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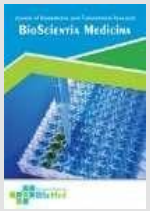

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Clinical Characteristics and Progression of Osteogenesis Imperfecta Type III: A Case Series

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A B S T R A C T

Background: Osteogenesis imperfecta (OI) is a rare genetic disorder primarily affecting bone formation, leading to increased bone fragility and fractures. OI Type III is characterized by severe clinical manifestations, including multiple fractures, skeletal deformities, and short stature. This case series describes the clinical characteristics and progression of three patients diagnosed with OI Type III, highlighting the impact of early intervention with zoledronic acid on their outcomes. **Case presentation:** This study presents three cases of OI Type III in female patients. Two patients (Patient A and Patient R) were diagnosed at birth with multiple fractures and received zoledronic acid treatment starting at three months of age. The third patient (Patient D) presented with fractures later in infancy and began treatment at one year of age. All patients demonstrated hallmark features of OI Type III, including blue sclerae, short stature, and progressive skeletal deformities. However, the two patients who received earlier treatment with zoledronic acid showed better mobility and fewer fractures compared to the patients who started treatment later. **Conclusion:** This case series emphasizes the importance of early diagnosis and intervention in OI Type III. Zoledronic acid appears to be effective in reducing fracture rates and improving mobility in these patients. Further studies with larger sample sizes are needed to confirm these findings and optimize treatment strategies for OI Type III.

1. Introduction

Osteogenesis imperfecta (OI), often referred to as "brittle bone disease," is a heterogeneous group of genetic disorders primarily characterized by defects in collagen synthesis. Collagen, a major protein in connective tissue, provides the structural framework for bones, tendons, ligaments, and other tissues. In OI, impaired collagen synthesis results in bone fragility, leading to an increased susceptibility to fractures. The clinical presentation of OI is highly variable, ranging from mild forms with few fractures to severe forms with perinatal lethal consequences. This variability is due to the diverse genetic mutations affecting collagen production and the extent of collagen deficiency.[1-3]

OI Type III is one of the most severe non-lethal forms of OI, characterized by multiple fractures at birth, progressive skeletal deformities, and significant growth retardation. Affected individuals often experience significant functional limitations and require lifelong medical care. The diagnosis of OI Type III is typically based on clinical findings, including a history of multiple fractures, blue sclerae, and skeletal deformities. Radiographic imaging plays a crucial role in confirming the diagnosis and assessing the extent of skeletal involvement.[4-6]

The management of OI Type III is complex and involves a multidisciplinary approach, including medical, surgical, and rehabilitative interventions. Medical management focuses on reducing fracture

rates, improving bone density, and promoting growth. Bisphosphonates, such as zoledronic acid, have emerged as a promising treatment option for OI. Zoledronic acid inhibits bone resorption and increases bone density, leading to a reduction in fracture rates and potential improvement in growth. Surgical interventions may be necessary to correct skeletal deformities, stabilize fractures, and improve mobility. Rehabilitation, including physical therapy and occupational therapy, plays a vital role in maximizing functional independence and improving quality of life. This case series presents three patients diagnosed with OI Type III who were followed at our pediatric endocrinology clinic.[7-10] The aim of this study is to describe their clinical characteristics, treatment course, and outcomes, with a particular focus on the impact of early intervention with zoledronic acid.

