Establishing biomarkers and clinical endpoints in myotonic dystrophy type 1 (END-DM1)

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

Summary

ID

NL-OMON50021

Source
ToetsingOnline

Brief title
Establishing biomarkers and clinical endpoints in DM type 1

Condition

- Neurological disorders congenital

Synonym
DM1; Steinerts disease

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Virginia Commonwealth University;Richmond;VA23219;VS

Intervention

Keyword: Myotonic Dystrophy 1

Outcome measures

Primary outcome

- Characterize baseline status and disease progression over two years in 700

DM1 patients with myotonic dystrophy type 1 (DM1).

Secondary outcome

Optimize sample collection and analysis procedures for use of muscle RNA

alternative splice events as biomarkers of DM1 severity

Study description

Background summary

Mechanistic studies of DM1 have recently revealed a novel RNA-mediated disease process. The field has reached consensus that RNA toxicity is the core mechanism for DM1 pathogenesis. Good molecular targets have been identified, and recently there has been rapid progress in developing targeted therapies. Studies have shown that RNA toxicity is reversible in mouse models, encouraging us to believe that targeted treatments may have transformative effects on DM1 patients. However, recent meetings of stakeholders, including representatives from FDA, industry, academia, and advocacy, have indicated that three obstacles stand in the way of capitalizing on this opportunity: (1) insufficient data on natural history; (2) lack of reliable biomarkers; and (3) incomplete characterization and limited biological understanding of the phenotypic heterogeneity of DM1.

Building on previous work of the Myotonic Dystrophy Clinical Research Network (DMCRN), the present study seeks to overcome these roadblocks. Previously we used long study visits and extensive data collection to assess small cohorts of patients (n = 113 in our most recent study). In the current study we are transitioning to focused data collection on a larger cohort. This will expand the scope of natural history data and help us develop strategies for managing patient heterogeneity going forward. For example, we hope to identify clinical measures or patient characteristics that predict future disease progression. In addition, we have made substantial progress in developing biomarkers of DM1

severity and therapeutic response, based on RNA alternative splicing in muscle tissue. We have carried out large
discovery studies to comprehensively identify DM1-associated splicing defects, and then develop highthroughput assays for candidate biomarkers. Further work is needed to assess test-retest reliability, examine associations with disease severity, and optimize methods for sample collection and RNA analysis.

Study objective

The overall goal of this study is to accelerate the development of new therapies for DM1 by validating new clinical assessments for measuring disease status and collecting data and biological samples to help understand disease progression and severity . This provides valuable information and material for further research on DM1, for the development of new therapies and for the future design of new drug investigators. The aim of the study is to determine the best way to assess how patients are affected by DM1. The research will investigate the effects of DM1 on muscles, heart, blood and nervous system. Walking speed, muscle strength, myotonia, heart rate and overall health will be assessed by trained study personnel. The way in which is thought and information is processed is assessed by means of an automated test. Using questionnaires, test subjects are asked to record their own ideas about the consequences of DM1. During the study, the condition will be evaluated over a 2-year period to determine how DM1 changes over time. The research also identifies the biomarkers of DM1. Biomarkers are needed for future research to determine how DM1 may respond to new treatments.

Study design

This study will enroll 700 adult patients (18 to 70 years old, inclusive) with DM1 in the United States and Europe. No treatment will be administered as part of this natural history study. Patients will receive standard of care as determined by their treating physician. Study visits occur at baseline/0 months, 12 months, and 24 months. Study visits can take place over two days, provided that day 2 is within 7 days of day 1.

Study burden and risks

Risks:
- During the collection of blood samples, the participant may experience pain and/or bruising at the needle site. Although rare, localized clot formation and infections may occur.
- Muscle strength testing may cause the participant*s muscles to be sore and the participant to feel weak.
- Breathing tests may cause the participant to have difficulty breathing or he/she may feel fatigued during the test.
Completing questionnaires about the participant's symptoms could cause the

participant to become tired after concentrating for a long period of time. Some questions may cause minor psychological stress.
- Release of medical information/genetic tests could result in a potential loss of privacy. There is a small chance that some research may yield results that will have a negative impact on participants, family members, other individuals, or groups. This impact may include ability to be insured or employed, or changes in family relationships
- The greatest risk to genetic testing is loss of confidentiality.

Benefits
There are no direct benefits that participants can expect to receive as a result of taking part in this study

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

- Age 18 to 70 years (inclusive)
- Competent to provide informed consent
- Clinical diagnosis of DM1 based on research criteria or positive genetic test

Exclusion criteria

- Symptomatic renal or liver disease, uncontrolled diabetes or thyroid disorder, or active malignancy other than skin cancer
- Current alcohol or substance abuse
- Concurrent enrollment in clinical trial for DM1, pr participation in trial within 6 months of entry
- Concurrent pregnancy or planned pregnancy during the course of the study
- Concurrent medical condition that would, in the opinion of the investigator or clinical evaluator, compromise performance on study measures
- Use of mexiletine or other anti-myotonia agents within 72 hours of baseline visit

Note: non-ambulatory participants are not excluded but are limited to <15% of enrollment

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-08-2022
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	11-01-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-06-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
ClinicalTrials.gov	NCT03981575
CCMO	NL71565.091.20