Zoledronic Acid in Non-Ambulatory Children and Young Adults with Fragility Fractures and Low Bone Mass Associated with Spastic Quadriplegic Cerebral Palsy and Other Neuromuscular Disorders

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Abstract: Non-ambulatory patients with neurological disorders such as spastic quadriplegic cerebral palsy often have low bone mineral density (BMD) and fragility fractures from disuse osteoporosis. Limited data exists on zoledronic acid (a third generation bisphosphonate) treatment in the pediatric population. We report a case series of 10 patients with spastic quadriplegic cerebral palsy (n=6), spinal muscular atrophy (n=2), and myelomeningocele (n=2) treated with zoledronic acid for fragility fractures and/or low BMD associated with the underlying conditions. The clinical and BMD outcomes were retrospectively studied and compared with a historical cohort of 32 patients treated with intravenous pamidronate. Mean lumbar BMD increased significantly (P< 0.01) by 28% at1 yearin zoledronic acid group, and by 19% in pamidronate group. Mean lumbar BMD weight-adjusted Z-scores improved from -4.31 at baseline to -2.55(P=0.003) at 1 year in zoledronic group, and from -3.66 to -2.30 in pamidronate group (P=0.001). Total number of fractures in the zoledronic group was 18 before treatment and reduced to zero after treatment with an average follow-up of 3.9 years. All patients tolerated zoledronic acid infusion with fever in 3 patients (30%) during the initial infusion and nohypocal cemianoted during the treatment cycles. Treatment with zoledronic acid is safe, significantly improves bone density and reduces fractures in children and young adults with fragility fractures and low bone mass secondary to neuromuscular disorders. Further follow up studies are needed to confirm safety and efficacy in long-term fracture prevention.

Keywords: Bisphosphonates, pamidronate, pediatric osteoporosis, osteopenia, bone density.

INTRODUCTION

Children with neuromuscular disorders that lead to quadriplegia or paraplegia are at risk for low bone density and fractures from minimal impact injuries. Multiple factors may contribute to bone fragility in this population, including immobilization, limited weight-bearing ambulation, lack of muscular forces on bone, decreased exposure to sunlight, nutritional deficiencies with low calcium and vitamin D intake and anticonvulsant therapy [1]. The prevalence of low bone mass was found in almost all (97%) children > 9 years with moderate and severe cerebral palsy [2], while fractures prevalence was 26% inchildren > 10 years [2], and increased with increasing age [3]. Several studies have shown benefits of intravenous pamidronate in improving bone mineral density (BMD) and reducing fractures in children with non-ambulatory neuromuscular disorders who suffered from osteopenia or fragility fractures [4-7]. Intravenous zoledronic acid, a third generation bisphosphonate, has been used widely in adult osteoporosis because of its superior anti-resorptive potency and efficacy in fracture reduction [8]. Zolendronic acid use in pediatric patients may also be more advantageous than pamidronate because of its shorter infusion time (20 minutes vs. 4 hours) and less total doses/treatment (1 dose vs. 3 consecutive day dosing). To date, a small number of studies have been published reporting benefits of zoledronic acid in children with primary osteoporosis, or osteogenesis imperfecta (OI) [9-12], and secondary osteoporosis from chronic corticosteroid treatment for chronic inflammatory conditions, or from immobility secondary to cerebral palsy [13, 14]. Data on the efficacy of zoledronic acid treatment in children and young adults with immobilization secondary to cerebral palsy or neuromuscular disorders are limited. In this study, we examine the treatment response to zoledronic acid in a cohort of 10 non-ambulatory pediatric patients suffering from fragility fractures and/ or low bone mass secondary to various neuromuscular disorders. The BMD and biochemical studies before and 1 year after the treatment with zoledronic acid are compared to those of a historical cohort of patients with fragility fractures and similar underlying conditions treated with intravenous pamidronate to evaluate whether the treatment outcomes are comparable between these 2 groups.

METHODS

Patients and Treatment Protocol

A retrospective study was carried out to analyse the clinical data of 42 non-ambulatory consecutive children

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and young adults (< 25 years of age) with fragility fractures associated with spastic quadriplegic cerebral palsy and other neuromuscular disorders treated with intravenous bisphosphonates and followed by the Pediatric Metabolic Bone Clinic at Nationwide Children's Hospital from 1999 to 2014. This study was approved by the Nationwide Children's Hospital Institutional Review Board.

