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ORIGINAL ARTICLE

Children and adolescents treated with neridronate for osteogenesis imperfecta show no evidence of any osteonecrosis of the jaw

Evelina Maines · Elena Monti · Francesco Doro · Grazia Morandi · Paolo Cavarzere · Franco Antoniazzi

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Abstract Over recent years, several reports have been published on unusual cases of osteonecrosis of the jaw (ONJ) in adults using second- and third-generation nitrogen-containing bisphosphonates such as pamidronate, alendronate, risedronate and zoledronate, but no case has ever been reported either in children or in adult patients taking neridronate. Children and adolescents affected by osteogenesis imperfecta (OI) could belong to a high-risk group for ONJ because bone fragility in OI is associated with a connective tissue malfunction. The purpose of this study is to evaluate the incidence of ONJ in a pediatric population treated with neridronate for OI. A total of 102 pediatric patients with OI who received neridronate infusions for a mean of 6.81 years (SD ± 3.06 years) were clinically assessed for possible ONJ. Eligibility criteria for participation included patients between 1.2 and 24 years old who received cyclical neridronate infusions for at least 1 year. All the patients were reviewed to determine duration, dosage and cumulative dose of their bisphosphonate therapy and were examined clinically to assess their oral health status. We have not demonstrated any occurrence of ONJ in our patients. In conclusion, at the moment insufficient data are available to prove a greater risk of ONJ in children with OI than in children affected by other forms of bone fragility. However, cases may emerge in future because the risk of ONJ seems to be related to the cumulative dose and the duration of therapy.

E. Maines (✉) · E. Monti · F. Doro · G. Morandi · P. Cavarzere · F. Antoniazzi
Department of Life Sciences and Reproduction Sciences, Pediatric Clinic, University of Verona, General Hospital "Giambattista Rossi", Piazzale Ludovico Antonio Scuro 10, 37134 Verona, Italy
e-mail: evelina.maines@gmail.com

Keywords Intravenous neridronate · Osteonecrosis of the jaw · Osteogenesis imperfecta

Abbreviations
ONJ Osteonecrosis of the jaw
OI Osteogenesis imperfecta

Introduction

Osteogenesis imperfecta (OI) is the most common genetic bone disorder and its prevalence is estimated to be between 1 in 10,000 and 1 in 20,000 births.

The great majority of OI cases are caused by a genetic defect in the quantitative or qualitative synthesis of the structural protein type I collagen; however, at the present time, a surprising genetic complexity of the molecular bases of OI has been revealed. To date, nine types of OI have been defined on the basis of a different phenotype correlated with each gene, but recently a new classification has emerged which classifies OI in 5 major types [1–3].

Until a gene therapy aimed at either replacement or silencing of the mutant allele is feasible, the causal defect of the disease cannot be corrected. At present, bisphosphonates are the most promising therapy and their use has become the widely accepted treatment both in adults and children affected by OI. Many studies on children with OI [4–8] suggest that intravenous infusions of bisphosphonates significantly raise the rate of increase in bone mass density and significantly decrease the risk of clinical fractures, because bisphosphonates given at adequate doses improve bone strength. The action mechanism of bisphosphonates is complex but these compounds act mainly on osteoclasts by inhibiting their activity through a direct toxic effect on these cells [9].

Intravenous bisphosphonate use in adult patients has been linked to osteonecrosis of the jaw (ONJ), a condition which has recently emerged as a significant complication in a subset of patients taking these drugs, typically > 60 years of age and with a history of malignancy [10–13]. However, increasing frequency of ONJ has also been reported recently in adults receiving oral bisphosphonates [12, 14].

In children osteonecrosis of long bones is a well-documented complication of intensive chemotherapy for acute lymphoblastic leukemia (ALL), including multiple courses of corticosteroids [15, 16]; however, no case of osteonecrosis, specifically of the jaw, has ever been reported in children.

Over the past few years, several reports have been published of unusual cases of ONJ in adults using second- and third-generation nitrogen-containing bisphosphonates such as pamidronate, alendronate, risedronate and zoledronate [10, 14, 17–22]. In the literature there are no reports on ONJ in patients using neridronate, a nitrogen-containing bisphosphonate structurally similar to alendronate and pamidronate. There are few studies that have assessed the incidence of ONJ in pediatric populations being treated with pamidronate, zoledronate or alendronate, but none concerning neridronate [23–25].

