Osteogenesis Imperfecta, Current and Future Medical Treatment

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Physiotherapy, rehabilitation, and orthopedic surgery are the mainstay of treatment in moderate to severe forms of osteogenesis imperfecta (OI). Nevertheless, medical treatment with bisphosphonates can bring significant additional improvements. 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. However, the optimal treatment regimen and the long-term consequences of pamidronate treatment in children are currently unknown. Given these uncertainties, treatment with bisphosphonates during growth should be reserved for patients who have significant clinical problems, such as vertebral compression fractures or long bone deformities. Medical therapies other than bisphosphonates, such as growth hormone and parathyroid hormone, play a minor role at present. Gene-based therapy currently remains in the early stages of preclinical research.

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INTRODUCTION

Osteogenesis imperfecta (OI) is a genetic disorder with increased bone fragility and low bone mass [Rauch and Glorieux, 2004]. Severity varies over a wide range, reaching from intrauterine fractures and perinatal lethality to very mild forms without fractures [Plotkin et al., 2003]. 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 distinguishes four clinical types, OI types I–IV [Sillence et al., 1979]. Recently, three additional groups of patients have been delineated who had a clinical diagnosis of OI, but who presented some distinct features [Rauch and Glorieux, 2004]. 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. 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.

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The clinical picture of OI type V is characterized by calcification of the interosseous membrane at the forearm...
and a predisposition to develop hyperplastic calluses. OI type VI was defined on the basis of bone histology, where an increased amount of osteoid and an abnormal pattern of lamellation (“fish-scale”) are observed. OI type VII is a recessive disorder with bone fragility, rhizomelia, and coxa vara, which so far has been observed only in a community of Native Americans in northern Quebec.

NONMEDICAL THERAPY
Physiotherapy, rehabilitation, and orthopedic surgery are the mainstay of treatment in OI [Engelbert et al., 1998; Zeitlin et al., 2003a]. Therapeutic efforts aim at maximizing mobility and other functional capabilities [Engelbert et al., 1998]. Physical activity programs are encouraged (as far as is compatible with the increased risk of fracture) to prevent contractures and immobility-induced bone loss [Zeitlin et al., 2003a]. Orthoses are used to protect the lower limbs during the earlier phases of mobilization [Gerber et al., 1998]. Standing and walking can often only be achieved after femora and tibiae have been straightened using intramedullary rods [Zeitlin et al., 2003a]. This traditional 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.

BISPHOSPHONATE THERAPY
Bisphosphonates are potent anti-resorptive agents that inhibit osteoclast function. 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.

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The use of these drugs in OI and other pediatric disorders became widespread after the 1998 publication of a series of children and adolescents with OI who had been treated with cyclical intravenous pamidronate [Glorieux et al., 1998]. Since then a number of groups have reported on their experience with intravenous and oral forms of bisphosphonate treatment [Rauch and Glorieux, 2004; Sakkers et al., 2004; Gatti et al., 2005; Letocha et al., 2005]. Most of these reports included a small number of subjects. Table I lists the publications that include more than 20 patients.

Intravenous Bisphosphonate Treatment
The majority of OI patients who were described in published reports received cyclical intravenous pamidronate in various dosages and treatment intervals. The use of these drugs in OI and other pediatric disorders became widespread after the 1998 publication of a series of children and adolescents with OI who had been treated with cyclical intravenous pamidronate [Glorieux et al., 1998]. Since then a number of groups have reported on their experience with intravenous and oral forms of bisphosphonate treatment [Rauch and Glorieux, 2004; Sakkers et al., 2004; Gatti et al., 2005; Letocha et al., 2005]. Most of these reports included a small number of subjects. Table I lists the publications that include more than 20 patients.

The majority of OI patients who were described in published reports received cyclical intravenous pamidronate in various dosages and treatment intervals. Most investigators observed that intravenous pamidronate infusions, given every 1–4 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 [Arikoski et al., 2004; Munns et al., 2005] (Fig. 1). The two largest studies reported improved mobility in more than half of the patients [Glorieux et al., 1998; Astrom and Soderhall, 2002]. 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 [Rauch et al., 2002; Munns et al., 2005] (Fig. 2). 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.

