Assess safety of intra-arterial autologous myogenic stem cell therapy for m.3243A>G mutation carriers

Published: 07-06-2019
Last updated: 09-04-2024

The phase I/IIa trial will consist of an intra-arterial injection (via catheter in femoral artery) of autologous MABs in the left lower leg of 5 m.3243A>G patients. The primary objective is assessing safety of administration of autologous MABs,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Muscle disorders
Study type	Interventional

Summary

ID

NL-OMON50120

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: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Prinses Beatrix Spierfonds;Metakids;Ride4Kids;UMDF

Intervention

Keyword: mesoangioblasts, mitochondrial myopathy, mtDNA, muscle regeneration

Outcome measures

Primary outcome

Primary endpoint: Safety

The planned i.m. MABs injections will provide knowledge on safety of autologous MABs as asCTMP by:

* Monitoring HR, BP, ECG, SaO2 to assess acute adverse events

* Angiography before and after cell infusion to asses vessel obstruction

* Assessment of systemic inflammation and muscle markers in venous blood samples collected within first 24 hours after infusion and after 28 days.

* Assessment of local inflammation in tibialis anterior muscle biopsies taken 24 hours and 28 days after infusion.

Secondary outcome

- Secondary endpoints:

*Assess homing by quantifying the number of IC-Green labelled autologous MABs in the muscle biopsy 24 hours after i.a. administration.

*Assess effectiveness of intra-arterial delivered autologous MABs at the tissue level by quantifying the number of new (eMHC-positive) muscle fibers and by assessing the mtDNA mutation load in muscle biopsies after 28 days.

Study description

Background summary

Mitochondrial disorders are progressive, often fatal multisystem disorders, in 20-25% of the cases caused by heteroplasmic mutations in the mitochondrial DNA (mtDNA). Epidemiological studies have shown that mtDNA disorders affect about 1 in 10,000 of the general population, inducing significant morbidity and mortality and high health and societal costs. Clinical manifestations are most prominent in organs with a high energy demand, like muscle and brain. At this moment, there is no effective treatment known to influence the disease process or manifestation. 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 (ATMP) for systemic treatment, namely good ex vivo proliferation capacity, high myogenic capacity and a capability to cross blood vessels, allowing intra-arterial (systemic) delivery towards affected muscle.
The only experience today is using allogeneic MABs transplantation in mice and dog models and in patients with Duchene muscular dystrophy (DMD). Treatment with ex-vivo expanded MABs resulted in significant regeneration of DMD positive muscle fibers in both mice and dog models. Intra-arterial delivery of allogeneic MABs in DMD boys (phase I/IIa clinical study) demonstrated that the treatment was relatively safe and that some dystrophin was produced by the new muscle fibers, although not sufficient for functional improvement. Our approach has key advantages as we use autologous MABs, which do not require an immunosuppressive regime. Also, mitochondrial function is partly preserved in mtDNA mutation carriers and partial supplementation by healthy fibres should suffice to ameliorate mitochondrial function. We have demonstrated that MABs of most m.3243A>G carriers contain no or only a low amount (<10%) of the mtDNA mutation, allowing direct ex vivo expansion of patient-derived MABs. The overall aim is to induce muscle regeneration using these autologous MABs with a mutation load of <10%, as advanced therapy medicinal product (ATMP).

Study objective

The phase I/IIa trial will consist of an intra-arterial injection (via catheter in femoral artery) of autologous MABs in the left lower leg of 5 m.3243A>G patients. The primary objective is assessing safety of administration of autologous MABs, which have not been used as treatment before in humans.
Secondary objectives are:
(1) to assess homing of the labelled autologous MABs to the tibialis anterior muscle after i.a. delivery
(2) assess effectiveness at the tissue level by measuring myogenesis and mtDNA mutation load

Study design

Mono-center prospective open label intra-subject controlled phase I/IIa

clinical study.

Intervention

Intra-arterial administration of 5*10E7 MABs/kg in left lower leg (total dosage: 1,9*10E8 MABs for treatment of one lower leg of a 75kg individual).

