Effectiveness and safety of the tri-iodothyronine analogue Triac in children and adults with MCT8 deficiency: an international, single-arm, open-label, phase 2 trial

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Summary

Background Deficiency of the thyroid hormone transporter monocarboxylate transporter 8 (MCT8) causes severe intellectual and motor disability and high serum tri-iodothyronine (T_3) concentrations (Allan–Herndon–Dudley syndrome). This chronic thyrotoxicosis leads to progressive deterioration in bodyweight, tachycardia, and muscle wasting, predisposing affected individuals to substantial morbidity and mortality. Treatment that safely alleviates peripheral thyrotoxicosis and reverses cerebral hypothyroidism is not yet available. We aimed to investigate the effects of treatment with the T_3 analogue Triac (3,3',5-tri-iodothyroacetic acid, or tiratricol), in patients with MCT8 deficiency.

Methods In this investigator-initiated, multicentre, open-label, single-arm, phase 2, pragmatic trial, we investigated the effectiveness and safety of oral Triac in male paediatric and adult patients with MCT8 deficiency in eight countries in Europe and one site in South Africa. Triac was administered in a predefined escalating dose schedule—after the initial dose of once-daily 350 µg Triac, the daily dose was increased progressively in 350 µg increments, with the goal of attaining serum total T_3 concentrations within the target range of 1·4–2·5 nmol/L. We assessed changes in several clinical and biochemical signs of hyperthyroidism between baseline and 12 months of treatment. The prespecified primary endpoint was the change in serum T_3 concentrations from baseline to month 12. The co-primary endpoints were changes in concentrations of serum thyroid-stimulating hormone (TSH), free and total thyroxine (T_4), and total reverse T_3 from baseline to month 12. These analyses were done in patients who received at least one dose of Triac and had at least one post-baseline evaluation of serum throid function. This trial is registered with ClinicalTrials.gov, number NCT02060474.

Findings Between Oct 15, 2014, and June 1, 2017, we screened 50 patients, all of whom were eligible. Of these patients, four (8%) patients decided not to participate because of travel commitments. 46 (92%) patients were therefore enrolled in the trial to receive Triac (median age 7·1 years [range 0·8–66·8]) . 45 (98%) participants received Triac and had at least one follow-up measurement of thyroid function and thus were included in the analyses of the primary endpoints. Of these 45 patients, five did not complete the trial (two patients withdrew [travel burden, severe pre-existing comorbidity], one was lost to follow-up, one developed of Graves disease, and one died of sepsis). Patients required a mean dose of 38.3 µg/kg of bodyweight (range 6·4–84·3) to attain T_3 concentrations within the target range. Serum T_3 concentration decreased from 4·97 nmol/L (SD 1·55) at baseline to 1·82 nmol/L (0·69) at month 12 (mean decrease 3·15 nmol/L, 95% CI 2·68–3·62; p<0·0001), while serum TSH concentrations decreased from 2·91 mU/L (SD 1·68) to 1·02 mU/L (1·14; mean decrease 1·89 mU/L, 1·39–2·39; p<0·0001) and serum free T_4 concentrations decreased from 9·5 pmol/L (SD 2·5) to 3·4 (1·6; mean decrease 6·1 pmol/L (5·4–6·8; p<0·0001). Additionally, serum total T_4 concentrations decreased by 31·6 nmol/L (28·0–35·2; p<0·0001) and reverse T_3 by 0·08 nmol/L (0·05–0·10; p<0·0001). Seven treatment-related adverse events (transiently increased perspiration or irritability) occurred in six (13%) patients. 26 serious adverse events that were considered unrelated to treatment occurred in 18 (39%) patients (mostly hospital admissions because of infections). One patient died from pulmonary sepsis leading to multi-organ failure, which was unrelated to Triac treatment.

Interpretation Key features of peripheral thyrotoxicosis were alleviated in paediatric and adult patients with MCT8 deficiency who were treated with Triac. Triac seems a reasonable treatment strategy to ameliorate the consequences of untreated peripheral thyrotoxicosis in patients with MCT8 deficiency.

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Introduction

Intracellular action of thyroid hormones requires membrane transporter proteins to facilitate their cellular entry. Monocarboxylate transporter 8 (MCT8) is a specific thyroid hormone transporter that is crucial for transport of tri-iodothyronine (T_3) and thyroxine (T_4) in several tissues, including the brain.[1] The *SLC16A2* gene (which is located on the X-chromosome) encodes MCT8, and mutations in this gene cause MCT8 deficiency (or Allan–Herndon–Dudley syndrome), a rare disorder with an estimated prevalence of one in 70 000 male individuals.[2–4] Because thyroid hormone entry into the brain is impaired, individuals with MCT8 deficiency have severe intellectual and motor disability and generally do not achieve early developmental milestones.

The endocrine hallmark of MCT8 deficiency is increased serum T_3 concentrations, reduced free T_4, and normal thyroid-stimulating hormone (TSH) concentrations. Peripheral tissues that rely on transporters other than MCT8 are exposed to high serum T_3 concentrations.[5] This chronic tissue thyrotoxicosis in patients with MCT8 deficiency leads to tachycardia, muscle wasting, hypermetabolism, and progressive reduction in bodyweight for age, causing substantial morbidity and mortality.[5] It is therefore imperative to treat the permanent hyperthyroidism present in this disorder. However, standard antithyroid drug therapy with thiamazole (also known as methimazole) has been shown to be ineffective.[4] The alternative antithyroid drug propylthiouracil has the potential to reduce serum T_3 concentrations through its inhibitory effect on type 1 deiodinase, but this treatment received a black box warning (the strongest drug safety warning) by the US Food and Drug Administration because of an associated risk of severe hepatotoxicity.[6] Accordingly, propylthiouracil is not recommended as therapy for hyperthyroidism and its use, particularly in children, is strongly discouraged by current guidelines.[7,8] The unfavourable safety profile of propylthiouracil is particularly relevant in the context of the frequent need to use other drugs with hepatotoxic side-effects (eg, anticonvulsants) in patients with MCT8 deficiency. An optimal therapy for MCT8 deficiency would safely alleviate peripheral thyrotoxicosis and restore euthyroidism in the brain, but, as yet, no such treatment is available. As a result, the majority of patients with MCT8 deficiency are currently left untreated.

