THERAPY OF ENDOCRINE DISEASE

Treatment of osteogenesis imperfecta in adults

Katarina Lindahl1, Bente Langdahl2, Östen Ljunggren1 and Andreas Kindmark1,3

1Department of Medical Sciences, Uppsala University Hospital, Ing 40, Str, SE-75185 Uppsala, Sweden, 2Department of Endocrinology and Internal Medicine THG, Aarhus University Hospital, DK-8000 Aarhus C, Denmark and 3Science for Life Laboratory, Department of Medical Sciences, Uppsala University Hospital, SE-75185 Uppsala, Sweden

Abstract

Background: Osteogenesis imperfecta (OI) is a heterogeneous rare connective tissue disorder commonly caused by mutations in the collagen type I genes. Pharmacological treatment has been most extensively studied in children, and there are only few studies comprising adult OI patients.

Objectives: i) To review the literature on the current medical management of OI in children and adults, and thereby identify unmet medical needs and ii) to present an overview of possible future treatment options.

Results: Individualization and optimization of OI treatment in adults remain a challenge, because available treatments do not target the underlying collagen defect, and available literature gives weak support for treatment decisions for adult patients.

Conclusions: Bisphosphonates are still the most widely used pharmacological treatment for adult OI, but the current evidence supporting this is sparse and investigations on indications for choice and duration of treatment are needed.

Introduction

General background

Osteogenesis imperfecta (OI) is a heterogeneous disorder of connective tissues with an incidence of 1/15 000 (1, 2, 3, 4) and disease severity spanning from subclinical osteoporosis to intrauterine lethality. Dominant mutation in collagen type I is the most common cause (>90%); however, in the last decade the molecular background of several recessive, an X-linked, and a non-collagen dominant form has been reported (5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30). The cardinal sign of OI is bone fragility, with subsequent fractures, deformities, and growth retardation. Most patients have a low bone mineral density (BMD), to some extent negatively correlated to clinical severity (31). Generally, the high fracture incidence observed in children with OI decreases after puberty. Collagen I is the most abundant protein in vertebrates, and is present in large quantities in many connective tissues. Thus, patients may have other signs and symptoms including blue sclerae, dentinogenesis imperfecta (DI), hearing impairment, hyperlaxity, scoliosis, and increased bruising and bleeding (32, 33, 34).

Invited Author’s profile

A Kindmark is a senior consultant at the Department of Endocrinology, Uppsala University Hospital, Uppsala, Sweden. His current areas of research interests include osteogenesis imperfecta, bone phenotypes of inborn errors of metabolism, and modulation of bone metabolism by miRNAs and gene therapy. He is the scientific secretary for the Swedish Endocrine Society, and a former president of the Swedish Osteoporosis Society.
Table 1  Classification of OI types.

<table>
<thead>
<tr>
<th>OI type</th>
<th>Affected gene</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant inheritance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical Sillence types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>COL1A1 or COL1A2</td>
<td>Mild, nondeforming</td>
</tr>
<tr>
<td>II</td>
<td>COL1A1 or COL1A2</td>
<td>Perinatal lethal</td>
</tr>
<tr>
<td>III</td>
<td>COL1A1 or COL1A2</td>
<td>Progressively deforming</td>
</tr>
<tr>
<td>IV</td>
<td>COL1A1 or COL1A2</td>
<td>Moderately deforming</td>
</tr>
<tr>
<td>COL1-mutation negative V</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XV</td>
<td>IFITM5</td>
<td>Moderate, distinct histology, and hyperplastic callus</td>
</tr>
<tr>
<td>Recessive inheritance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineralization defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>SERPINF1</td>
<td>Moderate to severe, distinct histology</td>
</tr>
<tr>
<td>3-Hydroxylation defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>CRTAP</td>
<td>Severe to lethal</td>
</tr>
<tr>
<td>VIII</td>
<td>LEPRE1</td>
<td>Severe to lethal</td>
</tr>
<tr>
<td>IX</td>
<td>PPIB</td>
<td>Moderate to lethal</td>
</tr>
<tr>
<td>Chaperone defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>SERPINH1</td>
<td>Severe</td>
</tr>
<tr>
<td>XI</td>
<td>FKBP10</td>
<td>Progressive deforming, Bruck syndrome</td>
</tr>
<tr>
<td>Zinc-finger transcription factor defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XII</td>
<td>SP7</td>
<td>Moderate</td>
</tr>
<tr>
<td>C-propeptide cleavage defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XIII</td>
<td>BMP1</td>
<td>Severe, high bone mass case</td>
</tr>
<tr>
<td>Cation channel defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XIV</td>
<td>TMEM38B</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>WNT signaling pathway defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XV</td>
<td>WNT1</td>
<td>Moderate, progressively deforming</td>
</tr>
<tr>
<td>Unclassified ER stresstransducer deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-linked inheritance</td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td>Unclassified suspected osteocyte defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclassified ER stresstransducer deficiency</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Classification

