

Renal safety in patients treated with bisphosphonates for osteoporosis: A review

Abbreviated title: Renal safety in osteoporosis

Paul D. Miller, MD¹; Sophie A. Jamal, MD, PhD, FRCP²; Pieter Evenepoel, MD³; Richard Eastell, MD, MD, FRCP, FRCPPath, FMedSci⁴; and Steven Boonen, MD, PhD⁵.

1. University of Colorado Health Sciences Center (P.D.M.), Colorado Center for Bone Research, Lakewood, CO 80277, USA; 2. Women's College Hospital (S.J.), University of Toronto, Ontario, Canada; 3. Nephrology Section (P.E.), Leuven University, B-3000 Leuven, Belgium; 4. Department of Human Metabolism (R.E.), University of Sheffield, Sheffield, UK.; and 5. Division of Gerontology and Geriatrics (S.B.), Leuven University, B-3000 Leuven, Belgium

Address all correspondence to:

Paul D Miller, M.D.

University of Colorado Health Sciences Center

Colorado Center for Bone Research

3190 S. Wadsworth Blvd

Lakewood, Colorado, 80227, USA

Telephone: 303-980-9985

Fax: 303-980-1367

Email: millercabr@aol.com

Address all requests for reprints to: Paul D Miller, M.D., University of Colorado Health

Sciences Center, Colorado Center for Bone Research, 3190 S., Wadsworth Blvd, Lakewood,

Colorado, 80227, USA. Email: millercabr@aol.com

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Abstract

Objective: Bisphosphonates are widely used for the treatment of osteoporosis and are generally well tolerated. However, the United States Food and Drug Administration safety reports have highlighted the issue of renal safety in bisphosphonate-treated patients. All bisphosphonates carry labeled “warnings” or a contraindication for use in patients with severe renal impairment (creatinine clearance <30 or <35 mL/min).

Methods: Data from pivotal trials and their extension studies of bisphosphonates approved for the management of osteoporosis were obtained via PubMed, and were reviewed with support from published perspective articles available on PubMed.

Results: Renal safety data in pivotal trials of oral alendronate and ibandronate for postmenopausal osteoporosis showed no short- or long-term effects on renal function. A study of risedronate reported decreases in urinary deoxyoyridineoline/creatinine in the treatment group but a retrospective analysis of phase III studies did not show any relationship between risedronate treatment and renal adverse events. Transient post infusion increases in serum creatinine have been reported in patients receiving intravenous ibandronate and zoledronic acid, however studies showed that treatment with zoledronic acid for up to 6 years did not result in long-term renal function deterioration in patients with osteoporosis.

Conclusions: All bisphosphonate therapies have “warnings” for use in patients with severe renal impairment. Clinical trial results have shown that even in elderly, frail osteoporotic patients with renal impairment, intravenous bisphosphonate therapy administration in accordance with the prescribing information did not result in long-term renal function decline. Physicians should follow guidelines for bisphosphonate therapies administration at all times.

Key terms: Bisphosphonates, renal impairment, osteoporosis, zoledronic acid, renal safety.

Introduction

Bisphosphonates effectively reduce fracture risk and have a high benefit to risk ratio for the treatment of osteoporosis. Bisphosphonates are commonly used in an aged population who often present with concomitant kidney diseases or age-related reductions in estimated glomerular filtration rate (eGFR). Given that bisphosphonates are eliminated from the body through the kidneys, it is important to understand the effect of long-term use of bisphosphonates on renal function. A United States Food and Drug Administration (FDA) safety newsletter reported 24 cases of renal impairment and acute renal failure between April 2007 and February 2009, associated with the use of zoledronic acid 5 mg in patients with osteoporosis (1). A second FDA drug safety communication reported an additional 11 cases of fatal acute renal failure and nine cases of renal injury requiring dialysis after zoledronic acid infusion between March 2009 and April 2011 (2). Subsequently, the prescribing information for zoledronic acid 5 mg was revised to include postmarketing surveillance data to reinforce existing warnings regarding renal safety, and to add a statement that zoledronic acid 5 mg is contraindicated in patients with creatinine clearance (CrCl) <35 mL/min and in those with evidence of acute renal impairment (the FDA accepted eGFR calculated by the Cockcroft-Gault formula (3) in lieu of a 24-hour urine collection for calculation of GFR by CrCl) (2,4).

Due to the mechanism of bisphosphonate excretion via the kidney, and the lack of clinical trial data in patients with osteoporosis and severe renal impairment (CrCl <30 mL/min), the oral bisphosphonates alendronate, risedronate and ibandronate and the intravenous (IV) bisphosphonates ibandronate and zoledronic acid all carry warnings regarding their use in patients with CrCl <30 mL/min (risedronate, oral and IV ibandronate) or <35 mL/min (alendronate) and recently for zoledronic acid, a “contraindication” for CrCl <35 mL/min (4,9).

