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REVIEW

The Role of Denosumab and Bisphosphonate in Osteogenesis Imperfecta: A Literature Review

El Papel del Denosumab y los Bisfosfonatos en la Osteogénesis Imperfecta: Una revisión de la Literatura

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ABSTRACT

Osteogenesis Imperfecta (OI) is a rare genetic disorder characterized by brittle bones and susceptibility to fractures. Management of OI focuses on minimizing fractures and improving bone strength. Denosumab and bisphosphonates have emerged as potential therapeutic agents in OI management due to their ability to modulate bone turnover. This literature review aims to explore the role of denosumab and bisphosphonates in the treatment of OI, highlighting their mechanisms of action, efficacy, and safety profiles. A comprehensive search was conducted across various databases, to identify relevant studies investigating the use of denosumab and bisphosphonates in OI management. The review discusses the molecular pathways underlying the pathogenesis of OI and how denosumab and bisphosphonates intervene in these pathways to improve bone quality. Furthermore, the review summarizes the findings from clinical trials and observational studies evaluating the effectiveness of denosumab and bisphosphonates in reducing fracture rates, improving bone mineral density, parathyroid hormone changes, calcium and phosphate quantity, and also enhancing functional outcomes in patients with OI. Additionally, considerations regarding optimal dosing, timing of initiation, and potential adverse effects of denosumab and bisphosphonates in individuals with OI are discussed. The synthesis of existing evidence underscores the promising role of denosumab and bisphosphonates as adjunctive therapies in the management of OI, although further research is warranted to elucidate their long-term efficacy and safety profiles in this patient population.

Keywords: Denosumab; Bisphosphonate; Osteogenesis Imperfecta.

RESUMEN

La osteogénesis imperfecta (OI) es un trastorno genético poco común caracterizado por huesos frágiles y susceptibilidad a fracturas. El manejo de la OI se enfoca en minimizar las fracturas y mejorar la resistencia ósea. El denosumab y los bifosfonatos han surgido como posibles agentes terapéuticos en el tratamiento de la OI debido a su capacidad para modular el recambio óseo. Esta revisión de la literatura tiene como objetivo explorar el papel del denosumab y los bisfosfonatos en el tratamiento de la IO, destacando sus mecanismos de acción, eficacia y perfiles de seguridad. Se realizó una búsqueda exhaustiva en varias bases de datos para identificar estudios relevantes que investiguen el uso de denosumab y bisfosfonatos en el manejo de la OI. La revisión analiza las vías moleculares subyacentes a la patogénesis de la IO y cómo el denosumab y los bisfosfonatos intervienen en estas vías para mejorar la calidad ósea. Además, la revisión resume los hallazgos de ensayos clínicos y estudios observacionales que evalúan la efectividad del denosumab y los bisfosfonatos para reducir las tasas de fracturas, mejorar la densidad mineral ósea, los cambios en la hormona paratiroidea, la cantidad de calcio y fosfato y también mejorar los resultados funcionales en pacientes con OI. Además, se discuten las consideraciones sobre la dosificación óptima, el momento de inicio y los posibles efectos adversos del denosumab y los bisfosfonatos en individuos con OI. La síntesis de la evidencia existente

subraya el papel prometedor del denosumab y los bifosfonatos como terapias complementarias en el tratamiento de la OI, aunque se justifica una mayor investigación para dilucidar sus perfiles de eficacia y seguridad a largo plazo en esta población de pacientes.

Palabras clave: Denosumab; Bifosfonatos; Osteogénesis Imperfecta.

INTRODUCTION

Osteogenesis Imperfecta (OI) is a disease characterized by bone fragility symptoms, leading to an increased risk of fractures. OI is caused by alterations in type I collagen and is genetic in nature. Clinically, this condition exhibits highly varied symptoms with an incidence rate of around 1:15,000-20,000 births. The natural course of this disease results in individuals with OI experiencing a variety of symptoms and complications that require multidisciplinary management. OI results in decreased bone mass and fragility, which can lead to morbidity due to pain, immobility, skeletal deformities, and growth deficiency. Reduced bone strength causes fractures from minor or trivial trauma, or fractures in atypical locations (such as the olecranon and compression fractures in the vertebrae). Extraskeletal manifestations include anomalies in the teeth (dentinogenesis imperfecta), blue sclerae, hearing loss, joint hypermobility, muscle weakness, and cardiovascular complications.

