Review

Renal tolerability of intermittent intravenous ibandronate treatment for patients with postmenopausal osteoporosis: a review

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ABSTRACT

While intravenous (IV) bisphosphonates are well established in managing metastatic bone disease and hypercalcemia of malignancy, oral bisphosphonates are the primary treatment for postmenopausal osteoporosis. The availability of a well-tolerated, effective, IV bisphosphonate regimen for postmenopausal osteoporosis would increase physicians' options, allowing treatment of patients who cannot tolerate oral therapy, for whom oral bisphosphonates should be avoided or patients who are unable to comply with the oral dosing recommendations.

Ibandronate is a potent, nitrogen-containing bisphosphonate, with proven efficacy and good tolerability when administered intermittently either orally or intravenously. Preclinical experience in animal models with IV ibandronate indicated that it had good renal tolerability. These data are supported by clinical pharmacology studies. Prolonged follow-up of patients receiving intermittent IV 15-30 second injections of 0.5-3 mg IV ibandronate has demonstrated no clinical evidence of renal toxicity in patients with postmenopausal osteoporosis. What is seen in controlled studies is not always the case in uncontrolled studies, however, no reports of renal failure have been received in post-marketing surveillance of >500,000 patients receiving IV ibandronate infusions in various indications including metastatic breast and prostate cancer. The good renal tolerability of IV ibandronate in patients with osteoporosis with glomerular filtration rates >30 mL/minute and without renal co-morbid conditions is reassuring.

Introduction

Osteoporosis is a common systemic skeletal disorder characterized by compromised bone strength, which predisposes patients to an increased risk of fracture (1). Oral nitrogen-containing bisphosphonates have been reported to reduce the risk of new vertebral fractures by 41-62% (2-5), and are the current mainstay of postmenopausal osteoporosis management. However, despite generally good tolerability, oral bisphosphonates are perceived to be associated with upper gastrointestinal (GI) side effects (6-10), and require patients to adhere to relatively stringent and disruptive posture and fasting guidelines when taking each oral dose.

In contrast, intravenous (IV) formulations need less frequent administration, have no potential for GI mucosal irritation and ensure 100% systemic bioavailability. Thus, there is likely to be an important role for a well-tolerated and effective IV bisphosphonate in the treatment of patients with osteoporosis who have relative contraindications for oral bisphosphonates such as symptomatic and poorly controlled esophageal reflux, or patients who may not absorb orally administered bisphosphonates, or patients who are generally intolerant to oral bisphosphonates or cannot comply with the stringent dosing guidelines.

Intermittent IV administration of bisphosphonates in postmenopausal osteoporosis

Rationale

The ability of the IV bisphosphonates ibandronate, zoledronic acid and pamidronate to reduce the risk of skeletal events, relieve pain, restore normal functioning and improve quality of life is well established in patients with metastatic bone disease (11-15). Due to their proven efficacy (11, 16), IV bisphosphonates are also recognized as the standard treatment for controlling hypercalcemia of malignancy (17). The role of IV bisphosphonates in the management of osteoporosis is becoming

better defined with the registration of the IV ibandronate injection and the annual zoledronic acid infusion.

Evolution of IV bisphosphonate therapy for postmenopausal osteoporosis treatment

As bisphosphonates are predominantly excreted by the kidney, there is potential for renal side effects. Indeed, acute renal failure has been associated with the rapid IV administration of high doses of etidronate, clodronate and tiludronate in the treatment of hypercalcemia of malignancy (18-20). Damage may result from direct interaction of the bisphosphonate with the intracellular metabolism of the epithelial cells of the convoluted tubules possibly through the same mechanism as their action on osteoclasts or possibly by a hemodynamic effect. The exact mechanism for tubular damage is not well defined.

To avoid renal damage, the older, high-dose bisphosphonates such as etidronate, clodronate and tiludronate must be administered by slow infusion, at no more than 200 mg/hour or 5 mg/minute when given intravenously (21, 22), which can often take several hours. The requirement for prolonged infusion time and renal function monitoring limits the utility of these medications in primary care. Healthcare resources may also be adversely affected: prolonged infusions are labor intensive for healthcare staff, adding to the cost of treatment delivery. The development of the higher-potency bisphosphonates (i.e. those that can inhibit bone resorption at doses that do not impair normal mineralization), opens the potential for a simpler, more convenient and less intrusive IV injection. Potency *in vitro* can be defined in two ways: by the affinity of the bisphosphonate to the crystal surface and the effect on the osteoclast mevalonic acid pathway enzyme, farnesyl pyrophosphate synthetase (FPPS) (23). These effects are divergent. For example risedronate has a low affinity for binding yet a strong effect on FPPS; while zoledronic acid has similar effects on FPPS yet a high affinity for binding to the crystal surface. How these differences translate into differences in clinical outcomes is unknown.

