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Full Length Article

Outcomes following intravenous bisphosphonate infusion in pediatric patients: A 7-year retrospective chart review

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ABSTRACT

Introduction: Intravenous bisphosphonates (IV BP) have been used to treat children with osteoporosis for many years. Favorable side effect profile and improvements in bone mineral density (BMD) have been demonstrated in patients with osteogenesis imperfecta (OI), a primary form of osteoporosis in pediatrics. Less is known about the safety of IV BP in children with secondary osteoporosis or glucocorticoid-induced osteoporosis (GIO). We aimed to determine the prevalence of both acute and long-term side effects and assess the efficacy of IV BP treatment to increase bone mineral density in pediatric patients with varying presentations of compromised bone health.

Methods: We conducted a retrospective chart review of pediatric patients (< 21 years old) treated for osteoporosis with intravenous pamidronate (PAM) or zoledronic acid (ZA) at Cincinnati Children's Hospital Medical Center from 2010 to 2017. Patient demographics, diagnosis, infusion type and dose, acute phase reactions (APR), electrolyte abnormalities, and bone density measurements were collected from the electronic medical records. Diagnoses were grouped into 3 categories: primary osteoporosis, secondary osteoporosis, and GIO. Descriptive characteristics and adverse events were compared among categories. Change in bone mineral density (BMD) over time was compared among groups.

Results: 123 patients (56% male) received 942 infusions (83% PAM and 17% ZA). APR was reported in 7% of all infusions and more common in secondary osteoporosis (16%, $p < 0.0001$). There was a higher percentage of acute adverse events after the first infusion (27% vs 5%, $p < 0.0001$). Hypocalcemia following IV BP infusions occurred in 7% (27/379) of infusions and was significantly associated with ZA use ($p = 0.04$). Severity of hypocalcemia was generally mild, requiring intravenous calcium in 3% (13/379) of infusions. Hypophosphatemia occurred frequently, however rarely required intravenous supplementation. In 468 patient years of IV BP exposure, there were no reports of osteonecrosis of the jaw (ONJ) nor atypical femoral fracture (AFF). Lumbar spine (LS) aBMD *Z*-score 1 year after IV BP initiation increased overall for all groups ($p < 0.0001$) but did not significantly differ for those who did or did not fracture following IV BP treatment.

Conclusions: APR due to intravenous BP treatment for pediatric osteoporosis were infrequent and generally mild. APR were more likely to occur in patients with secondary osteoporosis, a group who may require closer monitoring. A higher proportion of hypophosphatemia occurred in the patients with GIO. Long-term serious adverse events including ONJ and AFF were not identified in our patient population. LS aBMD *Z*-score increased following initiation of IV BP. However, the change in BMD was not associated with risk of fracture during the follow-up interval. These data provide reassurance and suggest that IV BP can be safely used in pediatric patients with osteoporosis.

1. Background

Low bone mineral density and fractures are increasingly recognized as complications of chronic pediatric medical conditions. Impaired mobility, chronic inflammation, inadequate nutrition, hormone disruption, and medication use (e.g., glucocorticoids, anti-epileptics and immunosuppressive agents) are all factors that affect bone size and microarchitecture and impair bone mineralization in children with

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chronic disease, potentially leading to the diagnosis of osteoporosis [1]. Treatment is first focused on addressing these risk factors. However, in some children, the extent to which these risk factors can be mitigated are limited.

Bisphosphonates have long been used on the basis of compassionate care treatment for osteogenesis imperfecta, the hallmark condition of primary osteoporosis in childhood, with a favorable safety profile and proven efficacy to increase bone mineral density (BMD) and decrease fracture frequency [2,3]. However, data on the safety and efficacy of intravenous bisphosphonate (IV BP) therapy for treatment of secondary osteoporosis, or osteoporosis due to another medical condition, is limited [4–6]. A common indication for bisphosphonate treatment in pediatric patients with secondary osteoporosis is fragility fracture with limited potential of spontaneous recovery [4]. Nevertheless, there is no current consensus on agent of choice, dose, duration and monitoring of IV BP therapy. Different protocols for IV BP infusions have been used for treatment of secondary osteoporosis based on diagnosis and age at diagnosis [7–11].

The main objective of this study was to determine the prevalence of both acute and long-term side effects following IV BP therapy for the compassionate care treatment of pediatric osteoporosis and concern for poor bone health in patients with chronic disease who may not strictly meet the International Society for Clinical Densitometry (ISCD) criteria for osteoporosis [12]. We then aimed to compare the frequency of these side effects among groups of patients with different etiologies of osteoporosis and poor bone health. Finally, we aimed to evaluate efficacy of IV BP therapy with regard to change in BMD and fracture frequency.

2. Methods

2.1. Study design

We conducted a retrospective chart review of patients < 21 years of age at initiation of IV BP therapy for treatment of osteoporosis at a large tertiary medical center (Cincinnati Children's Hospital Medical Center). We utilized the electronic medical records (EMR) to identify all instances of intravenous pamidronate (PAM) or zoledronic acid (ZA) infusion at our hospital between January 2010 and July 2017. A total of 1141 infusions from 169 unique patients were reviewed. Our aim was to study the safety and efficacy of bisphosphonate use in pediatric osteoporosis, therefore, we excluded patients who received these medications for other indications. Forty-six patients were excluded (hypercalcemia = 15, chemotherapy = 12, chronic osteomyelitis = 11, avascular necrosis = 6, tumoral calcinosis = 1, Gorham-Stout disease = 1). A total of 942 infusion encounters from 123 unique patients were included in this analysis.