As both osteoporosis and renal insufficiency become more prevalent with age (10) and bisphosphonates are the most widely prescribed treatment for osteoporosis, it is important for physicians to understand the impact of bisphosphonate therapies in osteoporotic patients with different levels of renal function. The aim of this review is to examine clinical data regarding renal safety in patients with osteoporosis treated with bisphosphonates and to discuss considerations for bisphosphonate use in osteoporotic patients with established CKD. Data from pivotal trials (including *post hoc* analyses) and their extension studies of approved bisphosphonates were obtained via PubMed, and were reviewed and discussed with support from published literature available on PubMed.

Bisphosphonates and the renal system

Bisphosphonates are not metabolized. Between 27% and 62% of the drug binds to bone mineral and the rest is excreted via the kidneys, predominantly within hours after administration (12,13). Renal excretion occurs by both passive glomerular filtration and active transport in renal proximal tubular cells (14,15).

In humans, early use of bisphosphonates to treat hypercalcemia due to malignancy highlighted three cases of renal failure following IV administration of high doses of etidronate and clodronate (16). Renal impairment such as toxic acute tubular necrosis, tubulointerstitial damage or focal segmental glomerulosclerosis has also been reported following administration of IV zoledronic acid every 3 to 4 weeks in patients with multiple myeloma or Paget's disease (Table 1)(21,22)(Joensuu TK Urol Int 2008;80:448-50; Henley Intern Med J 2005) However, all cases reported adopted the dosing regimen of zoledronic acid 4 mg once every 3 to 4 weeks, which is higher than the 5 mg once a year dosing for patients with osteoporosis (Zometa SmPC, Aclasta SmPC). No case reports of renal failures associating with once yearly zoledronic acid administration for osteoporosis have been published. Cancer patients are known to be at risk of

renal failure from compromised kidney function (17,18), and hypercalcemia, a consequence of multiple myeloma and some advanced solid tumors, can precipitate renal dysfunction (19,20).

Clinical data suggest that any potential renal damage associated with IV bisphosphonates may be infusion time– or dose-related. In a study comparing zoledronic acid with pamidronate in patients with bone lesions secondary to cancer, the dosing schedule of zoledronic acid was amended from 4 or 8 mg via a 5-minute infusion once every 3 or 4 weeks, to 4 mg via a 15-minute infusion owing to the high incidence of increased serum creatinine (SCr) levels among patients receiving zoledronic acid via a 5-minute infusion (23). After the amendments, no significant differences in changes in renal function were seen between the zoledronic acid 4 mg–treated and the pamidronate 90 mg–treated groups during the 25-month treatment period (23). A prostate cancer prevention trial also showed that a slower infusion rate (15 minutes) may improve renal safety compared with a rapid (5 minutes) infusion (24).

Concerns about the potential impact on renal function of IV bisphosphonates led to exclusion of patients with a SCr >1.27 mg/dL from the Fracture Intervention Trial (FIT) of alendronate (25); SCr >1.1 times the upper limit of normal from the Vertebral Efficacy with Risedronate Therapy MultiNational (VERT-MN) and VERT-North America (VERT-NA) studies of risedronate (26); and a SCr >2.4 mg/dL from the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE), Monthly Oral iBandronate in LadiEs (MOBILE)(Miller 2005 JBMR)(27) and. the Dosing IntraVenous Administration (DIVA) study of IV ibandronate (Eisman 2008 J Rheumatol). For trials of zoledronic acid, patients with a calculated CrCl <30 mL/min (3) were excluded from the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) clinical trial program (28–30).

Clinical evidence of the effect of bisphosphonates on renal function in patients treated for osteoporosis

Oral bisphosphonates

Alendronate was studied in the FIT and the FLEX studies but renal safety data were not specifically discussed in the primary publications of these studies. (Black 1998 Lancet; Black 2000 JCEM; Cummings 1998 JAMA; Black JAMA 2006) However, a *post-hoc* analysis of the FIT study of alendronate in women with postmenopausal osteoporosis, showed that alendronate (5 mg/day for 2 years and 10 mg/day for the third year) had no negative effect on renal function, even in patients with eGFR as low as 15 mL/min (Table 2)(25). A small but significant increase in SCr was seen between baseline and the 3-year follow-up ($P<0.00001$). However, the increase was the same across both the alendronate and placebo groups (mean increase in both groups: 0.01 ± 0.10 ; $P=0.88$) over the study period, and did not differ between patients with and without reduced renal function (25). No differences were found in bone mineral density (BMD) increases and antifracture efficacy for vertebral and all clinical fractures by renal function.

For risedronate, decrease in urinary deoxypyridinoline/creatinine by 26–33% from baseline to 6 months was reported in both risedronate 2.5 and 5.0 mg treatment groups in the VERT-MN study, compared with a reduction of up to 10% in the placebo group (Table 2; Reginster OI 2000); this difference was maintained throughout the 3-year study period. Renal safety results were not discussed specifically in the VERT-NA study publication, but a retrospective pooled analysis of phase III trials of risedronate 5 mg showed no significant differences between placebo and risedronate groups in changes from baseline in SCr at 6, 12 or 24 months. The overall incidence of renal function–related adverse events and the incidence of new vertebral fractures in risedronate-treated patients were similar across subgroups of patients with different levels of renal impairment (eGFR using the Cockcroft-Gault formula (3)), demonstrating that the vertebral antifracture efficacy of risedronate was not affected by the degree of renal impairment

(26). None of the oral bisphosphonate registration trials included patients with an eGFR <15 mL/min, so there are no data on patients with National Kidney Foundation (NKF)-defined stage 5 CKD.

