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Bisphosphonate treatment in osteogenesis imperfecta: Which drug, for whom, for how long?

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Abstract
Treatment with bisphosphonates has brought significant clinical improvements for children and adolescents suffering from moderate to severe forms of osteogenesis imperfecta (OI). Benefits include decreased pain, lower fracture incidence, and better mobility. Among the various bisphosphonates, intravenous pamidronate has been studied in most detail. It is unclear whether oral bisphosphonates are as effective as intravenous pamidronate. As the effect of bisphosphonates on the skeleton is largest during growth, it appears logical to start medical therapy of OI patients as early as possible. Nevertheless, the optimal treatment regimen and the long-term consequences of pamidronate treatment in children are currently unknown. Given these uncertainties, treatment with bisphosphonates should be reserved for patients who have significant clinical problems, such as vertebral compression fractures or long bone deformities. At present, bisphosphonate treatment has little justification in growing patients with mild forms of OI who have few or no clinical symptoms. Such patients should not be treated unless clear clinical benefit can be demonstrated in ongoing placebo-controlled trials.

Key words: *Bisphosphonate, children, collagen, osteogenesis imperfecta, osteoporosis*

Introduction

Osteogenesis imperfecta (OI) is a genetic disorder with increased bone fragility and low bone mass (1). Severity varies over a wide range, reaching from intrauterine fractures and perinatal lethality to very mild forms without fractures (2). Typical extraskeletal manifestations can be associated to a variable degree. These include blue sclera, dentinogenesis imperfecta, hyperlaxity of ligaments and skin, hearing impairment and the presence of Wormian bones on skull radiographs. The majority of patients with a clinical diagnosis of OI are positive for a mutation in one of the two genes that encode alpha chains of collagen type I (COL1A1 and COL1A2). However, a negative collagen type I study does not rule out OI, as it is possible that either a collagen type I mutation is present but was not detected, or that the patient has a form of OI that is not associated with collagen type I mutations.

The most widely used classification of OI was published by Sillence et al. in 1979 and distinguishes four clinical types, OI types I to IV (3). Recently, we have delineated three additional groups of patients who had a clinical diagnosis of OI, but who presented clearly distinct features (4–6). These disorders were named OI type V, VI and VII. The clinically most relevant characteristic of all types of OI is bone fragility, the severity of which decreases in the order type II > type III > types IV, V, VI, VII > type I.

OI type I comprises patients with mild disease and absence of major bone deformities (Table I). However, vertebral fractures are common and can lead to mild scoliosis. Type II is lethal in the perinatal period, often because of respiratory failure resulting from multiple rib fractures. OI type III patients have extremely short stature as well as limb and spine deformities secondary to multiple fractures. Patients with moderate bone deformities and variable short stature are classified as OI type IV.

Regarding the 'new' OI types, OI type V is an autosomal dominant disorder with moderate to severe bone fragility (5). Mutations affecting collagen type I are absent. The clinical picture is characterized by ossification of the interosseous membrane at the forearm and a predisposition to develop a hyperplastic callus. OI type VI is also a moderate to severe form of OI (4). This type was defined on the basis of bone histology, where an increased amount of osteoid and an abnormal pattern of lamellation ('fish-scale') are observed. The mode of inheritance has not yet been established and collagen type I mutation studies are negative (4). OI type VII is a recessive disorder, which

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Abbreviations

BMD	bone mineral density
OI	osteogenesis imperfecta

so far has been observed only in a community of Native Americans in northern Quebec (6). Apart from bone fragility, rhizomelia is a prominent clinical feature and coxa vara may be present even in infancy.

Bisphosphonate therapy in OI: What drugs to use?

Physiotherapy, rehabilitation and orthopedic surgery are the mainstay of treatment in OI (7,8). Therapeutic efforts aim at maximizing mobility and other functional capabilities (7,9). Physical activity programs are encouraged (as far as is compatible with the increased risk of fracture) to prevent contractures and immobility-induced bone loss (8). Orthoses are used to protect the lower limbs during the earlier phases of mobilization (10). Standing and walking can often only be achieved after femora and tibiae have been straightened using intramedullary rods (8,11,12). 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 longstanding search for medical approaches to strengthen the bones.

