Sulfonylurea Treatment for Cantú syndrome

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac and vascular disorders congenital
Study type	Interventional

Summary

ID

NL-OMON54600

Source
ToetsingOnline

Brief title
Treatment of Cantú syndrome

Condition

- Cardiac and vascular disorders congenital

Synonym
Cantu syndrome, hypertrichotic osteochondrodysplasia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cantu Syndrome, glibenclamide, treatment

Outcome measures

Primary outcome

Primary study parameter

The primary outcome parameter of the exploratory study will be the mean change in the number of hair follicle per cm2 in predefined body areas affected with hypertrichosis (cheek, forehead, arm).

Dermascopy pictures will be taken and evaluated using a computerized system (either Folliscope or Trichoscan). The system is able to pinpoint the area of interest, count the hairs and/or hair follicle present in this area as well as measure thickness, density and growth. Additionally, results can be compared over time.

Secondary outcome

Secondary study parameters:

Secondary outcome parameters will include parameters of safety (hypoglycemia, renal function) and efficacy of glibenclamide in treating cardiovascular, lymphatic, facial and dermatological effects of this condition. Based on our data from natural history studies collected over the past 5 years, we have identified a number of clinical characteristics whose possible reduction we intend to investigate during chronic exposure to glibenclamide.

1. Hypoglycemic events (safety parameter)

The prevalence of dose-related minor and major hypoglycemic events will be assessed. Patients will be provided with a continuous glucose sensor and

instructed by a specialized nurse how to handle in case of low blood glucose and recognize hypoglycemic symptoms. They will upload their 24h glucose profiles daily during the 2x2 weeks run-in period and weekly thereafter.

Hypoglycemia will be categorized as follows (EMA 2012): documented symptomatic hypoglycemia (blood glucose <3.9 mmol/L), asymptomatic hypoglycemia (blood glucose <3.9 mmol/L), severe hypoglycemia (requiring assistance from another person), relative hypoglycemia (blood glucose > 3.9 mmol/L).

2. Serum creatinine (safety parameter)

Serum creatinine is produced at a constant rate provided renal function is conserved and will be used as proxy for glomerular filtration rate and therefore an indicator of overall kidney function. Blood samples for creatinine measurements from serum will be taken.

3. Change from baseline in cardiovascular abnormalities

Cardiovascular abnormalities will be evaluated by MRI, echocardiography, 24-hour heart rhythm monitoring and standard cardiac exercise test.

4. Changes from baseline in swelling/edema in the leg

Edema will be measured applying method of Kuhnke (Kuhnke & Asdonk, 1986) where measurement of leg circumference by tape will be taken at the malleolar level and every 4 cm for eight leg segments.

5. Change from baseline in facial abnormalities

3D images of the face will be taken and analyzed using dense surface modelling and closest mean classification as described in Roessler et al. (2020).

6. Changes from baseline in dermatological abnormalities

We will take clinical photographs of body parts with hypertrichosis, collect

hair samples and take a scalp/forehead biopsy as described in Ohko et al. (2020). Patient satisfaction with hair growth and frequency of shaving necessary will be measured by asking patients to fill in a questionnaire including a Likert scale.

7. Change from baseline in skin-related phenotypes

During a physical exam, we will take clinical photographs of body parts revealing key skin abnormalities seen in CS. Clinical pictures will be blindly evaluated by specialists to give qualitative scores.

8. QOL questionnaire

The questionnaire will measure physical, social, and emotional aspects of functioning, and common symptoms of CS and GLB treatment.

9. Changes from baseline in vital signs

Heart rate, systolic (sitting down) and diastolic (standing up) blood pressure will be measured.

10. Anthropometric measurements.

We will measure height, weight and head size during every visit.

Study description

Background summary

Cantú syndrome (CS) is a rare autosomal dominant genetic condition that affects multiple organ systems. It is caused by gain-of-function mutations in ABCC9 and less commonly KNCJ8 which encode subunits of an ATP-sensitive potassium channel. Currently, there is no therapy for CS patients available yet. However, it is postulated that sulfonylureas, like glibenclamide, would close the overactive potassium channel present in patients. These compounds are already successfully used in clinic to treat patients with diabetes resulting from

missense mutations in ABCC8.

