A Randomized Controlled Trial in Duchenne Muscular Dystrophy

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Introduction

- Duchenne Muscular Dystrophy (DMD) is the most common X-linked recessive disorder, occurring in ***1/3,500*** live male births
- Lead to progressive degeneration of skeletal and cardiac muscle, and relentless deterioration in muscle function during childhood.

Introduction

- Long-term glucocorticoids (GC) therapy slows disease progression, prolonging ambulation by 2 years, and life expectancy has increased from 14 years in the 1960s to 25 years in the 1990s
- More recent unpublished experience suggests that many patients now live well into their fourth decade on long-term GC therapy.

Introduction

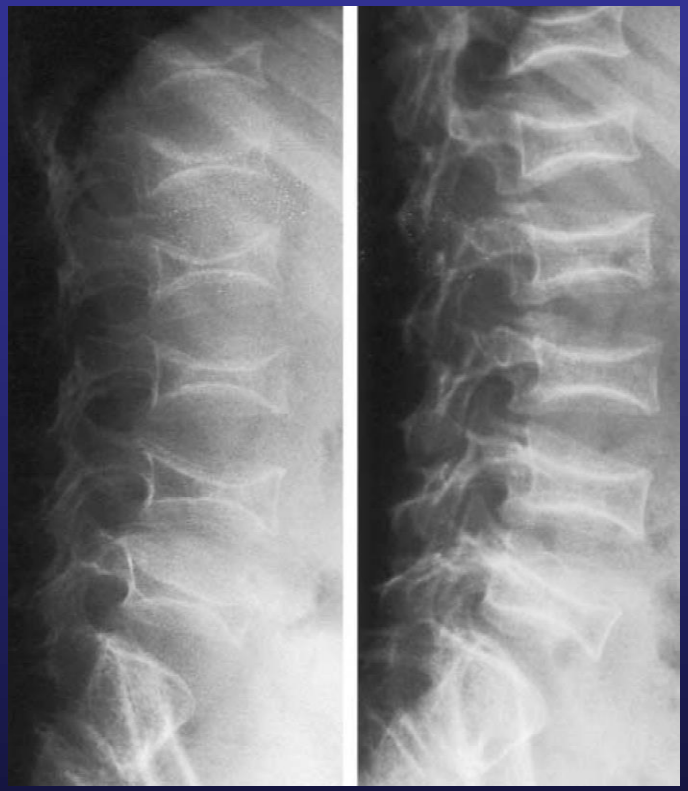
- Boys with DMD have numerous risk factors for osteoporosis:
  - Relentlessly progressive myopathy
  - Relative or complete immobilization
  - Treatment with high-dose glucocorticoids (GC) to slow disease progression

Introduction

- Boys with DMD can have quality of life-limiting back pain due to vertebral fractures
  - Bothwell JE…Cummings EA, Salisbury *et al.* Clin Pediatr. 2003;42;353
- Prevalent vertebral fracture rate has been shown to be as high as 39% in boys with DMD receiving deflazacort
  - Chabot G, Alos N, Vanasse M *et al*. JBMR, 2002; *17,* F419

Bisphosphonate (BP) Use in Pediatrics

- BP therapy is widely used for pediatric patients with fragility fractures, particularly in osteogenesis imperfecta (OI)
- Intravenous (IV) therapy can:
  - Increase bone mass and density
  - Improve bone pain
  - Stabilize vertebral fractures
  - Reshape fractured vertebral bodies (in the growing child)



Baseline **18 months**

Boy with OI, 6 yrs

Glorieux et al, *N Engl J Med* 1998;339:947

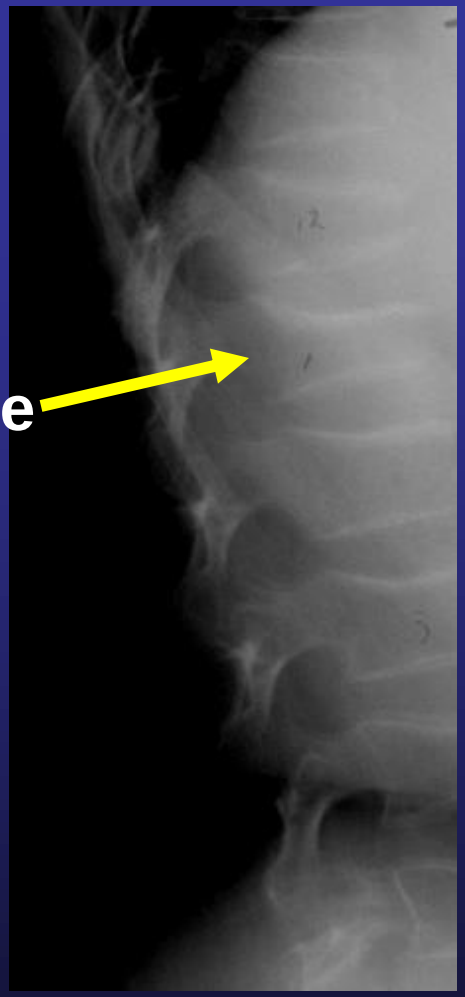
DMD and BPs

- Single previous study of BP use in DMD (Hawker et al. *Arch Phys Med* Rehabil 2005)
  - Oral alendronate (0.08 mg/kg/day) for 2 years in 16 boys
  - BMD-based entry criteria
    - Spine BMD Z-score worse than -1.0 SD
  - BMD-based outcome parameter
    - Mean spine BMD Z-score (unchanged)

