Overview of progress made, and lessons learnt in experimental therapies for other neuromuscular diseases”

Francesco Muntoni
Dubowitz Neuromuscular Centre
UCL Institute of Child Health
& Great Ormond Street Hospital
London, UK
Francesco Muntoni: disclosures

Duchenne trials
- CI of 3 AON clinical trials with AVI / Sarepta.
- PI of three Prosensa / Biomarin sponsored AON trials
- PI of PTC phase II and III sponsored trials.
- PI of Pfizer phase II clinical trial (myostatin inhibition)
- CI of Summit Phase I and II trials.
- CI of Esperare Phase I trial (2016-2017)

Spinal Muscular Atrophy trials
- PI of Trophos/ Roche SMA III trial (2013-14; 16-17)(1 SAB in 2014)
- PI of Ionis/ Biogen AON Phase III study (2015-17), SAB in 2015 and 2016

Other
- Member of Pfizer rare disease SAB
- Audentes natural history and AAV gene therapy UK Investigator
Structure of the presentation

1. Contribution of RYR1 to the CNM

2. Lessons learned from experimental therapies in other neuromuscular disorders: relevance for MTM/CNM
RYR1 studied in 24 CNM from South Africa (14) and Europe (10)

RYR1 mutations in 17/24 patients (12/14 of the South African population and 5/10 of the European population)

South African founder (common) RYR1 mutation

- How common CNM in patients with RYR1?
- Is the clinical course of these patients different from other RYR1 entities?
• We offer the diagnostic and clinical advisory service for England for these conditions
• We have diagnosed > 500 patients with RYR1 mutations over the years
• There is little information on the longitudinal natural history of patients with RYR1 related myopathies
• We have recently started to look in detail at the clinical presentation and functional changes over time of children with RYR1 related myopathies followed at our centre

• What is the proportion of patients with a CNM muscle pathology who have RYR1 mutations?
• Are these children any different from the remaining patients with RYR1 mutations?
Preliminary data: 35 RYR1 patients

- 7/9 CNM patients recessive inheritance, 2 dominant inheritance
- 8/9 CNM patients onset at birth, one at 1.5 years of age
- 7/8 walk; 1/8 lost ability to walk; 1/8 too young
- Opthalmoplegia: 7/9
- 3/9 PEG fed
- 1 sibling of a CNM had a muscle biopsy with unspecific myopathic changes (but no cores or CN)
Respiratory function (FVC) in CN patients (in red) vs non-CN pts (in grey)
Dramatic impact of genetic therapies for Duchenne muscular dystrophy (DMD) and Spinal Muscular Atrophy (SMA)

**Dealing with mutant RNA.**
Splice-switching antisense oligonucleotides for:
- exon skipping for DMD deletions
- exon inclusion in SMA

**Replacing genes with gene therapy**
- AAV gene therapy for DMD
- AAV gene therapy for SMA type I
The two most common neuromuscular diseases in children

**DMD**

- Most common muscular dystrophy of childhood
- X-linked, 1 in 3,500 male births
- 26,000 new cases each year, ~100 in UK
- De novo mutations hamper genetic efforts to reduce incidence
- Economic cost: at least $120,000 per year

**SMA**

- Most common lethal genetic disorder of childhood
- Autosomal recessive, 3 different levels of severity
- Cumulative incidence: 1 in 6,500 - 1,10,000 births
- Heterozygous carrier frequency: 1:37 - 1:60 in Caucasian populations

DMD

SMA
Antisense oligonucleotides: molecular patches that address the way the mutant SMN gene is processed by the cell

Skipping exon 51: 15% of all DMD boys carrying deletions

Or to induce an exon retention
Weekly intravenous infusions
Intrathecal administration of the antisense oligonucleotide spinraza

- AONs do not cross the blood brain barrier
- Intrathecal administration required
- After a loading phase (4 IT injection in 2 months), the long half life of the AON enables infrequent dosing
Motor performance

