Getting ready to test new targeted treatments for myotonic dystrophy

2013 Annual Conference

Myotonic Dystrophy Foundation

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University of Rochester
Rochester, New York

“targeted therapy”

If a new targeted therapy for myotonic dystrophy was created, what effects could it have in a clinical trials

a) No effect
b) Slow down/stop the progression
c) Improvement

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If there was a new drug for myotonic dystrophy, what should it do?

questionnaire

If you could pick one aspect of your condition that a drug would help, what would it be?

Person with DM1

Person with DM2

Family member

Interested person

if a drug made you better, would you be able to tell?

if a drug made you a little better (5%),

would you be able to tell?

if a drug made didn’t make you better,

but stopped you from getting worse,

would you be able to tell?

if a drug stopped you from getting worse,

would you be able to tell in 2 months?

if a drug made didn’t make you better,

but stopped you from getting worse,

would that be worthwhile?

Choosing the best measurements

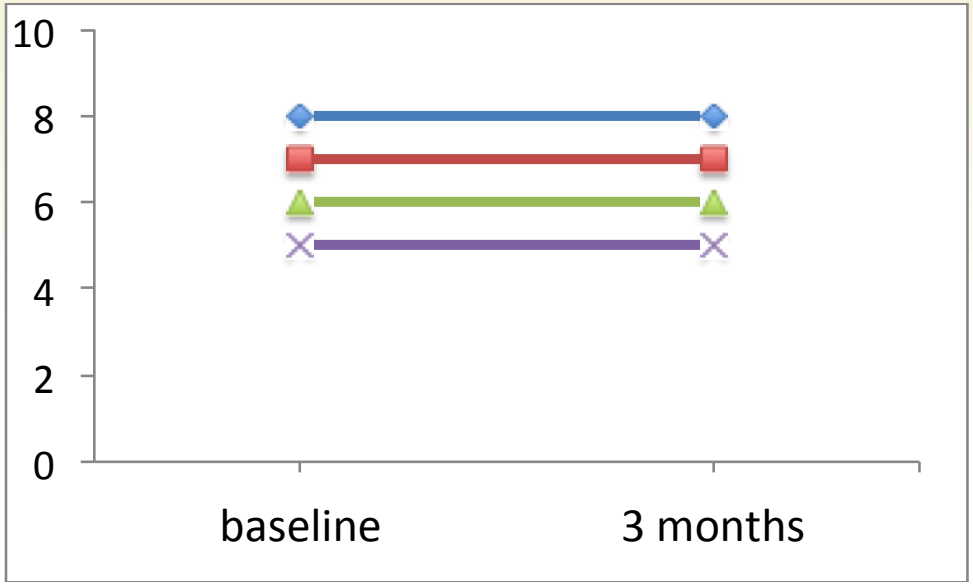
- Safe
- Acceptable to patients
- Not too costly
- Reliable
- Reflect something that’s important to a person’s life
- Responsive
  - ✧ Progression of the disease
  - ✧ To drug treatment