Triac (3,3',5-tri-iodothyroacetic acid; also known as tiratricol) is a thyroid hormone analogue the cellular entry of which is not dependent on MCT8.[9–11] Triac can inhibit TSH secretion in human beings, thereby lowering endogenous thyroid hormone production, but it has fairly weak thyromimetic activity in peripheral tissues.[12,13] Data from preclinical studies suggest that Triac restores abnormal neuronal development and myelination in animal models of MCT8 deficiency if given in early postnatal life.[9,14] We therefore aimed to evaluate the effectiveness and safety of Triac treatment for peripheral

Research in context

Evidence before this study

We searched PubMed for studies published between Jan 1, 2004, and Jan 1, 2019, using the key words "MCT8", "MCT8 deficiency", or "Allan-Herndon-Dudley syndrome" and "therapy", with no further restrictions. Among 36 results, we identified no clinical trials. Several case reports and small case series (with fewer than six participants) have described the effects of different therapeutic strategies that either further exacerbate the thyrotoxicosis (levothyroxine), are associated with an unfavourable safety profile (propylthiouracil), or have inconsistent effects (di-iodothyroproprionic acid). The tri-iodothyronine (T_3) analogue Triac (3,3',5-tri-iodothyroacetic acid) was reported to completely prevent the neurological signs in mouse models of MCT8 deficiency. Moreover, Triac is known to effectively suppress endogenous thyroid hormone production in men while providing an adequate level of thyroid hormone action in peripheral tissues. Therefore, we hypothesised that Triac treatment could effectively reduce serum T_3 concentrations, thereby improving the negative clinical sequelae of chronic tissue thyrotoxicosis in patients with MCT8 deficiency. Triac might also offer beneficial effects on neurodevelopment if treatment is commenced early in life.

Added value of this study

To our knowledge, this study is the first clinical trial to assess the effects of the thyroid hormone analogue Triac in patients with MCT8 deficiency. In this pragmatic, phase 2 trial, Triac was safe, effectively normalised the serum T_3 concentrations in paediatric and adult patients with MCT8 deficiency, and showed sustained improvements in clinically relevant outcomes, including bodyweight, heart rate, and blood pressure.

Implications of all the available evidence

In the absence of any other available effective therapies, our findings show that Triac is the first disease-modifying treatment for patients with MCT8 deficiency. Severe underweight and cardiovascular dysfunction are important clinical sequelae of chronic peripheral thyrotoxicosis, causing substantial morbidity and mortality in patients with MCT8 deficiency. Amelioration of the thyrotoxicosis with Triac treatment could benefit patients with MCT8 deficiency, irrespective of their age. A future clinical trial (NTC 02396459) in young infants will evaluate the effects of Triac on the neuro-cognitive phenotype once treatment is initiated early in life.

thyrotoxicosis in paediatric and adult patients with MCT8 deficiency. In view of the wide spectrum of patient age in our study, neurocognitive changes were assessed in an exploratory way only.

Methods

Study design and participants

In this investigator-initiated, multicentre, open-label, single-arm, phase 2, pragmatic trial, we investigated the effectiveness and safety of Triac in male patients with MCT8 deficiency. We enrolled patients at 11 sites (ten hospitals and one outpatient facility) in eight countries in Europe (Belgium, Czech Republic, France, Germany, Italy, the Netherlands, Romania, and the UK) and one site in South Africa (appendix p 3). All patients were assigned to receive Triac for 12 months. The trial was originally intended to be a national study in the Netherlands, but it was amended to allow additional enrolment of patients in other countries. To ascertain long-term effectiveness and safety, the patients enrolled in the Netherlands could enter an open-label treatment extension period, the endpoint of which was defined as the completion date of the last patient in other countries.

Patients with MCT8 deficiency (confirmed by the presence of a mutation in the *SLC16A2* gene) were eligible to participate, irrespective of their age and comorbidities. Patients were either known to the investigators through direct care or were enrolled in the trial after their doctors or parents became aware of the trial through its ClinicalTrials.gov registration. Exclusion criteria were major illness or major surgery within the past 4 weeks, enrolment in other randomised controlled trials, allergy to components in Triac tablets, and the presence of any contraindications to Triac treatment (appendix p 13). Patients could be withdrawn from the trial at the request of the parents or guardians, if continued participation was considered to be harmful to participants' health by the investigators because of dose-limiting toxicities, or because of non-adherence to the trial protocol, premature termination of the trial, or loss to follow-up (appendix p 13).

Parents or guardians provided written informed consent for individuals they legally represent. The institutional review board at each participating site approved the study protocol and all amendments (appendix).

Procedures

All participants discontinued treatment with antithyroid drugs, levothyroxine, or both (if applicable) before commencing treatment with the study drug. After a washout period of at least 4 weeks, baseline measurements were recorded. We treated all patients with Triac (Téatrois tablets [350 µg], taken orally; Rare Thyroid Therapeutics, Stockholm, Sweden) with individualised dose-escalation that followed a predefined dose-escalation protocol: after the initial dose of 350 µg Triac (one tablet) once per day was given and no predefined dose-limiting toxic effects were identified, the daily dose was increased progressively in 350 µg increments (one tablet) with no maximum dose defined, with a goal of attaining serum total T_3 concentrations within the target range of 1·4–2·5 nmol/L. The maintenance Triac dose was continued for the rest of the study period (appendix p 4), but it could be further adjusted according to the dose-escalation protocol if T_3 concentrations were outside the target range during control visits (appendix p 4).

Patients were assessed for study outcomes at baseline and 12 months after starting Triac treatment. Between these times, we screened patients for clinical and biochemical signs of hyperthyroidism, we recorded adverse events, and we assessed adherence to therapy (appendix p 14–16). All study procedures were specified in standard operating procedures, and they were performed by trained investigators. We did neuropsychological tests (Bailey Scales of Infant Development III, Gross Motor Function Measure 88, and Vineland Adaptive Behaviour II) according to their manuals (appendix p 16). We measured all blood components in a central laboratory (Erasmus Medical Centre, Rotterdam, The Netherlands), except for the blood count and serum glucose, which were measured locally in the participating centers at the baseline and month 12 visit. To account for any interference of Triac in the measurement of serum T_3 concentrations, we used an algorithm based on the different levels of cross-reactivity of Triac in two T_3 assays (appendix p 2). Bone mineral density was measured by total body or forearm dual-energy X-ray absorptiometry. Cardiac evaluations consisted of a routine electrocardiogram, trans-thoracic cardiac ultrasound, and 24 h ambulatory cardiac monitoring.

Outcomes

The prespecified main primary endpoint was the change in the serum T_3 concentrations between baseline and month 12. The prespecified co-primary endpoints were the change in serum TSH, free and total T_4, and total reverse T_3 concentrations between baseline and month 12.

The prespecified secondary endpoints were the change between baseline and month 12 in bodyweight (expressed as bodyweight-for-age *Z* score, to account for natural development in children); mean heart rate, measured by 24 h ambulatory cardiac monitoring, and resting heart rate, measured by electrocardiography, both in bpm; blood pressure (in mm Hg and percentiles, based on reference ranges in healthy people;[15,16] mean of two measurements); and established biochemical parameters that reflect thyroid hormone activity in the liver (sex hormone-binding globulin and total cholesterol) and muscle (creatine kinase). Bodyweight was assessed instead of BMI, because accurate height measurements can be hampered by scoliosis and contractures.