The BONE study of oral ibandronate (2.5 mg daily or 20 mg every other day for 12 doses every 3 months) in patients with postmenopausal osteoporosis did not report any clinically relevant changes in laboratory markers (including renal function tests) for the placebo or ibandronate treatment groups over a 3-year period (Table 2)(27). Renal safety results were not included in the publication of the MOBILE study.(Reginster 2006 Ann Rheum Dis)

IV bisphosphonates

In the randomized, double-blind, 2-year DIVA study, 1395 women with postmenopausal osteoporosis received intermittent IV ibandronate (2 mg every 2 months or 3 mg every 3 months) or daily oral ibandronate 2.5 mg (Eisman 2008)(32). At baseline, CrCl values (estimated using the Cockcroft-Gault formula (3)) were <90 mL/min in 95.0% of patients and <60 mL/min in 50.5% of patients (32). The proportion of patients with a decline in CrCl at any time point was similar between the three treatment groups. The overall incidence of renal adverse events was low and similar across the treatment groups. No cases of acute renal failure were reported. After 2 years of treatment, 12 patients experienced clinically relevant changes in SCr but none of these cases was considered to be treatment-related (32).

In the HORIZON-Pivotal Fracture Trial (PFT), 7765 women with postmenopausal osteoporosis (mean age, 73 years) were randomized to receive zoledronic acid 5 mg once yearly (IV administration over 15 minutes) or placebo for 3 years (Table 2) (28). Patients were excluded from the trial if they had an estimated CrCl <30 mL/min by Cockcroft-Gault formula (3,33) at baseline or urine dipstick results of more than 2+ for protein, without evidence of contamination

or bacteriuria. A detailed analysis of the safety population showed no association between annual infusions of zoledronic acid 5 mg and long-term deterioration of renal function in patients with postmenopausal osteoporosis (Figure 1A), and a similar frequency of long-term changes in renal adverse events, impairments and function in the zoledronic acid– and placebo-treated groups (33). A gradual deterioration of renal function with time was observed in both the treatment and placebo groups, consistent with age-related renal deterioration. SCr measurements were taken 9 to 11 days after each infusion (n=5035) (28). Transient but significant increases in SCr were observed in 12 patients in the zoledronic acid group after the second infusion, compared with one patient in the placebo group ($P<0.002$; Figure 1B). The proportion of patients experiencing an increase >0.5 mg/100 mL from pre-infusion value in the zoledronic acid group was greatest in those with baseline estimated CrCl between 30–34 mL/min. Follow-up of these patients showed that SCr returned to within 0.5 mg/100 mL of pre-infusion values within 12 months (33). There was also no significant difference between zoledronic acid group and placebo after the first or third infusions (13 vs 6, 8 vs 13, respectively). In the subsequent extension study, significantly more patients experienced short-term rises in SCr 9–11 days after infusion in the group that received zoledronic acid for 6 years than those who received zoledronic acid for 3 years followed by placebo for 3 years (n=18 vs. n=4; $P=0.002$); however, these increases were transient and resolved with no overall long-term impact on renal function (Figure 2)(36,37).

In the HORIZON-Recurrent Fracture Trial (RFT), 2127 men and women who had experienced a recent, low-trauma hip fracture received zoledronic acid 5 mg once yearly (IV administration over 15 minutes) or placebo (Table 2)(29). SCr levels were measured at baseline and within 4 weeks before each annual infusion of the study drug. Approximately 75% of patients were female and the average age of the total population was 74 years, an older population than in the PFT. Coexisting conditions reported by trial participants included: hypertension, coronary artery

disease, osteoarthritis, previous stroke, depression and diabetes mellitus. Following treatment, the incidence of renal adverse events was similar across the zoledronic acid– and placebo-treated groups (increase in SCr >0.5 mg/dL, calculated CrCl <30 mL/min) (29).

In the HORIZON-Glucocorticoid-Induced Osteoporosis (GIO) study, 833 men and women with glucocorticoid-induced osteoporosis were randomized to receive once-yearly zoledronic acid 5 mg (IV administration over 15–20 minutes) or daily risedronate 5 mg for 1 year (Table 2)(30). Renal function was assessed by monitoring serum creatinine and calculated CrCl before treatment, 9–11 days after treatment had started, and at 3, 6 and 12 months. Patients in this study had coexisting conditions, with rheumatoid arthritis the most common (~40%). The number of patients with a SCr increase >44 µmol/L (>0.50 mg/dL) or CrCl <30 mL/min after drug administration were comparable between the two groups ($P=1.000$). Confirmed adjudicated clinically significant renal events occurred in nine patients receiving zoledronic acid and six receiving risedronate. Acute renal failure was reported for two patients in the risedronate group and one patient in the zoledronic acid group; all cases were considered to be related to underlying diseases (30).

