Development of an Autologous Myogenic Cell Therapy against the Neuromuscular Phenotype of Myotonic Dystrophy type 1.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital and hereditary disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON43189

Source
ToetsingOnline

Brief title
Cellular therapy for DM1.

Condition

- Congenital and hereditary disorders NEC
- Muscle disorders

Synonym
inherited muscle disorder, Steinert disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cell therapy, Genetic editing, Myotonic Dystrophy, Pericytes

Outcome measures

Primary outcome

Isolate, culture and expand genetically corrected pericytes derived from a

human skeletal muscle biopsy

* Determine the efficiency of pericyte generation: number of pericytes/ mg

skeletal muscle biopsy

* Determine the percentage of edited pericytes generated by CRISPR-Cas9

modification: percentage of pericytes with complete *clean* removal of the

entire repeat sequence

* Determine the maximum amount of amplification: number of passages possible

with edited pericytes

Secondary outcome

Not applicable.

Study description

Background summary

Myotonic dystrophy (dystrophia myotonica, DM1) is a chronic progressive multisystemic disorder characterized by myotonia, muscular dystrophy and cognitive problems including; mild-severe intellectual disability, behavioural changes, speech disability and hypersomnia. It is the most common adult form of muscular dystrophy, with a prevalence of approximately 10 per 100,000 people. The genetic basis of DM1, a CTG-repeat expansion in the 3* untranslated region of the DMPK gene, was elucidated in 1992, but so far no treatment is available. However, cell-based therapies have recently emerged as an attractive therapeutic approach for neuromuscular disorders. Pericytes are progenitor cells that can be isolated from adult muscle tissue. They have the ability to

colonize muscle tissue and contribute to regeneration of the dystrophic muscle. These properties have prompted investigations towards the use of pericytes in the treatment of Duchenne Muscular Dystrophy and Limb-Girdle Muscular Dystrophy. Here, we propose to generate genetically modified autologous pericytes in which the disease-causing CTG-repeat has been removed by CRISPR/Cas9 genome editing. In consecutive research, these cells will form the basis for a therapeutic approach in DM1.

Study objective

In this project we use skeletal muscle biopsy tissue from DM1 patients and controls to isolate pericytes. These muscle-derived mesodermal cells can be genetically corrected by the novel powerful CRISPR-Cas9 technique, which will remove the disease causing repeat expansion. Pericytes have the potential to functionally integrate in skeletal muscle fibers and contribute to muscle regeneration. Human pericytes will be used for the proof-of-concept of generation of edited pericytes from human skeletal muscle biopsies. We are interested to see whether isolation, genetic manipulation and expansion will give us enough genetically corected autologous pericytes for therapeutic administration.

Study design

In this project we propose a preclinical study aimed to investigate the feasability of a cellular therapy against the neuromuscular phenotype in DM1. Pericytes obtained from DM1 patients by a quadriceps (vastus lateralis) muscle biopsy are genetically corrected by CRISPR-Cas9 and amplified to obtain the maximum number of genetically corrected autologous pericytes for therapeutic application.

Study burden and risks

When performed by a skilled physician in a defined clinical setting, the incidents associated muscle biopsy in volunteers are reasonable and rare. The van Engelen group routinely performs regular and MR-guided muscle biopsies, and has ample experience. There are no clinically defined major complications associated with the procedure. In extremely rare cases, infection or bleeding occurs after muscle biopsy. In some cases patients report pain, nausea, or dizziness.

There is no direct benefit for DM1 patients involved in this study. Treatment with autologous corrected pericytes will only be studied in animal models. In this feasibility study, human pericytes will only be used for the proof-of-concept of generation of edited pericytes. Therefore, the primary benefit will be better knowledge on the potential of a cellular therapy against the neuromuscular phenotype of DM1. No treatment is currently available for the

neuromuscular disorder. Performing this research will provide valuable information about the possibility to use autologous genetically corrected pericytes as a promising cellular therapy in DM1.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Written informed consent
- Age: 18+
- Sex: male/female
- Genetically confirmed diagnosis with DM1

Exclusion criteria

- Psychiatric or other disorders likely to impact on the informed consent
- Patients unable and/or unwilling to comply with the study instructions
- Concurrent illness
- Ongoing participation in other clinical trials
- Major surgery within 4 weeks of the visit

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-03-2018
Enrollment:	11
Type:	Actual

Ethics review

Approved WMO Date:	18-10-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL57509.091.16