2.2. Demographic data

Sex, race, age at each infusion, height, and weight were extracted from the EMR. Duration of follow-up was calculated from the date of the first IV BP infusion at our institution to the date of the last physical patient encounter or the recorded date of death.

2.3. Medical history

Charts were reviewed independently by NN and HW with any discrepancies being resolved by input from a third author (CMG) prior to analysis.

2.3.1. Diagnosis

The intent of this analysis was to review adverse events and outcomes following IV BP for treatment of patients whose history included threats to bone health (chronic glucocorticoids) or their history raised a significant concern for osteoporosis (low BMD with one fragility fracture, underlying disease associated with low BMD and bone pain). Therefore, we included patients in this study who did not strictly meet the ISCD criteria for pediatric osteoporosis [12]. The underlying etiology of low BMD or osteoporosis was extracted from the medical record. Patients were categorized as having primary osteoporosis, secondary osteoporosis, or glucocorticoid-induced osteoporosis (GIO). GIO was a distinct category from secondary osteoporosis for three reasons: 1. Glucocorticoids are detrimental to bone health by affecting both bone formation and resorption, a unique pathophysiology from other forms of secondary osteoporosis which primarily affect bone formation (disuse osteoporosis) or bone resorption (chronic inflammation) 2. Glucocorticoids affect linear growth and this needs to be considered in the DXA interpretation and 3. Fracture can occur sooner and at relatively higher aBMD value in children treated with glucocorticoids [13].

2.3.2. Bisphosphonate exposure

Type (PAM or ZA), dose, and frequency of infusion were based upon individual provider's discretion based on the age of the patient and underlying etiology of osteoporosis. PAM was used more frequently until 2016 when ZA became the preferred medication. Generally, infusion protocols for PAM followed a dosing schedule published for OI (9 mg/kg/year divided every 2–4 months) [14] whereas secondary osteoporosis and GIO received infusions every 3 months (yearly dose of approximately 4 mg/kg/year). ZA was primarily administered every 6 months (0.1 mg/kg/year) [15] regardless of underlying etiology. Duration of therapy was determined based on dates of first and last infusion recorded at our institution.

2.3.3. Fractures

Fracture history was obtained by review of EMR clinic visits and radiographic images for each patient. Documentation of fracture by a radiologist or evidence of healing fracture on subsequent radiographic imaging was used to determine number of fractures. As not all fractures were imaged radiographically at our institution, we also conducted a query of the EMR to identify the term “fracture” in the free text. Encounters including this term were further reviewed to determine if a fracture event had occurred. Shared external EMR data was also reviewed to verify fracture history when possible.

2.4. Adverse events

2.4.1. Acute phase reactions (APR)

Nitrogen-containing bisphosphonates such as PAM and ZA induce APR by stimulating a transient increase in pro-inflammatory, pro-resorptive cytokines [16]. APR may include low-grade fever, headache, myalgia, bone pain, nausea, vomiting, and rash, and decreased circulating lymphocyte counts [17]. APR is more common in bisphosphonate naïve patients, typically occurs within 48 h of IV BP infusion [16,18,19]. Half-doses for the first bisphosphonate infusion are sometimes used to mitigate this response. Our institution frequently hospitalized patients for the first infusion to observe for APR. Patients were considered to have an APR if a fever > 38 °C occurred within 48 h after infusion, respiratory distress resulted in need for supplemental oxygen or increased respiratory support within 48 h after infusion, or documentation in the EMR from patient or caregiver to the medical team of concerns for fever, headaches, abdominal pain or muscle aches within 1 week following the infusion. We included all reports of APR within one week of IV BP infusions for the analysis.

2.4.2. Electrolyte imbalances

Hypocalcemia and hypophosphatemia are common electrolyte abnormalities observed following IV BP infusions. Prescribers used varying approaches to monitor serum electrolytes (e.g., 24 h, 48 h, 72 h and/or 7 days post infusion). We reviewed laboratory data within one week of infusion (pre and post) including calcium, phosphorus, magnesium, creatinine, and albumin for the analysis. Episodes of hypocalcemia (serum calcium corrected for albumin < 8.0 mg/dL) and

hypophosphatemia (serum phosphorus below reference range for age) [20] occurring within one week after the infusion were recorded. The serum 25-hydroxyvitamin D (25OHD) level was linked to the IV BP infusion if it was obtained within 3 months prior or one week after the infusion. Vitamin D deficiency was defined as serum level of 25OHD < 20 ng/mL.

2.4.3. Long term adverse events

A query of the EMR for the terms, "osteonecrosis of the jaw" (ONJ) and "atypical femoral fracture" (AFF) was performed for each subject using natural language processing. Documentation for each occurrence of these terms was reviewed to determine whether it was used in the context of discussion of medication risk or a reported event.

