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Osteogenesis imperfecta and bisphosphonate

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Abstrak. Osteogenesis Imperfecta (OI) didefinisikan sebagai kelainan genetik yang ditunjukkan dengan berbagai kondisi klinis, seperti kelainan bentuk tulang, kelainan struktur gigi, tuli, sklera biru, gangguan pertumbuhan, dan kelemahan ligamen. Sebagian besar pasien OI mengalami mutasi pada gen rantai alfa kolagen tipe I, *COL1A1* dan *COL1A2*. Semua gen tersebut diekspresikan dalam osteoblas dan bertanggung jawab atas sebagian besar metabolisme langsung kolagen tipe I. Bisphosphonate (BP), sebagai agen antiresorptif yang kuat, menghambat resorpsi tulang melalui aksi langsung di dalam osteoklas. Obat ini memotong laju pergantian yang berlebihan dan mencegah hilangnya jaringan tulang. Pemilihan rejimen BP untuk pasien OI masih menjadi kendala yang signifikan karena kurangnya standarisasi terapi dan kurangnya bukti yang dipublikasikan untuk menentukan jenis yang paling tepat pada pasien OI yang berbeda. Penggunaan BP dan manfaatnya pada OI dibahas dalam ulasan ini.

Kata kunci: osteogenesis imperfecta, bisphosphonate, kepadatan mineral tulang, pembentukan tulang

Abstract. Osteogenesis Imperfecta (OI) is defined as genetic disorders presented by various clinical presentations, such as bone deformities, abnormalities in dental structure, deafness, blue sclera, growth retardation, and ligament laxity. Most OI patients have a mutation in collagen type I alpha chains genes, *COL1A1* and *COL1A2*. All those genes are expressed in osteoblasts and mostly responsible for the direct metabolism of collagen type I. Bisphosphonates (BPs), as potent antiresorptive agents, inhibit bone resorption through direct actions in the osteoclasts. They cut the excessive turnover rate and prevent bone tissue loss. The selection of BP regimens for OI patients is still a significant obstacle due to the lack of standardization of therapy and the lack of published evidence to determine the most appropriate type for different OI patients. The current use of BP and its benefit in OI are discussed in this review.

Keywords: osteogenesis imperfecta, bisphosphonate, bone mineral density, bone formation

Introduction

Osteogenesis Imperfecta (OI), which already presents since an infant, is defined as genetic disorders presented by several low trauma fractures[1]. Primary osteoporosis in children mainly caused by this disorder[2]. There are various clinical presentations shown in OI, such as bone deformities, abnormalities in dental structure, deafness, blue sclera, growth retardation, and ligament laxity[1].

Approximately, there are 1 of 100,000 children in the world suffered from OI since they were born. In the USA, there are around 500,000 people diagnosed with OI. Meanwhile, in Indonesia, the prevalence is yet to determine. The Endocrinology Division, Child Health Department of Cipto Mangunkusumo Hospital has treated 70 cases of Osteogenesis Imperfecta during the last five years[2].

Most OI patients have a mutation in 1 of 2 collagen type I alpha chains genes, *COL1A1* and *COL1A2*. Collagen type I as the major organic bone matrix element has a leading role in bone tissue integrity. Eighteen other gene mutations are associated with OI phenotypes. All those genes are expressed in osteoblasts and mostly responsible for the direct metabolism of collagen type I.

However, some of them are also involved in other osteoblast functions such as Wnt signaling[3].

Nearly all OI patients that present typical clinical findings are detected to have a well-known OI-related gene mutation. A current study with a total sample of 600 OI patients found 97% of patients with OI type I encountered disease-causing mutation (all with *COL1A1* or *COL1A2* mutations) and 99% of patients with severe OI types (77% with *COL1A1* or *COL1A2* mutations). Deficiency in the latest genes causes latent forms of OI. Meanwhile, gene *IFITM5* and *P4HB* are linked with dominant OI and the other two genes, *PLS3* and *MBTPS2*, cause X-linked bone fragility[3]. Other gene mutations are also found to result in OI, other than collagen type I mutation[4]. Even some OI genes yet to be found may only affect a small number of people with a typical OI phenotype[3]. The classification used in the clinical practice setting for OI is still formed on its phenotypical features. Sillence classification, as the original clinical-based classification, categorized OI into four types (type I to IV). Meanwhile, the Sillence Classification based on genetic mutations has developed into 18 groups and is expected to increase in the future[4].

