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Treatment of osteogenesis imperfecta with the bisphosphonate olpadronate (dimethylaminohydroxypropylidene bisphosphonate)

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Abstract Osteoporosis is an important feature of osteogenesis imperfecta (OI). So far, no effective medical treatment is available. We treated three boys with severe OI type III and vertebral deformities for 5–7 years with continuous oral administration of the bisphosphonate, olpadronate. Treatment resulted in a decreased number of bone fractures, an increased calcification of the long bones and an amelioration of vertebral shape. No side-effects were encountered.

Conclusion These preliminary but long-term observations suggest that the bisphosphonate olpadronate may be a useful treatment for patients with OI and vertebral fractures. Bisphosphonates may be promising drugs for children with OI.

Key words Bisphosphonates · Osteogenesis imperfecta · Osteoporosis

Abbreviation *OI* osteogenesis imperfecta

Introduction

Skeletal complications of osteogenesis imperfecta (OI), a genetic disorder of type I collagen, include osteoporosis, bone fractures and deformities, and short stature. There is no effective pharmacological treatment for the disorder. Bisphosphonates, synthetic stable analogues of natural pyrophosphate, which concentrate specifically in the skeleton and suppress osteoclastic bone resorption, have been effective in adults with osteoporosis [6]. A few case studies reported that these compounds may also be beneficial in the treatment of children with OI [1, 3, 5]. We report here long-term observations of three children with OI and multiple fractures treated with the new bisphosphonate olpadronate ((3-amino-1-hydroxyprolidene)-1,1-bis-phosphonate) which is more potent than pamidronate and has been shown in animal studies to improve the biomechanical properties of bone [2, 7].

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Patients and methods

Three boys, aged 1.0, 1.7 and 6.0 years, with OI type III (according to Sillence [10]) and vertebral deformities were treated with olpadronate after informed parental consent. Patients' details are given in Table 1. Olpadronate was given orally in tablets prepared by the pharmacy of the University Hospital Leiden, at a dose of 5 mg (patient 2) or 10 mg (patients 1 and 3) per day. The patients also received calcium (500 mg/day) and vitamin D (400–600 IU/day) supplements.

The patients were followed in the outpatient clinic at regular intervals. Fracture frequency was noted. Supine length and weight were measured. Growth was compared to the normal Dutch references and to the disease-specific 50th percentile as described by Vetter et al. [12]. At each visit blood was taken for the determination of parameters of calcium and bone metabolism (calcium, phosphate, alkaline phosphatase) and of safety parameters (total blood count, creatinine and liver function tests). Before treatment serum concentrations of vitamin D metabolites and parathyroid hormone were within normal limits. Radiographs of the spine, the long bones and the hand were obtained annually.

Results

The patients were treated continuously for 5–7 years. The yearly number of peripheral fractures before olpadronate treatment was six in patient 1, six in patient 2, and one to two in patient 3. During olpadronate treatment the patients had one to two fractures per year. During the treatment period all patients were treated

Table 1 Patient characteristics

	Patient 1	Patient 2	Patient 3
Family history of OI	–	–	–
Birth weight (g)	3305	2700	2750
Fractures at birth	Skull, ribs, femurs, tibias	Femurs, tibias	Femurs, tibias
Blue sclerae	+	+	+
Dentinogenesis imperfecta	+	+	+
Hearing loss	–	–	–
Bone deformities	+	+	+

surgically with metal pins in the femurs and tibias to stabilize the legs. At the last visit of the observation period all three patients were able to walk short distances, two of them with crutches. Treatment did not appear to affect the degree of kyphoscoliosis. No effect of the treatment on the dentinogenesis imperfecta could be documented.

The longitudinal growth of the patients is shown in Fig. 1. All patients were markedly smaller than the 3rd percentile of the normal population. Comparison with the OI-specific 50th percentiles suggests a catch-up growth. This should, however, be interpreted with caution in view of the difficulties in measuring height in such patients. The weights of patient 1 and 3 were appropriate for their length, while patient 2 was slightly underweight.

During treatment serum calcium, phosphate, alkaline phosphatase, parathyroid hormone, and vitamin D metabolites concentrations did not change and remained within the age-specific reference ranges.