2.5. Bone density

All DXA scans were acquired for clinical purposes on a Hologic densitometer (Delphi/Discovery/Horizon) calibrated to a common manufacturer standard, and scans were analyzed using software with the same bone detection algorithms (version 12.3). Lumbar spine (LS) scans were acquired using standard positioning and analysis procedures. The coefficient of variation (CV) at our center is < 1% for LS aBMD. LS aBMD *Z*-scores were calculated using reference data from Kalkwarf et al. [21] for ages 1 to 36 months, Kelly et al. [22] for ages 37 to 60 months, and Zemel et al. [23] for ages 5 to 20 years. Areal bone mineral density (aBMD) is influenced by height, however accurate measurements of height can be difficult to obtain in many children with bone disorders due to contractures. We therefore decided to include non-height adjusted LS aBMD *Z*-scores in the analysis of BMD change following IV BP treatment. Lateral distal femur (LDF) scans were obtained and three regions of interest (R1, R2 and R3) as described by Henderson et al. [24] and Zemel et al. [25]. We included R1, comprised of primarily trabecular bone, and R3, comprised of primarily cortical bone, in our analyses. R2 is difficult to interpret given it is an admixture of both bony tissue types. The CV for the LDF aBMD has not been reported and there are no height adjustment recommendations for this scan site. All scans were reviewed by HW for image quality, positioning and artifact (spinal instrumentation, ports and movement). LDF aBMD *Z*-scores were calculated for children ages ≥3 years using reference data from Henderson et al. [24]. Changes in aBMD *Z*-score were calculated for patients who had DXA scans both at baseline and 1-year post IV BP treatment. We studied the outcomes of age-, sex-, and race-specific aBMD *Z*-scores for each skeletal region of interest.

The study was approved by Cincinnati Children's Hospital Medical Center (CCHMC) Institutional Review Board.

2.6. Statistical analysis

Data were analyzed using SAS®, version 9.4 (SAS Institute, Cary, NC). Due to the distribution of variables, continuous data were summarized as medians with 25th and 75th percentiles (IQR: interquartile range), and categorical data were summarized as frequency counts and percentages. Chi-square and Fisher's exact tests were used, as appropriate, for group comparisons of categorical variables. Nonparametric Kruskal-Wallis tests were used to compare continuous variables between groups. $P < 0.05$ was considered statistically significant. A subanalysis was done on only those children who fulfilled strict ISCD criteria for osteoporosis ($n = 100$).

3. Results

3.1. Patients characteristics

One hundred twenty-three patients (56% male) were followed for an average of 3.8 years following first IV BP infusion at CCHMC. One hundred patients (81%) met the ISCD criteria for the diagnosis of pediatric osteoporosis. Eight patients (7%) had low BMD with a history of one long bone fracture prior to IV BP infusion. The remaining 15 patients (12%) were started on bisphosphonate therapy without a history of fragility fracture prior to first IV BP. The decision to initiate treatment in these cases were made on an individual basis between the patient/family and the provider. One patient had OI type I confirmed by genetic testing. Six had underlying genetic diseases associated with increased risk for fracture or overall poor clinical outcome [26,27]. Four had GIO and adult guidelines suggest patients on > 5 mg/day of prednisone equivalents for longer than three months should be starting on BP prophylaxis. One additional patient was started on treatment for acute bone loss after spinal cord injury [9]. Other patients were treated for low bone density and pain or low bone density in association with nephrocalcinosis.

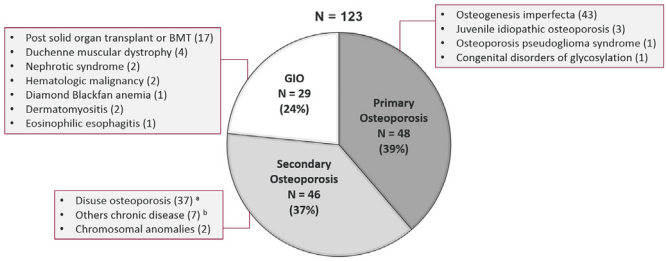

Fig. 1. Diagnosis.
[a]Disuse osteoporosis: Cerebral palsy = 15, spinal muscular atrophy = 6, spina bifida = 2, myelomeningocele 1, transverse myelitis = 2, spinal cord injury = 1, congenital myasthenia gravis = 1, mitochondrial diseases = 3, metabolic diseases = 2, dyskeratosis congenita = 1, kabuki syndrome = 1, Rubinstein Taybi syndrome = 1, chromosomal anomalies = 1.
[b]Other chronic disease: Epidermolysis bullosa = 3, Crohn's disease = 1, Alagille's syndrome = 1, Diamond Blackfan anemia with iron overload = 1, PKU with chronic hypercalciuria = 1.

Forty-eight patients had primary osteoporosis, 46 had secondary osteoporosis, and 29 had GIO (Fig. 1). Majority of patients with primary osteoporosis had osteogenesis imperfecta (44/48, 92%). Disuse osteoporosis was the most common diagnosis in secondary osteoporosis group (37/46, 80%). One patients with Crohn's disease and three with epidermolysis bullosa developed osteoporosis prior to glucocorticoid treatment. Therefore, they were categorized in the secondary osteoporosis group. In GIO group, most patients (17/29, 59%) received glucocorticoids following solid organ or bone marrow transplantation. Seven patients (3 with Spinal Muscular Atrophy (SMA) in secondary osteoporosis group and 4 with Duchenne muscular dystrophy in GIO) received alendronate treatment prior to IV BP.

