Neuromuscular disorders: outcomes in gene therapy and ethics

ACTION DUCHENNE

ANNUAL INTERNATIONAL CONFERENCE 2019

Francesco Muntoni

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

MRC Centre for Neuromuscular Diseases

NIHR | Great Ormond Street Hospital Biomedical Research Centre

Topic discussed (2)

- Micro-dystrophins in Becker MD
- Targeting the heart
- Durability
- Treating early or treating late?
- Second or more doses? Re-administration?
- Safety and clinical surveillance

Very mild muscular dystrophy associated with the deletion of 46% of dystrophin

S. B. England*, L. V. B. Nicholson†, M. A. Johnson†, S. M. Forrest*, D. R. Love*, E. E. Zubrzycka-Gaarn‡, D. E. Bulman‡, J. B. Harris§ & K. E. Davies*||

* Molecular Genetics Group, Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, UK
† Muscular Dystrophy Group Research Laboratories, Regional Neurological Centre, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne, NE4 6BE, UK
‡ Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada

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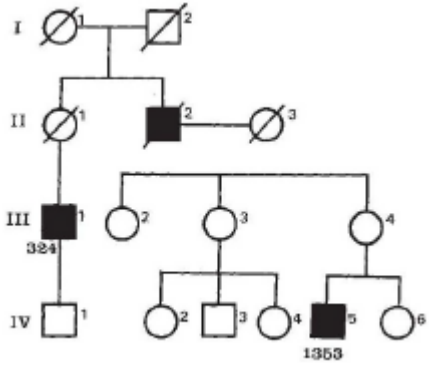


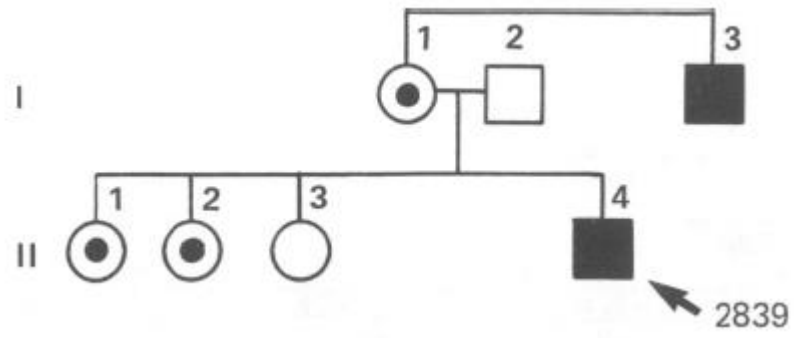
17-48 del

Weakness in the 30s, uses a stick in 60s
Uncle needed a stick in 50s

860 *J Med Genet* 1991; **28:** 860–864

Becker muscular dystrophy patient with a large intragenic dystrophin deletion: implications for functional minigenes and gene therapy

Donald R Love, Tracey J Flint, Sally A Genet, Helen R Middleton-Price, Kay E Davies



13-44 del

The proband presented at 21 years of age with proximal leg weakness
Difficulty in climbing stairs and rising from a squat position.
Aged 26 years continues to work as a panel beater
His maternal uncle, aged 44 years, is confined to a wheelchair.

Message

- These BMD patients (as the AAV treated patients) continue to have high CK, indicating a degree of ongoing muscle pathology

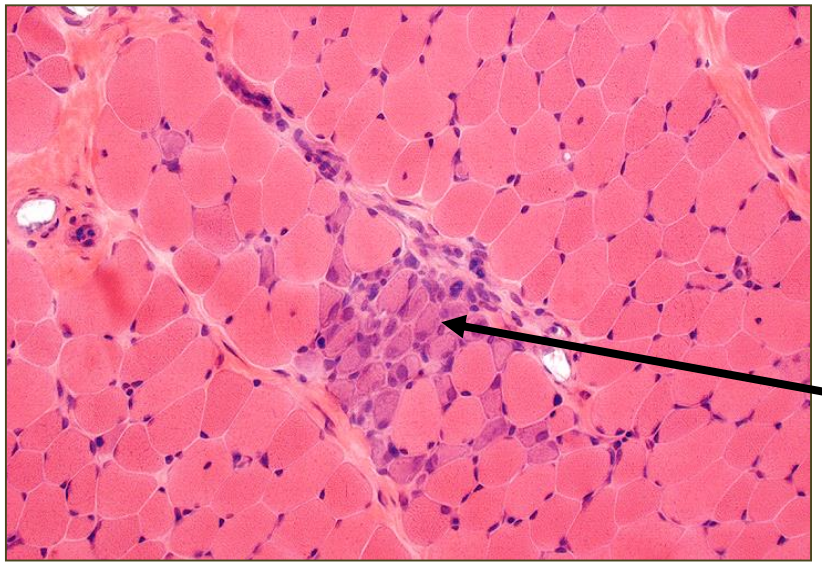
  → low level of ongoing muscle regeneration