The indications for bisphosphonate treatment were fragility fractures (at least one low impact fracture) and/or low BMD with decreasing BMD and BMD Z-scores at follow up BMD studies. Fracture history, bone density measurements, and biochemical studies including serum calcium, phosphorus, alkaline phosphatase, 25-hydroxy vitamin D (25-OHD), and PTH levels at baseline and 1 year after treatment were collected. Serum calcium levels obtained during the course of zoledronic acid treatment were reviewed to look for hypocalcemia. Before the commencement and throughout the course of therapy, all patients had normal liver and renal function studies. All patients were instructed to take calcium and vitamin D supplement at normal recommended dietary allowance. Patients with low 25-OHD levels < 30 ng/dL (<75 nmol/L) were given higher (1000-3000 IU/day) vitamin D intake to achieve 25-OHD levels> 30 ng/dL. In addition, patients were instructed to take 2 grams elemental calcium per day for 2 weeks before and after treatment.

Pamidronate was the only parenteral long acting bisphosphonate available prior to 2006 and all patients initiated between 1999 and 2006 received this agent. After 2006, 10 patients received zoledronic acid, although 3 patients received pamidronate during the period 2006-2008 due to family preference.

Intravenous pamidronate, 0.5 mg/kg/day was administered for 3 consecutive days during the first cycle and repeated at 1 mg/kg/day x 3 days at 3 month intervals during the first year. The maximal dose was 60 mg. Pamidronate was diluted in sterile 0.9% saline solution (with concentration less than 1 mg/10 ml normal saline) and intravenously infused over 4 hours. For young children aged 2-3 years, the standard pamidronate dose was reduced to 0.75 mg/kg/day (one patient in the pamidronate cohort was <3 years).

Intravenous zoledronic acid, at 0.025 mg/kg/dose, was given at the first dose, followed by 0.025-0.05 mg/kg/dose at 3-4 month intervals in the first year (total 0.1-0.15 mg/kg at 1 year). Patients > 18 years of age were treated at 6 month intervals. Zoledronic acid was diluted in normal saline (with concentration less than 0.04 mg/ml normal saline) and infused for 20 minutes.

All patients were given ibuprofen or acetaminophen at 10 mg/kg/dose 30 minutes prior to infusion and 6 hours later per our protocol which has been shown to reduce flu-like reaction [15]. All patients were hospitalized during the first infusion cycle for 3 days for pamidronate infusion and less than 24 hours (with one night stay) for zoledronic infusion. Subsequent infusions were given at the infusion clinic or given at home by a home health nurse.

Laboratory Studies

Serum 25-OHD was measured by a competitive protein-binding assay with an inter-assay coefficient of variation (CV) between 8.5-12.4%. The normal range is 10-55 ng/mL (or 25-137 nmol/L; conversion to SI unit is: 1 ng/mL x 2.496 = nmol/L). PTH was measured by two-site immunochemiluminometric method (ICMA), with inter-assay CV between 9.9-19%. The normal range is 10-65 pg/mL. All these were performed at Esoterix Laboratory, Calabasas Hills, CA. Routine chemistries were measured by a Hitachi multichannel analyzer.

Bone mineral density (BMD) of lumbar spine (L1-L4) and total bone mineral content (BMC) measurements were performed at baseline (before the commencement of treatment) and 1 year after, using Hologic dual-energy X-ray absorptiometry (Hologic Delphi, Waltham, MA). The Z-score of the lumbar spine BMD was determined using normative data based on the report by Southard *et al.* from our institution that studied 218 healthy children, age 1-19 years [16]. The lumbar bone mineral density is adjusted for weight and pubertal status, as the results of multiple regression analyses showed that Tanner stage and weight were the best predictive indicators of bone mass and bone mineral density [16].

In two patients with overlying gastrostomy tube over one vertebral body segment (L2 segment in one patient and L3 in the other), three lumbar vertebral body segments (excluding the obscured segment) were used in each BMD measurement to increase accuracy of the data [17].

