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PEDIATRICS (M LEONARD AND L WARD, SECTION EDITORS)

Osteogenesis Imperfecta: Diagnosis and Treatment

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Abstract Osteogenesis imperfecta (OI) is a genetic bone fragility disorder characterized by low bone mass, skeletal deformity, and variable short stature. OI is predominantly caused by dominant mutations affecting type 1 collagen synthesis, with a number of other genes implicated in OI over recent years. The clinical severity of OI can vary greatly, even within families who share a common mutation. Optimal management of OI requires a multidisciplinary approach involving pediatrician, endocrinologist (bone and mineral physician), rehabilitation specialist, orthopedic surgeon, dentist, geneticist, social worker/psychologist, physiotherapist, and occupational therapist. Bisphosphonate therapy remains the mainstay of medical treatment in OI and has been shown to decrease bone pain, enhance well-being, improve muscle strength and mobility and decrease fracture incidence. Novel therapies are beginning to emerge as more is understood about the signaling pathways involved in bone formation. The following summarizes the diagnosis, genetic heterogeneity and management of OI in pediatric practice.

Keywords Osteogenesis imperfecta · Bisphosphonates · Bone fragility · Fractures

Introduction

OI is characterized by increased bone fragility and decreased bone mass. There is significant variability in the clinical features and severity within OI, with presentation at any age from intrauterine life to adulthood. The extreme variability in OI results in part from genetic and biochemical heterogeneity. The diagnosis can be straightforward when there is a positive family history and the typical features of blue sclera, fractures and Wormian bones of the skull. However, a definitive diagnosis can be more difficult on clinical grounds alone in milder cases that lack these features and it is not uncommon for mildly affected adults to only be identified when their affected child presents with fractures. Some of the severe forms of OI eg, OI type VI, may also lack the classical phenotypic features of OI and, therefore, cause diagnostic difficulties. The classical features associated with OI can include joint hypermobility, hearing impairment, progressive skeletal deformity, basilar invagination, and brittle teeth (dentinogenesis imperfecta).

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Classification

Various classification systems have been proposed to describe the heterogeneity of OI. In 1979, Sillence proposed a classification of OI types I–IV based on clinical findings with radiological subclassification [1]. OI type I is the most common and mildest form of OI, and is characterized by distinctively blue sclera that persist into adulthood. Patients with OI type I tend to obtain a normal final height and have minimal if any long-bone or spinal deformity. Recurrent fracture can, however, cause significant and permanent disability if optimal orthopedic and medical management is not undertaken. Abnormal tooth dentin development, resulting in dentinogenesis imperfecta, is occasionally seen in OI type I. If present, the teeth are susceptible to breaking and cavities and children should undergo six-monthly dental reviews. OI type I is classically due to a reduction in the amount of collagen type 1 protein (quantitative deficiency) resulting from a stop, splice site, or frameshift mutation in *COL1A1* or *COL1A2*. Bisphosphonate therapy is most effective in a growing child, and, therefore, it tends to improve bone density readings in patients with OI type I where bone growth is not impaired. Hearing loss increases with age so adults require regular assessment.

OI type II is the most severe form of OI. It is perinatally lethal with very few reports of long-term survival. Neonates with OI type II present with multiple fractures, marked bone deformities, and significant respiratory distress from pulmonary hypoplasia. Skeletal survey reveals short, broad long-bones (sometimes described as 'crumpled') and multiple rib fractures that give the ribs a beaded appearance. Bisphosphonate therapy may improve bone fragility, but long-term survival is determined by the severity of the pulmonary hypoplasia. Both quantitative and qualitative defects in type 1 collagen have been described in OI type II, many of which involve glycine substitutions.

