Bisphosphonate nephrotoxicity

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Bisphosphonates are valuable agents for the treatment of post-menopausal osteoporosis (PMO), hypercalcemia of malignancy, and osteolytic bone metastases. Oral bisphosphonates are used mainly to treat PMO and are not associated with significant nephrotoxicity. In contrast, nephrotoxicity is a significant potential limiting factor to the use of intravenous (IV) bisphosphonates, and the nephrotoxicity is both dose-dependent and infusion time-dependent. The two main IV bisphosphonates available to treat hypercalcemia of malignancy and osteolytic bone disease in the United States are zoledronate and pamidronate. Patterns of nephrotoxicity described with these agents include toxic acute tubular necrosis and collapsing focal segmental glomerulosclerosis, respectively. With both of these agents, severe nephrotoxicity can be largely avoided by stringent adherence to guidelines for monitoring serum creatinine prior to each treatment, temporarily withholding therapy in the setting of renal insufficiency, and adjusting doses in patients with pre-existing chronic kidney disease. In patients with PMO, zoledronate and pamidronate are associated with significantly less nephrotoxicity, which undoubtedly relates to the lower doses and longer dosing intervals employed for this indication. Ibandronate is approved in the US for treatment of PMO and in Europe for treatment of PMO and malignancy-associated bone disease. Available data suggest that ibandronate has a safe renal profile without evidence of nephrotoxicity, even in patients with abnormal baseline kidney function.

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The bisphosphonates are a class of antiresorptive agents that are approved to treat multiple skeletal disorders including osteoporosis (postmenopausal and steroid-induced), malignancy-associated bone disease, and Paget's disease of bone. Bisphosphonates are available as oral and intravenous (i.v.) preparations. Oral preparations are effective in the treatment of postmenopausal osteoporosis (PMO) where they are associated with a significant reduction in fracture risk predominantly by reducing bone turnover and increasing bone mineral density. Oral bisphosphonates are generally considered to be safe and well-tolerated agents.[1] Exceptions include gastrointestinal intolerance, compliance issues, and contraindications to oral therapy due to underlying disorders such as achalasia and esophageal strictures.

Higher potency bisphosphonates, which are typically administered i.v., are effective therapies for malignancy-related bone disorders (multiple myeloma (MM), metastatic bone disease, hypercalcemia of malignancy) and Paget's disease of bone.[2] At lower doses, i.v. bisphosphonates also may be employed for PMO in patients with gastrointestinal intolerance or contraindications.[1] The use of i.v. bisphosphonates for PMO has the benefit of improved compliance compared to daily oral therapy. Due to the higher doses and potency, i.v. bisphosphonates have a greater potential for side effects than oral agents, including multiple forms of nephrotoxicity, osteonecrosis of the mandible, hypocalcemia, and postinfusion pyrexia and flu-like symptoms. Reports have described collapsing focal segmental glomerulosclerosis (FSGS) and other patterns of glomerular disease in patients treated with pamidronate. Zoledronate mainly has been associated with a toxic form of acute tubular necrosis (ATN).

The focus of this manuscript will be on the i.v. bisphosphonates, as these are the predominant forms that are associated with nephrotoxicity. A brief overview of the pharmacology and efficacy precedes a more detailed discussion on bisphosphonate nephrotoxicity.

PHARMACOLOGY OF BISPHOSPHONATES
General characteristics
The basic structure of all bisphosphonates is a P–C–P backbone with R1 and R2 side chains attached at the C position.[3] The composition of the side chains determines the specific characteristics of the molecule. An OH group at the R1 position enhances bone affinity, whereas the R2 side chain

Table 1 | Bisphosphonate dosing for malignancy-associated hypercalcemia or osteolytic disease

Drug	Dose/infusion time	Interval
	Estimated CrCl >60 cc/min	
Pamidronate	90 mg over 2–3 h	3–4 weeks
Zoledronate	4 mg over 15 min	3–4 weeks
	Estimated CrCl 30 <60 cc/min	
Pamidronate	90 mg over 2–3 h[a]	3–4 weeks
Zoledronate	Reduced dosage[b]	3–4 weeks
	Estimated CrCl <30 cc/min	
Pamidronate	90 mg over 4–6 h[a]	3–4 weeks
Zoledronate	Not recommended	

CrCl, creatinine clearance.
[a]Consider dose reduction (ASCO 2007; Kyle et al.[4]).
[b]3.5 mg (CrCl, 50–60 cc/min); 3.3 mg (CrCl, 40–49 cc/min); 3 mg (CrCl, 30–39 cc/min); Reference http://www.pharma.us.novartis.com/product/pi/pdf/Zometa.pdf.

can be either a non-nitrogen moiety or a nitrogen-containing moiety. Nitrogen-containing side chains (nitrogen-containing heterocyclic rings and tertiary nitrogen atoms) possess greater antiresorptive potency. *In vitro* studies[3] demonstrate an approximately 10,000-fold greater potency of nitrogen-containing bisphosphonates (pamidronate, zoledronate, and ibandronate) as compared with non-nitrogen-containing drugs (etidronate, clodronate).