3.2. Bisphosphonate utilization

Of 942 unique infusions, 779 (83%) were PAM and 163 (17%) were ZA. As expected, patients with primary osteoporosis had their first infusion at CCHMC at a younger age (median 7.2 years) and received more IV BP infusions (median 8.0 infusions per patient) (Table 1). PAM was frequently used as the bisphosphonate of choice for the first infusion (74%), especially in primary osteoporosis group. Twenty-three percent of patients switched from PAM to ZA at subsequent infusions and since 2016, ZA has become the preferred IV BP for first infusion in most patients (14/17, 82%). Among the multidisciplinary care teams who prescribed intravenous bisphosphonate, the Endocrinology and Genetics Services were the major prescribers (38% and 56% respectively). Other subspecialties included the Divisions of Gastroenterology (4%), Nephrology (1.6%), Rheumatology (0.1%), Immunology (0.1%), and Dermatology (0.1%).

Table 1
Bisphosphonate utilization.

		Primary osteoporosis N = 48	Secondary osteoporosis N = 46	GIO N = 29	P-value*
Baseline characteristics	Gender (male)	26 (54%)	24 (52%)	19 (66%)	0.50
	Follow-up time at CCHMC (years)	3.8 (1.6, 6.0) [0.1, 7.8]	5.1 (2.9, 6.6) [0.6, 7.7]	1.5 (0.6, 2.8) [0.1, 7.6]	**0.0001**
	Had at least one DXA scan	39 (81%)	44 (96%)	28 (97%)	**0.03**
Fracture data	Age at first fracture (years)	1.3 (0.1, 3.5)	7.8 (3.4, 10.5)	6.0 (3.1, 10.0)	< **0.0001**
	No long bone or vertebral fracture	0 (0%)	9 (20%)	3 (10%)	**0.002**
	No long bone or vertebral fracture prior to IV BP but fracture after	1 (2%)	1 (2%)	1 (3%)	1.00
	Long bone or vertebral fracture post 1st IV BP	37 (77%)	17 (37%)	5 (17%)	< **0.0001**
BP utilization	Age 1st Infusion at CCHMC (years)	7.2 (1.7, 12.2) [0.01, 18.4]	11.5 (8.5, 16.1) [2.0, 20.6]	12.7 (6.1, 15.2) [1.5, 18.3]	**0.002**
	Number of BP infusions per patient	8.0 (4.5, 17.5) [1.0, 48.0]	4.5 (2.0, 9.0) [1.0, 29.0]	2.0 (1.0, 5.0) [1.0, 9.0]	< **0.0001**
	BP type received				< **0.0001**
	PAM only	36 (75%)	13 (28%)	18 (62%)	
	ZA only	3 (6%)	15 (33%)	10 (34%)	
	Both	9 (19%)	18 (39%)	1 (3%)	
	BP type 1st infusion				**0.006**
	PAM	29/31 (94%)	24/36 (67%)	16/26 (62%)	
	ZA	2/31 (6%)	12/36 (33%)	10/26 (38%)	
	BP dose 1st infusion[a,b]				**0.02**
	Full	6/31 (19%)	18/36 (50%)	12/26 (46%)	
	Half	25/31 (81%)	18/36 (50%)	14/26 (54%)	

Data presented as n (%) or median (25th, 75th percentile) [min, max].
* *P*-value represents comparison between diagnosis groups.
[a] PAM full 1 mg/kg/dose, half 0.5 mg/kg/dose; ZA full 0.05 mg/kg/dose, half 0.025 mg/kg/dose.
[b] Only 93 patients who received 1st IV BP at our institution were included in the analysis of 1st infusion.

3.3. Adverse events

3.3.1. Acute phase reactions (APR)

A summary of acute adverse events is shown in Tables 2 and 3. APR occurred in 7% (68/942) of all infusions. Among 93 patients who initiated IV BP therapy at our institution, APR was reported in 27% following first infusion, a higher proportion when compared with subsequent infusions (43/849, 5.1%; $p < 0.0001$). BP type was not significantly associated with risk of developing APR within each of the osteoporosis groups for the first infusion but ZA was associated with higher proportion of overall acute adverse events in primary osteoporosis group (29% vs. 6%, $p = 0.0002$). Patients in secondary osteoporosis group were more likely to develop APR following any infusion (16%, $p < 0.0001$) (Table 2). Fever, which was the most common APR following the first infusion, was more common in secondary osteoporosis (12/36, 33% of patients). The second most common acute phase reaction was pain, which include bone pain and myalgia (20/942, 2% of all infusions). Tachycardia was noted in 7 infusions (0.7%), 3 of which occurred in one unique patient. Gastrointestinal symptoms (nausea, abdominal pain or diarrhea) were less common (8/942, 0.8% of all infusions). Respiratory symptoms included tachypnea, increased work of breathing or increased respiratory secretion were reported in 0.4% of all infusions (4/942); however, only one patient, who had concomitant acute bronchiolitis, required supplemental oxygen and suction. Other uncommonly reported symptoms such as dizziness or local swelling were mild and self-limited. Among 188 infusions that had

Table 2
Overall acute adverse events.

