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Workshop report

Clinical trial preparedness in facioscapulohumeral muscular dystrophy: Clinical, tissue, and imaging outcome measures 29–30 May 2015, Rochester, New York

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1. Introduction

Thirty six participants from seven countries representing academic centers, funding and regulatory agencies, pharma and advocacy groups met on May 29–30 2015 at the University of Rochester for a workshop on clinical trial preparedness in facioscapulohumeral muscular dystrophy (FSHD). The aim of the workshop was to reassess the state of trial readiness in FSHD two years after an initial workshop in Leiden in 2013 [1]. The elucidation of a unifying model for FSHD (see below) has provided several potential therapeutic approaches to treat FSHD. The potential for targeted clinical trials in the near future has heightened the interest of researchers and pharma in FSHD trial readiness. Indeed since the initial workshop in 2013, the results of two FSHD clinical trials have been published [2,3]. Another, ATYR1940 (aTyr Pharma) is actively recruiting study subjects.

FSHD is a dominantly inherited disease in its most common form, with a prevalence estimate ranging from 1:8000 to 1:20,000 [4–6]. A generally slowly progressive disease, FSHD causes significant lifetime morbidity, with up to 20% of those above age 50 requiring full time wheelchair use. FSHD has a distinct regional distribution of muscle weakness at onset [7]. Non muscular involvement in FSHD including hearing loss and retinal vascular disease is infrequent and restricted to patients with the most severe disease [8,9].

There are two genetically distinct but clinically identical forms of FSHD: FSHD1 and FSHD2. FSHD1, the most common form, is the result of partial loss of a number of D4Z4 macrosatellite repeat units in the subtelomeric region of chromosome 4 [10]. Individuals with FSHD1 have 1–10 repeats as opposed to 11–100 repeats in normal individuals. Each D4Z4 repeat contains a copy of the *DUX4* retrogene encoding for a double homeobox transcription factor [11,12]. The shorter repeat arrays have decreased epigenetic markers of repressive heterochromatin. There is now substantial evidence that the contraction of the repeats and the resulting chromatin changes result in aberrant reactivation of *DUX4* in skeletal muscle providing that the contraction occurs on a chromosome 4qA haplotype, which contains a polymorphic polyadenylation site for the DUX4 mRNA. Expression of DUX4 protein in skeletal muscle results in apoptotic cell death and induces the expression of numerous genes that might contribute to disease pathology [13–16]. In about 5% of FSHD cases (FSHD2), D4Z4 chromatin relaxation occurs in the absence of repeat contraction. In the majority of FSHD2 patients, this chromatin relaxation is the result of *SMCHD1* gene mutations, and digenic inheritance of an SMCHD1 mutation and an FSHD-permissive 4qA haplotype results in aberrant DUX4 expression in skeletal muscle and FSHD [17]. SMCHD1 is a chromatin modifier that binds to the D4Z4 repeat and is necessary to keep the repeat in a repressed state in somatic cells.

The first FSHD clinical trial preparedness workshop, held in Leiden, The Netherlands in April 2013, examined several aspects of clinical trial readiness including access to patients, clinical outcome measures, serum and tissue biomarkers, imaging biomarkers and the need for specific outcome measures for

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childhood-onset FSHD and FSHD2. The following recommendations were generated by the workshop: 1. Need for continued establishment of national registries utilizing the TREAT-NMD guidelines and recommended minimal dataset; 2. Whereas validated measures of impairment exist, there is a need for validated measures of activity impairment and validation of a new FSHD-specific patient reported outcome measure; 3. Identification and validation of additional tissue and serum biomarkers; 4. Need for longitudinal MRI studies using standardized imaging protocols and correlation of imaging with changes in muscle pathology and function; 5. Need for a trial network to facilitate the development and validation of FSHD outcome measures.

1.1. Access to patients for clinical trials

To date, nine national registries have been established (http://www.treat-nmd.eu/FSHD/patient-registries/FSHD-registries/), including those in the United States, Canada, United Kingdom, France, The Netherlands, Czech Republic, Italy, Egypt and New Zealand. Data from the UK FSHD registry (Evangelista) and the French National FSHD Database (Sacconi) were presented at the workshop. The UK registry was launched in May 2013 and currently has 521 registered patients. About 70% of the registered patients are genetically confirmed. It is a web-based self-reported registry with patient's own physician acting as curator. The French National FSHD Database has recruited 394 patients. In addition to curated medical records, French registry patients can opt to have a standard clinical evaluation performed by designated neuromuscular specialists.

