

# Effect of Intravenous Bisphosphonate Therapy among Boys with Duchenne Muscular Dystrophy and Vertebral Fractures due to Osteoporosis

## INTRODUCTION

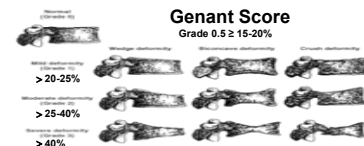
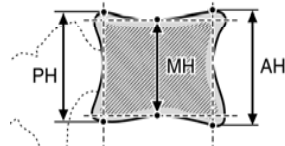
- Boys with Duchenne Muscular Dystrophy (DMD) can have quality of life-limiting back pain caused by vertebral fractures due to osteoporosis<sup>1</sup> (Prevalent vertebral fracture rate reported as 32%)<sup>2</sup>
- IV bisphosphonate (BP) therapy can increase bone mass and density, but more importantly improve bone pain, stabilize vertebral fractures, and reshape fractured vertebral bodies in pediatric patients<sup>3</sup>
- Only one previous report of BP use in DMD using PO alendronate (0.08 mg/kg/day) for 2 years in 16 boys with no change in spine bone mineral density (BMD) after 2 years of treatment<sup>4</sup>
- The impact of BP therapy on clinically relevant factors beyond BMD, such as *vertebral fractures and back pain*, has not been documented

## AIM

- To evaluate safety and efficacy of IV BP therapy in the treatment of painful vertebral fractures among boys with DMD

## METHODS

- 12 month, retrospective, observational study involving boys with DMD treated for spinal osteoporosis in the Pediatric Bone Health Clinic at CHEO from 2003 to 2009
- Spinal osteoporosis was diagnosed in the presence of two clinical criteria:
  - Vertebral Fracture, defined as  $\geq 20\%$  loss in height of vertebral body at any time point, or a minimum 15% loss in height of at least 1 vertebral body compared to a prior film
  - Back Pain localized to the site of fracture on palpation
- Treatment was either IV pamidronate (9 mg/kg/year) divided into 3 doses, q 4 months or IV zoledronic acid (0.1 mg/kg/year) divided into 2 doses, q 6 months
- Primary outcomes:**
  - Back pain: Improved, stable or worse compared to pre-treatment
  - Change in 6-point quantitative vertebral morphometry: Measurement of anterior, middle and posterior heights (AH, MH, PH) to calculate AP, MP and PP ratios. The worst of the 3 ratios  $\leq 0.85$  ( $\geq 15\%$  loss in height) was determined for T4-L4 and categorized as per the Genant scoring system at baseline and 12 months



- A statistically significant change in height ratio from baseline to 12 months was based on the Least Significant Change (LSC), calculated as the Precision error X 3.65 to give 99% confidence
- Existing fracture improved if change exceeded LSC, stabilized if change did not exceed LSC and deteriorated if the change in height loss was  $\geq 15\%$  and change exceeded LSC at 12 months

## Secondary outcomes:

- New fractures, defined as a change in height loss  $\geq 15\%$  at 12 months in a previously normal vertebral body and change exceeded LSC
- Change in lumbar spine BMD
- Clinical side effects

## Description of the Cohort at Baseline

Clinical Characteristics	N=7
<b>Demographic Data</b>	
Age	11.6 (8.5, 14.3)
<b>Anthropometry</b>	
Height Z-score	-1.7 (-4.2, -0.5)
Weight Z-score	0.4 (-2.4, 1.8)
Body mass index Z-score	1.2 (0.2, 2.3)
Pubertal stage, N	
Stage 1	6
Stage 2	1
<b>Ambulatory Status, N</b>	
Fully ambulatory	1
Partially ambulatory	6
<b>Glucocorticoid Treatment</b>	
Cumulative GC dose (mg/m <sup>2</sup> )*	15 291 (7700, 26 248)
<b>Lumbar Spine BMD</b>	
Areal Z-score <sup>1</sup>	-2.1 (-4.9, -0.4)
Volumetric Z-score <sup>2</sup>	-1.0 (-3.0, 0.9)

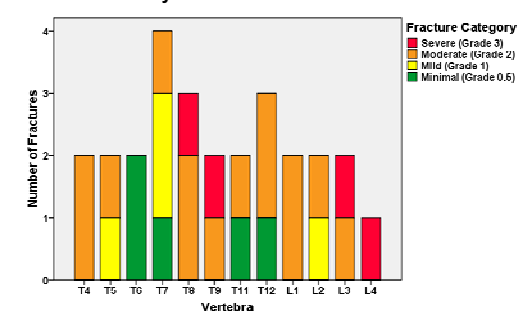
Values reported are median (min, max) unless otherwise specified. GC=Glucocorticoids; Cumulative GC dose reported in prednisone equivalents; \*N=6  
<sup>1</sup>Lunar machine reference data <sup>2</sup>VanderStuis reference data

## Description of the Vertebral Fracture Events

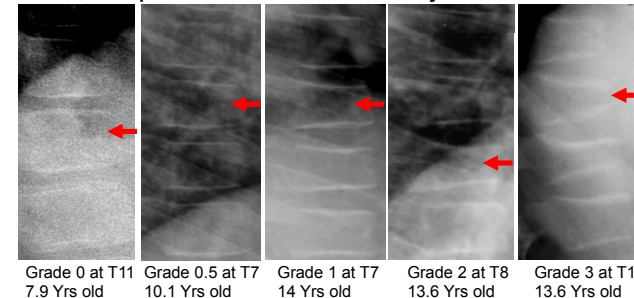
	N
<b>Number of Vertebral fractures</b>	
Grade 0.5	5
Grade 1	4
Grade 2	14
Grade 3	4
Total	27
<b>Number of Vertebral fractures per boy</b>	
1	3
2-4	2
$\geq 5$	2
<b>Fracture Severity per boy</b>	
Grade 0.5	2
Grade 1	1
Grade 2	2
Grade 3	2

