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Cholic acid treatment in Peroxisomal Biogenesis Disorders (Zellweger spectrum)

Submission date
20/11/2011

Recruitment status
No longer recruiting

Registration date
30/01/2012

Overall study status
Completed

Last Edited
04/08/2015

Condition category
Neonatal Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Zellweger spectrum disorder is a rare genetic disease that can affect most organs of the body. Progressive and irreversible damage starts in the womb and continues from birth onwards. Treatment from a young age is therefore important. Cholic acid is naturally found in the body in the bile. Our aim is to investigate the effect of cholic acid supplements in mild Zellweger spectrum patients. We think that cholic acid supplementation may improve intestinal fat absorption, liver function and neurological symptoms.

Who can participate?
Mild Zellweger spectrum disorder patients attending the outpatient clinic of the AMC Pediatric Neurology Department.

What does the study involve?
All participants will take cholic acid daily during meals for 9 months. Cholic acid can be taken as capsules or liquid depending on the participant's preference. Changes in diet and co-medication during the study period will be recorded.

What are the possible benefits and risks of participating?
Cholic acid is naturally found in the body and excellent safety reports of long-term use have been published. The burden to the subjects is limited as most tests are performed during four standard clinical visits and blood sampling is part of standard care during these visits. During the standard visits the extra interventions are providing stool and urine samples, neurological tests, fibroscan measurements, and completing a food diary and, in case of epilepsy, a convulsion diary. Fibroscan measurement is a one-minute, safe, non-invasive and painless liver test performed in the outpatient clinic. Only two extra visits to the hospital are required (week 36 and 40). Length and weight are measured during one visit, extra blood sampling is performed during another visit, and stools and urine are collected at both visits.

Where is the study run from?
Academic Medical Center (Netherlands).

When is the study starting and how long is it expected to run for?
From November 2011 to February 2016.

Who is funding the study?
Emma Paediatric Hospital (Netherlands).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
P1114

Study information

Scientific Title
Cholic acid treatment in Peroxisomal Biogenesis Disorders (Zellweger spectrum): biochemical and clinical effects

Study objectives
Cholic acid supplementation in mild Zellweger spectrum patients improves intestinal fat absorption and growth by increasing the amount of intraluminal bile acids, thus promoting micellar solubilization. In addition, we hypothesize that cholic acid supplementation improves liver function and alleviates neurological symptoms by suppressing the endogenous bile acid synthesis and stimulating bile flow, thus decreasing the production of potentially toxic and cholestatic bile acid intermediates.

Neurological milestones will be performed by a trained observer not blinded for the patients' treatment phase. Measurements of weight and height, fibroscan liver elasticity measurements and laboratory tests will be performed by operators blinded for the patients' treatment phase.

On 03/08/2015 the following changes were made to the trial record:
1. The overall trial end date was changed from 01/11/2013 to 01/02/2016.
2. The target number of participants was changed from 20 to 25.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Medical Ethical Committee AMC, March 2011 ref: MEC 10/276
2. Centrale Commissie Mensgebonden Onderzoek (CCMO), December 2010, ref: NL33339.018.10

Study design
Single-centre open label pilot study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Zellweger spectrum disorder

Interventions
Investigational product:
Cholic acid is the predominant human bile acid. In this study, cholic acid will be supplemented for 9 months in a regular dose. No placebo will be used.

Use of co-intervention:
Changes in diet during the study period will be recorded. Use of possible hepatotoxic medication should be avoided if an equally effective alternative drug is available. All changes in co-medication will be recorded.

Dosages, dosage modifications and method of administration:
Cholic acid will be administered in doses of 15 mg/kg/day in 2 or 3-divided doses daily orally during meals. In case of incomplete suppression of bile acid intermediates in week 36 the dosage will be increased to 20 mg/kg/day in 2 or 3 divided doses daily. Frequency of administration depends on the number of capsules needed daily, objective is to administer an equal dose over the day.

Cholic acid can de administered as capsules or liquid depending on the participants preference. Capsules of 250 and 50 mg will allow accurate dosing at 15 mg/kg/day in patients with body weight above 6 kilogram. In case the dosage is increased to 20 mg/kg/day or patients weighting less than 6 kg are included capsules will be prepared adapted to the patients weight by the AMC pharmacy. For this cutom-made preparation the same drug substance and addatives as described in the CMC will be used to prepare the drug product. As this is not a standardized preparation procedure, the storage life will be limited to 6 months after custom made preparation.

The medication will be provided by Asklepion Pharmaceuticals and it will be shipped to the pharmacy of the AMC pharmacy who will be responsible for capsule preparation and distribution of the product. At the end of the (premature) end of the studies the remaining medicinal product will be taken in by the treating physician and returned to the AMC pharmacy.

Intervention Type
Other

Phase
Not Specified

Primary outcome(s)
1. Degree of suppression of endogenous bile acid synthesis [Decrease in urine 3 alpha,7 alpha - dihydroxycholestanoic acid (DHCA) and 3 alpha,7alpha,12 alpha - trihydroxycholestanoic acid (THCA) bile acid intermediates and increase in FGF-19]
2. Increase in normal primary bile acids [increase in urine cholic acid (CA)]
3. Change in fat soluble vitamins levels (T= 24 weeks versus T= 42 weeks)
4. Change in weight gain (weight-for-height percentile) (T= 36 weeks versus T=72 weeks)
5. Change total body length growth rate (cm/year; only in those with remaining growth potential)
6. Feasiibility and side effects of cholic acid supplementation; diarrhea, vomiting, liver dysfunction and others
Measured at 0, 24, 36, 48, 72 weeks

Key secondary outcome(s))
1. Change in seizure frequency
2. Change in the obtained developmental mile stones
3. Change serum transminases and γ-glutamyltrans- peptidase levels
4. Change in fibroscan liver elasticity measurements
5. Change in liver protein synthesis
6. Change in markers of peroxisomal / mitochondrial functioning
Measured at 0, 24, 36, 48, 72 weeks

Completion date
01/02/2016

Eligibility

Key inclusion criteria
1. Zellweger spectrum disorder
2. At least one of the following hallmarks:
2.1. Steatorrhea
2.2. Elevated transaminases
2.3. Growth retardation
2.4. Neurological symptoms

Participant type(s)
Patient

Healthy volunteers allowed

No

Age group
Neonate

Sex
All

Key exclusion criteria
Short life expectancy (severe multiple organ dysfunction at the time of diagnosis)

Date of first enrolment
01/04/2012

Date of final enrolment
01/06/2012

Locations

Countries of recruitment
Netherlands

United States of America

Study participating centre
Academic Medical Center
Amsterdam
Netherlands
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Sponsor information

Organisation
Emma Paeditric Hosptial (Netherlands)

ROR
https://ror.org/00bmv4102

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Emma Paediatric Hospital (Netherlands)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration