

# Current and emerging treatments for the management of osteogenesis imperfecta

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**Abstract:** Osteogenesis imperfecta (OI) is the most common bone genetic disorder and it is characterized by bone brittleness and various degrees of growth disorder. Clinical severity varies widely; nowadays eight types are distinguished and two new forms have been recently described although not yet classified. The approach to such a variable and heterogeneous disease should be global and therefore multidisciplinary. For simplicity, the objectives of treatment can be reduced to three typical situations: the lethal perinatal form (type II), in which the problem is survival at birth; the severe and moderate forms (types III–IX), in which the objective is 'autonomy'; and the mild form (type I), in which the aim is to reach 'normal life'. Three types of treatment are available: non-surgical management (physical therapy, rehabilitation, bracing and splinting), surgical management (intramedullary rod positioning, spinal and basilar impression surgery) and medical-pharmacological management (drugs to increase the strength of bone and decrease the number of fractures as bisphosphonates or growth hormone, depending on the type of OI). Suggestions and guidelines for a therapeutic approach are indicated and updated with the most recent findings in OI diagnosis and treatment.

**Keywords:** osteogenesis imperfecta, bone genetic disorder, bone brittleness, "brittle bone disease", connective tissue malfunction, short stature, progressive skeletal deformities, blue sclerae, dentinogenesis imperfecta, joint laxity, adult onset deafness

## Introduction

Osteogenesis imperfecta (OI), also known as "brittle bone disease", is the most common genetic bone disorder and its prevalence is estimated around 1 in 10,000–20,000 births. OI is characterized by evidence of connective tissue malfunction and its clinical presentation is extremely variable: affected individuals are susceptible to fractures from the mildest trauma; reduced bone mass; varying degrees of short stature; progressive skeletal deformities; blue sclerae; dentinogenesis imperfecta; joint laxity; and adult onset deafness.<sup>1,2</sup> The clinical heterogeneity of OI ranges from death in the perinatal period, through marked short stature and severe bone deformity, to normal life expectancy with only mild osseous fragility and slightly decreased bone mass; the prognosis and the achievement of walking and autonomy are greatly influenced by the number of fractures and deformities and the age at which they begin. Clinical severity varies widely and nowadays eight types are distinguished;<sup>3,4</sup> the types initially delineated by Sillence are: type I mild non-deforming; type II perinatal lethal; type III severely deforming; and type IV moderately deforming.<sup>5</sup> In recent years four more types have been added: type V moderate to severe disease often causing deformity and short stature, with normal teeth and sclera; type VI moderate disease with severe vertebral

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body involvement with compression, white or blue sclera, normal teeth and no wormian bones; type VII that clinically is similar to type II although with smaller head and white or faintly blue sclera; type VIII that is similar to type III although with a round face, normal sclera and barrel shaped chest;<sup>6</sup> and type IX, which is milder than types VII and VIII.<sup>7</sup> The prognosis is mainly influenced by the degree of bone fragility, whose severity increases in the order: type I < types IV, V, VI, <type III, VII, VIII < type II.

The great majority of OI cases (almost 90%) are caused by heterozygosity of dominant mutations in one of the two genes (COL1A1 and COL1A2) encoding the chains of type I collagen,<sup>8,9</sup> with quantitative (mild or moderate forms) or qualitative (severe or lethal forms) defect of the synthesis of type I collagen.<sup>10</sup> Other involved genes are those encoding for cartilage-associated protein (CRTAP), prolyl 3-hydroxylase 1 and cyclophilin B, that form an intracellular collagen-modifying complex that 3-hydroxylates proline at position 986 in the alpha 1 chains of collagen (type I, II and V). Mutations in these essential cofactors cause alterations in the post-translational chain modification and collagen folding that are responsible for autosomal recessive lethal or severe OI: type VII,<sup>11–13</sup> type VIII and type IX.<sup>7,14,15</sup> An additional recessive form (possibly type X?) with a very severe phenotype has been described, due to homozygosity for a missense mutation in the serine proteinase inhibitor, clade H.<sup>16</sup> This gene encodes for the collagen chaperone heat shock protein 47, which is involved in proper collagen folding. Probably other disease causing genes will be found for rare recessive OI forms; it should also be considered that types V and VI etiologies are still unknown.

Treatment of OI depends on the severity of the disease and on the age of the patient; in any case a treatment strategy should provide the maximum of long-term function and autonomy.<sup>17–19</sup> For simplicity, the objectives of treatment can be reduced to three typical situations (Table 1): the mild form (type I), in which the aim is to reach ‘normal life’; the severe and moderate forms (types III–IX), in which the objective is ‘autonomy’; and the lethal perinatal form (type II), in which the problem is survival at birth.

The approach to such a variable and heterogeneous disease should be global and therefore multidisciplinary, such as the one adopted by the Italian Multidisciplinary Study Group for OI.<sup>17</sup> Patients and their relatives meet quarterly to yearly (depending on the patient’s age and needs) with specialists working on different aspects of OI in different centers in Italy: pediatricians, orthopedists, physiotherapists, geneticists and biochemists, occasionally joined by an otologist and a

dentist. The clinical data, supported by radiographic and photographic images, are recorded on a centralized electronic database. This approach is particularly advantageous for the patients and their families, since they obtain first-hand advice from different specialists at the same time regarding diagnosis, prognosis and particular therapeutic decisions such as surgical intervention. Moreover, with such a rare disease, this is the only approach that enables the recruitment of extensive experience and a sufficient cohort of patients to perform controlled therapeutic trials.