OI type III is the most severe form of OI that is associated with long-term survival. Patients with OI type III often sustain multiple in utero fractures that are detectable on antenatal ultrasound scan. Neonates, therefore, have multiple long-bone, rib fractures and limb deformities at birth. Despite multiple fractures, the neonatal x-rays of a child with OI type III tend not to show the crumpled long-bones and beaded ribs of a child with OI type II. Differentiating between these two types of OI can however be difficult with the clinical course determined by the underlying respiratory status of the child. Other features of OI type III include blue/grey sclera, triangular facies, and dentinogenesis imperfecta. A great majority of children with OI type III will have short stature and without a coordinated medical and orthopedic treatment program, will be wheelchair dependent from a young age. These children have ongoing bone fragility throughout life, which often results in limb and spinal deformities. As with OI type II, these children often have glycine substitutions in type 1 collagen resulting in a qualitative defect in the collagen protein.

OI type IV is characterized by bone fragility without the typical features of the type I phenotype (i.e. blue sclera and deafness). Fractures may present at any age and a majority of these patients have short stature. A small proportion experiences a severe, progressive lower limb deformity rather than recurrent fractures. Dentinogenesis imperfecta is variable but when present is associated with a greater frequency of fractures. Inheritance is autosomal dominant with mutations in *COL1A1* and *COL1A2*.

Genetic and Phenotypic Heterogeneity

The original Sillence classification was later extended to distinguish the above OI subtypes from those with noncollagen mutations and differential clinical findings [2]. OI type V was the first noncollagen OI type to be identified and mutations of the *IFITM5* gene have recently been shown to cause this autosomal dominant form of OI [3•]. Classically, patients have a distinctive phenotype with moderate to severe bone fragility, although family studies have shown the phenotype is variable [3•]. The hallmark of this subtype is the presence of hypertrophic callus formation and early calcification of the interosseous membrane between the bones of the forearm, which limits pronation and supination. Radial head dislocation can be identified from a young age and predates interosseous membrane calcification. Scleral color is normal. Upon histologic examination, the lamellar organization of the bone has an irregular mesh-like appearance, clearly distinct from the normal lamellar organization seen in OI types I and IV [4].

OI type VI clinically resembles other forms of moderate to severe OI but has a characteristic "fish-scale" pattern of bone lamellation on bone histology [5]. Children with OI type VI have severe long-bone and spine fragility, but lack blue sclera, dentinogenesis imperfecta, and Wormian bones of the skull. Mutations in *SERPINF1* have been shown to cause this subtype of OI [6•] and alkaline phosphatase may be elevated. In addition to the fish-scale pattern noted above, bone histomorphometry shows frank osteomalacia (in the absence of rickets), and so not surprisingly they have "looser zones" (the radiographic signs of bone fragility) of the scapula, ribs, and long bone shafts. There is evidence suggesting that response to bisphosphonate therapy, particularly gains in mobility scores and reductions in fracture incidence are less than in other types of OI [7].

OI type VII is a rare autosomal recessive condition that was described in the First Nations community in northern Quebec [8]. It is caused by mutations in *CRTAP* [9] and is associated with a moderate to severe phenotype involving fractures from birth, bluish sclera, early lower limb deformity, coxa vara, and osteopenia. Rhizomelia (proximal limb disproportion) is a prominent clinical feature that distinguishes this form of OI.

LEPRE1 [10•] (OI type VIII) and *PPIB* [11•] (OI type IX) are involved in the triple helix folding of type 1 collagen and result in a severe phenotype with autosomal recessive inheritance. Additional genes implicated in an OI phenotype include *SERPINH1* [12•], *SP7* [13•], *WNT1* [14•], *PLS3* [15•], *BMP1* [16•], *PLOD2* [17], *TMEM38B* [18•], and *FKBP10* [19•]. Of particular note, *FKBP10* mutations have been associated with significant pelvic abnormalities (protrusio acetabuli). Although the list of causative genes and OI subtypes has expanded over recent years [2], there has been a recent move to reduce the classification to five distinct subtypes based on phenotype only (Table 1) [20].