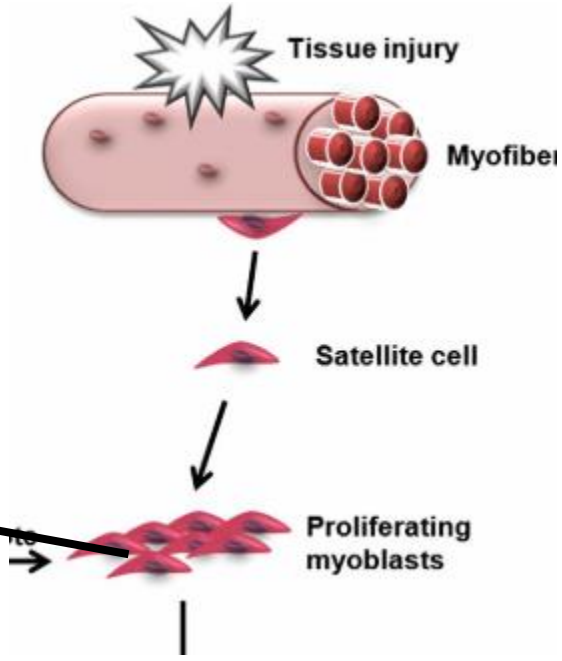
- In BMD patients, any new nucleus formed from activation of the muscle stem cells leads to a nucleus that is competent to produce the same BMD dystrophin

- In DMD patients following AAV therapy, any new nucleus does not have the AAV transgene, so will be dystrophin deficient

Durability of AAV in skeletal muscle: different aspects to consider

- 1. loss of non-integrating vector following cycles of degeneration/ regeneration, especially in muscles with low AAV transduction





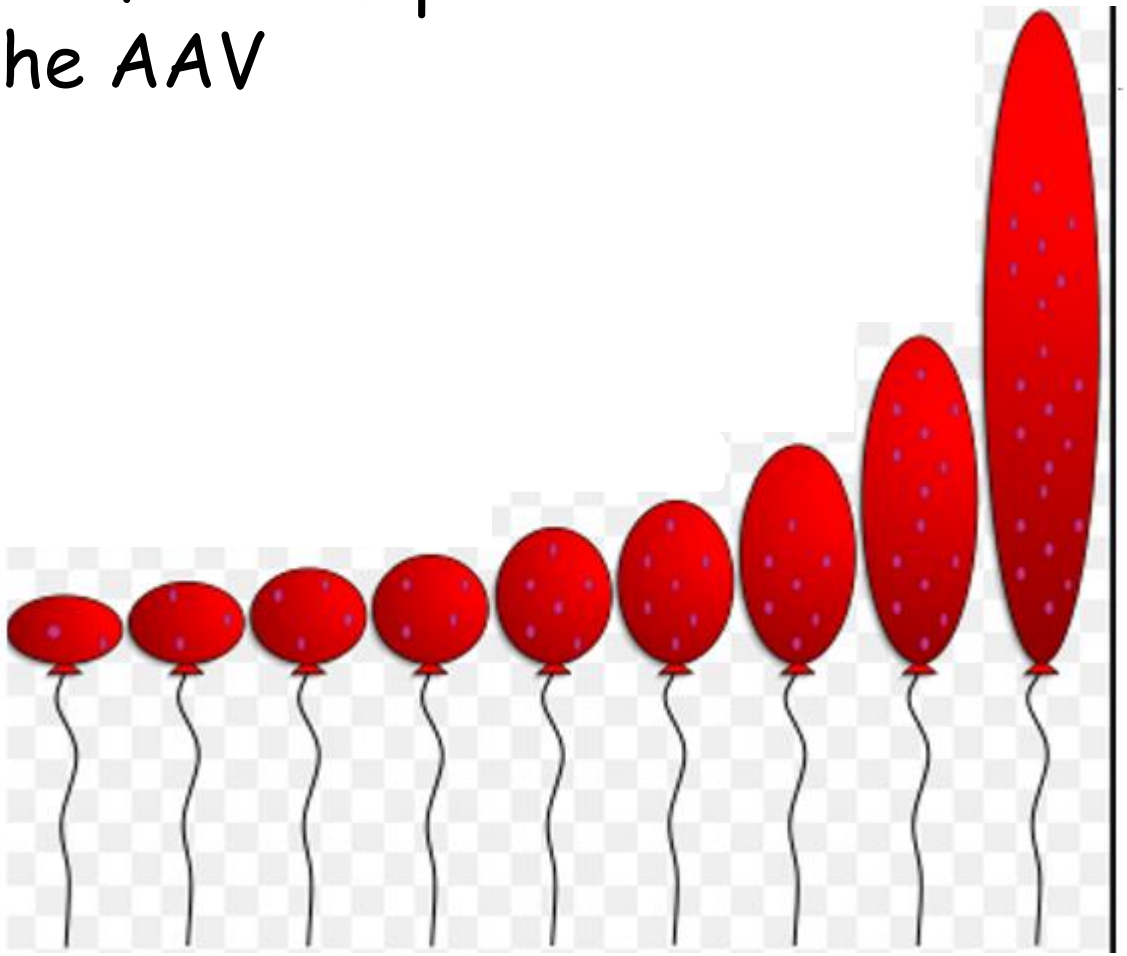
Molecular Therapy vol. 21 no. 8, 1551–1558