In the Intermittent Regimen intravenous Ibandronate Study (IRIS), IV ibandronate injections (1 mg and 2 mg every 3 months) produced increases in BMD (24) comparable to those seen with oral ibandronate in the oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE) (3) and similar to the effects observed with oral alendronate and risedronate (2-5, 25). Intermittent quarterly injections of 2 mg IV ibandronate also significantly reduced the risk of vertebral fractures by 62% in patients with corticosteroid-induced osteoporosis (26). The positive results from these studies led to the initiation of the Dosing IntraVenous Administration (DIVA) study, a registration trial investigating the optimal dose and dosing interval for intermittent IV ibandronate injections in postmenopausal osteoporosis. Non-inferiority analyses of the per-protocol population data at 1 year indicated that 3 mg every 3 months is at least as effective as the established daily oral ibandronate (2.5 mg) regimen that has proven fracture efficacy and is, in fact, superior to the daily regimen for increase in lumbar spine BMD (27). Increases in hip BMD at all sites were also greater in patients receiving IV rather than oral ibandronate. Corresponding intent-to-treat analyses supported these findings.

As renal adverse events have been observed with other IV bisphosphonates, this review aims to comprehensively examine the renal tolerability profile of IV ibandronate.

Measures of renal toxicity

There are various ways of assessing renal damage and toxicity, including tubular and glomerular damage (measured by urinary/serum markers) and renal failure (measured by creatinine clearance, serum creatinine levels or glomerular filtration rate [GFR]). The best biological sample for assessment of tubular and glomerular damage is a 24-hour urine collection. Measurements of the urinary excretion of high-molecular-mass proteins such as transferrin, IgG, and albumin are used as markers of glomerular damage and measurements of low-molecular-weight proteins, enzymes and kidney tissue proteins have been used to detect tubular damage (28, 29). Of the low-molecular-weight proteins excreted, measurement of retinol-binding protein or alpha-1-microglobulin is recommended for the detection of chronic renal tubular malfunction. Of the many enzymes that have been studied, urinary N-acetyl-beta-D-glucosaminidase or alanine aminopeptidase are recommended as being the most useful for the early detection of acute renal tubular damage.

GFR is accepted as the best overall measure of kidney function. Normal values, which are related to age, sex, and body size, are approximately 130 mL per minute per 1.73 m^2 in young men and 120 mL per minute per 1.73 m^2 in young women (30). Mean values decline as people age. GFR is measured as the urinary or plasma clearance of an ideal filtration marker such as inulin or of alternative exogenous markers. However, measuring clearance with the use of exogenous markers is complex, expensive, and difficult to do in routine clinical practice. Alternatively, urinary clearance of an endogenous filtration marker such as creatinine can be computed from a timed urine collection (for example, a 24-hour urine collection) and blood sampling during the collection period without the need for the administration of an exogenous marker.

Mechanisms of renal damage with bisphosphonate therapy

Currently, the mechanisms by which the bisphosphonates adversely affect renal tissue are unclear. However, differences between the bisphosphonates in the site and severity of action in the kidney are apparent in preclinical studies and these differences may be a result of the pharmacokinetic and pharmacological properties of the individual bisphosphonate (31, 32). Preclinical evidence has suggested that bisphosphonate-induced renal injury results from intracellular effects on the renal tubules, possibly mediated through the same mechanism as the bisphosphonates' action in osteoclasts (33). As such, renal tissue half-life, intracellular potencies and renal tissue kinetics are important considerations when examining differences in the bisphosphonates' renal tolerability.

It is possible that bisphosphonates that inhibit osteoclast function at low concentrations may have fewer effects on renal tubular cells (32). A relatively short renal half-life limits the exposure of renal cells to potentially high concentrations of drug and the possibility of accumulated cellular injury. In addition, intracellular concentrations of bisphosphonate could be influenced by factors affecting entry into and exit from cells, such as saturable cellular transport mechanisms and the extent of bisphosphonate-protein binding, which may result in intracellular accumulation of bisphosphonate and an increased risk of intracellular injury. These may be contributing factors in the differences observed in the bisphosphonates' renal tolerability, their margins of renal toxicity and the likelihood of accumulated damage (32).

Preclinical studies of renal tolerability with IV ibandronate

Findings from toxicology studies indicate that ibandronate is well tolerated, with a low potential for renal toxicity (34). Results from a preclinical study using very high nephrotoxic doses to investigate the patterns of renal injury, typical of different bisphosphonates, indicated that the degree and the pathological characteristics of renal toxicity differ between the bisphosphonates (21). In this study, signs of bisphosphonate nephrotoxicity, characterized by proximal convoluted tubule (PCT) degeneration and single cell necrosis, were seen in rats on day 4 after a single dose with ibandronate (1-20 mg/kg,) and zoledronic acid (3-10 mg/kg), and two doses of clodronate (two intraperitoneal injections of 200 mg/kg in 1 day). Ibandronate (≥10 mg/kg) and clodronate (2x200 mg/kg) showed tubular damage of similar severity and localization (P1 and P2 segments of the PCT), though mitoses and cytoplasmic vacuolation were increased with clodronate only. Zoledronic acid-induced damage was not restricted to this localization but extended further to the outer medulla, P3 segments of the tubules, and at the highest dose (10 mg/kg), to the distal tubules. The severity of damage was dose-dependent for both ibandronate and zoledronic acid, however, a stronger dose-effect relationship was observed with zoledronic acid.

