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Radiological Features of Zoledronic Acid Therapy in Saudi Children with Osteogenesis Imperfecta

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Abstract **Original Research Article**

Background: The majority of osteogenesis imperfecta (OI) cases have an autosomal dominant pattern of inheritance and are usually caused by mutations in genes encoding type I collagen. Patients with OI may have blue sclerae, dentinogenesis imperfecta, and growth deficiency. Zoledronic acid is a third-generation bisphosphonate which was reported to inhibit osteoclast-mediated bone resorption, improve bone density, and reduce incidence of fractures. ***Aim:*** To describe the radiographic features of cyclic Zoledronic acid administration on the growing skeleton in children with OI and to report the efficacy of Zoledronic acid on bone mineral density. ***Methods:*** We retrospectively reviewed the radiographs of 11 children treated with Zoledronic acid. The age of these children ranged from one to 13 years. Zoledronic acid was administrated intravenously at 6 months intervals at the Pediatric Endocrinology Day Medical Unit, King Faisal Specialist Hospital and Research Centre, and Security Forces Hospital, Riyadh, Kingdom of Saudi Arabia for 2 years. ***Results:*** During the course of treatment, a gradual increase in bone density was observed. The baseline mean lumbar BMDz score was -4.9SD ± 1.3, which improved to a mean score of -2.7SD ± 1.1, and a mean whole body BMDz score was -2SD ±1.2 and improved to a mean score of -1.1SD ± 1.3 by the end of therapy. Post treatment, there were multiple sclerotic metaphyseal bands seen in all children in the long bones paralleling to the growth plates and corresponding to the number of treatment cycles. ***Conclusion:*** Intravenous Zoledronic acid in children with osteogenesis imperfecta improved the bone mineral density and resulted in permanent sclerotic metaphyseal bands.

Keywords: Osteogenesis imperfect, fracture rate, Zoledronic acid, bone mineral density.

INTRODUCTION

Osteogenesis imperfecta (OI) is a common genetic disorder of collagen synthesis, which occurs in 1:20,000 newborns, that it affects the connective tissue, mainly the bones, decreasing their bone density and increasing their fragility [1, 2]. Depending on severity, the bone fragility may lead to perinatal death or cause severe deformities that persist into adulthood [3-6]. Most patients with OI have autosomal dominant inheritance caused by mutations in the COL1A1 or COL1A2 genes encoding collagen type α-1 and α-2 chains [7]. Additional mutations in at least 18 other genes can also cause brittle bones; these are typically clinically indistinguishable and are considered subtypes of osteogenesis imperfecta [8, 9].

Since most of the imaging characteristics of this disease are apparent on plain radiography, the preferred examination for the initial investigation of osteogenesis imperfecta is plain radiography. In cases of suspected osteogenesis imperfecta, postnatal radiographs should include views of the long bones, skull, chest, pelvis, and thoracolumbar spine [10].

Biphosphonates are potent inhibitors of osteoclastmediated bone resorption and have demonstrated clinical usefulness in the treatment of children with severe forms of OI [11]. The treatment usually consists of cyclic intravenous infusions and may be initiated after birth. Several studies have reported beneficial effects of biphosphonates on pain, mobility, growth, bone mineral density (BMD), and fracture rate [12-19]. However, long-term effects of these agents on Saudi children were not fully investigated.

METHOD

We retrospectively reviewed the radiographs of 11 children (4 males, 7 females) treated with Zoledronic acid intravenously at 6 months intervals at the Pediatric Endocrinology Day Medical Unit, King Faisal Specialist Hospital, Riyadh, Saudi Arabia for 2 years. The age of these children ranged from 1-13 years. The annual total dose was 0.1 mg/kg/year. Skeletal survey, lumbar and whole-body BMD were assessed annually. BMD determinations were performed using a Hologic QDR4500 dual-energy x-ray absorptiometer with pediatric scan and analysis functions. Z scores, the number of standard deviations (SD) for BMD above or below the mean for age-matched controls, were derived on the basis of the manufacturer's data. The study was approved by King Faisal Specialist Hospital Research Ethic Committee (RAC#2231169).

RESULTS

Initially, baseline radiographs showed osteopenia, bowing bones and bone deformities. Post-treatment, there were multiple sclerotic metaphyseal bands in the long bones parallel to the growth plates and corresponding to the number of treatment cycles (Figure 1).