The vast majority of Europeans with OI have mutations in *COL1A1* or *COL1A2* [21] whereas other populations (eg, Southern Asian or Samoan) have mutations in other genes as a cause of their OI [22]. Collagen type I has a triple helical structure consisting of two $\alpha 1$ and one $\alpha 2$ chains and in order for the triple helix to fold correctly, every third amino acid residue must be a glycine. The remaining amino acids are predominantly proline and hydroxyproline residues [21]. Genotype-phenotype correlations in OI, using *COL1A1* and *COL1A2* mutation analysis, have not been forthcoming. However, a general principle has been that mutations resulting in a

Table 1 Classification of OI illustrating five clinically distinct phenotypes

Type	Phenotype	Gene	Inheritance
I	Nondeforming OI with blue sclera.	COL1A1	AD
		COL1A2	AD
II	Perinatally lethal OI.	COL1A1	AD
		COL1A2	AD
		CRTAP	AR
		LEPRE1	AR
		PPIB	AR
III	Progressively deforming.	COL1A1	AD
		COL1A2	AD
		CRTAP	AR
		LEPRE1	AR
		PPIB	AR
		BMP1	AR
		FKBP10	AR
		PLOD2	AR
		SERPINF1	AR
		SERPINH1	AR
		TMEM38B	AR
		WNT1	AR
		CREB3L1	AR
IV	Common variable OI with normal sclera	COL1A1	AD
		COL1A2	AD
		WNT1	AD
		CRTAP	AR
		PPIB	AR
		SP7	AR
		PLS3	XL
V	OI with calcification of interosseous membranes	IFITM5	AD

AD autosomal dominant, *AR* autosomal recessive, *XL* X-linked.

quantitative defect in collagen type I production result in a milder phenotype compared with those that result in a qualitative defect [23]. With the introduction of next-generation sequencing techniques, a number of additional genes have been identified, which cause autosomal recessive forms of OI (see above). Some of these genes are involved in type I collagen trafficking and, therefore, indirectly affect type I collagen.

Disruption of collagen effects the mineral phase of OI bone: It is known that human OI bone has a higher material density than normal bone and that a murine model of OI (OIM mouse) has smaller and less well-aligned mineral crystals than its wild-type counterpart [24]. OI bone is brittle because of the combination of these abnormal organic (collagen) and inorganic (mineral) properties. Histomorphometric analysis of OI bone has shown a decrease in cortical thickness, core width, trabecular number, and trabecular thickness [25]. The net bone formation rate in OI is increased despite individual osteoblasts producing less bone. This is achieved by an increase in the total number of osteoblasts. Osteoclast activity is also increased so there is no overall gain in bone mass. OI bone is therefore in a high turnover state as reflected by an increase in markers of bone resorption (deoxypyridinoline and N-telopeptide) and bone formation (alkaline phosphatase, osteocalcin, and P1NP). The reduction in core width seen on trans-iliac bone biopsy illustrates that OI bone is thinner and more prone to fracture.

Management of Osteogenesis Imperfecta

Clinical management of OI requires a multidisciplinary approach involving pediatrician, endocrinologist (bone and mineral physician), rehabilitation specialist, orthopedic surgeon, dentist, geneticist, social worker/psychologist, physiotherapist, and occupational therapist. This list of health professionals is not exhaustive and highlights the multifaceted approach required for optimal management of children with OI. The aim of OI management is to maximize motor function and therefore improve functional outcome. Bisphosphonate therapy remains the mainstay of medical treatment in OI, the benefits of which complement the rehabilitation and surgical aspects of management. Novel therapies eg, RANKL antibodies, are also being explored for their use in OI.

Bisphosphonate Therapy

Bisphosphonates are synthetic analogues of naturally occurring inorganic pyrophosphates which act by inhibiting osteoclast function [26]. Their basic structure is a phosphate-carbon-phosphate bond that results in a very stable compound. Once administered, bisphosphonates avidly bind to the hydroxyapatite crystals of bone and are quickly removed from general circulation. They therefore, have a short plasma half-life but comparatively longer functional half-life as they are directly incorporated into bone mineral. As the bone is resorbed by osteoclast activity, the bisphosphonate is released and can act locally. Bisphosphonates inhibit the differentiation of osteoclast precursors and induce apoptosis of osteoclasts [27]. Newer bisphosphonates, such as pamidronate and zoledronate, also inhibit the mevalonate pathway of cholesterol synthesis and prevent post-translational prenylation of small guanosine triphosphate-binding proteins in osteoclasts [28].

