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TREATMENT WITH PAMIDRONATE IN CHILDREN AND ADOLESCENTS WITH OSTEOGENESIS IMPERFECTA IN SANTA CATARINA

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Abstract: Objectives: The aim of this study was to evaluate the clinical, laboratory and epidemiological profile of patients with OI undergoing early treatment with pamidronate compared to those who did not receive early treatment, at a Reference Center for Osteogenesis Imperfecta (CROI) in Santa Catarina. Methods: We retrospectively collected data from the medical records of patients with OI seen and treated with pamidronate between March 2005 and December 2022, resulting in 81 participants. Information such as age at start of treatment, clinical characteristics, laboratory parameters and number of fractures were analyzed. Results: It was observed that 48.2% of patients started treatment before 2 years, and 80.2% of patients before 6 years. The rate of fractures/year showed a median of 3.89 before and 0.53 after the start of treatment for all ages. In addition, patients who started treatment before the age of 2 showed a reduction in the median fracture rate/year from 33.97 before to 0.97 after starting treatment, with a p-value < 0.001. The median serum alkaline phosphatase for all ages went from 307.5 U/L before to 168 U/L after starting treatment, with statistical significance in patients who started treatment before the age of 6. Conclusion: Pamidronate was effective in reducing the fracture rate/year and serum alkaline phosphatase. It was found that, in all the types of OI analyzed, the earlier the start of treatment, the better the outcomes.
Keywords: Osteogenesis Imperfecta, pamidronate, bone fractures, children, quality of life

INTRODUCTION

Osteogenesis Imperfecta (OI), also known as glass bones, is a genetic connective tissue disease with a broad spectrum of phenotypes,[1] essentially affecting bone structure, characterized mainly by bone fragility and consequent fractures.[2] Its worldwide prevalence is between 1:15,000 and 1:20,000 births.[1]

OI is mostly caused by mutations in the autosomal dominant *COL1A1* and *COL1A2* genes, resulting in alterations in type 1 collagen.[3] A 2023 review showed that OI can be caused by mutations in 22 genes[4] involved in collagen biosynthesis or osteoblastic function, with dominant, recessive or X-linked inheritance.[5]

The clinical manifestations of the disease are heterogeneous, since all collagen-containing tissues are affected. The bone fragility caused by the disease makes the individual susceptible to fractures, bone deformities, growth deficiency and sarcopenia.[6] Some extra-osseous manifestations include bluish sclera, hearing loss, dentinogenesis imperfecta, joint hypermobility and muscle weakness.[7] In addition, the range of severity of the disease is very wide, since severe forms are lethal in the perinatal period, while milder forms may not be recognized until adulthood.[6] In less severe forms of the disease, it is necessary to consider abuse as a differential diagnosis, since both can present multiple fractures with no obvious explanation.[8]

In some cases, OI is diagnosed in utero, during prenatal care, which allows for early intervention in these patients. As the development of the fetal skeleton begins in the eighth week of pregnancy and the ossification centers become evident in the twentieth week, the second trimester is the most appropriate time to screen for this disease in the fetus.[9,10]

The classification of OI was first established by Sillence[11] in 1979, when it was divided into 4 subgroups: type I, characterized by OI of dominant inheritance with blue sclera, with a milder phenotype and no bone deformities; type II, by perinatal lethal OI; type III, progressively deforming OI with normal sclera, with a severe phenotype; and type IV, of dominant inheritance and normal sclera, with intermediate severity between types I and III.[12]

Sillence's classification has been expanded in recent years as new types of inheritance and genetic mutations have been discovered. Currently, 37 types of OI have been described.[4] However, most forms of OI fall into the described subgroups by Sillence, based on clinical criteria and the severity of the disease, which is still the most widely used classification in practice today to determine patient treatment and prognosis.[12]

Although there is no cure for the disease, a multidisciplinary approach often promotes good results in patients' condition, with improved pain and fewer fractures.[13] Early periodic multidisciplinary follow-up is essential for proper management of the disease, not only of bone deformities, but also of the multiple extraosseous manifestations that impair function and quality of life.[14]

The use of bisphosphonates, such as pamidronate, in the treatment of OI was first published in 1998, showing the drug's benefit in increasing bone mass, mobility, quality of life and reducing fractures and bone pain.[15] Its mechanism of action is to inhibit bone resorption by inactivating osteoclasts.[16] The drug was approved in Brazil in 2001. A Brazilian cohort study concluded that the first 10 years of treatment with pamidronate in children were safe and effective in terms of increased mobility and bone mineral density. It was also found that the earlier the start of treatment, the greater the benefit for the child.[3] It is important to mention that recent studies are exploring new therapeutic approaches, such as gene and cell therapy,

which have the potential to modify the course of the disease by acting directly on collagen production, unlike bisphosphonates, but are not yet approved.[17]

This study is justified by the need to illustrate the evolution of treatment with pamidronate in children and adolescents diagnosed with OI. By profiling these patients, it is possible to analyze potential changes in their quality of life, bone structure, the need for surgical interventions and laboratory changes caused by the disease before and after starting pamidronate, contributing to the understanding of this group of diseases and their treatment. Thus, this study aimed to analyze the treatment of OI patients with pamidronate in Santa Catarina between March 2005 and December 2022.

MATERIALS AND METHODS

This is a cross-sectional study conducted at the Joana de Gusmão Children's Hospital, which is the only Reference Center for Osteogenesis Imperfecta (CROI) in Santa Catarina analysis of a considerable number of cases. The research sample size was equal to the total number of patients with OI referred to the CROI in the state of Santa Catarina between March 2005 and December 2022, reaching a total of 114 patients.

The study included participants of both sexes, with no age limit, referred to the pediatric endocrinology service of the Joana de Gusmão Children's Hospital between March 2005 and December 2022 with a clinical diagnosis of OI, according to the Sillence criteria, and who underwent treatment with pamidronate at the hospital. The data collected was only from the participants' period of treatment with pamidronate. Patients who were not treated with this medication and those who were lost to follow-up after only 1 cycle of treatment were excluded, resulting in a total of 81 patients.

The data was collected through physical and digital access to the medical records of the Joana de Gusmão Children's Hospital, after authorization from the legal guardian. All the medical records of patients with OI were analyzed according to the inclusion and exclusion criteria. The records were analyzed for the presence of OI diagnosed using clinical criteria, based on anamnesis, physical examination, family history and imaging tests (X-rays). Patients with type 2 of the disease were not analyzed, as this is the perinatal lethal form of OI.

The data collected were: age at start of treatment (in years); age at last cycle of pamidronate (in years); gender (male/female); number of fractures before treatment; number of fractures after start of treatment; need for surgical treatment (yes/no); serum calcium before treatment (in mg/dl); serum calcium after start of treatment (in mg/dl); serum phosphorus before treatment (in mg/dl); serum phosphorus after starting treatment (in mg/dl); serum alkaline phosphatase before treatment (in U/L); serum alkaline phosphatase after starting treatment (in U/L); type of OI (1/3/4); number of pamidronate cycles; presence of bluish sclerae (yes/no); presence of dentinogenesis imperfecta (yes/no).

With regard to laboratory parameters, the reference values used were those of the laboratory where the tests were taken. For serum phosphorus: 0 to 5 days, 4.8 to 6.2 mg/dl; 6 days to 3 years, 3.8 to 5.5 mg/dl; 4 to 6 years, 4.1 to 5.4 mg/dl; 7 to 11 years, 3.7 to 5.6 mg/dl; 12 to 13 years old, 3.3 to 5.4 mg/dl; 14 to 15 years old, 2.9 to 5.4 mg/dl; from 16 years old, 2.7 to 4.7 mg/dl. For serum calcium: 0 to 3 years, 8.7 to 9.8 mg/dl; 4 to 9 years, 8.8 to 10.1 mg/dl; 10 to 11 years, 8.9 to 10.1 mg/dl; 12 to 13 years, 8.8 to 10.6 mg/dl; 14 to 15 years, 9.2 to 10.7 mg/dl; a from the age of 16, 8.9 to 10.7 mg/dl. For serum alkaline phosphatase: 0 to 5 days, 110 to 300 U/L; 6 days to 3 years, 145

to 320 U/L; 4 to 6 years, 150 to 380 U/L; 7 to 9 years, 175 to 420 U/L; 10 to 11 years, 135 to 530 U/L; 12 to 13 years, 200 to 465 U/L; 14 to 15 years, 130 to 525 U/L; from 16 years old, 55 to 260 U/L.

The number of fractures before starting treatment was obtained from the report of parents or guardians, described in the medical records. After the patient began to be monitored, fractures were diagnosed based on clinical history and radiographic examination. Using the number of fractures before and after the start of treatment and the age at the start of treatment, it was possible to calculate the rate of fractures/year before and after the start of treatment. Data on the need for orthopedic surgical treatment to correct fractures or deformities was obtained from medical records. Variables relating to the period after the start of treatment are mentioned in this way in order to make it clear that treatment may still be in progress.

Pamidronate was administered while the patient was hospitalized, and each hospitalization is equivalent to one cycle of intravenous medication, which varies in dose and frequency, according to the protocol adopted by the hospital, developed by Glorieux et al. in Montreal, Canada. Patients under 2 years old received 0.5 mg/kg/day for 3 consecutive days, with 2-month intervals between cycles. Between 2 and 3 years of age, the dose was 0.75 mg/kg/day for 3 consecutive days, at 3-month intervals. Children aged 3 and over received 1 mg/kg/day for 3 consecutive days, every 4 months. Depending on the response to treatment, some patients received a longer interval between cycles and even switched to treatment with other bisphosphonates.

The data was tabulated using *Windows Excel* software. The data was analyzed using the *IBM Statistical Package for the Social Sciences (IBM SPSS®) 18.0* program. Qualitative data was presented in the form of simple and relative frequencies. Quantitative data was presented as measures of central tendency (median and mean) and their respective measures of variability/dispersion (amplitude [maximum and minimum] and standard deviation) according to the distribution of the data. The chi-square test was used to analyze the association between categorical variables (exposure and outcome). The Wilcoxon test was used to compare variables with a non-normal distribution in relation to the outcome. Statistical significance was considered to be $p \leq 0,05$.

This research project was approved by the Research Ethics Committees of the Universidade do Sul de Santa Catarina - Unisul (Consubstantiated Opinion No. 5.674.376) and the Hospital Infantil Joana de Gusmão (Consubstantiated Opinion No. 5.735.000).

RESULTS AND DISCUSSION

The clinical, epidemiological and laboratory profile of OI patients in Santa Catarina between March 2005 and December 2022 is described in detail in Tables 1 and 2. Table 1 shows that 48.2% of patients started treatment before the age of 2, and 80.2% of patients started treatment before the age of 6. 59.3% required surgical treatment due to fractures. In addition, 96.3% of the patients had bluish sclerae and 43% had dentinogenesis imperfecta.

The age at which patients started treatment ranged from 4 days (0.01 years) to 14 years and 7 months (14.58 years), with a median of 2 years and 1 month (2.08 years) (Table 2). With regard to laboratory parameters, Table 2 shows that before pamidronate, serum alkaline phosphatase had a median of 307.5, while after starting treatment, this median was reduced to 168. Table 3 shows that there was a statistically significant reduction in serum alkaline phosphatase with the start

of pamidronate treatment in patients who started treatment before the age of 6. With regard to the number of pamidronate cycles, the median was 14, with a minimum of 2 and a maximum of 42 cycles.

Analyzing the number of fractures/year before and after starting treatment, the medians were 3.89 before treatment and 0.53 after starting treatment (Table 2). Table 4 shows the association between the age at the start of treatment and the number of fractures/year, differentiating between before and after the start of treatment. As a result, it was found that patients who started treatment before the age of 2 had a median of 33.97 fractures/year before treatment, and 0.97 after starting treatment, with a p-value < 0.001. There was also statistical significance in the other two groups who started treatment before 10 years.

Table 5 shows that of the patients who started treatment before the age of 2, 59.5% had type 3 OI, while in the other age groups there were more patients classified as type 1.

The data obtained in this study showed that early treatment with pamidronate had a positive impact on reducing the number of fractures and serum alkaline phosphatase in patients with OI.