2. Case Presentation

Case 1

Patient A is a 6-year-old female who was diagnosed with OI Type III at birth. She was born full-term via cesarean section with a birth weight of 3300 grams. At birth, she presented with multiple fractures in all four extremities, chest, and clavicle. She also had blue sclerae. There was no family history of OI. On physical examination, her height was 89 cm (below the 3rd percentile), weight was 12 kg, and lower segment length was 38 cm. She had normal mobility with supervision. Laboratory investigations revealed normal serum calcium and phosphate levels, but elevated serum alkaline phosphatase. A babygram showed multiple fractures in the extremities, chest, and clavicle. A skeletal survey confirmed generalized osteopenia, multiple healed fractures, and bowing deformities of long bones. Patient A started treatment with zoledronic acid at 3 months of age. The initial dosage regimen was monthly infusions for 6 months, then every 2 months until 1 year of age, and then every 3 months. She also received vitamin D and calcium supplements. She has not undergone any surgical interventions. Currently, Patient A receives zoledronic acid infusions every 3 months. She undergoes regular physical therapy sessions to improve muscle strength and mobility, and occupational therapy to facilitate daily activities. She is followed up every 3 months to monitor her height, weight, fracture incidence, mobility, pain, and quality of life. Since starting zoledronic acid treatment, Patient A has experienced a reduction in fracture incidence. Her mobility is normal with supervision, and her growth has improved, although she remains below the 3rd percentile for height. She attends school and participates in activities, and her quality of life is considered good. Patient R is a 6-year-old female who was also diagnosed with OI Type III at birth. She was born full-term via cesarean section with a birth weight of 2800 grams. At birth, she presented with multiple fractures in both legs and chest. She also had blue sclerae. There was no family history of OI. On physical examination, her height was 90 cm (below the 3rd percentile), weight was 14 kg, and lower segment length was 43 cm. She had normal mobility with supervision. Laboratory investigations revealed normal serum calcium and phosphate levels, but elevated serum alkaline phosphatase. A babygram showed multiple fractures in the legs and chest. A skeletal survey confirmed generalized osteopenia, multiple healed fractures, and bowing deformities of long bones. Patient R started treatment with zoledronic acid at 3 months of age. The initial dosage regimen was monthly infusions for 6 months, then every 2 months until 1 year of age, and then every 3 months. She also received vitamin D and calcium supplements. She has not undergone any surgical interventions. Currently, Patient R receives zoledronic acid infusions every 3 months. She undergoes regular physical therapy sessions to improve muscle strength and mobility, and occupational therapy to facilitate daily activities. She is followed up every 3 months to monitor her height, weight, fracture incidence, mobility, pain, and quality of life. Since starting zoledronic acid treatment, Patient R has experienced a reduction in fracture incidence. Her mobility is normal with supervision, and her growth has improved, although she remains below the 3rd

percentile for height. She attends school and participates in activities, and her quality of life is considered good. Patient D is a 15-year-old female who was diagnosed with OI Type III later in infancy. She was born full-term via natural delivery with a birth weight of 3000 grams. She did not present with any deformities at birth. However, she began experiencing fractures later in infancy. There was no family history of OI. On physical examination, her height was 138 cm (below the 3rd percentile), weight was 35 kg, and lower segment length was 81 cm. She is wheelchair-bound. Laboratory investigations revealed normal serum calcium and phosphate levels, but elevated serum alkaline phosphatase. A babygram was not available. A skeletal survey confirmed generalized osteopenia, multiple healed fractures, and severe bowing deformities of long bones. Patient D started treatment with zoledronic acid at 1 year of age. The initial dosage regimen was every 3 months. She also received vitamin D and calcium supplements. She has not undergone any surgical interventions. Currently, Patient D receives zoledronic acid infusions every 3 months. She undergoes regular physical therapy sessions to maintain range of motion and prevent contractures, and occupational therapy for adaptive equipment and wheelchair modifications to enhance independence. She is followed up every 3 months to monitor her height, weight, fracture incidence, mobility, pain, and quality of life. Since starting zoledronic acid treatment, Patient D has experienced a reduction in fracture incidence, but her fracture rate remains higher than that of Patients A and R. She is wheelchair-bound, and her growth has shown limited improvement, remaining below the 3rd percentile for height. She attends school but has limited social interaction due to her mobility restrictions. Her quality of life is considered fair.

Case 2

Patient A is a 6-year-old female who was diagnosed with osteogenesis imperfecta (OI) type III at birth. Her birth was full-term and occurred via cesarean section, with a birth weight of 3300 grams. Notably, she presented with multiple fractures at birth, affecting all four extremities, her chest, and clavicle. The presence of blue sclerae, a common clinical manifestation of OI, was also observed. There was no family history of OI, suggesting a sporadic mutation as the likely cause. A comprehensive physical examination revealed that Patient A's height was 89 cm, placing her below the 3rd percentile for her age. Her weight was 12 kg, and her lower segment length was measured at 38 cm. Despite the presence of skeletal deformities, she demonstrated normal mobility with appropriate supervision. Laboratory investigations were conducted to assess her overall health and rule out other potential conditions. Her serum calcium and phosphate levels were within the normal limits, indicating normal mineral homeostasis. However, her serum alkaline phosphatase level was elevated, which is a common finding in OI due to increased bone turnover. Imaging studies played a crucial role in confirming the diagnosis and evaluating the extent of skeletal involvement. A babygram, a radiographic examination performed shortly after birth, revealed multiple fractures in the extremities, chest, and clavicle. A subsequent skeletal survey, a series of X-rays encompassing the entire skeleton, confirmed generalized osteopenia (reduced bone mineral density), multiple healed fractures, and bowing deformities of the long bones. Patient A's treatment journey began at the tender age of 3 months with the initiation of zoledronic acid therapy. Zoledronic acid, a potent bisphosphonate, is a cornerstone in the management of OI. It acts by inhibiting bone resorption and increasing bone mineral density, thereby reducing fracture risk and potentially improving growth. The initial dosage regimen for Patient A consisted of monthly zoledronic acid infusions for the first 6 months, followed by infusions every 2 months until she reached 1 year of age. Subsequently, the frequency was adjusted to every 3 months. In addition to zoledronic acid, she received vitamin D and calcium supplements to support bone health. To date, Patient A has not required any surgical interventions. However, she has benefited