## RESULTS: BASELINE

### Site and Severity of the 27 Vertebral Fractures at Baseline

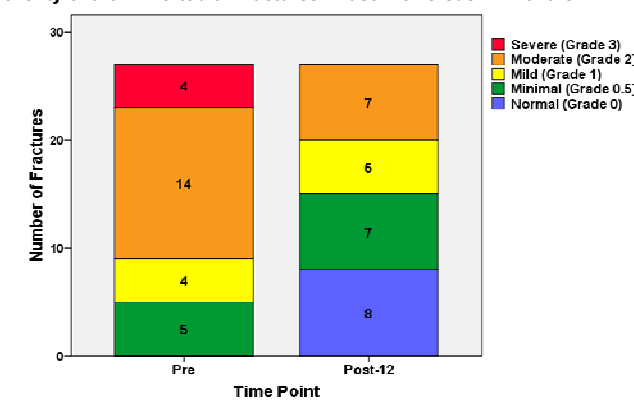


### Examples of Vertebral Fracture Severity



## RESULTS: 12 MONTHS

### Severity of the 27 Vertebral Fractures : Baseline versus 12 months



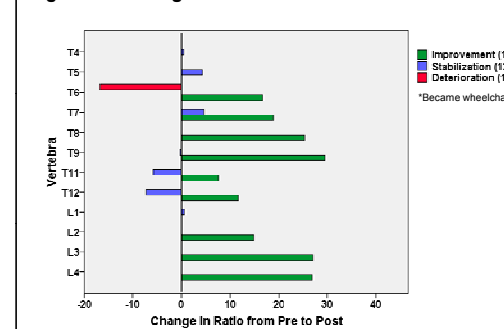
## Description of the Cohort at 12 months

Clinical Characteristics	N=7
<b>Back Pain, N</b>	
Resolved completely	4
Improved	3
<b>Anthropometry</b>	
Height Z-score	-2.0 (-3.5, -0.1)
Weight Z-score	-1.7 (-1.9, 1.9)
Body mass index Z-score	0.4 (-1.6, 2.3)
Pubertal stage, N	
Stage 1	5
Stage 2	2
<b>Ambulatory Status, N</b>	
Fully ambulatory	1
Partially ambulatory	5
Wheelchair bound	1
<b>Glucocorticoid Treatment</b>	
Cumulative GC dose (mg/m <sup>2</sup> )*	19 211 (11 425, 29 217)
<b>Lumbar Spine BMD</b>	
Areal Z-score <sup>1</sup>	-1.4 (-2.6, -0.2)
Volumetric Z-score <sup>2</sup>	-0.1 (-2.6, 1.4)
<b>Clinical Side Effects, N</b>	
Acute Phase Reaction	4
Hypocalcaemia**	2

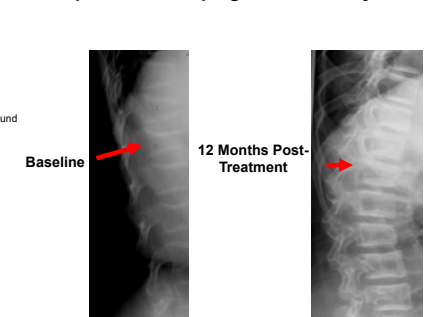
Values reported are median (min, max) unless otherwise specified. Cumulative GC dose reported in prednisone equivalents; \*N=6  
<sup>1</sup>Lunar machine reference data <sup>2</sup>VanderStuis reference data  
 \*\*Values 0.98 and 1.01 mmol/L; asymptomatic

## RESULTS: 12 MONTHS

### Evolution of vertebral fractures based on statistically significant changes



### Example of a re-shaping vertebral body



Boy with DMD treated with IV Pamidronate, 13 years of age

### Incident Vertebral Fractures

Number of incident fractures	2
Number of boys with incident fractures	2*
<b>Fracture Severity</b>	
Grade 0.5	2
<b>Percent Loss in Height, Pre/Post</b>	
T11	0/17
T6	2/18

\* 1 of the boys became completely wheelchair bound

## SUMMARY

- In boys with spinal osteoporosis and DMD, IV BP therapy administered over 12 months was associated with improvements not only in spine BMD, but also in the more clinically relevant back pain and vertebral morphometry
- Therapy was generally well-tolerated

## CONCLUSIONS

- This pilot study supports the use of IV BP therapy on compassionate grounds for boys with DMD and symptomatic vertebral fractures
- Provides background data for the development of larger BP trials in this population
- Contributes to the development of methodology for quantifying vertebral changes in growing patients undergoing osteoporosis therapy

## REFERENCES

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- Hawker GA, Ridout R, Harris VA, Chase CC, Fielding LJ, Biggar WD 2005 Alendronate in the treatment of low bone mass in steroid-treated boys with Duchennes muscular dystrophy. *Archives of Physical Medicine & Rehabilitation* 86(2):284-8.