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Research Article

EFFICACY AND SAFETY OF INTRAVENOUS PAMIDRONATE IN ADULTS WITH OSTEOGENESIS IMPERFECTA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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ABSTRACT

Osteogenesis imperfecta (OI) is a genetic disease which is rare, has fragile bones, low bone mineral density (BMD) and high tendency to fractures. This study aimed at assessing the effectiveness and safety of intravenous pamidronate in adults with OI. Those with OI were randomly divided into 75 patients with 38 receiving quarterly intravenous pamidronate (treatment group) and 37 were given a placebo (control group) at 36 months. The change in lumbar spine BMD was the main efficacy endpoint, and the secondary efficacy outcomes were changes in BMD at the hip, fracture rate, index of pain, functional mobility, and quality of life (QoL). The measurements of biochemical markers such as serum parathormone (PTH), vitamin D and urinary calcium levels were also taken. The treatment group recorded considerable improvements in lumbar spine BMD (+0.18 0.05 g/cm 2) and hip BMD (+0.12 0.04 g/cm 2) after 36 months as compared to the control group (+0.04 0.02 g/cm 2 and +0.03 0.01 g/cm 2, respectively). Fracture rate in the treatment group was reduced by -0.8 ± 0.6 per annum with a -0.2 ± 0.3 per annum in the control group. The secondary endpoints, such as pain management, functional mobility, and QoL improved significantly in the treatment group. These were reduced serum levels of PTH and an increase in serum vitamin D and urinary calcium excretion. The treatment was tolerable even though mild adverse effects were noted which included nausea, fatigue, and musculoskeletal pain. Finally, pamidronate intravenously is an effective treatment of OI in adults because it enhances bone health, bone fracture, and quality of life.

Keywords: - Osteogenesis imperfecta, Pamidronate, bone mineral density, fracture rate.

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INTRODUCTION

Osteogenesis imperfecta (OI) is a rare hereditary disease, which, in the first place, is characterized by defective bones, reduced bone mass and increased susceptibility to fractures. It is developed due to the mutation within COL1A1 and COL1A2 genes encoding two alpha chains of type I collagen. [1]. The type I collagen is very crucial in providing structural integrity to the bones and when the genes have mutations, then the bone matrix becomes weak and consequently, the bone becomes fragile and susceptible to fracture. Clinical presentation of the OI is varied because manifestations can be common bone fractures of mild diseases, or serious deformities of the skeleton, hearing loss and life-threatening fracture in severe forms. Treatment of fractures, bone density and fracture reduction through administration of various therapies has been done more in the management of OI. One of such treatments is bisphosphonates; the drugs inhibit bone resorption thereby increasing the bone mineral density (BMD). A number of studies have been conducted with the intravenous injection of pamidronate, a bisphosphonate,

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in the children, but not in adults, where the areas of improvement in BMD and prevention of fracture have been promising. [2]. However, the effect of pamidronate in adults with the OI has received minimal research in addition to no randomized, blind double-blind, placebo-controlled trials have been conducted to ascertain its effect in this category of individuals.

Other more recent bisphosphonates such as olpadronate and neridronate have also been studied in pediatric OI patients with some reducing the peripheral fracture rate. A lack of research evaluating the effectiveness of oral bisphosphonates such as alendronate in patients with OI in adulthood is however indicated. [3]. It has already been demonstrated that the Alendronate can increase the BMD, and reduce fractures in the osteoporotic patients, and the option of utilizing it in the treatment of OI is among the areas that are being studied. The study aims to compare the efficacy and safety of intravenous pamidronate to improve the bone development, reduce fracture, and improve the quality of life of patients with OI. At the expense of the comparison of the results of the pamidronate administration with the placebo, this study will provide the complete data about the treatment efficacy and the safety profile of this medication, which can be proposed as a potential remedy to cope with OI in adults. [4]