The early stages of tubular damage in the single-dose study were not detected by clinical monitoring of renal safety using biochemical parameters (33). Consequently, such subclinical histological renal changes could go unnoticed during routine renal monitoring of long-term treatment and may accumulate until they reach clinically relevant levels. Such accumulation of subclinical damage has been observed previously in a rat model of chronic toxicity with zoledronic acid, but not with ibandronate (34). With ibandronate, minimally nephrotoxic (1 mg/kg) IV doses, given to rats as either a single dose or every 3 weeks for 25 weeks, resulted in similar parameters of histopathology, serum biochemistry and urinalysis, demonstrating no signs of accumulation of renal damage with intermittent dosing. The 3-week period between doses (equivalent to a 3-monthly interval in humans) provided sufficient time for recovery from any induced subclinical changes.

Further evidence that repeated administration of ibandronate is not associated with deterioration in renal function at 'therapeutic' doses is provided by a study conducted to examine the ability of ibandronate to increase bone volume in rats with normal or moderately impaired renal function (35). Ibandronate (1.25 mg/rat) or vehicle were administered subcutaneously once weekly for 3 weeks to rats with mild renal failure (induced by two-thirds nephrectomy) and to sham-operated rats with normal renal function. After 3 weeks, serum creatinine levels in the renally impaired rats given ibandronate were comparable to those observed in the sham-operated rats. Absence of renal damage following ibandronate administration was also demonstrated in a study of thyroparathyroidectomized rats chronically infused with parathyroid hormone-related protein (36). Ibandronate (0.001, 0.003 or 0.01 P/kg, administered daily for 4-6 days) was effective in inhibiting bone resorption, without adversely affecting GFR or the renal handling of sodium. Together, these preclinical studies consistently demonstrate the good renal safety of ibandronate, and provided a sound footing for its clinical development.

Clinical studies of renal tolerability with IV ibandronate

Renal tolerability in healthy volunteers

A pharmacokinetic/renal safety study of ibandronate was conducted in 57 healthy male and female volunteers. Ibandronate was administered as a 6 mg IV infusion over 15-60 minutes. Renal safety was assessed by measuring creatinine clearance, serum creatinine levels and the urinary excretion of albumin, urine transferrin, β_2-microglobulin, a_1-microglobulin and N-acetyl-β-D-glucosaminidase (NAG) prior to and on several days following each infusion. The pharmacokinetic exposures following the 15- and 60-minute infusions were similar for area under the curve (AUC) but maximal concentrations (C_{max}) were significantly higher following the 15-minute infusion compared with the 60-minute infusion. Despite this, shortening the infusion time to 15 minutes did not adversely affect the measured renal parameters in those subjects following the 15-minute infusion (37) (Fig. 1). No changes in serum creatinine concentrations, in creatinine clearance, or in the markers of tubular or glomerular damage were found. GFR and renal blood flow (measured by inulin and para-aminohippuric acid clearance) were also unchanged post treatment, demonstrating no evidence of renal dysfunction following ibandronate infusion.

Patients with age- or disease-related renal impairment

Clinical pharmacology studies were also carried out in patients with age- or disease-related renal impairment. Single IV injections of ibandronate (0.5 mg) were investigated in a study of patients with varying degrees of renal impairment (38). As expected for a renally excreted drug, the clearance of ibandronate in this small sample of patients (n=32) was found to be directly related to creatinine clearance, especially in patients with renal impairment classified as severe (<30 mL/minute). In

this study the lowest level of creatinine clearance was <30 mL/minute, representing stage 4 chronic kidney disease (39). Nevertheless, this clinical study found that the two- to three-fold increase in average systemic exposure to ibandronate in patients with severe renal impairment was well tolerated, even at doses that exceed the therapeutic dose. To adjust for this increased systemic exposure, a three-fold dose reduction from 6 mg to 2 mg IV ibandronate infused for 1 hour (<30 mL/minute) every 3-4 weeks is recommended in patients with metastatic bone disease and severe renal impairment (creatinine clearance <30 mL/minute) (40). No adjustment of the IV ibandronate dose is needed in patients with mild or moderate renal impairment (creatinine clearance ≥30 mL/minute). Monitoring of renal function, serum calcium, phosphate and magnesium is recommended according to clinical assessment of the individual patient (40).

Renal tolerability of IV ibandronate is also maintained when administered to renal transplant recipients to prevent post-transplantation osteoporosis. Ibandronate IV injections (1 mg) given immediately before and 3, 6 and 9 months after renal transplantation to 40 male and female patients effectively prevented bone loss and did not negatively affect graft function. In fact, the group treated with ibandronate showed significantly fewer rejection episodes than the control group. Ibandronate injections were well tolerated in these patients, with no signs of renal toxicity or differences in serum creatinine from the control group (41).

Patients with postmenopausal osteoporosis

The renal safety of intermittent IV ibandronate in women with postmenopausal osteoporosis has been evaluated at various dose levels in four randomized double-blind, multicenter treatment trials; three placebo-controlled trials, [the fracture study (42), a BMD study (IRIS; 24) and a dose-finding study (43)] and DIVA, a double-dummy, phase III, non-inferiority trial comparing the efficacy and safety of two intermittent IV ibandronate regimens with daily oral ibandronate (27). Table I describes the ibandronate dose, patient numbers and age ranges, duration of follow up and renal function assessments in these trials. A pooled safety database of these IV treatment studies, together with the pivotal oral ibandronate study (BONE), has enabled the evaluation of

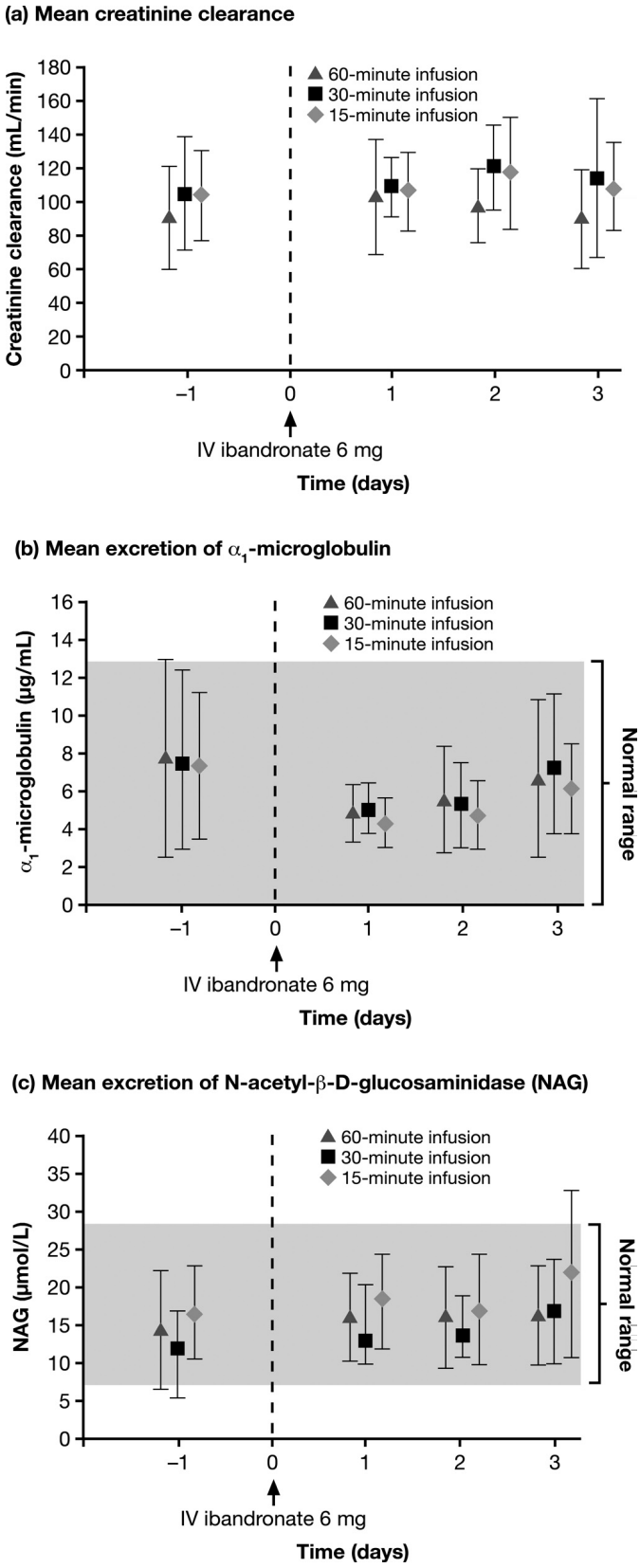

Fig. 1. Mean (±SD) creatinine clearance (a), mean excretion of α-microglobulin (b) and mean excretion of N-acetyl -β- -D-glucosaminidase (c) following infusion of IV ibandronate in healthy volunteers.

Table I. Overview of studies of women with postmenopausal osteoporosis who received 3-monthly IV ibandronate injections (0.25-2 mg) or placebo for 1-3 years.

