Long-term safety study of personalized cholic acid treatment in patients with bile acid synthesis defects

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Several reports on SED have shown the beneficial effects of CA supplementation on the down regulation of bile acid synthesis, increasing levels of primary bile acids and stimulating bile flow. Improvement in hepatic dysfunction, clinical improvement...

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON25657

Bron
Nationaal Trial Register

Verkorte titel
Cholzuur

Aandoening

Bile acid synthesis defects (BASD), 3β-hydroxy-Δ5-C27-steroid oxidoreductase, Δ4-3-oxosteroid-5β-reductase, cholesterol 7a-hydroxylase (CYP7A1), and α-methylacyl-CoA racemase (AMACR), Zellweger spectrum disorder

Ondersteuning

Primaire sponsor: Amsterdam UMC
Overige ondersteuning: VriendenLoterij

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

1. Degree of suppression of endogenous bile acid synthesis
2. Type and number of adverse events
3. Type and number of side effects

Toelichting onderzoek

Achtergrond van het onderzoek

This study is an open label single centre, non-randomized intervention study. Patients with a bile acid synthesis defect caused by 3β-hydroxy-Δ5-C27-steroid oxidoreductase, Δ4-3-oxosteroid-5β-reductase, α-methylacyl-CoA racemase (AMACR) deficiency or cholesterol 7a-hydroxylase (CYP7A1) deficiency will be recruited for this study. CA naive patients and Zellweger patients that had a positive response on CA treatment during a previous study may participate.

CA will be supplemented with personalized magistral prepared capsules for up to 5 years in daily doses of 5-15 mg/kg/day once daily or divided in 2 or 3 equal doses depending on the number of capsules needed daily. In case of incomplete suppression of bile acid intermediates the dosage will be increased to a maximum of 20 mg/kg/day. In case necessary due to adverse events (diarrhoea, vomiting, liver dysfunction and others), the dose can be reduced with 33% to 10 or 5 mg/kg/day.

Doel van het onderzoek

Several reports on SED have shown the beneficial effects of CA supplementation on the down regulation of bile acid synthesis, increasing levels of primary bile acids and stimulating bile flow. Improvement in hepatic dysfunction, clinical improvement and long term survival have been reported44,48-51. In several reviews CA is recommended as the preferred therapy in SED due to superior effects compared to CDCA (hepatotoxic) and UDCA (no suppression of bile acid synthesis and no micell function)41,43,44,51.

Because previous study shows that CA can be potentially harmful for patients with advanced liver disease, we discourage to treat this subgroup of ZSD patients with CA. In milder patients, the treatment period of 1 year and 9 months was too short to be able to conclude whether CA has an effect on the clinical progression in patients with a ZSD, since this is a slowly progressive disorder. Therefore further studies are needed to investigate the long-term efficacy and safety of cholic acid treatment.

Onderzoeksopzet

T = 0, 2 and 6 weeks after starting treatment, followed by tests performed every 3 months in the first year of treatment.
After the first year tests are performed every 6 months or yearly depending on the test.

Onderzoeksproduct en/of interventie

Cholic Acid

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

Bile acid synthesis defect due to:
o single enzyme deficiency in either:
- 3β-hydroxy-Δ5-C27-steroid oxidoreductase
- Δ4-3-oxosteroid-5β-reductase
- α-methylacyl-CoA racemase (AMACR)
- cholesterol 7a-hydroxylase (CYP7A1)
o OR Zellweger spectrum disorder

At least one of the following hallmarks: steatorrhea (confirmed per local protocol), elevated transaminases, developmental delay, neurological symptoms

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

Single enzyme deficiency patients will be excluded from participation when at least one of the following criteria is present:
- Short life expectancy of < 12 months (severe multiple organ dysfunction)
- Decompensated liver cirrhosis
- High bilirubin serum levels (conjugated bilirubin > 20 µmol/L)
- Prolonged prothrombin time (PT > 15s not due to vitamin K deficiency)
- Kidney dysfunction (eGFR < 60)
- Pregnancy and high total bile acid serum level (> 40µmol/L)
- Allergy to one of the components of CA capsules.

Zellweger spectrum disorder patients will be excluded from participation when at least one of the following criteria is present:
- Increased liver enzymes during previous CA treatment
- Normal biochemical parameters (THCA and/or DHCA ≤1.0 µmol/L)
- Short life expectancy of < 12 months (severe multiple organ dysfunction)
- Decompensated liver cirrhosis
- High bilirubin serum levels (conjugated bilirubin > 20 µmol/L)
- Prolonged prothrombin time (PT > 15s not due to vitamin K deficiency)
- Kidney dysfunction (eGFR < 60)
- Pregnancy and high total bile acid serum level (> 40µmol/L)
- Allergy to one of the components of CA capsules.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	18-05-2020

Aantal proefpersonen:	40
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	18-05-2020
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL8630
Ander register	METC AMC : 2019_192

Resultaten