METHODS

This was research aimed at determining the effectiveness and safety of an osteogenesis imperfecta (OI) treatment regimen. The study was done in 75 patients with OI, 38 in the treatment and 37 in control group. [5]. The research was done in a randomized, Double-Blind, as well as placebo, controlled fashion. The selection of participants was carried out with a set of inclusion and exclusion criteria, as well as similarity of the baseline traits between the two groups, the variables of age, gender, BMI, and fracture history were equally distributed. They could include patients with osteogenesis imperfecta (type I, type II, or type III). All the participants had experienced fractures in the last 12 months, and were aged between 18 and 70 years. The participants who had major comorbidities, including severe renal or liver or any other metabolic diseases, were not included. The Bone-drug (bisphosphonates) given to the treatment group was intravenous pamidronate used every 36 months (quarterly). The treatment was given to the control group in terms of a placebo of the same appearance and regimen of administration. Adverse effects and clinical outcomes of both groups were observed during the period of study. Both the subjects and the researchers were blinded on the group assignments to reduce bias. The change in bone mineral density (BMD) of the lumbar spine measured by the dual-energy X-ray absorptiometry (DXA) was taken as the primary efficacy endpoint. Secondary primary endpoint measure was also BMD of the hip. A secondary endpoint was recorded as the fracture rate per year, increases or decreases of the pain index, functional mobility score, and quality of life (QoL) score that were measured with standardized questionnaires. [7] All the patients were measured at baseline and during a follow-up visit after six months to measure the serum parathormone (PTH), 25OH vitamin D levels, and calcium levels in the blood. The serum PTH levels were evaluated with the enzyme-linked immunosorbent assay (ELISA), whereas serum vitamin D levels were assessed by means of high-performance liquid chromatography (HPLC). The excretion of urinary calcium was measured through 24-hour urine collection at the baseline and in the follow-up visits. The adverse events were observed during the research, and they entailed symptoms, i.e., nausea, vomiting, fatigue, headache, bone pain, musculoskeletal pain, gastrointestinal discomfort, hypertension, and skin rash. [8]. These undesirable effects were documented and the frequency and intensity of occurrence were compared between the treatment and control groups.

Statistical Analysis

The analysis of data was conducted in terms of descriptive and inferential statistics. Continuous variables were stated as the mean standard deviation (SD), and the categorical ones as percentages. The independent t-test was used to compare the treatment and the control group on the continuous variables and chi-square test was used when comparing the treatment and control groups on the categorical variables. A p-value that was less than 0.05 was taken to be statistically significant. An institutional ethics committee gave the nod to the study, and all the patients gave a written informed consent before taking part. The ethical rules of medical research were followed by keeping the treatment of a patient confidential. The proposed research design allowed a thorough analysis of the effect of the treatment in terms of its efficacy and safety, and offered solid results regarding its impact on bone mineralisation, risk of fractures and general health of the patients.

RESULT

The researchers used a sample size of 75 patients comprising of 38 patients who were treated and 37 patients who were not. The two groups were similar in the baseline characteristics of the study participants, such as age, gender, BMI, diagnosis, and history of fracture, which made them comparable. [9]. The mean age of the patients was 35 years, SD=12 at baseline. The gender distribution was 46.7 and 53.3 percent male and female respectively. The mean BMI was 23.4 ± 3.1 kg/m². The most frequent diagnosis was Osteogenesis imperfecta type I which was found to affect 73.3 percent of patients with type II (16.0 percent) coming in second and type III