OI has traditionally been classified according to Sillence, who published a revised classification system based on clinical, radiological, and hereditary findings in the late 1970s (33, 34, 35) (Table 1). The mildest, and most common, type of OI is denoted Sillence type I. This type is associated with fractures, blue sclerae, and hearing impairment. These individuals often have multiple fractures in childhood, but improve clinically after puberty and have a normal life expectancy (36). OI type II is a perinatal lethal variant. Affected fetuses and infants are usually stillborn, or die within a few days to weeks after birth due to multiple thoracic fractures causing respiratory complications, and possibly have an intrinsic pulmonary collagen pathology (37). The most severe OI type compatible with surviving the neonatal period is type III. Individuals with OI type III may suffer hundreds of fractures, and often have a markedly short stature, progressive deformities, severe scoliosis, and a shortened life span (36). OI is common and sclera has variable hue. Sillence type IV is a moderate form, with a phenotype spanning between types I and III in severity and clinical characteristics. The Sillence classification system is widely used, although recently discovered diversity in underlying molecular background as well as the phenotypic heterogeneity of collagen I mutations complicates classification. Roman numerals have been added for every new gene discovered to cause an OI-like phenotype, and to date 17 types have been described (Table 1) (5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30). The OI phenotypes caused by non-collagenous genes overlap with collagen I mutation-caused classical dominant OI, and there is no clear consensus on how to best define and classify this disorder.

Pathogenesis

Collagen type I constitutes ∼90% of the organic matrix of bone and supplies toughness, while the mineral...
component, hydroxyapatite, renders stiffness, and compression resilience. Collagen I is a heterotrimer composed of two \( \alpha 1 \) chains and one \( \alpha 2 \) chain encoded by the genes \( \text{COL1A1} \) and \( \text{COL1A2} \). The three chains associate C-terminally and in a zipperlike fashion create a highly structured triple helix that is 1014 amino acid residues long and composed of triplicate repeats of Gly-X-Y, flanked by globular N- and C-terminal ends. Mature collagen is formed when the globular ends are cleaved off peri-cellularly, and a meticulously ordered extracellular organic matrix can subsequently be developed and mineralized by hydroxyapatite. Principally, two types of mutations in collagen I cause classical dominant OI: quantitative and qualitative collagen defects.

Quantitative mutations are the result of haploinsufficiency of \( \text{COL1A1} \); patients have structurally normal collagen type I, but a reduced amount. Premature stop codons and splice-site mutations or insertion/deletions are commonly observed mutation types and all cause nonsense-mediated decay of mRNA from one \( \text{COL1A1} \) allele. Collagen type I is highly expressed in many connective tissue cell types, e.g. osteoblasts, and both alleles of \( \text{COL1A1} \) are required to meet the needs of the organism. Haploinsufficiency of \( \text{COL1A1} \) is usually associated with the milder type I phenotype, while \( \text{COL1A2} \) haploinsufficiency does not have an overt clinical bone phenotype (38).

Qualitative mutations are generally glycine substitutions (80%) or splice site mutations (20%); however, rare N- and C-terminal and X- and Y-position helical mutations have been described (39, 40, 41, 42, 43). Glycine is the only amino acid small enough to fit in the confined helical center of collagen I, and thus a prerequisite for correct folding. All described helical glycine substitutions cause OI phenotypes, with a severity depending on the position and specific substitution. Qualitative mutations cause a more heterogeneous phenotypic spectrum than quantitative mutations, ranging from mild disease similar to osteoporosis to perinatal lethal OI.

Non-collagenous genes causing OI are often involved in specific collagen modifications or function as collagen chaperones (29, 30, 44). Other examples of genes associated with OI phenotype may be involved in osteoblast differentiation and signaling or bone formation (19, 20, 22, 45). Many of the recently described non-collagenous OI types have phenotypes spanning from a moderate-to-lethal end of the spectrum; possibly due to ascertainment bias since severe cases are more thoroughly investigated.

### Heterogeneity of disease

Collagen mutations described so far illustrate a complex relationship between genotype and phenotype. Although some general principles can be discerned, it is virtually impossible to predict the phenotype of any given mutation with certainty. Varying phenotypes have been described for recurrent mutations, even when these are present within the same family. For example, specific glycine substitutions have been associated with both lethal and non-lethal OI (46). This phenotypic variability is thought to be caused by modifying elements, which are essentially unknown to date (46, 47). Similarly, this phenomenon has been described for non-collagenous OI; all known OI types V cases are caused by the same mutation in the \( \text{IFITM5} \) gene, but there is pronounced variability even within the same family regarding phenotypic severity (48). Also, individuals with OI type IX, caused by similar nonsense mutations in cyclophilin B (encoded by \( \text{PPIB} \)), exhibit a moderate-to-severe phenotype (9, 27). Generally, for collagen I mutations, it has been established that \( \text{COL1A1} \) mutations are more often associated with a lethal phenotype than \( \text{COL1A2} \) mutations (46). Glycine substitutions located at the N-terminal part are non-lethal in both genes (46). Glycine substitutions for large, branched, and charged amino residues are more often associated with a severe phenotype (46). In the collagen \( \alpha 1(1) \) chain at helical positions 691–823 and 910–964, consisting of major ligand-binding regions (MLRBs), essentially only lethal substitutions are identified. The MLRBs include sites important for collagen self-assembly and cleavage, as well as for binding by integrins, fibronectin, and other factors (46). For the non-collagenous mutations, only few cases have been reported and phenotypic variability has not been extensively studied, and therefore general principles have not been described yet.

### Treatment of OI

The focus of this review is on pharmacological treatment of adult OI. However, pharmacological treatment cannot stand alone, and physiotherapy, habilitation, and orthopedic care in the hands of an experienced surgeon from infancy are of utmost importance for more severe forms of OI.

#### Bone-specific treatments

There are a number of pharmacological agents available for effective fracture reduction in postmenopausal and...
male osteoporosis, such as bisphosphonates (e.g. alendronate and zoledronate), monoclonal RANKL antibody (denosomab), and rPTh (1–34) (teriparatide). These agents either attenuate loss of bone mass or increase bone mass, and thus decrease the risk of fracture. In OI, however, the pathophysiology of the disease causes a defective bone matrix, which does not necessarily respond to these pharmaceutical agents by a decrease in fracture rate. Generally, bone-specific treatments are prescribed together with calcium and vitamin D supplementation. Recent studies of treatment for postmenopausal osteoporosis have shown that adequate response to, for example, bisphosphonate treatment is correlated with circulating levels of 25(OH)D (49, 50). For treatment of OI, this would indicate that low serum 25(OH)D, as well as inadequate calcium intake, should be supplemented, unless contraindications are present.

There is currently no satisfactory treatment for severe OI, despite decades of research. Research in stem-cell transplantation (51, 52, 53) and various gene therapies (54, 55, 56, 57, 58) have not yielded clinically available applications. Individuals with mild OI are treated conservatively in most centers. In moderate-to-severe cases, with multiple long-bone fractures and/or vertebral compression fractures, bisphosphonate treatment is being used in children and often initiated at a young age, even in infancy (59, 60, 61, 62, 63). However, considerably less is known about how best to treat adults with moderate-to-severe OI, as only few trials, each comprising small numbers of treated patients with different OI types, have been published. As the patient population with OI grows older, the deleterious effects on the skeleton from aging are superimposed on the already present diminished bone mass and inferior bone quality due to the underlying disease. Furthermore, it is important to emphasize that the long-term effects of bisphosphonate treatment in pediatric and adult OI are not known.

**Bisphosphonate treatment for OI in childhood**

There is evidence from animal studies that bisphosphonate treatment leads to increases in BMD as well as decreases in fracture rate, as exemplified in the oim/oim mouse model of OI (64). In humans, bisphosphonates have been shown to increase lumbar spine BMD, ameliorate negative bone phenotypes, and improve vertebral height and areal measurements in children with OI (59, 61, 63, 65, 66, 67). However, initial reports on decreased pain and improved ambulation regrettably have not been possible to replicate in later controlled trials, and data on fracture reduction are equivocal (62, 63, 68). Recently a randomised, double-blind, placebo-controlled trial of orally administered riseredronate in children with predominantly mild OI has demonstrated a reduction in the rate of clinical fractures (69). Such trials have not been carried out with i.v. pamidronate for severe OI, and we therefore have no evidence for fracture reduction in this group of patients. Considering that i.v. bisphosphonates are routinely used in the treatment of severe OI (63), a randomized, placebo-controlled study would be difficult to perform. Regarding safety concerns with bisphosphonate treatment in OI, there have been no reports of osteonecrosis of the jaw neither in treated children, nor young adults up to age 25, despite the relatively high doses of bisphosphonate treatment given to children with OI (70, 71). Atypical femur fracture is another very rare condition that has been observed in patients on bisphosphonate therapy for osteoporosis (72). The only published observational study on this issue in OI for pediatric and adolescent patients highlights the need for further research regarding atypical femur fractures in bisphosphonate-treated patients with OI (73).

BMD treatment response in relation to BMD at onset and age at initiation has not been thoroughly studied in OI patients; however, there are reports supporting a negative correlation to BMD at onset (67, 74). Infants as young as 2 months have been treated with promising results and safety data (59, 60, 61, 75), and according to one study younger children did not gain as much bone compared with older children, explained by the fact that the deficit in BMD was smaller in younger children (67). Another study considered the response in infants to be faster and more pronounced than that in older children (75). Furthermore, although the majority of studies of bisphosphonate treatment are on children older than 3 years of age, there is support in observational trials with historical controls for increased BMD, improved vertebral shape, and attainment of motor milestones at an earlier age when treating severely affected infants with pamidronate (59, 61).

**Bisphosphonate treatment for OI in adults**

There are more studies on use of bisphosphonate in pediatric than in adult OI populations and some of the positive outcomes seen in children have been difficult to demonstrate in adults (76), although the overall goals of treatment are the same: reduction in fractures and chronic
bone pain and increase in BMD as a surrogate marker for treatment effect.

Table 2 summarizes the published Cochrane Systematic Reviews from 2008 (63), and studies on treatment of adult OI published since. In the Cochrane review from, the effectiveness and safety of bisphosphonates in treatment of OI in children and adults in randomized and quasi-randomized controlled trials comparing bisphosphonates with placebo, no treatment, or comparator interventions, in all types of OI was presented (63). Publications were included up to publication date of August 2008, with two studies available for analysis for the adult population (Table 2) (77, 78). The study by Chevrel et al. (78) on 64 adult OI patients in a 3-year randomized placebo-controlled study of alendronate showed a significant increase in total hip and lumbar spine BMD, but no significant difference in fracture rate, although the study was not statistically powered for analyses of fracture. Adami et al. (77) studied 46 OI adults, in which 31 received i.v. neridronate, compared with 15 patients who did not receive treatment until cross over after 12 months. Total follow-up time was 24 months, and a trend toward statistical significance was reported when pooling pre-recruitment and study period fracture rates, in favor of treatment.

After the publication of the Cochrane review, an additional four studies have been published on bisphosphonate treatment of adult OI patients. In a prospective non-randomized study of zoledronic acid in ten patients with osteoporosis or severe osteopenia (T score < −2) related to OI who could not tolerate oral bisphosphonates, Pavon de Paz et al. (79) found increases in lumbar spine BMD at 24 and 36 months and increase in femoral neck at 24 months. No fractures occurred in the patients during the study period. Shapiro et al. carried out an observational, nonrandomized study of 90 OI adults treated either with i.v. pamidronate (n = 28), oral alendronate (n = 10), or oral risendronate (n = 17). The untreated control group consisted of 35 patients (76). For type I OI, all bisphosphonates were associated with BMD increase in lumbar spine, and for the oral bisphosphonates increases in total hip were seen. A reduction in fracture rate was only seen for i.v. pamidronate in type III/IV patients (76). In a retrospective study of 16 adult patients with OI in Ireland, O’Sullivan et al. showed a large increase in BMD in patients on bisphosphonate treatment (median increase 15.1%; n = 10), and for two patients on PTH treatment (40.3 and 27.2% increase respectively) (80). No conclusions on fracture rate reduction could be drawn. In a prospective study by Bradbury et al. (81), 27 patients with type I OI treated with oral risendronate 35 mg weekly were assessed over 24 months. BMD increased significantly at lumbar spine (3.9%), with no change in total hip. Fracture rate remained at the level of historical controls.

