Intra-arterial autologous myogenic stem cell therapy for m.3243A>G mutation carriers

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Ethical review	Not approved
Status	Will not start
Health condition type	Muscle disorders
Study type	Interventional

Summary

ID

NL-OMON42959

Source
ToetsingOnline

Brief title
MABs therapy m.3243A>G mutation carriers

Condition

- Muscle disorders

Synonym
mitochondrial myopathy; mitochondrial muscular disease

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMW,Prinses Beatrixfonds;Metakids;Ride4Kids;UMDF

Intervention

Keyword: mesoangioblasts, mitochondrial myopathy, mtDNA, muscle regeneration

Outcome measures

Primary outcome

Assess safety

Secondary outcome

Assess effectiveness (strength tibialis anterior muscle, myogenesis (NCAM/eMHC+ fibers), the m.3243A>G mutation load in newly formed muscle (NCAM/eMHC+) fibers, OXPHOS capacity and muscle+mitochondrial morphology) and homing (inflammation markers blood) of the ATMP.

Study description

Background summary

Mitochondrial disorders are progressive, often fatal multisystem disorders, in a part caused by mutations in the mitochondrial DNA (mtDNA). Epidemiological studies have shown that mtDNA disorders affect about 1 in 10,000 of the general population, inducing high health and societal costs and loss of quality of life. Clinical manifestations most strongly affect organs with a high energy demand, like muscle and brain. At this moment, there is no effective treatment known to influence the disease process. Myogenic stem cell-based therapies complementing defective muscle cells and fibres, are highly promising to combat the myopathy and exercise intolerance which affect >50% of heteroplasmic mtDNA mutation carriers. Myogenic stem cells called mesoangioblasts (MABs), are currently the only myogenic precursors that fulfill all criteria to be used as advanced therapy medicinal product for systemic treatment, namely good ex vivo proliferation capacity, high myogenic capacity and a capability to cross blood vessels, allowing intra-arterially (systemic) delivery towards affected muscle. The only experience today is using allogeneic MABs transplantation in animal models and patients with Duchene muscular dystrophy. Treatment with ex-vivo expanded MABs resulted in significant regeneration of DMD positive muscle fibers in the mice and dog models. Intra-arterial delivery of allogeneic MABs in DMD boys (phase I/II clinical study) demonstrated that the treatment was relatively safe and that dystrophin was being produced by the new muscle fibers

but insufficiently for clinical improvement. Our approach is superior as we use autologous MABs, which do not required an immunosuppressive regime, and we need only partial correction. We have demonstrated that MABs of most m.3243A>G carriers contain no or only a low amount (<10%) of the mtDNA mutation, allowing ex vivo expansion of patient-derived healthy MABs. The aim of this project is to induce muscle regeneration using these autologous, healthy MABs, as an autologous somatic cell therapy medicinal product (asCTMP).

Study objective

In this phase I/II clinical study will assess the safety, effectiveness and homing of asCTMP, namely autologous mesoangioblasts, that will be injected 3x intra-arterially in right lower leg via catheter in 5 indivuals that carry the m.3243A>G mutation.

Study design

Mono-center prospective open label intra-subject controlled phase I/II clinical study.

Intervention

A vastus lateralis muscle biopsy will be collected for isolation and ex vivo expansion of mesoangioblasts. Intra-arterial administration of autologous mesoangioblasts in right lower leg. Total dosis is 6*10E7/kg, which will be administrated in 3 escalating dosis (1*10E7/kg, 2*10E7/kg and 3*10E7/kg) with one month interval. Four weeks after last administration, skeletal muscle biopsies in the tibialis anterior muscle of both legs will be collected.

Study burden and risks

All participants will visit the Erasmus MC five times.
- At the first visit, a routine clinical examination and eccentric exercise training of the lower legs will be performed, a skeletal muscle sample (~200mg) and blood sample (10 ml) will be collected.
- At the second visit, after a short eccentric exercise training of the lower legs, 1*10E7/kg autologous mesoangioblasts will be intra-arterially injected in right lower leg via catheter, followed by observation for 24 hours and 6 blood samples (10ml) will be collected.
- At the third visit, 4 weeks after second visit, after a short eccentric exercise training of the lower legs, 2*10E7/kg autologous mesoangioblasts will be intra-arterially injected in right lower leg via catheter, followed by observation for 24 hours and 6 blood samples (10ml) will be collected.
- At the fourth visit, 4 weeks after third visit, after a short eccentric exercise training of the lower legs, 2*10E7/kg autologous mesoangioblasts will be intra-arterially injected in right lower leg via catheter, followed by

observation for 24 hours and 6 blood samples (10ml) will be collected.
- At the fifth visit, after a short eccentric exercise training of the lower legs and venous blood sampling, 3 muscle biopsies (30mg) of the tibialis anterior in both legs will be collected

The burden and risk associated with participation will consist of the collection of in total 7 skeletal muscle samples (1x 200 mg en 6x 30mg) and injection of the asCTMP and buffer (procedure control). Muscle biopsies can be painful in some cases. Infections and bleeding afterwards are possible, but rare. To minimize patient burden, the six small (~30mg) muscle biopsies collected at visit 5 will be collected using the Mag I automatic biopsy instrument, which is a fast and routinely used procedure at the Erasmus MC to harvest a small muscle fragment with patient burden being limited to the time of the procedure (anecdotic information of multiple patients). No risks are known to be associated with intra-arterial injection of autologous mesoangioblasts. Autologous cells are not expected to trigger an immune response. However, in the unexpected case that an immune response would occur, this would result in inflammation that can be treated. Intra-arterial delivery of allogeneic MABs was shown to be safe in children with DMD. Bleeding and/or bruising at place of entry may occur.

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

Adult carriers of a m.3243A>G mutation in muscle >30%

Exclusion criteria

Significant concurrent illness
Pregnant or lactating women
Psychiatric or other disorders likely to impact on informed consent
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
Allergy contrast fluid

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Generic name:	Somatic cells autologous

Ethics review

Not approved

Date:	24-11-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2016-001258-16-NL
CCMO	NL56789.000.16