Seminar

Osteogenesis imperfecta

Frank Rauch, Francis H Glorieux

Osteogenesis imperfecta is a genetic disorder of increased bone fragility, low bone mass, and other connective-tissue manifestations. The most frequently used classification outlines four clinical types, which we have expanded to seven distinct types. In most patients the disorder is caused by mutations in one of the two genes encoding collagen type 1, but in some individuals no such mutations are detectable. The most important therapeutic advance is the introduction of bisphosphonate treatment for moderate to severe forms of osteogenesis imperfecta. However, at present, the best treatment regimen and the long-term outcomes of bisphosphonate therapy are unknown. Although this treatment does not constitute a cure, it is an adjunct to physiotherapy, rehabilitation, and orthopaedic care. Gene-based therapy presently remains in the early stages of preclinical research.

Osteogenesis imperfecta is a genetic disorder of increased bone fragility and low bone mass. Severity varies widely, ranging from intrauterine fractures and perinatal lethality to very mild forms without fractures.[1] Typical extraskeletal manifestations can be associated variably with the disorder. These include blue sclera, dentinogenesis imperfecta, hyperlaxity of ligaments and skin, hearing impairment, and presence of wormian bones on skull radiographs. Most patients with a clinical diagnosis of osteogenesis imperfecta have a mutation in one of the two genes that encode the α chains of collagen type 1 (*COL1A1* and *COL1A2*).

Diagnosis and classification

Diagnosis

The clinical diagnosis of osteogenesis imperfecta is based mainly on the signs and symptoms outlined above. Traditionally, much emphasis has been laid on the presence or absence of blue sclera and dentinogenesis imperfecta as diagnostic signs of osteogenesis imperfecta. This practice still holds true, but some limitations should be recognised. Dark or bluish sclerae are very typical in healthy infants, and therefore this finding is not of much diagnostic use in this age-group. Dentinogenesis imperfecta is more frequently clinically evident in primary than in permanent teeth of patients with osteogenesis imperfecta.[2] Radiological or histological examinations frequently show abnormalities, even in individuals whose teeth look normal on inspection.[3–5]

Clinically evident hearing loss is rare in the first two decades of life, even though subtle audiometric abnormalities can be recorded in a large proportion of children and adolescents with osteogenesis imperfecta.[6–8] About half of patients older than age 50 years report hearing loss, and an even higher proportion of adults have clearly pathological audiometric findings.[8,9]

Diagnosis of osteogenesis imperfecta is straightforward in individuals with a positive family history or in whom several typical features are present, but can be difficult in the absence of affected family members and when bone fragility is not associated with obvious extraskeletal abnormalities. The uncertainty in such cases is compounded by the fact that there are no agreed minimum criteria that establish a clinical diagnosis of the disorder. In this situation, analysis of the collagen type 1 genes can provide helpful information, which can be done by investigating the amount and structure of type 1 procollagen molecules that are derived from the patient's cultured skin fibroblasts.[10] Alternatively, genomic DNA can be extracted from white blood cells and the coding region of the *COL1A1* and *COL1A2* genes can then be screened for mutations.[11] Both of these approaches are thought to detect almost 90% of all collagen type 1 mutations.[12] A positive collagen type 1 study thus confirms the diagnosis of osteogenesis imperfecta. However, a negative result leaves open the possibility that either a collagen type 1 mutation is present but was not detected or the patient has a form of the disorder that is not associated with collagen type 1 mutations (see below). Therefore, a negative collagen type 1 study does not rule out osteogenesis imperfecta.

Classification

Even though the range of clinical severity in osteogenesis imperfecta is a continuum, categorisation of patients into separate types can be useful to assess prognosis and to help assess the effects of therapeutic interventions. The most widely used classification of osteogenesis imperfecta is by Sillence and colleagues[13] and distinguishes four clinical types. We have further delineated three additional groups of patients who had a clinical diagnosis of the disorder but who presented clearly distinct features (table 1).[14–16] The most

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Genetics Unit, Shriners Hospital for Children and McGill University, 1529 Cedar Avenue, Montréal, Québec, Canada H3G 1A6
(F Rauch MD, Prof F H Glorieux MD)

Correspondence to: Prof Francis H Glorieux
(e-mail: glorieux@shriners.mcgill.ca)

Search strategy and selection criteria

We searched PubMed with the keywords "osteogenesis imperfecta". On June 30, 2003, the database contained 680 such articles that were published in January, 1995, or later. We assessed all these database entries. This Seminar discusses topics where, from the authors' perspective, clinically relevant progress has taken place in recent years. The most important publications dealing with these topics were included in this Seminar. Frequently cited older published work was also taken into account. Articles in English, French, and German were used. As a result of space constraints, important contributions had to be left out if they could not be summarised under the main headings selected by the authors.

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

*May or may not be detectable in a given patient.

Table 1: **Expanded Sillence classification of osteogenesis imperfecta**

relevant clinical characteristic of all types of osteogenesis imperfecta is bone fragility, the severity of which increases in the order type I < types IV, V, VI, VII < type III < type II.

