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The Spine Fracture Burden in Boys with DMD Treated with the Novel Dissociative Steroid Vamorolone versus Deflazacort or Prednisone

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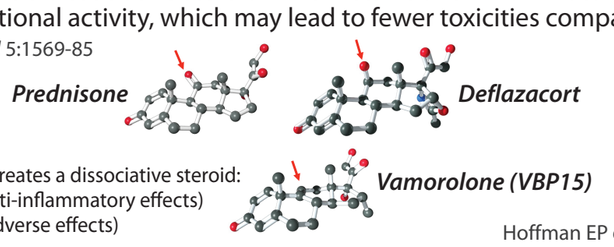
INTRODUCTION

- Glucocorticoids (GC) are standard of care for boys with Duchenne muscular dystrophy (DMD); however, they are associated with a high incidence of vertebral fractures (VF)
- Vamorolone (VAM/VBP15) is a dissociative steroid which retains anti-inflammatory properties but with reduced positive transcriptional activity, which may lead to fewer toxicities compared with classic GC

Heier et al. (2013) *AMBO Mol Med* 5:1569-85



Disruption of a key ligand H-bond creates a dissociative steroid:
Retains trans-repression activity (anti-inflammatory effects)
Reduces trans-activation activity (adverse effects)

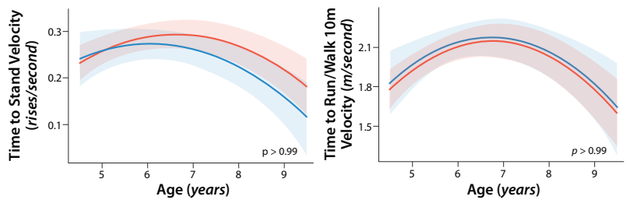
Hoffman EP et al. (2018) *Steroids* 134:43-52

BACKGROUND

- Results from prior dose-finding studies showed that ambulatory boys with DMD treated with vamorolone over 30 months had the following results compared with a classic steroid-treated historical control group (from the "Duchenne Natural History Study [DNHS])"

Muscle Function Assessments (verse DNHS*)

No significant difference in TTSTAND (quadratic comparison; p: >.99; linear comparison; p: .10) and TTRW predicted velocities (quadratic comparison; p: >.90; linear comparison; p: .94).

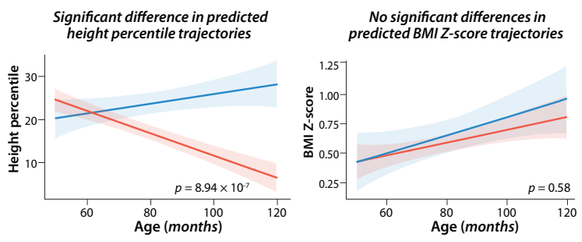


*Duchenne natural history study

Anthropometry Assessments

Significant difference in predicted height percentile trajectories

No significant differences in predicted BMI Z-score trajectories



DNHS Cohorts — Vamorolone High Dose (≥2 mg/kg/day)

Mah, J…Ward LM, Hoffman EP & Dang UJ. (2022) *JAMA Network Open* 5(1):e2144178

AIM

- To describe the skeletal phenotype in vamorolone-treated boys vs. boys who received daily deflazacort (DFZ_{Daily}), daily prednisone ($PRED_{Daily}$), and intermittent prednisone ($PRED_{Int}$)
  - Vertebral fracture outcomes
  - Serum bone turnover markers
  - Skeletal maturation status

METHODS

Study Populations and Interventions

48 GC-naïve boys, 4-7 years of age

6 countries, 11 sites

Consecutive, open-labelled, phase 2 longitudinal studies

2 weeks	*6 months*	*24 months*
002 Study	**003 Study**	**LTE Study**
0.25/0.75/2.0/6.0 mg/kg/day	0.25/0.75/2.0/6.0 mg/kg/day	0.25/0.75/2.0/6.0 mg /kg/day
NCT02760264	NCT02760277	NCT03038399