Pamidronate and zoledronate are the most widely used intravenous bisphosphonates in children with OI, with zoledronate being about 850 times more potent [29]. Zoledronate has a high affinity for bone and has a hundred-fold bone concentration compared with plasma. Adult studies have shown that the effects of zoledronate are also longstanding with only a slight decline after 6 months [30].

The use of bisphosphonates has been well established in adult patients for treatment of osteoporosis, Paget disease of bone, myeloma, hypercalcaemia and bone metastases. Its use

in children is relatively more recent but bisphosphonate therapy is now the mainstay of medical treatment for OI [31]. The aim of treatment in OI is to reduce fracture frequency, maximize mobility and improve functional outcomes [32]. The use of bisphosphonates to treat OI was first described in a case report in 1987 [33]. A 12-year-old girl with OI was treated with oral pamidronate. The dosing regimen comprised 250 mg daily for 2 months alternating with 2 months of abstinence for a total duration of 1 year. She showed a 33 % increase in lumbar spine bone mineral content by dual photon densitometry but still went on to sustain at least two low-trauma fractures within the following year. The first systematic assessment of bisphosphonates in OI was undertaken over a decade later when the effects of cyclic intravenous pamidronate were investigated in 30 children with severe OI [34].

In children with OI, intravenous pamidronate has been shown decrease bone pain, improve mobility and muscle strength, increase cortical thickness and vertebral size with vertebral reshaping, increase bone mass and bone mineral density, and decrease fracture incidence [34, 35]. Cyclical intravenous pamidronate has also been used in babies and infants with OI in order to prevent deformity and promote normal growth [36]. In this younger group, the response to treatment was greater than older children and there was also an improvement in the time taken to achieve gross motor milestones [37••]. Histomorphometric analysis of transiliac bone biopsy samples, has allowed the actions of pamidronate in children with OI to be investigated [38]. Pamidronate has been shown to increase cortical thickness and trabecular number and significantly reduce bone turnover below control values. Adults with OI have also shown positive effects with pamidronate therapy resulting in increased spine and hip areal bone mineral density and decreased fracture rates [39]. The changes seen in bisphosphonate-treated children are significantly greater than adults, suggesting that bisphosphonate therapy should be started during childhood to obtain maximal benefit through bone growth and thereby a positive impact of bisphosphonates on skeletal modelling. A prospective randomized trial of 23 children with OI was carried out to determine the dosage, efficacy, and safety of zoledronate compared with pamidronate [40]. Zoledronate can be given more rapidly and it has a longer biological half-life resulting in a longer dosing interval compared with other bisphosphonates. There was a similar response in terms of improvements in bone density and reported quality of life. However, there was an increase in fracture frequency in the zoledronate group, possibly due to the inclusion of children with more severe OI. There are no long-term data on the outcome of Zoledronate treatment in OI.

As mentioned above, the primary aim of bisphosphonate treatment in OI is to reduce fracture frequency in order to maximize mobility. The best possible functional outcome is the ability to walk, and bisphosphonates (along with appropriate long bone rodding surgery) have revolutionized this aspect of patient management, particularly in those with moderate to severe disease (Figs. 1 and 2).