There is less information on intravenously administered bisphosphonates other than pamidronate. A controlled trial on prepubertal OI patients who received intravenous neridronate, a bisphosphonate similar to pamidronate, yielded results that were comparable to those observed with pamidronate [Gatti et al., 2005]. Zoledronate is a newer intravenously applied bisphosphonate that has been used to treat postmenopausal osteoporosis [Delmas, 2002]. Its utility for the treatment of children and
adolescents with OI is currently under investigation in an international multicenter trial.

**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, and staying in an upright position for at least 30 min 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. It is currently unclear whether oral bisphosphonates are as effective as intravenous pamidronate in the treatment of OI patients.

A double-blind placebo-controlled trial in 139 children and adolescents found that 2 years of oral alendronate significantly decreased bone turnover, increased spine bone mineral density, and was generally well tolerated [Glorieux et al., 2004]. However, no significant effect on the incidence of fractures, bone pain or functional status was evident. Sakkers et al. [2004] tested oral olpadronate at a daily dose of 10 mg per m² body surface area in a randomized placebo-controlled study that comprised 34 children and adolescents with OI. After a treatment period of 2 years, the group receiving active therapy had a higher lumbar spine areal bone mineral density and a lower incidence of long-bone fractures. No difference in functional outcome such as mobility and muscle force was detected.

**Adverse Effects of Bisphosphonate Treatment**

Initially, there was a great deal of concern that bisphosphonates might affect growth, but no such effect has been detected in children with moderate to severe OI [Astrom and Soderhall, 2002; Zeitlin et al., 2003b]. Nevertheless, the main drawback of bisphosphonate treatment in growing individuals is that the long-term consequences of the treatment are unknown. Bisphosphonates are buried in the skeleton where they have a half-life of many years [Khan et al., 1997]. It is therefore possible that adverse effects may appear after a long time. This is a potential concern when bisphosphonate

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**TABLE I. Publications Describing the Overall Effect of Bisphosphonate Therapy in Osteogenesis Imperfecta**

<table>
<thead>
<tr>
<th>Article</th>
<th>N</th>
<th>Age at start (years)</th>
<th>Follow up time (years)</th>
<th>Stated criteria for starting treatment</th>
<th>Bisphosphonate used</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glorieux et al. [1998]</td>
<td>30</td>
<td>3–16</td>
<td>1.3–5.0</td>
<td>Severe OI (severe osteopenia)</td>
<td>Pamidronate iv</td>
<td>Observational</td>
</tr>
<tr>
<td>Astrom and Soderhall [2002]</td>
<td>28</td>
<td>0.6–18</td>
<td>2–9</td>
<td>1: Severe OI (short stature, and skeletal deformities, and pain), or 2: Moderate OI (compression fractures of vertebral bodies)</td>
<td>Pamidronate iv</td>
<td>Observational</td>
</tr>
<tr>
<td>Adami et al. [2003]</td>
<td>46</td>
<td>22–48</td>
<td>1.0–2.0</td>
<td>All OI patients of any type</td>
<td>Neridronate iv</td>
<td>Controlled</td>
</tr>
<tr>
<td>Sakkers et al. [2004]</td>
<td>34</td>
<td>3–18</td>
<td>2.0</td>
<td>Documented OI with restricted ambulation</td>
<td>Olpadronate oral</td>
<td>Controlled</td>
</tr>
<tr>
<td>Arikoski et al. [2004]</td>
<td>26</td>
<td>3.2–15.5</td>
<td>1.0</td>
<td>Moderate to severe OI</td>
<td>Pamidronate iv</td>
<td>Observational</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Munns et al. [2005]</td>
<td>29</td>
<td>0.5–1.9</td>
<td>3.0</td>
<td>1: Long-bone deformities, or 2: More than three fractures</td>
<td>Pamidronate iv</td>
<td>Historical controls</td>
</tr>
<tr>
<td>Gatti et al. [2005]</td>
<td>64</td>
<td>6–11</td>
<td>3.0</td>
<td>NA</td>
<td>Neridronate iv</td>
<td>Controlled</td>
</tr>
</tbody>
</table>

Only reports containing more than 20 patients are listed.