Osteogenesis imperfecta type I includes patients with mild disease and absence of major bone deformities (table 1). However, vertebral fractures are typical and can lead to mild scoliosis. Type II is lethal in the perinatal period, usually because of respiratory failure resulting from multiple rib fractures. Osteogenesis imperfecta type III is the most severe form in children surviving the neonatal period. These patients are of very short stature and have limb and spine deformities secondary to multiple fractures, which can lead to respiratory difficulties—identified as a leading cause of death in this patient group.[17,18] Patients with mild to moderate bone deformities and variable short stature are classified as osteogenesis imperfecta type IV. This last group includes all individuals who are not clearly part of the first three types. From this heterogeneous group we have identified three separate clinical entities on the basis of distinct clinical and bone histological features. These disorders have been named osteogenesis imperfecta type V, VI, and VII.[14–16]

Osteogenesis imperfecta type V is characterised by moderate to severe bone fragility.[15] Heredity seems to follow an autosomal dominant pattern, but we have no evidence of a collagen type 1 abnormality. The interosseous membrane at the forearm becomes calcified early in life. This occurrence severely limits movement of the hand and can lead to secondary dislocation of the radial head. On histological examination, bone lamellation is coarse or mesh-like (figure 1). Importantly, after fractures or surgical interventions, patients with osteogenesis imperfecta type V are predisposed to develop a hyperplastic callus, which can mimic osteosarcoma. MRI and CT can be useful to distinguish these two conditions in unclear cases.[19,20] At our institution, type V disorder has been diagnosed in 16 of 364 (4%) patients with osteogenesis imperfecta who have been assessed in the past 15 years (unpublished data). Brenner and colleagues[21] reported hyperplastic callus formation in ten of their 209 (5%) patients with this disorder. Thus, patients with osteogenesis imperfecta type V seem to constitute between 4% and 5% of individuals with this disorder who are seen in hospitals.

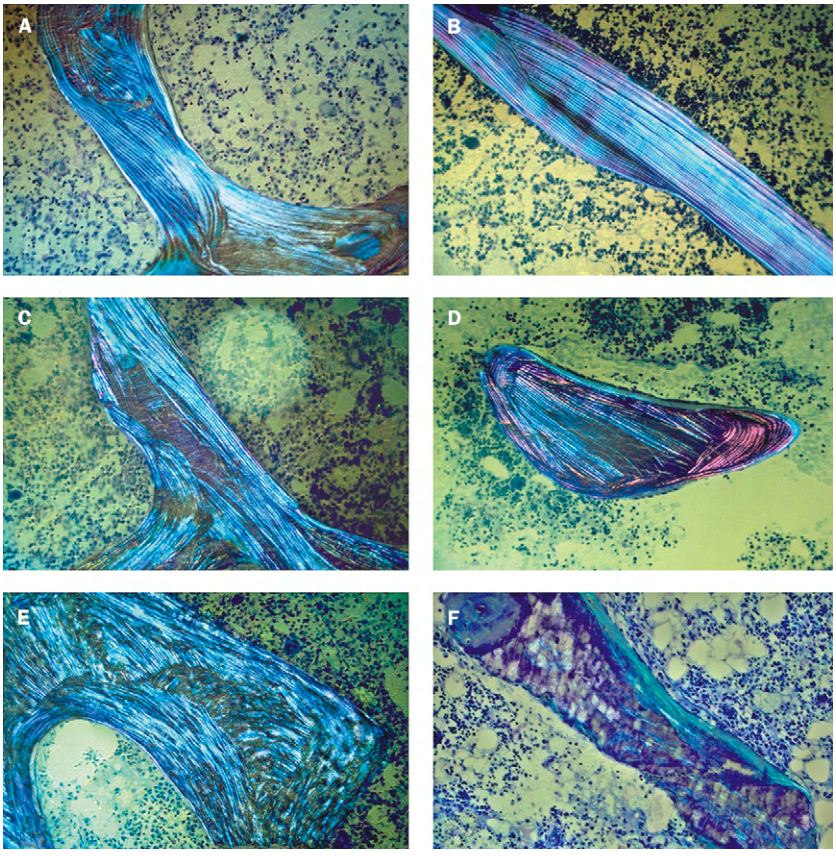

Figure 1: **Bone lamellation pattern as seen under polarised light**
(A) Healthy control. (B) Osteogenesis imperfecta type I; lamellae are thinner than normal, but lamellation is smooth. (C) Osteogenesis imperfecta type III; lamellation is slightly irregular. (D) Osteogenesis imperfecta type IV; lamellation is similar to type III disorder. (E) Osteogenesis imperfecta type V; mesh-like pattern. (F) Osteogenesis imperfecta type VI; fish-scale pattern.

Osteogenesis imperfecta type VI is also a moderate to severe form of the disorder.[14] This type was defined on the basis of bone histological findings, which show a higher amount of osteoid than usual and an abnormal pattern of lamellation (fish-scale; figure 1). These histological abnormalities suggest disordered mineralisation of bone tissue even though concentrations in serum of calcium and phosphorus are normal. Radiological signs of rickets are absent, indicating that mineralisation of the growth plate proceeds normally. The mode of inheritance has not yet been established and collagen type 1 mutation studies are negative.[14] Type VI disorder was diagnosed in eight of 195 patients (4%) with osteogenesis imperfecta who underwent bone biopsy

	Severity of bone fragility/deformity	Characteristics	Inheritance	Genetic defect
Disorder				
Bruck syndrome[24]	Moderate to severe	Congenital joint contractures	Autosomal recessive	Telopeptide lysyl hydroxylase deficiency[25]
Osteoporosis-pseudoglioma syndrome[26]	Moderate	Congenital blindness	Autosomal recessive	*LRP5*[27]
Panostotic fibrous dysplasia[28]	Severe	Cystic or ground-glass lesions in all bones	None (somatic mutation)	*GNAS*[29]
Idiopathic hyperphosphatasia[30]	Severe	Raised alkaline phosphatase activity; wide diaphyses; thick calvarium	Autosomal recessive	*TNFRSF11B*[30,31]
Hypophosphatasia[32]	Mild to severe	Low alkaline phosphatase activity	Autosomal recessive, autosomal dominant	*ALPL*[33]
Cole-Carpenter syndrome[34]	Severe	Craniosynostosis; ocular proptosis	Unknown	Unknown
Idiopathic juvenile osteoporosis	Mild to moderate	No extraskeletal abnormalities	Not hereditary	Unknown

Table 2: **Skeletal disorders resembling osteogenesis imperfecta**

at our institution during the past 15 years (unpublished data). Typical histological features of type VI disorder have been described by Sarathchandra and colleagues[22] in three of 36 patients (8%) with osteogenesis imperfecta.

Type VII osteogenesis imperfecta is a recessive disorder, which so far has been reported only in a community of Native Americans in northern Quebec.[16] Apart from bone fragility, rhizomelia is a prominent clinical feature, and coxa vara can be present even in infancy. The disease has been localised to chromosome 3p22–24.1, which is outside the loci for collagen type 1 genes.[23]

Several primary skeletal disorders can be confused with osteogenesis imperfecta (table 2).[24–34] The clinical resemblance is highlighted by the fact that Bruck syndrome and osteoporosis-pseudoglioma syndrome have previously been called "osteogenesis imperfecta with congenital joint contractures" and "ocular form of osteogenesis imperfecta", respectively.[24,35] Panostotic fibrous dysplasia is the extreme form of polyostotic fibrous dysplasia, in which all bones are affected.[28] Idiopathic autosomal recessive hyperphosphatasia, also known as juvenile Paget's disease, is characterised by strikingly raised bone turnover.[30,31] It is usually easily distinguishable from osteogenesis imperfecta on the basis of very high serum alkaline phosphatase activity. Hypophosphatasia is very variable in clinical expression, ranging from stillbirth without mineralised bone to pathological fractures that develop only late in adulthood.[30] Cole-Carpenter syndrome (features include osteoporosis, short stature, craniosynostosis, ocular proptosis, no type 1 collagen mutations) has been described in only a few patients, and therefore the mode of inheritance is not established. Idiopathic juvenile osteoporosis is a transient, non-hereditary form of childhood osteoporosis without extraskeletal involvement that typically develops in a prepubertal, previously healthy child of either sex.[36] Spontaneous recovery happens after 3–5 years, although spine deformities and severe functional impairment can persist.[36]

Child abuse is a frequent cause of fractures, with the highest incidence in the first year of life.[37] Clinical differentiation of mild osteogenesis imperfecta from child abuse can be difficult, especially if the family history is negative for the disorder. Bone-mineral density examinations with dual energy X-ray absorptiometry or CT have been proposed to help in the differential diagnosis.[38,39] However, little information is available on the range of bone-mineral density that is to be expected in infants with mild osteogenesis imperfecta. Collagen type 1 analysis can be very useful when the test is unequivocally positive, thus proving the diagnosis.[12] However, a negative collagen type 1 analysis evidently does not prove child abuse. Thus, in many cases, the distinction between mild osteogenesis imperfecta and child abuse still relies entirely on careful clinical evaluation.

Pathogenesis

This section focuses on forms of osteogenesis imperfecta that are positive for collagen type 1 mutations, since little is known about the pathogenesis of the other types of the disorder. A collagen type 1 molecule consists of three polypeptide chains (two α 1 and one α 2 chain) that form a triple-helical structure.[40] For the three chains to intertwine correctly they must have a glycine residue at every third position. The most typical sequence abnormality associated with osteogenesis imperfecta is a point mutation that affects a glycine residue in either *COL1A1* or *COL1A2*. Cells harbouring such a mutation produce a mixture of normal and abnormal collagen.[41,42] The resulting phenotype can vary from very mild to lethal depending on which of the two α chains is affected, the position in the triple helix at which the substitution arises, and which aminoacid is substituted for glycine. At the moment, genotype-phenotype correlations are too weak to predict with certainty the phenotypic effect of a particular glycine mutation.

Mutations that create a premature stop codon within *COL1A1* have a more predictable outcome than do other abnormalities, because in most cases they result in an osteogenesis imperfecta type I phenotype.[43] The transcription products of genes harbouring such a mutation are usually unstable and are destroyed by a process called nonsense-mediated decay.[44] As a result, only normal collagen type 1 chains are produced by fibroblasts of affected individuals, but the rate of collagen production is reduced.[41,42]

In most of these molecular studies, skin fibroblasts have been used to investigate collagen production. Much less is known about the effect of mutations on osteoblasts, which may differ from fibroblasts with respect to post-translational modifications of mutated collagen[45–48] and in the propensity to incorporate abnormal collagen molecules into extracellular matrix.[49] For most mutations we do not know how osteoblasts process mutated gene products, how much mutated protein is secreted, and whether it is incorporated into organic bone matrix. Osteoblasts harbouring a mutated collagen type 1 gene might have an abnormal expression pattern of other matrix proteins, such as proteoglycans, hyaluronan, decorin, fibronectin, and thrombospondin.[50–52]

These abnormalities in organic compounds also affect the mineral phase. Compared with age-matched controls, bone from patients with osteogenesis imperfecta shows a higher average mineralisation density.[53] The OIM (osteogenesis imperfecta murine) model of the moderate to severe disorder has smaller and less well aligned mineral crystals than normal mice.[54–56]

Disturbances in organic and mineral bone compounds are associated with altered biomechanical behaviour. Collagen from OIM mice has reduced tensile strength.[57] Mineralised osteogenesis imperfecta bone may be harder at the material level[56] but it breaks more easily than normal

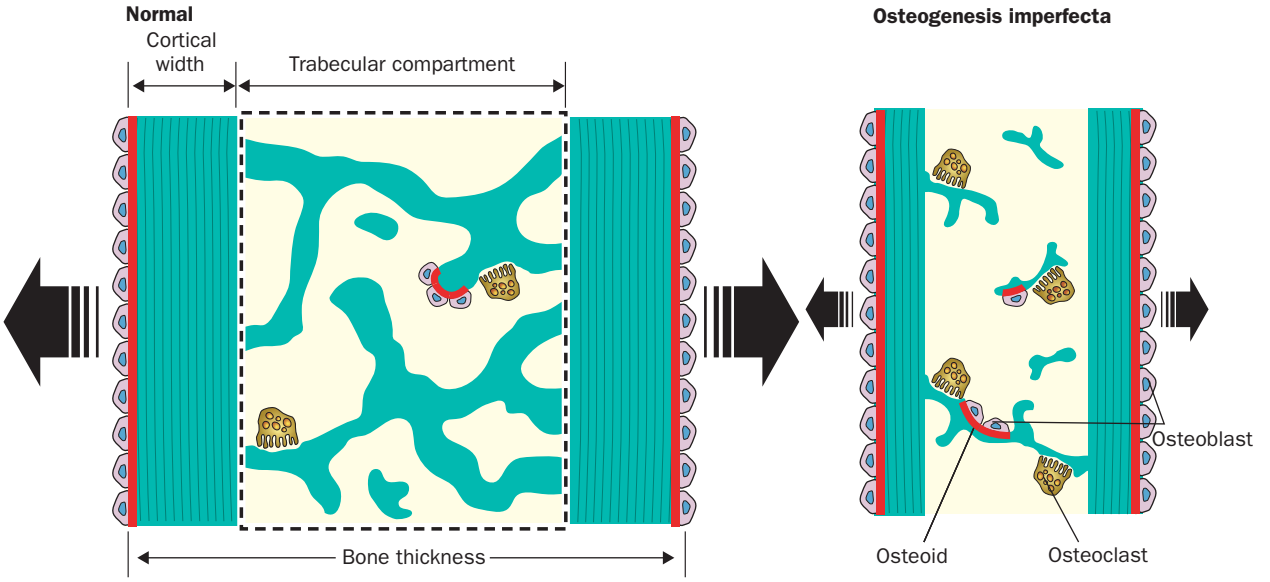

Figure 2: **Summary of histological bone abnormalities in osteogenesis imperfecta**[60]
Osteogenesis imperfecta bone has a smaller than normal external size (bone thickness) because of sluggish periosteal bone formation. Trabeculae are reduced in number and are abnormally thin. Although individual osteoblasts produce less bone than normal, the overall bone formation rate in the trabecular compartment is amplified, because the number of osteoblasts is raised. However, this increase does not lead to a net gain in trabecular bone mass, because the activity of bone resorption is also enhanced.

bone when deformed, and fatigue damage accumulates much faster on repetitive loading.[58,59] The sum of these abnormalities might account for the brittleness of osteogenesis imperfecta bone. Furthermore, the disorder is characterised by an insufficient amount of bone. Both cortical thickness and the amount of trabecular bone are low[60] (figure 2).

Medical management of osteogenesis imperfecta

Physiotherapy, rehabilitation, and orthopaedic surgery are the mainstay of treatment for patients with osteogenesis imperfecta.[61,62] Therapeutic efforts aim to get the most out of mobility and other functional capabilities.[61,63] Physical activity programmes are encouraged—as far as is possible with the raised risk of fracture—to prevent contractures and immobility-induced bone loss.[62] Orthoses are used to protect the legs during the early phases of mobilisation.[64] Standing and walking can sometimes only be achieved after femora and tibiae have been straightened with intramedullary rods.[62,65,66] This approach can be successful but does not alter the sometimes extreme bone fragility in these patients. For this reason, medical approaches to strengthen the bones have been sought for a long time.

Bisphosphonate treatment

Medical treatment in osteogenesis imperfecta is notoriously unsuccessful. Two decades ago, Albright[67] evaluated 96 reports of 20 different treatments including hormones (calcitonin, cortisone, oestrogens, androgens, and thyroxine), vitamins (A, C, and D), minerals (aluminium, calcium, fluoride, magnesium, phosphate, and strontium), and some more exotic approaches (such as arsenic, radiation, dilute hydrochloric acid, and calf-bone extract). Most researchers claimed some clinical effectiveness for their interventions but none stood the test of time.

This bleak picture started to brighten up with a 1987 case report by Devogelaer and colleagues,[68] who reported pronounced clinical and radiological improvement in a 12-year-old patient with osteogenesis imperfecta after 1 year of oral pamidronate treatment. Pamidronate is a member of the bisphosphonate family of drugs, which are potent

	N	Age at start (years)	Follow-up (years)	Data provided	Bisphosphonate used
Reference					
Brumsen et al[74]	4	12–17	5·1–8·1	Clinical summary	Olpadronate oral, pamidronate oral
Glorieux et al[82]	30	3–16	1·3–5·0	Clinical summary	Pamidronate iv
Plotkin et al[77]	9	0·2–1·8	1·0	Clinical summary	Pamidronate iv
Lee et al[86]	6	4–13	1·0–1·9	Clinical summary	Pamidronate iv
Astrom and Soderhall[83]	28	0·6–18	2·9	Clinical summary	Pamidronate iv
Zacharin et al[84]	14	1–14	1·8–2·0	Clinical summary	Pamidronate iv
Banerjee et al[87]	10	1–12	0·9–3·0	Clinical summary	Pamidronate iv
Giraud et al[88]	7	1–15	1·7	Clinical summary	Pamidronate iv
Rauch et al[80]	45	1–17	1·0–4·0	Histomorphometry	Pamidronate iv
Shapiro et al[89]	8	34–63	1·8–2·5	Clinical summary	Pamidronate iv
Adami et al[90]	46	22–48	1·0–2·0	Clinical summary	Neridronate iv
Rauch et al[81]	165	0·04–17	0·3–4·0	Biochemistry	Pamidronate iv
Rauch et al[78]	56	0·2–15	4·0	Densitometry	Pamidronate iv
Zeitlin et al[79]	116	0·04–15	1·0–4·0	Anthropometry	Pamidronate iv
Montpetit et al[85]	42	7–15	2·0	Grip force	Pamidronate iv
Grissom and Harcke[91]	19	1–17	NA	Radiography	Pamidronate iv
Falk et al[92]	6	1–14	2·3–3·3	Clinical summary	Pamidronate iv
Maasalu et al[93]	15	0·8–13	1–5	Clinical summary	Alendronate oral

Only reports containing more than three patients are listed. N=number of patients with osteogenesis imperfecta included in the report. NA=not available. iv=intravenously.

Table 3: **Studies on bisphosphonate treatment in osteogenesis imperfecta**

	Dosage	Frequency
Age (years)		
<2·0	0·5 mg/kg per day for 3 days	Every 2 months
2·0–3·0	0·75 mg/kg per day for 3 days	Every 3 months
>3·0	1·0 mg/kg per day for 3 days; maximum dose 60 mg/day	Every 4 months

An acute-phase reaction regularly happens after first exposure to pamidronate. In an attempt to reduce this reaction, only half the indicated dose is administered on the first day of the very first cycle of treatment. The maximum concentration of pamidronate in the infusion solution is 0·1 mg/mL. The infusion should be given over 3–4 h.

Table 4: **Pamidronate treatment schedule as used in the Shriners Hospital for Children, Montreal**

antiresorptive agents.[69] It interferes with the mevalonate pathway of cholesterol biosynthesis in osteoclasts,[70] inhibiting the function of these cells but not usually leading to apoptosis, as was believed previously.[71]

The encouraging observations by Devogelaer and colleagues,[68] and findings of subsequent pilot studies,[72–76] prompted investigators to treat large groups of patients with bisphosphonates. Available evidence on this treatment approach in children mostly stems from observational trials in moderately to severely affected patients with osteogenesis imperfecta (table 3).[74,77–93] None of the studies was placebo-controlled, but some included historical controls.[77–81] Most patients in these studies were treated with cyclic intravenous pamidronate (table 3). The most widely used treatment schedule is shown in table 4. At present, very little is known about the effect of oral bisphosphonate treatment, even though this regimen is under investigation in controlled trials. A pronounced decline in chronic bone pain can be seen within a few weeks after the start of intravenous pamidronate treatment.[72–84] This result is associated with an enhanced sense of well-being[83] and increased muscle strength in the grip force test.[85]

During pamidronate treatment, vertebral bone-mineral mass increases faster than in untreated patients.[82–84,86–88] Higher lumbar-spine bone mass is attributable to not only increased bone-mineral density but also larger vertebral size.[78] Several investigators have reported the impression that crushed vertebral bodies regain a more normal shape during pamidronate treatment.[82–84]

With respect to long bones, enhanced cortical thickness has been noted at the second metacarpal.[82] On the basis of CT analyses in two patients with osteogenesis imperfecta, researchers suggested that pamidronate might increase the mass of long-bone diaphyses but not geometric variables of bone stability.[94] However, our preliminary observations with peripheral quantitative CT in more than 20 patients with