A number of recent studies have assessed the use of oral bisphosphonates in the treatment of OI. In a placebo-controlled trial of 34 patients, olpadronate increased lumbar spine bone mineral density, but did not improve muscle strength, mobility, function, or vertebral height [41]. A randomized controlled study of 26 patients with OI type I showed that oral risedronate improved spine bone density and decreased bone turnover but did not alter bone biopsy findings [42]. A multicenter, double-blind, randomized, placebo-controlled trial of 139 patients looked at the effects of alendronate in children with moderate to severe OI. This study showed that while there was an improvement in bone density and decrease in bone turnover, there was no change in fracture rate, bone pain, vertebral height, iliac cortical width, or physical activity with treatment [43]. A large multinational placebo-controlled trial of 147 patients evaluated oral risedronate in children with generally milder OI. This study showed an increase in areal bone mineral density and reduction in overall long-bone fracture frequency [44••]. However, there were continued vertebral fractures in the risedronate group during treatment. These data would suggest that oral bisphosphonates should not be used in favor of intravenous bisphosphonates in the early treatment of children with moderate to severe OI. Oral therapy may be of benefit as initial therapy in mild OI to reduce the frequency of extremity fractures. Further studies are needed before this can be established as best-practice and monitoring for subsequent vertebral collapse is required for all patients on oral bisphosphonate therapy.

Bisphosphonate therapy has revolutionized the medical management of children with OI, but there is no consensus on an optimum treatment regimen. Intravenous bisphosphonates are commenced when faced with the clinical setting of low-trauma fractures rather than isolated reductions in bone mineral density. As a general rule, treatment is commenced in children with moderate-to-severe OI or in children with less severe OI if they sustain two or more long-bone fractures in a 12-month period or have significant vertebral compression fractures. There are a number of different treatment regimens used, with pamidronate doses of approximately 9 mg/kg/year and zoledronate doses of approximately 0.1 mg/kg/year. These doses are usually continued for 3–4 years until there are improvements in pain, mobility, vertebral shape, and fracture frequency. Longer duration may be indicated in severe OI. If bisphosphonate therapy is discontinued, there is minimal effect on the new bone produced following growth and modelling [45]. It would appear necessary therefore to continue children with OI

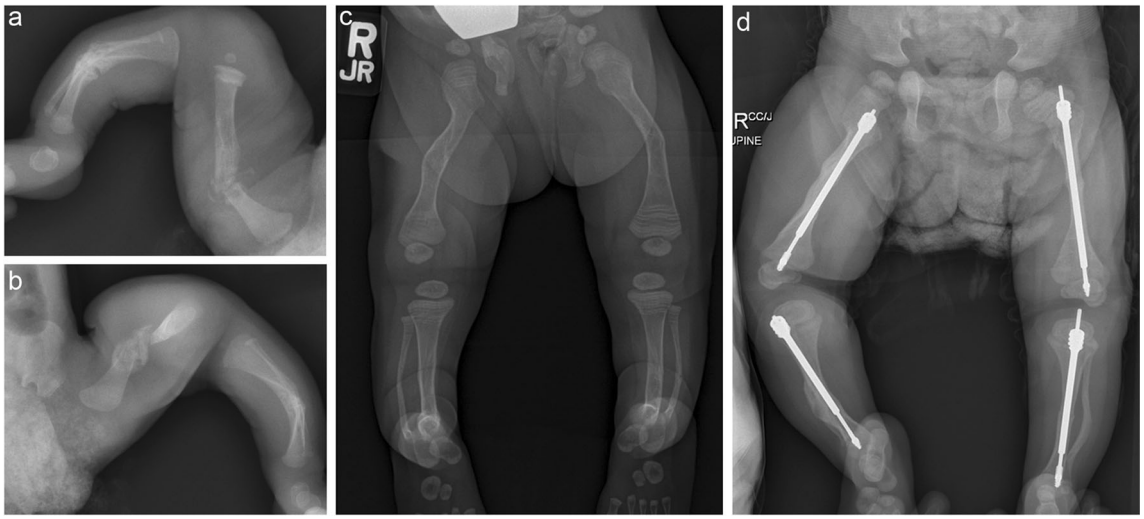

Fig. 1 Improvements in the appendicular skeleton following bisphosphonate treatment. Multiple fractures in the neonatal period of **a** right leg and **b** left leg in a child with moderate-severe OI. Cyclical intravenous bisphosphonate therapy aided fracture prevention and allowed linear growth (**c**). Note sclerotic bisphosphonate treatment lines, particularly in distal femur and proximal tibia. The bisphosphonate-treated bones were more amenable to orthopedic intervention allowing the insertion of Fassier-Duval telescopic rods (**d**) resulting in the ability to mobilize independently