### Teriparatide treatment in OI in adults

Teriparatide stimulates bone formation and reduces vertebral and non-vertebral fractures in postmenopausal osteoporosis (82). As OI is characterized by reduced collagen production and thereby bone formation, it seems obvious to investigate the effect of teriparatide in adult patients with OI. Observational studies have shown a positive effect on BMD in postmenopausal women (n = 13), with a statistically significant 3.5% increase in lumbar spine BMD (83). Orr woll et al. investigated in a randomized, placebo-controlled study comprising 79 adult OI patients, predominantly type I, the effect of teriparatide vs placebo over 18 months. Lumbar spine and hip BMD increased significantly in the patients treated with teriparatide compared with patients treated with placebo. Also markers of bone turnover increased significantly in the treated patients. No difference in self-reported fractures could be demonstrated between the two groups. Furthermore, although the number of patients with OI types III and IV were limited, subgroup analyses indicated that the effect was attenuated among these patients compared with type I OI patients (84). Further studies are needed to clarify whether treatment with teriparatide is superior to treatment with bisphosphonates or other antiresorptives in adult patients with different types of OI.

### Other potential treatments for OI

There are a number of therapies under evaluation for OI (e.g. the more recent osteoporosis treatments with denosomab and sclerostin antibodies), as well as therapies under development (e.g. cell-based therapies), and experimental models presently in vitro and in animals. These different areas of possible future therapies for OI are further described later.

### Cell-based therapy ▶ Parental somatic mosaicism is thought to underlie about 5% of classical OI, and the observation that these mosaic parents are phenotypically normal has provided rationale for different cell-based therapies. It has been proposed that normal osteoblasts in mosaic individuals have an advantage over osteoblasts
### Table 2  Clinical studies of bisphosphonate treatment of adult OI.

<table>
<thead>
<tr>
<th>References</th>
<th>Type of study</th>
<th>Study medication</th>
<th>Study period</th>
<th>Treatment arm (n)</th>
<th>n</th>
<th>Mean age (S.D.)</th>
<th>No fracture (n (%)</th>
<th>At least one fracture (n (%))</th>
<th>Outcome, mean % change LS BMD (S.D.)</th>
<th>Mean % change total hip BMD (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(78)</td>
<td>Double-blinded, placebo-</td>
<td>Oral alendronate</td>
<td>36 months</td>
<td>Treatment</td>
<td>31</td>
<td>36 (12)</td>
<td>21 (67.7)</td>
<td>10 (32.3)</td>
<td>10.1 (9.8)</td>
<td>3.3 (0.5)</td>
</tr>
<tr>
<td></td>
<td>controlled RCT</td>
<td>vs placebo</td>
<td></td>
<td>Placebo</td>
<td>33</td>
<td>37 (12)</td>
<td>22 (66.7)</td>
<td>11 (33.3)</td>
<td>0.7 (5.7)</td>
<td>−0.3 (0.6)</td>
</tr>
<tr>
<td>(77)</td>
<td>Double-blinded, placebo-</td>
<td>I.v. neridronate</td>
<td>12 (24)</td>
<td>Treatment</td>
<td>31</td>
<td>35.1 (7.1)</td>
<td>30 (96.7)</td>
<td>1 (3.3)</td>
<td>3.0 (4.6)</td>
<td>4.3 (3.9)</td>
</tr>
<tr>
<td></td>
<td>controlled RCT</td>
<td>vs no treatment</td>
<td>months</td>
<td>No treatment</td>
<td>15</td>
<td>34.7 (9.3)</td>
<td>13 (86.6)</td>
<td>2 (15.4)</td>
<td>−0.8 (7.7)</td>
<td>−0.5 (5.2)</td>
</tr>
<tr>
<td>(79)</td>
<td>Prospective non-randomized</td>
<td>I.v. zoledronic acid</td>
<td>36 months</td>
<td>Treatment</td>
<td>10</td>
<td>37 (12)</td>
<td>10 (100.0)</td>
<td>0 (0)</td>
<td>13.9b</td>
<td>3.8b,d</td>
</tr>
<tr>
<td>(76)</td>
<td>Observational, non-randomized</td>
<td>I.v. pamidronate, oral</td>
<td>&lt;161 months</td>
<td>Pamidronate</td>
<td>28</td>
<td>42.2 (12.1)</td>
<td>NA</td>
<td>NA</td>
<td>4.3 (2.5)b−15.9 (8.0)b,f</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>alendronate, oral</td>
<td></td>
<td>Alendronate</td>
<td>10</td>
<td>35.1 (9.9)</td>
<td>NA</td>
<td>NA</td>
<td>3.1 (2.8)b−6.2 (3.6)b,f,g</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>risedronate</td>
<td></td>
<td>Risedronate</td>
<td>17</td>
<td>40.0 (9.1)</td>
<td>NA</td>
<td>NA</td>
<td>3.1 (2.9)b−6.2 (3.6)b,f,g</td>
<td>NA</td>
</tr>
<tr>
<td>(80)</td>
<td>Retrospective cohort study</td>
<td>Alendronate, risedronate,</td>
<td>&lt;1–9 years</td>
<td>Not treated</td>
<td>35</td>
<td>38.2 (11.6)</td>
<td>NA</td>
<td>NA</td>
<td>8 (80.0)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>zoledronic acid, rhPTH</td>
<td></td>
<td>Bisphosphonate</td>
<td>10</td>
<td>32.3 (14.1)</td>
<td>2 (20.0)</td>
<td>0 (0)</td>
<td>2 (100.0)</td>
<td>NA</td>
</tr>
<tr>
<td>(81)</td>
<td>Prospective, observational</td>
<td>risedronate</td>
<td>24 months</td>
<td>Risedronate</td>
<td>27</td>
<td>39 (range 18–76)</td>
<td>13 (51.9)</td>
<td>14 (51.9)</td>
<td>3.8b,d</td>
<td>−1.8</td>
</tr>
<tr>
<td></td>
<td>study</td>
<td></td>
<td></td>
<td>rhPTH</td>
<td>2</td>
<td>32.5 (16.3)</td>
<td>0 (0)</td>
<td>2 (100.0)</td>
<td>27.2–40.3</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, data not available or not quantifiable; RCT, randomized controlled trial.