(10.7 percent) coming in third. A large percentage of the patients were experiencing previous fractures over the last 12 months (80%), of whom 60 percent had experienced spine fractures, 16 percent had hip fractures and 24 percent had forearm fractures. In addition, 33.3% of the patients had former bisphosphonates and 13.3% had former hearing deafness. Alterations of the primary efficacy endpoints showed a high degree of improvement in the treatment group compared to the control group in 36 months. [10]. The treatment group had a change in BMD at lumbar spine of +0.18 = 0.05 g/cm 2, which is significantly greater than the +0.04 = 0.02 g/cm 2 in control group (P <0.001). The same tendency was noted at hip whereby the treatment group experienced a change of BMD of +0.12 +0.04 g/cm 2, as compared to +0.03 - 0.01 g/cm 2 in the control group ($p < 0.01$). In addition, the treatment group showed a great decrease in fracture rate, -0.8 ± 0.6 per year as compared to the control group which had reduced by -0.2 ± 0.3 per year ($p < 0.05$). There were also significant positive changes in the treatment group in services such as secondary efficacy endpoints, such as pain index, functional mobility score, and quality of life score. Treatment group had the change in pain index of -2.5 plus or minus 1.1 which was significantly better than the change in pain index of the control group which was -0.5 plus or minus 0.8 ($p < 0.001$). The functional mobility also improved more in the treatment group (+5.2 ± 2.3) compared with control group (+1.1 ± 1.5) ($p < 0.01$). Concerning the quality of life, the change in treatment group was +10.3 ± 4.7 and the change in the control group was +2.7 ± 3.6 ($p < 0.001$). There was also significant change in the biochemical indices in the treatment group. The serum parathormone (PTH) levels of the treatment group decreased significantly with an effect of -5.6 ± 2.8 pg/mL, as opposed to that of the control group of -1.2 ± 1.4 pg/mL ($p < 0.001$). Likewise, the vitamin D levels of serum 25OH also rose significantly in the treatment group by +7.1 ± 2.5 ng/mL while it increased by +1.3 ± 1.6 ng/mL in the control group ($p < 0.001$). The most significant changes in treatment group were a significant lowering in the level of urinary calcium (-24.6 ± 15.4 mg/day) as compared to the control group (-5.8 ± 8.2 mg/day) ($p < 0.001$). As far as clinical adverse effects are concerned, the adverse events rate was relatively low in both groups. The treatment group and the control group had 13.2% and 5.4% patients respectively reporting nausea ($p = 0.14$). The treatment group (18.4% vs. the control group 10.8% was not statistically significant ($p = 0.25$). Other negative effects like vomiting, headache and musculoskeletal pains did not differ significantly between the groups. Treatment and control groups had no statistically significant differences in serum calcium, phosphorus, alkaline phosphatase, and creatinine concentrations. The treatment group registered serum calcium of 9.2 0.5 mg/dl and control group registered 9.1 0.4 mg/dl ($p = 0.41$). The groups were also similar with respect to serum phosphorus and alkaline phosphatase. [14]. Also, the serum vitamin D levels of both groups improved, but the improvement was much higher in the treatment group ($p < 0.001$). The level of serum PTH decreased in the treatment group more significantly than it decreased in the control group, which is also in line with the observed increases in bone health.

Table 1: Baseline Characteristics of the Study Patients (N = 75)

Characteristic	Total (N = 75)
Age (years)	35 ± 12
Gender	
- Male	35 (46.7%)
- Female	40 (53.3%)
BMI (kg/m²)	23.4 ± 3.1
Diagnosis	
- Osteogenesis Imperfecta Type I	55 (73.3%)
- Osteogenesis Imperfecta Type II	12 (16.0%)
- Osteogenesis Imperfecta Type III	8 (10.7%)
Medical History	
- Fractures (past 12 months)	60 (80.0%)
- Hearing loss	10 (13.3%)
- Previous bisphosphonate use	25 (33.3%)
Baseline BMD (g/cm²)	0.8 ± 0.2
Baseline Pain Index	6.2 ± 2.4
Physical Activity Level	
- Sedentary	45 (60.0%)
- Active	30 (40.0%)
Fracture Site (past history)	

- Spine	40 (53.3%)
- Hip	12 (16.0%)
- Forearm	18 (24.0%)
- Other	5 (6.7%)

Table 2: Baseline Characteristics of the Study Patients: Main Efficacy and Secondary Efficacy Endpoints, Serum Parathormone, Serum 25OH Vitamin D Concentrations, and Urinary Calcium (N = 75)

Characteristic	Total (N = 75)
Main Efficacy Endpoints	
- BMD (lumbar spine, g/cm²)	0.80 ± 0.22
- BMD (hip, g/cm²)	0.70 ± 0.18
- Fracture rate (per year)	1.2 ± 0.8
Secondary Efficacy Endpoints	
- Pain Index	6.4 ± 2.3
- Functional Mobility Score	60.5 ± 12.4
- Quality of Life Score	55.6 ± 13.2
Serum Parathormone (PTH, pg/mL)	44.1 ± 14.3
Serum 25OH Vitamin D Concentration (ng/mL)	20.3 ± 5.4
Urinary Calcium (mg/day)	180.2 ± 45.6
Baseline Fracture Site (history)	
- Spine	45 (60.0%)
- Hip	15 (20.0%)
- Forearm	12 (16.0%)
- Other	3 (4.0%)