significantly from regular physical therapy sessions aimed at improving muscle strength and mobility. Occupational therapy has also been instrumental in facilitating her daily activities and enhancing her independence. Patient A is closely followed up every 3 months to monitor her progress and make necessary adjustments to her treatment plan. The monitoring parameters include her height, weight, fracture incidence, mobility, pain levels, and overall quality of life. The initiation of zoledronic acid therapy has yielded positive outcomes. Her fracture incidence has reduced significantly, and she maintains normal mobility with supervision. While her growth has improved, she remains below the 3rd percentile for height. Importantly, she enjoys a good quality of life, attending school and participating in various activities. Patient R, a 6-year-old female, shares a similar diagnosis of OI Type III with Patient A. Like Patient A, she was born full-term via cesarean section, weighing 2800 grams at birth. Her initial presentation also included multiple fractures, specifically in both legs and chest, accompanied by blue sclerae. No family history of OI was reported. Patient R's physical examination revealed a height of 90 cm, placing her below the 3rd percentile for her age. Her weight was 14 kg, and her lower segment length was 43 cm. She exhibited normal mobility with supervision. Laboratory tests showed normal serum calcium and phosphate levels, but an elevated serum alkaline phosphatase level, consistent with the diagnosis of OI. Radiological imaging confirmed the clinical diagnosis. A babygram showed multiple fractures in the legs and chest, while a skeletal survey revealed generalized osteopenia, multiple healed fractures, and bowing deformities of the long bones. Patient R's treatment mirrored that of Patient A, commencing with zoledronic acid at 3 months of age. The initial dosage regimen was monthly infusions for 6 months, transitioning to every 2 months until 1 year of age, and then every 3 months. She also received vitamin D and calcium supplements. Surgical intervention has not been necessary for Patient R. She benefits from regular physical therapy to improve muscle strength and mobility, as well as occupational therapy to facilitate daily activities. Patient R's progress is closely monitored every 3 months, with assessments of her height, weight, fracture incidence, mobility, pain, and quality of life. Zoledronic acid therapy has been effective in reducing her fracture incidence and improving her growth, although she remains below the 3rd percentile for height. She maintains normal mobility with supervision, attends school, participates in activities, and enjoys a good quality of life. Patient D, a 15-year-old female, presents a contrasting picture to Patients A and R. While she was also diagnosed with OI Type III, her diagnosis came later in infancy, following the onset of fractures. Unlike the previous cases, she did not have any deformities at birth. Her birth was full-term and occurred via natural delivery, with a birth weight of 3000 grams. There was no family history of OI. Patient D's physical examination revealed a height of 138 cm, below the 3rd percentile for her age. Her weight was 35 kg, and her lower segment length was 81 cm. Notably, she is wheelchair-bound, highlighting the more severe impact of OI in her case. Laboratory investigations showed normal serum calcium and phosphate levels, but an elevated serum alkaline phosphatase level, consistent with OI. A babygram was not available for review. However, a skeletal survey confirmed generalized osteopenia, multiple healed fractures, and severe bowing deformities of the long bones, underscoring the progressive nature of the disease. Patient D's treatment with zoledronic acid began at 1 year of age, significantly later than Patients A and R. The initial dosage regimen was every 3 months. She also received vitamin D and calcium supplements. Surgical intervention has not been part of her management. She undergoes regular physical therapy sessions primarily focused on maintaining range of motion and preventing contractures, a common complication in OI. Occupational therapy is crucial for providing adaptive equipment and modifying her wheelchair to enhance her independence. Patient D's follow-up mirrors that of the other cases, with 3-monthly assessments of her height, weight, fracture incidence,

mobility, pain, and quality of life. While zoledronic acid therapy has reduced her fracture incidence, her fracture rate remains higher compared to Patients A and R. Her mobility is significantly limited, and she remains wheelchair-bound. Her growth has shown limited improvement, and she continues to be below the 3rd percentile for height. Her quality of life is considered fair, as she attends school but faces social interaction challenges due to her mobility restrictions.

