Treatment of osteogenesis imperfecta in adults

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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, since 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.
Background

General background

OI is a heterogeneous disorder of connective tissues with an incidence of 1/15 000 \(^1-^4\) and disease severity spanning from subclinical osteoporosis to intrauterine lethality. Dominant mutations 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 have been reported \(^5-^30\). 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 \(^32-^34\).

Classification

OI has traditionally been classified according to Sillence, who published a revised classification system based on clinical, radiologic and hereditary findings in the late 1970’s \(^33-^35\) (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 \(^36\). Dentinogenesis imperfecta is common and scleral hue variable. 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 phenotypes, and to date 17 types have been described (Table 1) \(^5-^30\). 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 approximately 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 \(COL1A1\) and \(COL1A2\). 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 COL1A1; patients have structurally normal collagen type I, but a reduced amount. Premature stop codons, splice-site mutations or insertion/deletions are commonly observed mutation types and all cause nonsense mediated decay of mRNA from one COL1A1 allele. Collagen type I is highly expressed in many connective tissue cell types, e.g. osteoblasts, and both alleles of COL1A1 are required to meet the needs of the organism. Haploinsufficiency of COL1A1 is usually associated with the milder type I phenotype, while COL1A2 haploinsufficiency does not have an overt clinical bone phenotype.

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. 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 substitution 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. Other examples of genes associated with OI phenotype may be involved in osteoblast differentiation and signaling, or bone formation. 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. This phenotypic variability is thought to be caused by modifying elements, which are essentially unknown to date. Similarly, this phenomenon has been described for non-collagenous OI; all known OI type V cases are caused by the same mutation in the IFITM5 gene but there is pronounced variability even within the same family regarding phenotypic severity. Also, individuals with OI type IX caused by similar nonsense mutations in Cyclophilin B (encoded by PP1B), exhibit a moderate to severe phenotype. Generally, for collagen I mutations it has been established that COL1A1 mutations are more often associated with a lethal phenotype than COL1A2 mutations. Glycine substitutions located at the N-terminal part are non-lethal in both genes. Glycine substitutions for large, branched and charged amino residues are more often associated with a severe phenotype. In the collagen □1(I) 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. 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 Osteogenesis Imperfecta

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, zoledronate), monoclonal RANKL antibody (denosumab), 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 e.g. bisphosphonate treatment is correlated with circulating levels of 25(OH)D. For treatment of OI, this would indicate that low serum 25(OH)D, as well as inadequate calcium intake, should be supplemented, unless contra indications are present.

There is currently no satisfactory treatment for severe OI, despite decades of research. Research in stem-cell transplantation and various gene therapies 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. 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 in osteogenesis imperfecta 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. 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. 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 is equivocal. Recently a randomised, double-blind, placebo-controlled trial of oral risedronate in children with predominantly mild OI did demonstrate a reduction of clinical fractures. Such trials have not been performed with IV pamidronate for severe OI, and we therefore have no evidence for fracture reduction in this group of patients. Considering that IV bisphosphonates are routinely used in the treatment of severe OI, 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 (ONJ) neither in treated children, nor young adults up to age 25, despite the relatively high doses of bisphosphonate treatment given to children with OI. Atypical femur fracture is another very rare condition that has been observed in patients on bisphosphonate therapy for osteoporosis. 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.

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. Infants as young as two months have been treated with promising results and safety data and according to one study younger children did not gain as much bone compared to older children, explained by the fact that the deficit in BMD was smaller in younger children. Another study considered the response in infants to be faster and more pronounced than in older children. 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.