	Primary osteoporosis N = 48	Secondary osteoporosis N = 46	GIO N = 29	P-value*
Total infusions	n = 567	n = 285	n = 90	
Overall acute adverse events[a]	38/567 (7%)	137/285 (48%)	48/90 (53%)	< **0.0001**
PAM	30/539 (6%)	80/176 (45%)	31/64 (48%)	< **0.0001**
ZA	8/28 (29%)	57/109 (52%)	17/26 (65%)	**0.02**
Hypocalcemia total	1/80 (1%)	20/221 (9%)	6/78 (8%)	**0.04**
Hypophosphatemia total	21/64 (33%)	117/220 (53%)	47/76 (62%)	**0.002**
Acute phase reactions total	17/567 (3%)	45/285 (16%)	6/90 (7%)	< **0.0001**
PAM	14/539 (3%)	27/176 (15%)	3/64 (5%)	< **0.0001**
ZA	3/28 (11%)	18/109 (17%)	3/26 (12%)	0.76
Acute phase reactions 1st infusion[b,c]				
PAM				
Full	2 (33%)	3 (33%)	0	
Half	4 (67%)	6 (67%)	1 (100%)	
ZA				
Full	0	4 (67%)	2 (67%)	
Half	0	2 (33%)	1 (33%)	

* *P*-value represents comparison between diagnosis groups.
[a] Comparing proportion of overall acute adverse events between PAM and ZA in primary osteoporosis *p*-value = 0.0002, secondary osteoporosis *p*-value = 0.26, and GIO *p*-value = 0.14.
[b] PAM full 1 mg/kg/dose, half 0.5 mg/kg/dose; ZA full 0.05 mg/kg/dose, half 0.025 mg/kg/dose.
[c] Only 93 patients who received 1st IV BP at our institution were included in the analysis of 1st infusion.

Table 3
Details of acute adverse events following IV BP infusions.

		Primary osteoporosis (*N* = 48)		Secondary osteoporosis (*N* = 46)		GIO (*N* = 29)	
		PAM (*n* = 539)	ZA (*n* = 28)	PAM (*n* = 176)	ZA (*n* = 109)	PAM (*n* = 64)	ZA (*n* = 26)
Total APR/Infusion		14/539 (3%)	3/28 (11%)	27/176 (15%)	18/109 (17%)	3/64 (5%)	3/26 (12%)
First infusion	**Acute phase reaction**						
	- Fever	3/29 (10.3%)	0/2 (0%)	7/24 (29.2%)	5/12 (41.7%)	1/16 (6.3%)	2/10 (20%)
	- Bone pain/myalgia	3/29 (10.3%)	0/2 (0%)	3/24 (12.5%)	3/12 (25.0%)	0/16 (0%)	1/10 (10%)
	- Respiratory	0/29 (0%)	0/2 (0%)	1/24 (4.2%)	0/12 (0%)	0/16 (0%)	1/10 (10%)
	- Cardiovascular	0/29 (0%)	0/2 (0%)	1/24 (4.2%)	0/12 (0%)	1/16 (6.3%)	1/10 (10%)
	- GI	0/29 (0%)	0/2 (0%)	2/24 (8.3%)	2/12 (16.7%)	0/16 (0%)	1/10 (10%)
	- Others	0/29 (0%)	0/2 (0%)	1/24 (4.2%)	0/12 (0%)	0/16 (0%)	0/10 (0%)
	Electrolyte abnormality						
	- Hypocalcemia	0/20 (0%)	0/2 (0%)	2/22 (9%)	2/11 (18%)	1/16 (6%)	2/10 (20%)
	- Hypophosphatemia	4/17 (24%)	1/2 (50%)	15/21 (71%)	6/11 (55%)	11/16 (69%)	6/10 (60%)
Subsequent infusions	**Acute phase reaction**						
	- Fever	5/510 (1.0%)	2/26 (7.7%)	8/152 (5.3%)	8/97 (8.2%)	1/48 (2.1%)	0/16 (0%)
	- Bone pain/myalgia	2/510 (0.4%)	1/26 (3.8%)	3/152 (2.0%)	3/97 (3.1%)	1/48 (2.1%)	0/16 (0%)
	- Respiratory	1/510 (0.2%)	0/26 (0%)	1/152 (0.7%)	0/97 (0%)	0/48 (0%)	0/16 (0%)
	- Cardiovascular	0/510 (0%)	0/26 (0%)	4/152 (2.6%)	0/97 (0%)	0/48 (0%)	0/16 (0%)
	- GI	0/510 (0%)	1/26 (3.8%)	1/152 (0.7%)	1/97 (1.0%)	0/48 (0%)	0/16 (0%)
	- Others	1/510 (0.2%)	0/26 (0%)	5/152 (3.3%)	0/97 (0%)	0/48 (0%)	0/16 (0%)
	Electrolyte abnormality						
	- Hypocalcemia	0/40 (0%)	1/18 (6%)	6/93 (6%)	10/95 (11%)	2/36 (6%)	1/16 (6%)
	- Hypophosphatemia	12/28 (43%)	4/17 (24%)	50/93 (54%)	46/95 (48%)	19/34 (56%)	11/16 (69%)

25OHD linked, vitamin D deficiency was not associated with APR ($p = 0.37$).

3.3.2. Hypocalcemia

Serum calcium was assessed following 379 infusions (40%) and 25OHD level was available for 164 of those. Routine post-infusion monitoring of calcium levels is not recommend for subsequent infusions in primary osteoporosis (mainly OI) patients and these accounted for 85% of our overall missing calcium lab data. Hypocalcemia occurred in 7% of infusions (27/379). The proportion of hypocalcemia among the three groups significantly differed for the data that were available ($p = 0.04$) (Table 2). Hypocalcemia was generally mild and managed with enteral calcium supplementation. Intravenous calcium infusions were required in 13 infusions (13/379, 3%) and 7 of these were following PAM. The prevalence of vitamin D deficiency was 20% (2/10) in patients who developed hypocalcemia and 3% (5/154) in those who did not develop hypocalcemia. There was a higher percentage of hypocalcemia for those on ZA in all groups (Table 3).