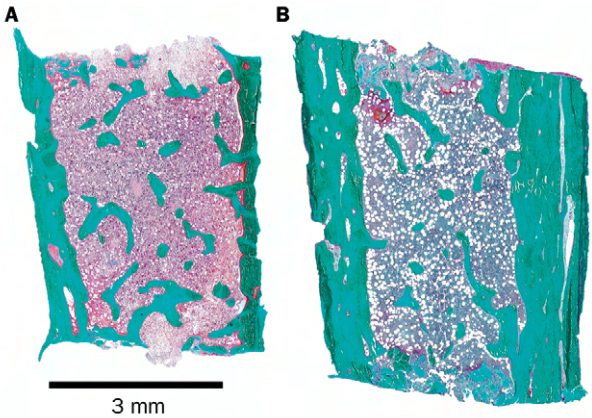

Figure 3: **Histological changes during pamidronate treatment**
(A) Complete iliac bone biopsy specimen from a 3·3-year-old boy with a moderately severe form of osteogenesis imperfecta type IV. (B) Biopsy sample after 2·0 years of pamidronate treatment. Note the striking increase in thickness of the bone cortex.

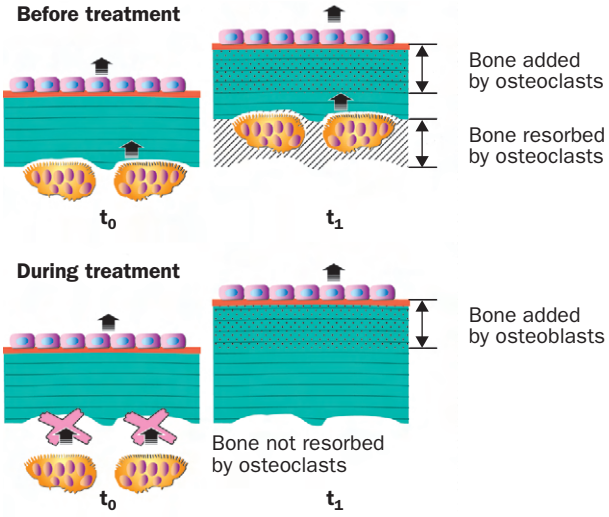

Figure 4: **Model of how pamidronate treatment increases cortical thickness in growing osteogenesis imperfecta patients[80]**
During the growth period, cortical width is determined by bone modelling. In this mechanism, osteoblasts and osteoclasts are active on opposite sides of the cortex and thus are not directly coupled.[95] Therefore, osteoclasts can be selectively targeted by pamidronate, and continuing bone formation can increase cortical width.

this disorder suggest that this drug also has a beneficial effect on indicators of long-bone stability (unpublished data).

Findings of histomorphometric studies of iliac bone samples showed that the main effect of pamidronate treatment was to enhance cortical thickness (figures 3 and 4).[80] By contrast, the drug had no detectable effect on the thickness of trabeculae (figure 5). The amount of trabecular bone nevertheless rose somewhat during therapy because the number of trabeculae increased (figure 6).

Most patients described in the above studies were older than 2 years of age when pamidronate treatment was started. In a congenital disease such as osteogenesis imperfecta, to start treatment as early as possible seems logical. Indeed, promising results were reported in a few children who received the drug in the first 2 years of life;[77] however, the clinical effect of an infusion, especially on bone pain, was short-lived. Pamidronate cycles were therefore repeated more frequently in infants than in older children (table 4).

Adults with osteogenesis imperfecta also benefit from intravenous pamidronate or a closely similar bisphosphonate, neridronate.[89,90] In an open-label controlled study, Adami and colleagues[90] noted that intravenous neridronate induced a relevant increase in areal bone-mineral density at the spine and hip. Importantly, the incidence of fractures was significantly lower during than before treatment.

The ultimate goal of medical treatment in children with severe osteogenesis imperfecta should be to reduce fracture rates, prevent long-bone deformities and scoliosis, and improve functional outcome. Published work on these issues is scarce. However, in two large observational studies, improved mobility was reported in more than half of patients.[82,83] In one of these studies, a 65% lower incidence of long-bone fractures was noted during treatment than in the pretreatment period.[82] However, this reduction may only be partly attributable to pamidronate treatment. Fracture incidence in osteogenesis imperfecta varies widely with age[98] and will probably depend on activity levels, correct use of mobility aids, and success of surgical interventions. At present, we do not know whether treatment with this drug prevents long-bone deformities or delays progression of scoliosis.

