Pharmacological Therapy in Osteogenesis Imperfecta: A Literature Review

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Abstract. O Osteogenesis Imperfecta (OI) is a rare condition characterized by bone fragility and deformities resulting from mutations in the COL1A1 and COL1A2 genes. This literature review emphasizes the clinical and pharmacological aspects associated with OI, with a special focus on the prognosis and impact on the lives of patients with this condition. Methodology: The literature review spanned from 2002 to 2022 and utilized four international databases. Nineteen articles addressing pharmacological interventions in humans with OI were selected, limited to the Portuguese and English languages. Results and Discussion: Pharmacological treatment with bisphosphonates, such as pamidronate, alendronate, and zoledronic acid, has shown benefits in bone density and fracture reduction, particularly in younger patients. However, the effectiveness of these treatments in adults, varying with the type of bisphosphonate and OI subtype, is less conclusive. Zoledronic acid has demonstrated promise in reducing clinical fractures, especially in children, suggesting its potential as an effective treatment. Conclusion: Advances in pharmacological treatment for OI offer hope for improving the quality of life of patients. Nevertheless, ongoing research is essential to develop more effective and personalized approaches. Collaboration among healthcare professionals, researchers, and patients plays a pivotal role in the management and treatment of this rare and challenging condition.

Keywords. osteogenesis imperfecta, bisphosphonates, therapeutics

1. Introduction

Osteogenesis Imperfecta (OI), also known as brittle bone disease or Lobstein's disease, is a rare condition characterized by bone fragility and deformities, often resulting in fractures from minimal trauma. OI has a genetic basis, with approximately 90% of cases attributed to mutations in the COL1A1 and COL1A2 genes, which encode the alpha chains of collagen type 1 produced by osteoblasts, leading to issues in bone matrix mineralization [1,2]. The classification of OI has evolved as knowledge of the disease has increased, resulting in various types ranging from type I to type XVIII, based on clinical criteria, severity, involved genes, and the type of mutation[3,4]. Typical symptoms across OI types include blue sclerae, dentinogenesis imperfecta, hyperextensible joints, hearing impairment, among others. While considered a rare disease, OI has an estimated incidence of approximately 1 in 15,000 and a prevalence in the United States among 25,000 to 50,000 affected individuals[5].

Diagnosis of OI is often made in childhood, but it can also occur later in adulthood. In addition to multiple fractures resulting from minimal trauma, individuals with OI may exhibit bone deformities in the skull,

pelvic girdle, and long bones such as the femur, tibia, and humerus[6]. Other signs and symptoms include bone pain, short stature, blue sclerae, hyperextensible joints, dentinogenesis imperfecta, aplasia or hypoplasia of the lungs. They may also experience lifelong comorbidities such as severe scoliosis with respiratory compromise, impaired mobility, cardiovascular changes, mitral valve prolapse, ocular anomalies, and deafness[7–9].

Literature review and the investigation of therapeutic innovations in the context of OI management play a pivotal role in the perspective of enhancing patients' quality of life, reducing debilitating symptoms, and driving medical advancements that could, in the long term, lead to effective control of this rare and challenging condition.

2. Methodology

This is a literature review using four databases: Google Scholar, Scielo, PubMed, and Embase, covering the period from 2002 to 2022. The keywords used were "osteogenesis imperfecta," "bisphosphonates," and "therapeutics." A total of 241 articles were selected, and the search was limited to articles in Portuguese and English, with studies conducted in humans. Inclusion criteria: Full-text articles involving pharmacological interventions for the prevention and treatment of osteogenesis imperfecta in different life stages. Exclusion criteria: Articles not related to the topic, other reviews, meta-analyses, and articles without scientific publication verification. Titles and abstracts were analyzed, and after applying the above criteria, a total of 19 articles were selected.

3. Results and Discussion

Pharmacological treatment is indicated for patients with OI who have long bone deformities, vertebral compression fractures, and a history of two or more fractures per year. It involves the use of bisphosphonates (oral alendronate and intravenous pamidronate), along with calcium and vitamin D supplementation [6].