In the United States, indications for zoledronate include hypercalcemia of malignancy and MM or bone metastases from solid tumors (Table 1). For these indications, zoledronate is administered at a dose of 4 mg i.v. monthly infused over at least 15 min. Zoledronate is not recommend for use in patients with a creatinine clearance (CrCl) <30 ml/min, and the dose should be adjusted for CrCl values between 30–60 cc/min. Indications for pamidronate include hypercalcemia of malignancy, osteolytic bone lesions from MM or breast cancer, and Paget's disease. For malignant indications, the recommended dose of pamidronate is up to 90 mg i.v. monthly infused over 3 h. For both pamidronate and zoledronate, serum creatinine should be measured prior to each administration and treatment should be withheld following a 0.5 mg/dl increase in serum creatinine in patients with normal renal function, or a 1.0 mg/dl increase in serum creatinine in patients with abnormal renal function at baseline. Intermittent evaluation of proteinuria is also recommended at 3–6 month intervals. Ibandronate is Food and Drug Administration approved for treatment of PMO but not malignancy-associated bone disease. The three approved regimens for PMO are 2.5 mg p.o. daily, 150 mg p.o. once per month, and 3 mg i.v. at 3-month intervals. Similar to the other agents, ibandronate is not recommended for use in patients with a CrCl <30 cc/min.

Outside the United States, i.v. ibandronate is approved by the European Union for the treatment of PMO and malignancy-associated bone disease. In general, the European Commission follows the same guidelines as the Food and Drug Administration for use of bisphosphonates to treat these disease states, but permits renal function monitoring to be utilized based on the clinical assessment of each patient at the discretion of the physician. Intravenous ibandronate is employed at 6 mg infused over 15 min for patients with CrCl >50 cc/min and the infusion time is increased to 1 h for patients with a CrCl between 30 and 50 cc/min. Although zoledronate is contraindicated in patients with severe renal impairment (CrCl <30cc/min), ibandronate can be used with a dose adjustment (2 mg over 1 h).[5]

Mechanism of action/pharmacodynamics

Bisphosphonates diminish bone resorption through several actions. Non-nitrogen-containing drugs primarily inhibit osteoclast activity by inhibiting ATP-dependent enzymes by forming nonhydrolyzable analogues of ATP.[3] In contrast, nitrogen-containing bisphosphonates act via extracellular and intracellular mechanisms. In the extracellular space, nitrogen-containing bisphosphonates act as calcium chelators, binding to and stabilizing calcium phosphate within bone matrix and preventing dissolution.[3] Second and more importantly, bisphosphonates exert multiple intracellular effects within osteoclasts, most notably inhibition of the mevalonate pathway. The mevalonate pathway is required for post-translational lipid modification (prenylation) and anchoring of small GTPases in cell membranes.[6] Subcellular compartmentalization and function of GTPases is critical for a variety of cellular processes, including integrin signaling, endosomal trafficking, membrane ruffling, and apoptosis.[7–11] Bisphosphonates also are able impair cell energetics through inhibition of ATP-dependent metabolic pathways[12] and to disrupt the osteoclast cytoskeleton by inhibiting actin assembly.[13]

Pharmacokinetics

Intravenous bisphosphonates are distributed between bone (50% is rapidly incorporated into the bone) and extracellular fluid.[3,14,15] They remain in bone for months to years depending on the associated bone tissue $T_{1/2}$ of the individual bisphosphonate. Once incorporated into bone, bisphosphonates are metabolically inactive until they are released by osteoclast activity. The drugs are released from osteoclasts via transcytosis, re-enter the circulation, and may later re-accumulate in bone. Negligible amounts of bisphosphonates are found in other tissues. Within the serum, protein binding is variable with ibandronate having the highest percentage of protein binding (87%), and zoledronate (56%) and pamidronate (54%) having similar but lower protein binding percentages. The i.v. bisphosphonates are not metabolized, do not interact with or affect the P450 enzyme system, and are excreted unchanged by the kidneys by glomerular filtration, without a significant component of tubular secretion.[3,14,15] As a result, impaired renal function reduces bisphosphonate excretion and can lead to excessive serum (and bone) levels with resultant toxicity. In addition to differences in protein binding, a notable difference between the bisphosphonates is a longer terminal renal tissue half-life with zoledronate (150–200 days) as compared with 24 days for ibandronate.[16]

EFFICACY OF BISPHOSPHONATES
Malignant osteolytic bone disease

Intravenous bisphosphonates are effective agents for the treatment of hypercalcemia of malignancy and malignancy-associated bone pain. In a phase III double-blind trial enrolling 1648 patients with MM or advanced breast cancer, zoledronate was shown to have greater efficacy than pamidronate with respect to reduction in skeletal-related events and event rate for radiation therapy, with a similar incidence of nephrotoxicity.[17] Intravenous bisphosphonates have also been employed less commonly for nonmalignant conditions such as Paget's disease of bone, osteogenesis imperfecta, and Langerhan's histiocytosis. Bisphosphonates are an important part of the therapeutic armamentarium for oncologists as they have been shown to effectively correct hypercalcemia, reduce osteolytic bone pain, and perhaps provide anti-tumor effects.