Table 1. Comprehensive overview of the clinical, laboratory, and imaging findings in the three cases of OI Type III.

Feature	Case 1 (Patient A)	Case 2 (Patient R)	Case 3 (Patient D)
Anamnesis			
Age	6 years old	6 years old	15 years old
Gender	Female	Female	Female
Birth	Full-term via cesarean section	Full-term via cesarean section	Full-term via natural delivery
Birth weight	3300 grams	2800 grams	3000 grams
Deformities at birth	Present in all four extremities, chest, and clavicle	Present in both legs and chest	None
Blue sclerae at birth	Yes	Yes	Yes
Family history of OI	No	No	No
Physical examination			
Height	89 cm (below 3rd percentile)	90 cm (below 3rd percentile)	138 cm (below 3rd percentile)
Weight	12 kg	14 kg	35 kg
Lower segment length	38 cm	43 cm	81 cm
Arm span	80 cm	73 cm	123 cm
Mobility	Normal activities with supervision	Normal activities with supervision	Wheelchair-bound
Laboratory			
Serum calcium	Within normal limits	Within normal limits	Within normal limits
Serum phosphate	Within normal limits	Within normal limits	Within normal limits
Serum alkaline phosphatase	Elevated	Elevated	Elevated
Imaging			
Babygram	Multiple fractures in the extremities, chest, and clavicle	Multiple fractures in the legs and chest	Not available
Skeletal survey	Generalized osteopenia, multiple healed fractures, bowing deformities of long bones	Generalized osteopenia, multiple healed fractures, bowing deformities of long bones	Generalized osteopenia, multiple healed fractures, severe bowing deformities of long bones
Diagnosis			
Clinical diagnosis	Osteogenesis Imperfecta Type III	Osteogenesis Imperfecta Type III	Osteogenesis Imperfecta Type III
Genetic testing	Not performed	Not performed	Not performed

Table 2. Overview of the treatment and follow-up protocols for the three cases of OI Type III.

Feature	Case 1 (Patient A)	Case 2 (Patient R)	Case 3 (Patient D)
Treatment			
Zoledronic acid	Started at 3 months of age	Started at 3 months of age	Started at 1 year of age
Initial dosage regimen	Monthly infusions for 6 months, then every 2 months until 1 year of age, then every 3 months	Monthly infusions for 6 months, then every 2 months until 1 year of age, then every 3 months	Every 3 months
Current dosage regimen	Every 3 months	Every 3 months	Every 3 months
Other medications	Vitamin D and calcium supplements	Vitamin D and calcium supplements	Vitamin D and calcium supplements
Surgical interventions	None	None	None
Physical therapy	Regular sessions to improve muscle strength and mobility	Regular sessions to improve muscle strength and mobility	Regular sessions to maintain range of motion and prevent contractures
Occupational therapy	Adaptive equipment and strategies to facilitate daily activities	Adaptive equipment and strategies to facilitate daily activities	Adaptive equipment and wheelchair modifications to enhance independence
Follow-up			
Frequency of follow-up visits	Every 3 months	Every 3 months	Every 3 months
Monitoring parameters	Height, weight, fracture incidence, mobility, pain, quality of life	Height, weight, fracture incidence, mobility, pain, quality of life	Height, weight, fracture incidence, mobility, pain, quality of life
Outcomes			
Fracture incidence	Reduced since starting zoledronic acid	Reduced since starting zoledronic acid	Reduced since starting zoledronic acid, but higher than Cases 1 and 2
Mobility	Normal activities with supervision	Normal activities with supervision	Wheelchair-bound
Growth	Below 3rd percentile, but improved since starting zoledronic acid	Below 3rd percentile, but improved since starting zoledronic acid	Below 3rd percentile, limited improvement
Quality of life	Good, attends school and participates in activities	Good, attends school and participates in activities	Fair, attends school but limited social interaction due to mobility restrictions