Study	Ibandronate dose	Annual IV ibandronate dose (mg)	Patients evaluable for safety (n)	Mean age (years)	Duration of follow-up (years)	Measures of renal function (assessment times)
Thiebaud *et al*. 1997 (43) (dose finding)	Placebo 0.25mg q3mo 0.5 mg q3mo 1 mg q3mo 2 mg q3mo	 1 2 4 8	125	50-75	1	Adverse events (throughout) Serum creatinine (baseline and every 3 months)
Recker *et al*. 2004 (42) [fracture prevention]	Placebo 0.5 mg q3mo 1 mg q3mo	 2 4	2,860	52-76	3	Adverse events (throughout) Serum creatinine (baseline and every 3 months)
Adami *et al*. 2004 (24) [IRIS]	Placebo 1 mg q3mo 2 mg q3mo	 4 8	520	55-77	1	Adverse events (throughout) Serum creatinine Blood urea nitrogen Urine total protein Urine albumin a1-microglobulin (baseline and at 12 months)
Delmas *et al*. 2006 (27) [DIVA]	Oral 2.5 mg IV 2 mg q2mo IV 3 mg q3mo	 12 12	1,382	54–80	2 (1 year reported)	Adverse events (throughout) Serum creatinine (baseline and 4, 8 and 12 months (q2mo arm) or 3, 6, 9 and 12 months (q3mo arm). Blood urea nitrogen

q3mo once every 3 months, q2mo once every 2 months, IV intravenous.

Table II. Summary of absolute change in creatinine clearance per year by annual IV dose and proportion of patients with significant change in creatinine clearance over 1 year in pooled safety population (44).

		Ibandronate				
Change in creatinine clearance (mL/minute) per year	Placebo (n=2,078)	ACE 5.5 mg 2.5 mg daily (n=1,442)	ACE 2 mg IV 0.5 mg q3mo (n=977)	ACE 4 mg IV 1 mg q3mo (n=1,118)	ACE 8 mg IV 2 mg q3mo (n=283)	ACE 12 mg IV 2 mg q2mo or 3 mg q3mo (n=917)
n	1,959	1,373	928	1,059	275	886
Mean	-0.91	-0.28	-1.40	-0.72	-4.48	-0.90
SD	14.266	13.141	12.878	15.414	15.805	9.008
Median	0.00	0.00	0.00	0.00	–0.18	-0.82
Range	-121.3 to 119.1	-96.9 to 127.5	-68.4 to 75.8	-144.3 to 90.4	-51.8 to 85.1	-90.8 to 127.3
Patients with significant change in creatinine over 1 year (n, %)						
(a) Baseline <1.4 mg/dL and increased by ≥0.5 mg/dL	10 (0.5%)	3 (0.2%)	4 (0.4%)	3 (0.3%)	1 (0.4%)	6 (0.7%)
(b) Baseline ≥1.4 mg/dL and increased by ≥1.0 mg/dL	0	0	0	0	0	0
(c) Increased 2x baseline	2 (0.1%)	3 (0.2%)	0	0	0	1 (0.1%)
Total patients in (a), (b) or (c)	11 (0.5%)	3 (0.2%)	4 (0.4%)	3 (0.3%)	1 (0.4%)	6 (0.7%)

ACE annual cumulative exposure, q3mo once every 3 months, q2mo once every 2 months.

data from 3,295 patients exposed to IV ibandronate, 1,442 patients exposed to daily oral ibandronate (2.5 mg), and 2,078 patients who received placebo (44). Patients with severe renal impairment (serum creatinine >2.4 mg/dL [>210 mmol/L]) were excluded from the studies per-protocol but, due to the age-specific inclusion for recruiting patients, only 4.9% of patients had normal creatinine clearance (>90 mL/minute), whereas 44.5% and 50%, respectively, had mild (60-<90 mL/minute) or moderate (30-<60 mL/minute) renal impairment, and 0.4% had creatinine clearance below 30 mL/minute in post-hoc analysis of estimated GFR (eGFR).

From the pooled database (44), renal adverse events were reported in 2.5-5.6% of patients receiving IV ibandronate (2-12 mg annually) compared

