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Treatment of Osteogenesis Imperfecta: Who, Why, What?

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Osteogenesis imperfecta · Bisphosphonates · Collagen type I · Osteoporosis

Abstract
Introduction: Osteogenesis imperfecta (OI) is a heritable disorder characterized by bone fragility and reduced bone mass. It may present with a wide range of severity. About 85% of the cases are linked to mutations in one of the two genes encoding type I collagen. In other cases of OI, there are mutations in the expression of a cartilage-related protein or of 3-prolyl-hydroxylase. Increased bone turnover rate, due to the repair activity triggered to replace weak tissue, is the rule. Often, disuse bone loss further compounds the decrease in bone mass. These findings justify the use of bisphosphonates to reduce osteoclast-mediated bone resorption, and so tilt the remodeling balance towards an increase in bone mass. ***Conclusions:*** Cyclical intravenous pamidronate administration reduces bone pain, and increases bone mass and density. No negative effects on growth or fracture repair have been observed. There is an increase in size of vertebral bodies and thickening of cortical bone, which translates into decreased fracture incidence and improved ambulation. However, the long-term consequences of low bone turnover in children with OI are unknown at the present time. Innovative surgery and specific occupational and physiotherapy programs are integral parts of the treatment protocol. This approach will prevail until gene-based therapies become clinically applicable.

Introduction

Osteogenesis imperfecta (OI) is a heritable disorder characterized by increased bone fragility and low bone mass [1]. Extraskeletal manifestations, which are not always present, include blue sclera, dentinogenesis imperfecta, ligament hyperlaxity, hearing impairment and the presence of Wormian bones on skull radiographs. Approximately 85% of the patients with OI are positive for dominant mutations in one of the two genes encoding the alpha chains of collagen type I. In addition, recessive mutations in the genes encoding a cartilage-associated protein and a 3-prolyl-hydroxylase, two key components in the processing of type I collagen, have recently been characterized [2].

There is a wide spectrum of clinical severity in OI [3]. Some patients have a mild form of the disease and an absence of major bone deformities. However, vertebral fractures are common and can lead to mild scoliosis. In other patients, the trait is lethal in the perinatal period, often because of respiratory failure due to multiple rib frac-

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tures. Some patients have very short stature as well as limb and spine deformities secondary to multiple fractures, while others have moderate bone deformities and variable short stature. It has been evident (and somewhat frustrating) that there is no precise correlation between genotype and phenotype. Even among patients sharing the same mutation, the clinical picture may vary widely.

Bisphosphonate Therapy in OI

Physiotherapy, rehabilitation and orthopedic surgery are the mainstays of treatment in OI [4, 5]. Therapeutic efforts are aimed at maximizing mobility and other functional capabilities [4, 6]. Standing and walking can often only be achieved after femora and tibiae have been straightened using intramedullary rods [5, 7, 8]. This treatment approach can be successful, but does not alter the often extreme bone fragility in these patients. For this reason, there has been a long-standing search for medical approaches to strengthen the bones.

Bisphosphonates are potent antiresorptive agents that inhibit osteoclast function [9]. The hypothesis underlying the use of these drugs in an osteoblast disorder such as OI is that a decrease in the activity of the bone resorption system might compensate for the weakness of the bone-forming cells. Increased turnover rate, established by histological studies, and disuse osteoporosis also substantiate the rationale for using bisphosphonates in OI. The first case report on the use of the oral bisphosphonate pamidronate in a child with OI appeared in 1987 [10]. The use of these drugs in OI and other pediatric disorders became more widespread after the 1998 publication of a larger study of children and adolescents with OI who had been treated with cyclical intravenous pamidronate [11]. Since then, a number of groups have reported on their experience with intravenous pamidronate and, more recently, with oral forms of bisphosphonates.

Intravenous Pamidronate

The majority of OI patients who were described in published reports received cyclical intravenous pamidronate. None of these pamidronate studies was placebo-controlled. Nevertheless, the studies consistently showed that pamidronate infusions, given every 1 to 4 months, led to a marked and rapid decrease in chronic bone pain, an increased sense of well-being and a rapid rise in vertebral bone mineral mass. Collapsed vertebral bodies were also noted to regain a more normal size and shape. There was also improved mobility in more than half of the patients, and a significant reduction in fracture incidence [11–17].