Nearly until ten years ago, management of OI mainly includes rehabilitation, physiotherapy, and corrective surgery. The main goal of therapy in OI is to achieve maximum potential mobility and functional capabilities. Several attempts to increase bone formation have not shown promising results. As potent antiresorptive agents, Bisphosphonates may become the answer because it offered a high bone turnover rate in OI patients[5]. Currently, the selection of bisphosphonate therapy regimens for OI patients is still a significant obstacle due to the lack of standardization of therapy and the lack of published evidence to determine the most appropriate type for different OI patients. No studies have directly compared the efficacy and safety of different therapeutic regimens.

Bisphosphonates

Bisphosphonates (BPs) are synthetic and pyrophosphate analogues consisting of two groups of phosphonates attached to a carbon atom that replaces oxygen in pyrophosphate (P-O-P to P-C-P). Metabolically, they are stable and have a healthy bone affinity, particularly in areas with high turnover rates. Based on their side chains, BPs are classified into three generations[6]:

1. The first-generation bisphosphonates consist of minimal-modified side chains (Clodronate, Etifronate, and Medronate) or chlorophenyl typed (Tiludronate).
2. The second-generation bisphosphonates or Amino BPs consist of an N-atom in the side chain (Alendronate, Ibandronate, and Pamidronate). These chains are 10 to 100 times more potent than the first generation.
3. The third-generation bisphosphonates consist of an N-atom within the heterocyclic ring (Risedronate and Zoledronate). They are almost 10,000 times more potent than the first generation.

Bisphosphonates, as antiresorptive agents, inhibit bone resorption through direct actions in the osteoclasts. They cut the excessive turnover rate and arrest or prevent the progressive fall of the microarchitecture and bone tissue loss. Bisphosphonates bind to the exposed bone minerals to respond the active bone remodelling so that they inhibit osteoclasts-mediated bone resorption in a dose-dependent manner[6]. There will be an improvement to the existing bone microarchitecture and mineralization and

advanced loss prevention of structural elements. Regular treatment with N-containing BPs affects the rapid progress in bone microarchitecture, along with the increment in bone mass leads to enhanced mechanical strength and lessened risk of fracture events. Latest N-containing bisphosphonates also affect the GTPase formation by preventing the intracellular mevalonate pathway of protein prenylation and cholesterol biosynthesis. They also cause disturbance of ameliorated protein-membrane transfer, membrane loss, integrin signalling, cytoskeleton disruption, and apoptosis induction of osteoclasts[3,6].

Until today, there are eight types of bisphosphonates approved by the US-Food and Drugs Administration (FDA) for clinical benefit. They are alendronate, clodronate, etidronate, ibandronate, pamidronate, tiludronate, risedronate, and zolendronic acid. Those 8 BPs can improve bone mass and reduce the risk of fractures in osteoporotic patients. BPs also be used in Paget's disease, bone metastases and cancers such as multiple myeloma and hypercalcemia of malignancy which is useful in controlling the elevated levels of blood calcium[6].

Osteoporosis

Recently, osteoporosis treatment using BPs is established. They can be used either in men with idiopathic osteoporosis or women postmenopausal osteoporosis and other kinds of osteoporosis. Routine oral formulations are available for both prevention and treatment[7]. A study found an annual infusion of 5 mg zolendronic acid reduces vertebral fracture risk by 70% and vertebral fractures by 40% within three years. Bisphosphonate usage also decreases the mortality rate in patients post-hip fractures by 28% over three years[6].