Osteoporosis

There are limited data available on i.v. bisphosphonates for the treatment of postmenopausal and steroid-induced osteoporosis. For these indications, substantially lower doses are employed. Although not approved for treatment of PMO, a regimen of pamidronate 30–60 mg i.v. at 3-month intervals has been shown over a 2-year period to increase bone mineral density of the spine and hip by 11 and 5.5%, respectively,[18] with an efficacy similar to oral alendronate.[19]

Clinical trials have demonstrated that i.v. zoledronate and ibandronate are effective treatments for PMO which reduce bone resorption (as measure by biochemical markers) and increase bone mineral density.[20,21] In two trials, i.v. quarterly ibandronate increased bone mineral density to a similar or greater degree than oral alendronate and risedronate or monthly ibandronate,[22,23] In a large trial enrolling 7765 women with PMO, once yearly infusion of zoledronate (5 mg) reduced the risk of vertebral (70%), hip (41%), and other fractures, increased bone mineral density, and reduced markers of bone turnover as compared with placebo over a 3-year period.[24] Intravenous zoledronate and ibandronate have also been shown to be effective agents in reducing the incidence of fracture in patients with recent hip fractures[25] and in patients with corticosteroid-induced osteoporosis.[26]

BISPHOSPHONATE NEPHROTOXICITY
### Animal studies

Animal studies have been employed to evaluate the relative antiresorptive efficacy and nephrotoxicity of the high potency i.v. bisphosphonates. A single dose of i.v. pamidronate in rats leads to an increase in urinary malate dehydrogenase, a sensitive marker of renal injury which can be detected prior to the development of histopathologic changes.[27] When exposed to higher doses of i.v. pamidronate (5–50 mg/kg), elevations in serum blood urea nitrogen and creatinine are seen.[28] Mice exposed to greater than 10 mg/kg of pamidronate may exhibit histopathologic changes of kidney injury including focal cellular necrosis, increased cellular vesicles, and loss of tubular cell brush border.[29]

Zoledronate was developed with the goal of finding a bisphosphonate with maximum potency with respect to inhibiting bone resorption and minimal nephrotoxicity. A panel of bisphosphonates was studied in two rat models.[27] Zoledronate emerged as having greater antiresorptive capacity, similar renal tolerability, and thus a superior therapeutic ratio than the six available bisphosphonates and five other novel compounds tested in thyroparathyroidectomized rats.[27] Specifically, the therapeutic ratio for zoledronate was 790, as compared to 40 for Ibandronate and 0.88 for pamidronate. An important observation in this study was the lack of correlation between antiresorptive capacity and renal tolerability. One-hour infusions of varying doses of zoledronate or pamidronate were then compared with respect to renal tolerability. Pamidronate was found to be more nephrotoxic, requiring 10 mg/kg to increase the serum urea nitrogen by 100% at 4 h, as opposed to 38 mg/kg for zoledronate.[27]

Other animal studies have suggested that ibandronate may be safer than zoledronate with respect to nephrotoxicity. A study in rats comparing the two agents showed that intermittent dosing of zoledronate (every 3 weeks) induced more frequent and more severe renal histopathologic injury than similar doses of ibandronate.[30] The difference in nephrotoxicity was also noted when only a single dose of each agent was administered. The authors proposed that the safer renal profile of ibandronate with repetitive dosing might relate to the shorter renal tissue half-life of ibandronate (24 days) as compared with zoledronate (150–200 days).[31] The same authors went on to administer supratherapeutic i.v. doses of zoledronate and ibandronate to rats in an attempt to determine the minimally nephrotoxic dose, defined as the dose required to promote kidney injury.[32] In this single-dose study, 1 mg/kg of zoledronate as compared with 3 mg/kg of ibandronate caused renal proximal tubular damage with loss of brush border, cytoplasmic swelling, and cellular necrosis. Distal tubular injury and necrosis occurred only in rats treated with 10 mg/kg of zoledronate. The ratio between the lowest lethal dose and the minimally nephrotoxic dose was 25 for ibandronate and 3.3 for zoledronate.