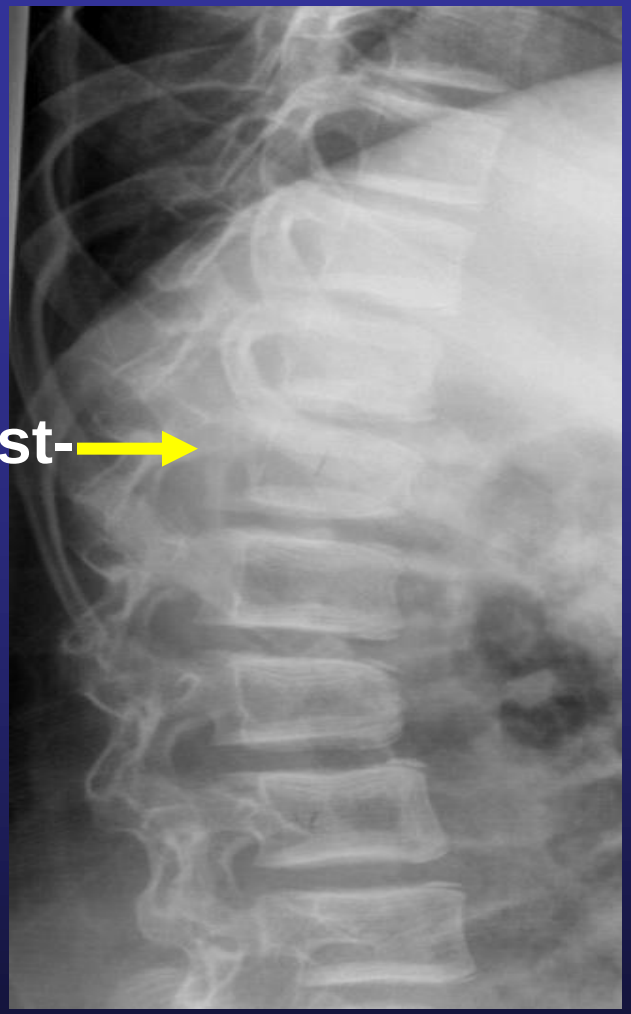
DMD and BPs

The impact of BP therapy on clinically relevant factors beyond BMD, i.e., *vertebral fractures and back pain*, has not been documented

Baseline



12 Months Post-Treatment



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

Objective

- To evaluate the effect of intravenous zoledronic acid, a bisphosphonate agent, on the prevention of incident vertebral fracture among boys with DMD.

Patients and Methods

- Study Design:
  - 12 months, two-center, single-blinded, randomized controlled trial
  - Randomization is ***stratified*** by age and site
  - Boys with DMD treated at the Children's Hospital of Eastern Ontario (Ottawa) and Bloorview Hospital (Toronto)

Patients and Methods

- Inclusion Criteria:
  1) Boys aged ≥ 4.0 and < 18.0 years at the time of enrolment;
  2) With DMD confirmed by dystrophin immunofluorescence or immunoblot, gene deletion test, or complete dystrophin gene sequencing;
  3) With osteoporosis;
  4) Currently receiving or initiating GC treatment for DMD.

Patients and Methods

- Exclusion Criteria:
  - Use of an osteoporosis or other bone treatment agent such as bisphosphonates, calcitonin, calcitriol, fluoride etc.; or
  - Other conditions apart from DMD affecting muscle and/or bone development (i.e. cerebral palsy, rickets).