An overview of prespecified exploratory measures, including neuropsychological tests and for which the

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See Online for appendix

endpoint was the change from baseline to month 12, is shown in the appendix (p 14–16) and the statistical analysis plan (appendix).

The prespecified assessments were the documentation of adverse events; echocardiography and 24-h monitoring of heart rhythm; bone mineral density measurement; and biochemical evaluations, including renal and liver function tests and bone turnover markers (appendix).

Post hoc, we also assessed the change in all available primary and secondary endpoints between baseline and the end of the treatment extension period in the participants treated for this time. Other post-hoc endpoints that we assessed between baseline and month 12 were the changes in total fat mass and percentage and lean body mass by dual-energy X-ray absorptiometry; the number of premature atrial contractions per 24 h; the ratio of HDL to LDL cholesterol; and the change in bodyweight (in kg). We also examined changes in neuropsychological test results after post-hoc stratification by age.

Although the measurement of energy expenditure (secondary endpoint) and hair cortisol concentrations (exploratory endpoint) were prespecified endpoints, their acquisition was compromised by technical difficulties and are, therefore, not reported.

Statistical analysis

We did a power calculation based on a one-sample *t* test to estimate the difference in serum T_3 concentrations after 12 months of treatment, by use of a mean serum T_3 concentration of 4·3 nmol/L (SD 1·2), which we derived from a historical group of 31 patients with MCT8 deficiency (unpublished data). With ten patients we would have 80% power (at a significance level of 0·05) to detect a mean decrease in serum T_3 concentrations from 4·3 nmol/L to 3·3 nmol/L. We thereby ensured sufficient power to detect a decrease in T_3 concentrations to the upper limit of the intended target range (1·4–2·5 nmol/L). This range was based on the reference range for healthy individuals in the Erasmus Medical Center at time of design of the trial protocol. After approval by all relevant ethical committees, we recruited additional patients to ascertain uniform documentation of the effects of Triac in this rare disorder and to provide more meaningful data on secondary outcomes and safety measures. Since, to our knowledge, this study represents the first clinical trial in patients with MCT8 deficiency, the number of withdrawals and effect sizes were difficult to predict beforehand.

Analyses of the prespecified primary endpoints were based on the full analysis dataset, which included all patients who received at least one dose of Triac and who had at least one control visit after the baseline assessment (appendix p 4). As such, patients who withdrew were included in the analyses, with their last available measurement used. The main analyses of the prespecified secondary endpoints were done in all patients who completed 12 months of treatment. In post-hoc analyses, the prespecified secondary endpoints were also done on the full analysis dataset, which included all patients who received at least one dose of Triac and who had at least one control visit after the baseline assessment. The analyses of prespecified exploratory endpoints and the post-hoc analyses were done in all patients who completed 12 months of treatment and for whom relevant data were available. Analyses of safety endpoints were done in the safety population, which included all patients exposed to at least one dose of the study drug.

For all prespecified primary and secondary endpoints, p values and 95% CIs were calculated for the mean change between baseline and month 12 by use of paired Student's *t* tests. Serum TSH and creatine kinase concentrations were first log-transformed to normalise the distribution. For all prespecified exploratory and safety measures, 95% CIs were calculated for the mean change between baseline and 12 months of Triac treatment. Post-hoc analyses of neurocognitive endpoints after stratification by age are descriptive only. Longitudinal analyses of the primary and secondary endpoints in the treatment extension period were done in all patients who received at least one dose of Triac after enrolment into the long-term treatment extension period, done with paired *t* tests, and they compared baseline versus the end of the treatment extension period.

Missing data can mainly be attributed to the poor clinical condition of patients, poor adherence to trial instructions, and common manifestations of MCT8 deficiency, such as scoliosis and dystonic posturing that hamper investigations for which patients needed proper positioning. With the assumption that omission of data occurred randomly, and given the broad age range of the participants and small group size, pairwise deletion was used to adjust for missing data that were only captured at baseline and 12 months; for missing data that were captured throughout the study, the last available measurement was used.

We used GraphPad Prism (version 6) for all statistical analyses. Two-sided p values of less than 0·05 were considered to denote statistical significance.

An independent data safety monitoring board monitored patient safety.

This trial is registered with ClinicalTrials.gov, number NCT02060474.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Between Oct 15, 2014, and June 1, 2017, we screened 50 patients for eligibility for the trial, all of whom were eligible. Of these 50 patients, four declined to participate; 46 patients were therefore enrolled and assigned to receive

Triac (appendix p 5), but one (2%) patient was withdrawn before the first control visit because of non-compliance to study procedures. This patient was included in safety analyses, but not primary efficacy analyses. 45 (98%) participants received Triac and had at least one follow-up measurement of thyroid function and thus were included in the analyses of the primary endpoints and in the post-hoc analyses of the secondary endpoints (appendix p 17). Five of these patients did not complete the study intervention: two were withdrawn due to parental choice (one because of travel time to the study centre, one because of severe comorbidity [severe epileptic seizures and hydrocephalus]), one was lost to follow-up, one developed Graves' disease, and one patient died from sepsis. 40 (87%) patients completed the 12-month intervention period and thus were included in the analyses of secondary and exploratory endpoints. Ten (22%) patients who completed the follow-up were also included in the long-term (median 40·4 months, IQR 38·1–41·3) treatment extension period (appendix p 5).

At baseline, the median age of the overall study population (n=46) was 7·1 years (range 0·8–66·8) and the mean serum T_3 concentration was 4·91 nmol/L (SD 1·57), which was more than 1·6-times the upper limit of the normal range for age (table 1). The mean weight-for-age *Z* score was –2·84 (1·88) and 30 (65%) of the 46 enrolled patients were underweight (*Z* score less than –2). All patients had severe intellectual and motor disability: 41 (89%) of 46 patients were wheelchair-bound and had not reached early developmental milestones such as independent sitting. Resting heart rate was very high (>90th percentile)[17] in 19 (43%) of 44 patients with data available and systolic hypertension was present in 12 (34%) of 35 patients with baseline blood pressure measurements. The median daily Triac dose remained stable after the dose-escalation phase, although seven (16%) of 45 patients required further dose adjustments to maintain T_3 concentrations within the target range (appendix p 6). The median daily Triac dose during the final study visit, either at month 12 or at time of withdrawal, was 37·0 µg/kg bodyweight (IQR 28·9–47·2).

In the 45 patients assessed for the primary endpoint, serum T_3 concentrations had significantly decreased by month 12 (median 13·1 months [IQR 12·4–13·9]), with a mean decrease of 3·15 nmol/L (95% CI 2·68–3·62; p<0·0001; figure 1; table 2), equivalent to 61% (56–66) from baseline. We also identified significant reductions in serum free T_4 concentrations (mean decrease 6·1 pmol/L, 5·4–6·8; p<0·0001) and serum TSH concentrations (mean decrease 1·89 mU/L, 1·39–2·39; p<0·0001). Additionally, serum total T_4 concentrations decreased by 31·6 nmol/L (28·0–35·2; p<0·0001) and reverse T_3 by 0·08 nmol/L (0·05–0·10; p<0·0001; (appendix p 7).