Study objective

The principal aim of this proof-of-concept exploratory study is to determine whether a full randomised controlled trial to test glibenclamide in a large cohort of CS patients is justifiable and feasible and to optimize its design. We specifically intend to assess the efficacy and safety of glibenclamide in individuals with CS.
Primary objective:
To determine whether giving glibencamide to CS patients can efficiently reverse hypertrichosis. Thus, we will perform dermascopy pre-, and post-baseline in order to assess changes in the amount of hair follicle in predefined body areas as well as measure thickness, density and growth of hair.
Secondary objectives:
Secondary objectives involve safety, further evidence of efficacy and collecting of experience and data a pivotal study can be based on.
1. Although safety has already been checked in healthy individuals, we will determine safety of glibenclamide in CS patients. The main concern of treating CS patients with glibenclamide is that individuals who do not have diabetes are potentially at risk to develop hypoglycemia as a side effect.
2. To determine efficacy of glibenclamide in reversing (i) cardiovascular abnormalities focusing on cardiomegaly, aortic dilation, tortuosity, high-state output and exercise intolerance, (ii) swelling/edema in the leg, (iii) distinctive facial features as described in Roessler et al. and (iv) further skin- and hair-related abnormalities associated with CS.
2. To collect data to inform sample size calculations for the primary outcome measures for use in a future full-scale phase II/III trial.
3. To estimate treatment period, appropriate outcome measurements and effect size for future trial.

Study design

We intend to perform a proof-of-concept early phase exploratory clinical study which will be an open- label, single-arm, non-randomized, uncontrolled intervention study for only a limited number of Dutch patients due to the overall rarity of CS. Thus, all participating patients will receive glibenclamide and we will not include a control group. Baseline measurements will be performed before commencement of glibenclamide treatment and patients will be their own controls. The study will last for 9 months. After undergoing baseline measurements, CS patients will start on a low dose of glibenclamide (2.5 mg) and patients will monitor their blood glucose with a common glucometer for hypoglycemia, which is the most likely adverse effect expected in non-diabetic patients. Patients will be seen monthly for the first 6 months and one more time after another 3 months.

Intervention

The study drug glibenclamide, also called Glyburide, is a second-generation sulfonylurea drug working as an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus. It belongs to the sulfonylurea class of insulin secretagogues, which promote increased insulin secretion and reductions in blood glucose due to its inhibitory action on pancreatic-expressed SUR1-dependant KATP channel isoforms (ABCC8). Glibenclamide was approved by the EMA for use in Type II diabetes nearly 30 years ago, is readily available at pharmacies and is inexpensive. The drug is available in scored 5 mg tablets and therefore easily divided in two 2.5 mg doses. It has been successfully used for long-term treatment of Type II diabetes in children and adults. It is generally well tolerated and hypoglycemia is its main side effect.
The usual starting dose of glibencamide in adults with type 2 diabetes is 2.5 mg once a day. During the exploratory study we propose to start at a lower dose in CS patients as they do not have diabetes and therefore are at risk to develop hypoglycemia. We will start with a run-in period of 2 weeks with 1.25 mg once a day and monitor closely for signs and symptoms of hypoglycemia and we will monitor blood glucose using a continuous glucose sensor. Patients will be instructed by a specialized nurse how to recognize hypoglycemic symptoms and how to handle them in case of a hypoglycemia. In case patients develop hypoglycemia on this dose, they will be excluded from the study. In case they tolerate 1.25 mg per day well, we will increase the dose after 2 weeks to 2.5 mg a day for another 2 weeks.

Study burden and risks

Most tests, except for the skin biopsy and the continuous glucose sensor, will be non-invasive. Patients will be carefully instructed how to recognize hypoglycemia and how to handle when blood glucose drops < 3.9 mmol/L. 24h glucose profiles will be uploaded and evaluated daily in the run-in period and weekly thereafter. Hence, we believe that although hypoglycemia is a serious adverse event, the 24h glucose monitoring and the instructions will mitigate this risk substantially. Other side effects reported with Glibenclamide are seen in less than 2% of treated patients. Given the promising pre-clinical data, CS patients might directly benefit from treatment if glibenclamide ameliorates CS related features.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
1. As the majority of CS patients reveal a mutation in ABCC9 and we aim to create a homogenized study population, only, otherwise healthy, patients with a confirmed diagnosis of CS via molecular genetic testing, with a mutation in ABCC9 will be eligible.
2. 16 years of age or older.
3. No history of sulfonamides or thiazides allergies.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. All patients without a molecularly proven diagnosis of Cantú syndrome are excluded from this study.
2. Patients with a history of a sulfonamides or thiazides allergy
3. CS patients who are deemed poor candidates by the PI for the study based on additional medical concerns, not related to CS, including epilepsy, diabetes

mellitus, intellectual deficit. As far as we are aware there are no cases in our cohort who are now suffering from additional medical concerns.
4. Pregnant women.
5. Patients with known G6PD deficiency.
6. Patients with known chronic kidney or liver disease.
7. Patients who take non-selective beta-blockers due to a possible interaction with the study drug glibenclamide.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-01-2023
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Glyburide
Generic name:	Glibenclamide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	18-02-2021
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-05-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-004651-36-NL
CCMO	NL71289.018.20