Patients and adolescents affected by OI could belong to a high-risk group for ONJ because bone fragility in OI is associated with a connective tissue malfunction.

The purpose of our study is to investigate any possible relationship between intravenous neridronate treatment and ONJ in a pediatric population affected by OI and, eventually, to establish an incidence of this complication.

Materials and methods

A retrospective survey of 102 pediatric patients who received neridronate infusions for OI at the Pediatric Clinic of the University of Verona was carried out between August 2009 and March 2011. Indications for treatment were either severe forms of OI with fractures and skeletal deformities, or milder forms with pain, low growth velocity, and vertebral compressions.

We included patients having received only neridronate therapy and no other bisphosphonate treatment.

Eligibility criteria for participation included OI children or adolescents between 1.2 and 24 years of age who had received neridronate infusions for at least 1 year.

All the patients were reviewed to determine the type, treatment starting age, dosage, cumulative dose and duration of their bisphosphonate therapy; the patients were also investigated and examined clinically by a dental surgeon to assess their oral health status.

A confirmed case of ONJ was defined, according to the American Association of Oral and Maxillofacial Surgeons (AAOMS), as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after being identified by a health care provider in a patient who is currently receiving or has been exposed to a bisphosphonate and who has not had radiation therapy to the craniofacial region [19, 20]. To further distinguish ONJ from other health conditions, the patients must have taken or be currently taking bisphosphonate, while other potential confounding conditions (e.g., radiotherapy to the craniofacial region, corticosteroids, diabetes, malignant disease and cytostatic treatment) must be absent.

A history of any dental procedure, a known risk factor for osteonecrosis, was carefully reviewed. We looked for the presence of non-healing ulcers, exposed bone, infections and abnormal mobility of teeth in the maxilla or mandible and recorded any cases.

The study was approved by Ethical Committee of the Hospital and written informed consent was obtained from each patient and/or guardian.

Results

By the end of the survey, there were 55 female patients between 3.7 and 23.1 years of age (mean 11.8 ± 5.0 years) and 47 male patients between 3.1 and 23.4 years (mean 12.8 ± 5.2 years).

Seventy-five patients were suffering from OI type I, 20 patients from OI type III, 4 patients from OI type IV, and 3 patients suffered other rare forms of OI (Table 1).

At the time neridronate treatment began the age varied from 2 months to 19.6 years of age (mean 5.4 ± 3.9 years).

Fifteen patients started treatment in the first year of life (mean 4.8 months); nine patients with type III OI, five patients with type I OI, and one patient with type VII OI. These patients were treated with neridronate infusions once every 3–4 months at a dose of 1 mg/kg/day, for two consecutive days. All other patients received neridronate infusions once every 3–6 months at a dose of 2 mg/kg/dose in a single session. The mean cumulative dose was 1,679 mg (range 144–5,307) and the mean cumulative dose/kg was 50 mg (range 10–100).

Neridronate treatment lasted from 1.0 to 12.9 years (mean 6.8 ± 3.0 years); the treatment period ranged from 2.0 to 11.5 years (mean 6.9 ± 2.7 years) in type III OI patients, from 1.2 to 12.9 years (mean 6.7 ± 3.0 years) in type I OI patients, and from 1.0 to 12.5 years (mean 7.0 ± 4.2 years) in patients suffering from the other forms of OI.

Only six patients had suspension of the therapy longer than 3–4 months during the treatment period (one patient

Table 1 Neridronate intravenous treatment in our patients

Type of OI	Patients (*n*)	Mean age at the start of treatment (years)	Mean length of treatment (years)
I	75	5.6 ± 3.6	6.7 ± 3.0
III	20	4.3 ± 4.3	6.9 ± 2.7
IV	4	9.6 ± 3.8	6.6 ± 5.5
Other types	3	2.0 ± 1.1	7.7 ± 2.7

for 3 years, one patient for 2 years, one patient for 1.24 years, one patient for 1 year, one patient for 9 months, and one patient for 6 months). Eight patients stopped neridronate infusions before the analysis (one patient from 4 years, three patients from 3 years, three patients from 2 years, and one patient from 1 year).

Only two patients affected by type I OI had a history of an invasive dental procedure (abscess of tooth with pulpectomy) during bisphosphonate treatment. The most common dental finding was clinically apparent dentinogenesis imperfecta that was detected in 28 patients.

ONJ was not seen in any of the patients who were assessed. We have not reported evidence that ONJ is a side-effect of intravenous neridronate use in children and adolescents with OI.

Discussion

The use of bisphosphonates has become the widely accepted treatment for children and adolescents affected by OI.

In recent years, several reports have been published on unusual cases of ONJ in adults using second- and third-generation nitrogen-containing bisphosphonates such as pamidronate, alendronate, risedronate and zoledronate [10, 14, 17–24], but in the literature there are no reports of ONJ in patients taking neridronate.

In this survey, we have not demonstrated any evidence of ONJ as a side-effect of intravenous neridronate use in children and adolescents treated for OI for a mean of 6.81 years and with a mean cumulative dose of 50 mg/kg.

We have not seen ONJ in patients treated with neridronate who are still growing and who are often teething, a potential risk factor for osteonecrosis due to the rapid remodeling of jaw bone.

The most commonly reported initiating factor of ONJ is tooth extraction, although periodontal disease and denture trauma have been implicated [10, 11].

In the survey conducted by the Myeloma Foundation, the mean time of osteonecrosis onset was 6 years in patients receiving pamidronate and 18 months in patients receiving zoledronic acid. Other reports suggest shorter mean onset times, but few studies report onset when the patient has been on treatment for <1 year. Long-term studies of intravenous bisphosphonates have generally covered approximately 2 years, which may have been too short a time to identify this event [26].

In our study, we did not find cases of ONJ even in patients who had been treated for nearly 13 years. ONJ is probably not frequently found in OI patients because, in spite of lengthy duration of therapy, low neridronate doses are used. It is possible, however, that high cumulative doses are needed to observe ONJ; cancer patients are treated for bone metastasis with higher doses even if for a shorter time.

The lack of comorbidities and the lower doses used in children and adolescents probably reduce the risk of osteonecrosis.

Most reported cases of ONJ are in adult cancer patients, who are at a significantly higher risk of ONJ for several reasons [10–13].

In adults, even though the incidence of ONJ is not known, there seems to be a difference in prevalence depending on the mode and frequency of administration, drug potency, cumulative dose and the duration of treatment.

The agents described in the literature as involved in ONJ belong exclusively to the class of potent nitrogen-containing bisphosphonates (zolendronic acid, alendronate, risedronate and pamidronate) and it is evident that the incidence of ONJ associated with parenteral bisphosphonates is higher than that with oral bisphosphonates [27].

Among the clinically-relevant bisphosphonates there are significant differences in mineral binding affinities that influence their differential distributions within bone, their biological potencies and their duration of action. Neridronate is a bisphosphonate that is structurally similar to alendronate and pamidronate, but its retention time within bone and the expression of its mineral binding affinity has been reported as being lower than the retention time of alendronate and pamidronate [28, 29].

Studies on adults taking neridronate will be important to establish if the lower relative bone mineral-binding affinity of neridronate might restrict osteoclastic function less severely than other bisphosphonates, contributing to reduce the risk of ONJ.

In children, only osteonecrosis of long bones has been reported in patients treated for ALL [15, 16]. Corticosteroids are integral to the management of childhood ALL and are probably what contributes to the dramatic increase in the occurrence of osteonecrosis in children.

No case of ONJ has ever been reported in children; therefore, the true incidence of this complication remains unknown.

We advise the use of less potent bisphosphonates such as neridronate in pediatric patients affected by OI.

It is recommended that prior to the initiation of bisphosphonate therapy, an evaluation of the dental status should be performed to identify existing infections, compromised teeth and ill-fitting dentures. If bisphosphonate therapy can be delayed, preventive surgery to eliminate potential sites of infection should be performed.

The patients should be referred to a dentist for routine examination, education and instruction.

Optimal dental health during treatment is essential and all patients should be informed of the importance of good oral hygiene [27, 30].

The requirement for dental treatment is higher in children suffering from OI due to the frequent association with dentinogenesis imperfecta.

In conclusion, at the moment there are insufficient data available to prove a link between the use of neridronate and ONJ in children. Young patients affected by OI do not seem to be at a greater risk of ONJ than children and adolescents affected by other forms of bone fragility. However, clinicians have to report every occurrence of ONJ in children and adolescents treated with bisphosphonates because cases may emerge in future. Prospective studies are also needed to determine the safety of neridronate in adults.

Conflict of interest All authors have no conflicts of interest.

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