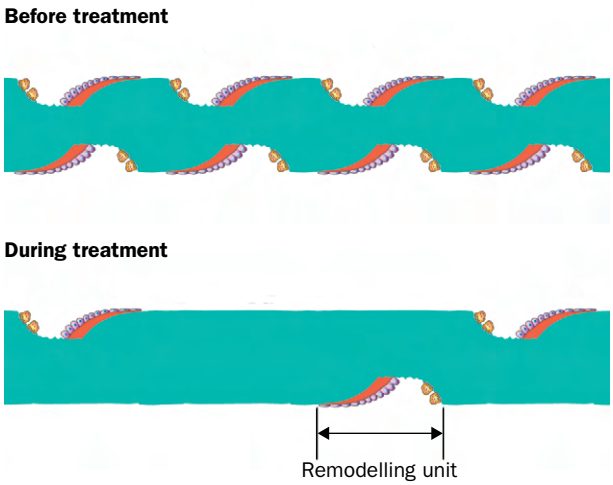

Figure 5: **Model of why pamidronate has no effect on the thickness of trabeculae[80]**
Trabecular thickness is determined by remodelling. In this process, osteoblasts are directly coupled to osteoclasts thus forming so-called remodelling units.[96] Inhibition of osteoclast action by pamidronate reduces the number of remodelling units, but does not alter the thickness of trabeculae.

Despite encouraging results, safety issues are a concern when bisphosphonates are administered to children and adolescents. The immediate effect of pamidronate infusions is a drop in serum calcium concentrations, which in calcium and vitamin D replete patients is rapidly corrected via the expected counter-regulatory rise in parathyroid hormone and production of 1,25 vitamin D.[81] Many children have an influenza-like reaction after their first pamidronate infusion that can be accompanied by fever, rash, and vomiting.[82–84] These symptoms typically arise 12–36 h after initiation of the infusion, are usually controlled with standard antipyretic therapy, and do not recur in later treatments. Nevertheless, this reaction could be of concern in infants and young children who are in a compromised general condition or who have respiratory difficulties.

With respect to long-term safety in children and adolescents, the possible detrimental effect of bisphosphonates on longitudinal bone growth is high on the list of concerns.[99] Suppression of longitudinal growth in rats has been used as a marker of the biological activity of bisphosphonate compounds;[100] further, alendronate in high doses inhibits longitudinal growth in OIM mice.[101] The early impression of clinical investigators was that intravenous pamidronate therapy, in presently used doses, did not have a detrimental effect on growth in patients with moderate to severe forms of osteogenesis imperfecta.[82–84,86] Detailed analysis of 41 such patients showed that after 4 years of treatment with this drug they had a significant increase in height compared with historical controls.[79]

Unexplained rapid weight gain has been noted in several children during pamidronate treatment.[79] This change interferes with rehabilitation and adds to the general negative results of obesity. Another potential side-effect of pamidronate is uveitis, which we have recorded in two of 215 patients who have received this drug at our institution (unpublished data). Bisphosphonates persist in bone tissue for many years.[102] At present we do not know whether such drugs released from the maternal skeleton have any effect on the fetus.

Antiresorptive drugs such as bisphosphonates inevitably diminish bone remodelling (figure 5) and can interfere with bone modelling (shaping).[78,81,103] This occurrence was highlighted in a case report of a teenage boy who, for unclear reasons, received large doses of pamidronate over a period of 3 years and developed abnormally shaped long-bone metaphyses.[104] A sustained decline in remodelling activity during growth can also be harmful. Remnants of mineralised growth-plate cartilage accumulate within trabecular bone.[80,101,104,105] Calcified cartilage has a high mineral density and therefore contributes to enhance densitometric results,[78,106] but is less resistant to fractures than is normal bone. Low remodelling activity can also delay the repair of microdamage in bone tissue.[107] Finally, fracture repair might be impaired when bone metabolism is suppressed too much. This possibility must be closely monitored in clinical trials.

Several important unresolved questions thus surround bisphosphonate treatment of moderate to severe forms of osteogenesis imperfecta. What are the long-term benefits of this treatment approach? How long should pamidronate treatment be continued to make the most of these benefits and to keep potential long-term side-effects to a minimum? What happens after therapy is discontinued? Are other bisphosphonates—either given intravenously or orally—as effective as pamidronate? These questions can only be answered if treatment effects continue to be systematically assessed in large groups of patients within defined protocols.

We should note that in the above studies, children with mild forms of osteogenesis imperfecta (two or fewer fractures per year, no vertebral compression fractures, and no long-bone deformities) were not included. Observational trials on pamidronate have evolved from compassionate use of this drug in desperate cases; these results cannot be simply extrapolated to mild forms of the disease. Children with mild osteogenesis imperfecta have less to gain from treatment than severely affected patients, but have more to lose from potential adverse effects. In our view, bisphosphonate therapy is not justified in children with mild forms of the disorder until placebo-controlled