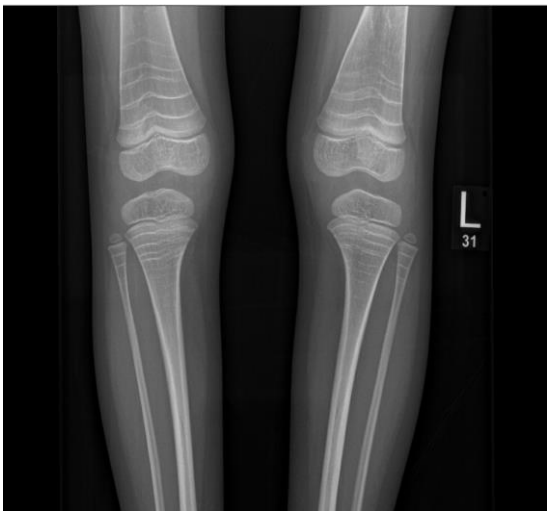

Figure 1: Radiograph showing distal ends of the femur and proximal end of the tabia, which are parallel to the growth plates and correspond to the number of treatment cycle (Zebra Lines)

The metaphyseal bands were seen as early as 3 months after the first treatment cycle and became more visible over time as the growth separated them from the zone of provisional calcification.

During the course of treatment, a gradual increase in bone density was observed in all patients. Before treatment, the mean lumbar BMDz score was -4.9SD $\pm$ 1.3, which improved to a mean score of -3.1SD + 1.2 one-year post treatment, to a mean score of -2.7SD $\pm$ 1.1 at the end of therapy. The mean whole body BMDz score was -2SD $\pm$1.2 at the start of therapy. After one year of therapy, the mean whole body BMDz score was -1.7SD $\pm$ 1.1. At the end of treatment, the whole body BMDz score was -1.1SD $\pm$ 1.3.

DISCUSSION

The objective of this study is to prove the benefit of Zoledronic acid on the bone turnover and subsequent increase in bone mass in Saudi children with OI. As a third-generation bisphosphonate, Zoledronic acid had high binding affinity for hydroxyapatite and played strong inhibiting roles on bone resorption, which could be administered annually or biannually or more frequently [15-19]. Recently, a study included 82 children with OI treated with Zoledronic acid 0.05 mg/Kg/day for a median duration of 60 months showed an annual fracture rate decrease from 2.8±1.5 to 0.2±0.5. Z-score on DEXA scan showed improvement in BMD overall from -3.9±2.0 to -2.2 ±1.7 [20] which is more or less similar to our Saudi results and response. A 2-year prospective observational study from Egypt showed a significant increase in BMD Z-score as well, together with a significant drop-in fracture rate, relief of pain, and improvement in ambulation [21]. Another paper from China tried to find a relationship between pathogenic mutations and responses to Zoledronic acid in a Cohort of 201 children with OI. They concluded that patients with non-AD inheritance or with pathogenic mutations leading to collagen structural defects may have relatively poor responses to Zoledronic acid, which is possibly associated with their more severe phenotypes [22]. Another study aimed to compare the efficacy and safety of intravenous zoledronic acid and oral alendronate in patients with OI. A once-yearly 5 mg infusion of Zoledronic acid and weekly oral alendronate had similar effects in increasing BMD and reducing bone resorption in children and adolescents with OI. Zoledronic acid was superior to oral alendronate in reducing the clinical fracture rate [23]. one of the extensive institutional experience studies aimed to characterize the short-term safety profile of Zoledronic acid and identify risk in

young patients included 81 patients with a median age of 12 years. The adverse events were mild and more common after the first infusion. Hypophosphatemia was reported in 25% of infusions, and hypocalcemia in 16%. Symptomatic hypocalcemia requiring intravenous calcium infusion [24]. In our small group, none of the patients developed serious side effects such as hypocalcemia, however all children were given a short course of calcium supplementation 5 days before and 5 days after Zoledronic acid infusion.

CONCLUSION

The effect of Zoledronic acid in Saudi children with OI is encouraging and we need to evaluate zoledronic acid treatment in a larger size sample from Saudi Arabia and Gulf countries for longer duration to allow discriminating the differences that can exist between different groups.

Author Contributions:

All the authors were equally involved in the curation and development of this manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest: No conflict of interest.

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