Adding to data from the HORIZON-PFT, RFT and GIO studies are the results from the zoledronic acid male fracture study, in which there were no significant differences in long-term parameters of renal function (Table 3)(38).

Discussion

Subsequent to the approval of zoledronic acid 5 mg in 2007 for the treatment of postmenopausal osteoporosis, by April 2011, the FDA Adverse Event Reporting System had received 44 evaluable spontaneous postmarket cases of renal impairment and acute renal failure associated with zoledronic acid 5 mg(1,2). Details of these cases have been reported in

full in the FDA reports and are detailed below: More than half of the patients described in the first report (14/24) had underlying medical conditions that may have contributed to their risk of renal impairment or acute renal failure, or had concurrent exposure to known nephrotoxic medications (e.g. nonsteroidal anti-inflammatory drugs). Thirteen cases had documented transient increases in SCr following drug administration. Most patients improved following IV fluid administration or other supportive care. Four patients died from acute renal failure; however, these patients also had other comorbidities (such as chronic diabetic renal disease, chronic pulmonary obstructive disease or hypertension) that may have contributed death due to acute renal failure (1).

Whilst the cases of acute renal function reported above are important for clinicians to be aware of, there are a number of factors related to renal function that should be taken into consideration in treating patients with osteoporosis. Renal function is known to decline with age, with the reduction in GFR usually beginning after 30–40 years of age, with the potential for acceleration after 50–60 years. This decline is associated with structural and functional changes in the kidneys (40). There may also be differences in the pathophysiology of age-related reductions in GFR compared with reductions in GFR due to intrinsic renal disease, proteinuria or ongoing kidney damage (41). Recent studies have indicated that combining proteinuria with eGFR may provide a better predictive model for progression of chronic kidney disease (42). In addition, the NKF classification of chronic kidney disease categorizes eGFR >90 mL/min (up to 110 mL/min) as Stage 1 and 90–60 mL/min as stage 2, only if the patient also has proteinuria (34). However, data on proteinuria have not been included in the publications of the pivotal trials of bisphosphonates.

Regardless of treatment, data from the third National Health Assessment and Nutritional Examination Survey (NHANES III) indicates that impaired renal function is seen in a high proportion of both men and women aged ≥ 20 years, who have osteoporosis (10). Early CKD

(GFR <60 mL/min) may also be associated with an approximate doubling of the hazard ratio for hip fractures as compared with patients (age-adjusted) exhibiting normal renal function (43–45). The reasons why fracture risk appears to be greater in early stages of CKD (eGFR <60 mL/min) are unknown, but the effect of elevated PTH levels,(Hruska K 2004 Seminar Nephrology) and early phosphorus retention on bone might, in part, explain the increase in bone resorption or altered bone strength in these patients (46–48). In addition, fibroblast growth factor 23, which rises in serum in early CKD before PTH increases and is a strong risk factor for all-cause mortality, may impair bone mineralization and be an additional factor explaining the greater fracture risk in early CKD (49–51). Hypothetically, these are interesting associations since fracture risk reduction as well as reduction in all-cause mortality has been observed with bisphosphonates even in an elderly and frail population (28,52).

In patients with more severe (stage 4-5) CKD, clinicians should also be aware of the possibility of adynamic bone disease, an indication that shares many clinical features with osteoporosis such as, low bone mass risk of fractures, but is associated with low PTH and bone turnover.(Cannata-Andía JB, et al. J Nephrol 2012) In these cases, further suppression of bone turnover is not recommended.(Miller 2011 Bone) Calcium and vitamin D treatment may also need to be used cautiously because they may enhance vascular calcification in these patients who have very low capacity of calcium uptake in the bone compartment.(Frazão JM, Martins P. Curr Opin Nephrol Hypertens 2009;18:303-7) Given that BMD are poorly correlated with fracture risk in patients with CKD,(Cannata-Andía JB, et al. J Nephrol 2012) PTH measurement and histomorphometry assessment are recommended for patients with CKD stage 4-5 (eGFR, 30–60 mL/min).; and, perhaps more severe stage 3B CKD (GFR 45-30 ml/min) especially if they have PTH levels < 100 pg/ml.(Miller 2011 Bone) Potential management of adynamic bone disease include reduction of calcium and vitamin D load to restore parathyroid activity, and prevention of other risk factors known to induce PTH oversuppression.(Cannata-Andía JB, et al.

J Nephrol 2012; Frazão JM, Martins P. Curr Opin Nephrol Hypertens 2009;18:303-7). While anabolic agents (e.g. parathyroid hormone) have been used in subjects with idiopathic adynamic bone disease, there are no well designed studies in this area.

