

Oral bisphosphonates for paediatric osteogenesis imperfecta?

Children and adolescents with osteogenesis imperfecta have numerous fractures, often after what would otherwise seem trivial trauma. Even in mild disease, the risk of breaking a long bone (femur, tibia, fibula, humerus, radius, or ulna) is about 100 times higher than in the general population.¹ Almost three-quarters of young people with mild osteogenesis imperfecta have at least one fracture of a vertebral body.¹ Children with severe forms of the disease have additional complications such as tibia and femur deformities that require correction by intramedullary rodding surgery before walking is possible.² Osteogenesis imperfecta is most often caused by mutations that directly or indirectly affect type I collagen, the most prevalent protein in the skeleton.³

No existing treatment for osteogenesis imperfecta addresses the underlying genetic defect. Symptomatic treatment with intravenous bisphosphonates has been widely used since a landmark report from 1998 by Glorieux and colleagues,⁴ which described positive effects of pamidronate infusions in children and adolescents with severe forms of osteogenesis imperfecta, including rapid relief from bone pain, absence of new vertebral fractures, reshaping of previously fractured vertebral bodies, and a reduction in the number of long-bone fractures. Another study of an intravenous bisphosphonate for treatment of paediatric osteogenesis imperfecta also showed a decrease in long-bone fractures.⁵ Intravenous bisphosphonate treatment in children with osteogenesis imperfecta leads to a rapid increase in bone mass through modulation of growth-dependent processes.⁶ Therefore, treatment effects are much larger in children than in adults with the disease.⁷

Although many studies have focused on intravenous bisphosphonate treatment, several of these drugs are available for oral administration. The bioavailability of oral bisphosphonates is low and variable,⁸ but the greater ease and potentially lower costs of administering the drugs orally are appealing. Several randomised controlled trials have reported on the effects of orally administered bisphosphonate compounds in paediatric osteogenesis imperfecta.^{9–12} In one trial with 139 participants, we reported that 2 years of oral alendronate for children and adolescents with mostly moderate and severe disease had no significant effect on long-bone fracture rates

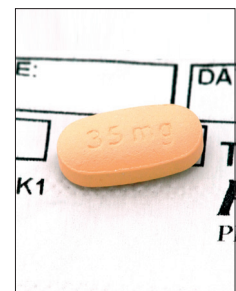
or reshaping of fractured vertebral bodies, despite a substantial effect on spine bone density.¹²

In *The Lancet*, Nick Bishop and colleagues¹³ report the results of a randomised, double-blind, placebo-controlled trial of oral risedronate, for which they recruited 147 children aged 4–15 years, mostly with mild osteogenesis imperfecta. Risedronate treatment was associated not only with the expected increase in spine and total body bone mineral densities—mean increase in lumbar spine areal bone mineral density at 1 year, the trial's primary endpoint, was 16.3% with risedronate and 7.6% with placebo (difference 8.7%, 95% CI 5.7–11.7%; $p < 0.0001$)—but also with a reduced number of non-vertebral fractures. However, no difference was seen in the frequency of new vertebral fractures. As in other paediatric bisphosphonate studies, the short-term safety profile of oral risedronate was favourable.

This study adds to the debate on oral bisphosphonate for the treatment of paediatric osteogenesis imperfecta. The most important study finding, that risedronate reduced the risk of fractures by 47% (hazard ratio 0.53, 95% CI 0.31–0.92), is encouraging. The observation that the effect on fracture incidence was evident after only 6 weeks of treatment is remarkable, and suggests that the antifracture effect does not depend on changes in bone density, but rather results from the decrease in bone turnover.

To assess the clinical benefit associated with risedronate treatment fully, additional information about the types of fractures prevented would be necessary. For example, our previous trial of oral alendronate¹² showed a non-significant prolongation of time to first fracture in the alendronate group ($p = 0.07$), but no difference from placebo in the number of long-bone fractures ($p > 0.50$).¹² Since prevention of femur and tibia fractures is a clinically more desirable outcome than prevention of toe and finger fractures, fracture location is an important consideration in assessment of the clinical utility of a treatment approach.

Fractures of the arms and legs are the most frequently reported bone-fragility outcome measure in studies of paediatric osteogenesis imperfecta. However, this outcome is fraught with challenges, since numerous determinants, such as activity level, risk-taking behaviour, and the presence of long-bone deformities,



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can affect numbers of arm and leg fractures in children. Vertebral fractures are also an important marker of reduction or improvement in bone strength in children with osteogenesis imperfecta. In this respect, the low efficacy of oral risedronate for prevention of new vertebral fractures is a disappointing finding, since most children with even mild disease will frequently manifest new vertebral fractures during childhood.¹

Where do these new data leave us with respect to the treatment of children with osteogenesis imperfecta? Bishop and colleagues' study included few children with severe osteogenesis imperfecta, and therefore does not provide substantial new evidence for the treatment of severe disease. For children and adolescents with mild osteogenesis imperfecta, oral risedronate emerges from this study as an option to reduce the number of non-vertebral fractures, although whether it reduces long-bone fractures, which have the highest clinical morbidity, remains unclear. Additionally, the study did not find that oral risedronate will protect against the development of new vertebral fractures. As a result, whether the benefits of this treatment provide a strong enough rationale for prescribing daily oral risedronate to children with osteogenesis imperfecta remains open to debate.

*Leanne M Ward, Frank Rauch

Children's Hospital of Eastern Ontario, Ottawa, ON, K1H 8L1, Canada (LMW); and Shriners Hospital for Children, Montreal, QC, Canada (FR)
lward@cheo.on.ca

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