An overview of therapeutic strategies for Duchenne Muscular Dystrophy

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Duchenne muscular dystrophy (DMD)

Disease causing muscle wasting

X-linked inheritance

Frequency 1:3500 boys
20 years ago:
Natural history of Duchenne muscular dystrophy without treatment:

- Disease onset at the **age of 2-5 years**: motor delay, muscle weakness
- Loss of ambulation at the **age of 7-13 years**.
- Thereafter: decline of respiratory function cardiomyopathy
- Mean age of death at the **age of 18-19 years**.
Lack of dystrophin as the underlying cause of DMD

Expression of dystrophin in a control muscle

Missing dystrophin in Duchenne muscular dystrophie
Histopathological hallmarks of muscular dystrophy

fibre necrosis  fibre regeneration  fatty fibrosis
Researchers often say there is no therapy for Duchenne muscular dystrophy.

The clinicians and the patients know that this is not true.
Combat against progressing scoliosis - spinal arthrodesis

- Rapidly progressing scoliosis
- Loss in respiratory function with Vital Capacity: **0.89 liter** (29% of normal)

Before operation

- no further progression of scoliosis
- Amelioration of respiratory function
  - VC: **1.33 liter** (41% of normal)

After operation
Combat against decline in respiratory function – the benefice of noninvasive ventilation (NIV)

Before ventilation

- severe weight loss
- fatigability
- sleep-disorderd breathing
  morning pCO2: **7.13 kPA**
  (normal 4.5-5.5)

After start of ventilation

- weight gain
- less fatigable
- normalisation of sleeping pattern
- normalisation of blood gases

**Importantly:**
Less broncho-pulmonary infections!!!
Managing Duchenne muscular dystrophy -- the additive effect of spinal surgery and home nocturnal ventilation in improving survival.

Eagle M, Bourke J, Bullock R, Gibson M, Mehta J, Giddings D, Straub V, Bushby K.
University of Newcastle

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<th>No treatment</th>
<th>NIV only</th>
<th>NIV and spinal surgery</th>
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<tr>
<td>Median age of survival</td>
<td>17 years</td>
<td>22 years</td>
<td>30 years</td>
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Combat against heart failure
– the benefice of heart protective treatment

depression of left ventricular function and dilated cardiomyopathy

heart failure

40% of DMD patients die from heart dysfunction

electrocardiographic abnormalities

arrhythmia
Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up.


Department of Cardiology, Cochin Hospital, APHP, Paris V René Descartes University, Paris, France.

10 years Perindopril treatment: **93%** of patients still living

10 years Placebo treatment: **65%** of patients still living
Duchenne muscular dystrophy: survival by cardio-respiratory interventions.

Yakumo Byoin National Sanatorium, Department of Paediatrics, Hokkaido, Japan

Non-invasive ventilation and cardioprotection
+/- back surgery, +/- glucocorticoids

Median age of survival

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<th>no treatment</th>
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<td>18 years</td>
<td>40 years</td>
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Standards of Care for Duchenne muscular dystrophy


Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management.
Bushby K et al.; DMD Care Considerations Working Group.


Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care.
Bushby K et al.; DMD Care Considerations Working Group.
Researchers often say there is no therapy for Duchenne muscular dystrophy.

Julien plays Piano. However, Julien would like to do many things that he can’t do.
- he can’t stand up,
- he can’t play football,
- he can’t lift up a book....

Yes, it is also true that there is no real therapy, because doctors can’t make patients walk again.
Many prospective therapies to treat muscular dystrophy

1. Medicaments to restore expression of dystrophin
   - e.g. Exon skipping
   - e.g. Stop codon read through

2. Medicaments to stimulate muscle growth
   - e.g. Myostatin blockade
   - e.g. ActRIIB blockade

3. Medicaments that alleviate alterations of muscle cell function
   - e.g. Idebenone
   - e.g. SERCA-overexpression
How to develop novel therapies for Duchenne muscular dystrophy

Proof of principle of the therapeutic strategy

Preclinical trial

Clinical trial

Duchenne patient

Mdx mouse

GRMD dog
Upcoming novel therapy: Restoration of Dystrophin expression by Exon skipping