Bisphosphonates are potent anti-resorptive agents that inhibit osteoclast function (13). All bisphosphonate compounds have a backbone that resembles pyrophosphate, which explains the affinity of these drugs for mineralized surfaces. The various members of the bisphosphonate family differ in the two side chains that are attached to this backbone molecule. Importantly, all bisphosphonates are incorporated into bone mineral and remain there for many years (14). The hypothesis initially underlying the use of an anti-osteoclast medication in an osteoblast disorder such as OI was that a decrease in the activity of the bone resorbing system might compensate for the weakness of the bone forming cells. After a case report on the use of oral pamidronate in a child with OI appeared in 1987 (15), various investigators started to treat small groups of pediatric OI patients with bisphosphonates. The use of these drugs in OI and other pediatric disorders became more widespread after the 1998 publication of a larger series of children and adolescents with OI who had been treated with cyclical intravenous

Key messages

- Cyclical intravenous pamidronate is the best characterized form of bisphosphonate treatment in osteogenesis imperfecta, whereas little information is available on the utility of oral bisphosphonates.
- The long-term safety profile of bisphosphonate given during growth is unknown.
- At present, bisphosphonate treatment in children and adolescents should be reserved for patients with significant clinical problems, such as vertebral compressions and long-bone deformities.

Table I. Expanded Sillence classification of OI.

Type	Clinical severity	Typical features	Typically associated mutations
I	Mild non-deforming OI	Normal height or mild short stature; blue sclera; no DI	Premature stop codon in COL1A1
II	Perinatal lethal	Multiple rib and long-bone fractures at birth; marked deformities; broad long bones; low density of skull bones on x-rays; dark sclera	Glycine substitutions in COL1A1 or COL1A2
III	Severely deforming	Very short; triangular face; severe scoliosis; grayish sclera; DI	Glycine substitutions in COL1A1 or COL1A2
IV	Moderately deforming	Moderately short; mild to moderate scoliosis; grayish or white sclera; DI	Glycine substitutions in COL1A1 or COL1A2
V	Moderately deforming	Mild to moderate short stature; dislocation of radial head; mineralized interosseous membrane; hyperplastic callus; white sclera; no DI	unknown
VI	Moderately to severely deforming	Moderately short; scoliosis; accumulation of osteoid in bone tissue, fish scale pattern of bone lamellation; white sclera; no DI	unknown
VII	Moderately deforming	Mild short stature; short humeri and femora; coxa vara; white sclera; no DI	unknown

Note: The 'typically associated mutations' may or may not be detectable in a given patient. DI=dentinogenesis imperfecta

pamidronate (16). Since then a number of groups have reported on their experience with intravenous pamidronate and, more recently, oral forms of bisphosphonate treatment (Table II).

Intravenous pamidronate

The majority of OI patients who were described in published reports received cyclical intravenous pamidronate (Table II). None of these pamidronate studies was placebo-controlled and none of these studies compared various dosing regimen against each other. Consequently, the optimal dose of pamidronate and the best treatment interval are unknown. Nevertheless, investigators agreed that intravenous pamidronate infusions, given every one to four months, led to a marked and rapid decrease of 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 (16–22). The two largest studies reported improved mobility in more than half of the patients (16,17). It is unknown at present, whether pamidronate treatment prevents long-bone deformities or delays the progression of scoliosis.

Histomorphometric studies of iliac bone samples showed that the main effect of pamidronate treatment was to increase cortical thickness (Figure 1) (23). The amount of trabecular bone also increased, which was due to a higher number of trabeculae. In contrast, pamidronate therapy had no detectable effect on trabecular thickness.

With regard to long-term safety, there was initially a great deal of concern regarding the effect on growth, given the well-known growth-suppressive effect of high-dose bisphosphonates in animals (24). Fortunately, no negative effect of pamidronate on growth has been detected in children with moderate to severe OI (17,19,25).

Other intravenously administered bisphosphonates

Neridronate, a bisphosphonate which is similar to pamidronate, was used in an open-label controlled study on adults with OI (26). This resulted in a significant increase in areal bone mineral density (BMD). Zoledronate is a newer intravenously applied bisphosphonate that has been used to treat postmenopausal osteoporosis (27). Its utility for the treatment of children and adolescents with OI is

Table II. Publications describing the overall effect of bisphosphonate therapy in osteogenesis imperfecta.