Human studies: case series and renal biopsy findings

Insights into the patterns and mechanisms of bisphosphonate nephrotoxicity have been gained from case reports and short series which highlight clinical and renal biopsy findings (Figure 1). The first report described seven patients with acute kidney injury (AKI) and nephrotic syndrome following long-term treatment with pamidronate[33] (Table 2). The cohort consisted of five women and two men with a mean age of 62.7 years. Six patients had MM and one had a history of breast cancer. At the time of presentation and renal biopsy, the mean serum creatinine was 3.6 mg/dl and the mean 24 h urine protein was 12.4 g/day. All seven patients had received monthly i.v. pamidronate for 15–48 months. Five of the seven patients received doses of pamidronate that exceeded recommended levels, including 360 mg/month in three patients and 180 mg/month in two patients. Renal biopsy
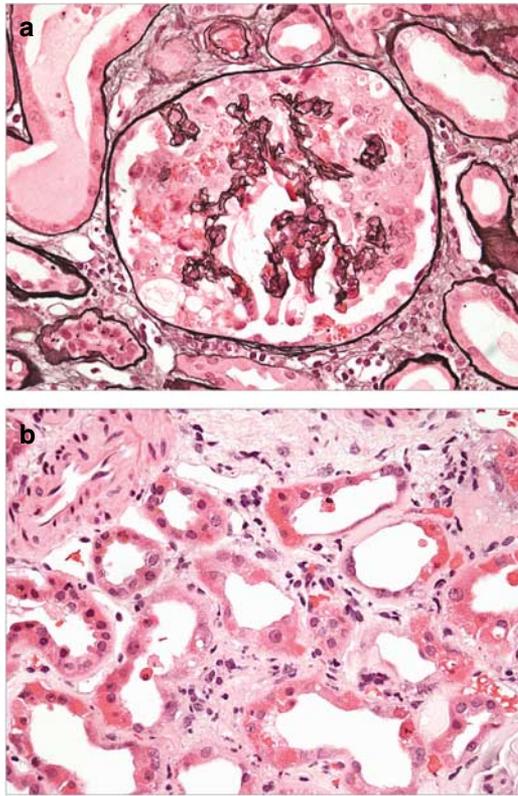
Figure 1 | Renal biopsy findings in bisphosphonate nephrotoxicity. (**a**) A glomerulus from a patient who had been treated with pamidronate exhibits collapsing focal segmental glomerulosclerosis with global wrinkling and retraction of the glomerular basement membrane. There is global swelling and proliferation of overlying visceral epithelial cells which contain protein resorption droplets. (Jones methenamine silver, × 400.) (**b**) In this example of toxic acute tubular necrosis following treatment with zoledronate proximal tubules exhibit severe degenerative changes including luminal ectasia, cytoplasmic simplification and hypereosinophilia, irregular luminal contours, extensive loss of brush border, prominent nucleoli, and focal apoptotic figures. (Hematoxylin and eosin, × 400.)

revealed collapsing FSGS associated with severe tubular degenerative changes. Collapsing FSGS is a pattern of glomerular disease that most commonly occurs in young, African-American patients. The finding of collapsing FSGS in a group of older Caucasian patients with a history of malignancy was the initial observation that led to the recognition of an association between pamidronate and this pathologic lesion. Following discontinuation of pamidronate, renal function improved in two of five patients.

Subsequent reports have reaffirmed the association of pamidronate with nephrotic syndrome and a spectrum of glomerular lesions ranging from collapsing FSGS to non-collapsing forms of FSGS to minimal change disease.[34–36] Barri *et al.*[34] described five patients with MM who developed nephrotic syndrome following treatment with pamidronate. Three patients received a standard dose of 90 mg/month i.v. for at least 1 year. The remaining two patients were part of an experimental protocol whereby they received 50 mg continuous infusion daily for 7 days every other week for 2 months

followed by a maintenance dose of 50 mg/month. Among the five patients, the mean 24 h urine protein was 8.1 g/day and the mean creatinine was 1.7 mg/100 ml. Renal biopsy revealed minimal change disease in two patients, non-collapsing FSGS in two patients, and a single patient with collapsing FSGS. Following renal biopsy, pamidronate was discontinued. The patient with collapsing FSGS progressed to ESRD, whereas the two patients with minimal change disease had a remission of proteinuria. Among the remaining two patients with non-collapsing FSGS, one had persistent proteinuria with normal renal function and the other had resolution of proteinuria in the setting of worsening renal function.[34] Desikan *et al.*[35] described five patients with MM who developed severe proteinuria (mean 13.5 g/day; range 2.96–25 g/day) following treatment with pamidronate at a dose of 180 mg/month. Two of the five patients underwent biopsy and were found to have FSGS. Although a single patient became dialysis-dependent, the remaining four patients had a marked reduction in proteinuria following cessation or reduction in dose of pamidronate. The authors of the study noted that none of 55 patients at their center who had been treated with pamidronate at a dose of 90 mg/month had developed progressive nephrotic proteinuria.[35] Shreedhara *et al.*[36] reported four patients with breast cancer and one with MM who developed proteinuria and renal insufficiency following treatment with pamidronate (90 mg/month in four patients; 180 mg/month in the single remaining patient). Three of the five patients underwent renal biopsy and were found to have collapsing FSGS. In all five patients, discontinuation of pamidronate led to significant improvement in renal function and a decline in proteinuria.

There has also been multiple individual case reports of nephrotic syndrome associated with pamidronate.[37–40] In one report, a patient's 24 h urine protein declined from 28.7 to 3.4 g/day after discontinuation of pamidronate.[37] Due to life-threatening thoracic and lumbar disease, pamidronate was restarted and soon after, proteinuria increased to 6.4 g/day. The authors of this report, who also described the initial seven cases of pamidronate-associated collapsing FSGS, noted that they had seen 10 additional cases since their original report, bringing the total to 17 from a single referral center.[37] From these reports, it appears that pamidronate-associated nephrotic syndrome mainly occurs in patients who have MM and have received pamidronate at higher than recommended doses. The most frequent pathologic lesion is collapsing FSGS although less aggressive patterns of podocyte injury, including minimal change disease and non-collapsing FSGS, may be seen. In many cases, nephrotic syndrome associated with pamidronate is at least partially reversible following discontinuation of the offending agent.