3.3.3. Hypophosphatemia

A serum phosphorous level was available for review following 360 infusions. Similar to the serum calcium level, there were less data on serum phosphate in primary osteoporosis group. The overall percentage of hypophosphatemia in those who have serum phosphate measured was 51% (185/360) and significantly differed among the 3 groups ($p = 0.002$) (Table 2). Hypophosphatemia was usually mild and intravenous phosphate replacement was rarely required (2%, 8/360).

3.3.4. Long-term adverse events

In 468 patient years of bisphosphonate exposure, there were no reports of osteonecrosis of ONJ or AFF in medical record.

3.4. Bone density

DXA scans were available for review and included in the analysis for 111 patients (90%).

Median baseline LS aBMD *Z*-scores prior to IV BP infusion were similar across the groups ($p = 0.53$; Table 4) and tended to increase in all 3 groups (Fig. 2). A significant increase in LS aBMD *Z*-score (median Δ *Z*-score 0.79, IQR: 0.51–1.63, $p < 0.0001$) at 1 year following bisphosphonate infusion was noted among the 42 patients, from all groups, who had at least 2 scans available for comparison (Table 4). Patients with a baseline LS aBMD *Z*-score ≤ -4.0 had a significantly greater increase in *Z*-score 1 year after initiating BP treatment compared to those who had a baseline LS aBMD *Z*-score > -4.0 (median Δ *Z*-score:1.56 vs 0.64 respectively; $p = 0.005$). When adjusted with height, there was significant difference in baseline height-adjusted LS aBMD *Z*-score ($p = 0.03$) with higher median in patients with GIO. However, the change in height-adjusted LS aBMD *Z*-score over time remained similar to non-height corrected *Z*-score.

Baseline LDF aBMD *Z*-score was shown in Table 4. The majority of these data was acquired in patients in secondary osteoporosis group. There was also a trend of increasing LDF R1 aBMD *Z*-score one year after BP initiation; however, this change was not statistically significant (median Δ *Z*-score 0.08, IQR −0.16–0.47, $p = 0.49$).

A sub-analysis was done on 100 patients who met full criteria for pediatric osteoporosis [12] (Supplemental Table S1). This decreased the primary osteoporosis group by 1, the secondary osteoporosis group by 16 patients and the GIO group by 6 patients. In this sub-analysis, there were no significant between group differences found at any DXA skeletal site, though a trend toward significance was observed for height-adjusted LS aBMD *Z*-score at baseline and 1 year ($p = 0.05$ for both) similar to findings in the full analysis. Overall median *Z*-scores for each group did not substantially change.

3.5. Fractures

Among 123 patients, 108 (88%) had history of long bone or vertebral fractures prior to initiation of IV BP treatment on record. Patients with primary osteoporosis were significantly younger at the time of their first fracture (median age 1.3 (IQR: 0.1–3.5) years) when compared with other groups ($p < 0.0001$). Approximately half of patients (53%) continued to have fractures following IV BP therapy and 20% (25/123) had fractures during the first year following initiation of BP therapy. Three patients who did not have fracture prior to IV BP treatment sustained long bone fracture later (primary osteoporosis = 1, secondary osteoporosis = 1, GIO = 1). Change in LS aBMD *Z*-score at one year did not differ in patients who did or did not continue to

Table 4
Baseline bone mineral density and change over the time.

	Primary osteoporosis	Secondary osteoporosis	GIO	*P*-value*
Baseline				
Spine *Z* BMD	−3.75 (−5.15, −1.62) *n = 24*	−3.95 (−4.58, −3.08) *n = 28*	−3.18 (−4.14, −2.32) *n = 21*	0.53
HAZ[a] Spine *Z* BMD	−2.23 (−3.33, −1.37) *n = 19*	−2.35 (−3.78, −1.78) *n = 22*	−1.29 (−2.33, −0.85) *n = 18*	**0.03**
Femur R1 *Z* BMD	–	−4.24 (−4.95, −3.33) *n = 12*	−3.88 (−5.41, −2.77) *n = 6*	0.61
Femur R3 *Z* BMD	–	−4.95 (−5.42, −4.49) *n = 12*	−4.62 (−5.20, −3.38) *n = 6*	0.54
1 year				
Spine *Z* BMD	−2.05 (−3.32, −1.25) *n = 18*	−2.88 (−4.46, −1.74) *n = 28*	−1.78 (−3.19, −1.34) *n = 11*	0.38
HAZ Spine *Z* BMD	−0.94 (−2.39, −0.04) *n = 12*	−1.68 (−2.64, −1.29) *n = 23*	−0.39 (−1.78, 0.12) *n = 11*	0.08
Femur R1 *Z* BMD	−4.60 *n = 1*	−4.82 (−5.74, −3.34) *n = 12*	−4.67 (−5.59, −3.75) *n = 2*	–
Femur R3 *Z* BMD	−5.96 *n = 1*	−5.26 (−6.50, −3.92) *n = 12*	−7.20 (−7.77, −6.62) *n = 2*	–
Δ *Z*-score: Baseline to 1 year[b]				
Spine *Z* BMD	1.91 (0.29, 2.44) *n = 11*	0.78 (0.51, 1.29) *n = 21*	0.61 (0.52, 1.09) *n = 10*	0.17
HAZ Spine *Z* BMD	1.00 (0.41, 2.22) *n = 8*	0.74 (0.46, 1.23) *n = 16*	0.74 (0.67, 0.91) *n = 9*	0.43
Femur R1 *Z* BMD	–	0.22 (−0.15, 0.70) *n = 8*	−0.02 (−0.18, 0.14) *n = 2*	–
Femur R3 *Z* BMD	–	0.11 (−0.21, 0.92) *n = 8*	−1.04 (−1.68, −0.39) *n = 2*	–

Data presented as median (25th, 75th percentile).
* *P*-value represents comparison between diagnosis groups.
[a] Height Adjusted *Z*-score.
[b] To be included in the Δ *Z*-score analysis, patients had to have DXA data at both time points.