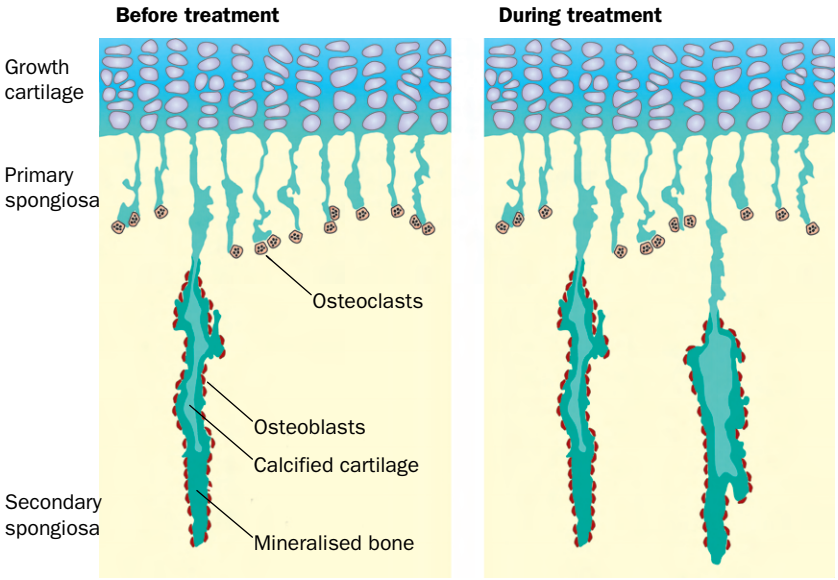

Figure 6: **Model of how pamidronate affects the number of trabeculae[80]**
During the endochondral growth process, most of the primary trabeculae are lost during the conversion of primary into secondary spongiosa.[97] Pamidronate treatment increases the number of secondary trabeculae, presumably because more primary trabeculae survive to become secondary trabeculae.

trials have established the efficacy and safety of this approach in this group of patients.

Other medical treatments

Growth hormone was proposed as a possible treatment for osteogenesis imperfecta almost three decades ago.[108] Findings of small studies suggest that growth-hormone treatment might accelerate short-term height velocity in some patients.[109–111] In calcium kinetic studies, after 1 year of growth-hormone therapy bone turnover increased but calcium retention was unchanged compared with pretreatment.[110] Enhanced bone turnover during growth-hormone treatment was also reported in histomorphometric studies of iliac bone samples.[111] Since bone turnover is already abnormally high in untreated children with osteogenesis imperfecta,[60] further stimulation does not seem to be a desirable goal. Growth hormone might be more useful in combination with bisphosphonates, but this regimen remains to be tested.

Parathyroid hormone is a potent bone anabolic agent that reduces fracture incidence in postmenopausal osteoporosis.[112] These results suggest parathyroid hormone as an attractive candidate for treating children with osteogenesis imperfecta. However, a substantial proportion of young rats receiving parathyroid hormone subsequently developed osteosarcoma,[113] and a similar effect could happen in human beings.[114] Thus, parathyroid hormone should not be used in children until these issues have been resolved.

Potential treatments

Bone-marrow stromal cells can differentiate into various cell lineages, including osteoblasts.[115] This observation led to the straightforward hypothesis that transplanting bone-marrow stromal cells from healthy people might improve the clinical course of osteogenesis imperfecta. For this approach to be successful, intravenously infused bone-marrow stromal cells must find their way into the skeleton and differentiate into osteoblasts that start producing normal bone. Also, we must hope that the bone produced by transplanted cells is not subjected to the same rapid removal as that formed by the patient's original osteoblasts.

These hopes formed the rationale for undertaking bone-marrow transplantation in a small group of children with severe osteogenesis imperfecta:[116,117] the reported results elicited mixed reactions. Bone-marrow transplantation experts were excited, because some of the patients' osteoblasts seemed to be of donor origin.[118] Bone-disease specialists remained sceptical, because no convincing evidence was presented to show that the patients had actually benefited from the procedure.[41,115,119–121]

Whatever the clinical effects might have been, the researchers conceded that they were short-lived.[117] Therefore, they re-treated the same patients with a modified approach—this time, isolated marrow stromal cells were infused.[122] Similar to the first study, a few transplanted cells were detectable in several tissues, including bone. Clinical benefit was claimed, based mainly on increased growth velocity in the 6 months after the procedure. However, the difficulty of measuring short-term growth velocity in children with bone deformities is obvious.

In our view, enthusiasm about an innovative technique should not be a substitute for scientific stringency and objective evaluation of results. Techniques based on marrow stem cells could offer therapeutic potential for patients with osteogenesis imperfecta in the future. Therefore, we should not discredit this approach by premature clinical application; basic science and technical issues should be worked out in animals before further studies are undertaken in human beings.

Presently, medical treatment options at best achieve symptomatic improvement of osteogenesis imperfecta. The only hope for actually curing the disease is by elimination of the mutated gene or gene product. Unfortunately, major obstacles to gene-based therapy of osteogenesis imperfecta exist. Most severe cases result from the presence of abnormal collagen molecules. Thus, we cannot simply replace a missing protein as is the case in many recessive enzyme disorders. Rather, we need to first inactivate the mutant allele and then substitute for its product.[123] Research is still grappling with the first of these two tasks. Various investigators are studying so-called hammerhead ribozymes,[124–126] small RNA molecules that can cut mRNA in the absence of protein cofactors.[127] Various viruses have been tested that allow for transfection of mesenchymal progenitor cells.[126,128] When ribozymes were transfected into such cells, *COL1A1* mRNA amounts could be suppressed by about 50%.[126] Such results are encouraging, but nevertheless they represent only a first step on a long and difficult path.

Conflict of interest statement

F H Glorieux has received support for research into use of bisphosphonates in osteogenesis imperfecta from Merck Research Laboratories and honoraria for lectures in the area of paediatric bone diseases at academic meetings organised by various pharmaceutical companies. None of these sources has contributed to the content of this Seminar. F Rauch has no conflict of interest with respect to this Seminar.

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