Individualized trajectories of upper arm disease progression in Duchenne muscular dystrophy patients

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Main objective1. To assess the longitudinal trajectories of upper arm flexor muscle MRI parameters, muscle force and upper arm function in a cohort of ambulant and non-ambulant DMD patients, to assess the value of this muscle as target for...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neuromuscular disorders
Study type	Observational non invasive

Summary

ID

NL-OMON52311

Source
ToetsingOnline

Brief title
Individualized disease trajectories in DMD

Condition

- Neuromuscular disorders

Synonym
Duchenne, Duchenne muscular dystrophy

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Prinses Beatrix spierfonds

Intervention

Keyword: Duchenne muscular dystrophy, MRI, Muscle, Upper arm function

Outcome measures

Primary outcome

The main study parameters at the four different timepoints (0, 6, 12 and 18 months) are the mFF of the upper limb flexor muscles, measured by qMRI, the muscle force of the upper limb (elbow flexion strength) and upper arm function as measured with the PUL2.0. These datapoints will be used to construct the individual disease trajectories.

Secondary outcome

Secondary endpoints are:

- The clinical elbow flexion endpoint, defined as the loss of the ability to bring the hand to the mouth with a 200g weighing cup (supporting elbow on table is allowed).
- Upper limb strength: shoulder abduction, elbow flexion and extension strength and wrist flexion- and extension strength measured using hand held dynamometry (HHD; N);
- Absolute grip strength (kg), pinch strength (kg), measured using MyoGrip and MyoPinch;
- The DMD Upper Limb patient*reported outcome measure (PROM; score 0-64);
- The PedsQL3.0 Neuromuscular questionnaire (score 0-100);

Study description

Background summary

Duchenne muscular dystrophy (DMD) is a rare, progressive neuromuscular disorder that primarily affects boys and men due to recessive X-linked mutations in the dystrophin gene, which results in progressive degeneration of the muscle fibers, with fibrosis, fat replacement and eventually atrophy of the muscles. The clinical course of DMD is characterized by progressive muscle weakness and cardiac and/or respiratory failure eventually cause a premature death.

To date, no medicinal products have received full marketing authorization for Duchenne. Several antisense oligonucleotide (AON) mediated exon skipping therapies are currently being studied with systemic dosing, mainly in ambulant DMD patients. In the LUMC, new preclinical research is focused on another delivery method of therapy for DMD patients: intramuscular injections. Firstly because so far, results of systemic delivery of AONs have been limited due to relatively poor delivery of AONs to target tissues. The proof-of-concept studies with local intramuscular AONs (AVI-4658 and PRO051) showed safe and induced dystrophin synthesis. Based on these promising results, the exon-skip group from prof. dr. Annemieke Aartsma-Rus (Human Genetics, LUMC) is currently working on optimal dosing and frequency of intramuscular injections of AONs in animal models. Secondly because local therapy would reduce the risk of off-target effects. The research group of prof. dr. N. Geijssen (Anatomy and Embryology, LUMC) is working on a novel intramuscular CRISPR-Cas9 endonuclease therapy with an unique way of delivery by the method of iTOP.

The aim of both approaches is the development of a therapy using local intramuscular injections in selected muscles with the goal to preserve muscle function. To overcome the lack of treatment development in non-ambulant patients we aim to design a clinical trial targeting the elbow flexor (EF) muscles.

To be able to measure response to local intramuscular therapy, careful characterization of the natural history of the disease in the EF muscles, using relevant biomarkers, in relationship to function, is needed in younger and ambulant patients to expand previous findings. Moreover, longitudinal trajectories are needed to determine the *window of opportunity* for treatment of the EF muscles and to help us to determine the inclusion- and exclusion criteria for prospective trials. Finally, as the trial is envisioned to be a self-controlled trial, data about the symmetry between the trajectories of both EF muscles (left vs. right) are needed.

Study objective

Main objective
1. To assess the longitudinal trajectories of upper arm flexor muscle MRI parameters, muscle force and upper arm function in a cohort of ambulant and

non-ambulant DMD patients, to assess the value of this muscle as target for intramuscular therapy.

Secondary objectives
2. To assess (establish) the relation of these trajectories to a major disease milestone, ie the loss of hand to mouth movement.
3. To assess the relationship between arm function and patient*s perspective on performance of activities of the daily living and experienced health related quality of life.
4. To assess the annual decline of each parameter for both the left and right arm, to substantiate the feasibility of a self-controlled trial design.
5. To define the inclusion and exclusion criteria and primary endpoint for participants in the self-controlled trial.

Study design

The study design of this study is an observational, prospective cohort study and will be conducted at the LUMC. Patients will undergo a MRI of both upper arms, functional tests (by hand-held-dynamometry (HHD), Biodex, Myotools and assessment of the Performance of the Upper Limb (PUL)), the functional questionnaire *DMD upper limb patient-reported outcome measure (PROM)* and the QoL questionnaire *PedsQL Neuromuscular* at baseline, 6 months, 12 months and 24 months follow-up. Clinical follow-up will be done by telephone calls every six months to determine if the elbow flexor endpoint has been reached and to assess the PROM upper limb DMD.

For every included study patient under treatment at the LUMC, we will try to incorporate the study visits in the in their (yearly) routine follow-up visit at the hospital as much as possible. Their routine visit will then be lengthened with roughly 2 hours to undergo the MRI examination, functional assessments and questionnaires. Several functional tests mentioned above are already part of their routine follow-up visits, except the measurements by the Myotools and Biodex. For every included study patient under treatment at another hospital, we will ask the study patients to visit the LUMC independently from their routine follow-up visits. We expect their visits to take up a maximum duration of 2,5 hours (including short breaks and time for reposition).

The maximum duration of follow-up is 4 years. The physical follow-up ends for each patient after the 24 month follow-up visit. The study will be ended when all patients have finished their telephonic follow-up.

Study burden and risks

This study has no invasive procedures. Subjects with contraindications for MRI will be excluded. There are no known risks associated with the use of MRI or

the functional tests (HHD, Biodex, Myotools, PUL2.0). The burden for each participant (and his parents) will consist of roughly 1,5 - 2,5 hours per study visit (at 0, 6, 12 and 24 months), and a maximum of five telephonic follow-up calls, with a maximum duration of 15 minutes. Participants have no direct personal benefit from participating in this study. However, the results of this study will support the design of a future clinical trial for a new local intramuscular therapy for Duchenne patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

- Confirmed diagnosis of DMD through genetic testing;

- Age five years and older.

Exclusion criteria

- Lack of confirmed mutation in the dystrophin gene or patients with a secondary (neuro)muscular or metabolic disease that affect muscle function;
- Intake of investigational medications or exposure to an investigational drug within 6 months prior to the start of the study;
- Cognitive problems that would make it difficult to follow directions and participate in testing;
- Contraindications to MRI exposure (such as a metal implant).

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-10-2022
Enrollment:	35
Type:	Actual

Ethics review

Approved WMO

Date:	19-08-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

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	NL78546.058.21