Article	*n*	Age at start (years)	Follow-up time (years)	Stated criteria for starting treatment	Bisphosphonate used
Glorieux et al. 1998 (16)	30	3–16	1.3–5.0	Severe OI (severe osteopenia)	Pamidronate iv
Plotkin et al. 2000 (18)	9	0.2–1.8	1.0	Severe OI (no details given)	Pamidronate iv
Lee et al. 2001 (43)	6	4–13	1.0–1.9	OI (no details given)	Pamidronate iv
Astrom et al. 2002 (17)	28	0.6–18	2–9	1) severe OI (short stature, skeletal deformities, and pain), or 2) moderate OI (compression fractures of vertebral bodies)	Pamidronate iv
Zacharin et al. 2002 (19)	14	1–14	1.8–2.0	Severe OI: (history of multiple fractures, and restriction of ambulation, and chronic back pain)	Pamidronate iv
Banerjee et al. 2002 (44)	10	1–12	0.9–3.0	OI with decreased quality of life, and low bone density	Pamidronate iv
Giraud et al. 2002 (45)	7	1–15	1–7	Definite OI (no details given)	Pamidronate iv
Shapiro et al. 2003 (34)	8	34–63	1.8–2.5	OI type IA	Pamidronate iv
Adami et al. 2003 (26)	46	22–48	1.0–2.0	All OI patients of any type	Neridronate iv
Falk et al. 2003 (46)	6	1–14	2.3–3.3	Moderate to severe OI (>1 fracture in previous 12 months, or progressive long-bone deformity, or lumbar spine BMD z-score <-3)	Pamidronate iv
Maasalu et al. 2003 (28)	15	0.8–13	1–5	OI (no details given)	Alendronate oral
Sakkers et al. 2004 (29)	34	3–18	2.0	Documented OI with restricted ambulation	Olpadronate oral
Arikoski et al. 2004 (21)	26	3.2–15.5	1.0	Moderate to severe OI: 1) frequent, disabling fractures, or 2) two or more crush-fractured vertebrae, or 3) chronic, disabling bone pain, or 4) bone deformity requiring surgical intervention	Pamidronate iv

Only reports containing more than five patients are listed. *n*=number of OI patients included in the report; NA=information not available

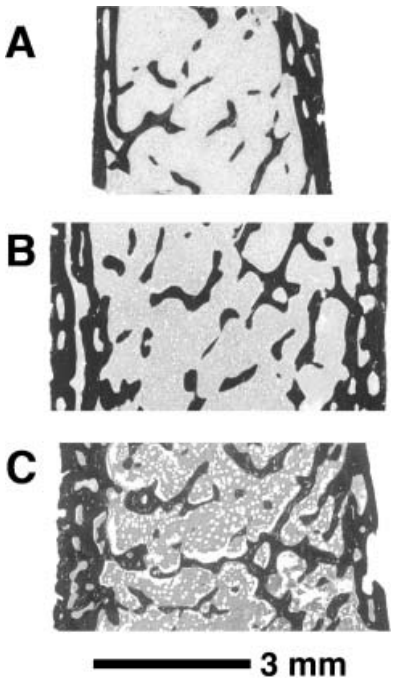

Figure 1. Series of iliac bone samples in a boy with OI type I caused by a Gly to Ser substitution at position 901 of the COL1A1 gene. **A**. Before treatment (cortical width 427 μm, cancellous bone volume 12.3%). **B**. After 2.8 years of pamidronate treatment (cortical width 774 μm, cancellous bone volume 21.3%). **C**. After 6.4 years of pamidronate treatment (cortical width 643 μm, cancellous bone volume 23.7%).

currently under investigation in an international multicenter trial.

Oral bisphosphonate therapy

In an observational trial, 15 children and adolescents received alendronate pills at a dose of 1 mg/kg per week in 3 to 7 doses per week, combined with calcitriol 0.25 μg once or twice per week (28). This treatment was reported to increase lumbar spine areal BMD and decrease the number of fractures, compared to the pretreatment period.

Sakkers et al. tested oral olpadronate at a daily dose of 10 mg per m^2 body surface area in a randomized placebo-controlled study that comprised 34 children and adolescents with OI. After a treatment period of two years, the group receiving active therapy had a higher lumbar spine areal BMD and a lower incidence of long-bone fractures. No difference in functional outcome such as mobility and muscle force was detected (29).

Synthesis: Intravenous or oral therapy?

There is currently little published evidence to help in the selection among different bisphosphonate regimes for an OI patient. No study has directly compared the efficacy and safety of different therapeutic approaches. Nevertheless, it is the impression of many clinicians that intravenous pamidronate has a more marked effect on bone pain than oral bisphosphonate therapy.