on a 'maintenance' bisphosphonate regimen following the initial treatment phase. The best maintenance regimen is uncertain but is likely to be around 30 % of the acute treatment dose [46]. Oral bisphosphonate therapy may be an alternative to IV bisphosphonates as maintenance treatment. Further collaborative studies are required to determine the optimal treatment regimen in the management of children with OI.

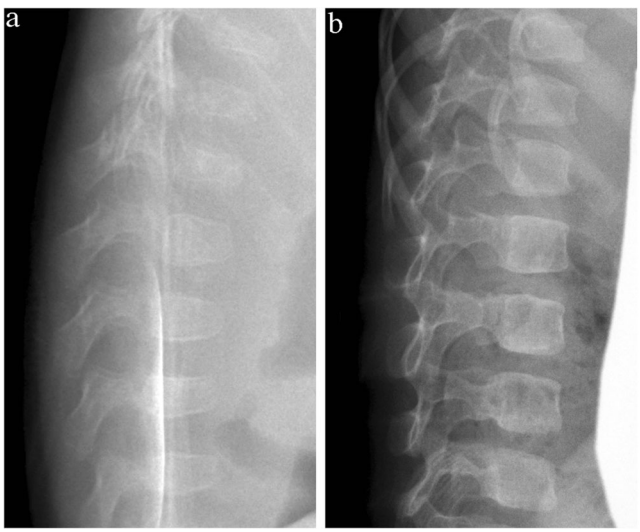

Fig. 2 Improvements in the axial skeleton following bisphosphonate treatment. Lateral thoracolumbar spine radiograph showing generalized osteopenia and anterior wedging of all lumbar vertebral bodies in a 3-month old with moderate-severe OI (**a**). Improvements in osteopenia and vertebral morphology were evident following 1 year of bisphosphonate therapy (**b**)

Side Effects and Complications of Bisphosphonate Therapy

There have been numerous reports of serious adverse effects associated with bisphosphonate therapy in adults [47]. These include acute systemic inflammatory reactions, ocular complications, renal failure, nephrotic syndrome, electrolyte abnormalities, and osteonecrosis of the jaw. By far the most frequent adverse effect seen in children is an acute-phase reaction following the first dose. This typically includes fever, nausea, diarrhea, malaise, muscle, and bone pain. These symptoms begin 24–48 hours following the initiation of treatment and rarely recur with subsequent doses [48]. This appears to be mediated by T-cell release of interferon gamma and tumor necrosis factor [49]. These side effects can be minimized by the administration of acetaminophen (paracetamol) or the anti-inflammatory medication Ibuprofen [50]. Serum calcium levels drop with each dose of bisphosphonates, particularly after the first dose, making it necessary to monitor calcium levels following the first infusion [51]. If however, that patient is vitamin D replete and has a normal dietary calcium intake, the hypocalcaemia is usually self-remitting.

Severe respiratory distress has been described in children with severe OI and pre-existing respiratory compromise [52]. The precise etiology of this is uncertain, but highlights the underlying fragility of neonates and infants with severe OI and the necessity for close monitoring during bisphosphonate treatment.

Animal studies have shown that bisphosphonates given in high doses can suppress growth and this has led to concerns of growth failure in children. Despite these concerns, the effect

of pamidronate in the prevention of limb and spine deformity has been shown to improve growth in patients with moderate to severe OI (compared with historical controls) over a 4-year treatment period [53]. Weight gain has also been reported in children with severe OI [53].