Histomorphometric studies of iliac bone samples showed that the main effect of pamidronate treatment was an increase in cortical thickness. The amount of trabecular bone also increased, which was due to a higher number of trabeculae [18]. With regard to long-term safety, no negative effect of pamidronate on renal function or growth has been detected in children with moderate to severe OI [12, 14, 19].

Another bisphosphonate, neridronate, was used intravenously in an open-label controlled study of adults with OI, with similar results [20]. Zoledronic acid is one of the newer bisphosphonates that is being used to treat postmenopausal osteoporosis [21]. Its utility for the treatment of children and adolescents with OI is currently under investigation in an international multicenter trial.

Oral alendronate [22] and olpadronate [23] have also been used. With the latter, a randomized placebo-controlled study showed that the group receiving active therapy had a higher lumbar spine bone mineral density (BMD) and a lower incidence of long-bone fractures. No difference in functional outcomes such as mobility and muscle force was detected [23].

Currently, there is little published evidence to help in the selection among different bisphosphonate regimens for OI patients. Nevertheless, it seems that intravenous pamidronate has a more marked effect on bone pain than oral formulations. Oral medication is easier to administer, but drawbacks are uncertain compliance, low and variable bioavailability and possible gastrointestinal side effects. In a controlled study, it was shown that alendronate increased BMD but had little effect on pain, mobility and fracture incidence in moderate-to-severe OI [28].

The results from studies in moderate-to-severe OI cannot be simply extrapolated to mild forms of the disease (defined as two or fewer fractures per year, no vertebral compression fractures and no long-bone deformities). Children with mild OI have less to gain simply because their functional status is better even without treatment. At this time, it is recommended that children with mild OI not be treated.

Most of the patients described in the above studies were older than 2 years of age when pamidronate treatment was started. In a congenital disease such as OI, it appears logical to start treatment as early as possible. Indeed, promising results were reported in a small group of

patients who received pamidronate in the first 2 years of life [13]. The effect of bisphosphonates on the skeleton is clearly growth-dependent [18]. Thus, postpubertal adolescents and adults cannot be expected to benefit as much as younger patients do.

Should the treatment ever be stopped? If so, when? There is little published evidence that answers these questions in one way or another. One might tackle the problem by addressing it from three different angles: (1) What is the benefit of prolonged therapy? (2) What are the drawbacks of continuing therapy? (3) What is the effect of discontinuing therapy?

What is the benefit of prolonged therapy? Most reports invariably focus on the initial treatment effect. However, a densitometric study of 56 pediatric OI patients indicates that the rate of change in BMD slows down during pamidronate therapy [15]. For example, the age-specific Z-score for lumbar spine BMD increased by 2.0 during the first 2 years of treatment, but only by 0.6 between 2 and 4 years of treatment. Similarly, histomorphometric studies have shown that the cortical width of the iliac bones almost doubles during the first 2.4 years of pamidronate treatment, but changes little when therapy is continued for another 3 years thereafter [18].

What are the drawbacks of continuing therapy? Antiresorptive drugs such as the bisphosphonates inevitably decrease the activity of bone remodeling and also have the potential to interfere with bone modeling (shaping) [15, 24, 25]. Low remodeling activity might also delay bone healing after injury. Pamidronate treatment has been shown to delay the healing of osteotomy sites after surgical insertion of intramedullary rods [26]. This can lead to pain and fracture at the affected site and may necessitate further surgical procedures.

What is the effect of discontinuing therapy? In a group of 70 OI patients between 1 and 3 years of age who had stopped pamidronate treatment, BMD remained stable or continued to increase in most cases. However, new metaphyseal bone added by growth after pamidronate therapy discontinuation has a lower density than treated bone, and this may produce zones of fragility, e.g., around the wrist, in growing children [27]. Therefore, it appears that some form of therapy has to be maintained throughout the growth period.

Conclusions

Bisphosphonate therapy does not constitute a cure of OI, but rather is an adjunct to physiotherapy, rehabilitation and orthopedic care. These drugs have brought clear improvements in the lives of patients with moderate to severe OI. In contrast, children and adolescents with OI who have few fractures and no functional limitations have less to gain from treatment. It therefore appears advisable not to treat such patients unless clinical benefit can be demonstrated in placebo-controlled studies.

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