

## **Risedronate in children with osteogenesis imperfecta: a randomized, double-blind, placebo-controlled trial.**

Bishop N, Adami S, Ahmed SF, Antón J, Arundel P, Burren CP, Devogelaer JP, Hangartner T, Hosszú E, Lane JM, Lorenc R, Mäkitie O, Munns CF, Paredes A, Pavlov H, Plotkin H, Raggio CL, Reyes ML, Schoenau E, Semler O, Sillence DO, Steiner RD.

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### **Abstract**

#### **BACKGROUND:**

Children with osteogenesis imperfecta are often treated with intravenous bisphosphonates. We aimed to assess the safety and efficacy of risedronate, an orally administered third-generation bisphosphonate, in children with the disease.

#### **METHODS:**

In this multicentre, randomised, parallel, double-blind, placebo-controlled trial, children aged 4-15 years with osteogenesis imperfecta and increased fracture risk were randomly assigned by telephone randomisation system in a 2:1 ratio to receive either daily risedronate (2.5 or 5 mg) or placebo for 1 year. Study treatment was masked from patients, investigators, and study centre personnel. Thereafter, all children received risedronate for 2 additional years in an open-label extension. The primary efficacy endpoint was percentage change in lumbar spine areal bone mineral density (BMD) at 1 year. The primary efficacy analysis was done by ANCOVA, with treatment, age group, and pooled centre as fixed effects, and baseline as covariate. Analyses were based on the intention-to-treat population, which included all patients who were randomly assigned and took at least one dose of assigned study treatment. The trial is registered with ClinicalTrials.gov, number NCT00106028.

#### **FINDINGS:**

Of 147 patients, 97 were randomly assigned to the risedronate group and 50 to the placebo group. Three patients from the risedronate group and one from the placebo group did not receive study treatment, leaving 94 and 49 in the intention-to-treat population, respectively. The mean increase in lumbar spine areal BMD after 1 year was 16.3% in the risedronate group and 7.6% in the placebo group (difference 8.7%, 95% CI 5.7-11.7;  $p < 0.0001$ ). After 1 year, clinical fractures had occurred in 29 (31%) of 94 patients in the risedronate group and 24 (49%) of 49 patients in the placebo group ( $p = 0.0446$ ). During years 2 and 3 (open-label phase), clinical fractures were reported in 46 (53%) of 87 patients in the group that had received risedronate since the start of the study, and 32 (65%) of 49 patients in the group that had been given placebo during the first year. Adverse event profiles were otherwise similar between the two groups, including frequencies of reported upper-gastrointestinal and selected musculoskeletal adverse events.

#### **INTERPRETATION:**

Oral risedronate increased areal BMD and reduced the risk of first and recurrent clinical fractures in children with osteogenesis imperfecta, and the drug was generally well tolerated. Risedronate should be regarded as a treatment option for children with osteogenesis imperfecta.