Antitumor Activity – Solid Tumors and Metastasis

Bone metastases may be the metastatic disease that shows most symptoms, affecting the patient's quality of life, mobility, and independence. More than 80% of patients with breast, prostate, or kidney malignancies develop metastases to bones[8]. BPs are believed to directly influence antitumor activity and act synergistically when combined with other anticancer agents. BPs work in several different mechanisms to reduce bone resorption formation in cancers[6].

Hypercalcemia

BPs are proven to be effective in the release of calcium-mediated by osteoclasts and hypercalcemia control. A single zolendronic acid administration can maintain serum calcium at a normal level in 88% of cases in an average of 10 days. In life-threatening conditions, the combination of BPs and calcitonin is effective in hypercalcemia normalization by increasing renal calcium excretion[6,9].

Fibrous Dysplasia

BPs cause progressive thickening and ossification, improvement in pain, and N-telopeptide levels. Intravenous pamidronate has been used in the most worker, with numerous reports of pamidronate and oral alendronate combination usage and only oral alendronate[6].

Arthroplasty

In arthroplasty, the main goal of BPs administration is to reduce the further revision surgeries possibility by preventing aseptic loosening, periprosthetic osteoporosis, and fractures. Many authors

claimed a density improvement in periprosthetic bone and decreased stress shielding after oral or local bisphosphonates administration. A reduced rate of implant migration is also found[6,10]. Moreover, BPs are also expected to suppress debris-induced osteolysis and activation of osteoclasts. A clinical study reported that postoperative oral alendronate for six months had shown significant bone mineral density improvement in patients who underwent total knee arthroplasty[6].

Heterotopic Calcification and Ossification

In the clinical setting, BPs have been reported to affect both mineralization inhibition of soft tissue and heterotopic ossification inhibition. A study stated that BPs are useful for prophylaxis after the trauma with an initial slow dose, but bone matrix mineralization will continue after the drug usage stopped[6].

Paget's Disease

Bone turnover in patients can be normalized with Bisphosphonates and cause lesions healing. Zoledronate demonstrates very long biochemical remission durations, and high response rate in the long term follow up study[6].

Complex Regional Pain Syndrome (CRPS)

In some clinical research, bisphosphonate treatment in CRPS has been proven to improve clinical response with symptoms of spontaneous pain, swelling, tenderness, and reduce the local acceleration of bone remodelling[6].

Avascular Necrosis of Femoral Head (AVNFH)

Bisphosphonates, specifically alendronate, have been proven to suppress avascular necrosis lesions progression, but excellent progress has only been shown in the pre-collapse stages. Therefore, it is recommended to initiate therapy early because the later stages prove to be less responsive[6,9].

Perthe's Disease

A study in rats showed that zoledronic acid could ameliorate femoral head sphericity in Perthe's disease[11]. Another study also showed similar results in children with Perthe's disease. A recent study also proved that alendronate modified gold nanoparticles as useful media to study the femoral head treatment's osteonecrosis *in vitro* models of Perthe's disease[6,9].

Bisphosphonate & Osteogenesis Imperfecta

Bisphosphonate (BP) therapy is the most common medical treatment used for osteogenesis imperfecta (OI). This BP therapy in OI has been the focus of discussion in several recent reviews. Many studies have shown evidence that BP therapy can increase bone mineral density in patients with OI. Of the few randomized controlled trials that have been conducted on the treatment of BP in OI, most of them have only assessed bone mineral density and have had only a short treatment duration. Systematic reviews of randomized trials on OI concur that there is insufficient evidence to assess whether BP therapy improves outcomes other than bone mineral density. Nevertheless, some long-term follow-up data from observational studies provide some clinically relevant information about BP treatment outcomes[1,3].

In a study conducted by Falk et al., it was found that the periodic administration of intravenous pamidronate to children with OI had beneficial effects on BMD z scores and physical disability[8]. These results are

consistent and confirm the results of the study conducted by Glorieux et al.[5] However, long-term follow-up is still needed to determine whether this BP therapy can reduce fracture rates and improve mobility in children with moderate to severe OI[8].