Management of OI aims to prevent deformities and fractures through medical, surgical, medical rehabilitation, and counseling interventions. Recent research in pharmacological therapy for OI may increase bone mass and improve bone architecture, but it has not yet targeted the matrix abnormalities that are the main source of bone fragility. Several studies are currently being developed to understand the genetic defects and pathophysiological mechanisms of OI.

Several options for pharmacological therapy can be used and have been proven beneficial in managing OI, including Bisphosphonates and Denosumab. Among the effective therapy options for managing OI, Denosumab, which is an anti-RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand) drug, is an antibody that inhibits the differentiation and function of osteoclasts. This is similar to bisphosphonates, which work by inhibiting osteoclasts to suppress bone resorption and increase bone mineral density in OI, especially in type IV, which is less responsive to bisphosphonate therapy. There are two different types of bisphosphonates: nitrogen and non-nitrogen. Nitrogen-containing bisphosphonates interfere with the formation, survival, and cytoskeletal dynamics of osteoclasts. Non-nitrogen-containing bisphosphonates induce osteoclast apoptosis.

Both denosumab and bisphosphonates specifically target osteoclasts; their effects on osteoblasts are mostly indirect because of the coupled mechanism between bone resorption and formation. One key to understanding the difference between these antiresorptive agents is their disposition in the body. Bisphosphonates have a strong affinity for bone and become embedded in bone mineral, persisting until released during bone resorption. Although bisphosphonates typically do not cross cell membranes, they will pass through them in the acidic environment created by osteoclasts during bone matrix resorption, thus specifically targeting osteoclast cells. Bisphosphonates are cleared from the circulation through renal excretion or adsorption to bone mineral. Initial clearance of a bisphosphonate dose is rapid, but the drug bound to bone must first be released by osteoclast-mediated bone resorption, and its elimination can last from weeks to several years. However, significant recycling of bisphosphonates in bone occurs, resulting in measurable retention for several years. Among antiresorptive and anabolic therapies for osteoporosis, only bisphosphonates bind to bone matrix, thus influencing the onset and offset of their action. Therefore, differences in bone affinity can affect the required dose of bisphosphonates and their reversibility of effects.

Unlike bisphosphonates, denosumab does not embed within bone tissue. Instead, by binding to RANKL in the extracellular fluid and circulation, denosumab inhibits the formation, function, and survival of osteoclasts. As an antibody, denosumab is cleared from the bloodstream through the reticuloendothelial system, with a half-life of about 26 days, and appears not to induce the formation of neutralizing antibodies. For this reason, bisphosphonates are more prone to causing long-term side effects, such as osteonecrosis, over suppression of bone remodelling, and even atrial fibrillation.

Based on the description above, the importance of studying the choice of OI management therapy with lower complication risks has piqued researchers' interest in understanding the differences between Denosumab and Bisphosphonates in treating OI cases and the potential for Denosumab to become a therapy option for OI.

METHODS

We also explore the comparative efficacy and potential synergistic effects or limitations of combining denosumab and bisphosphonate therapies in the context of OI management. We conducted a literature search related to an overview of OI, then carried out a review regarding the treatment of OI which has a lower risk. We collect scientific articles from 2019 to 2024 from scientific search engines, such as PubMed, ScienceDirect, and ResearchGate.

RESULTS

Pathophysiology

OI is a rare genetic disease. In most cases, this occurs due to mutations in the COL1A1 and COL1A2 genes. Recently, more diverse mutations associated with OI have been identified. The classification of OI according to the International Society of Skeletal Dysplasia is based on the disease inheritance model and associated genes.

OI syndrome names	Type	Inheritance	Genes
Nondeforming OI	Type I	Autosomal Dominant (AD)	COL1A1, COL1A2
Perinatally lethal	Type II	Autosomal Recessive (AR)	COL1A1, COL1A2, CRTAP, LEPRE1, PPIB, BMP1
Progressively deforming	Type III	AD, AR	COL1A1, COL1A2, CRTAP, LEPRE1, PPIB, FKBP10, SERPINH1, SERINF1, WNT1
Moderate	Type IV	AD, AR	COL1A1, COL1A2, CRTAP, FKBP10, SP7, SERPINF1, WNT1, TMEM38B
Calcification of interosseous membrane or hypertrophic callus	Type V	AD	IFITM5

Table 1. The genes associated with Osteogenesis Imperfecta

Two pro-alpha-1 chains and one pro-alpha-2 chain form type 1 collagen, which constitutes the main protein in the extracellular matrix of skin, bone, tendon, and others, forming a rigid triple helix structure. Each alpha chain consists of an amino-terminal pro-peptide and a carboxyl-terminal pro-peptide, and a central pro-peptide consisting of 338 glycine residues. Glycine is the smallest residue occupying the axial position of the triple helix. The triple helix structure of type 1 collagen is possibly due to the presence of glycine at every third amino acid residue.