Oral medication has obvious practical advantages over intravenous infusions, at least in patients who are able to swallow pills and who can take the precautions that are required with oral bisphosphonates (such as drinking a large glass of water with the pill, staying in an upright position for at least 30 minutes thereafter). However, oral therapy also has a number of drawbacks, such as uncertain compliance, low and variable bioavailability, as well as the possibility of gastrointestinal side effects. Oral treatment exposes the skeleton to frequent small doses of medication, whereas intravenous treatment acts with lower frequency but at higher doses. In growing children this difference leads to specific radiographic features: oral treatment causes a continuous dense band in metaphyses, whereas intravenous treatment leads to discrete metaphyseal lines (Figure 2) (30,31). It is currently unknown, whether other skeletal effects differ between oral and intravenous bisphosphonate therapy in OI patients.

Which patients?

The observational trials on pamidronate discussed earlier have evolved from the compassionate use of this drug in desperate cases. As experience with this treatment approach increased, it was also used in less severe ('moderate') forms of OI. Nevertheless, most reports on intravenous pamidronate therapy state that this treatment was offered only to patients who had long-bone deformities, vertebral compression fractures and frequent fractures (Table II). The treatment decisions of most investigators thus appear to be dictated by clinical severity rather than collagen mutations status, BMD, or OI type. However, given that OI types III and IV (as well as the newly described types V and VI) represent the more severe part of the spectrum of the disorder, most patients who are classified in these categories will probably fulfill the stated criteria for intravenous pamidronate treatment.

The results from studies in moderate to severe OI cannot be simply extrapolated to mild forms of the disease (with two or fewer fractures per year, no vertebral compression fractures and no long-bone deformities). Children with mild OI have less to gain from therapy than severely affected patients, simply because their functional status is better even without

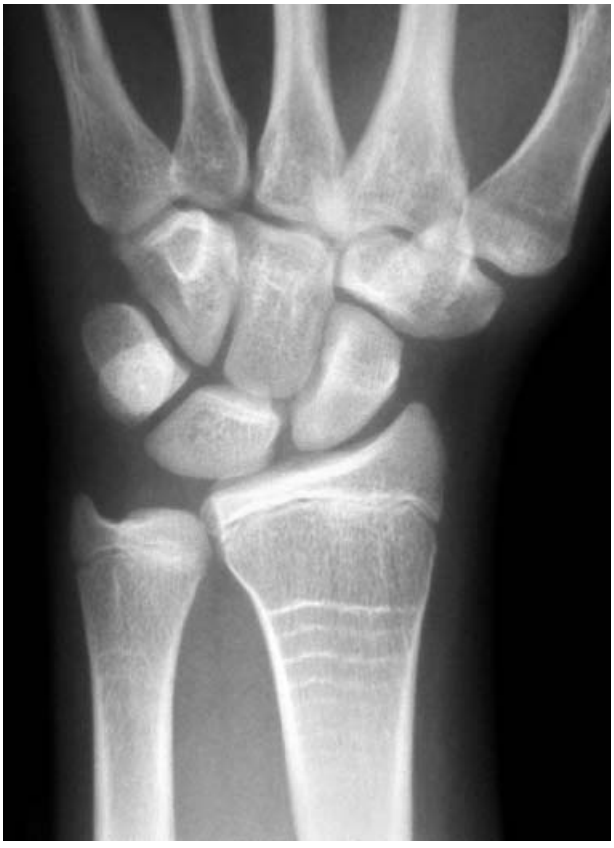

Figure 2. Radiograph of the wrist of a 15 year old girl with OI type I. Cyclical intravenous pamidronate had been given every four months from age 8 to 12 years. Metaphyseal lines corresponding to the last few treatment cycles are clearly visible in the radius. Bone that was added after the last pamidronate cycle does not contain any transverse lines and appears to be of normal density.

treatment. Therefore, the fact that the long-term side effects of bisphosphonate therapy in growing subjects are unknown weighs more heavily in the risk-benefit balance of mildly affected patients. In our view, bisphosphonate therapy is not justified in children with mild forms of OI unless ongoing placebo-controlled trials can establish the efficacy and safety of this approach in this particular patient group.