Statistical Analysis

Descriptive data are presented as mean and standard deviation (SD). Change in BMD and BMC are

expressed as a percentage of baseline BMD or BMC. Example: percent increase in BMD at 1 year = (BMD at 1 year – baseline BMD)/baseline BMD. Categorical data were compared between the groups by using likelihood ratio Chi-Square test or Fisher's Exact test when appropriate. Continuous data were compared using either nonparametric Wilcoxon two-sample test or t test when appropriate. Paired t test was used to compare the response of BMD at 1 year with baseline. *P* value < 0.05 was considered significant. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Ten non-ambulatory children and young adults (mean age 12.5 ± 7 years, range 3.5-24.8 years, 50% male) received zoledronic acid from the period of 2006 to 2012. Six of these patients had spastic quadriplegic cerebral palsy, 2 had spinal muscular dystrophy, and 2 had myelomeningocele. Mean weight Z score at baseline was -4.25 (range -0.90 to -8.22) and mean height Z score at baseline was -5.10 (range 0.94 to -8.22). There were 18 fractures in 9 patients before treatment, 10 of which were femur, 1 humerus, 6 tibia and 1 fibula. Fractures occurred during transfer manoeuvre, clothes changing, physical therapy, low impact fall or unknown mechanism. One patient, a 10 year old male with spinal muscular atrophy and severe scoliosis of 43 degree and kyphosis of 90 degree, did not have fractures but was noted to have 'soft bone' by his orthopaedist during his first spinal surgery. His lumbar BMD decreased from 0.388 to 0.34 during a period of 1 year, with a reduction in his Z score from -2.4 to -3.24. The decision was made to treat him with zoledronic acid to improve his bone density before his second spinal surgery. All patients tolerated the treatment well with no significant adverse effects, except for fever which was noted in 3 patients (30%) within 48 hours of the initial zoledronic infusion. Fever ranged from 39 to 39.8 degree Celsius, and resolved with additional ibuprofen or acetaminophen. There was no hypocalcemia noted during any infusion cycle.

The BMD and biochemical studies at pretreatment baseline and 1 year after the treatment with zoledronic acid were compared to those of a historical cohort of patients with fragility fractures associated with similar neuromuscular disorders treated with pamidronate to evaluate the effects of treatment on these parameters. There were 32 non-ambulatory patients treated with intravenous pamidronate from1999 to 2008, 25 of whom had spastic quadriplegic cerebral palsy, 4 spinal muscular atrophy, and 3 myelomeningocele. There were a total of 53 fragility fractures in this pamidronate cohort, with similar mechanism as the zoledronic acid

Table 1: Clinical Characteristics, and Bone Measurements at Baseline and 1 Year after Treatment Inzoledronic Acid and Pamidronate Groups. There were no Statistically Significant Differences between 2 Groups

Clinical characteristics	Zoledronic acid	Pamidronate
Total N	10	32
Clinical Characteristics		
Age at baseline	12.6 ± 7.0	8.7 ± 3.7
Male [n (%)]	5 (50%)	17 (53%)
Spastic quadriplegic cerebral palsy [n (%)]	6 (60%)	25 (78%)
Spinal muscular atrophy [n (%)]	2 (20%)	4 (12%)
Myelomeningocele [n (%)]	2 (20%)	3 (10%)
Lumbar BMD at baseline	0.43 ± 0.17	0.43 ± 0.13
Lumbar BMD at 1 year	0.52 ± 0.17	0.51 ± 0.17
Lumbar BMD Z score at baseline	-4.31 ± 1.46	-3.67 ± 1.68
Lumbar BMD Z score at 1 year	-2.55 ± 1.99	-2.30 ± 1.85
Total BMC at baseline	814 ± 195	722 ± 272
Total BMC at 1 year	894 ± 284	869 ± 383
Percent increase in lumbar BMD at 1 year	28% ± 33%	19% ± 24%
Percent increase in BMC at 1 year	17% ± 17%	19% ± 11%

Results were expressed in means ± standard deviations unless otherwise noted.