We assessed the secondary endpoints in the 40 patients who completed the 12-month treatment. We identified a significant increase in weight-for-age *Z* score at month 12 (0·27 SDs, 95% CI 0·03–0·50; p=0·0253; figure 1; table 2; appendix p 8), equating to a mean increase in bodyweight

	Triac (n=46)
Age (years)	7·1 (0·8–66·8)
Age group	
<4 years	11 (24%)
4–10 years	19 (41%)
11–18 years	11 (24%)
Adults (>18 years)	5 (11%)
Sex	
Female	0
Male	46 (100%)
Race	
White	44 (96%)
Other	2 (4%)
Ethnic origin	
European	39 (85%)
North Africa	3 (7%)
Middle Eastern	2 (4%)
Asian	1 (2%)
Other	1 (2%)
Country	
Netherlands	14 (30%)
UK	10 (22%)
France	7 (15%)
Italy	5 (11%)
Germany	3 (7%)
Romania	3 (7%)
Belgium	2 (4%)
Czech Republic	1 (2%)
South Africa	1 (2%)
Living location	
At home	34 (74%)
Institution	5 (11%)
Home and institution	7 (15%)
Developmental stage reached	
Wheelchair-bound	41 (89%)
No or poor head control	32 (70%)
Able to sit independently	5 (11%)
T_3 concentration (nmol/L)	4·91 (1·57)
Weight-for-age *Z* score	–2·84 (1·88)
Underweight*	30 (65%)
Uses a feeding tube	20 (43%)
Tachycardia at rest†	19 (43%)
Systolic hypertension‡	12 (34%)

Data are median (range), n (%), or mean (SD). T_3=triiodothyronine. *Underweight was based on WHO criteria (*Z* score <–2). †Tachycardia was defined as a resting heart rate above the 90th percentile for the corresponding age, with cut-offs described by Fleming and colleagues;[17] resting heart rate data were available for 44 patients (denominator for percentage calculation). ‡Systolic hypertension was based on guidelines from the American Academy of Pediatrics[15] and the American College of Cardiology and American Heart Association;[16] baseline blood pressure was measured in 35 patients (denominator for percentage calculation).

Table 1: **Baseline characteristics**

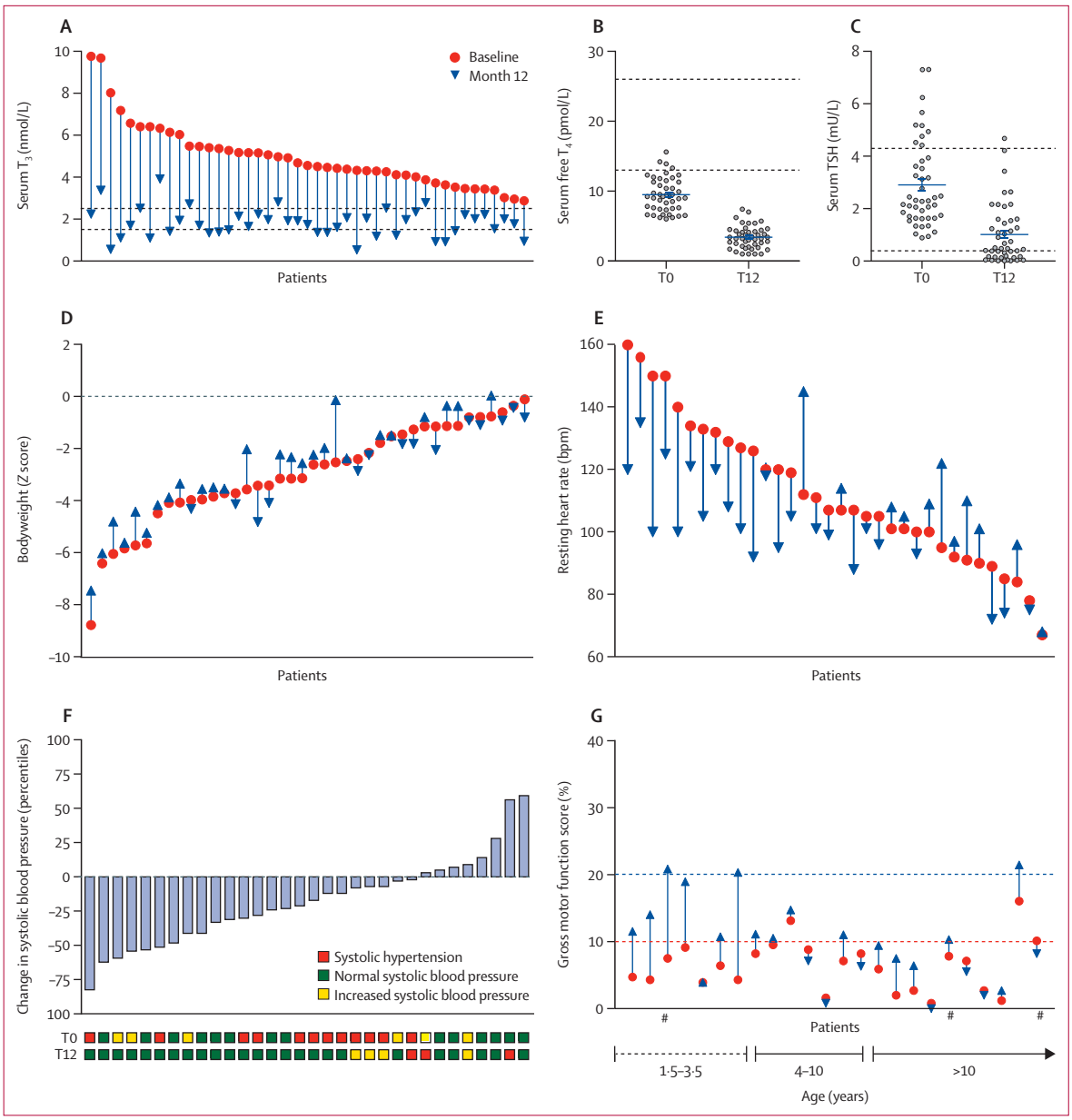

Figure 1: **Change from baseline to month 12 in prespecified primary and secondary and exploratory outcome measures**
Data are changes between baseline (T0) and month 12 (T12) of treatment with tri-iodothyroacetic acid in serum concentrations of T_3 (by patient; A), free T_4 (B), and TSH (C); bodyweight, as bodyweight-for-age *Z* scores (D); resting heart rate (by patient), determined by electrocardiogram (E); mean systolic blood pressure (by patient), expressed in percentiles after correction for age and height (F); and gross motor function (by patient), determined with the Gross Motor Function Measure 88. Gross motor function scores of 10% are indicated by the red dotted line, and 20% by the blue dotted line. Patients with the same inactivating F230del mutation are indicated with #. Data and p values are indicated in table 2. T_3=tri-iodothyronine. T_4=thyroxine. TSH=thyroid-stimulating hormone.