At least 90 % of OI patients have genetic defects causing quantitative and/or qualitative abnormalities in their type I collagen molecules. These defects are inherited in an autosomal dominant, autosomal recessive manner, or by spontaneous mutation. Autosomal dominant forms are caused by direct defects in type 1 collagen, while autosomal recessive forms are caused by non-collagenous proteins, which play a role in post-translational modification or triple helix formation.

Defects involving type 1 Collagen

Frameshift mutations (involving premature stop codons in the affected allele) can result in a quantitative decrease in the amount of normal type 1 collagen. When patients are heterozygous in this condition, they may secrete half the normal amount of type 1 collagen. Additionally, errors in substitutions or deletions involving glycine peptide residues along the polypeptide chain can lead to the production of ineffective, abnormal collagen both structurally and quantitatively. Phenotypic expression in these defects depends on the substitution position, whether glycine is substituted at the carboxyl-terminal (severe form) or amino-terminal (milder form) of the polypeptide chain. Substitutions at the carboxyl end of the peptide have the potential to be more severe due to cross-linking in the triple helix that begins at the carboxyl terminus of the polypeptide chain. Patients with mutations of glycine residues affect the quality of collagen chains (commonly known as defects in Sillence types II, III, IV), leading to more severe bone manifestations.

Other Mutations

In addition to mutations in type I collagen, other genetic mutations can also produce autosomal recessive OI types (VI, VII, VIII, IX, X, and XI). These mutations may involve components that encode collagen 3-hydroxylation complexes, which aid in assembling the triple helix. These recessive mutations account for 5 % of the total OI cases.

Diagnosis

The diagnosis is based on clinical and family history, pregnancy history, physical examination, bone mineral density (lumbar vertebrae), bone biochemistry, and radiographic examination. In general, the diagnosis can be established clinically. Only in some situations are special examinations required such as collagen and DNA examinations, namely when after clinical examination including history taking, physical examination, and radiological examination, the diagnosis of OI cannot be established or remains doubtful.

History Taking

History taking that needs to be considered includes the following:

      a. Prenatal history: Long bone fractures were found in the fetus during the ultrasound.

    b. Perinatal history: presence of fractures.

    c. Family history: presence of perinatal death, family members with recurrent fractures, brittle teeth (dentinogenesis imperfecta), blue sclera, early onset hearing impairment.

    d. Disease history: onset, progressiveness, history of growth, and presence of recurrent fractures.

Physical Examination

Patients typically present with four main clinical features:

    a. Decreased bone mass, increased bone fragility.

    b. Blue sclera.

    c. Dentinogenesis imperfecta (normal enamel with dentin abnormalities).

    d. Hearing impairment.

    e. Other features include ligament weakness, increased joint mobility, short stature, and easy bruising.

The manifestations depend on the type of OI. The classification of OI is as follows (Table 1)

