

Letter to the Editor: Therapies for Osteogenesis Imperfecta

Carta ao Editor: Terapêuticas para a Osteogénese Imperfeita

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Osteogenesis imperfecta (OI) is a rare genetic disorder characterized by bone fragility, increased risk of fracture, and skeletal deformities, which occurs in 1:20 000 newborns. Based on clinical findings, OI was classified by Sillence *et al* in 1979, in types I, II, III, and IV. Progress in molecular studies has added several new types to this syndrome. The most common mutations are in the COL1A1/ COL1A2 genes that lead to defects in type 1 collagen. There is no cure for OI. Rehabilitation, orthopedic surgery and pharmacologic therapies are the mainstay of treatment.¹

Bisphosphonates (BP) are potent antiresorptive agents that inhibit osteoclast function and may reduce fracture rate in OI patients. Its use became widespread after the publication in 1998 of a large series of OI children treated with pamidronate.² Although pamidronate administered every four months remains the most widely used BP, zoledronate, given its superior antiresorptive potency and more convenient administration (every six months), emerges as an alternative for OI children.¹

We recently started zoledronate, in a 4-years-old boy with a history of non-traumatic fractures since the age of 1.5 years, blue sclera and ligamentous laxity associated with reduced growth and low stature. Investigations were performed for suspected OI. The findings on genetics [variant c.3825G > A (p.Trp1275*) gene COL1A1], bone densitometry (lumbar spine BMD Z-Score: -4.4) and radiographs (wormian bones in lambdoid suture and cortical thickening of long bones) were strongly suggestive of OI type I (Fig. 1). After 4 infusions, he showed improvements in lumbar spine BMD Z-Score (-4.4 > -2.7), fracture rate (6 > 0) and mobility.

Nowadays zoledronate is the more convenient option for OI children starting therapy. Nevertheless, a systematic review summarizing the evidence on bisphosphonates in OI concluded that the available evidence is insufficient to judge whether BP therapy improves outcomes other than bone density, namely fracture risk.³

Emerging therapies include denosumab, a RANK ligand antibody. A recent trial demonstrated significant increase in lumbar spine BMD after 48 weeks of therapy and no serious adverse events.⁴ Regarding stimulators of bone formation, a randomized controlled trial on teriparatide in adults with *osteogenesis imperfecta*, showed increased BMD in mild OI. Sclerostin antibody treatment has shown promise in OI mouse models but there is no clinical experience reported in OI patients.⁴ Fresolimumab, anti-TGF-beta neutralizing antibody, seems to correct the bone phenotype and improve lung abnormalities in OI mouse models.⁵

New therapies are needed for OI in order to reduce morbidity and provide patients a better quality of life.



Figure 1 - Skull (A) and leg (B) x-ray: presence of wormian bones in lambdoid suture and marked cortical thickening of long bones in OI patient (arrows).

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Sandra SOUSA✉¹, Fátima GODINHO¹, Maria José SANTOS^{1,2}

1. Rheumatology Department. Hospital Garcia de Orta. Almada. Portugal.

2. Rheumatology Research Unit. Instituto de Medicina Molecular. Lisbon. Portugal.

Autor correspondente: Sandra Sousa. sandrainsousa@gmail.com

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