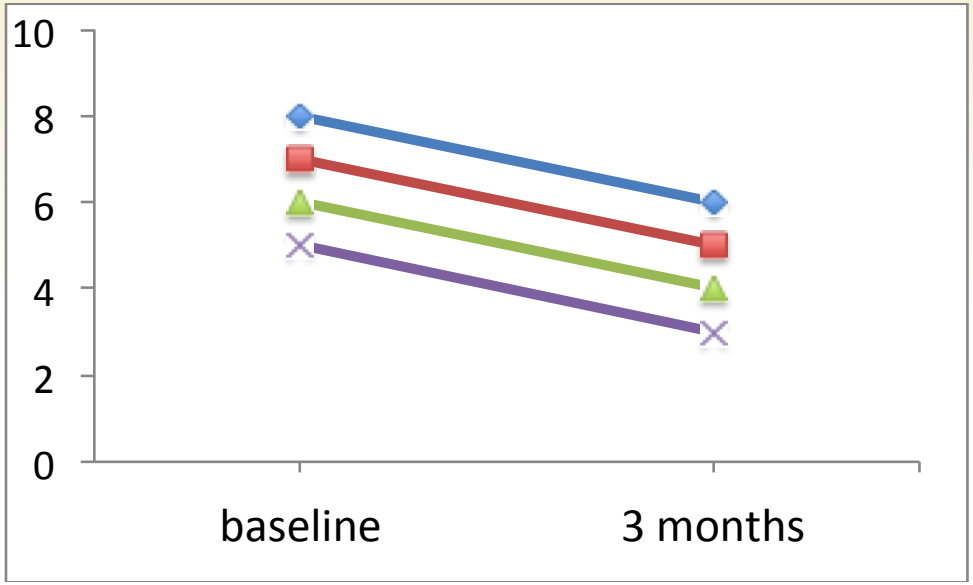
Natural History Study

Make a set of measurements in a group of people

No specific treatment

Repeat over time


10
8
6
4
2
0
baseline
3 months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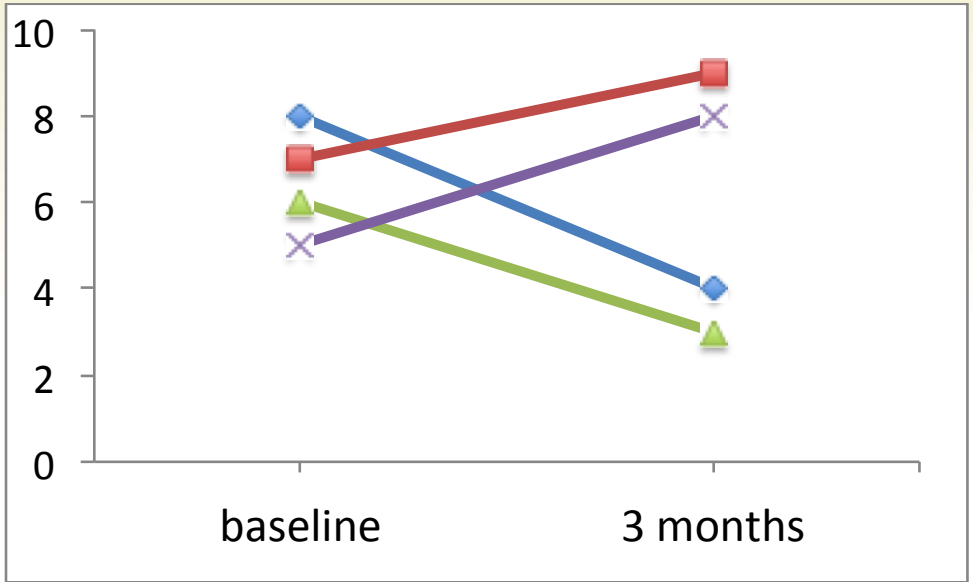
10
8
6
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2
0
baseline
3 months

Study of Progression in DM (STOP DM)

Richard Moxley
Charles Thornton
Chad Heatwole
Mike McDermott
Araya Puwanant
Masayuki Nakamori
Jeanne Dekdebrun
Kate Eichinger
Shree Pandya
Bill Martens
Nuran Dilek
Bharati Shah
Kirti Bhatt

80 people with DM1
20 people with DM2
20 healthy people

Baseline
1 year
3 year

Many different measurements
Muscle strength
Muscle function, myotonia
EKG, questionnaires, EMG,
Muscle biopsy

What have we learned from STOP DM study

1. That it is possible to do a study
2. Which measurements are best for showing change
   - one answer: hand grip is best single measurement
3. How to measure myotonia
4. Very good biomarkers
5. Very good Patient Reported Outcome

Chad Heatwole and the DM-specific Patient Reported Outcome (MDHI)

1. Years in the making
2. In accordance with methods/recommendations FDA
3. Input from hundreds of people affected by DM
4. Extensively validated
5. Just published

Finding good biomarkers

- Laboratory measurements
- Using samples from people
- Showing that:
  - ✧ Drug went to the right place
  - ✧ Had the intended effect

Biomarkers

1. Muscle biopsy
2. Specimen placed in BioBank (if person gave permission)
3. Lab analysis

Distribution from BioBank

Biomarkers

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3. Lab analysis

- Largest, most intensive study of muscle biopsies in muscular dystrophy
- First study to systematically compare changes in biomarkers with changes of strength
- Results compared to DM1 mouse models
- How did the biomarker respond to treatment in mice

Biomarker measurements in muscle biopsies

- Big effect
- Quite precise
- Correlated with muscle weakness
- Similar changes in DM mice
- In DM1 mice, changes are completely normalized by antisense drug

Comments and Recommendation of Reviewer

This is a very comprehensive and detailed look at splicing patterns in DM and the findings show novelty in enlarging the number of DM-affected splice events and by providing insight into the functional correlation with splicing misregulation. *The major weakness of this manuscript is the shear bulk of information presented to potential readers. Only a select group of researchers would consider wading through all of this material after publication.*

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Splicing Biomarkers of Disease Severity in Myotonic Dystrophy

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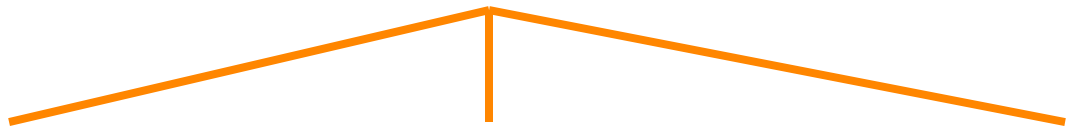
Scrambling toward trial readiness: Myotonic Dystrophy Clinical Research Network

1. Like minded researchers
2. Additional natural history data
3. Further validation of PRO and biomarkers
4. Multicenter experience

Scrambling toward trial readiness: Myotonic Dystrophy Clinical Research Network

Supported by all the major stakeholders



NIH	Advocacy	Companies
	Myotonic Dystrophy Foundation	Isis
	MDA	Biogen Idec
	Marigold Foundation	

Scrambling toward trial readiness: Myotonic Dystrophy Clinical Research Network

1. Ohio State University
    - Kissel, Arnold, King
2. Kansas University Medical Center
    - Barohn, Dimachkie, Herbelin
3. University of Florida
    - Ashizawa, Subramony
4. Stanford University
    - Day, Hagerman
5. University of Rochester
    - Moxley, Thornton, Heatwole, Pandya, Eichinger

Scrambling toward trial readiness: Myotonic Dystrophy Clinical Research Network

Initial study:

- 100 people
- 3 study visit over 1 year
- Measurements of DM1 severity
- Biomarker