| Table 2. Classification of OI	
Classification of OI	**Explanation**
Based on the severity	OI with mild symptoms (type A) OI with progressive and lethal deformities in the perinatal period (type B)
According to the International Nomenclature group for Constitutional Disorders of the Skeleton (INCDS) in 2010	Type 1: OI without deformities with blue sclerae Type 4: Common form of OI without blue sclerae Type 5: OI with calcifications in the intraosseous membrane Type 3: OI with progressive deformities Type 2: Lethal OI in the perinatal period
Note: Types 1, 4, and 5, based on their mild severity, are classified as OI type A. Types 2 and 3 are classified as OI type B.	
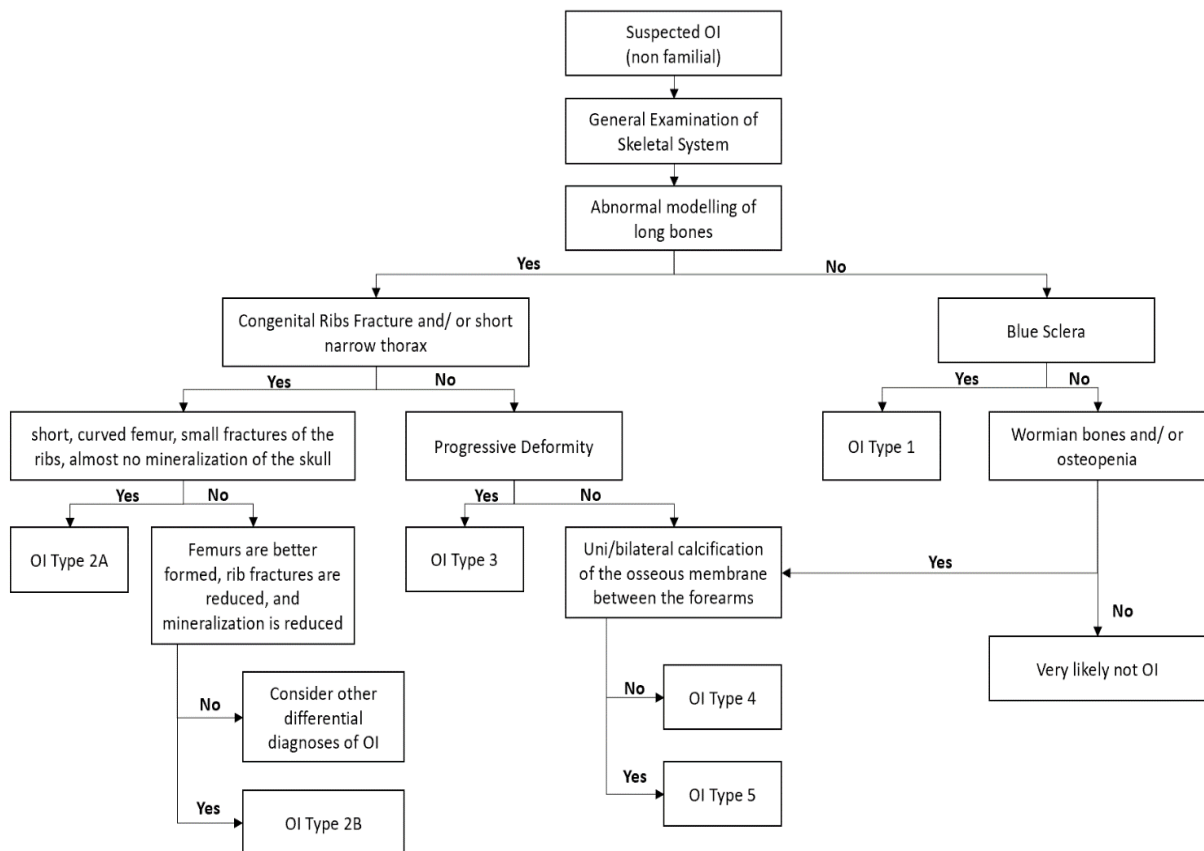
Figure 1. The Diagnostic Algorithm for Osteogenesis Imperfecta

Additional Examinations

Radiological examinations may reveal signs of fractures or decreased bone mineral density (osteopenia or osteoporosis) from plain radiographic surveys, prenatal ultrasonography (USG), Bone Mineral Density (BMD) (if age-specific normal standards are available for children). Computed tomography (CT) scans and Magnetic Resonance Imaging (MRI) are not routinely performed.

Plain Radiography:
- Head, neck, and Spine: Wormian bones, basilar invagination, kyphoscoliosis (39 to 100 %), platyspondyly.
- Chest: Pectus excavatum or carinatum.
- Pelvis: Acetabular protrusion, coxa vera.
- General: Osteoporosis, lack of long bone shafts, cortical thinning, hypertrophic callus formation, popcorn calcification involving metaphysis and epiphysis, pseudoarthrosis at fracture sites.

Prenatal Ultrasound (USG): Decreased calvaria ossification, shortening and angulation of long bones, multiple fractures, rib bones appearing like beads (beaded appearance), polyhydramnios.
   a. CT scan:
      - Wormian bones.
      - Basilar invagination.
      - Otosclerosis.
      - Long bone fractures.
   a. MRI: to evaluate basilar invagination.

Laboratory additional examinations can be performed with bone biochemistry tests including calcium, vitamin D, phosphate, ALP, and magnesium. If clinical suspicion persists and resources allow, fibroblast culture and mutation analysis are highly recommended

Treatment

Management varies with age, severity level, and patient's functional status :
   a. Mild: mild activity restriction, avoid contact sports, management for each fracture.
   b. Moderate: medical rehabilitation and orthopaedic interventions, management of acute fractures and scoliosis.
   c. Severe: intramedullary nailing with osteotomy used to correct severe long bone bowing.