Figure 2 shows the X-ray of the hand of patient 2 at the age of 4 months (before treatment), and after 1 month and 6 years of olpadronate therapy. Already after 1 month of treatment calcification lines were clearly visible in the metaphyses. Later X-rays showed that the zone of increased calcium deposits was limited to the metaphysis. Figure 3 shows the X-ray of the lumbar spine of patient 1 at the start, and after 3 and 6 years of treatment with olpadronate. Vertebral height clearly increased during treatment and there was restoration of the shape of some vertebrae. Similar findings were observed in the other two boys.

Treatment was well tolerated and the patients did not encounter any side-effects. There were no abnormalities in blood count, serum creatinine or liver function tests during treatment with olpadronate.

Discussion

The present study suggests that long-term continuous administration of the bisphosphonate olpadronate to patients with OI and vertebral deformities is effective and devoid of side-effects. Radiologically, there was a tendency for restoration of normal vertebral shape and increased calcification of the long bones. Linear growth paralleled the 50th percentile of OI-specific growth curves and the number of yearly fractures decreased. It should be noted, however, that fracture frequency is a rather weak efficacy parameter in open therapeutic studies of patients with OI as this can be influenced by external factors (e.g. mode of handling, mobility) and

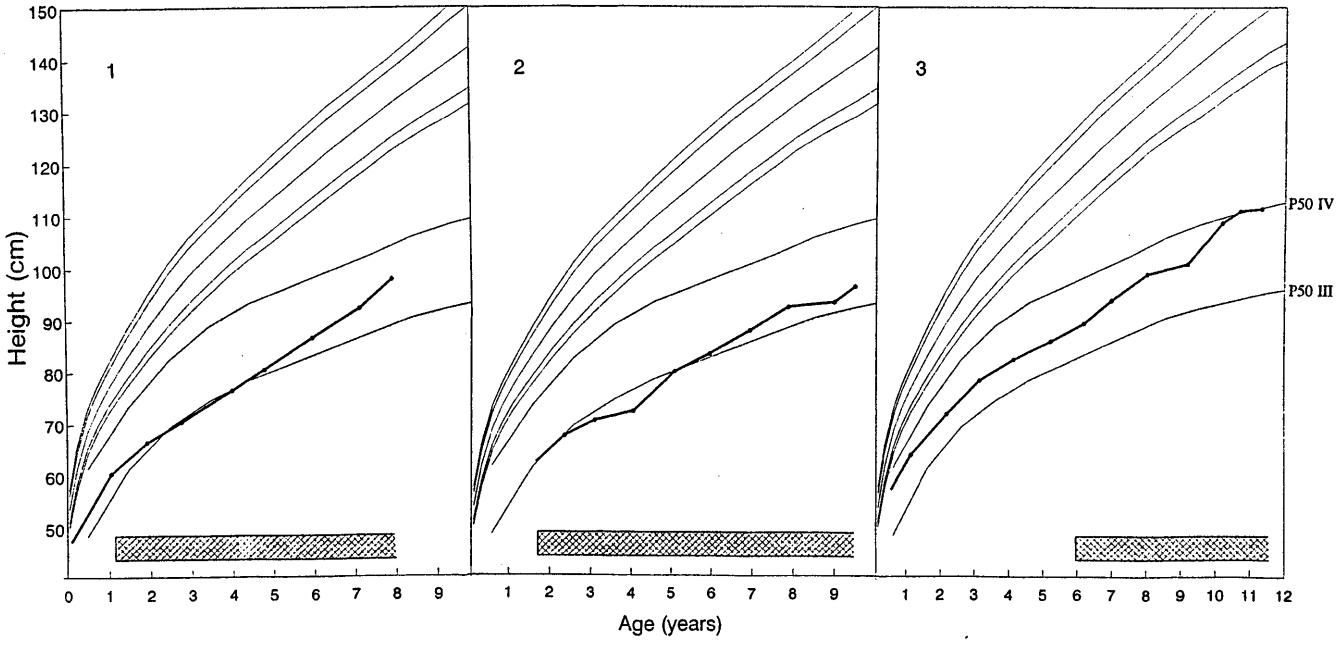

Fig. 1 Growth charts of three patients with OI treated continuously with oral olpadronate (indicated by *hatched bar*) for 5–7 years. *Upper lines* represent normal percentiles. *P50III* and *P50IV* represent 50th percentile for children with respectively type III and type IV OI according to Vetter et al. [12]