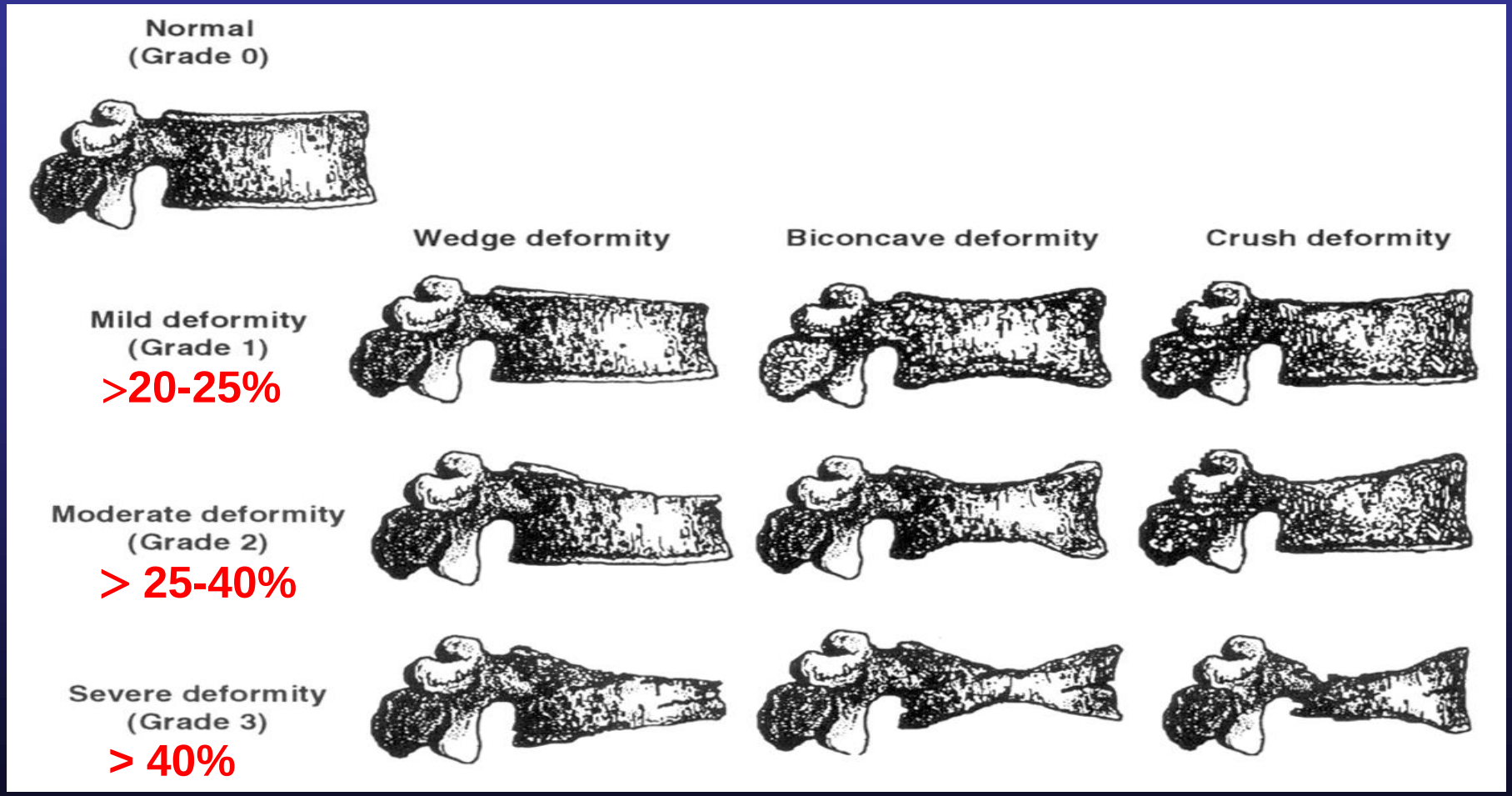
Patients and Methods

- Patients are randomized to receive either intervention or control
- Intervention
  - IV **zoledronic acid** (0.1 mg/kg/year)
  - Divided into 2 doses, q 6 months
  - Routine supportive bone health care (calcium and vitamin D supplementation, as needed)
- Control
  - Routine supportive bone health care (calcium and vitamin D supplementation, as needed)

Patients and Methods

- Primary outcome
  - A lateral spine radiograph taken at the time of enrolment (***baseline***) and ***12 months*** after enrolment
  - An incident fracture is defined as an **increase in Genant grade** by at least 1 compared to baseline

Genant Semi-Quantitative Score (Morphology and Severity)



Patients and Methods

- Other clinical data collected at baseline, 6 and 12 months
  - Lumbar spine bone mineral density
  - GC Exposure
  - Calcium and Vitamin D Intake
  - Bone biomarkers: PINP (bone formation) and CTX (bone resorption), 25OHD (vitamin D stores)

Feasibility

- The 2 participating centres are currently providing care to ***150*** boys with GC-treated DMD between 4 and 18 years of age.
- An additional ***15*** boys will begin GC therapy at the two sites.
- A total of ***165*** boys can be approached for enrolment.

Feasibility

- Meet eligibility criteria: 40%
- Consent rate: 80%
- Retain to 1 year : 90%

Total sample size: ***47***

Sample Size Consideration

- We anticipate a vertebral fracture incidence of ***20%*** after one year of follow-up for the ***control group***.
- This incidence is conservative:
  - Vertebral fracture incidence of 16% in the first year of GC-treatment in children with leukemia where the average daily dose of GC was 10-50% less than the typical dose for boys receiving DMD care in Canada

Sample Size Consideration

- Incidence in control group: 20%
- Incidence in intervention group: 5%

Δ = 15%

- Statistical Power: 0.8
- Significance level: 0.05
- Randomization ratio: 1:1

Minimum required Sample size:

76 per group

Questions

- Is there an adaptive design appropriate for this trial? Why?
- How to use the data collected at baseline and 6 months to guide the trial as it moves forward?
- Are there any concerns about the validity and integrity of the trial?