3. Discussion

Osteogenesis imperfecta (OI) Type III, a severe form of brittle bone disease, presents a significant challenge due to its wide-ranging clinical manifestations and unpredictable progression. While the hallmark of the disease is bone fragility leading to recurrent fractures, the specific presentation can vary considerably from one individual to another. This heterogeneity, even within the same OI type, underscores the complexity of the disease and the need for personalized

management strategies. The skeletal system bears the brunt of OI Type III, with multiple fractures often evident at birth or in early infancy. These fractures can occur with minimal or no apparent trauma, a stark indicator of the severe bone fragility that characterizes this condition. As the child grows, the risk of fractures persists, leading to a cumulative burden of skeletal deformities. The frequency and severity of fractures can fluctuate, with some individuals experiencing near-constant fractures, while others have longer periods of relative stability. The location and type of fractures can also vary, affecting long bones, ribs, and even skull bones. This variability can be influenced by factors such as the specific genetic mutation, the child's age and developmental stage, and environmental factors such as nutrition and activity level. Repeated fractures and the inherent weakness of the bone structure contribute to the development of progressive skeletal deformities. These deformities can involve bowing of the long bones, particularly in the legs, leading to significant mobility challenges. Spinal deformities, such as scoliosis (lateral curvature) and kyphosis (exaggerated forward curvature), can also occur, compromising respiratory function and overall quality of life. The severity and progression of these deformities can vary widely among individuals with OI Type III, and they may require surgical intervention to correct or stabilize. Short stature is a common feature of OI Type III, with affected individuals often falling significantly below the average height for their age and gender. This growth retardation can be attributed to a combination of factors, including impaired bone growth, recurrent fractures, and potential hormonal imbalances. The degree of growth retardation can vary, and some individuals may benefit from growth hormone therapy to improve their final adult height. While the skeletal manifestations dominate the clinical picture of OI Type III, extra-skeletal complications can also arise, adding to the complexity of the disease. A classic sign of OI, blue sclerae (the white part of the eyes) results from the thinning of the scleral collagen, allowing the underlying choroid to show through. While often present in OI Type III, the intensity of the blue color can vary. This feature is not unique to OI and can also be seen in other connective tissue disorders. Dentinogenesis imperfecta condition, characterized by abnormal dentin formation, can lead to discolored, brittle, and misshapen teeth. The teeth are prone to wear and tear, potentially causing functional and aesthetic concerns. Dentinogenesis imperfecta can occur in isolation or in association with OI, and its severity can vary. Hearing impairment can develop in some individuals with OI Type III, typically due to abnormalities in the middle ear bones (conductive hearing loss) or the inner ear (sensorineural hearing loss). The onset and severity of hearing loss can vary, and regular hearing evaluations are recommended for individuals with OI Type III. Dilatation of the aortic root, the base of the aorta where it exits the heart, can occur in OI Type III, increasing the risk of aortic dissection or rupture. Valvular abnormalities may also arise, potentially compromising cardiovascular function. Regular cardiac evaluations are recommended for individuals with OI Type III to monitor for these complications. Chest deformities, such as pectus excavatum (sunken chest), can restrict lung expansion, leading to respiratory difficulties. Muscle weakness can further compromise respiratory function, increasing the susceptibility to respiratory infections. Pulmonary function tests may be used to assess respiratory function in individuals with OI Type III. Laxity in the ligaments and tendons can result in joint hypermobility, making the joints more prone to dislocations and subluxations (partial dislocations). Joint hypermobility can contribute to pain, instability, and functional limitations. OI Type III is primarily caused by mutations in the COL1A1 gene, which encodes the alpha 1 chain of type I collagen. However, the specific location and type of mutation can influence the severity of collagen deficiency and the resulting clinical manifestations. Different mutations can affect collagen production, structure, or assembly, leading to a wide range of phenotypic variability. Type I collagen is a crucial component of bone and other connective tissues, providing strength and resilience.