Patients with OI require multidisciplinary management. Medication therapy is given after consultation with a paediatric endocrinologist. In some cases, management needs to begin at birth. As this disease is based on genetic abnormalities, there is no definitive treatment for OI, and it mainly focuses on reducing symptoms, which include.

Medication

Medication therapy can be administered promptly after the diagnosis is established. The selection of medication therapy includes the following

Bisphosphonates
   a. Pamidronate. The minimum age for intravenous pamidronate administration is 2 weeks. The commonly used dose is 9-12 mg/kg/year given cyclically every 1-4 months, with the following protocol (Table 3).
   b. Zoledronic acid. The minimum age for intravenous zoledronic acid administration is 3 months (for ages below 3 months, therapy is based on expert team consideration, minimum of 2 experts). Infusion preparation for zoledronic acid is shown in Table 4

For the first cycle of AZ administration, patients must undergo a 2-day hospitalization for close monitoring of potential acute complications. Subsequent administrations of AZ require only a 1-day hospitalization. All patients are advised to maintain adequate oral calcium intake with a daily dose of 1200 mg along with a daily dose of vitamin D (400-800 IU).

Denosumab
There are several reports of denosumab use in OI, but no randomized trials. The first case series of denosumab treatment published in OI was by Hoyer-Kuhn et al, who administered denosumab at a dose of 1 mg/kg every 12 weeks for 6 months to 10 children with OI over a 4-year period. All individuals had previously been treated with bisphosphonates but discontinued treatment 6 months before entering the study. Calcium and vitamin

D supplements were routinely given. The average age of participants was 7 years old, and most had OI type 1. Bone density increased during the study, but there were no changes in vertebral morphometry or general mobility. Urinary Deoxypyridinoline/Creatinine values (a bone resorption marker) significantly decreased after the first denosumab administration, reaching a nadir on day 8 and then rising again so that by 10 weeks, values approached pre-treatment levels. Various side effects were reported, including one case of hypocalcaemia.

Table 3. Protocol for administering sodium pamidronate		
Initial Assessment		
Serum	Calcium. Phosphate, ALP, Creatinine, DPL	
Urine	Calcium, Creatinine	
Radiology	Skull (AP/Lateral), Vertebrae (AP, Thorax Lateral, Lumbar segment, Upper and lower extremity (AP or Lateral)	
BMD	DXA	
Dosage (Maximal Dosage 60 mg/days)		
Age	**Dosage**	**Frequency**
<2 years old	0,5 mg/kg/day for 3 days	2 months
2-3 years old	0,75 mg/kg/days for 3 days	3 months
>3 years old	1,0 mg/kg/days for 3 days	4 months
Dilution		
Drugs (mg)	**Normal Saline Volume (ml)**	**Infusion rate (ml/hour)**
0 – 0,5	50	15
5,1 – 10	100	30
10,1 – 15,0	150	45
15,1 – 25,0	250	75
25,1 – 50,0	500	150
50,1 – 60,0	600	180
Maximum concentration 0,1 mg/ml		

Table 4. Protocol for administering zoledronic acid infusion				
	Zoledronic Acid Dosage	**NaCl volume required**	**Duration**	**Interval Cycle**
Neonates	0,0125 mg/kg/dosage	50 ml	45 minutes	-
Infants	0,025 mg/kg/dosage	50 ml	45 minutes	3 months
Pediatrics	0,05 mg/kg/dosage	100 ml	30 minutes	6 months

Orthopaedic intervention
   Surgical management is aimed at treating fractures and correcting deformities that occur in OI.

Medical Rehabilitation
   Physical rehabilitation should begin as early as possible so that patients can achieve optimal functional levels, including muscle and joint strengthening and optimizing mobility.

Genetic Counselling
   Patients and families are explained about the possibility of inheriting this disease.

DISCUSSION
The Role of Bisphosphonates in the Management of Osteogenesis Imperfecta
   There is no cure for OI, and therapy mainly consists of supportive measures at present. Therapy varies and is individualized depending on the severity of OI, the degree of impairment, and the individual's age. Orthopaedic management is paramount; surgical intervention or bracing of the lower limbs, or both, are often necessary. Physical and occupational therapy are primary therapies. Pharmacological agents including growth hormone, calcitonin, parathyroid hormone, sodium fluoride, and vitamins have been given in an effort to reduce fractures and deformities in OI. Oral and intravenous (IV) bisphosphonates are currently the most promising pharmacological therapy and routinely used for OI, as clinical trials of these agents consistently demonstrate increased BMD in individuals with OI. Previous versions of this review and other systematic reviews since have

found consistent increases in BMD in individuals with OI treated with various bisphosphonates. Some trials also indicate a reduction in fracture risk and improved growth.