Table 2: Biochemical Studies at Baseline and 1 Year after Treatment in each Treatment Group

Laboratory values	Zoledronic acid Group			Pamidronate Group		
Serum	**Baseline**	**1 year**	***P* value[a]**	**Baseline**	**1 year**	***P* value[a]**
Calcium (mg/dL)	9.7 ± 0.3	9.5 ± 0.5	0.68	9.6 ± 0.5	9.2± 0.4	0.004
Phosphorus (mg/dL)	4.6± 0.6	3.8 ± 1.0	0.004	4.9± 0.6	4.3 ± 0.6	0.006
Alkaline phosphatase (U/L)	197± 90	155± 77	0.12	214± 122	162 ± 60	0.01
25-OHD (ng/mL)	34.2± 15.0	32.1± 12.2	0.34	30.3± 14.7	33.0±17.5	0.73
PTH (pg/mL)	17.6± 11.1[b]	26.2± 27.6	0.14	29.8± 12.5[b]	28.7±13.1	0.79

[a]*P* value reflects comparison of laboratory values at baseline vs. 1 year within each group. For each dependent variable, the baseline and 1 year values were compared between the zoledronic acid and pamidronate groups. [b]The only value that was different between 2 groups was baseline PTH (*P*=0.01).

cohort. The clinical characteristics and BMD parameters were similar in both cohorts (Table **1**). Biochemical studies at baseline were also similar between 2 groups, except for baseline PTH levels being lower in zoledronic group (Table **1**). Comparing within group, there were no significant differences between vitamin D and PTH levels from baseline to 1 year after treatment in both groups (Table **2**). However, there were significant reductions seen from baseline to 1 year post treatment in serum calcium, phosphorus and alkaline phosphatase levels (*P*<0.01) in the pamidronate group, but only in serum phosphorus (*P*=0.01) in the zoledronic acid group (Table **2**). Serum alkaline phosphatase levels decreased at 1 year but did not reach significance in the zoledronic acid group.

Mean lumbar BMD and BMD Z scores at baseline were similarly low in both pamidronate and zoledronic groups (Table **1**). Mean lumbar BMD increased significantly at 1 year in the zoledronic group (*P*=0.0006) and the pamidronate group (*P*=0.002) (Figure **1**). In the zoledronic acid group, mean lumbar BMD Z-score increased significantly from -4.31± 1.46 at baseline to -2.55 ±1.99 at 1 year (*P*=0.001), while in the pamidronate group, mean lumbar BMD Z score also increased significantly from -3.66 ± 1.68 at baseline to -2.30 ± 1.85 at 1 year (*P*=0.001) (Figure **2**). The percent increase in lumbar BMD (28% vs. 19%) and total BMC (17% vs. 19%) were similar between zoledronic and pamidronate groups.

No fractures were reported in the zoledronic group during the course of follow up (mean follow up of 3.9 years, range 2-8.8 years). No fractures were reported during the first 2 years after treatment initiation in the pamidronate group. However, 9 patients (28%) in the pamidronate group had fractures during long term follow up, 3 to 8 years after the treatment initiation.