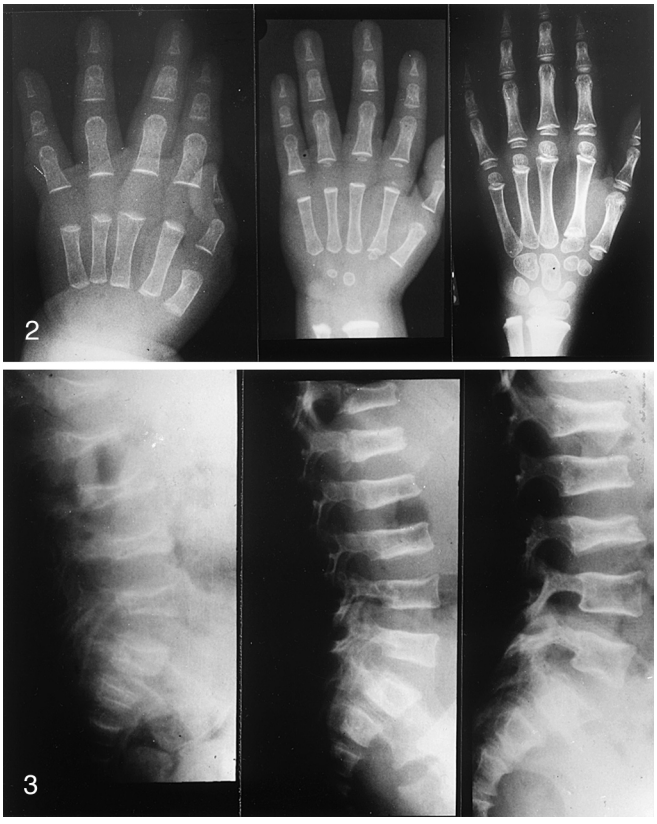

Fig. 2 X-ray of the hand of patient 2 at the age of 4 months (before treatment), and after 1 month and 6 years of olpadronate therapy. Note metaphyseal calcification lines after 1 month of treatment

Fig. 3 X-ray of the lumbar spine of patient 1 at the start, and after 3 and 6 years of treatment with olpadronate. Note increase in vertebral width and restoration of the shape of some vertebrae during treatment

may also decrease spontaneously with age. Our results conform with previous short-term studies [1, 3, 5] of patients with OI treated with pamidronate. Although spontaneous recovery of vertebral shape has been previously reported in patients with idiopathic juvenile osteoporosis after puberty [11] no such data are available for young patients with OI and vertebral osteoporosis.

There is limited experience with the use of bisphosphonates in children and in all reports, nitrogen-containing compounds, as in the present study, have been applied [4, 8]. These bisphosphonates have a wide therapeutic margin and do not induce mineralisation defects as the first developed bisphosphonate, etidronate. The dose of olpadronate used in the present study was chosen empirically on the basis of our experience in treating older children with bisphosphonates as well as on preclinical and clinical data with the use of this bisphosphonate in adults [7]. Independently of the primary diagnosis, all available studies have reported encouraging results with bisphosphonates, and most importantly, lack of serious side-effects.

Although in OI the primary abnormality is a genetically determined defect in the synthesis of collagen type I, most studies agree that there is also an imbalance between bone formation and resorption leading to bone loss and osteoporosis [9, 13]. Bisphosphonate therapy by suppressing bone resorption reduces bone loss and increases the accumulation of calcium in the skeleton. When appropriate doses are applied there is no excessive suppression of bone turnover, as has been demonstrated in adult patients with osteoporosis during long-term treatment with alendronate or pamidronate [6].

In conclusion, this long-term as well as the previously reported short-term studies provide provisional but encouraging results in the management of a crippling condition for which no medical treatment is currently available. We believe that these results justify larger therapeutic controlled trials of bisphosphonates in patients with OI.

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