Data from the NHANES surveys suggest that the prevalence of moderate renal impairment is underestimated when SCr is used instead of eGFR to screen for CKD (53). Use of eGFR may, therefore, be of particular importance in older adults who are more likely to have lower creatinine values due to lower muscle mass (53) or poor protein intake (54). Many commercial laboratory reports automatically report eGFR using the Modification of Diet in Renal Disease (MDRD) equation (11,55). Both the Cockcroft-Gault formula and the MDRD are accurate, practical predictors of eGFR but neither has a linear relationship to the most accurate eGFR measurements, inulin clearance or iodothalamate determinations (56). If either eGFR result needs clinical confirmation, well-hydrated and carefully collected 24-hour urine for CrCl could be considered (57). A recently developed Chronic Kidney Disease Epidemiology Collaboration eGFR equation has been shown to have improved precision, accuracy and mortality risk prediction compared with MDRD, and is recommended for routine clinical use (58–60).

Given the prevalence of kidney impairment in patients with osteoporosis, it is critical that clinicians know which patients are suitable for treatment with specific bisphosphonates (61). Although the oral bisphosphonates carry warnings on their use in patients with severe renal impairment, renal function did not change between treatment and placebo groups in clinical studies on alendronate, risedronate and oral ibandronate (25,26). A prospective, randomized trial in women with osteoporosis or osteopenia found no significant differences in blood urea nitrogen, creatinine and eGFR between baseline and 12 months for patients receiving risedronate, alendronate or raloxifene, suggesting that use of these agents in patients with osteoporosis did not cause a change in renal function (31). A recent retrospective cohort study

in 122,727 patients aged ≥ 66 years with a fragility fracture also found that oral bisphosphonate use was not associated with acute kidney injury (62).

Clinical studies of IV bisphosphonates reported cases of transient increases in SCr following drug administration but no long-term impact in kidney function has been reported. In a prospective, randomized open-label study of IV ibandronate (3 mg every 3 months) given by bolus injection versus 15-minute infusion versus oral alendronate (70 mg/week) in 801 postmenopausal women considered to be at increased risk for renal disease; the effect of the three therapies on renal function were similar, suggesting that injection of ibandronate had a similar renal safety profile as a slower infusion (35). For zoledronic acid, similar incidences of renal adverse events, impairments and function were reported for the zoledronic acid- and placebo-treated groups (28), even in an older study population and in those who had received IV zoledronic acid for up to 6 years (35). As none of the patients in the zoledronic acid pivotal studies had biochemical changes that could suggest CKD-MBD, it is unknown whether the responses observed in these trials would vary in patients with known intrinsic kidney disease or unresolved secondary hyperparathyroidism (42,63,64). Although the renal tissue half-life of ibandronate is shorter than zoledronic acid (24 vs 150–200 days), (Perazella 2008 Kidney Int) no data comparing the renal effects of IV ibandronate with IV zoledronic acid in a randomized population have been published, and there is no scientific evidence establishing any differences on renal effects between these two bisphosphonates.

Clinicians wishing to prescribe bisphosphonates to patients with osteoporosis are advised to check their patients' CrCl or eGFR prior to initiating treatment and ensure that they adhere to prescribing instructions. We recommend that in patients with marginal eGFR values, a well-hydrated 24-hour CrCl should be performed for GFR calculation before clinical management decisions are made with regard to bisphosphonate use. For zoledronic acid IV administration

should be over a period of no less than 15 minutes and patients must be adequately hydrated prior to the infusion. In addition, clinicians should make an assessment of any concomitant medication that a patient may be taking, with special regard to potentially nephrotoxic therapies.

Conclusion

All bisphosphonates have registration “warnings” for use in patients with severe renal impairment (CrCl <30 or <35 mL/min). IV zoledronic acid has included a “contraindication” in the registration labels for patients with eGFR <35 mL/min (2). This contraindication is primarily due to the way bisphosphonates are excreted from the body, via glomerular filtration and tubular secretion, and from the post-marketing reports of acute renal failure and deaths in a small number of patients. There is little evidence that oral bisphosphonates are associated with renal impairment in clinical trials, and these medications are effective in reducing fracture risk and increasing BMD in patients (by *post hoc* analysis) with eGFR >15 mL/min. Results from clinical trials of IV bisphosphonates for osteoporosis have shown that even in elderly patients with existing fracture, administration in accordance with the prescribing information does not result in long-term renal function decline and is efficacious in preventing fracture at all skeletal sites over 6 years of administration. The parenteral formulations of therapies for postmenopausal osteoporosis are invaluable for patients intolerant to oral bisphosphonates, patients with pre-existing esophageal disease, or in whom there is uncertainty regarding the absorption, given that most oral bisphosphonates are poorly absorbed in the gastrointestinal tract. In order to maximize this benefit to risk ratio of bisphosphonates, it is important that physicians follow the registered guidelines for administration at all times. When used according to the label, IV bisphosphonates are well tolerated and can even be used in elderly patients whose eGFR is >35 mL/min.