Pamidronate also has been rarely associated with diseases of the tubules and interstitium. Banerjee *et al.*[42] described a patient with hypercalcemia of unclear etiology who developed AKI, requiring dialysis after three 60 mg doses of pamidronate administered over 2 weeks. Renal biopsy

Table 2 | Renal biopsy findings in bisphosphonate-associated nephrotic syndrome

Author/ reference	Patient no.	Clinical presentation	Bisphosphonate	Renal biopsy findings	Bisphosphonate withdrawal?	Outcome following bisphosphonate withdrawal
Markowitz[33]	1	NS/RI	Pamidronate	Collapsing FSGS	No	HD
	2	NS/RI	Pamidronate	Collapsing FSGS	Yes	HD
	3	NS/RI	Pamidronate	Collapsing FSGS	No	HD
	4	NS/RI	Pamidronate	Collapsing FSGS	Yes	Increase in sCr
	5	NS/RI	Pamidronate	Collapsing FSGS	Yes	Decline in sCr
	6	NS/RI	Pamidronate	Collapsing FSGS	Yes	HD
	7	NS/RI	Pamidronate	Collapsing FSGS	Yes	Decline in sCr
Barri[34]	1	NS	Pamidronate	MCD	Yes	Remission of NS
	2	NS	Pamidronate	FSGS NOS	Yes	Persistent NS
	3	NRP/RI	Pamidronate	MCD	Yes	Remission of NRP; decline in sCr
	4	Proteinuria	Pamidronate	FSGS NOS	Yes	Decline in proteinuria; increase in sCr
	5	NS/RI	Pamidronate	Collapsing FSGS	Yes	HD
Desikan[35]	1	NRP	Pamidronate	FSGS	Yes	Remission of proteinuria
	2	NRP	Pamidronate	FSGS	Yes	Persistent NRP
Shreedhara[36]	1	NS/RI	Pamidronate	Collapsing FSGS	Yes	Remission of NS & RI
	2	NS/RI	Pamidronate	Collapsing FSGS	Yes	Decline in proteinuria & sCr
	3	NS/RI	Pamidronate	Collapsing FSGS	Yes	Decline in proteinuria & sCr
Markowitz[37]	1	NS	Pamidronate	Collapsing FSGS	Yes	Decline in proteinuria
Lockridge[38]	1	NS/RI	Pamidronate	MCD	Yes	HD
Kunin[39]	1	NS/RI	Pamidronate	Collapsing FSGS	Yes	HD
Nasr[40]	1	NS/RI	Pamidronate	Collapsing FSGS & MCN	Yes	Decline in proteinuria & sCr
Bodmer[41]	1	NS/RI	Zoledronate	Collapsing FSGS	Yes	HD

FSGS NOS, FSGS not otherwise specified; FSGS, focal segmental glomerulosclerosis; HD, hemodialysis; MCD, minimal change disease; MCN, myeloma cast nephropathy; NRP, nephrotic range proteinuria; NS, nephrotic syndrome; RI, renal insufficiency; sCr, serum creatinine.

revealed ATN and renal function subsequently recovered. Similarly, Smetana *et al.*[43] described a woman who was treated with pamidronate 90 i.v. monthly for PMO and developed progressive renal failure during the initial 20 months of therapy. Over that time period, the serum creatinine increased from 1.1 to 2.7 mg/dl. Renal biopsy revealed toxic ATN, pamidronate was discontinued, and her serum creatinine declined over 4 months to 1.9 mg/dl.[43] Buysschaert *et al.*[44] reported a patient with hyperparathyroidism who was treated with up to 360 mg/month of i.v. pamidronate and developed a severe chronic tubulointerstitial nephropathy associated with Fanconi syndrome. Following discontinuation of pamidronate, Fanconi syndrome resolved but there was minimal improvement in renal function.

In contrast to pamidronate, zoledronate appears to be mainly associated with injury to the tubules, resulting in a toxic form of ATN. The initial report of toxic ATN following treatment with zoledronate included four men and two women with a mean age of 69.2 years.[45] Five patients had a history of MM and one had Paget's disease. The mean baseline serum creatinine was 1.4 mg/dl. Patients received zoledronate at the recommended dose and infusion time (4 mg/month i.v. over at least 15 min) and were found to have AKI with a mean serum creatinine of 3.4 mg/dl and only subnephrotic proteinuria following a mean of 4.7 months of treatment (range 3–9 months). Renal biopsy revealed toxic ATN, without evidence of collapsing FSGS. Discontinuation of zoledronate led to improvement in renal function, with a mean serum creatinine of 2.3 mg/dl at a mean of 3.2 months following renal biopsy. Of note, only a single case of

nephrotic syndrome and collapsing FSGS following treatment with zoledronate has been reported.[41]

It is important to note that the large trials which report incidences of renal insufficiency following treatment with pamidronate or zoledronate do not provide information on proteinuria or mention renal biopsy findings. As a result, it would be inaccurate to conclude that the patterns of nephrotoxicity seen in case reports and clinical series are entirely reflective of the patterns of nephrotoxicity seen in large clinical trials. For instance, it is possible that pamidronate is associated with ATN as often or even more often than collapsing FSGS, but that the findings of collapsing FSGS have gained attention due to the distinctive clinical presentation of full nephrotic syndrome.