Pamidronate

Pamidronate is one type of bisphosphonate (BP) that is widely used in children with OI. The use of pamidronate increased after an observational study conducted by Glorieux et al., who gave an intermittent infusion of pamidronate for 1 to 5 years using a dose of 1.5-3.0 mg/kg for three consecutive days at 4-6 monthly intervals in 30 children with severe OI[5].

The study results showed that there were striking differences after treatment in increased bone pain associated with mobility, increased bone mineral density as assessed by DEXA examination, and a 75% reduction in fracture rates from 3.2 fractures per patient per year to 0.6 fractures per patient per year. The authors also noted an increase in bone density in the spinal area after treatment[12].

According to research conducted by Marginean et al., it was found that the osteodensitometry examination of children over 12 years showed a decrease in bone mineral density (BMD) with a significant improvement of it after pamidronate treatment. Besides, the bone alkaline phosphatase and osteocalcin values also changed after pamidronate treatment. OI treatment with pamidronate is beneficial for patients by increasing bone density, increasing mobility and quality of life, and reducing family dependence on children with OI[13].

In children with OI, periodic intravenous pamidronate therapy will gradually reduce pain and improve functional ability. The pain will subside immediately after infusion, with the functional improvement observed four weeks later. Both pain and physical function will return to pre-treatment levels with subsequent infusion[10].

Alendronate

There are not many studies on alendronate therapy in OI. At least there are three randomized trials have been published, two in children and one in adults. DiMeglio and Peacock conducted a randomized, open study of 18 children with OI who were given oral alendronate at a dose of 1 mg/kg/day or intravenous pamidronate at a dose of 4 mg/kg every four months for two years. From these studies, it was found that bone density in the spine and the body generally increased at the same rate as the two therapies. The therapeutic response was higher in OI type I than OI type III and IV for both alendronate and pamidronate administration[14].

Another randomized, double-blind study by Ward et al. demonstrated a significant increase in bone mineral density (BMD) in the spine and a significant reduction in urinary N-telopeptide from collagen type I (uNTX/Cr) after the administration of oral alendronate to children with OI. The dose of alendronate given was 5 mg daily for patients weighing under 40 kg and 10 mg daily for patients weighing over 40 kg[15].

Chevrel et al. also performed a randomized, double-blind trial using 10 mg oral alendronate daily in 64 adult patients with type I OI for three years. All patients were also given calcium and vitamin D supplements[16]. Chevrel et al. reported a significant increase in hip and spinal bone mineral density (BMD) in patients who were treated alendronate routinely and a decrease in biochemical markers of bone turnover[12,16].

Risedronate

Risedronate administration as an OI therapy has been studied in at least three randomized trials in children. The first study by Bishop et al. compared the effects of various doses of risedronate (0.2, 1, and 2 mg/kg) on bone density and fracture risk in 53 children with OI. The result of the study showed a 75% reduction in fracture rates with risedronate[17]. A further study by Bishop et al. studied the effect of administering risedronate 2.5 or 5 mg daily in 147 children with OI for one year. In line with the previous study results, there was an increase in BMD of 5% in the risedronate group compared to the placebo group at one year. The risedronate group also had a lower proportion of patients with new fractures at 30.8% than the placebo group at 48.9%. A time-to-event analysis showed that the fracture hazard ratio of risedronate compared to placebo was 0.53[17].
In another study, Rauch et al. randomized 26 pediatric patients with type I OI to receive risedronate or placebo. The dose of risedronate administration was 15 mg weekly for patients weighing less than 40 kg and 30 mg weekly for patients weighing more than 40 kg for two years. The results showed that the risedronate group experienced a significant increase in BMD and decreased serum NTX by 30%[12,18].