*Significant vs baseline.

Data at 36 months.

Data at 12 months.

Data at 24 months.

*01 type I.

*01 type II/IV.

Alendronate and risedronate combined.
producing mutated collagen. Thus, if normal osteoblasts could be introduced to an OI patient, these may mimic the situation in a mosaic carrier of OI, with the normal cells outperforming mutation-harboring cells (85, 86). Along these lines, bone marrow transplantation has been carried out in OI patients in clinical trials, aiming at introducing normal osteoblasts through differentiation of mesenchymal stem cells. A few positive reports have been published, despite low numbers of engrafted cells (51, 52, 53). Induced pluripotent cells could be another possible option (87); these could potentially be engineered to produce any desired tissue, including bone-forming cells for OI patients. This approach has been studied in vitro in mesenchymal cells from OI patients (88).

Gene therapy ▶ Allele-specific gene silencing ▶ For severe dominant OI, a therapeutic vision is silencing the mutated allele by gene therapy, i.e. allele-specific silencing. For a COL1A1 mutation, the consequence would be COL1A1 haploinsufficiency, thus converting a severe phenotype to mild OI (similar to type I). Heterozygous COL1A2 null alleles have no overt phenotype. There are several publications that report successful allele-specific gene silencing using siRNAs discriminating between single-nucleotide variants within specific mRNAs (89, 90, 91, 92, 93, 94, 95, 96, 97). These studies suggest that siRNAs may be interesting to explore as therapeutics in dominant monogenic disorders such as dominant OI as well and the first steps toward allele-specific silencing in OI were taken in 2004 in a study which reports that COL1A1 was silenced in mesenchymal progenitor cells (98). A recent publication has reported that allele-specific silencing of COL1A1 using short hairpin RNAs (shRNAs) reduced the amount of mutant collagen in BrtI/+ mice, a murine model for classical dominant OI (58). Targeted cell delivery is a challenge, and it will be necessary to guide siRNAs specifically to the cells in sufficient quantity. Possible avenues investigated include viral vectors expressing target tissue-specific shRNAs, aptamer-shRNA chimeras as well as atelocollagen-bound siRNAs (58, 99, 100).