Human studies: nephrotoxicity observed in clinical trials and government reporting systems

Malignant bone disease. Intravenous pamidronate is recommended for use at a dose of 90 mg i.v. monthly infused over 3 h for treatment of malignancy-associated bone disease. A phase III trial that employed i.v. pamidronate 90–120 mg i.v. monthly for 9 cycles in 203 patients with MM found no adverse renal effects as compared with 189 placebo-treated patients.[46] A similar renal safety profile was noted at a similar dose and schedule for treatment of patients with breast cancer and osteolytic bone metastases.[47] In this trial, 367 patients received i.v. pamidronate (90 mg) and 387 patients received placebo. Serum and urine chemistries as well as urinalysis were followed at regular intervals and no adverse renal events were noted. A retrospective study examined long-term renal safety of i.v. pamidronate (or pamidronate

before/after zoledronate) in 57 patients with various forms of metastatic cancer (breast, 48; renal cell, 1; prostate, 1) or MM[8] over a median of 34 months of therapy.[2] Patients who had normal kidney function at baseline (median 0.89 mg/dl, range 0.4–1.4 mg/dl) received pamidronate (90 mg every 3–4 weeks) or pamidronate/zoledronate (4 mg every 3–4 weeks). Seven patients (12%) developed an increase in serum creatinine concentration (>0.5 mg/dl or doubling over baseline). Six patients continued on therapy with two improving and four having no further rise in serum creatinine, whereas treatment was discontinued in one patient. Thus, i.v. pamidronate does maintain some nephrotoxic risk.

In contrast to pamidronate, renal safety concerns were noted with i.v. zoledronate in two phase III oncology trials involving patients with breast, lung, and other cancers with bone metastases that used doses of 4 and 8 mg i.v. infused over 5 min every 3–4 weeks.[17,48] In a phase III trial comparing zoledronate to pamidronate that enrolled 1648 patients with MM or advanced breast cancer, two protocol adjustments were required to reduce the incidence of renal insufficiency with zoledronate to a rate similar to that seen with pamidronate. Initially, patients were treated with zoledronate 8 mg i.v. infused over 5 min. The first protocol change increased the infusion time from 5 to 15 min, whereas the second reduced the dose from 8 to 4 mg.[17] Following the two protocol adjustments, the incidence of nephrotoxicity, defined as an increase in serum creatinine of at least 0.5 mg/dl, was 9.3% with zoledronate as compared to 8.1% for pamidronate. It should be noted that although these percentages may appear alarmingly high, this study did not include a placebo group; AKI may occur from a variety of etiologies and with some frequency in patients with myeloma or metastatic carcinoma. Another trial in patients with bone metastases from various malignancies noted a statistically insignificant difference in the incidence of abnormal kidney function between zoledronate (10.9%) and a placebo group (6.7%).[48] Importantly, this study included only patients with lung cancer and other solid tumors (except breast and prostate cancer) and did not include patients with MM.

In 2003, the Food and Drug Administration Adverse Event Reporting System reported 72 cases of renal failure associated with i.v. zoledronate identified over an 18-month period.[49] The 72 patients had a mean age of 71 years. Indications for zoledronate included MM and solid organ malignancies in 42 and 22 patients, respectively. The mean baseline serum creatinine was 1.7 mg/dl, which increased to a mean of 6.5 mg/dl with zoledronate treatment and decreased to a mean of 2.7 mg/dl following drug discontinuation. Renal failure was noted an average of 56 days after commencing therapy, following a mean of 2.4 i.v. doses. Risk factors for nephrotoxicity were advanced cancer, previous bisphosphonate exposure (mainly pamidronate), and exposure to nonsteroidal anti-inflammatory drugs. Most patients were left with chronic kidney disease, 27 patients required renal replacement therapy, and 18 patients expired. The French

Adverse Effect Reporting Database similarly noted renal toxicity associated with i.v. zoledronate utilized to treat cancer.[50] They identified seven patients who developed AKI (four de novo; three superimposed on chronic kidney disease). Clinical follow-up after discontinuation of zoledronate was available for six patients, including three that completely recovered and three who were left with permanent renal impairment. Risk factors for renal failure were similar to those previously noted. Further evidence of increased nephrotoxicity associated with i.v. zoledronate (median treatment 9.8 months) was demonstrated in a retrospective study of 122 patients with metastatic prostate cancer followed over a median of 11.7 months.[51] In this study, the median patient age was 70 years, 59% of patients had hypertension, and 91% of patients had a baseline serum creatinine <1.4 mg/dl. Using standard definitions of renal toxicity, 23.8% of patients developed nephrotoxicity based on increased serum creatinine concentration and 41.8% based on a decline in CrCl. Renal toxicity increased with duration of therapy using either serum creatinine increases (<6 month, 11.1%; >12 months, 21.8%; >24 months, 26.3%) or declines in CrCl (<6 month, 23.9%; >12 months, 45.5%; >24 months, 36.8%) as well as with prior pamidronate therapy (increase in serum creatinine 45.5 vs 19%, decrease in CrCl 72.7 vs 35%) and older age.