N, number of OI patients included in the report; NA, information not available.
treatment is given to girls and premenopausal women, as an adverse effect on future pregnancies cannot be ruled out categorically [Munns et al., 2004a].

Antiresorptive drugs such as bisphosphonates can interfere with bone modeling (shaping) during growth [Rauch et al., 2003a,b]. 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 3 years and who developed abnormally shaped long-bone metaphyses [Whyte et al., 2003]. Bisphosphonates inevitably decrease the activity of bone remodeling, which can lead to the accumulation of growth plate residues within trabecular bone tissue [Rauch et al., 2002; Whyte et al., 2003]. Calcified cartilage has a high mineral density and therefore contributes to increase densitometric results, but is less resistant to fractures than is normal bone. Low remodeling activity might also delay bone healing after injury. In fact, pamidronate treatment delayed the healing of osteotomy sites after intramedullary rodding procedures [Munns et al., 2004b]. This can lead to pain and fracture at the affected site and may necessitate further surgical procedures.

Who Should Receive Bisphosphonates?

Most reports on bisphosphonate treatment in children and adolescents with OI state that this treatment was offered only to patients who had long-bone deformities, vertebral compression fractures, and frequent fractures. Treatment decisions thus appear to be dictated by clinical severity rather than collagen mutations status, bone mineral density, or OI type. However, some investigators feel that a low areal bone mineral density reading alone provides sufficient arguments to commencement bisphosphonate therapy in children and adolescents with OI [Batch et al., 2003]. Yet, 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, because their functional status is better even without treatment. In our view, bisphosphonate therapy is not justified in children with mild forms of OI until a clearer picture of the long-term risks emerges.

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Regarding the best age for treatment, it appears logical to start therapy as early as possible in order to optimize the developmental potential. Indeed, promising results were reported in a small group of patients who received pamidronate in the first 2 years of life [Munns et al., 2005]. 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 [Rauch and Glorieux, 2004]. The effect of bisphosphonates on the skeleton is clearly growth-dependent [Rauch et al., 2002]. 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 [Adami et al., 2003; Shapiro et al., 2003]. In the larger of these studies, intravenous neridronate induced a significant increase in areal bone mineral

Figure 1. Lateral lumbar spine radiograph of a boy with OI type III who started pamidronate treatment at 6 years of age. Left panel: At start of treatment. All lumbar vertebral have sustained compression fractures. Right panel: After 18 months of pamidronate treatment. Reshaping is evident in all vertebral bodies. The bone mineral content of lumbar vertebra 1–4 has increased by 238% compared to the start of treatment.
density at the spine and at the hip and, more surprisingly, led to a larger cross-sectional bone area at the radial diaphysis [Adami et al., 2003; Gatti et al., 2005]. The incidence of fractures was significantly lower during than before neredronate treatment.

**How Long Should Bisphosphonate Treatment be Given?**

Given the fact that the long-term consequences of the treatment are unknown, it appears desirable to limit the exposure of young OI patients to pamidronate. Also, the treatment effect appears to become less evident with increasing duration of therapy. For example, the age-specific z-score for lumbar spine areal bone mineral density increased by 2.0 during the first 2 years of treatment, but only by 0.6 between 2 and 4 years of treatment [Rauch et al., 2003b]. 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 (Ref [Rauch et al., 2002] and unpublished observations).

Yet, it is unclear at present whether bisphosphonate treatment should be discontinued after a given period of time or whether, for instance, it would be preferable to continue with a lower dose of the drug. This topic needs to be addressed in future studies.

**OTHER MEDICAL THERAPIES**

Growth hormone has long been proposed as a possible treatment for OI [Kruse and Kuhlencordt, 1975]. A few studies suggest that growth hormone treatment may accelerate short-term height velocity in some patients [Antoniazzi et al., 1996; Vieira et al., 1999; Marini et al., 2003]. Calcium kinetic studies after 1 year of growth hormone therapy revealed that bone turnover had increased, but that calcium retention was unchanged compared to the pretreatment situation [Vieira et al., 1999]. Increased bone turnover during growth hormone therapy was also found in histomorphometric studies of iliac bone samples [Marini et al., 2003]. As bone turnover is already abnormally high in untreated children with OI [Rauch et al., 2000], further stimulation does not appear to be a desirable goal. Possibly, growth hormone would be more useful in combination with bisphosphonate therapy, but this remains to be tested.