Restoration of dystrophin expression

Improvement of eccentric force

Improvement of muscle pathology...and.........muscle function
Local dystrophin restoration with antisense oligonucleotide PRO051.  
van Deutekom JC, et al.
Department of Human and Clinical Genetics, Leiden University Medical Center, The Netherlands

Recently started: Phase III trial, GSK, on exon 51 skipping:

- Clinical Study to Assess the Efficacy and Safety
- Randomised - Double-Blind - Placebo-Controlled
  - 180 subjects, 48 weeks treatment
- Primary efficacy analysis: 6 min walking test
Upcoming novel therapy: Soluble Actin Receptor IIB (sAcRIIB)

Stimulation of muscle growth

Stimulation of muscle function??

Results of preclinical trial currently analysed.

Pistilli et al. (2011)
Rational of therapy targeting Activin receptor IIb signalling: Increased muscle growth following mutations in Myostatin (GDF-8)
Rational of therapy targeting Activin receptor IIb signalling:

Soluble Activin receptor IIb inhibit Myostatin (GDF-8) and homologue factors
Study of ACE-031 in Subjects With Duchenne Muscular Dystrophy

Upcoming novel therapy:
Soluble Actin Receptor IIB (sAcRIIB)

- **Sponsor:** Acceleron Pharma
- Phase II – Randomized – Double blind – Placebo controlled
- Ascending dose study to evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics
- Subcutaneous application of ACE-031
- 88 Patients
Upcoming novel therapy: Idebenone


Buyse GM et al.
Department of Pediatric Neurology, University Hospitals Leuven, Hereestraat, Leuven, Belgium.

Improvement of heart function

Improvement of exercise capacity
Rational for therapy with Idebenone

- Dystrophin deficiency
- Abnormal Ca^{2+} handling
- [Ca^{2+}]_i ↑
- [Ca^{2+}]_{mit} ↑
- Oxidative phosphorylation
- ATP production
- Oxidative stress
- Mitochondrial dysfunction
- Reduced oxidative phosphorylation
- Impaired energy (ATP) production
- Apoptosis

DMD: cascade of cellular pathology

A clear scientific rationale for Idebenone in DMD
Idebenone: Mode of Action

Idebenone

- facilitates transport of electrons within mitochondria
- increases cellular energy production
- protects from oxidative stress in impaired mitochondria
- is cell permeable due to optimized lipophilicity

Diagram:

- Succinate → Complex II (FAD-FeS)
- Glutamate; pyruvate & malate → Complex I (FMN-FeS)
- NADH → Complex I (FMN-FeS)
- Idebenone
- Oxidative stress: $O_2^-$ → Lipid peroxidation
- ATP generation: Complex IV
The DELOS Study (Idebenone)

Sponsor: Santhera

- Phase III - Double-Blind – Randomised - Placebo-Controlled

- Study of the Efficacy, Safety and Tolerability of Idebenone in 10 – 18 Year Old Patients with Duchenne Muscular Dystrophy

- 240 patients

- **Primary Objectives**: To study efficacy of idebenone in improving or delaying the loss of respiratory function
The consequence of treating skeletal muscle without treating cardiac muscle

Emergent dilated cardiomyopathy caused by targeted repair of dystrophic skeletal muscle.

Townsend D, Yasuda S, Li S, Chamberlain JS, Metzger JM.
Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, Michigan, USA.

Restoration of dystrophin expression by minidystrophin only in skeletal muscle

Heart muscle damage
Summary

Duchenne muscular dystrophy is a severe muscle wasting disease.

Over the last 20 years, therapies have been established that
- tremendously increased quality of life
- delayed the progression of the disease
- extended life expectancy by decades

However, no established therapy exists that prevents the progression of the disease or reverses loss of muscle function.

Currently, many new therapeutic approaches are developed.

Exon skipping to restore dystrophin expression is the most promising therapeutic strategy to cure Duchenne muscular dystrophy patients.

A phase III trial on Exon skipping is ongoing.

**Very important:** A successful therapy requires that skeletal muscle and cardiac muscle is treated simultaneously!