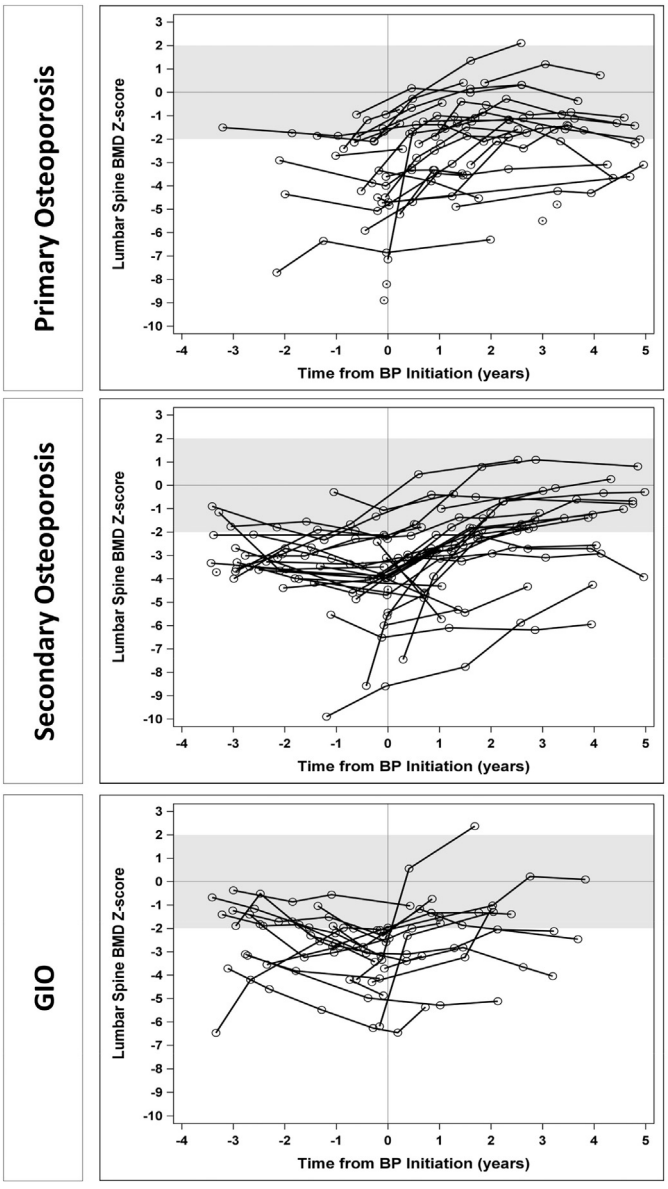

Fig. 2. LS aBMD *Z*-score change over time.

fracture following IV BP treatment (median Δ LS aBMD *Z*-score 0.68 vs 0.74 respectively, $p = 0.78$). Patients who had lower LS aBMD *Z*-score at baseline (≤ -4) were not at higher risk of sustaining subsequent fractures compared to those with higher LS aBMD *Z*-score at baseline (> -4) (61.5% had no record of fracture post BP initiation vs 61.7% respectively, $p = 0.99$).

In the sub-analysis of patients who strictly met the ISCD criteria for osteoporosis, the characteristics of fracture for each group were similar to the full analysis (Supplemental Table S2).

4. Discussion

Favorable efficacy and safety profiles for IV BP therapy have been well described in patients with primary osteoporosis; however, less is known about the safety and efficacy of IV BPs in children with secondary osteoporosis or GIO. This study reviewed the use of IV BP therapy at a tertiary care center in a diverse cohort of patients with impaired bone mineralization. We aimed to add to the available literature on the safety and efficacy in children with secondary bone disease. In our cohort, PAM was used in the majority of patients. However, there has been an increasing trend in ZA use at our center since 2016 due to its shorter infusion time and longer dosing interval when compared with PAM.

A recent retrospective study comparing inpatient and outpatient (PAM and ZA) infusion protocols revealed comparable safety profiles for these two skeletal agents [28]. In this study, no direct comparison between underlying etiology of bone disease and adverse event was done. However, the majority of patients receiving outpatient infusions had OI (60%) or low bone density for age (35%) and an adverse event occurred in 20% of this cohort. This differed from those receiving inpatient infusions of which 89% had disuse osteoporosis and adverse events were reported in 50% of patients. Our data found similar safety profiles for type of IV BP as reported in previous studies [6,19,29] and confirmed the observation that patients with secondary osteoporosis are more likely to report an adverse event then those with primary bone disease. We hypothesized that this was because those patients are at higher risk for rapid remineralization of bone following IV BP coupled with their underlying disease pathology that is characterized by chronic inflammation. APR were generally mild and occurred more frequently in bisphosphonate naïve patients. In several cases four occurrences of fever were likely associated with other etiologies rather than IV BP (concurrent intravenous immunoglobulin infusion, dysautonomia, sinusitis, and viral infection). Moreover, two respiratory events were believed to be associated with concurrent diphenhydramine use and

acute bronchiolitis.