The American Society of Clinical Oncology 2007 Clinical Practice Guideline Update recommends that pamidronate (90 mg over no less than 2 h) and zoledronate (4 mg over 15 min) be employed for patients with normal kidney function.[4] In patients with mild-to-moderate kidney disease (estimated CrCl 30–60 cc/min), the dose of zoledronate should be reduced with no change in pamidronate, although the committee suggests that clinicians 'consider reducing the initial dose of pamidronate' (Table 1). For more severe kidney disease (estimated CrCl <30 cc/min), zoledronate is not recommended whereas the infusion time for pamidronate should be increased to 4–6 h, again with a consideration for reducing the dose. Serum creatinine should be monitored before each dose of bisphosphonate and the drug withheld in patients who develop an otherwise unexplained increase in serum creatinine concentration. The drug can be restarted if the serum creatinine returns to within 10% of baseline. Also, the development of albuminuria (confirmed by 24 h urine collection) should be monitored for at 3–6 month intervals, with a similar drug withhold if unexplained albuminuria develops.

Ibandronate appears to have less nephrotoxic potential than other available i.v. bisphosphonates. In 25 patients with metastatic prostate cancer, severe bone pain, and a creatinine <2.5 mg/dl, ibandronate infused at a dose of 6 mg i.v. over 1 h for 3 consecutive days followed by a single 6 mg infusion every 4 weeks was not associated with nephrotoxicity over an undefined period of follow-up.[52] In another study, both 2 mg and 6 mg i.v. ibandronate doses infused over 1–2 h every 3–4 weeks for metastatic breast cancer did not cause renal toxicity.[53] In this study, 158 patients received placebo,

whereas 154 patients received 2 mg and 154 patients received 6 mg doses. The percentage of patients with increased serum creatinine concentrations was similar between all groups. A *post hoc* analysis of a trial in 309 patients with breast cancer treated with either i.v. ibandronate ($n = 152$) or placebo ($n = 157$) also showed similar adverse renal effects in both groups (ibandronate 6%; placebo 12%) over 2 years of follow-up.[54] In this study, a renal event was defined as increase in serum creatinine concentration of 0.5 mg/dl in patients with a baseline serum creatinine < 1.4 mg/dl and 1.0 mg/dl if baseline serum creatinine was > 1.4 mg/dl. Finally, a short-term study in 18 patients with advanced metastatic cancer employing ibandronate 4 mg infused over 2 h on 4 consecutive days was not associated with nephrotoxicity.[55]

The renal safety of ibandronate has also been examined in patients with underlying kidney disease. In an open-label study, i.v. ibandronate (6 mg over 30 min) was administered to 21 MM patients with baseline renal insufficiency (CrCl 8–120 cc/min, 17 of 21 with underlying kidney disease) and the short-term renal effects were measured.[56] No changes in serum creatinine or urinary markers of tubular injury were noted. Seven MM patients with AKI due to hypercalcemia/nephrocalcinosis received i.v. ibandronate (6 mg over 30 min in 6 patients, 2 mg in 1 patient followed by 4 or 6 mg every 3–4 weeks) and were followed for correction of serum calcium concentration and renal function parameters.[57] Hypercalcemia was corrected and renal function improved or normalized in all patients. In contrast to pamidronate and zoledronate, currently published clinical studies suggest that IV ibandronate does not exhibit significant nephrotoxicity and is well tolerated, even in patients with underlying kidney disease.

Postmenopausal osteoporosis. Treatment of PMO with i.v. bisphosphonates requires lower doses and longer dosing intervals which, not surprisingly, results in less nephrotoxicity. The limited data on oral pamidronate (4.8–6.0 mg/kg daily) for osteoporosis reflect a safe renal profile.[58] Similarly, i.v. pamidronate for PMO is understudied but appears to have a relatively safe renal profile at doses that range from 30 mg every 3 months up to 60 mg monthly.[18,19]

Three large studies have examined the efficacy and safety of i.v. zoledronate in the treatment of PMO or as an agent to reduce mortality in patients who have had a recent hip fracture. In a 12-month study of 351 women with PMO who received zoledronate 4 mg i.v. annually in single or divided doses, no adverse effects on renal function were reported.[21] A subsequent double-blind, placebo-controlled trial enrolled 7765 women with PMO who were administered zoledronate 4 mg i.v. or placebo once per year.[24] In this 3-year follow-up study, a transient decline in renal function (increase in serum creatinine concentration > 0.5 mg/dl) occurred more frequently in the i.v. zoledronate group (1.3% vs 0.4%; $P = 0.001$). However, renal function was not significantly different between the two groups at the end of 3 years. A third study examined the efficacy of zoledronate 5 mg i.v.

once per year to reduce the incidence of new fractures among patients with a recent hip fracture. This double-blind, placebo-controlled trial enrolled 2127 patients. An increase in serum creatinine of > 0.5 mg/dl was seen in a similar percentage of patients in both groups (6.2% in zoledronate group vs 5.6% in placebo group; $P = 0.62$).[25] Of note, the efficacy of zoledronate as a treatment for PMO or to reduce postfracture mortality was well established in each of the three studies.

Ibandronate administered at a dose of 2 mg i.v. every 2 months or 3 mg i.v. every 3 months has been compared to daily oral ibandronate in a study of 1395 women with PMO.[59] In this 2-year randomized, double-blind, noninferiority study, both i.v. ibandronate dosing schedules were as effective as oral ibandronate. No cases of AKI, defined as either an increase in serum creatinine concentration of > 0.5 mg/dl (baseline creatinine < 1.4 mg/dl) or 1.0 mg/dl (baseline creatinine > 1.4 mg/dl) or twofold increase in serum creatinine during treatment, were reported. In more than 3000 patients with PMO treated with i.v. ibandronate (2–12 mg annually), pooled safety data demonstrate a safe renal profile with no adverse renal effects or cases of renal failure.[60] In this analysis, the mean decline in estimated glomerular filtration rate in patients exposed to 12 mg of i.v. ibandronate (-0.72 ml/min) was similar to patients treated with 2.5 mg of oral ibandronate (-0.28 ml/min) and placebo (-0.91 ml/min).