Bisphosphonates are analogues of pyrophosphate that strongly bind to bone surfaces. The basic structure of bisphosphonates consists of a carbon-phosphorus-carbon backbone that makes them resistant to chemical hydrolysis. Bisphosphonates exert their effects through several mechanisms including directly inhibiting osteoclast precursor differentiation, osteoclast apoptosis, and inhibiting the mevalonate pathway. Commonly used drugs include second-generation bisphosphonates, alendronate, and pamidronate, which have amino-terminal groups. Third-generation bisphosphonates, such as risedronate and zoledronate, have cyclic side chains resulting in enhanced anti-resorptive properties.

A systematic review from 2009 confirmed increased bone density in children with OI treated with bisphosphonates. Not all studies included in that review showed reductions in fracture rates, improvements in pain, or increased quality of life with the treatment. A recent Cochrane review found 14 of 21 trials (819 participants) assessing the effectiveness and safety of bisphosphonates in increasing bone mineral density, reducing fractures, and improving clinical function in children and adults with OI. These studies were published between 2003 and 2013, and many of the questions raised in the initial systematic review resurfaced in subsequent reviews.

Bisphosphonate therapy is not a perfect therapy for OI management because it does not directly address the underlying issue, namely, the quality of the bone itself. However, it is undoubtedly true that bisphosphonate therapy increases bone density in OI, especially in growing children, as illustrated by the Cochrane review.

Intravenous bisphosphonate treatment with continued growth allows for the correction of vertebral compression fractures through bone remodelling processes. This effect is time-dependent, so the longer the treatment/growth period, the better the results in terms of normal or near-normal vertebral body dimensions. The use of bisphosphonates does not appear to alter the occurrence of scoliosis but may slow its progression in severe forms of OI. There is also improved mobility and functional outcomes in some studies. A recent meta-analysis showed a 20 % decrease in long bone fractures in paediatric patients with OI treated with bisphosphonates. While others show a statistically insignificant reduction trend. As the underlying abnormal nature of OI bone is not altered with bisphosphonate therapy, ongoing fractures remain a challenge to manage. Oral bisphosphonate treatment has not been associated with improvements in vertebral body morphology but has shown the same reduction in paediatric fractures compared to intravenous therapy, so its use may be limited to mild OI or maintenance of moderate OI without compression fractures.

Intravenous bisphosphonate therapy has also been widely used to treat bone fragility in children with OI. This is largely based on studies of patients with severe bone fragility who mostly received intravenous pamidronate for 2 to 4 years. Other bisphosphonates, such as etidronate and zoledronic acid, have also been used, with almost similar outcomes. Reported bone effects of intravenous bisphosphonate therapy in children with OI include a significant increase in BMD in the lumbar vertebrae, increased cortical thickness, and trabecular bone volume per tissue volume on iliac bone histomorphometry, radiologically evident remodelling of compressed vertebral bodies, and reduced rates of long bone fractures.

Currently, although with limited reference evidence, both oral and intravenous bisphosphonates have been shown to increase bone mineral density in children and adults with this condition. There appears to be no difference in their ability to improve bone mineral density. It is unclear whether oral or intravenous bisphosphonate treatment consistently reduces fractures, although some studies have reported this independently, and no studies have reported an increase in fracture rates with treatment. The studies included here do not convincingly show bisphosphonates improve clinical status (reduce pain; improve growth and functional mobility) in people with OI. Given their widespread current use and expected continued use, optimal methods, duration of therapy, and long-term safety of bisphosphonate therapy require further investigation. Moreover, attention should be given to reducing long-term fractures and improving indicators of quality of life.

Bisphosphonates work by deactivating osteoclasts, the cells that break down bone tissue, thus inhibiting bone resorption. There are two different types of bisphosphonates, nitrogen and non-nitrogen. Nitrogen-containing bisphosphonates interfere with osteoclast formation, survival, and cytoskeletal dynamics. Non-nitrogen bisphosphonates initiate osteoclast apoptosis. Bisphosphonates vary in efficacy and absorption when taken orally, making direct comparisons challenging.