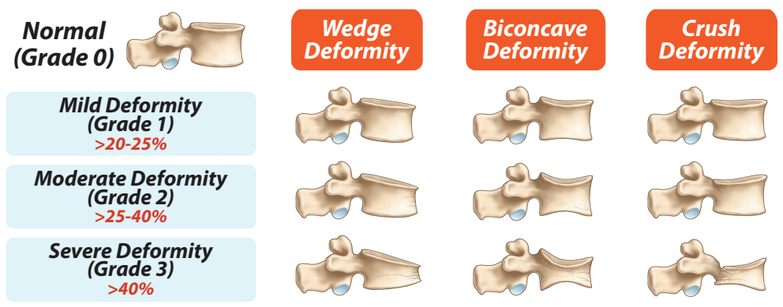
*LTE = Long-term extension

Total duration = 30 months

- Vamorolone study (VBP15-LTE, NCT03038399)
  - 39 boys 4 to <7 years-old all ambulatory
  - Treatment: 0.25, 0.75, 2.0, or 6.0 mg/kg/d for 6 months, followed by permitted dose (de)escalations for 2 years
  - Total treatment duration 30 months
- Finding the Optimal Regimen for DMD (FOR-DMD, NCT01603407) study
  - 70 boys on classic GC, 4 to <8 years-old
  - Treatment arms: randomized to one of the following:
    - DFZ_{Daily} (0.9mg/kg/d)
    - $PRED_{Daily}$ (0.75mg/kg/d)
    - $PRED_{Int}$ (0.75mg/kg/d 10 days on/off)
  - Total treatment duration 36 months

Vertebral Fractures Evaluations:

- Vertebral fracture outcomes on vamorolone-treated patients were benchmarked to 70 boys receiving $PRED_{Daily}$, DFZ_{Daily} and $PRED_{Int}$ as part of the FOR-DMD study
  - Patients were matched for:
    - Baseline age 4 to <7 years
    - Ability to walk independently
    - Ability to complete the time to stand test without assistance
- Central analysis of lateral spine x-rays was carried out according to a triple read protocol using the Genant SQ method



Genant et al. (1993) *J Bone Miner Res* 8:1137–1148

METHODS (cont'd)

- Vertebral fracture outcomes were adjusted for shorter duration in vamorolone by a factor of 1.2 (36/30 months)
- Skeletal maturation was evaluated descriptively as bone age (BA) relative to chronological age (CA)

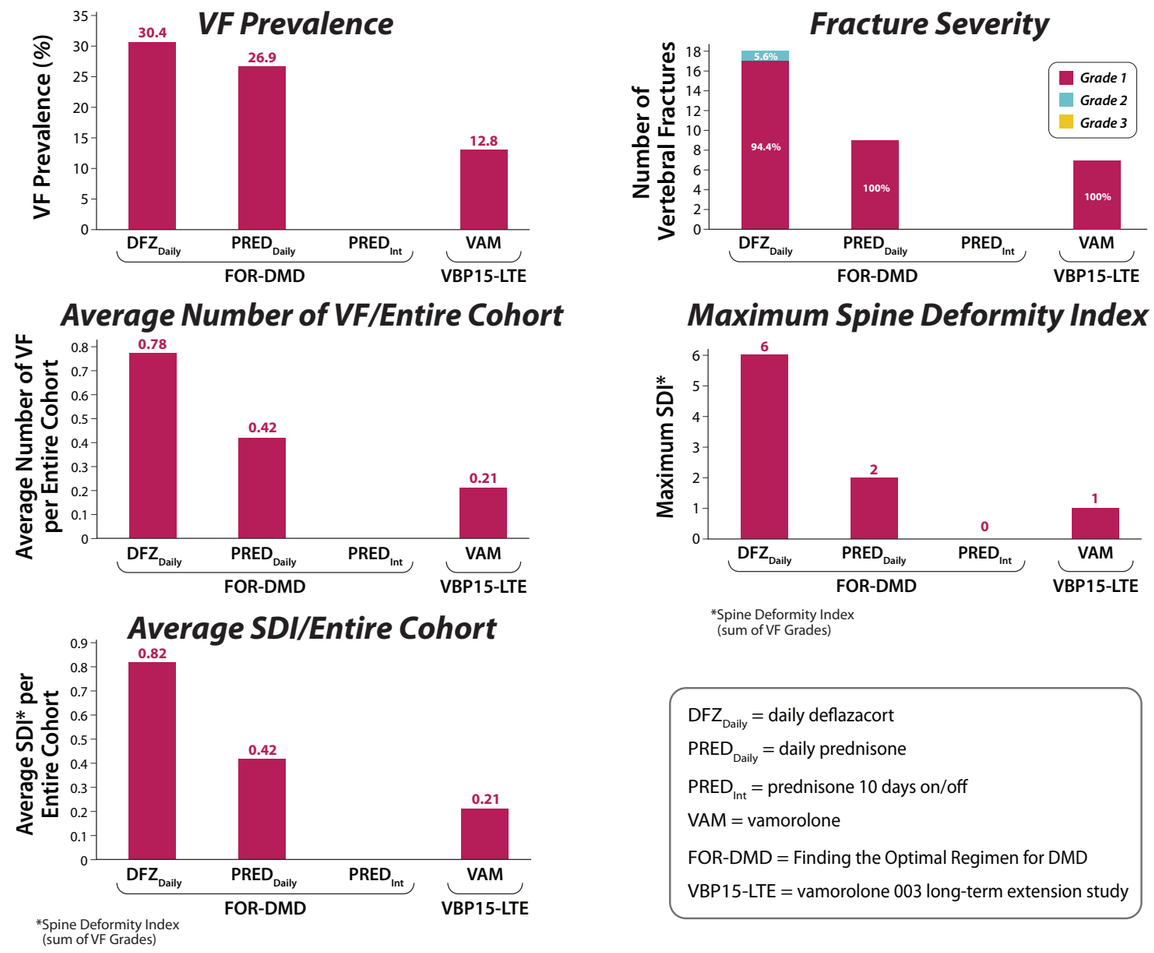
Bone Turnover Markers:

- Between baseline and 30 months (longitudinal)
- Serum bone turnover marker Z-scores were evaluated (adjusted for age <6 vs ≥6 years at baseline, and change in height Z-score at each visit)
  - Bone formation
    - Procollagen1 N-propeptide (PINP)
    - Osteocalcin
  - Bone resorption
    - Type I collagen c-telopeptides (CTX)

RESULTS

Fig 1: Vertebral Fracture Outcomes

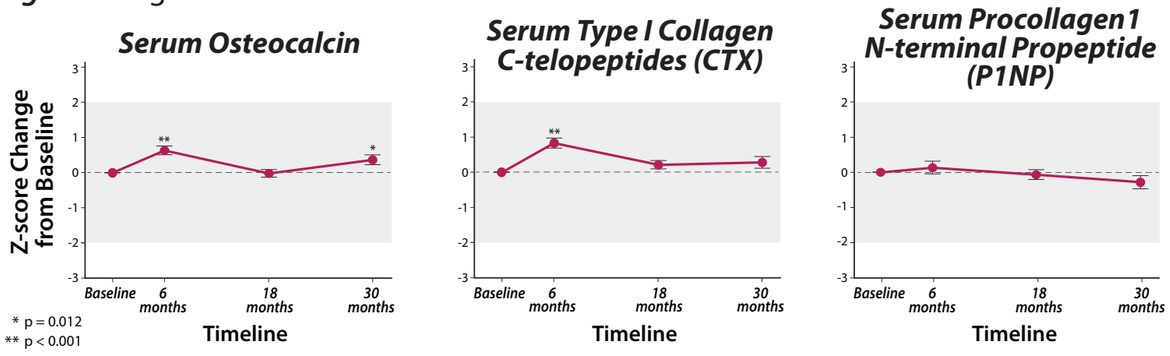
Mean age (in years) of boys on classic GC was 8.9±1.0 and on VAM 8.0±1.0 years at evaluation.



*Spine Deformity Index (sum of VF Grades)

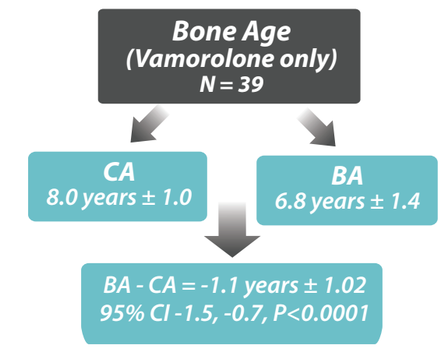
DFZ_{Daily} = daily deflazacort
$PRED_{Daily}$ = daily prednisone
$PRED_{Int}$ = prednisone 10 days on/off
VAM = vamorolone
FOR-DMD = Finding the Optimal Regimen for DMD
VBP15-LTE = vamorolone 003 long-term extension study

Fig 2: Change from Baseline in Serum Bone Turnover Markers



* p = 0.012
** p < 0.001

Fig 3: Bone Age



CA = Chronological Age
BA = Bone Age

CONCLUSIONS

- After 2.5 years of vamorolone, bone turnover markers were not suppressed, bone age delay was minimal, and the vertebral fracture burden appeared to be lower compared with DFZ_{Daily} and $PRED_{Daily}$
- Vertebral fracture burden was lowest on $PRED_{Int}$; however, this has been linked to reduced muscle strength
  - Guglieri M, et al. (2022) *JAMA*. 327(15): 1456-1468
  - Crabtree NJ et al. (2018) *Bone*. 116: 181-186
- These results suggest vamorolone may be relatively bone-sparing in ambulatory boys with DMD compared with classic daily GC therapy
- These observations merit further investigation over the longer-term

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