

Long-term follow-up in an open-label trial of triheptanoin in GLUT1 deficiency syndrome: a sustained dramatic effect

BACKGROUND

Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is caused by heterozygous mutations in the *SLC2A1* gene. Glucose transport is impaired across the blood–brain barrier and into astrocytes. This eventually results in cerebral energy deficiency.¹ Typically, GLUT1-DS is associated with developmental delay, permanent motor disorders and paroxysmal manifestations including epileptic and non-epileptic paroxysmal episodes.^{1 2} The phenotypic spectrum is however much wider: exercise-induced paroxysmal dyskinesia may sometimes be the main or sole manifestation of the disease.^{3 4}

Ketogenic diet is the standard of care in GLUT1-DS,^{1 5} providing ketone bodies as an alternate source of energy to the brain. Other alternative treatments are needed as

many patients have difficulties following the heavy constraints of this diet. Triheptanoin (UX007; Ultragenyx Pharmaceuticals, Novato, USA) is a medium odd-chain triglyceride containing three 7-carbon fatty acids with anaplerotic properties.⁶⁻⁸ Unlike even-chain fatty acids that can only generate acetyl-CoA, triheptanoin provides indeed both acetyl-CoA and propionyl-CoA, two key carbon sources for the Krebs cycle.^{9,10}

We recently showed that triheptanoin dramatically reduced by 90% the number of non-epileptic paroxysmal manifestations over 2 months in GLUT1-DS and improved patient's brain energy profile.⁹ Here, we wished to evaluate the long-term clinical efficacy of triheptanoin in children and adults with GLUT1-DS.

METHODS

We extended our study protocol (NCT02014883) based on the striking short-term response with triheptanoin.⁹ All participants and/or their legal guardians signed a new informed consent. Among the six patients previously reported who completed the initial study,⁹ five patients (P1, P3-P6) opted to participate in the study extension. Patient P2, who prior to the study failed being on a ketogenic diet after a few months, declined the extension due to her strong appetite for glucose. Patient's characteristics were the same as in the

initial trial.⁹ Triheptanoin was reintroduced after the withdrawal phase from the initial study (figure 1A). The study was extended for 3 years, divided into four phases: (1) resumption short-term (6 months); (2) resumption mid-term (6 months); (3) second year of follow-up (1 year); and (4) third year of follow-up (1 year).

Patient's diet was isocaloric, but restricted in fast sugars, and triheptanoin, distributed during meals, represented about 30% of patient's calorie intake.^{9,10} Dietary and therapeutic compliance was assessed by a trained dietitian at each visit.

During each study phase, the patients and/or their caregivers filled a comprehensive diary to record all motor and non-motor paroxysmal events, as well as their approximate duration in minutes.⁹ At each visit, diaries were comprehensively reviewed by the evaluating physician. The primary endpoint was the total number of paroxysmal events normalised over a month. Secondary endpoints were their mean duration, the number of motor events and the clinical Global Impression Severity Scale (CGI-S, range 0-7) completed by the patient at each visit. Compliance was verified with dosage of triheptanoin-derived metabolites in plasma (acylcarnitines and C5-keto acids) collected after an overnight fast.

For clinical parameters, Friedman tests were used to test the global hypothesis that study phases were equal. If significant,

Dunn's multiple comparison tests were applied for pairwise phase comparisons with an α of 0.05.

RESULTS

Compared with baseline, triheptanoin reduced the number of monthly total paroxysmal events during the resumption mid-term phase ($p=0.048$) as well as during the second and third year of follow-up ($p=0.036$ and 0.004 , respectively) (figure 1B, online supplementary table e1). This therapeutic response was similar to what we previously demonstrated during the initial treatment phase with triheptanoin.⁹ Furthermore, triheptanoin significantly reduced the number of monthly motor paroxysmal events during the second and third year of follow-up ($p=0.028$ and 0.016 , respectively) (figure 1B, online supplementary table e1). Notably, compared with baseline, the number of paroxysmal events decreased during the resumption short-term phase of the study but that decrease did not reach significance (figure 1B).

Triheptanoin tended to reduce the mean duration of total paroxysmal events, particularly during the second and third year of follow-up (online supplementary table e1). The same trend of improvement on triheptanoin was observed on the CGI-S score: on average, patients evolved from moderately ill at baseline to mildly ill after 2 or 3 years of treatment with