AAV Genome Loss From Dystrophic Mouse Muscles During AAV-U7 snRNA-mediated Exon-skipping Therapy

Maëva Le Hir[1,2], Aurélie Goyenvalle[2], Cécile Peccate[1], Guillaume Précigout[2], Kay E Davies[3], Thomas Voit[1], Luis Garcia[2] and Stéphanie Lorain[1]

Durability of AAV in skeletal muscle

- Dilution of non-integrating vector following muscle growth
- Every cell division of a AAV positive cells leads to a + and a – cell for the AAV vectors



Dose escalating studies

- Children in the lower cohorts unlikely to have the same level of benefit as children receiving the highest dose.
- In current AAV trial, low dose could nevertheless be expected to produce some benefit
- At variance with other therapies, these children cannot be re-dosed, i.e. receive another AAV administration at the optimal dose
- Substantial cross reactivity between different AAV serotypes makes it currently not possible to redoes using a different vector

- It is hoped these difficulties will be overcome in the future

Ethical issues

- Considerations for informed consent (and assent…)
- Uncertainty on how long treatment will last for, and what to do if loss of therapeutic efficacy after several years
- Implication for recruitment of treated patients in future clinical trials
- Optimal timing window for intervention (in myopathies):
  - → early and better preserved muscle ?
  - → or late with less dilution effect of the transgene?

Why not only to use high AAV doses in all?

AAV related Adverse Events

- Frequent "flu-like" malaise following the i.v. injection
- Transient liver transaminitis, requiring preventive corticosteroid administration, occasionally requiring increased and prolonged dosing

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- More severe liver involvement
- Platelet depletion
- Troponin elevation with cardiac involvement
- Complement mediated nephropathy requiring hemodyalisis

Conflict of interests

- Physicians may be misguided by the therapeutic misconception or in some instances have financial conflict of interest
- Some families are heavily involved in raising money and in companies for initiating AAV gene therapy for their children
- Pressure on affected children in these families

Evolving pharmacopeia, knowledge and expertise for post AAV gene therapy

- UCL AAV Gene therapy working group
- Corticosteroids
- Complement targeting drugs (eculizumab):
- Combinations of T cell targeting drugs (steroids, sirolimus, tacrolimus, etc.)
- Combination of B and T cell targeting drugs (sirolimus + rituximab)
- Addition of rapamycin for potential transgene re-administration
- Vaccination policies
- Exposure to infectious agents policies

PRACTICAL CONSIDERATIONS FOR PROVIDING AAV-MEDIATED GT

Consider your clinics today

- Number of patients
- Age and range of severity of patients with DMD
- Expertise of the multidisciplinary teams involved in delivering care

Consideration for delivery of AAV GT when commercially available

- Expertise / facilities required for AAV administration
- Networks of treatment centers and follow up centers

We are well placed in the UK for a network approach for AAV gene therapy deployment

There is a long standing and well functioning tradition of collaboration between different tertiary neuromuscular centres in the UK

23 centres have been working together for more than a decade under the auspices of the North Star network

More than 1500 DMD boys longitudinally followed up in the North Star network

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Good flow of patients between sites for clinical trials, although the increase in number of trials puts new demands on the network

Hub and spoke model for the safe delivery of AAV explored between different sites and also with some of the companies

- Likely hub and spoke model
- Centres involved in the delivery of the AAV and the management of rare adverse events
- Local centres involved in the general care of the patient and in the common complications

Incredibly dynamic times for neuromuscular AAV therapeutic developments
Size of response to intervention will be transformative for patients, especially if treated early

Important ethical issues for which we need to be prepared
We need to rapidly improve our knowledge and capacity to deal with the likely profile of AAV Aes, to be able to effectively and safely use these products in clinic

Acknowledgment

NIHR | Great Ormond Street Hospital Biomedical Research Centre

UCL GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

Muscular Dystrophy UK
Fighting muscle-wasting conditions

NorthStar Clinical Network

MRC Medical Research Council
Centre for Neuromuscular Diseases

DUCHENNE UK

DMD HUB
EXPANDING TRIAL CAPACITY

SMA REACH UK

The SMA Trust

wellcome trust

MRC Medical Research Council

Great Ormond Street Hospital Charity

Great Ormond Street Hospital for Children NHS
NHS Trust