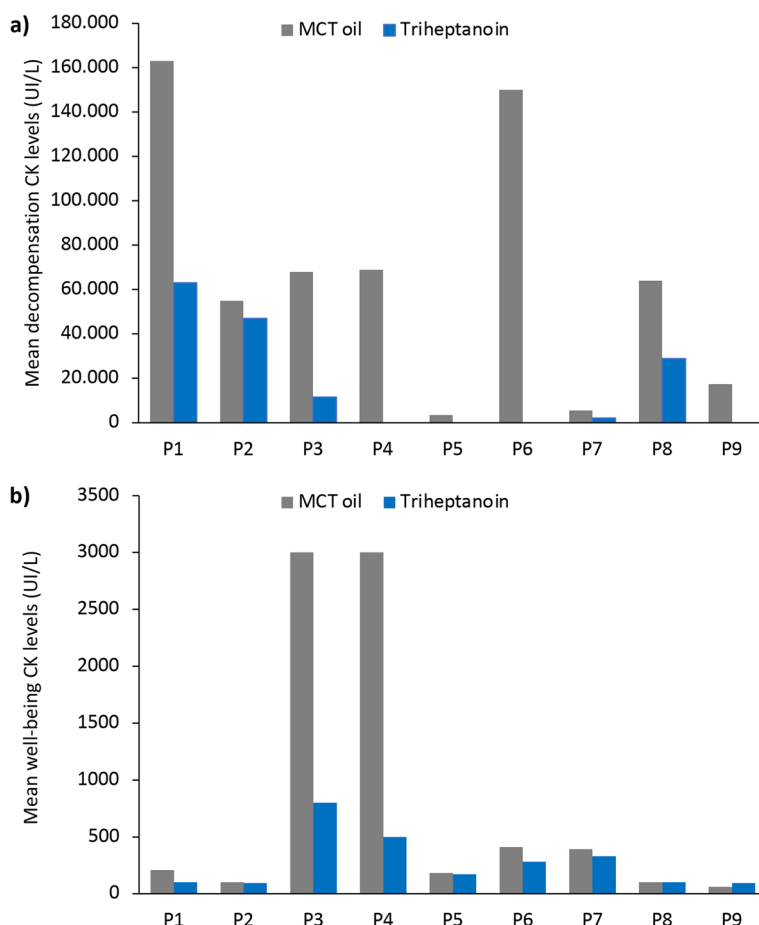
Similarly, a previous study of three US patients with LC-FAOD reported fewer hospitalisations related to metabolic crises, as well as lower annualised rates and durations of hospitalisation, after the start of triheptanoin treatment [19]. In the current study, we observed a 77.4% reduction in the annualised hospitalisation rate during the triheptanoin treatment period, in line with the final results of a previous open-label extension study, which found an 85% reduction in this outcome measure [16]. In addition, patients with LC-FAOD who received triheptanoin in the previous study had reduced rates of hospitalisation due to rhabdomyolysis, cardiomyopathy and hypoglycaemia; these beneficial effects were sustained with long-term triheptanoin treatment [16].

CK levels, both during metabolic decompensation and steady-state conditions, were lower with triheptanoin versus MCT oil, although these differences did not reach statistical significance. These findings are consistent with those of a similar retrospective observational study of 12 patients with LC-FAOD in Austria, in which the total number of hospitalisation days decreased by 82% and the episodes of elevated CK levels (i.e. >500 UI/L) decreased by 45% after initiation of triheptanoin (mean treatment duration 5.3 years) compared with the pre-treatment period [13]. Similar to our study, rhabdomyolysis also

occurred in one patient during MCT oil therapy, but there were no cases of rhabdomyolysis recorded with triheptanoin treatment in the Austrian study [13]. Another retrospective US study of 52 patients with LC-FAOD reported that episodes of rhabdomyolysis requiring hospital admission were reduced from 85 to 31% after switching from MCT to triheptanoin treatment [20].

Current guideline recommendations specify that patients with severe LC-FAOD should receive their total caloric intake from MCT [15]. However, high-dose administrations of MCT may cause gastrointestinal symptoms (e.g. cramping, diarrhoea and vomiting) [21]. In our study, the only treatment-related adverse effects with triheptanoin were gastrointestinal in nature (i.e. epigastric pain and diarrhoea) and were similar to those observed during MCT treatment. Although triheptanoin is generally well tolerated [17, 22], the documented adverse effects in other studies were also predominantly mild gastrointestinal symptoms (e.g. diarrhoea, abdominal or gastrointestinal pain, nausea and vomiting, abdominal distension and flatulence) [10, 16].

In this study, molecular confirmation was obtained for all patients either diagnosed by NBS or clinically. To this purpose, the use of next generation sequencing can be useful to provide counseling to the family on genetic



**Fig. 4** Mean **a** decompensation and **b** well-being creatine kinase (CK) levels during medium-chain triglyceride (MCT) oil and subsequent triheptanoin treatment in each patient (P)

diseases, establishing the risk of recurrence and advancing potential genotype–phenotype correlations [23, 24].

The limitations of this study include its retrospective, open-label and uncontrolled design, and the relatively small and heterogeneous study population. Since the total daily caloric intake provided by MCT and triheptanoin treatment differed between patients, a dose-dependent effect on clinical outcomes could not be ruled out.

**Conclusions**

Treatment with triheptanoin provided significant improvement of clinical outcomes compared with standard MCT therapy in patients with LC-FAOD, with decreases in intercurrent catabolic episodes, metabolic decompensation episodes requiring hospitalisation and the annualised rate and duration of hospitalisations in these patients. Triheptanoin treatment was well tolerated, with few adverse effects. These results highlight that

triheptanoin is a safe and more effective treatment option compared with MCT in patients with LC-FAOD.

**Abbreviations**

- AIFA Agenzia Italiana del Farmaco
- BMI Body-mass index
- CACTD Carnitine-acylcarnitine translocase deficiency
- CK Creatine kinase
- CoA Coenzyme A
- CPT1D Carnitine palmitoyltransferase type 1 deficiency
- CPT2D Carnitine palmitoyltransferase type 2 deficiency
- ICU Intensive care unit
- LC-FAOD Long-chain fatty acid oxidation disorders
- LCHADD Long-chain hydroxyacyl-coenzyme-A dehydrogenase deficiency
- LCT Long-chain triglyceride
- MCT Medium-chain triglyceride
- MTPD Mitochondrial trifunctional protein deficiency
- SD Standard deviation
- US United States
- VLCADD Very long-chain acyl-coenzyme A dehydrogenase deficiency

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### Authors' contributions

FP, AM, VG, EP, SG, RT, MS, CD-V and AB contributed towards the study design, patient enrolment, data collection and analysis. FP participated in the drafting of the manuscript and AM, VG, EP, SG, RT, MS, CD-V and AB revised and approved all drafts of the manuscript.

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### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Declarations

#### Ethics approval and consent to participate

Ethics approval for this study was obtained from the ethics committee of AOU Città della Salute e della Scienza di Torino, Italy (0069665–109/2023). Written consent to participate in this study was obtained from all study participants or their legal guardians. We confirm that all methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

#### Consent for publication

Not applicable.

#### Competing interests

VG received honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events from Sanofi and Nutricia; and financial support for attending meetings and/or travel expenses from Sanofi, Nutricia, Amicus and PIAM. SG, EP, FP, AM, CD-V and AB received fees for participation on the advisory board following personal experience in using triheptanoin. MS declares they have no competing interests.

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