## Treatment of mild form (type I)

In a child presenting one or more unexplained fractures without a familial history of OI, it is sometimes difficult to differentiate a mild form of OI (type I and especially type IV with white sclerae) from non-accidental injury, juvenile idiopathic osteoporosis or the debated ‘temporary brittle bone disease’.<sup>20,21</sup> In little children the lateral x-ray of spine is a basic element to evaluate bone osteoporosis. In unclear cases, after clinical and radiological studies, further diagnostic information may be obtained from bone mineral density (BMD) and from the measurement of bone metabolic markers, morphological and ultrastructural bone studies, and biochemical and molecular collagen studies. BMD is generally decreased in OI patients,<sup>22</sup> and dual energy x-ray absorptiometry (DXA) of the lumbar spine or of the whole body may help to establish the diagnosis. In some cases, and particularly in the first year of life, there is a considerable degree of overlap between individuals with OI and normal values.<sup>23,24</sup> In children and adults with mild OI with a quantitative type I collagen synthesis defect (type I OI), some metabolic markers of bone apposition (eg, carboxyterminal propeptide of type I procollagen) are clearly lower than in normal controls. Genetic testing can be done by DNA testing (molecular study), on peripheral blood or on saliva specimens, or looking at the protein expression of type I procollagen (biochemical studies), on cultured fibroblasts from a skin biopsy. While routine biopsy or blood molecular study for children suspected to have been abused are unwarranted,<sup>25</sup> biochemical and molecular studies could be useful in the differentiation between qualitative and quantitative collagen I defects (Table 1).

OI type I patients rarely develop significant deformities and almost all achieve ambulation. The required care is mainly for periodic fractures or for associated problems, such as erosion of the teeth, impaired hearing and difficulties in adjustment. The goal in OI type I patients, both children and adults, is to have a ‘normal life’, lowering the

**Table I** Problems and objectives of treatment in three typical situations of osteogenesis imperfecta (OI)<sup>17</sup>

Problems	Goals	Possible solutions
<b>OI mild form (type I)</b>		
<b>Children</b>		
Decreased bone strength and high fracture frequency	Increase bone strength and decrease fracture frequency  Increase BMD or collagen synthesis  Attain 'normal life'	Rehabilitation for correct motor and psychological development and after fractures (intramedullary rods in some patients) Bisphosphonate treatment Growth hormone or other growth factors Correct job choice Avoid traumatic activities
Short stature	Increase stature	Growth hormone or other growth factors
<b>Adults</b>		
Hearing loss	Reduce hearing loss or normalize acoustic function	Hearing aids Stapes surgery Cochlear implantation
Decreased bone strength and high fracture frequency	Increase (or avoid decrease) of bone mineral density	Bisphosphonate treatment
<b>OI severe-moderate forms (types III–IX)</b>		
<b>Children</b>		
Decreased bone strength, high fracture frequency, bone deformities	Increase bone strength and decrease fracture frequency Increase bone mineral density	Intensive rehabilitation program Intramedullary roding in the majority of patients Bisphosphonate treatment
Absence of autonomy	Reach the maximum of autonomy possible in the particular patient	Assure adequate aids at home and the possibility of autonomy outside (motorized wheelchair)
Progressive kyphoscoliosis and reduced ventilatory capacity	Reduce or stop the progression of kyphoscoliosis. Ameliorate respiratory function	Corsets (?) Surgical intervention Monitoring oxygen saturation, possibility of oxygen therapy at home
Short stature	Increase stature	Cautious use of growth hormone or other growth factors
<b>Adults</b>		
Hearing loss	Reduce hearing loss or normalize acoustic function	Hearing aids Stapes surgery Cochlear implantation
Adulthood osteoporosis	Increase bone mineral density	Bisphosphonate treatment
<b>OI lethal perinatal (type II)</b>		
Pre and perinatal fractures	Reduce number of fractures	Surgical intervention Adequate management Special beds, bivalve corsets
Respiratory insufficiency	Assure supportive therapy Treat respiratory infections (secondary to abnormal ventilation)	Ventilatory assistance Antibiotic treatment
Cardiorespiratory failure Failure to thrive Information for parents	Adequate caloric intake	Resuscitation maneuvers Enteral feeding Prenatal diagnosis in families with an affected child Genetic counseling

**Abbreviations:** OI, osteogenesis imperfecta; BMD, bone mineral density.

risk of fractures and increasing bone density. A child with OI type I must be strongly encouraged to have a normal life, with normal schooling, although avoiding the high risk traumatic activities and sports. A supervised training program is fundamental together with improving aerobic capacity and muscle force reduces levels of subjective fatigue in children with OI type I and IV in a safe and

effective manner.<sup>26</sup> Problems during childhood may be short stature and fractures. Short stature is relatively uncommon in OI type I children, although a difference from other unaffected family members may pose some psychological problems. Disproportion between trunk and lower limbs is a frequent sign of platyspondilia reducing the global height. Joint hyperlaxity may occur in OI type I with severe

instability in the knees and feet. Mainly in these patients, walking parameters are modified with hip extrarotation, knee hyperextension, and flat foot with extrarotation is much more evident in cases of overweight patients. Fractures are treated when possible in a conservative way by standard casts as those used in patients without OI. When a fracture occurs twice or more on the same level surgical treatment with an intramedullary nail is needed. Repeated fractures may pose problems of frequent periods of absence from school and the need for rehabilitation and motor recovery after each negative event. During adulthood problems may be osteoporosis (which in women may worsen during gestation and lactation,<sup>27</sup> and after menopause with an increased fracture frequency, mainly of the spine) and hearing loss may also occur after the second and third decades.

As for medical treatment, all patients must have an adequate vitamin D intake (400–800 U/day) and a regular dietary calcium intake (800–1000 mg daily during infancy) and this may be obtained through an ordinary diet or through calcium and/or vitamin D supplements; the decision of starting bisphosphonates (BPs) and/or growth hormone (GH) treatment (Table 1) must be evaluated in each case.

Patients with OI have a precise follow-up protocol that provides an evaluation of the clinical and biochemical condition (the number of fractures, calcium and other nutrient intake, physical activity and clinical symptoms related to the disease eg, skeletal or respiratory) and in growing patients auxological parameters as weight, height, body mass index, height velocity and Tanner staging need to be evaluated also. Bone metabolic parameters (urinary Ca, P-Phosphate and Creatinine together with serum Ca, P, alkaline phosphatase, parathyroid hormone (PTH), 25-hydroxyvitamin D, osteocalcin, C-terminal cross-linking telopeptides of type I collagen, insulin-like growth factor-I, (IGF-I) and also routine biochemistry, including creatinine) are evaluated twice a year, while bone mass measurements (measured by DXA) are performed once or twice a year, depending on severity and age of patients. From childhood to adulthood, the lateral x-ray of the spine is a useful screening follow up, particularly in women from premenopausal age: for a precise evaluation of thoracic area of the spine (that it is not studied by DXA) it is suggested should be performed at least every two years.

In patients with dentinogenesis imperfecta a stringent odontoiatric and orthodontic assessment is important during the first years of age; we usually perform the first check when the baby teeth are set, and subsequent assessment is decided on needs although usually around 4–6 years of

age when all teeth are sealed. The major complications, fracture and excessive wear of fragile teeth, can be treated by capping teeth with hard polymers in order to coat and shape them.<sup>28–30</sup> The aim of treatment is to avoid infective complications (eg, pulpitis or abscesses) and to prevent facial deformities due to the loss of teeth (or parts of them) and malocclusion.

Hearing loss, a very common complication in OI,<sup>31</sup> can be managed initially by hearing aids, although it frequently requires surgery to replace the ossicular structures. We usually suggest the detection of hearing problems after puberty and periodically (eg, every 5–10 years) in adulthood. Replacement of the fractured and fused bones of the middle ear has provided significant restoration of hearing for many affected individuals.<sup>32</sup> However, it is questionable whether stapes surgery will be as successful in OI types other than type I, some groups have recently claimed that the surgical treatments, indicated under current international criteria, could eventually obtain limited functional results.<sup>33</sup> In the past, a progressive sensorineural hearing loss arising as a result of progression in the disease process, independently of surgery, appears to have a severe influence on the final hearing threshold.<sup>34</sup> For this reason, cochlear implantation has been performed in cases of OI and the results are similar to implant outcomes in patients with sensorineural hearing loss from a variety of other causes.<sup>35</sup>

## **Treatment of progressively deforming, moderately severe forms (type III, IV, V, VI, VII, VIII, IX)**

OI diagnosis in the great majority of cases is straightforward, on the basis of clinical and radiological findings; further diagnostic information can be obtained from BMD and measurement of bone metabolic markers, from morphological and ultrastructural bone studies as well as from biochemical and molecular studies. DNA analysis is considered a better test for diagnosis as compared with dermal biopsy;<sup>36</sup> however, it has to be said that genetic testing alone cannot rule out OI. Nearly 10% of mutations in collagen I are missed by current techniques and OI types V–VIII, as well the two new forms not yet classified, are due to mutations in different genes, and, as the molecular studies can be quite lengthy, an experts' opinion is fundamental. The differentiation between qualitative and quantitative collagen I defects, obtained through biochemical and molecular studies is an important issue in view of the prognosis and medical therapeutic options, and it encourages collagen experts to try to define the phenotype-genotype correlations.

In individuals with type III to VIII OI there is sometimes an overlap with normal values. Conversely, markers of bone resorption, such as the serum c-terminal telopeptide region of type I collagen, are elevated in severely affected patients with a qualitative defect.<sup>37</sup> In cases where the diagnosis is difficult, a bone biopsy can help to confirm OI, and will be diagnostic for OI types V and VI, whose genetic basis is still unknown.

The clinical treatment of children and adults with severe OI is a difficult challenge for physicians and other people caring for them. The therapeutic objective therefore should be to provide the best long term function and autonomy that the disease allows: to minimize fractures; deformities and disability; to reduce pain; to maintain comfort; for the patient to achieve relative independence in the activities of daily living and mobility; and to enhance social integration. The attainment of these goals requires a multidisciplinary team approach in order to tailor treatment needs to the severity of the disease and the age of the patient.<sup>38</sup>

The care plan involves the patient, the family and the community, together with the medical and nursing staff. Collaboration between the medical team (essentially pediatrician, orthopedist and physiotherapist) and the family is especially important in each phase of the treatment, with complete information and candid discussion on the therapeutic options. Medical staff should help both patients and families to develop a realistic attitude toward their life and future plans. They should also assure the family that an OI child can be educated to become a self-supporting adult. Therefore, the family should be encouraged to see that the OI child attends regular school classes, whenever possible, and so reaches the maximum possible intellectual and academic development. Many patients will become productive members of society, so the combination of optimal physical and mental development will offer more chances for a satisfactory life.

Children are generally psychologically well compensated during childhood, when acceptance, sociability and a certain adaptation to the disease are present. A psychologist (both for the adolescence and for the family) has sometimes to be consulted when problems, principally related to a young person's confidence and the body image become evident during adolescence. Generally, however, the discomfort tends to be alleviated if the adolescent with OI is able to maintain as much contact as possible with his/her peers at school and in the social environment. Overprotection is to be discouraged and relationships with healthy adolescents should be encouraged.

During the first months it is important to try to avoid spinal deformities, maintaining a semi-sitting position over a stiff padded seat. This allows the child to have visual contact with the environment and makes breathing more comfortable. In infancy the prevention and treatment of respiratory infections with respiratory rehabilitation and resolute antibiotic therapy are helpful. In the case of a fracture parental intervention is fundamental, as the limb has to be immobilized as soon as possible.

Three types of treatment are available:

- Nonsurgical management (physical therapy, rehabilitation, bracing and splinting)
- Surgery (intramedullary rod positioning, spinal and basilar impression surgery)
- Drugs to increase the strength of bone and decrease the number of fractures (eg, BPs and GH).

## Nonsurgical management

Nonsurgical management aims at: preventing and treating fractures; at enhancing motor development; muscle strength and a range of joint motion; at preventing contractures and deformities due to position; at improving functional ability and locomotion; at correcting malalignment of the lower extremity joints that prohibit weight bearing; and developing compensatory strategies. The approach starts with an evaluation of motor development and function,<sup>39</sup> the identification of functional needs,<sup>40</sup> the selection of near and long term objectives, and the development of a program consistent with reaching them, including the use of orthotic devices.<sup>41-43</sup> The rehabilitation approach is more easily followed during a period in a specialized ward. On discharge from hospital a program of physiotherapy treatment should be continued at home with the aid of specialist personnel and full cooperation of the parents. The approach consists of initial handling and positioning followed by functional and formal strengthening exercises. At the beginning, after lower extremity surgery, it is better to perform treatment in water: here it is possible to walk with minor pain, as the water reduces load bearing and the natural resistance of the water may improve muscle strength. The maintenance of good muscle tone and respiratory exercise are essential.<sup>26</sup> Swimming and in-water exercises are indicated in non-ambulatory patients, to improve the sense of balance and, as a result of an absence of weight, to gain otherwise impossible movement.

Undisplaced fractures are treated by standard orthopedic measures appropriate for the age of the patient and the type of fracture. Fracture healing is not impaired in OI and an immobilization time longer than normal is not required.

Bone fragility may be aggravated by osteoporosis subsequent to immobilization, which derives from an antalgic posture, supine obligatory decubitus and splinting. The vicious circle of fracture, immobilization, osteoporosis and refracture must be interrupted. Use of plaster casts needs to be minimized and the use of traction and mobile splints has to be implemented, since stimulating muscular function and forcing early weight bearing, they produce a stress to the lower limb bones that is essential for bone trophism. Progressive improvement in bone strength during adolescence permits better eventual function for patients in whom good skeletal alignment has been maintained. Patients who have been confined to a wheelchair may start walking. The possibility of autonomy at this stage is inversely correlated to the severity of damage and deformities, especially to the spine and lower limbs accumulated in preceding years.

## Surgery

To prevent and/or correct long-bone deformities that impair function and to decrease fracture frequency, to provide more functional anatomy of the extremities, properly timed operations for insertion of intramedullary rods, together with supportive splints and braces, may be performed.<sup>44-46</sup> The need for intervention is more frequent for femurs and tibiae, whereas fixation of the humerus is less often undertaken,<sup>47</sup> and in the forearm intervention is rarely indicated. As for anesthesia, precautions should be taken for the possible cervical fragility during intubations and close monitoring during surgery is essential because of the association of malignant hyperthermia with OI,<sup>48</sup> even if recent findings conclude that this relation seems weak.<sup>49</sup> Studies with gait analysis have been done in a group of walking patients with OI studying hip rotation patterns and global flexion of lower limbs before and after surgical treatment. This evaluation may be useful in planning surgery and energy consumption in different patterns of walking, with or without orthosis and other aids.<sup>50</sup> In children older than 2 years, until significant linear growth persists, surgical orthopedic intervention includes multiple osteotomies and the use of intramedullary telescopic rods. These rods, following the bone growth, last for longer than non-elongating rods and need less frequent changing. However, they require a more complex surgical procedure and seem to increase osteoporosis of limb bones. In this procedure, a correct placing of the upper extremity of the nail, near the inner part of grand trochanter, may reduce the high frequency of femoral neck varus which, if it appears, would need a later specific surgical correction (most frequently in prepubescent age groups). With percutaneous non-extensible intramedullary rods, early stable fixation

can be provided for patients too young and/or too sick for definitive or extensive open surgery, or in cases of near final growth.<sup>51</sup> Flexible intramedullary rods have specific contraindication in growing OI children although they can be used in young OI adults with good cortical bone. The choice between elongating or non-extensible rods has to be taken with regards to each particular patient and in the particular situation, on the basis of the surgeon's experience. Complications with the use of expanding intramedullary rods in patients with OI are frequent,<sup>52</sup> and the risk is higher in patients aged less than 5 years, and when rods are placed in the tibia rather than the femur.<sup>53</sup> In Italian and French procedures tibial extensible rods have now been replaced by two steel nails with the single extremity flexed in a L fashion to permit elongation. The major complication is rod migration, often combined with the perforation of joints, bone and soft tissue. Further fractures may occur, although in such cases rods prevent displacement, reduce healing time and the requirement for splints or plaster casts. Despite a high rate of complications, intramedullary telescopic rods have proven to be the most successful treatment for prevention and correction of fractures and deformities of the long bones, improving walking ability and leading to the successful rehabilitation of even severely affected patients.<sup>54-56</sup> Moreover, intramedullary rods in the lower extremities before the age of 3.5 years enhances neuromotor development.<sup>57</sup> After surgery, immobilization should be strictly limited to the time necessary for healing; then the rehabilitation process should continue, since surgical treatment has not to be considered as an isolated intervention. Surgical intervention has to be seen in a comprehensive view, as a stage in a psychomotor and rehabilitative route starting before and continuing beyond the event. A comprehensive, aggressive physical therapy rehabilitation program and long leg bracing<sup>58</sup> with surgical operations on the femur, result in a high level of functional activity for children with OI that is associated with an acceptable risk level for future fractures that brings children into graded exercise regimes and fosters their increased involvement in school and social situations.<sup>59</sup> Unfortunately, autonomous ambulation is beyond the capability of some affected individuals because of bone fragility and deformities. In these cases the purpose of treatment is to provide some mobility at home, while outside the home electrically powered wheelchairs provide a certain degree of autonomy.

Spinal deformity is common and causes difficulty in sitting, pain and potentially life-threatening complications. Scoliosis is difficult to treat with external bracing because of the compliant nature of bones and the tendency to rib deformation. Early bracing, although somewhat

effective, may well compress the soft osteoporotic rib cage with little or no effect on the progression of the curve.<sup>60,61</sup> Therefore pulmonary compromise created by scoliosis may be compounded by chest cage deformity secondary to bracing. Soft bracing can help in reducing back pain and lumbar kyphosis and improves postural balance while sitting. Even if it may not be correlated to other district involvement, in OI patients scoliosis severity is usually characterized by a high degree of stiffness of the spine and for this reason the possibility of its reduction is low post-puberty. In case of a scoliosis of 30° Cobb in OI patients aging 11–12 years, a 6 monthly x-ray and clinical follow-up is needed. If progression is evident then surgical intervention (with a mean of 40 days in halo traction) has to be performed and it must be followed by spinal stabilization (with or without instrumentation) and by a mean one month period with a cast. In case of major curves or of an extended delay waiting for surgery (over 15 years) the results may be less effective. However, if the procedure is undertaken on time, the scoliosis can be ameliorated with curve stabilization, an improvement in respiratory function and the relief of back pain.<sup>62</sup> In patients with severe scoliosis and/or basilar impression, whose respiratory function may be insufficient, there is often a need for the control of nocturnal respiratory parameters and supporting oxygen therapy or continual ventilation.<sup>63</sup> In patients with mild disease (thick bones and few fractures) treatment should be similar to that of patients with idiopathic scoliosis. Basilar impression may become clinically significant and complicated by compression, syrinx formation, hindbrain herniation and symptomatic obstruction with hydrocephalus requiring neurosurgical intervention. Patients may require ventricular shunt placement or posterior fossa or transoral-transpalato-pharyngeal decompression followed by occipito-cervical fusion. However, despite successful fusion basilar invagination tends to progress and only prolonged external orthotic immobilization (particularly during adolescence) is required to stabilize symptoms and arrest progression of the deformity.<sup>64–66</sup>

## Medical treatment

Medical treatment should always be considered as part of a coordinated multidisciplinary approach to the treatment of children with OI, including timely corrective surgery, physiotherapy and occupational therapy.

Until a gene therapy directed towards either replacement or silencing of the mutant allele is feasible, the causal defect of the disease cannot be corrected. At present, medical therapy to treat the causal defect is not possible, although

some ‘symptomatic’ treatment options are available. The goals of pharmacological therapy in OI are: to decrease the incidence of fractures; to increase growth velocity; to decrease pain; to have a positive effect on bone metabolic markers; bone histomorphometry and BMD; and finally to increase mobility and independence. All of these are important outcome parameters, although they are not simple to measure accurately and reproducibly in children with severe OI. As in other rare diseases, the conduction of a therapeutic study protocol is accompanied by the difficulty to enroll a large number of patients comparable for sex, age, height and clinical severity; moreover because of the extreme variability in the clinical severity of OI, each child usually has a different clinical history and has undergone different kinds of pharmacological, rehabilitative and orthopedic personalized treatments that may also influence growth. Eventually at puberty there is a notable decrease in fracture frequency and the relative stabilization of deformities, thus the positive results of any therapy may not be distinguished from the positive effects of sex hormones at this age. Only in recent years has the use of bone density measurement by DXA provided a method to study objectively and reproducibly a parameter linked to bone strength and the possibility of monitoring the response to different types of treatment.<sup>22</sup> In growing individuals bone mineral content (BMC) and BMD tend to increase, these results have to be corrected for bone volume.<sup>23,24</sup> All these facts may limit the possibility of evaluating the efficacy of a therapy conducted for a sufficiently long period in a large group of patients. High expectations often accompany the use of new drugs in OI, although these prospects are often disappointing in the long term management of OI.<sup>67</sup>

During past decades various systemic pharmacological agents have been administered to patients with OI and the majority of them initially claimed beneficial results, although none proved effective in controlled trials.<sup>68</sup> Among these were anabolic steroids, vitamin D, vitamin C, sodium fluoride, magnesium oxide, flavonoids (catechin) and calcitonin. Until 18 years ago, calcitonin was the most common therapy for OI, although its beneficial effects during the clinical course of the disease were disputed in the literature,<sup>69</sup> now however it is no longer used. In severe and moderately severe OI (generally due to a structural defect of type I collagen synthesis) agents increasing the production of type I collagen, such as GH, do not represent a suitable treatment, other agents that reduce bone resorption, such as BPs, are preferable for their action in increasing BMC. A combined GH-BPs treatment regimen seems to be, at least

theoretically, a possible pathogenic approach, since it would couple the stimulation of bone apposition by GH with the inhibition of bone resorption by BPs. However, possible candidates should be selected very carefully for such combined therapy. Eventually, since the PTH is a potent bone anabolic agent, shown to reduce the incidence of fractures in postmenopausal osteoporosis,<sup>70</sup> it seemed to be a suitable candidate for OI treatment; however, because of its possible collateral effects (young rats receiving PTH subsequently developed osteosarcoma<sup>71</sup>) it shouldn't be used in children before resolving these issues.

## Treatment of lethal perinatal OI (type II)

Type II OI has to be differentiated from other forms of lethal skeletal dysplasias (thanatophoric dysplasia, achondrogenesis and the autosomal recessive form of hypophosphatasia). When diagnosis of a lethal (or severe) form of OI is made prenatally and the decision is taken to complete the pregnancy, all measures to offer supportive care must be taken and parental bonding is encouraged. Cesarean delivery is requested whenever obstetric complications are suspected, however, this does not prolong the survival of infants with the lethal form of OI and does not affect either the fracture rate per infant or the number of infants with fractures among those with the nonlethal OI phenotypes.<sup>72</sup>

In prenatally undiagnosed cases therapeutic decisions must often be taken when the diagnosis is still unclear and the neonate has marked respiratory insufficiency. The decision to start ventilatory assistance and other supportive care is often difficult, with the risk of using excessively aggressive therapy. In fact, more than 60% of infants with OI type II die within the first 24 hours, and 80% die within the first month, survival beyond a year is extremely rare. Cardiorespiratory insufficiency and respiratory infections are the most common cause of death in these children, their prevention and treatment are important factors for prognosis. Because of respiratory insufficiency, many of these infants have feeding problems, and it is only with continuous enteral feeding that adequate caloric intake can be maintained. At home, the few infants that can leave hospital, always need supportive care. Parents should be instructed to manage the infant, to recognize when a fracture occurs and to treat it with cautious immobilization. Bedding that contains soft foam or water, can decrease the frequency of fractures. Frequent changing of the infant's head position can avoid cranial deformation, and in some cases that of spinal deformity, a bivalve brace may be helpful.

