Excellence in Clinical Research Seminars

October 27th, 2021
Motivation and Goal

• Genetics is both a diagnostic and therapeutic specialty

• We aim to discuss interventional clinical research

• We welcome active participation and suggestions

Voretigene FDA approved in 2017

Onasemnogene FDA approved in 2019
Topics

- Study design
- Preclinical research
- Regulatory Affairs
- Data Management
- Funding/Budgets
- Working with Industry
- Ethics
Building a Study

- Research Question
- Building a Team
- Trial Design
- Eligibility Criteria
- Outcomes and Endpoints
- So many other considerations
  - regulatory, operation, reporting and publication
Clinical Trials in Rare Disorders: Teriparatide in Adults with Osteogenesis Imperfecta

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Evaluation of teriparatide treatment in adults with osteogenesis imperfecta

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**Background.** Adults with osteogenesis imperfecta (OI) have a high risk of fracture. Currently, few treatment options are available, and bone anabolic therapies have not been tested in clinical trials for OI treatment.

**Methods.** 79 adults with OI were randomized to receive 20 μg recombinant human parathyroid hormone (teriparatide) or placebo for 18 months in a double-blind, placebo-controlled trial. The primary endpoint was the percent change in areal bone mineral density (aBMD) of the lumbar spine (LS), as determined by dual-energy X-ray absorptiometry. Secondary endpoints included percent change in bone remodeling markers and vertebral volumetric BMD (vBMD) by quantitative computed tomography, estimated vertebral strength by finite element analysis, and self-reported fractures.

**Results.** Compared with the placebo group, the teriparatide group showed increased LS aBMD (6.1% ± 1.0% vs. 2.8% ± 1.0% change from baseline; \( P < 0.05 \)) and total hip aBMD (2.6% ± 1.0% vs. −2.4% ± 1.0% change; \( P < 0.001 \)). Vertebral vBMD and strength improved with teriparatide therapy (18% ± 6% and 15% ± 3% change, respectively), but declined with placebo (−5.0% ± 6% and −2.0% ± 3% change; \( P < 0.05 \) for both comparisons). Serum procollagen […]
Why We Feature This Clinical Trial

• It is the largest placebo-controlled, randomized trial in adults with OI
• It was the first trial in OI involving an anabolic agent
• Sufficiently powered to detect difference in primary outcomes
• But is it enough to progress from IND to NDA?
Osteogenesis Imperfecta (OI)

- Heritable connective tissue disorder
- Incidence: 1:15,000 live births
- Variable presentation

Fractures  Blue Sclera  Dentinogenesis Imperfecta  Hearing loss

Illustrations: courtesy of Dr Nagamani et al
Genetic Heterogeneity of OI

Illustrations: courtesy of Dr Nagamani et al
Molecular Mechanisms Leading to Fractures

- COL1A1
- COL1A2

Abnormal fibrils → Altered interaction with matrix proteins → Decreased bone mass → Fractures

Illustrations: courtesy of Dr. Nagamani et al
Study Rationale: Bone Resorption vs Bone Formation

Bone resorption

- Osteoclasts
- Bisphosphonates
  - Decreased turnover
  - Increased BMD
  - Decrease in pain
  - Increased quality of life

Bone formation

- Osteoblasts

Illustrations: courtesy of Dr Nagamani et al
Study Rationale: Teriparatide as Anabolic Agent to Stimulate Bone Formation

• 1-34 amino acids of the N-terminus of parathyroid hormone

• Regulatory status:
  • Approved for treatment of osteoporosis women after menopause
  • Robust increase in lumbar spine BMD
  • Modest increase in the hip BMD
  • Decrease in fractures

• Can it increase BMD in subjects with OI by stimulating bone formation?
Critical Decisions

- A regulatory pathway
- Study design
- Sample power calculations
- Cohort
  - Inclusion and exclusion criteria
- Outcomes
  - Primary
  - Secondary
  - Exploratory
Study Design: Randomized, Double-Blind, Placebo-controlled, Parallel-Group, Non-Crossover

78 Patients were randomized

40 assigned to placebo

32 (80%) completed study

38 assigned to teriparatide

31 (81.6%) completed study

Illustrations: courtesy of Dr Nagamani et al
Power Calculation

• 5% difference between treatment and placebo groups
• Assumptions
  • 80% power
  • 2-tailed $\alpha = 0.05$
  • 15% subject dropout rate
• 90 participants
Study Cohort

• Inclusion criteria
  • Adults with a clinical diagnosis of OI and fused epiphyses

• Exclusion criteria
  • Bisphosphonate therapy with 12 months of enrollment
  • Abnormal ALP, AST, ALT, elevated serum creatinine, hypo- and hypercalcemia
Trial Endpoints

• Primary endpoint
  • Change in the areal BMD at the spine and hip measured by DEXA

• Secondary endpoint
  • Volumetric change in BMD at vertebrae measured by high resolution qCT
  • Estimated vertebral strength by finite element analysis
  • Self-reported fractures
Results
Teriparatide Increases BMD

LS BMD

TH BMD

Mean % change from baseline

Time in months

Teriparatide

Placebo

NIH NHGRI
Teriparatide Increases Bone Strength

![Bar chart showing the comparison of Teriparatide and Placebo effects on bone strength measures.](Illustrations: courtesy of Dr Nagamani et al)
Outcomes May Vary Depending on the OI Type

LS BMD OI type I

Mean % change from baseline

Time in months

LS BMD OI types III/IV

Mean % change from baseline

Time in months

Illustrations: courtesy of Dr Nagamani et al
Safety

- Teriparatide’s safety profile
  - No differences were observed between the intervention and placebo groups
  - Serious adverse events?
  - Safety outcomes
- Follow up studies on the risk of osteosarcoma?
Teriparatide Increases Bone Remodeling

Illustrations: courtesy of Dr Nagamani et al