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Table 1. Case reports of renal events in patients receiving zoledronic acid (21,22)(Joensuu 2008; Henley 2005)

Patient	Renal-related comorbidities	Bisphosphonate treatment	Clinical presentation and histology
59-year-old male with multiple myeloma (21)	Long-standing renal insufficiency	Pamidronate 90 mg monthly for 13 months then switch to zoledronic acid 4 mg monthly	4 months after switching to zoledronic acid: <ul style="list-style-type: none"> • SCr increased from 1.9 to 4.0 mg/dL • 24-hour urine protein, 1.08 g/day • Biopsy revealed toxic ATN
73-year-old female with Paget's disease (21)	Acute renal failure	Pamidronate 90 mg monthly for 21 months then switch to zoledronic acid 4 mg monthly	After 4 doses of zoledronic acid: <ul style="list-style-type: none"> • SCr increased from ~1.5 to 3.8 mg/dL • 24-hour urine protein, 2 g/day • Biopsy revealed toxic ATN
57-year-old female with multiple myeloma (21)	NR	Pamidronate 90 mg monthly for 2 years and 9 months then switch to zoledronic acid 4 mg monthly	8 months after switching to zoledronic acid: <ul style="list-style-type: none"> • SCr increased from 1.3 to 2.5 mg/dL • 24-hour urine protein, 194 mg/day to 1.3 g/day • Biopsy revealed toxic ATN
75-year-old male with multiple myeloma (21)	NR	Pamidronate 90 mg monthly for 22 months then switch to zoledronic acid 4 mg monthly	By the 4 th dose of zoledronic acid: <ul style="list-style-type: none"> • SCr increased from 1.4 to 1.7 mg/dL (levels continued to increase to 2.6 mg/dL after treatment discontinuation for 2 months) • Urinalysis showed absence of protein • Biopsy revealed toxic ATN
85-year-old male with multiple myeloma (21)	NR	Pamidronate 90 mg for 2 doses then switch to zoledronic acid 4 mg monthly	After 3 doses of zoledronic acid: <ul style="list-style-type: none"> • SCr increased from 1.6 to 3.8 mg/dL • Biopsy revealed toxic ATN 1 month after zoledronic acid discontinuation <ul style="list-style-type: none"> • SCr reached 5.5 mg/dL • 24-hour urine protein, 1.7 g/day

66-year-old male with multiple myeloma (21)	NR	Pamidronate 90 mg monthly for 4 months then switch to zoledronic acid 4 mg monthly	After 4 doses of zoledronic acid: <ul style="list-style-type: none"> • SCr increased from 1.0 to 2.0 mg/dL • 24-hour urine protein, 2.6 g/day • Biopsy revealed toxic ATN
65-year-old male with multiple myeloma (22)	NR	Zoledronic acid 4 mg (9 doses), 3.3 mg (1 dose)	After 9 doses of zoledronic acid, SCr levels was 2.39 mg/dL Shortly after the 10 th dose: <ul style="list-style-type: none"> • SCr levels reached 4.6 mg/dL • Patient reported heavy proteinuria, hypoalbuminemia and acute renal failure with nephrotic syndrome • Biopsy showed focal segmental glomerulosclerosis
74-year-old male with bone metastases (Joensuu 2008)	NR	Zoledronic acid 4 mg infused over 15 minutes every 3 or 4 weeks for 14 months	Steady increase in SCr that reached above normal range after 10 months of therapy; increases continued over the subsequent 4 months until treatment discontinuation month
72-year-old female with multiple myeloma (Henley 2005)	NR	Zoledronic acid 4 mg monthly	After 5 th dose of zoledronic acid, SCr increased from 0.67 to 4.28 mg/dL but subsequently stabilized after 2 weeks at 1.88 mg/dL with CrCl of 23 mL/min
57-year-old male with multiple myeloma (Henley 2005)	NR	Zoledronic acid 4 mg monthly	4 weeks after zoledronic acid administration, SCr increased from 2.49 to 12.22 mg/dL; biopsy showed tubulointerstitial damage

ATN, acute tubular necrosis; CrCl, creatinine clearance; NR, not reported; SCr, serum creatinine .
Conversion factor for SCr from mg/dL to $\mu\text{mol/L}$ is 88.4.

Table 2. Clinical evidence of the effect of bisphosphonates on renal function (25–33)

Study details	Dosage	Renal function effects
<i>Oral bisphosphonates</i>		
FIT subanalysis in women with postmenopausal osteoporosis (n=6438)(25)	Alendronate vs. placebo; 3-year follow-up	Small significant increase in SCr from baseline to 3 years in both groups
VERT-MN study in women with postmenopausal osteoporosis (n=1226)(Reginster OI 2000)	Risedronate 2.5 mg, risedronate 5 mg vs placebo; 3-year follow-up	Decrease in urinary deoxypyridinoline/creatinine by 26% and 33% from baseline to 6 months in the risedronate 2.5 and 5 mg groups, respectively; decrease up to 10% was reported in the placebo group; the difference remained throughout the study period
Risedronate pooled analysis of Phase III studies (n=9883) in women with osteoporosis (91% renal impairment at baseline – subdivided into severe, moderate and mild)(26)	Risedronate 5 mg daily or placebo for up to 3 years	No significant difference in SCr changes between placebo and risedronate groups; overall incidence of renal function-related adverse events similar across all renal impairment subgroups
BONE study in women with postmenopausal osteoporosis (n=2946)(27)	Oral ibandronate 2.5 mg daily or 20 mg every other day for 12 doses every 3 months	No clinically relevant changes in laboratory markers (including renal function tests) reported for placebo or ibandronate groups over 3 years