For OI, more than 800 qualitative mutations have been described in COL1A1 and COL1A2 (46, 101), making it prohibitively laborious to create unique siRNAs for each mutation. A mutation-independent approach is desirable, and targeting of heterozygous SNPs (102) or insertion/deletion polymorphisms (indels) (103) in the COL1A1 and COL1A2 genes has now been successfully carried out in human bone cells in vitro. By specifically targeting both alleles of a common heterozygous position, all heterozygous individuals carrying a mutation on the same allele (in cis) could be treated, and design of a limited number of highly specific siRNAs with minimal off-target effects would potentially treat a majority of patients.

Viral vectors as a potential approach for recessive OI ▶ For many recessive disorders even a moderate increase in gene product can have a crucial effect on biological activity and function, and for OI such an increase could potentially rescue the recessive phenotypes. The most common approach for this would be utilizing a viral vector introducing a cDNA copy of the missing allele, with the largest conferred risk being turning on an oncogene or turning off a tumor suppressor gene. Several studies using viral vectors are ongoing for a multitude of disorders (104); however, to date there are no publications describing the use of viral vectors in recessive OI.

Ex vivo correction of mutated allele ▶ OI type I is often due to a quantitative collagen defect, and gene correction of the mutated allele or enhanced activity of the functioning allele would be the desirable goal. However, COL1A1 is a highly expressed large gene, and the viral vector approach described earlier would most likely not be optimal for classical dominant OI type I. Furthermore, for qualitative mutations, enhanced activity of the functioning allele would have to be combined with silencing of the mutated allele as OI is a dominant disorder. An attractive avenue for dominant OI would be a correction of the mutant allele with subsequent return of the corrected cells to the affected individual. Steps in this direction are ongoing through use of e.g. zinc-finger nucleases (105) and TALEN systems (106) and hopefully this approach can be applied for patients with OI in the future.

Other pharmaceutical approaches ▶ Over the years many different treatment regimes for OI have been studied with equivocal clinical effects following on initially positive publications; e.g. cortisone, vitamin A, vitamin D, fluoride, and strontium ranelate, as well as the hormones calcitonin, thyroxin, estrogens, and androgens. The combination of recombinant growth hormone (rGH) and bisphosphonates is still under investigation and may be beneficial for OI types I, IV, and III to increase linear growth, although these patients are not endogenously GH deficient (107).

Little is known about the benefits of other osteoporosis therapies for OI patients. The RANKL antibody, denosumab, was well tolerated in a small scale study in recessive OI
(108), and sclerostin antibody, an emerging osteoporosis therapeutic, has been shown to act as an anabolic agent in the type III OI murine model Brlt/+ (109).

Future perspectives

Larger study cohorts are needed to properly investigate the efficacy of pharmacological intervention, and efforts are underway to have national and international OI registries to make this possible.

Such registries/cohorts could also be the basis for further research into genotype vs phenotype for prediction of disease severity, and pharmacogenetic studies on the choice of medical treatment based on the patient’s mutation.

Summary

Bisphosphonates are the most widely investigated and used treatment option for OI, and have been shown to increase BMD in both children and adults, while effects on fracture incidence remain equivocal. For adults, there are few randomized controlled studies for treatment of OI, and the evidence for treatment is therefore limited. A recently published study of the effects of teriparatide in adult OI has shown positive effects on BMD, at least in mild disease. Despite the lack of evidence, bisphosphonates are being used for the prevention of fractures in adult OI, although dosing and duration of treatment remain to be studied further.

Trials investigating the effects of novel bone-specific treatments approved for use in postmenopausal osteoporosis in adult patients with OI are ongoing. Gene therapy may be a possible future treatment option for severe OI. Larger cohorts of patients with OI are necessary to obtain the statistical power to perform genotype/phenotype studies, pharmacogenetic studies and to assess fracture efficacy of bone-specific medications.

Declaration of interest

The authors declare the following association with the companies: K Lindahl disclosures: speaker’s bureau for Amgen. B Langdahl disclosures: received research grant from Eli Lilly, advisory boards and speaker’s bureau for Eli Lilly, Merck, Sharp & Dohme, and Amgen. O Ljunggren disclosures: speaker’s bureau for Eli Lilly and Amgen. A Kindmark disclosures: research grant and speaker’s bureau for Shire HGT, speaker’s bureau for Amgen and Glaxo Smith Kline. Inventor on patents WO2007039724, WO2007039718, WO2007039722, and WO2007039721.

References


Received 7 January 2014
Revised version received 16 April 2014
Accepted 22 April 2014