Therapy with pamidronate showed a significant reduction in the fracture rate/year in patients with OI, as has been shown in numerous studies.[15,18,19] In the present study, for all age groups, the median was 3.89 fractures/year before treatment to 0.53 fractures/year after starting treatment. As expected, this result was more significant in the children who received pamidronate earlier, in the under-2 age group, with a median fracture rate of 33.97 fractures/year before treatment and 0.97 after starting treatment, with p < 0.001. Furthermore, the only age group that did not show a significant reduction in the number of fractures after starting treatment was that containing children aged 10 and over, which could suggest that treatment started earlier is capable of having a greater impact on reducing the number of fractures. Although significant, one theory that could explain why the rate of fractures/year after starting treatment is not even more significant is that, after starting treatment, the patient's mobility improves, making them more active and consequently more susceptible to fractures.[15]

Frequent fractures are often the cause of recurrent pain in OI.[2] Recent studies have shown significantly reduced levels of referred pain after treatment with pamidronate,[18,20] which may be related to a reduction in the number of fractures, as well as a reduction in exacerbated bone formation.[21]

In this study, there were more patients who required surgical treatment (48 patients) than patients who did not (33 patients). In all age groups, a substantial proportion of patients required orthopaedic surgery. Surgical intervention may be necessary both to correct fractures, since the bone callus formed after a fracture has a defective bone matrix, and to correct deformities that occur as a result of OI, which can interfere with the functionality of the affected limb and predispose to fractures.[22]

The use of intravenous bisphosphonates, such as pamidronate, is known to have several benefits for bone metabolism.[23,24] Serum alkaline phosphatase levels are usually increased in OI, especially during periods of bone callus formation, since it is a biochemical marker of bone remodeling.[21,25] Serum calcium and phosphorus levels are usually within the normal range in the disease.[15,26] This study showed a reduction in serum alkaline phosphatase values in all age groups after starting treatment with pamidronate, with a significant result especially in those who started treatment earlier. In addition, mean serum calcium and phosphorus values remained within the reference values before and after starting treatment. In a study of

patients under the age of 2 undergoing treatment with

In the same study, a significant reduction in serum alkaline phosphatase was observed after cyclic intravenous pamidronate for at least 3 years. In the same study, no significant differences were found in serum calcium and phosphorus before and after treatment.[25]

This study also showed that milder cases of OI are diagnosed later. It was observed that 42 (51.9%) patients started treatment after the age of 2, and of these, 9 had type 3 of the disease, considered to be the most severe type compatible with life. This may be due to the fact that there were patients with the disease prior to the creation of the CROI at the Joana de Gusmão Children's Hospital in March 2005, who were left untreated or treated in other services until then.

This study had limitations in terms of methodology, such as the fact that the data collected was restricted to medical records, which are subject to errors or subjectivity, the fact that the group of patients studied was heterogeneous in terms of the number of cycles of pamidronate and the types of disease, and the different levels of evidence of the methodologies used in the references. The sample of cases collected, although relatively small when compared to other similar studies, proved to be adequate for evaluating most of the parameters, and comparable to the reference samples used in the discussion.

TABLES

Variable	n	%
Sex Male	44	54,3
Female	37	45,7
Total	81	100,0
Age at start of treatment < 2 years	39	48,2
≥ 2 < 6 years	26	32,1
≥ 6 < 10 years	10	12,3
≥ 10 years	6	7,4
Total	81	100,0
Type		
1	33	43,4
3	31	40,8
4	12	15,8
Total		76100.0
Need for surgical treatment		
Yes	48	59,3
No	33	40,7
Total	81	100,0
Bluish sclerae Yes		
	78	96,3
No	3	3,7
Total	81	100,0
Dentinogenesis imperfecta		
Yes	34	43,0
No	45	57,0
Total	79	100,0

Table 1 - Description of the clinical and epidemiological profile of patients with OI at the CROI Hospital Infantil Joana de Gusmão between March 2005 and December 2022.

CONCLUSION

In conclusion, the results indicate that treatment with cyclic intravenous pamidronate is a beneficial therapeutic approach for children diagnosed with OI, providing a better overall prognosis for these patients. It was observed that the earlier the start of treatment, the better the outcomes, with significant results in reducing the number of fractures and serum alkaline phosphatase.