<i>IV bisphosphonates</i>		
DIVA study in women with postmenopausal osteoporosis (n=1395) (32)(Eisman 2008)	Intermittent IV ibandronate (2 mg every 2 months or 3 mg every 3 months) or daily oral ibandronate (2.5 mg) for 2 years (only 1-year data are shown)	Low incidence of renal adverse events; no acute renal failure reported; 12 cases of clinically relevant changes in SCr from baseline but none was considered to be treatment-related
HORIZON-PFT: Women with postmenopausal osteoporosis (n=7765) (28,33)	Zoledronic acid 5 mg once yearly (IV administration over 15 minutes) or placebo for 3 years	No significant between group differences in SCr or CrCl at 3 years. No association between zoledronic acid 5 mg and long-term renal function deterioration; Age-related deterioration of renal function over time observed in both zoledronic acid and placebo groups
HORIZON-RFT: Men and women with low-trauma hip fracture (n=2127) (29)	Zoledronic acid 5 mg once yearly (IV administration over 15 minutes) or placebo	Renal adverse events similar across zoledronic acid 5 mg and placebo groups
HORIZON-GIO: Men and women with glucocorticoid-induced osteoporosis (n=833); Prevention/treatment cohorts (30)	Once-yearly zoledronic acid 5 mg (IV administration over 15–20 minutes) or daily risedronate 5 mg for 1 year	Clinically significant renal events in 2% zoledronic acid patients + 1.4% risedronate patients; 3 cases acute renal failure related to underlying disease

CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; FIT, Fracture Intervention Trial; GIO, Glucocorticoid-induced Osteoporosis; PFT, Pivotal Fracture Trial; RFT, Recurrent Fracture Trial; SCr, serum creatinine

Table 3. Renal laboratory values and changes in the male fracture study of zoledronic acid (37)

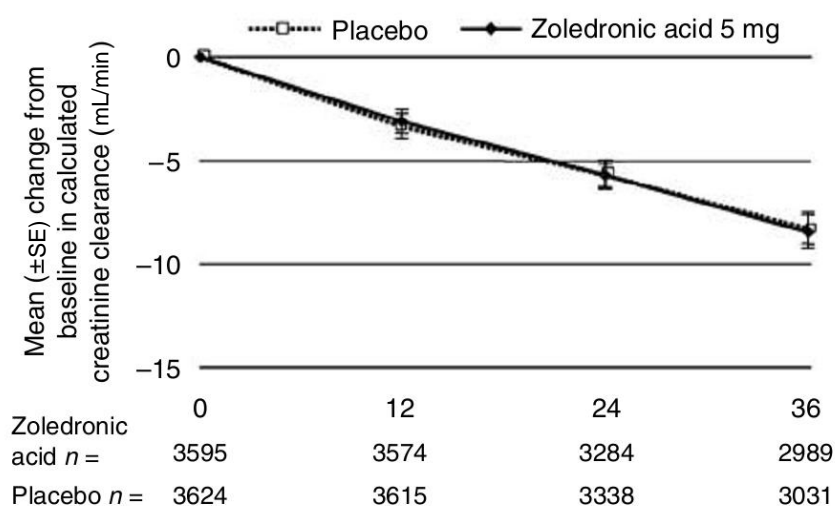
	Zoledronic acid, N=588 n/N (%)	Placebo, N=611 n/N (%)
Increase in SCr >0.5 mg/dL	14/584 (2.4)	18/610 (3.0)
Treatment emergent CrCl <30 mL/min	3/557 (0.5)	9/577 (1.6)
Baseline CrCl ≤60 mL/min and decreased at least 30%	6/90 (6.7)	10/112 (8.9)

For the criterion of CrCl <30 mL/min, only subjects with a baseline CrCl ≥30 mL/min are included; the criterion of baseline CrCl ≤60 mL/min and decreased at least 30%, only subjects with a baseline CrCl ≤60 mL/min are included.

CrCl, creatinine clearance; SCr, serum creatinine.

Renal safety during the 3 year HORIZON-PFT

(A)



(B)