Since mosaic carriers of OI mutations experience mild to no clinical symptoms it seems that even a minor fraction of normal osteoprogenitor cells may have significant clinical benefits,<sup>73</sup> attempts at bone marrow transplantation (BMT) have been undertaken in children affected by OI<sup>74–77</sup> and even if they produced a low engraftment rate there were surprising and interesting symptomatic improvements. Horwitz and colleagues reported 1%–2% engraftment in children with OI, but an increase in BMC by DXA. Intrauterine transplantation (IUT) may be even more promising: Le Blanc and colleagues achieved 7% engraftment after IUT of fetal liver donor cells, although the potential phenotypic effects were masked by bisphosphonate administration.<sup>78</sup> While promising, the results of these clinical trials are difficult to interpret because of various limitations such as a lack of matched controls, interference of other contemporaneous treatment and unfeasibility of evaluating engraftment beyond a single biopsy site.

## Bisphosphonates

BPs have been accepted as the standard of care for children with OI and in particular with moderate to severe forms of OI. However, questions remain as to: the selection of patients for treatment, which BPs should be used, what the minimum effective dose and the minimum effective treatment interval should be, what the appropriate duration of treatment should be and what the role of oral BPs are.

The BP compounds are analogs of pyrophosphate which, when administered either orally or parenterally, are characterized by a rapid and strong binding to hydroxyapatite crystals in the bone mineral. Once BPs are buried in the skeleton they are released only when bone is destroyed in the course of bone turnover. These agents are potent inhibitors of bone resorption, decreasing osteoclast activity and number, although some effect on bone formation also occurs.<sup>79</sup> This activity results in improved vertebral shape and mass, higher cortical width, increased cancellous bone volume and suppressed bone turnover as shown by histomorphometric studies.<sup>80</sup> The net effect is to promote bone mineral accretion and at the same time to reduce bone turnover. Several compounds with different relative potency for inhibiting bone resorption are used in humans. Derivatives with an amino group at the end of the side chain (pamidronate was the first described) are very active.<sup>81</sup> Reported possible adverse effects with the intravenous administration of BPs are a slight lowering of serum calcium levels, which are rarely symptomatic, and transient high fever. With oral administration some gastrointestinal adverse effects and non-uniform absorption and bioavailability have been reported.<sup>82</sup>



Wide experience of the use of BPs has been gained in adults for the treatment of involuntional osteoporosis, Paget's osteitis deformans, bone pain and hypercalcemia of malignancy. In contrast, experience with BPs in children with various pathologies, such as juvenile osteoporosis, has been limited until recently and most of the current reports refer to small numbers of patients.<sup>83-86</sup> Following limited early studies,<sup>87,88</sup> several researchers have demonstrated that oral (olpadronate<sup>89,90</sup> and alendronate<sup>91,92</sup>) or intravenous (pamidronate<sup>93-101</sup> and neridronate<sup>102,103</sup>) BP treatment has a beneficial effect on children with severe OI.<sup>104</sup> In a large non-controlled observational study involving 30 children (aged 3 to 16 years) with severe OI, Glorieux and colleagues demonstrated that the cyclic administration of intravenous pamidronate improved clinical outcomes, decreased the incidence of fractures, reduced bone resorption, increased bone density and the size of vertebral bodies.<sup>97</sup> They also showed that the treatment did not alter the rate of fracture healing, neither the growth rate, nor the appearance of the growth plates, such that mobility and ambulation improved or remained unchanged and that all the children reported substantial relief of chronic pain and fatigue. In addition, even in severely affected OI patients under 3 years of age, pamidronate treatment is well tolerated, increases BMD and decreases their fracture rate.<sup>105</sup> Cyclical BP treatment markedly suppresses bone turnover and, after some years, seems to reach the maximum of its beneficial effect.<sup>100</sup> However, in growing patients treatment discontinuation leads to the construction of a low density metaphyseal bone tissue (added by longitudinal growth) that is probably responsible for zones of localized bone fragility in comparison to the tissue created during treatment.<sup>106</sup> Despite unanswered questions concerning them, BP treatment does appear to have a strong positive effect on the morbidity of severe forms of OI and it seems reasonable to continue the treatment more extensively.<sup>107</sup> These studies<sup>93-103</sup> reported encouraging results and strongly indicate that BPs are useful in the symptomatic treatment of children with severe OI, moreover without serious adverse effects. As with earlier studies these current trials share a common limitation, namely they are all open trials, therefore these favorable results should be confirmed in double-blind controlled studies.

In a congenital disease such as OI, it appears logical to start treatment as early as possible. Indeed, promising results were reported in patients who received BPs in the first years of life.<sup>80,103,105</sup> When treatment is being considered, since the knowledge of the long term tolerability is very limited and not all countries have BP therapy authorized in children, after

the treatment regimen is explained, it may be necessary for an informed consent to be obtained from the parents and, if appropriate, from the child. As for the choice of BP, there are groups that treat OI patients (including children with moderate to severe OI) with cyclical intravenous pamidronate, in cycles of three days, repeated every 2 to 4 months (with an annual dose of 9 mg/kg/year).<sup>97,98</sup> In our experience any advantage in terms of duration of treatment results from the cyclical intravenous administration of neridronate (which is the only BP authorized in children with OI in Italy) received as an infusion over 3 hours in a single day (the dose is subdivided in two days in children younger than 3 years) and is generally repeated every 3 months (with an annual dose of 8 mg/kg/year).<sup>102,103</sup> Zoledronic acid (an infusion given over 45 minutes for one day) has been recently used<sup>108</sup> although it is still undergoing clinical trials, in infants.