1.2. Clinical outcome measures

The International Classification of Impairment, Disability and Health (ICF: http://www.who.int/classifications/icf/en/) will be used to describe clinical outcome measures discussed at the workshop. Measures of impairment, activity limitation, participation limitations and quality of life were discussed.

Measure of Impairment and Activity Limitation: A fifteen item FSHD-specific outcome measure currently under development (FSHD-COM), composed of individually validated measures mostly of function (activity) with a few items of impairment (weakness), was presented (Eichinger). The validation of the FSHD-COM is currently underway in a prospective 18-month study of 40 subjects. Test–retest reliability for the FSHD-COM was high (ICC 0.99) as well as the test–retest reliability of many of the individual items. Additionally, preliminary results of the measure's responsiveness were also presented. On completion of the longitudinal study the most reliable and responsive components of the FSHD-COM will be identified and included in the final instrument.

Measure of Activity and Participation: The outlines of a multicenter Dutch project to develop a functional outcome measure for FSHD based on Rasch analysis were presented (Mul). A review of the literature showed that most clinical outcomes used in FSHD studies were measures of impairment, used ordinal scales and were not validated. Responses from 200 patients to a list of 150 items, based on WHO ICF classifications, will be used to select approximately 20 items through Rasch analysis. The functional outcome measure will then be compared to existing scales and then studied longitudinally to determine responsiveness.

Measure of Impairment and Participation: The FSHD Health Index (FSHD-HI) is an FSHD-specific patient reported measure of disease burden consisting of a questionnaire with 116 items developed from qualitative interviews of patients followed by a national cross-sectional validation study (Heatwole) [18]. The measure was designed to meet FDA guidance for use in drug labeling claims and consists of 14 subscales that measure a patient's perception of their ambulation and mobility, hand function, shoulder and arm function, emotional health, back/chest/abdomen strength, fatigue, pain, eating function, ability to do activities, communication ability, satisfaction in social situations, performance in social situations, body image and cognition. Currently, the responsiveness of the FSHD-HI is being evaluated in an 18 month prospective study of 40 subjects. Test–retest reliability of the FSHD-HI was excellent in a sample of 22 subjects (interclass correlation coefficient = 0.945). Early data on 20 participants also demonstrate that the FSHD-HI is capable of measuring a small decrement of disease-burden over a 6–12 month period.

Measure of Impairment: The Astrand test, a submaximal cycle test which aims to measure aerobic capacity, appeared to be not feasible for use in patients with FSHD (Voet) [19]. Many patients use beta blocker medication, which is a contra-indication for the test, and the more severely affected patients are not able to reach the target heart rate because of muscle atrophy. A maximal exercise test is only suitable for the young, not severely affected patients. At present, a valid and reliable test to measure aerobic capacity is not available for the severely affected FSHD patients. The assisted 6-minute cycle test could be validated for use in the FSHD population to measure aerobic capacity and prescribe exercise. Assisted bicycle training delays functional deterioration in boys with Duchenne muscular dystrophy: the randomized controlled trial "no use is disuse" [20].

1.3. Tissue and serum biomarkers

Skeletal Muscle Biomarkers: Data on using DUX4 and DUX4 targets as potential biomarkers were presented (Tapscott). *DUX4* misexpression in skeletal muscle causes FSHD [21]. As a transcription factor *DUX4* activates expression of many other genes, including genes associated with stem cells and germline cells [22]. DUX4 mRNA is detected in FSHD muscle but at extremely low abundance [23]. Many DUX4 target genes are normally present in testis but absent in skeletal muscle. In a study of muscle needle biopsies from 14 FSHD and 10 control individuals, deep sequencing of RNA showed that DUX4 induced gene expression is the major molecular signature in FSHD with a more minor additional component attributable to genes expressed in infiltrating immune cells [24]. Further validation of these results is underway in a prospective study looking at correlations among measures of muscle pathology, biomarker expression and MRI outcomes. As this study will involve repeated