Mechanism of nephrotoxicity

Although the mechanism(s) by which bisphosphonates are associated with nephrotoxicity are not well understood, inferences can be drawn from the pathologic findings.

Collapsing FSGS is the most severe histologic variant of FSGS[61] and results from direct podocyte injury, whereby visceral epithelial cells leave their terminally differentiated state, enter the cell cycle, lose expression of markers of differentiation, and exhibit an immature phenotype.[62] In the initial report of seven cases of pamidronate-associated collapsing FSGS, similar alterations were seen, including loss of podocyte synaptopodin and increased expression of proliferation marker Ki-67, in both podocytes and tubular epithelia.[33] Based on the pathologic findings, pamidronate toxicity appears to target podocytes and possibly tubular epithelium.

Toxic ATN, the main pattern of renal injury seen in patients treated with zoledronate, is characterized by toxicity directed at tubular epithelium, as evidenced by the increased tubular expression of Ki-67 and diminished and altered expression of tubular Na $+$, K $+$ -ATPase. The concept that zoledronate toxicity targets tubular epithelia whereas pamidronate targets visceral epithelial cells and possibly tubular epithelia is likely to be an oversimplification in that rare cases of pamidronate-associated toxic ATN and a single case of zoledronate-associated collapsing FSGS have been reported. Furthermore, renal biopsy findings are not provided in any of the large trials that have documented renal insufficiency following treatment with pamidronate or zoledronate.

Bisphosphonate nephrotoxicity may result from similar mechanisms to that in which these agents exert their therapeutic effects in osteoclasts. Inhibition of the mevalonate pathway within the osteoclast is thought to be an important mechanism of action of bisphosphonates, leading to alterations in integrin signaling, endosomal trafficking, and membrane ruffling, as well as induction of apoptosis.[7–11] Nitrogen-containing bisphosphonates exert this effect on osteoclasts by direct inhibition of farnesyl diphosphate synthase, an enzyme present in the mevalonate pathway. Recent experiments have shown that zoledronate and ibandronate inhibit farnesyl diphosphate in a human proximal tubular cell line, and that this step may be followed by decreased levels of prenylated proteins and later cytotoxicity, an observation that strongly supports the concept that the therapeutic effect of bisphosphonates on osteoclasts may have an identical mechanism to the toxic effect on the kidney.[63] Bisphosphonates also impair cellular energetic and disrupt cytoskeleton assembly within osteoclasts.[12,13] Bisphosphonates may exert similar effects in tubular and visceral epithelial cells, thereby producing toxic ATN and collapsing FSGS, respectively. This concept is supported by the high renal exposure to bisphosphonates and the finding that bisphosphonates can induce apoptosis in other cell types including cancerous cells.[64] Furthermore, podocytes, much like osteoclasts, have a highly complex cytoskeleton and disruption of this cytoskeleton plays a role in the development of collapsing FSGS. A recent case report raises the possibility that in some cases, pamidronate-associated FSGS may result from drug-induced mitochondrial toxicity targeting visceral epithelial cells and tubular epithelia.[65]

It is unclear as to why ibandronate has a safer renal profile than the alternative i.v. bisphosphonates, although this finding clearly argues against a class effect. The difference in nephrotoxic potential may relate to two pharmacokinetic differences. Compared to pamidronate and zoledronate, ibandronate is more highly protein bound (87% vs 54 and 56%), which may limit renal exposure to free drug.[16] Second, the renal tissue half life of ibandronate is much shorter than zoledronate,[16] possibly allowing for more time for injured cells to undergo repair between repeat dosing.

CONCLUSION

Intravenous bisphosphonates are highly effective agents for the treatment of osteoporosis, hypercalcemia of malignancy, and osteolytic bone metastases. Nephrotoxicity is an important potential limiting factor in the use of these agents, in particular pamidronate and zoledronate. Bisphosphonate nephrotoxicity is dose-dependent and infusion time-dependent, and can be limited by increasing the time interval between doses. The two main i.v. bisphosphonates in use for these indications in the United States are zoledronate and pamidronate. Patterns of nephrotoxicity seen with these agents include toxic ATN and collapsing FSGS. With both of these agents, severe nephrotoxicity can often be avoided by strict adherence to guideline for monitoring serum creatinine prior to each treatment, withholding therapy in the setting of renal insufficiency, and adjusting doses in the setting of pre-existing chronic kidney disease. Currently, ibandronate is approved in the US for treatment of PMO and in Europe for treatment of PMO and complications of cancer. In contrast to pamidronate and zoledronate, ibandronate appears to have a safer renal profile with no evidence of nephrotoxicity, even in patients with abnormal baseline kidney function. Future studies and accumulated clinical experience are needed to better determine whether ibandronate is an agent with any significant nephrotoxicity.

DISCLOSURE

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