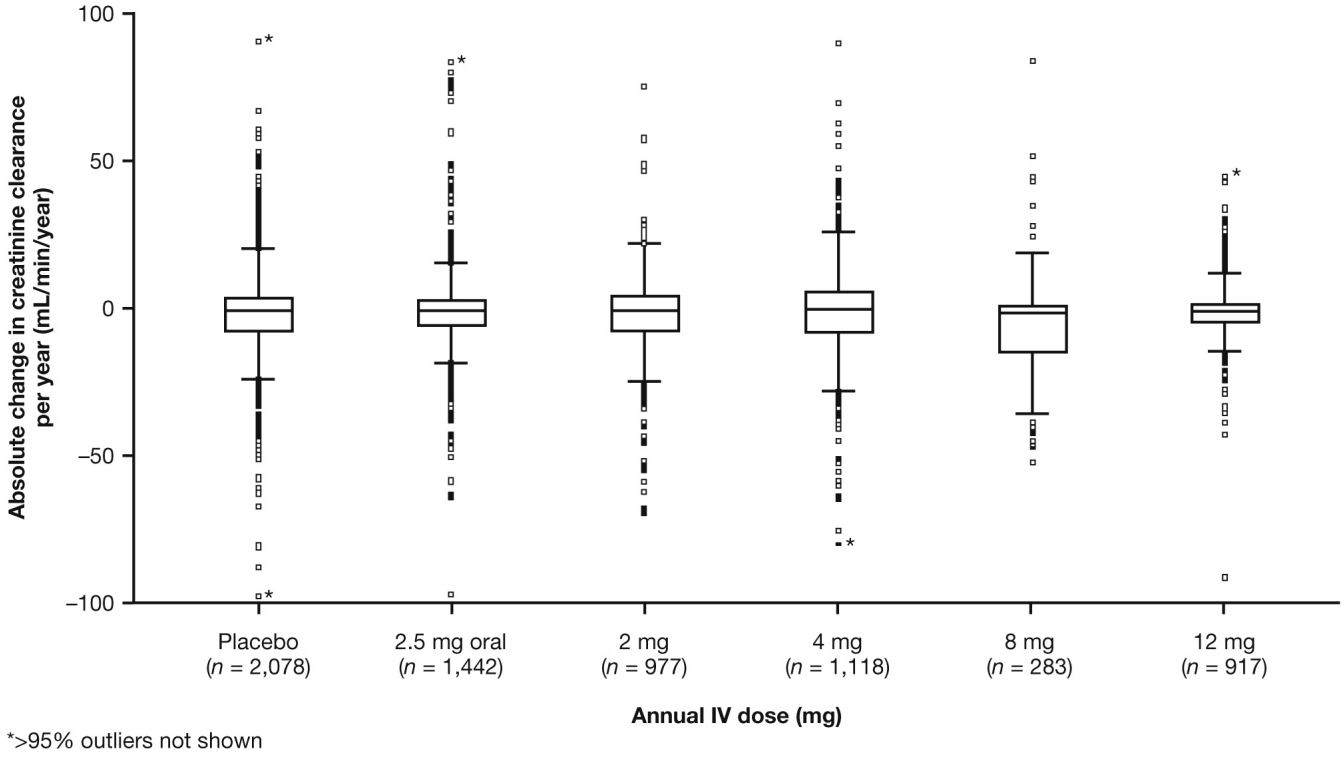

Fig. 2. Box and whiskers plot showing annual rate of change in creatinine clearance (median and interquartile range ±SD) with each total annual dose over 1 year (pooled studies) in women with postmenopausal osteoporosis.

with 5.3% of patients receiving oral daily ibandronate and 3.7% of patients receiving placebo. The most common renal adverse event was urinary tract infection, occurring in 1.1-3.7% of patients in the IV treatment groups and 3.2% and 2.4% of patients receiving daily oral ibandronate and placebo, respectively. Overall, no cases of acute renal failure were reported.

Estimated creatinine clearance was calculated using the Cockroft-Gault formula. The change in estimated creatinine clearance seen in patients treated with 12 mg IV ibandronate annually was similar to that of patients receiving oral ibandronate (2.5 mg) or placebo (Table II, Fig. 2). Across the studies, very few patients (0.2-0.7%) experienced a clinically relevant change in estimated creatinine clearance (Table II). The rate of change in estimated creatinine clearance was also assessed in relation to patients' renal function at baseline. As expected for a population of elderly women, the baseline creatinine clearance for almost all patients suggested mild or moderate renal impairment (60-<90 mL/min or 30-< 60 mL/minute, respectively). The proportion of patients with a shift of grade from moderate to severe was 7 out of 998 (0.7%) in the placebo group compared with 5 out of 437 (1.1%) in patients receiving the highest IV ibandronate dose of 12 mg annually (Table III).

These analyses indicate a lack of any negative effect of IV ibandronate on the renal function of women with postmenopausal osteoporosis, in the range of doses studied and for a 3-year treatment duration in patients with a baseline serum creatinine concentration <2.4 mg/dL or estimated creatinine clearance >30 mL/minute. Quarterly IV ibandronate injections (3 mg) were recently approved for the treatment of women with postmenopausal osteoporosis in the USA and the EU. Monitoring of renal function is not required in the EU. The US license recommends that patients who receive IV ibandronate injections should have serum creatinine measured prior to each dosage administration (45). It is also recommended that patients with concomitant medications that have the potential for adverse effects on the kidney should be assessed, as clinically appropriate, and that treatment should be withheld for renal deterioration (32). While there are no guidelines in the FDA label concerning the timing of measurement of the serum creatinine concentration or the level of any potential increase that should be of clinical concern, our opinions are that creatinine should be measured 1-2 weeks after ibandronate injection, and that a rise in serum creatinine concentration of >0.5 mg/dL should be considered clinically relevant and managed by clinical judgment. The same principle should be applied to monitoring the use of IV zoledronic acid. With zoledronic acid 5 mg/year there was an increase in serum creatinine concentration (day 9-11 after administration) of >0.5 mg/dL in 1.3% of patients compared with 0.4% receiving placebo (p=0.001) (46). These increases were transient and returned to baseline within 12 months.