Pamidronate markedly suppresses bone turnover in children with OI [38] and at high doses it can interfere with bone modelling to cause an undertubularization of long-bones. Acute suppression of bone turnover at the growth plate leads to an accumulation of mineralized cartilage within the bone, therefore, increasing bone density [54]. This leads to the characteristic sclerotic metaphyseal lines (horizontal trabeculae) seen on long-bone radiographs of children that may act as a stress riser for subsequent fractures [55] (Fig. 1). Pamidronate therapy has also been associated with delayed healing of osteotomy sites after intramedullary rodding procedures [56] but multivariate analysis did not show a significant delay in healing after fractures. However, when children with OI sustain a fracture and are due a scheduled bisphosphonate dose, the general pragmatic approach is to delay treatment until there is radiological evidence of callus formation.

Bisphosphonate related osteonecrosis of the jaw (BRONJ) has emerged as a major issue in adult patients treated with high dose or potent bisphosphonates, but to date, there has been no report of osteonecrosis of jaw in children. BRONJ is characterized by painful, nonhealing jaw wounds that occur either spontaneously or following a dental procedure such as tooth extraction. It does not appear to occur following normal loss of deciduous teeth in children. A study of 278 patients treated with intravenous pamidronate during childhood or adolescence did not exhibit jaw osteonecrosis [57]. Current clinical practice varies but a pragmatic approach is for all children to undergo dental review and have necessary extractions and reparative work undertaken prior to starting bisphosphonate treatment. This is then followed by annual review by a pediatric dentist. There are no data to guide recommendations on timing of dental extractions once bisphosphonate treatment has commenced. A suggested approach is for all children to have a dental review before starting bisphosphonate treatment and for dental procedures to be undertaken prior to the start of treatment [58••]. Once on bisphosphonate therapy teeth should be preserved where possible, but if extraction is required to undertake this as late in the treatment cycle as possible with primary closure of the gingiva, allowing at least 3 weeks for healing before the next bisphosphonate dose [58••].

Bisphosphonates should only be used under extenuating circumstances during pregnancy, with many centers insisting that all females of reproductive age have a negative pregnancy test before each bisphosphonate treatment cycle or before commencing oral bisphosphonates. Because bisphosphonates persist in mineralized bone for many years, concern has also been expressed that bisphosphonates administered before conception could be released from the maternal skeleton during the pregnancy and affect the fetus [59]. Reports have been published of two women with OI who became pregnant after 5 years of pamidronate therapy. No pamidronate was administered following conception. Both pregnancies went to term and there were no maternal complications noted. It could not be excluded however, that the adverse events noted in the babies, hypocalcaemia and talipes equinovarus, were related to maternal pamidronate therapy [60]. There has been no conclusive report to-date that bisphosphonate therapy during pregnancy has been detrimental to fetal development [61]. Clearly, further systematic follow-up of pregnancy outcome in this cohort is required and females should be counselled about the uncertainty surrounding this aspect of bisphosphonate treatment.

Rehabilitation and Physical Therapy

In order to maximize function and prevent fractures a multidisciplinary rehabilitation program is required. The phenotypic diversity of OI dictates a personalized approach to rehabilitation and physical therapies, starting with a comprehensive assessment of gross and fine motor function. Goals and treatment strategies are personalized and generally address motor development, strength, joint contractures, and mobility [62]. The use of orthotics can also be useful in optimizing mobility [63]. A 4-year follow-up study of rehabilitation in OI showed an increase in self-care and social function with all types of OI but mobility level plateaued in moderate-severe OI [64]. Preliminary data on the use of whole body vibration in severe OI suggested functional benefit with this treatment modality [65]. The objectives of rehabilitation and physical therapy can change with time as the focus shifts from obtaining motor milestones to optimization of learning at school.

Orthopedic Surgery

Advances in orthopedic surgical techniques, particularly the use of intramedullary telescopic rods, have made a significant impact on the surgical management of OI (Fig. 1). This approach has helped with maintaining function and managing fracture recurrence. Orthopedic intervention in combination with bisphosphonate therapy has resulted in improvements in patient mobility [66].