of 2·7 kg (1·9–3·5; p<0·0001); by contrast, in untreated patients, the bodyweight-for-age *Z* score has been shown to progressively reduce over time (appendix p 8). Between baseline and month 12, resting heart rate, as measured by electrocardiography, decreased by 9 bpm (95% CI 2–16; p=0·010), and mean heart rate, as measured by 24-h cardiac monitoring, decreased by 5 bpm (1–9; p=0·012; appendix p 9). Mean systolic blood pressure decreased over the 12-month study from the 78th percentile to the 61th percentile, equating to a change of 18 percentile points (95% CI 6–29; p=0·0037; table 2). The proportion of patients with systolic hypertension decreased from 34% (n=12/35) at baseline to 9% (n=3/32 at month 12). The serum concentrations of sex hormone-binding globulin decreased by 35 nmol/L (15–55; p=0·0013). However, mean serum total cholesterol concentration did not significantly change between baseline and month 12 (difference 0·2, 95% CI

0·0–0·3; p=0·056). Finally, serum creatine kinase concentrations increased by 53 U/L (27–78; p<0·0001) by month 12 (table 2; appendix p 10).

The greatest increase in gross motor function was in patients in whom Triac treatment was started before age 4 years (figure 1). At baseline, none of the 24 patients with a completely inactivating MCT8 mutation and available data had a score of more than 20% on the Gross Motor Function Measure 88 scale,[18] which would roughly reflect the ability to sit independently and achieve full head control in different postural positions. From the seven patients with a completely inactivating mutation who had started with Triac treatment before the age of 4 years, two reached this developmental stage by month 12 of treatment. One of these two patients has the completely inactivating F230del mutation. Other neurological and neuropsychological findings are reported in the appendix (p 18–20).

In the post-hoc analyses to assess only the patients who completed 12 months of treatment, we found that 34 (85%) of 40 patients had attained serum T_3 concentrations within the target range by month 12, and the remaining patients had concentrations just above the target range, but that their T_3 measurements had been within the target range during the previous study assessment visit. All withdrawals had T_3 concentrations within target range at the time of the last available measurement (median follow-up time 7·0 months [IQR 3·9–9·3]). The median time to achieve serum T_3 concentrations within the target range was 2·5 months (IQR 1·5–3·7), which required a mean daily Triac dose of 38·3 µg/kg of bodyweight (SD 15·3; range 6·4–84·3), administered as a median of three doses per day (IQR 2–3; appendix p 6). By month 4, 35 (78%) of 45 patients had attained T_3 concentrations within the target range (appendix p 6). Serum free T_4 concentrations decreased during the dose-escalation phase and were maintained throughout the rest of the study (appendix p 6).

All 46 patients who received at least one dose of Triac were included in drug safety analyses. 43 (93%) patients had at least one adverse event (table 3; appendix p 22). Triac treatment was continued during hospital admission in all but one patient. All seven adverse events that were suspected to be related to Triac treatment, which occurred in six (13%) patients, were mild: three patients had a transient increase in perspiration and three patients reported transient irritability. The onset of these events coincided with the start of Triac treatment or modification in Triac dose and resolved spontaneously after a few days. No patients required a dose reduction or discontinued participation because of drug-related toxicity. Most adverse events that occurred during the study period were classified as mild and required symptom relief or no treatment, and resolved while the patients continued to receive Triac. Of the safety measures prespecified in the protocol (appendix p 14–16), no clinically relevant changes in cardiac structure or function were identified.

	Baseline mean (SD)	12-month mean (SD)	Mean change (95% CI)	p value
Primary outcomes (n=45)				
T_3 (nmol/L)	4·97 (1·55)	1·82 (0·69)	−3·15 (−3·62 to −2·68)	<0·0001
TSH (mU/L)*	2·91 (1·68)	1·02 (1·14)	−1·89 (−2·39 to −1·39)	<0·0001
Free T_4 (pmol/L)	9·5 (2·5)	3·4 (1·6)	−6·1 (−6·8 to −5·4)	<0·0001
Total T_4 (nmol/L)	56·0 (13·0)	24·4 (9·4)	−31·6 (−35·2 to −28·0)	<0·0001
Reverse T_3 (nmol/L)	0·12 (0·10)	0·04 (0·04)	−0·08 (−0·10 to −0·05)	<0·0001
Secondary outcomes				
Weight-for-age *Z* score (n=40)	−2·98 (1·93)	−2·71 (1·79)	0·27 (0·03 to 0·50)	0·025
Resting heart rate (bpm; n=34)	112 (23)	104 (17)	−9 (−16 to −2)	0·010
Mean heart rate over 24 h (bpm; n=31)	102 (14)	97 (9)	−5 (−9 to −1)	0·012
Blood pressure (n=32)				
Systolic (mm Hg)	108 (8)	102 (10)	−5 (−9 to −1)	0·0086
Systolic (percentile)†	78 (24)	61 (29)	−18 (−29 to −6)	0·0037
Diastolic (mm Hg)	64 (9)	62 (9)	−2 (−6 to −2)	0·35
Diastolic (percentile)†	74 (22)	67 (22)	−6 (−17 to 4)	0·24
Sex hormone-binding globulin (nmol/L; n=39)	212 (91)	178 (76)	−35 (−55 to −15)	0·0013
Total cholesterol (mmol/L; n=40)	3·2 (0·7)	3·4 (0·7)	0·2 (0·0 to 0·3)	0·056
Creatine kinase (U/L; n=40)*	108 (90)	161 (117)	53 (27 to 78)	<0·0001
Exploratory outcomes (n=40)				
Height (m)	1·20 (0·23)	1·26 (0·22)	0·06 (0·04 to 0·07)	..
Height-for-age *Z* score	−1·96 (1·5)	−1·98 (1·5)	−0·02 (−0·19 to 0·16)	..
BMI (kg/m²)	14·2 (2·7)	14·6 (2·9)	0·3 (−0·09 to 0·77)	..
BMI-for-age *Z* score	−2·56 (2·56)	−2·24 (2·60)	0·32 (−0·14 to 0·77)	..
Thyroxine-binding globulin (mg/L)	18·2 (3·3)	19·7 (4·6)	1·5 (0·3 to 2·8)	..
Albumin (g/L)	46 (2·2)	46·8 (2·1)	0·9 (−0·1 to 1·9)	..
Creatinine (µmol/L)	33 (12)	38 (14)	5 (3 to 7)	..
LDL cholesterol (mmol/L)	1·80 (0·53)	1·85 (0·53)	0·06 (−0·07 to 0·19)	..
HDL cholesterol (mmol/L)	1·20 (0·30)	1·37 (0·31)	0·18 (0·10 to 0·26)	..
Triglycerides (mmol/L)	0·69 (0·34)	0·72 (0·35)	0·02 (−0·14 to 0·09)	..
Ferritin (µg/L)	45 (40)	29 (19)	−16 (−27 to −4)	..
Thyroglobulin (µg/L)‡	11·7 (7·1–28·9)	4·1 (1·5–6·8)	−9·2 (−23·6 to −2·7)	..
Post-hoc outcomes				
Weight (kg; n=40)	21·8 (12·2)	24·5 (12·6)	2·7 (1·9 to 3·5)	..
Body fat (kg; n=15)	5·1 (3·9)	6·2 (4·2)	1·1 (0·2 to 2·1)	..
Body fat (%; n=15)	22·8% (9·8)	25·1% (10·0)	2·3 (−1·0 to 5·6)	..
Lean body mass (kg; n=15)	15·7 (6·9)	16·9 (6·8)	1·2 (0·8 to 1·7)	..
Ratio of HDL to LDL cholesterol (n=40)	0·70 (0·19)	0·78 (0·22)	0·08 (0·02 to 0·14)	..
Premature atrial complexes (n=31)‡	48 (1–1322)	0 (0–12)	−22 (−1150 to 0)	..