Patients with secondary osteoporosis

The safety of intermittent IV ibandronate injections has also been investigated in patients with corticosteroid-induced osteoporosis and osteoporosis secondary to Crohn's disease. In a

Table III. Shifts of grade in creatinine clearance in the pooled database (44).

a) Placebo groups (n=2,078). From	<30	30–<60	60–<90	≥90	Missing
To					
<30	6	7	0	0	1
30 – <60	1	945	271	2	13
60 – <90	0	46	619	47	8
≥90	0	0	11	40	0
Missing	2	27	23	7	2
b) Ibandronate 12 mg annually (n=917) From	<30	30–<60	60–<90	≥90	Missing
To					
<30	2	5	0	0	0
30 – <60	2	412	103	0	0
60 – <90	0	20	297	21	0
≥90	0	0	7	21	0
Missing	0	19	8	0	0

3-year study in 115 men and women with established corticosteroid-induced osteoporosis, the adverse-event profile of 58 patients given 3-monthly ibandronate IV injections (2 mg) was comparable with that of patients given oral daily alfacalcidol, the active control (26). No cases of acute renal failure or clinically relevant changes in laboratory values were observed. Similarly, in a 27-month study, no cases of acute renal failure, nor any renal toxicity concerns, were observed in 35 men and women with Crohn's disease-related osteoporosis or osteopenia treated with 3-monthly IV ibandronate injections (1 mg) (47).

Patients with hypercalcemia of malignancy and metastatic bone disease

Extensive experience in hypercalcemia of malignancy and metastatic bone disease supports the good renal tolerability of IV ibandronate. In these indications, higher doses of bisphosphonate than those recommended in osteoporosis are required to relieve bone pain, reduce the frequency of skeletal complications and correct hypercalcemia. Nevertheless, in clinical trials conducted in both these indications, no evidence of renal toxicity has been observed regardless of dose administered and irrespective of whether given by a short infusion or an injection. In particular, the good renal tolerability profile of IV ibandronate is supported by the findings from a phase III trial in patients with newly diagnosed metastatic bone disease due to breast cancer (11). There was no major difference in adverse events in this 2-year trial amongst patients receiving placebo (n=158) or IV ibandronate every 3-4 weeks, given by infusion over 1-2 hours (6 mg, n=154). No evidence of renal toxicity was observed: the incidence of renal adverse events was comparable between the groups (4.5% and 4.0% in placebo and 6 mg IV ibandronate groups, respectively). The frequency of participants with an increase in creatinine levels was low and similar between treatment arms (2.6% for ibandronate 6 mg *vs.* 1.3% for placebo), and no patients withdrew due to renal adverse events. Post-hoc analysis examined time to renal function deterioration in this study, defined as an increase in serum creatinine of ≥1.0 mg/dL from a baseline of ≥1.4 mg/dL or an increase above baseline of twice the baseline value (48). Kaplan-Meier analysis showed similar rates of increases in serum creatinine in the ibandronate 6mg group and the placebo group: 2% *vs.* 4%, respectively, at 48 weeks and 6% versus 12%, respectively, at 96 weeks of treatment (NS, p=0.22).

In an additional, smaller treatment trial, the effects of a single IV injection of ibandronate (3 mg) on renal function were intensively studied in 15 normocalcemic breast cancer patients with bone metastases (49). No adverse clinical effects on kidney function were observed beyond slight transient proteinuria (highest protein concentration: 30 mg/dL). Serum creatinine and creatinine clearance, assessed at 2, 4, 7, 14, 21 and 28 days after the IV injection, were not significantly different from baseline (Table IV).

Post-marketing surveillance

In total, >500,000 patients with hypercalcemia of malignancy or bone metastases have been treated with IV ibandronate outside clinical trials. No cases of acute renal failure related to IV ibandronate treatment have been reported in patients without myeloma as a confounding diagnosis. The risk of acute renal failure is generally increased in patients with myeloma. Acute renal failure has been reported in a small number of ibandronate-treated patients with myeloma. Due to the presence of confounding factors, none are considered to definitely relate to ibandronate, although a contribution cannot be definitively ruled out.

Discussion

Intermittent IV bisphosphonates are well established in the treatment of metastatic bone disease and hypercalcemia of malignancy, and they are now becoming more established in the

Table IV. Serum creatinine and clearance following ibandronate IV injection (3 mg) in patients with bone metastases (mean [SEM]) (44).