3.1 Pamidronate Disodium

Pamidronate disodium belongs to the class of intravenously administered bisphosphonate medications and has demonstrated efficacy in increasing bone mineral density (BMD) [10]. The impact of this medication on bones is influenced by various factors, including matrix composition, the quantity and distribution of cortical and trabecular bone, and bone geometry [10,11].

In a clinical trial involving OI patients under 18 years of age, pamidronate was shown to increase BMD and reduce the incidence of upper limb fractures in the first year of treatment [11]. Comparative studies also demonstrated improvements in spine BMD and motor function after pamidronate use. Therefore, intravenous pamidronate is recommended for OI patients under 18 years of age who suffer from chronic pain, bone deformities, or fractures [12]. The incidence of fractures in OI patients varies throughout life, suggesting that bisphosphonate treatment may not be clinically beneficial for adults with OI [10].

A retrospective cohort study in OI patients over 18 years of age evaluated the use of pamidronate compared to non-use of bisphosphonates. The results showed that pamidronate increased BMD in the lumbar spine (L1-L4), but this improvement was not statistically significant. There were no significant differences in total hip BMD between the groups [10]. Regarding fractures, the effects of pamidronate in adult OI patients were inconclusive. For OI patients of types III or IV, there was a non-significant reduction in fractures after treatment, while patients with OI type I did not show a statistically significant reduction in fractures, and in some cases, the fracture ratio even increased compared to untreated patients [10].

3.2 Alendronate

Alendronate, an oral bisphosphonate, increases BMD in the spine and hip and reduces vertebral, hip, and forearm fractures in postmenopausal women and men with osteoporosis[10]. Studies in children and adolescents with OI do not recommend the use of alendronate, although it increased BMD in pediatric OI patients[13].

Comparing oral alendronate and intravenous pamidronate in pediatric OI patients, both increased total BMD, with a better response in patients with milder OI[14]. The incidence of fractures decreased in both groups. Intravenous pamidronate resulted in adverse events such as fever, myalgia, and vomiting, while oral alendronate had no adverse events[14].

For OI patients over 18 years old, a study compared oral bisphosphonates (alendronate or risedronate) and intravenous pamidronate. There were no significant differences in lumbar and hip BMD[15]. Oral bisphosphonates showed a slight benefit in adult patients with OI type I, III, or IV[15].

Oral bisphosphonates did not reduce the incidence of fractures in type I or types III or IV patients, while pamidronate reduced fractures in type III or IV patients. This Protocol recommends the use of alendronate for OI patients over 18 years old, despite some study limitations[10].

3.3 Zoledronic Acid

Zoledronic acid, a third-generation bisphosphonate with high anti-resorptive potency, has been studied to treat various bone disorders, including OI types I, II, and IV, in both adults and children [15–17]. Clinical studies compared zoledronic acid with pamidronate in OI patients under 18 years of age. Both drugs increased BMD in the lumbar spine, but there was no significant difference between them. However, zoledronic acid showed a slight increase in the percentage change in BMD compared to

pamidronate [18].

Comparing zoledronic acid with weekly oral alendronate in studies, both had similar results in increasing BMD and reducing bone loss in children and adolescents with OI [19]. However, zoledronic acid was more effective in reducing the occurrence of clinical fractures, suggesting it may become an effective treatment option for children, adolescents, and adults with OI [19].

4. Conclusion

Osteogenesis Imperfecta is a rare condition characterized by bone fragility. This review focused on pharmacological options, such as bisphosphonates, for treating OI, with an emphasis on younger patients. Bisphosphonates have shown benefits in bone density and fracture reduction, especially in children and adolescents. However, their effectiveness in adults is less clear, varying with the type of bisphosphonate and OI subtype. Zoledronic acid shows promise, but further research is needed. These advancements offer hope, but ongoing research is crucial to develop more effective and personalized treatments. Collaboration among healthcare professionals, researchers, and patients is essential in addressing this challenging condition.

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6. References

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