Parathyroid hormone is a potent bone anabolic agent and has been shown to reduce the fracture incidence in postmenopausal osteoporosis [Delmas, 2002]. These results made parathyroid hormone look like an attractive candidate for treating children with OI. However, a substantial proportion of young rats receiving parathyroid hormone subsequently developed osteosarcoma [Vahle et al., 2002]. It cannot be excluded that a similar effect could happen in humans. Thus, parathyroid hormone should probably not be used in children until these issues have been resolved.

**POTENTIAL FUTURE THERAPIES**

Currently available medical treatment options at best achieve symptomatic improvement of OI. The only hope for actually curing the disease is by eliminating the mutated gene or the gene product. Unfortunately, there are major obstacles to gene-based therapy of OI. The majority of severe OI cases result from the presence of abnormal collagen molecules. Thus, it is not sufficient to replace a missing protein, as is the case in many recessive enzyme disorders. Rather, it is necessary to first inactivate the mutant allele and then substitute for...
its product [Niyibizi et al., 2004; Millington-Ward et al., 2005].

Current research is still grappling with the first of these two tasks. Some investigators have tested so-called hammerhead ribozymes, small RNA molecules that can cut mRNA in the absence of protein cofactors [Millington-Ward et al., 2005; Peace et al., 2005]. More recently, short interfering RNAs have been evaluated as a means to downregulate the expression of the defective collagen allele [Millington-Ward et al., 2004]. Another approach is to disrupt gene expression by inserting a targeting vector through homologous recombination [Chamberlain et al., 2004]. When mesenchymal stem cells from two OI patients were treated in that manner, they retained their ability to differentiate into osteoblasts and produce bone. The quality of the bone thus formed was better than that of untreated cells from the same patients [Chamberlain et al., 2004]. Such results are encouraging. However, until now these techniques have been able to “treat” cells in culture systems, but have not been shown to improve the course of OI in whole organisms.

Rather than trying to modify the molecular defect within osteoblasts, it is conceivably easier to put normal cells in the place of disease carrying ones. This is the idea underlying the transplantation of mesenchymal stem cells. Indeed, when marrow stromal cells from wild-type mice were introduced systemically into irradiated OI mice, a small increase in collagen content was detected in bone 1 month after the infusion [Pereira et al., 1998].

These results formed the rationale for performing bone marrow transplantation in a small group of children with severe OI [Horwitz et al., 1999, 2001]. Although some transplanted cells were detected in the bone marrow of the recipients, it is unclear whether these patients derived any benefit from the procedure. Similar results were found when the same patients were retreated with isolated marrow stromal cells [Horwitz et al., 2002]. Clinical benefit was claimed, based mainly on increased growth velocity in the 6 months following the procedure. However, this widely cited piece of data will hardly convince anyone who has tried to measure short-term growth velocity in children with bone deformities. In a further case, marrow stromal cells were infused into the umbilical vein of a fetus with severe OI [Le Blanc et al., 2005]. A few months after birth a small number of surviving cells were detectable in the bone marrow, but again, the clinical benefit for the patient was not obvious.

CONCLUSIONS

The recent advent of bisphosphonate therapy has brought clear improvements to the lives of children and adolescents suffering from moderate to severe OI. However, this form of treatment does not constitute a cure, but rather is an adjunct to physiotherapy, rehabilitation, and orthopedic care. The case for bisphosphonate treatment during growth is less strong in mildly affected patients who have a good functional status even without treatment. Uncertainty about long-term side effects remains a concern when any bisphosphonate is used in growing individuals. Medical treatment other than bisphosphonates are of minor clinical importance at present. Gene-based therapy offers the hope for a curative treatment of OI, but still remains in the early stages of preclinical research. New therapeutic avenues in severe OI will have to be evaluated against the results obtained with bisphosphonates.

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