Inflammation in Duchenne muscular dystrophy

Rationale for anti-inflammatory therapy in DMD

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Why is anti-inflammatory therapy important for DMD
Why is anti-inflammatory therapy important for DMD

Currently, steroids are the only drug available for all boys with DMD that have been shown to slow the decline of muscle strength.

Corticosteroids are anti-inflammatory medicine.
Corticosteroids: mechanism of action

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Corticosteroids in Duchenne Muscular Dystrophy

Side effects

- Weight gain
- Growth restriction
- Bone fragility
- Adrenal suppression
  - Adrenal failure
  - Delayed puberty
- Immune suppression
- ........................................
- ........................................
FOR DMD study
Find the Optimum corticosteroid regime for Duchenne Muscular Dystrophy

Kate Bushby

Michela Guglieri

Robert ‘Berch’ Griggs
The FOR-DMD steroid trial

Multi-centre, double-blind, parallel group, comparing three corticosteroid regimens in wide use in DMD:

- daily prednisone (0.75 mg/kg/day)
- intermittent prednisone (0.75 mg/kg/day, 10 days on, 10 days off)
- daily deflazacort (0.9 mg/kg/day)

Duration: minimum of 36 months

Study population: 200 boys
The FOR-DMD steroid trial

- 36 sites
- Recruitment completed: September 2016 (196 boys)
- Study will close in September 2019
- Results expected in early 2020
The FOR-DMD steroid trial: Rationale for study

- Prescribing chaos:
  - Patients will be being treated suboptimally/ higher risk of side effects
  - Potential threat to new studies where steroid treatment is allowed

- To allow informed decision making about the dosage regimens of corticosteroids with regard to efficacy and tolerability
Corticosteroids: mechanism of action

1. DNA-Dependent Regulation
   - Glucocorticoid Responsive Element
   - NFκB Response Element
   - Protein Interference Mechanisms

2. Beneficial Effects
   - Anti-inflammatory Effects
   - Metabolic Side Effects

Cytoplasm

GR

p65
p50
IκB

C-Jun
Fos

GR-C-Jun-Fos

Corticosteroids: mechanism of action

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VBP15

- **Efficacy (good layers)**
  - Anti-inflammatory
  - NFkB inhibition

- **Side effects (bad layer)**
  - Mineral-corticoid agonist

- Peel away layers
- Keep or enhance the ‘**good layers**’
- Reduce or remove the ‘**bad layers**’

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Corticosteroids: mechanism of action

1. DNA-Dependent Regulation

2. Metabolic Side Effects

3. Plasma membrane

Membrane Stabilization

Cytoplasm

Anti-inflammatory Effects

Beneficial Effects

GR

Corticosteroids: mechanism of action

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Vamorolone pre-clinical efficacy and safety
VPB15: Clinical program

Phase 1 study: Healthy adult volunteers. August 2015-December 2015

- Single Ascending Dose (SAD)
  0.1, 0.3, 1.0, 3.0, 8.0, 8.0 fed, 20.0 mg/kg
- Multiple Ascending Dose (MAD)
  1.0, 3.0, 9.0, 20.0 mg/kg/day 14 days

Study design very similar to phase 2a study

VBP15 – Vamorolone:
Oral syrup suspension
Once daily administration
Phase 1 data results

- Excellent dose proportionality
- Short half-life (2 hrs) – similar to prednisolone
- No dose accumulation

- A food effect was observed, with an increased absorption by 2.5-fold by the high fat meal, consistent with the lipophilic character of vamorolone

Figure 1: Arithmetic mean ± standard error plasma concentrations of VBP15 after oral administration of 0.1, 0.3, 1, 3, and 8 mg/kg to healthy subjects under fasted conditions — linear (top panel) and semi-logarithmic (bottom panel) axes.
Phase 1 data results

- No adverse events precluding further escalations in dosing were observed.
- One subject (20 mg/kg/day cohort) showed mild elevations of liver enzymes, and drug dosing was halted.
Phase 1 data results

- Safety blood biomarkers showed that Vamorolone had an improved side effect profile for:
  - Adrenal suppression (100-fold increase in therapeutic window),
  - Insulin resistance
  - Immune suppression, compared to prednisone studies reported in the literature.
VPB15: DMD Clinical program

Phase IIa Open-Label, Multiple Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Exploratory Efficacy of Vamorolone in Boys with Duchenne Muscular Dystrophy (DMD)

<table>
<thead>
<tr>
<th>Planned Dose Level Group</th>
<th>No. Subjects in Dose Level Group</th>
<th>Vamorolone Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>0.25 mg/kg</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>0.75 mg/kg</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>2.0 mg/kg</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>6.0 mg/kg</td>
</tr>
</tbody>
</table>
VBP15-002 study (Phase IIa)

- 12 sites: US (7), Canada (1), UK (1), Sweden (1), Israel (1) and Australia (2)

- Dose escalation SAFETY study (4 doses)

