A nationwide natural history study in Becker muscular dystrophy: Modeling a slowly progressive neuromuscular disease to prepare for clinical trials.

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

Summary

ID

NL-OMON52088

Source
ToetsingOnline

Brief title
Natural history BMD 2022

Condition

- Neuromuscular disorders

Synonym
Becker muscular dystrofie / BMD

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Becker muscular dystrophy, MRI, Muscle, Natural history

Outcome measures

Primary outcome

The main study endpoint is a model to predict the disease course of individual BMD patients based on the following parameters: clinical parameters (e.g. loss of ambulation), functional parameters (e.g. North Star Ambulatory assessment, strength measures), pulmonary parameters (e.g. forced vital capacity), cardiac parameters (e.g. left ventricular ejection fraction), muscle MRI characteristics (e.g. fat fraction) and biomarkers in serum (e.g. creatine/creatinine ratio).

Secondary outcome

Main clinical parameters at each time point:

- Weight (kg)

- Height (meters)

- Blood pressure (mmHg)

- Heart rate (beats/min)

- Ulna length (cm)

- ACTIVLIM and the PROM upper limb DMD

- Loss of ambulation (date, whenever applicable)

- Other clinical endpoints (first symptoms, diagnosis, use of walking aids, occasional use of wheelchair, loss of function arm to mouth, start use of respiratory support, cardiomyopathy, start use of cardiac support; date,

whenever applicable)

Main pulmonary parameters at each time point:

- Forced Vital Capacity (FVC) in percentage

- Forced Expiratory Volume in 1 second (FEV1) in percentage

- Peak Cough Flow (PCF) in percentage

Main functional parameters at each time point:

- North Star Ambulatory Assessment (NSAA) in points

- Timed tests (6 minute walk test (meters), 10 meter run test (seconds), time to rise from floor (seconds), time to climb 4 stairs (seconds), time to descend 4 stairs (seconds))

- Performance of the Upper Limb (PUL) 2.0 in points.

- Pinch strength (kg), grip strength (kg) measured using Myopinch and MyoGrip.

- Strength (kg) of at minimum: both flexion and extension of knee hip and elbow

Main cardiac parameters at each time point:

- Left ventricular (LV) ejection fraction (LVEF) in percentage

- Left ventricular end diastolic volume (LVEDV) in ml

- Left ventricular end systolic volume (LVESV) in ml

- Left ventricular global longitudinal strain (LVGLS) in percentage

Main qMRI characteristics at each time point

- Multiple MRI parameters including muscle volume, fat fraction and DTI

parameters.

Main parameters of muscle biopsy:

- Fibre size and other structural parameters

- Dystrophin quantification

Study description

Background summary

Becker muscular dystrophy (BMD) is a rare X-linked recessive disorder caused by a mutation in the dystrophin gene resulting in progressive muscle weakness. Cardiac involvement occurs in around 70% of the BMD patients and in some cases lung function is affected. Disease progression is slow making chances of observing clinically relevant end points during a clinical trial low. This in combination with the rarity of the disease and the large heterogeneity in symptoms makes research for possible therapies challenging. A model to predict disease progression based on biomarkers could potentially provide a solution to this problem in two ways. Firstly, it would enable researchers to select the patients in whom measurable disease progression is expected, thereby increase the chances of observing clinical endpoints within the duration of a trial. Secondly, this model could potentially be used to compare the predicted disease progression at the beginning of a trial with the observed progression at the end of a trial. This difference can then be used as a measure for the effect of the intervention.
Previous research has identified several potential serum and MRI biomarkers. In 2014, a 4 year natural history study was initiated at the LUMC collecting biomarkers as well as clinical parameters such as strength measures and the 6 minute walking distance. Preliminary data indicated that a longer follow-up and expansion of the cohort to include a larger disease spectrum are essential to be able to predict long term changes in BMD and to facilitate trial readiness. Therefore, this study aims to extend the follow-up in this cohort and expand the cohort also including children.

Study objective

The primary objective is to develop a disease model predicting clinical meaningful changes based on a combination of results of tests on clinical function, muscle MRI, echocardiography and circulating biomarkers applicable in various stages of disease in BMD patients.

The secondary objective is to link biomarkers to biology in BMD patients by spatial transcriptomics and quantitative muscle MRI.

Study design

Prospective observational cohort study

Study burden and risks

Patients will not benefit directly from participating in this study, but will contribute to the knowledge on BMD of which they may benefit in the future. The burden consists of 4 annual visits lasting a complete day. For patients under treatment at the LUMC, the study visits will be combined the regular follow-up as much as possible.
For the vast majority of the investigations in this protocol, there is no risk.
A MRI maybe considered unpleasant, for which there is an opt-out possibility.
Muscle biopsy may result in an hematoma and/or a 1-2 cm scar, for which in general no treatment is required. Also for muscle biopsy, there is an opt-out possibility.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

BMD patient cohort:
• Male
• Confirmation of diagnosis of BMD by DNA analysis
• Age >=5 years

In order to be eligible to partake in the muscle biopsy part of this study, the following additional inclusion criteria apply:
• Age >= 18 years

BMD trial participants cohort:
• Male
• Confirmation of diagnosis of BMD by DNA analysis
• Age >=5 years
• Inclusion in the phase II study of EDG-5506 in BMD (P22-064)

Healthy controls:
• Male
• Age >=5 years
In order to be eligible to partake in the muscle biopsy part of this study, the following additional inclusion criteria apply:
• Age >= 18 years

Exclusion criteria

Patients will not undergo MRI or muscle biopsy if they have contraindication for the MRI (such as a metal implant) or muscle biopsy (such as use of anticoagulation) respectively. If this is the case, it is still possible to partake in the other parts of this study.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-12-2022
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO Date:	24-11-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	05-08-2024
Application type:	Amendment
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	NL77823.058.22