Study burden and risks

15 participants will be included, of which 5 will be selected for the clinical study.
- At the first visit (inclusion visit), a routine physical and neurological examination will be performed and a vastus lateralis skeletal muscle biopsy (~30mg) will be collected for quantification of the m.3243A>G mutation load in MABs and muscle.

The 5 participants, who have the lowest m.3243A>G mutation load in MABs (max 10%) and highest mutation load in muscle (min. 40%) will be selected for participation in the clinical study and will visit the Maastricht UMC four additional times. For the other 10 participants, the study ends after the first visit.

- At the second visit (5 patients), a routine clinical physical examination and will be performed, and a vastus lateralis skeletal muscle biopsy (~100mg) and a venous blood sample (~10 ml) will be collected and they will try-out the bout of eccentric exercise on the Biodex machine.
- At visit 3: routine physical examination, a bout of maximal eccentric exercise will be performed and a venous blood sample (10 ml) will be collected.
- At visit 4: routine physical examination, intra-arterial administration of 5*10E7 MABs in one lower leg, followed by 24hrs observation in the hospital including regular blood sampling (4x ~10ml) and a ~30mg tibialis anterior muscle biopsy of both leg 24 hours after infusion of the asCTMP.
- Visit 5 consists of a neurological and routine clinical physical examination, a venous blood sample (~10ml) and a ~30mg muscle biopsy in the tibialis anterior muscles of both legs.

The burden and risk associated with participation in the clinical study (5 patients) will consist of the collection of in total 6 skeletal muscle samples, 7 times venous blood sampling (10ml) and the intra-arterial administration of 1,9*10E8 labelled MABs (based on a 75kg person). Muscle biopsies can be painful in some cases. Infections and bleeding afterwards are possible, but rare. To minimize patient burden, the five small (~30mg) muscle biopsies collected at visit 1, 4 and 5 will be collected using the Pro-Mag I automatic biopsy instrument, which is a fast and routinely used procedure to harvest a small muscle fragment with patient burden being limited to the time of the procedure (anecdotic information of >500 patients). Intra-arterial

injection can cause bleeding and an allergic reaction to the contrast agent is possible. Intra-arterial injection of autologous cells are not expected to trigger an immune response, especially, because no missing protein is introduced as in DMD. Migration of MABs is possible when injected intra-arterially, and allogeneic i.a. delivery of 1.6-9 x10E8 allogeneic MABs in femoral artery was shown to be safe in children with DMD. Intra-arterial infusion of 1,9x10E8 MABs may cause obstruction of a blood vessel. To prevent formation of cell aggregates, 5 IU/ml heparin is added to the medicinal product and a bolus of 3,000 IU heparin is given at insertion of the catheter. The total dose of heparin is <3,200 IU, which is far below the maximum of 40,000 IU/day. After i.a. infusion, patients are monitored for 24 hrs and medication to react in case of an adverse event (thrombosis, anaphylactic shock, allergic reaction) is available.
The burden and risk associated with the first visit, for the 10 persons that are excluded from participation in the clinical study, is one visit the MUMC at which a small (~30mg) muscle biopsy will be collected using the Pro-Mag I automatic biopsy instrument.
The expected benefit of the current study for mtDNA patients is the characterization of the safety of autologous MABs as treatment for myopathy and secondly, an indication of the homing and effectiveness at the tissue level of the labelled asCTMP (myogenesis and m.3243A>G mutation load). This cannot be studied in animal models, as no model is available for the specific mtDNA mutation studied.

Contacts

Public
Medisch Universitair Ziekenhuis Maastricht

Universiteitssingel 50
Maastricht 6229ER
NL
Scientific
Medisch Universitair Ziekenhuis Maastricht

Universiteitssingel 50
Maastricht 6229ER
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Adult carriers of >40% m.3243A>G mutation in muscle

Exclusion criteria

- 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
- Deficient immune system or autoimmune disease
- Significant concurrent illness
- Ongoing participation in other clinical trials
- Major surgery within 4 weeks of the visit
- Vaccination within 4 weeks of the visit
- 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
- Stokes
- Allergy for contrast fluid
- Peripheral signs of ischemia or vasculopathy
- Any other factor that in the opinion of the investigator excludes the patient from the study

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-11-2020
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	07-06-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-08-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	06-03-2023
Application type:	Amendment
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	NL68732.000.19