Neridronate

Neridronate is another type of bisphosphonate that contains a nitrogen atom and is structurally similar to pamidronate and alendronate. Neridronate has six carbon atoms on the side chain, whereas pamidronate has three carbon atoms, and alendronate has four carbon atoms. Currently, neridronate is licensed for the treatment of bone disease in Italy. Gatti et al. have studied the effect of administering neridronate intravenously in one randomized controlled trial of children with OI. In this trial, patients were given neridronate at a dose of 2 mg/kg body weight by intravenous infusion every three months for three years. Patients whose vitamin D levels were less than 50 nmol/l were also given vitamin D supplements. The results showed a significantly higher increase in spine and hip BMD in the neridronate group than placebo. Increased height and bony area in the lumbar spine were also reported to be greater during the first year in the neridronate group[19].
Adami et al. also performed an open study by randomizing 46 adult patients with OI to receive neridronate 100 mg intravenously every four months. The results showed a more significant increase in spine and hip BMD in the neridronate group than in the untreated control group. There was a decrease in biochemical markers of bone turnover such as bone-specific ALP, serum CTX, and urinary deoxypyridinoline/creatinine in both groups, although the neridronate group tended to have a greater decrease in these markers[12,20].

Olpadronate

Olpadronate is a bisphosphonate group structurally similar to pamidronate but has an additional methyl group on the nitrogen atom. Sakkers et al. conducted a randomized study of 34 children with OI[21]. They randomized and gave olpadronate 10 mg daily or placebo to children with various OI types. The results showed an increase in spinal BMD in the olpadronate group compared to placebo, but there was no improvement in grip strength, mobility, and biochemical markers of bone turnover between groups[12].
The decision to choose bisphosphonate therapy appears to be determined by clinical severity rather than collagen mutation status, BMD, or type OI. However, in OI types III

and IV, which represent a more severe portion of the spectrum disorders, most patients in this category will meet the indication criteria for intravenous pamidronate treatment. Results from previous studies indicate that moderate to severe OI cannot be extrapolated to a mild form of diseases such as no vertebral compression fracture or no long bone deformity. Patients with mild OI will benefit less from bisphosphonate therapy than patients with more severe degrees because simply the functional status of patients with mild OI is better even without treatment[12,7].
There is no definite time to start bisphosphonate therapy. In congenital diseases such as OI, it is essential to start treatment as early as possible. Several studies reported satisfactory results in OI patients who received pamidronate early in the first two years of life. The clinical effect of intravenous pamidronate administration, especially for bone pain, is shorter in children than in the elderly, so the pamidronate administration needs to be repeated more frequently. The effect of bisphosphonates on the bone also depends on the process of bone growth. Adolescents who have no bone growth may not benefit from treatment as much as do younger patients[12].

The benefit and drawback of prolonged therapy

No studies have specifically addressed the effects of bisphosphonate on long-term administration. However, one study showed a slowing down effect of pamidronate therapy overtime on pediatric patients' bone density with OI. For example, the age-specific z-score for the lumbar spine BMD increased by 2.0 during the first two years of pamidronate treatment but only increased by 0.6 in the second two years of treatment[6,12]. Although bisphosphonates can generally increase bone density, they also have the drawback of being antiresorptive. Long-term use of bisphosphonate will decrease bone remodelling activity and potentially interfere with bone modelling or shaping[8]. This effect has been reported in a teenage boy who received large doses of pamidronate for three years, where he developed abnormally-shaped long-bone metaphyses[12].

The effect of discontinuing therapy

There are no accurate reports on the effect of discontinuation therapy. A study followed by 70 young patients with OI showed that most of them had stable or even increased lumbar and spinal bone mineral density after one to three years of discontinuation of pamidronate[12]. However, some patients complained of a lack of stamina and recurrent bone pain after not using pamidronate for several months[4].

Conclusion

Bisphosphonate is a therapy that has been used for more than 50 years to treat various bone diseases in children, especially to treat bone fragility, avascular necrosis, and other bone pathologies. Most studies have shown that bisphosphonate therapy can increase bone density, reduce fracture risk, and decrease pain due to bone abnormalities. Bisphosphonate can be used as an adjunct therapy for physiotherapy, rehabilitation, and orthopaedic care. This drug has shown marked improvements in patients suffering from moderate to severe OI. In contrast, children and adolescents with OI who experience fractures and minimal functional limitations benefit less from this treatment.

Conflict of Interest

The authors of this work have nothing to disclose

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