- Subjects: 48 subjects (12 subjects per cohort)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Subjects</th>
<th>Duration</th>
<th>DSMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25mg/kg</td>
<td>12</td>
<td>2 weeks</td>
<td>DSMB</td>
</tr>
<tr>
<td>0.75mg/kg</td>
<td>12</td>
<td>2 weeks</td>
<td>DSMB</td>
</tr>
<tr>
<td>2.0mg/kg</td>
<td>12</td>
<td>2 weeks</td>
<td>DSMB</td>
</tr>
<tr>
<td>6.0mg/kg</td>
<td>12</td>
<td>2 weeks</td>
<td>DSMB</td>
</tr>
</tbody>
</table>
Main Inclusion criteria
1. Confirmed diagnosis of DMD
2. Age ≥ 4 years and < 7 years
3. Steroid naïve
4. Chicken pox immunity

Main Excusion criteria
1. Contro-indications to corticosteroids
2. Treatment with Idebenone
3. Other investigational drug with 3 months from first dosing
Primary Objective
To evaluate the safety and tolerability of multiple ascending doses of vamorolone in ambulant boys ages 4-< 7 years with DMD.

Secondary Objectives
To investigate the single-dose and multiple-dose PK of vamorolone at multiple dose levels in ambulant boys ages 4-< 7 years with DMD;
To investigate the effects of single and multiple oral doses of vamorolone on serum PD biomarkers in ambulant boys ages 4-< 7 years with DMD
VBP15-003 study (Phase IIa extension)

- All subjects who complete the 2 week treatment period and the 4 week follow up visit will be offered to continue vamorolone in an extension study.

- The objectives of the Phase IIa extension study are to evaluate the long term safety and efficacy of vamorolone versus natural history data.

- A long term access extension study will follow the Phase IIa extension study.
VBP15-002 study (Phase IIa)

Update

- 2 active sites (US and Canada)
- 8 expected to be activated by the end of the year (US, Sweden, Australia)
- 2 expected to open in Jan/Fen 2017 (Newcastle, UK)
- 6 subjects enrolled so far (4 in Phase IIa extension)
- No AE related to study drug reported
A Phase IIb Randomized, Double-blind, Parallel Placebo- and Active-controlled Study to Assess the Efficacy and Safety of Vamorolone in Ambulatory Boys with Duchenne Muscular Dystrophy (DMD)

- Vamorolone, 2.0 mg/kg/day
- Vamorolone, 6.0 mg/kg/day
- Prednisolone, 0.75 mg/kg/day
- Placebo
VBP15-004 study (Phase IIb)

- 30 sites (EU, Israel, Australia)
- Safety and Efficacy study
- 100 boys
- Expected to open in Summer 2017
Main Inclusion criteria
1. Confirmed diagnosis of DMD
2. Age ≥ 4 years and < 7 years
3. Steroid naïve
4. Chicken pox immunity
5. *Ability to rise from the floor in > 3 seconds and < 10 seconds*

Main Exclusion criteria
1. Contro-indications to corticosteroids
2. Treatment with Idebenone
3. Other investigational drug with 3 months from first dosing (*including* Ataluren)
VBP15-004 study (Phase IIb)

Study design
4 weeks screening period
24 week treatment period
2-6 week follow up tapering period

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Study Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vamorolone (4% oral suspension)</td>
</tr>
<tr>
<td>Dose Group 1</td>
<td>2.0 mg/kg</td>
</tr>
<tr>
<td>Dose Group 2</td>
<td>6.0 mg/kg</td>
</tr>
<tr>
<td>Dose Group 3</td>
<td>Placebo</td>
</tr>
<tr>
<td>Dose Group 4</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

All subjects who complete the treatment period and the tapering period will be offered the possibility to continue vamorolone in the long term access extension study.
# VBP15-004 study (Phase IIb)

| **Primary Objectives** | 1. To evaluate the efficacy, as measured by the time to Stand of vamorolone vs. placebo  
2. To evaluate the safety, as measured by body mass index (BMI) z-score, of vamorolone vs. prednisolone 0.75 mg/kg/day |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| **Secondary Objectives** | 1. To evaluate the safety and tolerability of vamorolone  
2. To compare the efficacy, as measured by Time to run/walk 10 meter, Time to Climb Test, North Star Ambulatory Assessment, 6-minute walk test and myometry of vamorolone vs. placebo  
3. To compare the effects of vamorolone vs prednisolone on serum (PD) biomarkers of safety (Insuline resistance, adrenal insufficiency, bone health) |
### Exploratory Objectives

1. To compare the efficacy of vamorolone vs. daily prednisolone
2. To evaluate the satisfaction with treatment of vamorolone vs daily prednisolone; and
3. To evaluate the effect of vamorolone on Quality of Life,
4. To explore the feasibility and clinical relevance of a shorter and simplified lower limb muscle MRI protocol for the assessment of the effect of vamorolone on muscle pathology
VBP15: Timelines

- **Phase 2a**
  - 4-7 yr old DMD
  - 2016

- **Phase 2b**
  - 1-3 yr old DMD
  - 2016

- **Phase 2b**
  - 4-7 yr old DMD
  - 2017

- **Phase 2b**
  - 0-1 yr old DMD
  - 2018

- **Phase 2b**
  - 1-3 yr old DMD
  - 2018

- **Phase 2b**
  - 0-1 yr old DMD
  - 2019

- **Phase 2b**
  - 7-18 yr old DMD
  - 2019

- **Phase 2b**
  - 3-17 yr old Pediatric Ulcerative Colitis
  - 2020

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VBP15: Made possible by the community