Primary outcomes were assessed in all patients who received Triac and had at least one follow-up measurement of thyroid function, including five patients who withdrew (in whom the last available measurement was used in place of the 12-month measurement). Secondary, exploratory, and post-hoc outcomes were assessed in all patients who completed the 12-month intervention period and for whom relevant data were available. If 12-month measurements were not available, the last available observation in the same patient was used (<3% of included datapoints). CIs for exploratory measures have not been adjusted for multiplicity and these data should not be used to infer definitive treatment effects. T_3=tri-iodothyronine. TSH=thyroid-stimulating hormone. T_4=thyroxine. *TSH and creatine kinase concentrations were log-transformed to ensure a normal distribution before paired *t* tests were done (non-transformed means [SDs] and mean changes [95% CIs] are presented for the sake of interpretability). †Percentile scores were based on age and height.[15,16] ‡Data for thyroglobulin and premature atrial complexes are median (IQR) instead of mean (SD) because of violation of normality assumptions.

Table 2: **Effects of Triac on prespecified and post-hoc outcome measures**

	Patients with at least one event (n=46)	Number of events
Total adverse events	43 (93%)	150
Adverse events occurring in >10% of patients		
Gastrointestinal disorders		
Diarrhoea	5 (11%)	5
Gastroenteritis	11 (24%)	12
Vomiting	5 (11%)	5
General disorders and administration-site conditions		
Influenza or influenza-like illness	9 (20%)	12
Infections and infestations		
Bronchitis	6 (13%)	6
Otitis media	5 (11%)	5
Respiratory, thoracic, and mediastinal disorders		
Nasopharyngitis	11 (24%)	14
Upper-respiratory-tract infection	9 (20%)	9
Serious adverse events*	18 (39%)	26
Gastrointestinal disorders		
Gastroenteritis	2 (3%)	3
Enterocolitis	1 (2%)	1
General disorders and administration-site conditions		
Multiple organ dysfunction syndrome	1 (2%)	1
Hepatobiliary disorders		
Hepatic failure	1 (2%)	1
Infections and infestations		
Bronchitis	2 (3%)	2
Pneumonia	2 (3%)	2
Clostridium difficile infection	1 (2%)	1
Investigations		
Gastroscopy	1 (2%)	1
Nervous system disorders		
Increased seizures	2 (3%)	2
Product issues		
Device malfunction†	2 (3%)	2
Renal and urinary-tract disorders		
Urinary-tract infection	1 (2%)	1
Respiratory, thoracic, and mediastinal disorders		
Bronchiolitis	3 (7%)	3
Respiratory distress	1 (2%)	2
Upper-respiratory-tract infection	1 (2%)	1
Surgical and medical procedures		
Hip surgery	1 (2%)	1
Drug therapy (bisphosphonates)	1 (2%)	2
(Continued from previous column)		
Fatal adverse events‡	1 (2%)	1
Adverse events leading to premature treatment discontinuation	1 (2%)	1
Immune system disorders		
Autoimmune thyroid disorder	1 (2%)	1
Grade of adverse events		
Severe	4 (9%)	4
Moderate	4 (9%)	5
Mild	40 (87%)	141
Relation of adverse events to study drug		
Probable**	6 (13%)	7
Unlikely	43 (93%)	143

Data are n or n (%). Adverse events were classified according system organ class and preferred term with the Medical Dictionary for Regulatory Activities and were defined as those occurring between the administration of the first dose and 30 days after administration of the final dose of study drug. At baseline, seizures were present in 15 (37%) of 41 patients with available data. *A serious adverse event was defined one that resulted in death, was life-threatening, resulted in hospital admission or prolonged hospital treatment, resulted in persistent or clinically significant disability or incapacity other than might be expected by the effects of the disease-specific mutation, or was otherwise considered medically significant by the investigators. †Device malfunctions were hospital admissions for a dysfunctional ventriculoperitoneal drain or percutaneous enteral feeding tube. ‡One patient died from pulmonary sepsis leading to multi-organ failure; post-mortem examination confirmed the clinical diagnosis and other causes were excluded. **Adverse events with a probable relation to the study drug as deemed by the investigators (adverse reactions) were those for which a causal relation with Triac could not be excluded.

Table 3: **Adverse events**

Serum β-carboxy-terminal collagen crosslinks increased by 0·14 µg/L (95% CI 0·03–0·25) and bone-specific alkaline phosphatase concentrations increased by 8·4 µg/L (2·7–14·1), without affecting bone mineral density (appendix p 23), consistent with the physiological increase of bone turnover markers in paediatric patients during development. We identified no notable changes in serum electrolytes, serum urea, or random plasma glucose concentrations (appendix p 23). Hematopoietic parameters did not differ except in three patients, in whom mild anaemia, which was ascribed to nutritional deficiency, was detected at month 12 (not linked to the intervention). 25 (54%) of 46 patients showed mildly increased serum concentrations of alanine aminotransferase, aspartate aminotransferase, or γ-glutamyl transferase at baseline, which was attributed to the concomitant use of hepatotoxic medications, and these concentrations did not increase further during the study. Two (4%) patients showed an increase in aminotransferase concentrations that were attributed to commencement or dose adjustment of anticonvulsant drugs with known hepatotoxicity (levetiracetam and lamotrigine).