The extent of collagen deficiency and the impact on collagen structure can vary depending on the specific mutation, leading to differences in bone fragility and other clinical features. Even subtle changes in collagen structure can have significant functional consequences. While the primary defect lies in the COL1A1 gene, other genes may modify the expression of the disease, contributing to the variability in clinical presentation. These modifying genes can influence bone metabolism, collagen synthesis, and other factors that affect bone health. The complex interplay between genes can make it challenging to predict the clinical course of OI Type III. Environmental factors, such as nutrition, physical activity, and exposure to certain medications, can also influence the course of OI Type III. Adequate nutrition, particularly calcium and vitamin D intake, is essential for bone health, while regular physical activity can help maintain muscle strength and bone density. Certain medications, such as corticosteroids, can have adverse effects on bone health and should be used with caution in individuals with OI Type III. The clinical heterogeneity of OI Type III underscores the need for a personalized approach to management. Treatment strategies should be tailored to the individual's specific needs, taking into account the severity of bone fragility, the presence of extra-skeletal complications, and the overall health status. Early diagnosis is crucial to initiate timely interventions that can help minimize fractures, prevent deformities, and optimize growth and development. Regular monitoring and proactive management of complications are essential to maintain quality of life. Early intervention may involve physical therapy, occupational therapy, bracing, and medications to improve bone density. The management of OI Type III often requires a multidisciplinary team, involving pediatricians, orthopedists, geneticists, physical therapists, occupational therapists, and other specialists. This collaborative approach ensures comprehensive care that addresses the diverse needs of the individual. Regular communication and coordination among team members are essential for effective management. Educating patients and their families about OI Type III, its potential complications, and management strategies is crucial for empowering them to actively participate in their care and make informed decisions. Patients and families should be provided with information about the disease, its inheritance pattern, and available treatment options. They should also be encouraged to connect with support groups and other resources. The three cases presented in this study provide real-world examples of the clinical heterogeneity of OI Type III. Patient A and patient R were diagnosed at birth with multiple fractures, highlighting the severe end of the OI Type III spectrum. However, their specific fracture patterns differed, with Patient A having more extensive fractures involving all four extremities, chest, and clavicle, while Patient R's fractures were primarily in the legs and chest. This difference may reflect variations in the underlying genetic mutations or other modifying factors. Despite their initial severe presentation, both patients responded well to early intervention with zoledronic acid and have achieved good functional outcomes. In contrast to Patients A and R, Patient D's fractures appeared later in infancy, suggesting a milder form of OI Type III. However, the subsequent development of severe bowing deformities and wheelchair dependence underscores the progressive nature of the disease and the potential for significant functional limitations even in those with a less severe initial presentation. Patient D's case highlights the importance of ongoing monitoring and proactive management of complications to prevent long-term disability.[11-14]

The three cases presented in this study provide compelling evidence for the potential benefits of early intervention with zoledronic acid in improving outcomes for patients with OI Type III. Zoledronic acid, a potent bisphosphonate, has emerged as a cornerstone in the management of OI, particularly in its more severe forms. Its mechanism of action involves inhibiting bone resorption and promoting bone mineralization, leading to increased bone density and reduced fracture risk. Zoledronic acid has revolutionized the treatment of OI, offering a much-