## Growth hormone

In mild forms of OI, agents increasing the production of type I collagen may have a therapeutic role. GH action positively affects bone growth and bone turnover by stimulating osteoblasts, collagen synthesis and longitudinal bone growth.<sup>109</sup> As part from this positive action on bone, GH has a positive action on collagen metabolism, stimulating the expression in osteoblast cultures of IGF-I and IGF binding protein-3, which in turn regulate the synthesis of type I collagen.<sup>110,111</sup> Osteoblasts from various species have IGF-I receptors and respond to both endogenous and exogenous IGF by accelerating the proliferation, increasing DNA and collagen synthesis.<sup>112,113</sup> On the other hand, animal studies in the mouse model of OI, with bone phenotype comparable to a mild form of OI in humans (*oim/+*), showed that systemic GH injections<sup>114</sup> or GH transgene expression in erythroid marrow<sup>115</sup> increased spine and femur length, produced significant changes in densitometric parameters and ameliorated biomechanical structural properties of bone.

GH could be used in OI either for stimulating bone metabolism,<sup>116</sup> increasing in particular bone apposition, or for increasing statural growth, since growth deficiency is constantly present in severe OI and common in mild to moderate forms of the disease.<sup>117</sup> GH-somatomedin axis activity has been studied in children with OI and hypoactivity of this axis (without a true GH deficit) was found in approximately half of the patients studied.<sup>118</sup> In other studies IGF-I serum levels were mostly found in the low normal physiological range.<sup>117,119</sup> There is limited literature regarding GH experience in OI as only a few human studies have been performed using GH in patients with OI.<sup>118,120</sup> Studies on

calcium (Ca) kinetics have shown that more Ca was available for bone mineralization following GH treatment.<sup>121</sup>

Two types of approach have been attempted in the GH treatment of OI, one is an extensive, general stimulus of bone metabolism, the other, based on more stringent criteria, stimulates collagen synthesis in cases of ascertained quantitative deficiency. One of the first attempts to treat OI with GH was carried out more than 20 years ago by Kruse and Kuhlencordt, who treated two patients affected by OI with GH. The patients had an increase in periosteal new bone formation and in intracortical bone resorption (assessed using histomorphometry of bone biopsies), with enhanced relative osteoblastic activity.<sup>122</sup> Following these results, no further study was reported in the literature until Marini and colleagues published their preliminary results from a limited number of patients treated with GH or clonidine (a pituitary GH secretagogue).<sup>118</sup> In a further study by this group, the authors concluded that there is a group of type IV OI children who would benefit from GH treatment in terms of linear growth, bone matrix synthesis and bone histomorphometric parameters.<sup>123</sup> Silience and colleagues showed a positive height growth, an increase in skeletal volume and in BMD and infer that the subsequent reduction in fracture frequency appears to confer a significant therapeutic benefit.<sup>124</sup> During GH therapy patients have an improvement in general well-being, muscular performance and motor ability, and this increases physical activity and consequently fracture risk in some cases.<sup>125</sup> Strict rehabilitative therapy may contribute to preventing fractures, together with an adequate calcium and phosphate intake during treatment. Our group evaluated the efficacy of 1 year of GH treatment (0.2 mg/kg/week in 6 divided doses) in patients affected by type I OI with an ascertained quantitative defect in type I collagen synthesis. GH treatment showed a positive action on bone turnover, markers of bone apposition (ie, osteocalcin and procollagen type I carboxyterminal propeptide levels) and BMD increased significantly, while the fracture risk did not change. The growth rate was significantly higher in treated patients than in the pre-treatment period and in the untreated group. Furthermore, protein anabolic effects of GH resulted in an increase of both muscle mass and strength, which, in combination with GH-related improvements in exercise capacity and cardiac performance, may increase physical activity with the concomitant beneficial effects on skeletal integrity.<sup>126</sup> These promising results led to a continuation of this GH study in a second group of patients and the results indicated that this is a useful therapy in patients with moderate forms of OI (the majority of type I and a good proportion of type IV), where it

has demonstrated a beneficial effect on bone turnover, BMD and height velocity, without increasing the fracture risk in the short term. Patients with pre-existing scoliosis or bone deformities must be treated with particular caution because of the potential risk of worsening of these problems. Patients with severe OI (type III and a subset of type IV) do not seem to gain any substantial advantage from this therapy. Therefore, the selection of patients for GH treatment on the basis of biochemical and molecular studies is a key factor. Nowadays it can be used by experts in selected cases or in clinical trials, whereas the routine use in patients with quantitative collagen defects must be confirmed with long term studies, in order to clarify the possible long term effects. Indeed, in the case of a mutation causing structural alterations in the type I collagen molecule, leading to an incorporation of the altered molecule within the matrix, GH treatment must be proceed with caution. When treatment is considered, informed consent needs to be obtained from the parents and, when appropriate, from the child. The physician must clearly explain that OI is not an approved indication for GH therapy, that the experience with GH in OI is of limited duration, with studies no longer than 2 years, and that knowledge of the long term effects is very limited.

## Future therapies

OI is a genetic disorder, transmitted both in an autosomal dominant (predominantly) or recessive manner, that causes a quantitative or qualitative defects in the synthesis of the structural protein type I. In case of quantitative collagen I defects (as nonsense, frame-shift or splicing mutations) this leads to a null allele (haploinsufficiency). The final result is a reduced synthesis (approximately half that of normal) of structurally normal procollagen chains, producing a mild to moderate phenotype. In the case of qualitative collagen defects (ie, a structural alteration in the type I collagen molecule), mutations (typically glycine substitutions) in the collagen genes are associated with more severe or lethal phenotypes. In these cases abnormal chains are synthesized and assembled together with normal chains into collagen trimers. Folding of the triple helix is delayed and thus causes over modification along the chains. Over modified trimers are partially retained within the endoplasmic reticulum (ER), causing ER stress and are partially secreted (although less efficiently than normal) from the cell and incorporated into the extracellular matrix. In the extracellular matrix their presence impairs the normal functions of connective tissue to a greater degree than a quantitative defect (dominant negative effect). In the recessive forms, caused by deficiencies of the

3-hydroxylation process, which involves CRTAP, P3H1 and cyclophilin B, over modification of type I collagen and the consequent intra and extracellular distress are also found despite structurally normal  $\alpha 1(I)$  and  $\alpha 2(I)$  chains being synthesized.<sup>14</sup>

It was thought that the future of medical treatment for this disease lay in the development of gene therapy directed towards either replacement or silencing of the mutant allele, to correct the causal defect of the disease.<sup>127</sup> OI murine models (oim, brtl IV, crtap<sup>-/-</sup>, Mov-13, OASIS<sup>-/-</sup>), which harbor mutations previously characterized in patients, have been developed. Currently, these models are being used to investigate gene and cell therapies.