Table 3: Comparisons at 36 Months Between Treatment and Control Groups in Changes of Main Efficacy and Secondary Efficacy Endpoints, Serum Parathormone, Serum 25OH Vitamin D Concentrations, and Urinary Calcium

Characteristic	Treatment Group (N = 38)	Control Group (N = 37)	P-Value
Main Efficacy Endpoints			
- Change in BMD (lumbar spine, g/cm²)	+0.18 ± 0.05	+0.04 ± 0.02	<0.001
- Change in BMD (hip, g/cm²)	+0.12 ± 0.04	+0.03 ± 0.01	<0.01
- Change in fracture rate (per year)	-0.8 ± 0.6	-0.2 ± 0.3	<0.05
Secondary Efficacy Endpoints			
- Change in Pain Index	-2.5 ± 1.1	-0.5 ± 0.8	<0.001
- Change in Functional Mobility Score	+5.2 ± 2.3	+1.1 ± 1.5	<0.01
- Change in Quality of Life Score	+10.3 ± 4.7	+2.7 ± 3.6	<0.001
Serum Parathormone (PTH, pg/mL)			
- Change in Serum PTH	-5.6 ± 2.8	-1.2 ± 1.4	<0.001
Serum 25OH Vitamin D Concentration (ng/mL)			
- Change in Vitamin D Levels	+7.1 ± 2.5	+1.3 ± 1.6	<0.001
Urinary Calcium (mg/day)			
- Change in Urinary Calcium	-24.6 ± 15.4	-5.8 ± 8.2	<0.001

Table 4: Clinical Adverse Effects and Biochemical Indices in Treatment and Control Groups

Adverse Effect	Treatment Group (N = 38)	Control Group (N = 37)	P-Value
Clinical Adverse Effects			
- Nausea	5 (13.2%)	2 (5.4%)	0.14
- Vomiting	3 (7.9%)	1 (2.7%)	0.22
- Fatigue	7 (18.4%)	4 (10.8%)	0.25
- Headache	4 (10.5%)	2 (5.4%)	0.31
- Bone pain	6 (15.8%)	3 (8.1%)	0.21
- Musculoskeletal pain	8 (21.1%)	5 (13.5%)	0.32

- Gastrointestinal discomfort	4 (10.5%)	3 (8.1%)	0.63
- Hypertension	2 (5.3%)	1 (2.7%)	0.50
- Rash	1 (2.6%)	0 (0%)	0.38
Biochemical Indices			
- Serum Calcium (mg/dL)	9.2 ± 0.5	9.1 ± 0.4	0.41
- Serum Phosphorus (mg/dL)	3.5 ± 0.3	3.6 ± 0.3	0.58
- Serum Alkaline Phosphatase (IU/L)	120 ± 28	118 ± 25	0.74
- Serum Creatinine (mg/dL)	1.0 ± 0.2	1.1 ± 0.2	0.35
- Serum Vitamin D (ng/mL)	22.1 ± 5.4	21.2 ± 5.1	0.51
- Serum Parathormone (PTH, pg/mL)	45.6 ± 14.2	44.9 ± 13.5	0.80
- Urinary Calcium (mg/day)	180.3 ± 40.5	175.8 ± 42.1	0.60

DISCUSSION:

Osteogenesis imperfecta (OI) is a rare inherited disease, which is characterized by weak bones, low bone density which often can result in frequent fractures and physical disability. The study was aimed to establish whether intravenous pamidronate was effective in preventing fractures and bone mineral density (BMD) in adults with OI. [15]. Our findings indicated that pamidronate has considerable positive impact on BMD, fewer incidences of fracture and possesses considerable advantage in terms of pain management, functional mobility, and quality of life compared to control group. One of the most significant findings of the study was a significant increment of the BMD of treatment group, particularly, hip and lumbar spine. The improved changes were +0.18 +0.05 g/cm 2 at the lumbar spine and +0.12 +0.04 g/cm 2 at the hip at 36 months post-treatment in the treatment group over the minor changes in the control (+0.04 +0.02 g/cm 2 at the lumbar spine and +0.03 +0.01 g/cm 2 at the hip, respectively). [16]. These findings agree with those of the other studies which have shown that the bisphosphonates like pamidronate may be useful in raising the BMD of the OI patients who have lower bone density usually owing to the reduced ability to generate collagen. In the treatment group, the rate of fractures was statistically lower in cases of decrease of -0.8 + 0.6 fractures/year but the decrease was lower in the control group as -0.2 + 0.3 fractures/year. [17]. The fact that the fracture rate has been decreased is particularly important as fractures are among the typical aspects of OI and have a massive impact on the quality of life of the patient. The only thing that can be done is to reduce the debilitating influence of the frequent fractures by reducing the rate of fractures, using pamidronate that can lead to mobility issues and long-term disability. [18]. Other secondary endpoints of efficacy (pain index, functional mobility score and quality of life (QoL)) also showed significant improvement in the treatment group, in addition to the BMD and rate of fracture. Treatment group showed much better pain management because the index of pain changed as compared to the control group which changed by -2.5 ± 1.1 ($p < 0.001$). The most common OI symptom is chronic, and in most cases, debilitating pain, and normally occurs after fractures, bone abnormalities, and musculoskeletal difficulties. The fact that pain experienced by the treatment group was minimized is a pointer that pamidronate could be a very crucial component in the management of pain, likely because of the strength that is gained on the bone and the frequency of the breakage. Treatment group also showed a strong improvement of functional mobility score (+5.2 + 2.3) as opposed to the control group (+1.1 + 1.5, $p < 0.01$). This improvement means that this treatment has done not only strengthened the bones but also contributed to the increase in physical functioning and the ability of patients to engage in more physical activities and the limitation of OI. [21]. Similarly, QoL also improved significantly in the treatment group (10.3 4.7) relative to control group (2.7 3.6) which is also indicative of the overall positive effect of pamidronate on QoL of OI patients. The strong influence of Pamidronate on the bone metabolism was also demonstrated by the significant change of the biochemical indices. [22]. Serum parathormone (PTH) decreased significantly (-5.6 ± 2.8 pg/mL) in the treatment group both of which are indicators of bone remodelling and decreased bone resorption. The excessive levels of PTH in OI patients are the common compensatory measure to the diminished bone mass and reduction in the levels of PTH contributes to the fact that pamidronate may be a potential inhibitor of excessive bone resorption. In addition, the serum 25OH vitamin D in the treatment group (+7.1 ± 2.5 ng/mL) which is crucial in the calcium absorption and growth of bones was significantly improved. Patients with OI are also prone to vitamin D deficiency, which makes bones weak, thus, the improvement of vitamin D levels is another sign of the beneficial effect on bone state produced by pamidronate. [23]. The amount of urinary calcium excretion was also significantly reduced in the treatment group (-24.6 ± 15.4 mg/day), and it denotes a higher retention of calcium and bone mineralization. The reduction of the urinary calcium also indicates a reduction of the bone turnover and increase of the bone mineralization that is an excellent outcome among patients with OI. Although the results of

the study were favorable, there were some negative results within the two groups, which were in general mild, and statistically non-significant. There was a significantly greater number of 13.2% patients in the treatment group who experienced nausea than 5.4% of the patients in the control group who experienced nausea but this was not a statistically significant value (p = 0.25). The other adverse effects such as vomiting, headache and musculoskeletal pain were also reported but they were not significantly different when compared to the groups. The findings are consistent with the side effect profile previously known about bisphosphonates and it might contain gastrointestinal discomfort, fatigue and musculoskeletal pain. However, these adverse effects were quite uncommon and did not lead to the discontinuation of treatment, which means that pamidronate can be regarded as well-tolerated even in OI patients. [25]. Although the effectiveness of pamidronate in OI is useful information that has been provided in this study, the study is limited by various factors. First, the researchers lacked sufficient time to study the long-term outcomes to establish the long-term benefits and safety of pamidronate in patients with OI; the researchers had only 36 months to study the matter. In addition, the study design may limit the generalization to the populations because the sample size used was appropriate. Future studies that may be conducted to prove the validity of the results with a larger sample size and extended follow-up are needed to examine the potential benefits of the combination of pamidronate and other treatment methods, such as physical therapy and exercise programs, to improve the outcomes of OI patients.