Most serious adverse events were intermittent infections that were treated with antibiotics and supportive care. All serious adverse events were considered to be secondary to MCT8 deficiency and, thus, unrelated to Triac (table 3). In three patients with pre-existing seizures, an increase in seizure frequency was reported. In one patient, this increase coincided with a gastrointestinal infection; and the other two patients had a history of seizures that were difficult to control. Hospital admission was required in two patients with pre-existing seizures to treat prolonged seizure or to optimise

anticonvulsant therapy. In the patient with a history of seizures in whom Triac treatment was stopped, hepatic insufficiency resulted in hospital admission, during which time Triac treatment was temporarily withheld; this hepatic insufficiency resolved with reduction in anticonvulsant drug dose and supportive measures. One patient died from pulmonary sepsis leading to multi-organ failure; post-mortem examination confirmed the clinical diagnosis, and other causes were excluded.

Post-hoc analyses showed that premature atrial contractions largely subsided in most patients in whom these were present at baseline (appendix p 9). The effects of Triac treatment on secondary outcomes were maintained when the post-hoc analyses were done with the full analysis set population, including patients who did not complete the 12 months of treatment (appendix p 17). Post-hoc analyses of the treatment extension endpoints included ten patients. During the long-term treatment extension period, the reductions in T_3 concentrations persisted in all patients (figure 2; appendix p 21) and reductions in TSH and free T_4 concentrations were maintained (appendix pp 11,21). The reduction in mean heart rate was sustained (figure 2) and premature atrial contractions were reduced to fewer than 100 per 24 h (figure 2) in all patients enrolled in the treatment extension period; the premature atrial contractions completely subsided in three (43%) of seven children assessed over the treatment extension period. Atrial fibrillation was present in one child at baseline, but not at months 12 or 36. The improvement in bodyweight-for-age *Z* score was maintained, with a mean increase of 0·52 SDs (95% CI 0·02–1·02) at month 12 and 0·62 (0·12–1·12) at month 32, relative to baseline. Bodyweight (figure 2), height, and BMI trajectories improved relative to their anticipated natural course in seven (88%) of the eight paediatric patients (appendix p 12). Improvements on circulating tissue markers of thyroid hormone action were maintained in the long-term treatment extension period.

Discussion

In this investigator-initiated, international, multicentre trial in patients with MCT8 deficiency, Triac treatment resulted in effective reduction in serum T_3 concentrations, as well as improvements in clinically relevant outcome measures, including bodyweight, heart rate and rhythm, blood pressure, and biochemical markers of thyroid hormone action in different tissues.

During treatment with Triac, serum T_3 concentrations decreased, with 78% of patients achieving serum T_3 concentrations within the normal range by 4 months of treatment, requiring a mean dose of 38·3 µg/kg per day. This effect was maintained in those patients enrolled in the treatment extension period.

Many key clinical outcomes improved during the 12 months of Triac treatment, of which 8 months was at a maintenance dose. Bodyweight-for-age *Z* score increased and patients enrolled in the treatment extension period showed a reversal of the natural course of the disorder, which is typically accompanied by progressive

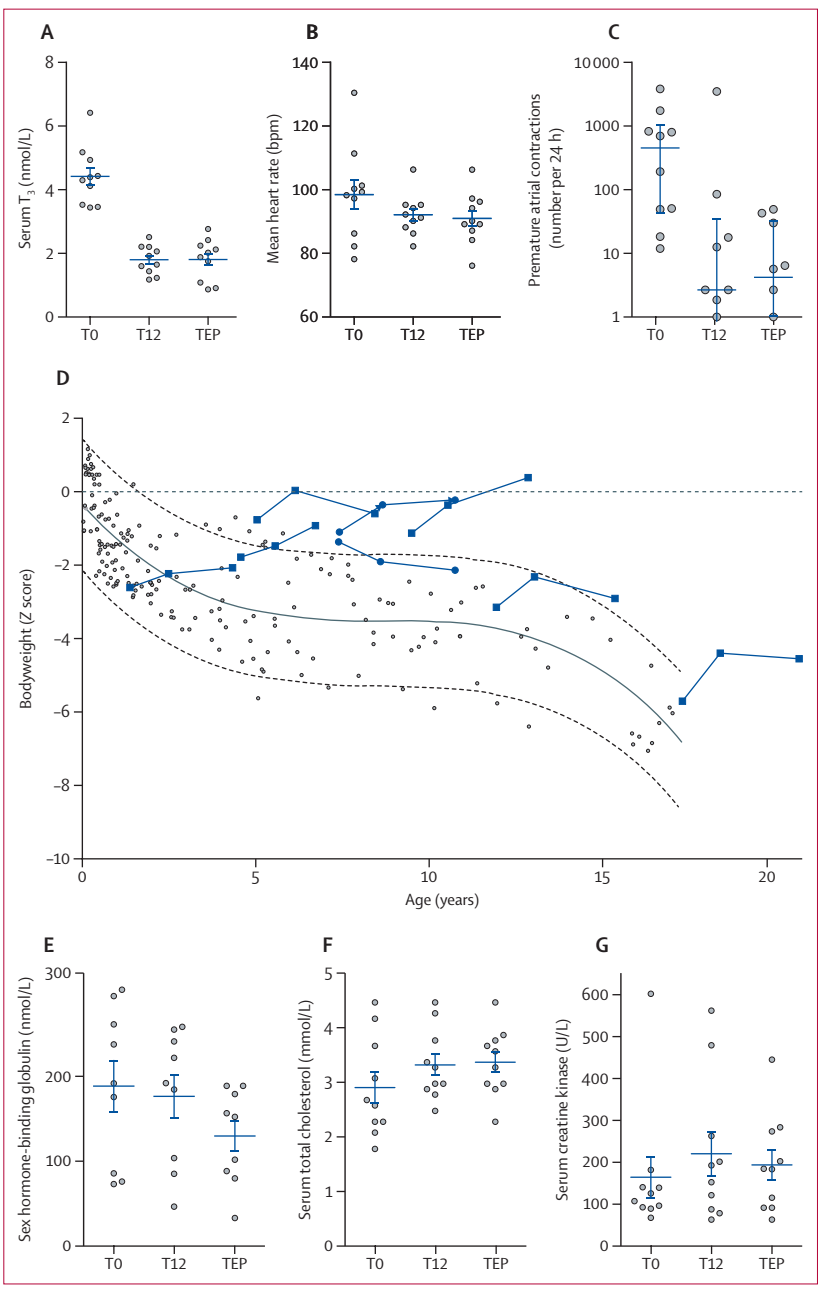

Figure 2: **Change from baseline to month 12 and to the end of the treatment extension period in post-hoc outcome measures**