needed therapeutic option for a condition that was once considered largely untreatable. Its efficacy in reducing fracture rates and improving bone health has been demonstrated in numerous studies, making it a standard of care for many individuals with OI. Osteoclasts, the cells responsible for breaking down bone tissue, play a key role in the pathogenesis of OI. Zoledronic acid acts by binding to hydroxyapatite, the mineral component of bone, and inhibiting osteoclast activity. This inhibition of bone resorption leads to a net increase in bone mass and improved bone strength. By suppressing osteoclast activity, zoledronic acid helps to preserve bone tissue and prevent further bone loss, which is critical in OI where bone fragility is a major concern. In addition to inhibiting bone resorption, zoledronic acid may also promote bone mineralization, the process by which calcium and other minerals are deposited into the bone matrix. This further contributes to increased bone density and improved bone quality. Enhanced mineralization not only strengthens the existing bone but also improves its overall structure and resilience, making it less susceptible to fractures. Studies have suggested that zoledronic acid may also have a positive impact on growth in children with OI. By improving bone health and reducing fracture frequency, zoledronic acid may create a more favorable environment for growth and development. Fewer fractures mean less disruption to the growth plates, the areas of active bone growth in children, allowing for more consistent and robust skeletal development. The findings of this case series suggest that early intervention with zoledronic acid may be particularly beneficial in OI Type III. Patients A and R, who were diagnosed at birth and started treatment at 3 months of age, demonstrated better mobility and fewer fractures compared to Patient D, who was diagnosed later and started treatment at 1 year of age. This observation highlights the importance of early diagnosis and prompt initiation of treatment to maximize the potential benefits of zoledronic acid. Early intervention with zoledronic acid may help prevent or mitigate the severe skeletal deformities that often characterize OI Type III. By strengthening bones and reducing fracture risk, zoledronic acid may allow for more normal growth and development, minimizing the long-term impact of the disease on mobility and function. This is particularly crucial in the early years of life when bone growth and development are most rapid and when the skeletal system is most vulnerable to the damaging effects of recurrent fractures. Early initiation of zoledronic acid may also help optimize growth potential in children with OI Type III. By improving bone health and reducing fracture-related growth disturbances, zoledronic acid may allow children to achieve closer to their full growth potential. This can have a significant impact on their overall quality of life, as height is often a major determinant of self-esteem and social acceptance. Early intervention with zoledronic acid can significantly enhance the quality of life for individuals with OI Type III. By reducing fracture frequency and severity, zoledronic acid can minimize pain, disability, and healthcare utilization, allowing individuals to participate more fully in daily activities and social interactions. This can lead to greater independence, improved self-confidence, and a more fulfilling life. The timing of zoledronic acid initiation appears to be a crucial factor in its effectiveness. Starting treatment early, ideally within the first year of life, may offer the greatest benefits in terms of preventing deformities, optimizing growth, and improving overall outcomes. The first few years of life are a critical period for bone development, with rapid bone growth and modeling taking place. Early intervention with zoledronic acid during this critical period may have a more profound and lasting impact on bone health and growth trajectory. This is because the young skeleton is more responsive to the effects of zoledronic acid, allowing for greater gains in bone density and improved bone architecture. Early intervention may also help minimize the cumulative damage to the skeletal system that can occur with repeated fractures. By reducing fracture frequency and severity, zoledronic acid can help preserve bone structure and function, preventing the development of severe deformities and

disabilities. Each fracture carries the risk of further complications, such as malunion (improper healing), nonunion (failure to heal), and growth disturbances, all of which can contribute to long-term disability. While the benefits of early intervention with zoledronic acid are promising, there are also challenges and considerations that need to be addressed. The long-term safety of zoledronic acid in children is still under investigation. While short-term studies have shown a favorable safety profile, more research is needed to assess the potential long-term effects of zoledronic acid on bone health, growth, and other organ systems. This includes monitoring for potential adverse effects on kidney function, dental health, and bone turnover. The optimal dosage and duration of zoledronic acid treatment in children with OI Type III are still being determined. Further research is needed to establish individualized treatment protocols that maximize benefits while minimizing risks. Factors such as age, weight, severity of disease, and response to treatment need to be considered when determining the appropriate dosage and duration of therapy. Access to zoledronic acid therapy can be limited in some settings due to cost and availability. Efforts are needed to improve access to this important medication for all children who could benefit from it. This may involve advocating for greater affordability, exploring alternative treatment options, and developing strategies to ensure equitable access to care.[15-17]

The management of OI Type III necessitates a comprehensive and individualized approach that addresses the multifaceted challenges faced by individuals with this condition. A multidisciplinary team, comprising medical specialists, surgeons, therapists, and other healthcare professionals, plays a crucial role in coordinating care and optimizing outcomes. The primary goals of management are to minimize fractures, prevent or correct deformities, enhance mobility and function, and improve overall quality of life. Medical management forms the cornerstone of OI Type III treatment, focusing on strategies to improve bone health and reduce fracture risk. Bisphosphonates, such as zoledronic acid, are the mainstay of medical management for OI Type III. These medications act by inhibiting bone resorption and promoting bone mineralization, leading to increased bone density and reduced fracture rates. The choice of bisphosphonate, dosage, and frequency of administration are individualized based on factors such as age, severity of disease, and response to treatment. Adequate calcium and vitamin D intake are essential for bone health, particularly in individuals with OI Type III who have compromised bone density. Calcium is the primary mineral component of bone, while vitamin D facilitates calcium absorption and utilization. Supplementation with calcium and vitamin D may be recommended to ensure adequate intake and optimize bone mineralization. In some cases, other medications may be used to address specific complications or symptoms of OI Type III. For example, pain management may involve the use of analgesics or non-steroidal anti-inflammatory drugs (NSAIDs). Growth hormone therapy may be considered for individuals with significant growth retardation. Surgical interventions play a crucial role in the management of OI Type III, particularly in addressing skeletal deformities and stabilizing fractures. Intramedullary rodding is a common surgical procedure used to stabilize long bones and prevent or correct bowing deformities. This involves inserting a metal rod into the medullary canal, the hollow cavity within the bone, to provide internal support and alignment. Telescoping rods, which can lengthen as the child grows, are often preferred to minimize the need for repeated surgeries. Osteotomy involves cutting and realigning a bone to correct a deformity. This procedure may be used to address angular deformities, such as those affecting the legs or spine. Osteotomy can improve alignment, reduce pain, and enhance mobility. Spinal fusion is a surgical procedure used to stabilize the spine and prevent or correct scoliosis. This involves fusing two or more vertebrae together using bone grafts and instrumentation. Spinal fusion can improve spinal stability, reduce pain, and prevent further progression of scoliosis. Rehabilitation, including physical therapy