CONCLUSION

Osteogenesis imperfecta (OI) is a challenging genetic condition, which has thin bones, reduced bone mass, and numerous fractures that could catastrophically impact the quality of life of patients. The article aimed to determine the efficacy and safety of intravenous pamidronate when used to treat adults with OI. The findings demonstrate that pamidronate possesses significant clinical outcomes with regard to the bone mineral density (BMD), fracture, pain, functional mobility, and overall quality of life (QoL), and can be considered an effective treatment in patients with OI. In terms of alterations in BMD, treatment group was highly enhanced especially in the lumbar and hip regions which are the sensitive areas where bone frailty is experienced in OI. Improvement in the BMD of the treatment group (lumbar spine +0.18 + -0.05 g/cm 2 and hip +0.12 + -0.04 g/cm 2) was significantly greater than the control condition. The results are similar to the results of the previous studies, which have also attached significance to the application of bisphosphonates like pamidronate in improving the bone density of the individuals affected by OI. Pamidronate enhances the BMD, thus bone strengthening by reducing the probability of fractures, which is a trait of OI. Other than BMD improvement, pamidronate treatment was also reported to result in a reduction of fracture rate. The treatment group indicated the fracture rate had fallen by -0.8 +/-0.6 fractures per year compared to the control group, which was much lower (-0.2 +/- 0.3 fractures per year). This is very crucial, as fractures is one of the most disabling factors of OI. Pamidronate assists in the alleviation of mobility by averting both fractures and decreasing pain and suffering due to frequent breaks in the bones that enhances the quality of life among patients. The other important area in this study was the pain management and the results showed that pamidronate worked well in management of the pain on the group under treatment. The difference between the change of the index of pain in the treatment group was -2.5 +-1.1 compared to the change of the control group of -0.5 +-0.8. The causes of pain among patients of OI include fractures, deformities and musculoskeletal complications, management of the pain is important in improving the patient overall health. The given pain reduction demonstrates that pamidronate may become a significant aspect in enhancing the quality of life and the level of comfort of a patient. Functional mobility and QoL were also significant in the treatment group. Treatment group (+5.2 +2.3 and +10.3 +4.7) and control group (+1.1 +1.5 and +2.7 +3.6) showed great improvements in functional mobility and QoL respectively (T). The improvement of the QoL and mobility implies that the treatment has not been intended to improve only the bone health but the overall physical health since the patients are able to carry out more activities and have their normal functioning in the daily life. It is particularly necessary in the case of OI patients since they can exercise with a limited capacity due to the fragility of bones. Biochemical markers were also useful in achieving the positive effects of pamidronate. There was the reduction of serum parathormone (PTH) levels in all cases in a treatment group which is the indication of a reduction in bone resorption and increase in bone metabolism. The vitamin D concentrations of the 25OH in the treatment group also increased significantly and plays a critical role in the absorption of calcium and building of bones. The fact that there is a reduced rate of urinary calcium excretion is also a pointer that it may be true that pamidronate improves the retention of calcium in the body as well as bone turnover and this is crucial in raising the bone strength and stability of the individuals with OI. Although the study has demonstrated numerous benefits of pamidronate, some side effects have also been established to be experienced based on the study and they include nausea, fatigue and musculoskeletal pains. These were not serious side effects that would lead to the termination of treatment. This implies that pamidronate is

a treatment option that patients have high tolerance towards in OI and the benefits of this drug outweigh the side effects in most patients. Regardless of the positive results, the study had certain limitations. The study had a limitation of being limited to 36 months, and there is no indication as to how the study would have evolved over time. In addition, the sample size is too limited, and it consists of 75 patients, which significantly limits the generalizability of the findings. These findings need to be confirmed through more comprehensive research on bigger samples and extended follow-ups into the validity of pamidronate in the long-term and whether it is a safe agent. Future research could also examine possible advantages of dual therapy (pamidronate and other approaches to treatment such as physical therapy, exercise regimens, and oral bisphosphonates) to achieve better patient outcomes. Even though there have been some mild adverse effects associated with the treatment, it is generally well-tolerated, and that is why in this manner, it is a promising treatment approach of OI management. The findings will contribute to the available literature that endorses the use of bisphosphonates in the management of OI as well as serve as a foundation in the other studies to refine and improve subsequent management strategies to deal with the dreadful disease.

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