Complications specifically arising from the use of telescoping rods (eg, Fassier-Duval) include rod migration into the joint space and the rod pulling out of metaphyseal bone and no longer extending [67]. However, these rods can be inserted without having to perform complete osteotomies which results in minimal trauma, faster healing, and quicker recovery for early rehabilitation [68]. A coordinated approach to the timing of orthopedic surgery and bisphosphonate administration is

required to minimize the risk of delayed osteotomy healing [56]. A pragmatic approach is to withhold the next dose of bisphosphonate after orthopedic surgery until there is radiological evidence of callus formation at the osteotomy site. Many centers take a similar approach following a fracture, although this is not always possible given the fracture frequency and the symptoms of a child.

Orthopedic management may also be required in the treatment of scoliosis in patients with OI [69]. Combined orthopedic, spinal and neurosurgical input may also be required in the management of basilar invagination although the specific management strategies employed are usually made on a case by case basis. Occipito-cervical repair is technically difficult and is reserved for subspecialized surgeons in expert centers [70].

Psychological Care

The psychological care of the child with OI, and their family, is an important aspect of management that is often overlooked. Reactions of parents, care providers, and siblings of a child with OI vary and this sometimes overwhelming experience requires ongoing support from experienced professionals. For a child with OI, it is also important to consider the psycho-social aspects of this diagnosis on the different developmental stages of childhood and adolescence. A comprehensive plan for transition to adult services is also an important aspect of management. Community-based help groups and societies can provide additional support for patients and their families and are often valuable adjuncts to medical care [71].

Novel Therapies on the Horizon

Novel therapies are beginning to emerge as the signaling pathways involved in bone formation are being further elucidated. OI type VI is caused by mutations in *SERPINF1* leading to an activation of osteoclasts via the RANK/RANKL pathway. Patients with this type of OI tend to respond poorly to conventional bisphosphonate treatment. This is probably due to the fact that patients with OI type VI tend to have unmineralized osteoid and bisphosphonates bind to mineralized bone to exert their effect. Denosumab is a RANKL antibody that has been shown to reversibly reduce bone resorption in four children with OI type VI [72•]. The use of sclerostin antibody to stimulate osteoblasts via the canonical Wnt signaling pathway has also been investigated as a novel therapeutic agent. In a murine model of moderate-severe OI, 2 weeks of sclerostin antibody therapy resulted in improved bone mass and reduced long-bone fragility [73]. These therapies represent novel treatment strategies to improve bone mass, reduce fractures and improve quality of life in children with OI.

Summary

The diagnosis of OI remains clinically driven and its optimal management requires the input from a specialized multidisciplinary team. In the vast majority of cases OI is a dominant disorder caused by mutations in one of the type I collagen genes. Recent advances in molecular genetics has increased our understanding of bone development and identified a number of additional genes responsible for the OI phenotype. The use of bisphosphonates has proven to be very effective in the treatment of OI. It has led to a reduction in fracture rate, pain and disability in children with this disorder. Through a multidisciplinary approach and the appropriate use of bisphosphonate therapy, the quality of life for children with OI and their families has been significantly improved. Despite the widespread use of bisphosphonates in the management of patients with OI, there remain a number of unanswered questions. Key areas requiring further elucidation include: the long-term effects of treatment, the optimal treatment regimen to maximize benefit and minimize potential long-term side effects, the use of newer bisphosphonate preparations, and the outcome following cessation of therapy. These issues can only be addressed through the continued systematic evaluation of patients receiving bisphosphonate therapy and ability to obtain long-term follow-up data on these individuals. Animal models of OI and advances in the understanding of the Wnt pathway may lead to the development of new therapeutic strategies. Gene therapy may also permit silencing of mutant alleles to transform a severe form of OI to a milder phenotype [74].

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Compliance with Ethics Guidelines

Conflict of Interest A. Biggin and C. F. Munns declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent All studies by the authors involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

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