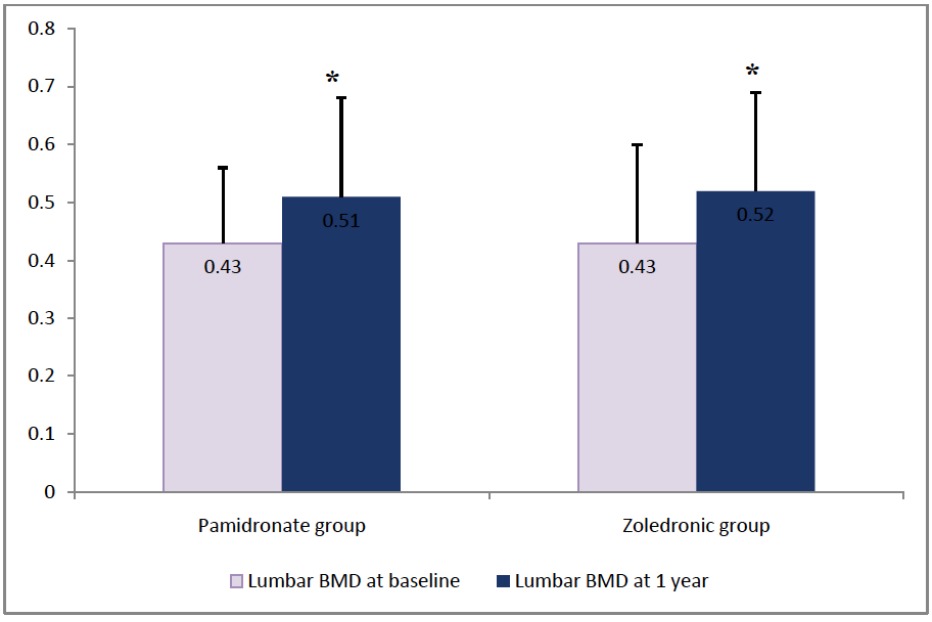

Figure 1: Lumbar BMD at baseline and 1 year in pamidronate (n = 32) and zoledronic acid group (n = 10). *represents *P*< 0.01 within group.

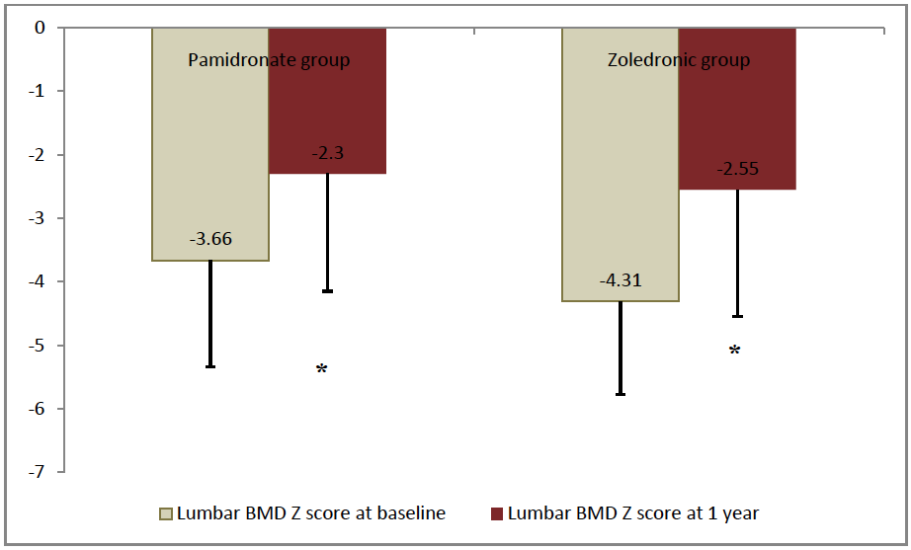

Figure 2: Lumbar BMD Z-score at baseline and 1 year in Pamidronate and Zoledronic group. *represents *P*<0.01 within group.

DISCUSSION

We report our experience with zoledronic acid in pediatric and young adults patients with secondary osteoporosis associated with immobilization from various neuromuscular disorders, and compare the treatment outcomes with those of patients treated with pamidronate infusion. We found that zoledronic acid was safe, and effective in improving BMD and reducing fractures in this patient population. These results are important for clinicians as zoledronic acid has been increasingly used in place of pamidronate in recent years, owing to its rapid and convenient administration, but more data is still needed to establish the safety and efficacy of zoledronic acid. To date, there have only been 2 comparative pediatric studies between pamidronate and zoledronic acid specifically in patients with OI [11, 12], but no comparative studies reported in pediatric patients with secondary osteoporosis from neuromuscular disorders.

Very low bone mass was observed in both zoledronic acid and pamidronate groups at baseline. The BMD reference used in our study was adjusted for weight and pubertal status [16], which appears to be most suitable because of significantly diminished growth and low body size generally seen in this patient population. Using age-adjusted Z-score would likely underestimate Z-scores values and over-diagnose low bone mineral density for age in this group of patients. The diagnosis of osteoporosis in pediatric patients is unequivocal when patients have fragility fractures that occur after low impact injury, as observed in the 2 cohorts in this study. Bisphosphonate therapy is undoubtedly warranted in such patients with clinical bone fragility. Although one patient in the zoledronic acid cohort did not have fractures before treatment, the decision to start treatment was justified by the observation of 'soft bone' by his orthopedic surgeon during his first spinal surgery and also due to a steep decline in his BMD measurements noted at follow up. Previous studies using intravenous pamidronate or oral alendronate have shown benefits of improving BMD in non-ambulatory children with cerebral palsy who had significant osteopenia but without fractures [6, 18]. Noting that the lifetime risk of fractures in this population is high, the approach of providing treatment in patients with worsening BMD parameters without fractures seems to be reasonable. The timing of therapy commencement, whether when bone loss is detected or only after a fracture occurs, continues to be a subject of debate. A randomized controlled study with a long term follow up is needed to prove the benefits of treatment for primary prevention of bone fragility in this population.