Infants on nusinersen achieved motor milestones unexpected for individuals with Type I SMA
Dramatic impact of genetic therapies for Duchenne muscular dystrophy (DMD) and Spinal Muscular Atrophy (SMA)

Dealing with mutant RNA. Splice-switching antisense oligonucleotides for:
- exon skipping for DMD deletions
- exon inclusion in SMA

Replacing genes with gene therapy
- AAV gene therapy for DMD
- AAV gene therapy for SMA type I
DMD AAV gene therapy programs

Single IV administration

Highly internally deleted dystrophins (AAV capacity 4.7Kb max)
AAV9 for SMA gene therapy

Jerry Mendell (Columbus, Ohio) is pursuing AAV gene therapy in infants with SMA I

Single IV injection

Two doses used:
A. Cohort 1: $6.7 \times 10^{13}$ vg/kg
B. Cohort 2: $2.0 \times 10^{14}$ vg/kg

Inclusion
- 9 months/6 months of age or younger at infusion
- Bi-allelic SMN1 gene deletions or point mutations
- 2 copies of SMN2
- Onset of disease at birth to 6 months of age
AVXS-101: CHOP-INTEND Motor Function Scores

Infants with SMA type 1 older than 6 months of age do not score >40 (Finkel et al. 2014)

Infants with SMA1 decline >10 points from 6 to 12 months of age on average (NeuroNEXT; Kolb 2016)

COHORT 1 (n=3)
Baseline Age (months): 5.9 [median], 6.3 [mean]
Current Age (months): 30.8 [median], 30.4 [mean]
Mean CHOP INTEND Increase: 7.7 points
AVXS-101: CHOP-INTEND Motor Function Scores

**COHORT 2 (n=12)**

Baseline Age (months): 3.1 [median], 3.4 [mean]  
Current Age (months): 20.2 [median], 20.7 [mean]  
Mean CHOP INTEND Increase: 24.7 points

Rapid Response in Cohort 2
- CHOP INTEND Increase at Month 1: 9.8 [mean]  
- CHOP INTEND Increase at Month 3: 15.4 [mean]

Max score is 64

Early intervention and dose appear to affect response

Dashed lines for individual patients denote missed or partial CHOP-INTEND assessments
AAV gene therapy take home message

On the whole the side effect profile of AAV so far has been manageable

Improvement of at least some function is encouraging, as suggests that at least some of the muscle weakness can be reversed

Issues to consider:
- Pre-existing immunity might preclude treatment in some kids
- Administration of very high viral doses almost invariably determines transient inflammation of the liver that requires administration of high doses of steroids to avoid severe liver damage
- Longevity of effect?
- Hurdle of re-administration
Concluding remarks

- The progress made in the last few years in the therapeutic approaches for neuromuscular disorders is simply outstanding.
- Early data in some of the conditions indicate a size of therapeutic response that is unprecedented (for example in spinal muscular atrophy).
- Complete reversibility is not achievable. Optimal management of children and adherence to anticipatory standards of care necessary.
- Reducing the diagnostic delay for these conditions now has very tangible implications.
- Consider newborn screening.
Concluding remarks (2)

• While success and tolerability of these approaches encourages their continuing development, both their long term safety, and cost/benefit will require careful analysis

• The cost of some of these intervention is considerable, and this might preclude their access to our patients

• NHSE and NICE do not currently have a swift system to allow the assessment of emerging therapies for these devastating childhood conditions

• It is an important priority the careful documentation of the burden of disease for children and their families, as these “hidden costs” are not easily available and this is an obstacle for the adoption of costly drugs
Acknowledgment
Clinical and research team at GOSH/ICH

Great Ormond Street Hospital for Children NHS
National Institute for Health Research

Muscular Dystrophy Campaign
NorthStar Clinical Network

wellcome trust

Duchenne Parent Project

AFM

MDEX

Medical Research Council Centre for Neuromuscular Diseases

Seventh Framework Programme

Association Française contre les Myopathies

Great Ormond Street Hospital Charity