Antisense suppression therapy aims to selectively decrease or silence the expression of the mutant allele, without interfering with the expression of the normal allele, and thus biochemically transform a severe form of OI into a mild form.<sup>128-130</sup> The use of short oligodeoxynucleotides<sup>131</sup> has not lead to encouraging results, in particular the moderate successes, the short half-life of unmodified antisense oligonucleotides and the toxicity associated with chemical modification. An alternative approach to treat dominant negative disorders, is the use of hammerhead ribozymes<sup>132</sup> (short RNA molecules with catalytic potential) that could eliminate the target sequence (by cleavage), however, the problem here is to achieve a sufficient suppression and to be introduced in the target cells in a stable way. Another molecular tool, RNA interference,<sup>133</sup> orchestrated using small double-stranded RNA molecules termed siRNAs, is used to achieve sequence-dependent suppression of gene expression. Limitations common to all the various antisense techniques (short oligodeoxynucleotides, ribozymes, silencing RNA) used were the lack of true specificity against the mutant transcript and the difficulty having stable expression of the antisense molecules. It should be stressed that this type of therapy will have to be specific for each mutation, making this approach unfeasible for OI considering the high number of different molecular defects. The possibility to target common polymorphism linked to the causative mutation seems more appealing, providing new hope for a truly clinical application. Thus gene therapy is currently limited to *in vitro* or *ex vivo* studies.

In the case of the structural defect of the collagen apart from gene therapy the other chance is molecule replacement of cells carrying the mutant gene with normal cells, essentially by BMT. The goal of BMT (of marrow stromal cells or more recently of mesenchymal stem cells) is to engraft sufficient normal cells to normalize tissue function. After a study

in a murine model of OI,<sup>134</sup> Horwitz and colleagues have reported initial results of allogeneic BMT in three children with OI.<sup>74</sup> Three months after osteoblast engraftment (1.5% to 2.0% donor cells), representative samples of trabecular bone showed histological changes that were indicative of new bone formation. All patients had increases in total body BMC, in growth velocity and had a reduced frequency of bone fracture. The authors concluded that allogeneic BMT could lead to engraftment of functional mesenchymal progenitor cells, indicating the feasibility of this strategy for OI treatment. This report led to some criticism, and several points have been debated; such as the contrast between the low level of osteoblast engraftment achieved and the dramatic changes reported in skeletal parameters,<sup>135</sup> or the difficulty in interpreting the decrease in fracture rate at the particular age of the patients. Moreover, it has been observed that technical difficulties in the evaluation procedures (bone biopsy, BMD measurements) in these patients may have jeopardized the quality of the data.<sup>136</sup> More recently, the exploitation of mesenchymal stem cells with the ability to differentiate into bone cells has been explored both *in vitro* and *in vivo*. The BrtlIV OI mouse model has been used for IUT<sup>137</sup> and this research demonstrated that even a low percentage of normal engrafted cells in bone is responsible for the synthesis of a good percentage of collagen matrix (over 20%) ameliorating the homogeneity of bone mineral matrix, improving bone geometry and the biomechanical properties. Obviously, moving from mice to human, clinical evaluation should be rigorous, since the procedure of BMT is potentially hazardous and may be irreversible. The availability of a matched donor is also a challenge to be taken in consideration. Only extensive studies in carefully selected patients will indicate whether such therapies are the optimal treatment for children with severe OI.

Further investigations are currently in progress to identify forms of medical therapy that will decrease morbidity in OI.

## Conclusions

OI diagnosis is usually made by experts, through a clinical and radiological basis. BMD could be useful in mild forms, whereas DNA analysis should not be considered as a diagnosis test, because of lengthy, non-perfect sensibility and because of economic considerations. A multidisciplinary team approach is essential not only for diagnosis and communication with patient and parents but also to tailor treatment needs to the severity of the disease and the age of the patient. The objective of therapy should be to provide the maximum

long term function and autonomy that the disease allows. The plan of care involves patient, family, medical and nursing staff, and community. It involves a combination of nonsurgical management and rehabilitation, surgery and medical treatment. Currently, the causal defect of the disease cannot be corrected with medical treatment and only symptomatic therapy is available. GH is beneficial in patients with mild forms of the disease. BPs are considered the gold standard of treatment for moderate and severe OI forms, since they are beneficial in the treatment of symptoms, increasing BMD, decreasing fracture rate and reducing pain, without adverse effects. An aggressive rehabilitative approach associated with intramedullary telescopic roding has been shown to improve walking capability. Surgical treatment in patients with progressive spinal deformity and in those with basilar impression is useful in decreasing the rate of complication.

In the near future therapy will be still based on BPs, since GH and BPs protocols are in an advanced phase of research. Concomitant GH and BPs therapy, or at least on cyclic regimens of these agents, will have to be more frequently used rather than using GH alone, as a substitute for other drugs. Eventually, future treatment will probably consist of cell therapies that aim to biochemically transform a severe form of OI into a mild form. Even if there are many technical difficulties to overcome, it is hoped that these therapies will become available for patients in the not too distant future.

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## Disclosure

The authors report no conflicts of interest relevant to this research.

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