	Baseline	Day 2	Day 4	Day 7	Day 14	Day 21	Day 28
Serum creatinine (mM)	87.5 (7.07)	84.9 (6.19)	82.2 (5.30)	80.4 (7.95)	85.8 (6.18)	82.2 (7.07)	84.9 (7.07)
Creatinine clearance (mL/minute)	62.2 (6.3)	65.2 (7.0)	64.3 (6.5)	68.1 (7.5)	61.6 (5.7)	65.4 (5.7)	64.8 (7.1)

management of postmenopausal osteoporosis.

Ibandronate has not been associated with renal failure or renal toxicity in patients randomized according to criteria for inclusion into the clinical trials. This good renal tolerability profile was predicted by preclinical toxicity studies, in which single and intermittent doses in excess of therapeutic levels in postmenopausal osteoporosis produced no clinically relevant renal damage in dogs and rats. Numerous clinical studies in various subjects and patient groups have confirmed that ibandronate has a favorable renal tolerability profile. In addition, studies of intermittent IV ibandronate injection in the management of postmenopausal osteoporosis have consistently demonstrated the tolerability of this regimen in patients with serum creatinine concentrations less than 2.4 mg/dL and eGFR >30 mL/minute (24, 42, 43, 50): no clinically significant renal concerns have been identified in approximately 4,000 women administered IV ibandronate injections in clinical trials. More specifically, estimated creatinine clearance in patients receiving IV ibandronate injections (0.25-3 mg over 15-20 seconds) remains stable, similar to that of patients receiving oral ibandronate and close to placebo values throughout the duration of treatment. A limited number of patients experienced a marked shift in creatinine clearance during the studies, with no evidence of a dose effect of IV ibandronate on renal function. These findings may not apply to patients with pre-existing conditions that predispose to renal adverse effects: patients with hypertension or diabetes, or to patients with age-related eGFR <30 mL/minute. More data are needed to assess renal safety in these latter populations.

Renal safety was also seen in the clinical studies in patients with metastatic bone disease or hypercalcemia of malignancy. No adverse renal effects of IV ibandronate (up to 6 mg every 3-4 weeks) were observed in these studies, despite the administration of high doses relative to those given for the treatment of postmenopausal osteoporosis. Similarly, no renal safety concerns or reports of renal failure have been identified in post-marketing surveillance of more than 500,000 patients with hypercalcemia of malignancy or bone metastases.

Importantly, the renal tolerability of IV ibandronate is maintained in patients with differing degrees of renal function (creatinine clearance >90 mL/minute, 40-70 mL/minute and in small sample sizes in a few patients with eGFR <30 mL/minute but not below 15 mL/minute [stage 5 CKD]) (37). Therefore, no IV ibandronate dose reduction is required in patients with mild or moderate renal impairment with eGFR >30 mL/minute. The effect of IV ibandronate in patients with severe renal impairment (GFR <30 mL/minute) requires additional evaluation. Good tolerability was also observed in studies of patients undergoing renal transplantation and in those undergoing hemodialysis. For the treatment of postmenopausal osteoporosis with IV ibandronate, monitoring renal function is not mandatory in Europe but left to the physician's discretion. In the USA, the FDA states that treatment with IV bisphosphonates has been associated with renal toxicity manifested as deterioration in renal function (*i.e.*, increased serum creatinine) so physicians should measure serum creatinine prior to each bisphosphonate injection, including ibandronate. It should be noted that IV ibandronate is contraindicated for patients with severe renal impairment. For the prevention of skeletal events in patients with breast cancer and bone metastases and for the treatment of tumor-induced hypercalcemia, again monitoring renal function is not mandatory in Europe.

The mechanisms that may be associated with the potential differences in renal damage among bisphosphonates have yet to be clarified. However, differences in their pharmacokinetic and pharmacological properties, such as tissue half-life and protein binding, may be contributing factors. Head-to-head studies between the IV bisphosphonates would be the best scientific means of comparing any potential differences in effects on GFR. In addition, more data are needed for all IV bisphosphonates in populations at higher risk for renal impairment (*e.g.*, hypertensives, diabetics, and patients with proteinuria or GFR <30 mL/minute).

In summary, the good renal tolerability of intermittent IV ibandronate injection in patients with an eGFR >30 mL/minute and without renal co-morbid conditions is reassuring. More data are needed to study the renal safety with all of the IV bisphosphonates in patients with hypertension and diabetes or other co-morbid conditions that might pre-dispose to adverse renal effects as well as in patients who fracture due to osteoporosis and have eGFR <30 mL/minute (51). More data are also needed from patients who are not part of a controlled clinical study to determine if their renal tolerability profiles differ from clinical trial patients. In addition, head-to-head studies among the IV bisphosphonates in comparable populations would be the most scientific manner to assess if there are clear-cut differences in renal effects.

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