In regards to electrolytes abnormalities, patients who received ZA were more likely to develop hypocalcemia and the prevalence of vitamin D deficiency was higher in those who developed hypocalcemia. Both hypocalcemia and hypophosphatemia were mild and rarely required intravenous supplementation. Hypophosphatemia requiring intravenous replacement occurred in one patient and was believed to be related to Neocate as it developed prior to bisphosphonate infusion [30]. There were less data available for patients with primary osteoporosis receiving PAM as the Montreal protocol recommends only pre-infusion calcium [14]. This could potentially lower the incidence of electrolyte abnormalities in primary osteoporosis group.

While data on long-term serious adverse events (ONJ and AFF) following IV BP are limited, our 468 patient years provides additional evidence of the long-term safety of these medications in pediatric patients.

Data on the efficacy of IV BP in pediatric patients is most robust in those with OI where treatment has been shown to increase BMD and decrease fracture frequency. In children with secondary osteoporosis, data on the efficacy of IV BP is more limited. In these small studies, IV BP has been shown to increase BMD at trabecular sites [31–33]. We report similar findings where aBMD at the lumbar spine increased over one year of IV BP treatment in all 3 groups. At R1 of the LDF, a similar trend toward increased aBMD after 1 year of IV BP treatment was also observed for patients with secondary osteoporosis. This finding at the LDF, a measure of appendicular bone density, is important because many non-ambulatory patients have spinal rods placed in later childhood rendering the recommended scan sites of the LS and whole body unusable for comparison in the future.

IV BP may reduce fracture risk in pediatric patients with secondary osteoporosis [31,33]. These studies are limited by small numbers and lack of control groups to adequately compare the natural history of fracture risk. In our study, we were unable to determine fracture risk reduction given the small numbers and heterogeneity of patient follow up. However we did find that change in LS aBMD *Z*-score was not associated with fracture occurrence while on IV BP treatment. This is similar to findings from other studies where aBMD response to bisphosphonate therapy did not fully correlate with fracture outcomes [34,35]. DXA acquired BMD may not adequately represent the changes in bone strength that portend to decreased fracture risk after IV BP therapy. In addition, median baseline height-adjusted LS aBMD *Z*-score in our GIO group was within normal range, suggesting that glucocorticoids can cause fracture even at a normal bone density. This re-emphasizes the limitation of DXA in predicting fracture risk.

Limitations and strengths of our study merit consideration. APR could potentially have been underestimated as we relied on data provided by the family and included in EMR documentation. However all acute adverse events were thoroughly reviewed from all forms of communication in medical record, such as telephone and email encounter, decreasing the possibility of recall bias. Seven patients with neuromuscular diseases in our cohort were previously treated with oral BP which could blunt the incidence of adverse effects following first IV BP infusion even though the bioavailability of oral BP is low and IV BP treatment is considered more effective in children with known impaired bone mineralization pre-treatment. With regard to fractures, we included only those reported in the EMR and/or a radiology report. The fracture history may be lacking some data on referral patients, especially information on those fractures that were managed at a facility closer to home. We found that change in LS aBMD *Z*-score at one year following intravenous bisphosphonate was not predictive of future fracture risk. However, only a limited number of patient had both baseline and one-year LS aBMD *Z*-score for comparison, and there was not enough data on cortical bone density, potentially a more important measure in predicting fracture risk in non-ambulatory patients [36]. Direct causal relationships between bisphosphonate use and bone mineral density is also difficult to conclude as there was variation in bisphosphonate dose and frequency in our study. Severity of disease may limit the ability to obtain follow-up DXA scans, or conversely patients with milder disease may not present for follow up. Lastly, consideration of puberty, which plays a significant role in bone mass accrual, was not included in our analyses.

Strengths of our study included large number of IV BP infusions for pediatric patients with concerns of osteoporosis or impaired bone health. While treatment with IV BP is generally reserved for pediatric patients with low BMD and at least one fragility fracture, the heterogeneous group of prescribers at our institution highlights the need for establishment and distribution of consistent best practice guidelines. Our retrospective study design suggested, but limited the ability to elucidate, direct causal relationship of IV BP use and its efficacy in regards to change in bone mineral density and fracture outcome. Careful and systematic long-term monitoring of bone health outcomes (change in aBMD and fracture outcomes) is needed to understand the efficacy of IV BP treatment in pediatric patients, especially those with secondary osteoporosis and GIO.

5. Conclusion

In pediatric patients with osteoporosis, adverse events due to IV BP treatment were mild and generally would not require inpatient management. APR and electrolyte abnormalities were more likely to occur in patients with secondary osteoporosis, a group who may require closer monitoring. Long-term serious adverse events including ONJ and AFF were not identified in 468 patient years of monitoring our cohort. IV BP treatment increased aBMD of trabecular bone but change in LS aBMD *Z*-score at one year was not predictive of future fractures. These data suggest that IV BP can be safely used in pediatric patients with osteoporosis, but further study is necessary to determine the efficacy of this intervention to decrease fracture risk in patients with secondary osteoporosis. Importantly, as bone disease spans medical disciplines, the development and dissemination of best practice guidelines for monitoring and treatment of children at risk for bone fragility and osteoporosis are essential.

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Appendix A. Supplementary data

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