Ex vivo genetic correction of LAMA2 mutations in myogenic stem cells of patients with merosin-deficient congenital muscle dystrophy type 1a (MDC1a)

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Ethical review	Approved WMO
Status	Completed
Health condition type	Muscle disorders
Study type	Observational invasive

Summary

ID

NL-OMON52746

Source
ToetsingOnline

Brief title
Genetic correction LAMA2

Condition

- Muscle disorders

Synonym
merosin-deficient congenital muscular dystrophy; congenital muscle dystrophy

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: stichting voor Sara

Intervention

Keyword: LAMA2, MDC1a, mesoangioblasts

Outcome measures

Primary outcome

Assessment of the effect of LAMA2 mutations on skeletal muscle LAMA protein quality and quantity and in vitro analysis of CRISPR-Cas9 genetically corrected mesoangioblasts of MDC1a/LAMA2-MD patients compared with control mesoangioblasts.

Secondary outcome

- Blood markers muscle inflammation, damage and regeneration: CK, TNFa, IL-6, SDF1 (ELISA assay).

- DNA analysis for verification of the LAMA2 mutations or exclusion of LAMA2 mutations in controls.

Study description

Background summary

Merosin-deficient congenital muscle dystrophy type 1a (MDC1a), or LAMA2 muscular dystrophy (LAMA2-MD) is a severe autosomal recessive form of muscular dystrophy that is caused by homozygous or compound heterozygous mutations in the laminin alpha 2 (LAMA-2) gene. Many different LAMA-2 mutations have been reported. In most cases, MDC1a is diagnosed within the first year of life, and is characterized by hypotonia, delayed motor development and white matter abnormalities. Currently, no efficient treatment is available for this patient group. Generally, MDC1a patients with mutations causing a premature stop codon are most severely affected (early onset LAMA2-MD) and patients with missense

mutations are generally affected more mild affected and more late-onset (late onset LAMA2-MD). However, large variation in disease severity and clinical course is observed, even between individuals with the same mutation, e.g. the LAMA2 c.5562+5G>C mutation, which is frequently observed in Dutch MDC1a patients.

Study objective

This study aims to isolate and culture myogenic stem cells called mesoangioblasts from the muscle biopsies to explore if genetic correction of LAMA2 mutations using CRISPR-Cas9 can be achieved and subsequently assess the effect in vitro, as a first step towards therapy development.

Study design

Mono-center observational study

Study burden and risks

Participation does not result in direct benefit for the participant.
The risk of complications associated with the muscle and skin biopsy (1 procedure). In some cases, the muscle biopsy can be painful. Infections and bleeding afterwards are possible, but rare. Collection of a skin biopsy during the muscle biopsy procedure does not increase burden or risk of complications. Only difference in procedure for combined collection of skin and muscle biopsy is that instead of a 0.5cm incision in the skin for collecting only a muscle biopsy, a circular punch of 3mm diameter will be made in the anesthetized skin.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

LAMA2 mutation carriers:
- Age >18 years
- Heterozygous or homozygous LAMA2 c.5562+5G>C mutation
- Written informed consent

Controls:
- Written informed consent
- Age >18 years
- No muscular dystrophy or other disease known to affect muscle morphology or function

Exclusion criteria

MDC1 patients and controls:
- No informed consent
- Use of anti-coagulants, anti-thrombotics and other medication influencing coagulation
- Have a weekly alcohol intake of >= 35 units (men) or >= 24 units (women)
- Current history of drug abuse
- A history of strokes
- Significant concurrent illness
- Ongoing participation in other clinical trials
- Major surgery within 4 weeks of the visit
- Pregnant or lactating women
- Patients unable and/or unwilling to comply with treatment and study instructions
- Any other factor that in the opinion of the investigator excludes the patient

from the study

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-06-2021
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	05-08-2020
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-03-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
CCMO	NL70962.068.20