and occupational therapy, is an integral part of OI Type III management. These therapies focus on maximizing functional independence, improving mobility, and enhancing quality of life. Physical therapy aims to improve muscle strength, flexibility, range of motion, and overall physical function. Exercises and activities are tailored to the individual's needs and abilities, taking into account their skeletal deformities and fracture risk. Physical therapy can help individuals with OI Type III maintain or improve their mobility, reduce pain, and prevent complications such as contractures (muscle shortening) and joint stiffness. Occupational therapy focuses on helping individuals with OI Type III adapt to their environment and perform daily activities. This may involve the use of adaptive equipment, such as splints, braces, or assistive devices, to facilitate dressing, eating, bathing, and other tasks. Occupational therapy can also address cognitive and psychosocial challenges that may arise due to the chronic nature of the condition. The primary care physician plays a central role in coordinating care, monitoring overall health, and addressing medical complications. The orthopedic surgeon specializes in the surgical management of bone and joint conditions, including intramedullary rodding, osteotomy, and spinal fusion. The geneticist provides genetic counseling, confirms the diagnosis through genetic testing, and assesses the risk of recurrence in future generations. The physical therapist helps individuals with OI Type III improve their strength, flexibility, range of motion, and overall physical function. The occupational therapist assists individuals with OI Type III in adapting to their environment and performing daily activities. Other specialists may be involved in the care of individuals with OI Type III depending on their specific needs. This may include dentists, ophthalmologists, audiologists, cardiologists, pulmonologists, and psychologists. Early intervention is crucial in the management of OI Type III. Starting treatment early, ideally within the first year of life, can help minimize fractures, prevent deformities, optimize growth, and improve overall outcomes. Early intervention often involves a combination of medical, surgical, and rehabilitative strategies, tailored to the individual's specific needs. Patient and family education is an essential component of OI Type III management. Educating patients and their families about the condition, its potential complications, and management strategies empowers them to actively participate in their care and make informed decisions. This includes providing information about the importance of medication adherence, safe exercise practices, and strategies to prevent falls and injuries.[18-20]

4. Conclusion

This case series underscores the profound impact of early diagnosis and intervention in mitigating the severe complications of Osteogenesis Imperfecta (OI) Type III. The findings suggest that zoledronic acid is effective in reducing fracture rates and improving mobility, especially when initiated early in life. The cases of Patient A and Patient R, who received zoledronic acid at three months of age, demonstrated a significant reduction in fracture incidence and improved mobility compared to Patient D, who began treatment later at one year of age. The earlier the treatment, the better the outcome, particularly in preventing skeletal deformities and optimizing growth potential. However, the long-term safety profile and optimal treatment protocols for zoledronic acid in children with OI Type III require further investigation. Additionally, addressing the challenges of cost and access to this essential medication remains crucial. The management of OI Type III necessitates a comprehensive and individualized approach, encompassing medical, surgical, and rehabilitative strategies. Bisphosphonates, such as zoledronic acid, are the mainstay of medical management, while surgical interventions address skeletal deformities and stabilize fractures. Rehabilitation, including physical and occupational therapy, focuses on maximizing functional independence and enhancing quality of life. The findings of this case series, while limited by the small sample size, provide valuable insights into the clinical characteristics and

progression of OI Type III. Further research with larger cohorts is needed to confirm these findings and optimize treatment strategies for this challenging condition.

5. References

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