Outcome measures in Duchenne Muscular Dystrophy: A Natural History Study

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON50307

Source
ToetsingOnline

Brief title
Duchenne natural history study

Condition

- Musculoskeletal and connective tissue disorders congenital
- Muscle disorders

Synonym
Duchenne Muscular Dystrophy

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Association Française contre les Myopathies

(AFM)

Intervention

Keyword: DMD gene, Duchenne muscular dystrophy, Natural history

Outcome measures

Primary outcome

Functional tests assessing pulmonary function and upper- and lower limb performance. These includes spirometry (FVC, MIP, MEP, PEF, Peak cough flow), timed and graded functional tests, 6 minute walk test (6MWT) , NorthStar Ambulatory Assessment (NSAA), myometry and goniometry, and PUL assessment. Furthermore, questionnaires regarding quality of life and disease specific milestones will be filled out.

Secondary outcome

Occurrence of antidystrophin antibodies in serum and autoreactive T-cells to dystrophin during the course of the disease in relation to functional outcome measures. Proteomics in serum and urine to search for disease biomarkers. Genome wide SNP analysis.

Study description

Background summary

Duchenne Muscular Dystrophy (DMD) is a fatal X-linked inherited muscle disorder, affecting 1 in 3,600 live male births. It classically presents in the first decade with proximal muscle weakness, which leads to progressive loss of ambulation before the age of 13 years. DMD occurs as a result of mutations in the dystrophin gene on chromosome Xp21. Characteristically, the muscle enzyme serum creatinine kinase is markedly increased and muscle biopsy shows absent dystrophin protein. To date there is no cure. In the recent years, there have been promising advances for new potential genetic treatments (including the

development of exon skipping with anti-sense oligomers producing dystrophin restoration). Because of the relative rarity of the disease and its progression over many years, it is not always feasible to test these potential therapies in randomized, blinded and placebo controlled trials. Therefore, it is required to expand our understanding on the natural history of DMD and to develop outcome measures, especially for the more advanced stages of the disease. In the last years, genetic modifiers have been identified in other genes than the DMD gene that influence the course of the disease.

Study objective

The primary aim of this study is to document with quantified measurements the natural history of Duchenne Muscular Dystrophy. Several validated tools will be used to describe motor, orthopedic and respiratory functions, and quality of life along a 6 years follow-up study in ambulant and non-ambulant patients. Objective is to determine the most sensitive outcome measures to use in the assessment of efficacy of future therapies. Secondary objectives are to understand how specific dystrophin responses are to DMD and to search for disease biomarkers in blood and urine.
Study of genetic disease modifiers in the DNA.

Study design

This prospective longitudinal natural history study will be performed in two cohorts of patients with DMD according to their level of functional motor ability (ambulant/non-ambulant). This study is designed as a large multi-institution study including 6 centres in 3 European countries: Netherlands (Leiden and Nijmegen), France (Paris) and UK (London (2 centres) and Newcastle).

Study burden and risks

The burden for patients and their families are six extra visits to the clinic in 6 years taking up to 1,5 hours, answering a quality of life questionnaire taking 5 minutes. The optional study of disease modifiers will be done via a SNP analysis on stored DNA. No incidental findings are to be expected.

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

NON AMBULANT DMD PATIENTS
1. Children, teenagers and adults from the age of 5 with DMD, who have lost the ability to walk 10 meters with no support
2. The diagnosis of DMD must be documented by genetic testing.
3. Patients should preferably have deletions amenable of skipping of exons 51 or 53 or 45 or 44 or 46 or 50 or 52.
4. Patients should be capable of sitting upright in a wheelchair for at least an hour
5. Patients should be stable from a respiratory point of view., AMBULANT DMD PATIENTS
Inclusion criteria:
1. Ambulant children from 5 years old and teenagers with DMD, and potential candidates for future genetic therapies with antisense oligomer (AO) exon skipping
2. The diagnosis of DMD must be documented by MLPA or a standard genetic test for the disorder, genotypically confirmed to have an out-of-frame deletion(s) that could be corrected by skipping exon 51 or 53 or 45 or 44 or 46 or 50 or 52

(Table1).
3. Ability to walk independently for at least 10 meters at recruitment.
4. Patients should receive the standard of care for DMD as recommended by the NorthStar UK and TREAT-NMD (ie: on glucocorticoids treatment)
5. Sufficiently preserved pulmonary function (FVC >30%) and absence of symptoms of cardiac failure.

Exclusion criteria

NON AMBULANT DMD PATIENTS:, 1. Patients who are currently involved in interventional clinical trials aimed at restoring dystrophin will be excluded, as their data could not be used to establish natural history of the disease (participation in a previous interventional clinical trial prior to 6 months from being recruited in the study is not an exclusion criterion)
2. Patients with severe intellectual impairment, who would be unable to cooperate with examination
3. Patients/families we anticipate may have emotional/ psychological problems if recruited in into a natural history study
4. Symptomatic cardiac failure
5. Recent (< 6 months) upper limb surgery or trauma
6. Anticipated surgery for anytime during the duration of the study
7. For the MRI substudy, patients with metal/metallic surgically inserted equipment incompatible with MRI scan and patients suffering from claustrofobia.
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Study design

Design

Study type:	Observational invasive

Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-07-2015
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	15-06-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	11-08-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	05-08-2020
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	NL51560.058.14