Bisphosphonate treatment in osteogenesis imperfecta in adults

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

Table 2 summarizes the published Cochrane systematic review from 2008, 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 to placebo, no treatment, or comparator interventions, in all types of OI was presented. Publications were included up to publication date of August 2008, with 2 studies available for analysis for the adult population (table 2). The study by Chevrel et al 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 studied 46 OI adults, where 31 received IV 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 towards 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 10 patients with osteoporosis or severe osteopenia (T score < -2) related to OI who could not tolerate oral bisphosphonates, Pavon de Paz et al 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 performed an observational, non-randomized study of 90 OI adults treated either with intravenous pamidronate (n = 28), oral alendronate (n = 10), or oral risedronate (n = 17). The untreated control group consisted of 35 patients. For type I OI, all bisphosphonates were associated with BMD increase in lumbar spine, and for the oral bisphosphonates increases in total hip was seen. A reduction in fracture rate was only seen for IV pamidronate in type III/IV patients. 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). No conclusions on fracture rate reduction could be drawn. In a prospective study by Bradbury et al, 27 patients with type I OI treated with oral risedronate 35mg 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 osteogenesis imperfecta in adults

Teriparatide stimulates bone formation and reduces vertebral and non-vertebral fractures in postmenopausal osteoporosis. As osteogenesis imperfecta is characterized by reduced collagen production and thereby bone formation it seems obvious to investigate the effect of teriparatide in adult patients with osteogenesis imperfecta. 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. Orwoll et al. investigated in a randomized, placebo controlled study comprising 79 adult OI patients, predominantly type I, the effect of teriparatide versus 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 type III and IV was limited, subgroup analyses indicated that the effect was attenuated among these patients compared with type I OI patients. Further studies are needed to clarify if 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 for OI under evaluation (e.g. the more recent osteoporosis treatments with denusomab 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 below.
Cell based therapies

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 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. Along these lines, bone marrow transplantation has been performed 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. Induced pluripotent cells could be another possible option, 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.

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 short interfering RNAs (siRNAs) discriminating between single nucleotide variants within specific mRNAs. 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 2004 in a study where COL1A1 was silenced in mesenchymal progenitor cells. In a recent publication allele-specific silencing of COL1A1 using short hairpin RNAs (shRNAs) reduced the amount of mutant collagen in Brtl/+ mice, a murine model for classical dominant OI. 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.

For OI, more than 800 qualitative mutations have been described in COL1A1 and COL1A2, making it prohibitively laborious to create unique siRNAs for each mutation. A mutation independent approach is desirable, and targeting of heterozygous SNPs or insertion/deletion polymorphisms (indels) in the COL1A1 and COL1A2 genes have now been successfully performed 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 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\textsuperscript{104}; however to date there are no publications describing the use of viral vectors in recessive OI.

\textit{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, \textit{COL1A1} is a highly expressed large gene, and the viral vector approach described above 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\textsuperscript{105} and TALEN systems\textsuperscript{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\textsuperscript{107}.

Little is known about the benefits for OI patients of other osteoporosis therapies. The RANKL antibody; denosumab was well tolerated in a small scale study in recessive OI\textsuperscript{108}, and sclerostin antibody, an emerging osteoporosis therapeutic, has been shown to act as an anabolic agent in the type III OI murine model Brtl\textsuperscript{+/+}\textsuperscript{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 osteogenesis imperfecta, 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 showed 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

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ÖL disclosures: speaker’s bureau for Eli Lilly and Amgen.
AK 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, WO2007039721.

References:


fragility associated with an Amish COL1A2 variant and a knock-in mouse model. *J Bone Miner Res* 2010 **25** 247-261.


101. Dalgleish R. (http://www.le.ac.uk/ge/collagen/).
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<tr>
<th>OI Type</th>
<th>Affected Gene</th>
<th>Phenotype</th>
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<td>Classical Sillence types</td>
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<tr>
<td>I</td>
<td>COL1A1 or COL1A2</td>
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<td>II</td>
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<td>VI</td>
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* significant vs baseline, ¹ data at 12 months, ² data at 24 months, ³ data at 36 months, ⁴ OI type I, ⁵ OI types III/IV, ⁶ alendronate and risedronate combined, NA: data not available or not quantifiable

RCT: Randomized Controlled Trial