Variable	Mean (SD)	Median (range)	n
Age at start of treatment	-	2,08 (0,01 - 14,58)	81
Fractures/year before treatment	-	3,89 (0,00 - 469,28)	77
Fractures/year after starting treatment	-	0,53 (0,00 - 6,42)	81
Calcium before treatment	9,64 (1,16)	-	61
Calcium after starting treatment	9,77 (0,54)	-	73
Phosphorus before treatment	5,18 (1,24)	-	65
Phosphorus after starting treatment	4,67 (0,72)	-	71
Serum alkaline phosphatase before treatment	-	307,50 (98,80-5.300,00)	64
Serum alkaline phosphatase after starting treatment	-	168,00 (42,70-930,00)	73
Cycles	-	14,00 (2,00 - 42,00)	81

Table 2 - Description of the laboratory profile, fracture rate per year and number of pamidronate cycles of patients with OI at the CROI Hospital Infantil Joana de Gusmão between March 2005 and December 2022.

	Serum alkaline phosphatase before treatment		Serum alkaline phosphatase after starting treatment		p
Age of onset treatment	n	Median (range)	n	Median (range)	
< 2 years	29	358,0 (147,0 - 2.432,0)	36	164,5 (65,0 - 620,0)	< 0,001
≥ 2 < 6 years	20	300,5 (117,0 - 5.300,0)	24	168,5 (59,0 - 930,0)	< 0,001
≥ 6 < 10 years	9	245,0 (141,0 - 891,0)	8	162,0 (42,7 - 362,0)	0,069
≥ 10 years	6	158,5 (98,8 - 471,0)	5	192,0 (64,1 - 296,0)	0,225
Total	64	307,5 (98,8 - 5.300,0)	73	168,0 (42,7 - 930,0)	-

Table 3 - Comparison of serum alkaline phosphatase before and after the start of treatment with pamidronate in OI in relation to age at the start of treatment at the CROI Hospital Infantil Joana de Gusmão between March 2005 and December 2022.

Variable	Fractures/year before treatment		Fractures/year after start of treatment		p
Age of onset treatment	n	Median (range)	n	Median (range)	
< 2 years	38	33,97 (0,00 - 469,28)	39	0,97 (0 - 6,42)	<0,001
≥ 2 < 6 years	24	1,48 (0,00 - 14,29)	26	0,42 (0 - 2,32)	0,001
≥ 6 < 10 years	10	0,74 (0,40 - 4,86)	10	0,16 (0 - 1,05)	0,022
≥ 10 years	5	0,69 (0,22 - 2,06)	6	0,07 (0 - 1,66)	0,08
Type					
1	32	1,00 (0,00-12,00)	33	0,11 (0 - 1,87)	< 0,001
3	28	34,59 (2,06 - 469,28)	31	1,01 (0 - 6,42)	< 0,001
4	12	14,50 (0,67 - 108,00)	12	0,94 (0 - 4,17)	0,003

Table 4 - Comparison of the rate of fractures per year before and after the start of treatment with pamidronate in relation to age at the start of treatment and type of OI at the CROI Hospital Infantil Joana de Gusmão between March 2005 and December 2022.

Variable	Age at start of treatment									
Need for surgical treatment	< 2 years		≥ 2 < 6 years		≥ 6 < 10 years		≥ 10 years		Total	
Yes	25	64,1	13	50,0	6	60,0	4	66,7	48	59,3
No	14	35,9	13	50,0	4	40,0	2	33,3	33	40,7
Total	39	100,0	26	100,0	10	100,0	6	100,0	81	100,0
Type										
1	7	18,9	15	62,5	8	80,0	3	60,0	33	43,4
3	22	59,5	6	25,0	1	10,0	2	40,0	31	40,8
4	8	21,6	3	12,5	1	10,0	0	0,0	12	15,8
Total	37	100,0	24	100,0	10	100,0	5	100,0	76	100,0

Table 5 - Data regarding the need for surgical treatment and the type of OI classified into age groups according to the age at which treatment began at the CROI Hospital Infantil Joana de Gusmão between March 2005 and December 2022.

Despite the improvements observed, it is important to recognize that the sample of patients is heterogeneous and the variables analyzed are strongly influenced by the types of disease, since they represent different levels of severity. It is therefore essential to take them into account when assessing the individual prognosis of each patient, and a multidisciplinary approach is necessary.

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