Data are changes in serum T_3 concentration (A); mean heart rate, determined by 24-h cardiac monitoring (B); premature atrial contractions (C); bodyweight, as bodyweight-for-age *Z* scores, relative to the natural course of bodyweight development in MCT8 deficiency (represented by a trend line with 95% error band and grey dots of individual historical measurements) and based on historical measurements from growth charts and medical records of the enrolled patients before starting treatment. The trend line (blue) consists of baseline, month 12, and TEP values. (D); sex-hormone binding globulin concentrations (E); serum total cholesterol (F); and creatine kinase concentrations, all across T0, T12, and the TEP following treatment with tri-iodothyroacetic acid. Grey dots represent individual patient measurements, and the mean and SE (A, E, F) and the median and IQR (B,C,G) are shown in blue. The TEP ranged from 26 to 42 months (median length 40·4 months [38·1–41·3]). Data and p values are shown in table 2. T_3=tri-iodothyronine. T0=baseline. T12=month 12. TEP=treatment extension period.

deterioration of bodyweight and often necessitates enteral tube feeding. In this vulnerable population, being severely underweight is associated with adverse clinical outcomes, including an increased risk of infections.[19] Heart rate decreased predominantly in patients who had an increased heart rate at baseline, in whom such a reduction is the most clinically relevant. Systolic blood pressure decreased, and hypertension was resolved in most patients receiving Triac treatment. Premature atrial complexes, which are more prevalent in patients with hyperthyroidism,[20] also subsided in most participants. The high frequency of premature atrial complexes that is present in untreated patients is uncommon in healthy individuals, particularly in children,[21] and premature atrial complexes predispose individuals to other arrhythmias and cardiac death.[22–24] Indeed, sudden death is a frequent cause of death in patients with MCT8 deficiency and, in one patient in our study, an episode of atrial fibrillation was recorded during baseline assessment. Thus, improving bodyweight and cardiovascular status could ameliorate important risk factors for premature death in MCT8 deficiency.

Triac treatment was associated with reversal of the hypermetabolic state in different tissues (liver, kidney, and muscle), reflected by a reduction in serum sex hormone-binding globulin concentrations and an increase in serum creatinine and creatine kinase concentrations. The positive clinical and biochemical outcomes were sustained in the subgroup of patients in the long-term treatment extension period. Apart from a decrease in serum T_3 concentrations, consistent positive clinical and biochemical outcomes were not seen in an observational study[25] in which four patients were treated with di-iodothyropropionic acid (DITPA); with this treatment, free T_4 and reverse T_3 concentrations increased and TSH concentrations remained unchanged, whereas, with Triac treatment, TSH concentrations decreased with a concomitant reduction in free T_4, T_3, and total reverse T_3 concentrations. These differential changes in thyroid function tests might point to a different mode of action of DITPA versus Triac.

The consistent reduction in serum T_3 concentrations coincided with improvements in bodyweight, cardiovascular status, and markers of thyroid hormone action in different tissues. Although our study design, including the absence of a control group and open-label design, does not enable us to prove causality, the observed unidirectional changes in serum T_3 concentrations can likely be attributed to Triac treatment, given the substantial evidence from preclinical and clinical studies on the effects of Triac.[11]

The mean Triac dose used in our trial was within the range used in previous clinical studies to restore euthyroidism in patients (23–48 µg/kg per day).[11,26,27] Therefore, the thyromimetic effects of Triac in peripheral organs probably compensate adequately for the observed reduction in serum T_4 concentrations. This suggestion is supported by the absence of clinical and biochemical signs of hypothyroidism, which was actively monitored for throughout the study.

It is unknown whether the further reduction in circulating T_4 concentrations under Triac treatment aggravates the hypothyroid state in the brain in people with MCT8 deficiency.[28,29] Although MCT8 is believed to be the primary transporter that facilitates both T_3 and T_4 transport across the human blood–brain barrier, we cannot exclude a contribution of other factors.[30] In several animal models that recapitulate the neuromotor phenotype of human MCT8 deficiency, Triac has resolved brain hypothyroidism and enabled brain development to progress as normal.[9,14] Our trial was not designed to detect whether Triac also modulates neurodevelopment in human MCT8 deficiency, since the study did not include specific neurodevelopmental outcomes and enrolled patients of all ages. Therefore, most patients studied would have passed the small window of opportunity to modulate brain development. A phase 2 trial (NCT02396459; not yet recruiting) will investigate the effects of Triac on neurodevelopmental outcomes in very young children.

The most commonly reported adverse events were all deemed to be consequences of MCT8 deficiency and unrelated to the intervention. Triac treatment only transiently increased signs of mild hyperthyroidism (perspiration and irritability) after commencement or dose adjustment of treatment in a few patients. Although data from some previous studies[27,31] have suggested that Triac could increase bone resorption, we identified only marginal increases in bone turnover markers that followed the physiological changes observed during development in children and were not accompanied by noticeable changes in bone mineral density. Although our findings suggest that Triac treatment is generally well tolerated, the acquisition of additional safety data in consecutive trials is warranted to extend knowledge of drug safety in this population.

Since we did not select for patient characteristics, the study population comprises a heterogeneous sample that constitutes a large proportion of identified patients with the condition—as such, the study population is representative of routine clinical practice. Inherent to studies in such a heterogeneous population, the effect size of outcomes varied within the study cohort, suggesting inter-individual variation in degree of benefit between patients. The small sample size did not allow identification or statistical control for factors other than the intervention that might modulate treatment effects. Another limitation was the small number of adult patients enrolled in the study, as a consequence of high mortality during childhood. Moreover, the low physical and cognitive abilities of the participants, a feature that is inherent to the disorder, precluded recording some study parameters in all patients. Together with study withdrawals, this issue might have, unavoidably, caused selection bias in the data used for statistical analyses.

Severe underweight and cardiovascular dysfunction are important clinical sequelae of chronic peripheral thyrotoxicosis, causing significant morbidity and mortality in patients with MCT8 deficiency. The results of our study suggest that several key features related to the peripheral phenotype of MCT8 deficiency are alleviated under Triac treatment in paediatric and adult patients.

Contributors

SG, RPP, IFMdC, FKA, MCYdW, YBdR, TJV, and WEV designed the study. SG was the study coordinator. WEV was the overall principal investigator and AS, SD, JL, MC, LDM, HK, DC, FZ, IOP, MP, and KC were the principal investigators at trial sites. All authors made substantial contributions to the coordination and execution of study procedures, data acquisition, interpretation of data, or all three. SG and WEV analysed the data and wrote the initial draft of the report. All authors critically reviewed and revised the report and have read and approved the final version, apart from MMa, LDM, and TJV, who died before completion of the study.

Declaration of interests

The Erasmus Medical Centre (Rotterdam, Netherlands), which employs SG, RPP, IMvB, MMvdK, CAU, MCZ, MCYdW, YBdR, MMe, and WEV, might receive royalties from Rare Thyroid Therapeutics (the manufacturer of Triac) in the future, dependent on any future commercialisation. None of the authors will benefit personally from any royalties. Rare Thyroid Therapeutics had no influence on the conduct or analysis of this study. All other authors declare no competing interests.

Data sharing

Because of the rarity of monocarboxylate transporter 8 deficiency and the small number of participants in our trial, individual participant data beyond that reported here will not be shared, to safeguard patient privacy.

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