Bisphosphonates are widely used in postmenopausal women to treat osteoporosis where they have been shown to increase bone density, reduce bone turnover, and decrease fractures. Although an increase in BMD is not expected to change the defective Type I collagen in OI, it is anticipated that increased BMD may lead to a decrease in fracture rates analogous to bisphosphonate therapy in postmenopausal women with osteoporosis. Animal models provide reasons for optimism as increased BMD in OI mouse models is accompanied by a decrease in fracture rates. However, caution is advised as OI biology differs from osteoporosis, and increasing bone density without altering strength may not lead to desired functional improvements. A report on bisphosphonate-induced osteopetrosis validates these concerns.

The optimal dose, frequency, and duration of bisphosphonate treatment for OI are still undetermined. Treatment approaches vary from center to center, depending on drug availability and the treating physician's experience. There is an approach using intravenous pamidronate in children under 2 years old, switching to zoledronate in older children with moderate to severe OI. However, other centers only use pamidronate or zoledronate. To date, no data shows one form of intravenous bisphosphonate to be superior to another. Not all children with OI require intravenous bisphosphonate therapy. There is an extremely conservative approach considering using intravenous bisphosphonates in children with OI type III or children who have two or more long bone fractures per year or vertebral compression fractures. Other centers initiate bisphosphonate therapy in children with a confirmed OI diagnosis after one major long bone fracture (such as a femoral fracture). Annual pamidronate doses range from 9 to 12 mg/kg/year, depending on the regimen used. In bisphosphonate-naive patients, the initial zoledronate dose can be reduced to 0,0125 mg/kg to reduce the risk of hypocalcaemia and acute-phase response. The greatest increases in BMD, cortical thickness, and trabecular number occur in the first 2-4 years of bisphosphonate therapy.

The Role of Denosumab in the Management of Osteogenesis Imperfecta
The FDA-approved treatment regimen for OI includes drugs used for other conditions such as osteopenia and osteoporosis, such as bisphosphonates, which have shown positive effects in improving the quality of life of people with OI. Physical therapy and rehabilitation also play a crucial role in maintaining the mobility of these patients. Additionally, in some cases, orthopaedic surgery may be required.

In 2010, the FDA approved denosumab (a monoclonal antibody) for the treatment of osteoporosis in postmenopausal women at high risk of fractures and in 2011 by the European Commission.

Denosumab is a monoclonal antibody directed against Receptor Activator of Nuclear Factor Kappa B ligand (RANKL), a molecule that plays a crucial role in osteoclast activation. Through this action, denosumab acts as a potent inhibitor of osteoclastic bone resorption. The dose is 60 mg subcutaneous (s.c.) every six months for postmenopausal osteoporosis treatment and male osteoporosis. The dose used is 1 mg/kg s.c. every 3 months. All studies reported a significant increase in BMD and no significant side effects of treatment over a two-year period. A systematic review of denosumab in children with OI, identified and evaluated the three studies mentioned above and concluded that further research is needed to evaluate its role in treatment. In some studies, the use of Denosumab has similar effectiveness to bisphosphonates, with improvement in BMD in some cases, especially in OI type IV.

Denosumab is well tolerated and generally provides a good response in terms of BMD markers and bone turnover along with the potential for fracture prevention in OI patients with osteoporosis, thus representing a good treatment option for such cases. In 2010, denosumab as a fully human IgG2 antibody that binds RANK ligand was approved for treating osteoporosis in postmenopausal women. By inhibiting the interaction of RANK ligand with its receptor RANK, denosumab is a potent anti-resorptive agent, reducing pre-osteoclast differentiation and osteoclast survival, and therefore reducing bone resorption. The beneficial effects (reduced bone resorption) are comparable to bisphosphonate therapy in postmenopausal women, but subcutaneous application is more convenient, and the potential risk of long-term side effects can be reduced due to complete antibody degradation after several months.

Denosumab is well tolerated even in children. No growth impairment is observed. The most important concomitant effect of denosumab is the alteration of calcium homeostasis (hypocalcaemia after injection followed by rebound hypercalcemia at the end of each treatment interval). Oral calcium and vitamin D supplementation adjusted by body weight continuously are mandatory to avoid severe hypocalcaemia within the first 14 days after injection as reported in adults and children treated with denosumab. A clinically significant hypercalcemia was recently reported after discontinuation of denosumab treatment in a male child with fibrous dysplasia and two children with giant cell tumours and interpreted as a rebound effect. At the end of our trial, only a few cases of hypercalcemia without clinical significance were observed in our patients. Previous bisphosphonate treatment may have attenuated this rebound effect in our patients