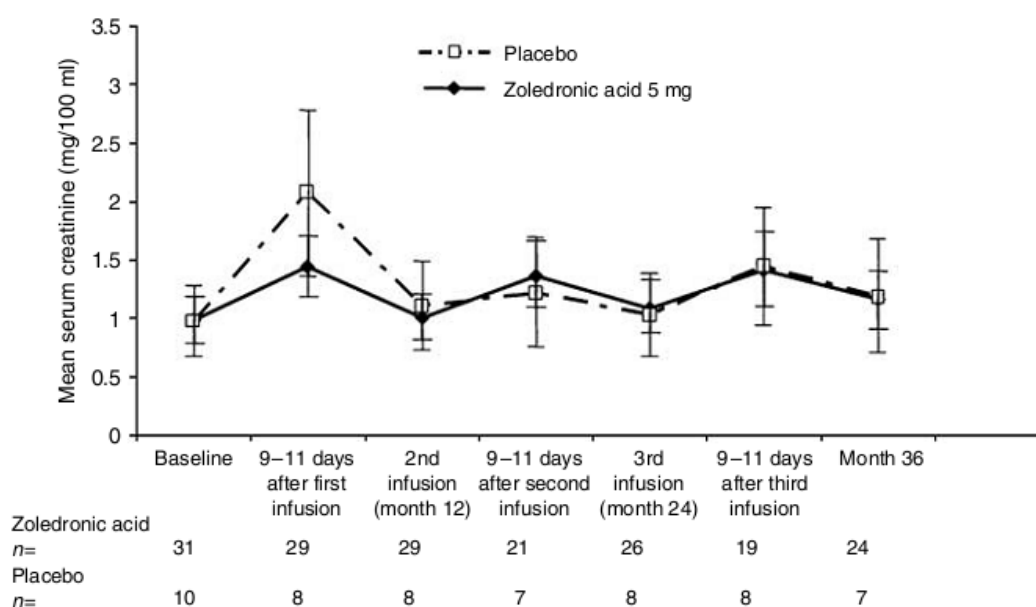


Figure. 1(A) Mean change in estimated creatinine clearance (safety population) during the HORIZON-PFT (33). At month 36, the mean (\pm SE) decrease from baseline in estimated creatinine clearance was similar between patients treated with 5 mg of zoledronic acid (-8.75 ± 0.175 mL/min) and those treated with placebo (-8.67 ± 0.175 mL/min). **(B)** Mean serum creatinine levels in patients with pre- to post- infusion change of >0.5 mg/100 mL from baseline

to 36 months in the HORIZON-PFT (33). For each infusion, the patients treated with 5 mg of zoledronic acid showed similar mean serum creatinine levels at 9–11 days post-infusion and also at 12 months post-infusion. Figures reprinted from Boonen and colleagues, with permission from the International Society of Nephrology.

HORIZON-PFT, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial; SE, standard error.

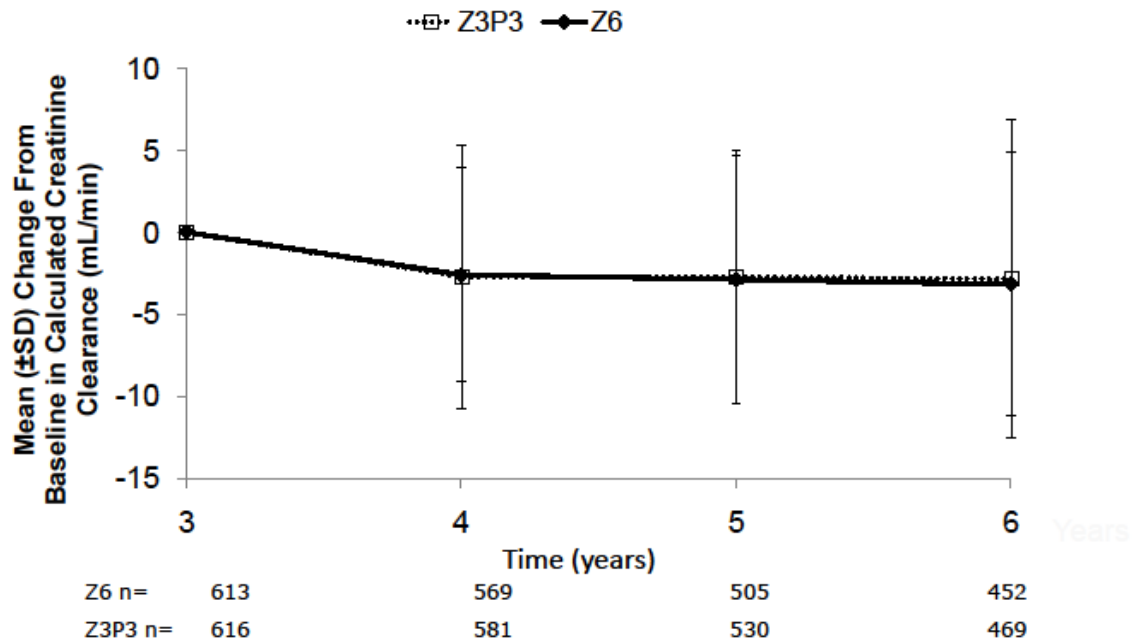


Figure. 2 Mean changes in calculated creatinine clearance from the baseline of the HORIZON-PFT extension study (year 3 of the HORIZON-PFT trial) to year 6 were comparable for zoledronic acid vs. placebo (safety population) (37). Figure reprinted from Miller and colleagues, with permission from Springer.

HORIZON-PFT, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial; Z6, patient group receiving zoledronic acid 5 mg for 6 years; Z3P3, patient group receiving zoledronic acid 5 mg for 3 years followed by placebo for 3 years.