It is unclear what, if any, role BMD measurements should have in the decision to treat an OI patient with bisphosphonates. The many limitations of BMD measurements by dual-energy X-ray absorptiometry, in particular the dependency of results on bone size, have been highlighted in a number of recent reviews (32,33). In moderate to severely affected OI patients, lumbar spine areal BMD is usually very low, but such patients would receive treatment based on their clinical picture alone. In milder cases BMD may also be low, but the predictive value of such results in OI patients is not established. Despite the lack of evidence that BMD results actually provide relevant information in OI patients, a clinician may feel that stagnant or decreasing BMD values in a growing child should be taken as an additional argument for starting bisphosphonate therapy. Nevertheless, it is unclear whether there is any benefit in treating young and asymptomatic OI patients whose only 'problem' is low BMD.

At what age?

Most of the patients described in the above studies were above two 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 two years of life (18). As the clinical effect of a pamidronate infusion, especially on bone pain, was more short-lived in these young children than in older patients, pamidronate cycles were repeated more frequently (1).

The effect of bisphosphonates on the skeleton is clearly growth-dependent (23). Therefore, postpubertal adolescents and adults cannot be expected to benefit as much from treatment as do younger patients. Nevertheless, two studies suggest that adults with OI also may have some benefit from intravenous pamidronate or neridronate, a bisphosphonate which is similar to pamidronate (26,34). In the larger of these, Adami et al. found that intravenous neridronate induced a significant increase in areal BMD at the spine and at the hip. The incidence of fractures was significantly lower during than before treatment.

Although these are the only two studies that have evaluated bisphosphonate treatment of adults with OI, it is our experience that many adult patients receive oral bisphosphonates from their family physicians or from osteoporosis clinics. As systematically collected information is not available, it is impossible to judge whether adults with OI benefit from oral bisphosphonate therapy.

When to stop?

Should the treatment be stopped at all? If so, when? There is little published evidence that would allow answering these questions in one way or another. However, one might try to tackle the problem by addressing it from three different sides: 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?

None of the studies listed in Table II have specifically looked at this problem, as these reports invariably focused on the initial treatment effect. However, a densitometric study on 56 pediatric OI patients indicated that the rate of change in BMD is slowing down with the duration of pamidronate therapy (20). For example, the age-specific z-score for lumbar spine areal BMD increased by 2.0 during the first two years of treatment, but only by 0.6 between two years and four years of treatment. Similarly, histomorphometric studies have shown that the cortical width of iliac bone almost doubles during the first 2.4 years of pamidronate treatment, but changes little when therapy is continued for another 3 years thereafter (23) (and unpublished observations) (Figure 1).

What are the drawbacks of continuing therapy?

Antiresorptive drugs such as bisphosphonates inevitably decrease the activity of bone remodeling and also have the potential to interfere with bone modeling (shaping) (20,35,36). This was highlighted in a recent case report of a teenage boy who for unclear reasons received massive doses of pamidronate over a period of three years and who developed abnormally shaped long-bone metaphyses (37).

A sustained decrease in remodeling activity during growth may also be harmful, as it can lead to the accumulation of growth plate residues within trabecular bone tissue (23,24,37,38). Calcified cartilage has a high mineral density and therefore contributes to increase densitometric results (20,39), but is less resistant to fractures than is normal bone. Low remodeling activity might also delay bone healing after injury. In fact, we found that pamidronate treatment delayed the healing of osteotomy sites after intramedullary rodding procedures (40). This can lead to pain and fracture at the affected site and may necessitate further surgical procedures.

Bisphosphonates are known to persist in bone tissue for many years. Therefore, bisphosphonate treatment of girls and premenopausal women might have an effect on future pregnancies (41). In two young women with OI who received intravenous pamidronate before conception we did not detect any maternal ill effects (42). Both of their babies inherited OI from their mother. One baby had transient asymptomatic hypocalcemia on the first day of life and the other had bilateral talipes equinovarus. However, it is unclear whether these adverse events in the babies were related to the previous pamidronate treatment of the mothers. It will be important to collect such cases in far greater numbers to gain some certainty on the effect of bisphosphonate treatment on future pregnancies.

What is the effect of discontinuing therapy?

There is no published information on this question. However, we are following a group of 70 young OI patients who have stopped pamidronate treatment between one and three years ago. In most of these children and adolescents lumbar spine areal BMD remained stable or continued to increase after pamidronate was stopped. However, a few patients requested that pamidronate treatment be restarted, as they complained about a lack of stamina and recurrence of bone pain after they had been off pamidronate for several months.

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 to the lives of patients suffering from 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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