The first prospective clinical trial of denosumab application in children with OI provides evidence that, on average, denosumab leads to significant changes in areal bone mineral density in the lumbar spine, that children undergoing denosumab treatment show increased height. Denosumab appears to suppress bone resorption in children over 10-12 weeks and is safe over a one-year treatment course if adequate calcium and vitamin D substitution is provided

Semler et al. also studied the use of denosumab in patients with OI type VI, showing good results over a 2-year period. During this process, deoxypyridinoline (also called pyrilinks-D) was measured to verify its effectiveness. Deoxypyridinoline or pyrilinks-D is one of two pyridinium cross-links that provide structural rigidity to type I collagen found in bone. The substance is excreted and measured unchanged in urine and is a specific marker of bone resorption and osteoclastic processes. The results of the study conducted by Semler et al. showed a decrease in bone resorption with a decrease in deoxypyridinoline levels in urine.

The interval between denosumab injections is chosen based on experience from adults with osteoporosis. However, the results of studies conducted by Semler and Hoyer et al. suggest that a 6-month interval may be too long for patients with OI. An 8-10week interval seems more appropriate to ensure constant suppression of bone resorption by osteoclasts.

In addition to its effectiveness in normalizing bone resorption in patients with OI, denosumab potentially offers other advantages compared to bisphosphonates. Humanized antibodies degrade within 3-4 months after injection and therefore do not remain in the body. Bisphosphonates are retained in the human body for years, a fact that has led to debate about their safety in long-term therapy for children.

According to Hoyer-Kuhn et al., treatment with denosumab should be continued until the end of children's growth, similar to the current use of bisphosphonates. Bone turnover is very high during childhood and adolescence, and the strong effect of antiresorptive treatment with denosumab can be expected to reduce the risk of rebound effects after the end of therapy.

There are also studies stating inconsistent findings regarding the administration of denosumab in children with OI. There are two prospective studies and one case report involving a total of 15 children. One trial consisted of four children diagnosed with OI type VI who had a poor response to bisphosphonate treatment but then showed a remarkable increase in BMD as well as bone resorption and formation biomarkers with denosumab. Two children subsequently experienced bone fractures due to mild trauma. Another trial focused on 10 children diagnosed with OI types I, III, and IV and reported that denosumab significantly increased BMD at week 48. Four bone fractures due to trauma were reported. However, N-terminal telopeptide levels of type I collagen tended to increase, while osteocalcin levels tended to decrease. The case report is a clinical observation in a child with OI type VI, with a mutation in SERPINF1, who received denosumab at 23 months and did not show clinical improvement in BMD or bone fractures.

The optimal management of OI remains a puzzle. Denosumab can degrade within three to four months, avoiding the long-term accumulation effects of bisphosphonates. Compared to intravenous bisphosphonate injections, subcutaneous denosumab injections may be more convenient and acceptable to patients and families. Given its potential clinical applications, it is worthwhile to explore the long-term benefits and safety of denosumab for patients with OI.

Two studies appear comparable, where denosumab was tested on patients with the same recessive OI type VI. One key characteristic of OI type VI is increased unmineralized osteoid, which reduces bisphosphonate binding to mineralized bone surfaces and its inability to inhibit osteoclastic activity. Denosumab may be considered a new treatment option for OI type VI through the RANK ligand approach. However, these studies yielded inconsistent findings for BMD and fracture incidence rates, and further investigation is needed to clarify the effects of denosumab on OI type VI, due to the lack of control groups, short-term observations, differing management, and small sample sizes in these two studies. Another prospective trial involving children diagnosed with OI types I, III, and IV reported promising benefits and safety effects for denosumab, but once again, the lack of control groups and small sample sizes weaken their findings and hinder their validity and generalizability.

It can be concluded that the quality of evidence regarding the effects of denosumab treatment in children with OI is scarce, limited, and inconclusive. Comparative randomized head-to-head trial designs using a bisphosphonate control group may be necessary to assess the equivalence and/or superiority of denosumab. Dosage and dosing intervals may also require further investigation to achieve optimal treatment effects. Sample size is a common challenge in research for rare diseases like OI, where the prevalence is less than one per 10,000 live births.

CONCLUSIONS

Denosumab and Bisphosphonate treatments are effective in enhancing BMD and managing bone turnover markers in OI patients. Denosumab inhibits bone resorption, potentially reducing fracture risk, particularly in OI type III and IV patients. Bisphosphonates also improve BMD, but concerns exist about long-term safety, including atypical fractures and jaw osteonecrosis. Treatment choice should be individualized, considering factors like disease severity and patient characteristics, with further research needed to optimize outcomes and safety in OI patients.

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