The lumbar BMD and BMD Z-score gain was significantly large in both zoledronic acid and pamidronate groups and was comparable between groups (28% vs. 19% percent increase and net Z score gain of 1.76 vs. 1.36, respectively). This gain is similar to that of a similar patient population by Allington *et al.* [5], with an increase of 27% after 1 year of pamidronate, and another study by Plotkin *et al.* [6], with an increase of 1.5 point in Z-score after 1 year of pamidronate. This gain exceeds that described in untreated patients, a 3.8% change, as observed in a control group of non-ambulatory patients with cerebral

palsy aged 1-16 years in a study by Iwasaki *et al*. [19]. In a natural history study in children and adolescents with cerebral palsy by Henderson *et al.* where an average of 2%-4% annualized BMD increase was observed, the increase was less than that seen in healthy children, causing a decrease in BMD Z-score with age [20]. These observations provide more evidence that the substantial gain in BMD observed in our study was by the pharmacologic intervention.

Similar to other studies of pamidronate treatment in this same population [2, 5, 7], the absence of fractures observed during the course of follow up in zoledronic acid group in our study is certainly the most fundamental functional outcome measure and also the most important indicator of success of therapy. More long term studies are needed to see if this positive outcome persists and whether the bisphosphonate therapy should be continued up to 3-4 years or until completion of growth as in the case for children and adolescents with OI.

We observed a decrease in serum alkaline phosphatase (a measure of bone osteoblast activity) in the pamidronate group, which is similar to previous reports of pamidronate treatment in children with OI [21, 22]. We did not observe a significant reduction in serum alkaline phosphatase with zoledronic acid. In contrast, a recent comparative study reported by Barros *et al.* in children with OI showed a significantly greater reduction in serum alkaline phosphatase with zoledronic acid treatment than that seen in a pamidronate treated group [11]. This study utilized much higher zoledronic acid doses (0.25-0.4 mg/kg/year) than our study (0.1-0.15 mg/kg/year). The reduction in alkaline phosphatase represents some degree of bone formation suppression, but, in our population, did not compromise bone density parameters or clinical response. Whether changes in biochemical markers are related to bisphosphonate doses warrants further studies in children.

It is important to note that, while the pamidronate dose at 9 mg/kg/year used in this study was one of the most common dosing regimens described in the literature, there has not been a consistent or unified dosage of zoledronic acid in children reported in the literature. The dose has varied greatly in reported studies: 0.15 mg/kg/year by Munns *et al.* [23], 0.2 mg/kg/year by Hölger *et al.* [24], 0.25-0.4 mg/kg/year by Barros *et al.* [11]. The frequency of infusion in most studies was every 3-4 months [11, 23, 24], but more recent studies reported very good outcome with every 6 month interval doses [10, 14]. There is still the need to define the minimal appropriate effective dosage of zoledronic acid for safety, convenience and cost-effectiveness.

The limitations of this study are that it was not a randomized controlled study and the number of patients receiving zoledronic acid was small. Despite these limitations, our data provides good evidence that zoledronic acid is safe and effective in improving BMD and reducing fractures in children and young adults with fragility fractures and low bone mass secondary to non-ambulatory neuromuscular disorders. Long term follow up study is needed to determine the length of bisphosphonate treatment to maintain these positive effects and to evaluate and confirm safety and efficacy in fracture reduction and prevention.

LIST OF ABBREVIATIONS

BMD	=	Bone mineral density
BMC	=	Bone mineral content
OI	=	Osteogenesis imperfecta
25-OHD	=	25 Hydroxyvitamin D
1,25-OHD	=	1,25 Dihydroxyvitamin D
PTH	=	Parathyroid hormone
CV	=	Coefficient of Variation

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