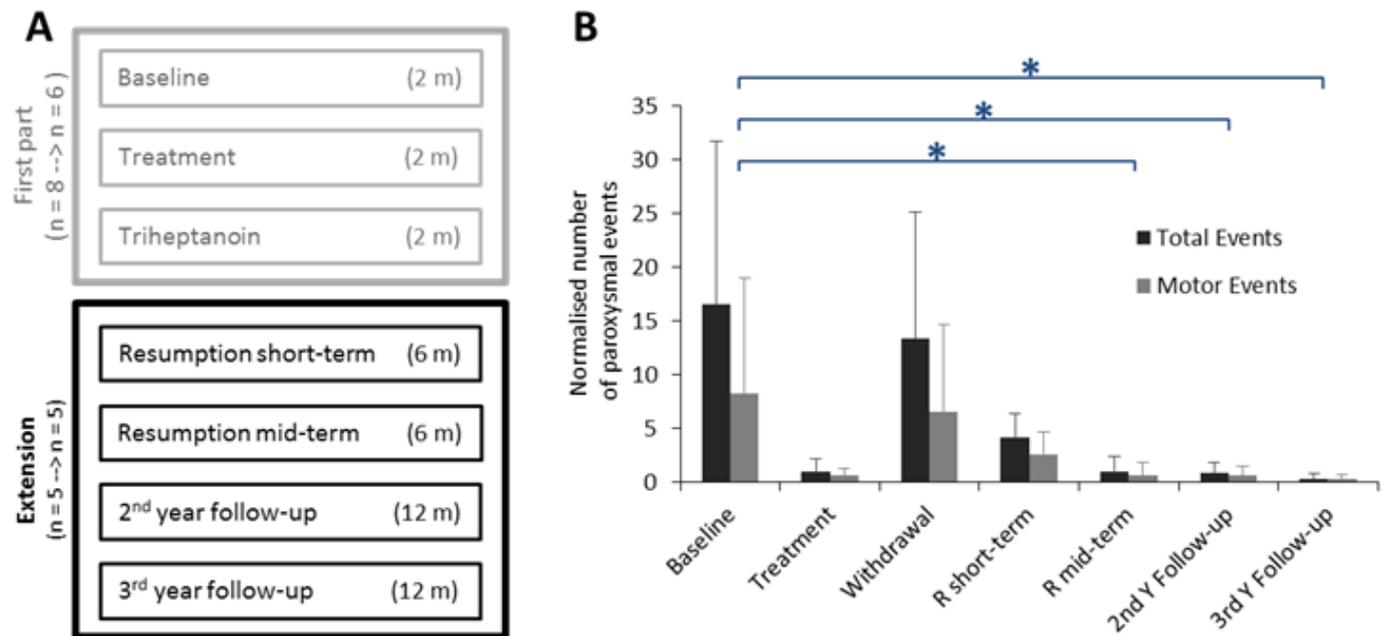


Figure 1 (A) Flow chart. (B) Normalised number of paroxysmal events in patients with glucose transporter type 1 deficiency syndrome (GLUT1-DS) during the different phases of the study. Total and motor numbers of paroxysmal events are expressed in mean per month. Error bars represent SEM. * $P<0.05$ (Dunn's tests). m, number of months; n, number of patients.

trihéptanoïn (online supplementary table e1).

Plasma propionylcarnitine and C5-keto acid levels measured at the end of each period were higher after trihéptanoïn treatment (data not shown), reflecting proper metabolism of trihéptanoïn.

Although our study was not designed to evaluate cognitive performances, we observed an improvement of cognitive performance during the study extension. Compared with before baseline, P1 improved her total IQ (63 to >72), verbal IQ (62 to >72) and performance IQ (67 to >75) after 2 years of treatment with trihéptanoïn, and P3 improved his school performance.

DISCUSSION

In five patients with GLUT1-DS, treatment with trihéptanoïn led to a dramatic (97%) and sustained reduction of motor and non-motor paroxysmal events over 3 years. The magnitude and duration of this response confirm the therapeutic benefit of trihéptanoïn and eliminate a placebo effect.

Proper compliance is key to obtaining good results. It means compliance to the prescribed trihéptanoïn dosage and to a low-sugar diet. Indeed, when trihéptanoïn was reintroduced, we observed that paroxysmal events were reduced compared with baseline but without reaching statistical significance, suggesting that the magnitude of the effect was less pronounced than in the initial study. We realised that the remaining events were associated with increased intake of fast sugars due to relaxed habits during the withdrawal phase. Renewed explanation and closer monitoring of sugar intake led to a significant reduction of paroxysmal events during the subsequent study phases. Over the last year of treatment, patients have become almost free of events. As for any dietary intervention, proper diet instructions and monitoring are mandatory for trihéptanoïn to provide its best efficacy. This is a major lesson for future trials using trihéptanoïn in GLUT1-DS or other diseases. Continued treatment with trihéptanoïn is currently provided to our patients through a temporary use of authorisation, but a study on a larger patient group should be encouraged.

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Competing interests FM holds a patent on the use of trihéptanoïn in GLUT1-DS (WO2014093901).

Patient consent for publication Not required.

Ethics approval The extension study was sponsored by INSERM and approved by the local ethical committee (ID RCB: 2013-A01300-45).

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