

Renal Safety in Patients Treated With Bisphosphonates for Osteoporosis: A Review

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ABSTRACT

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). 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 articles available on PubMed. Renal safety analyses of pivotal trials of oral alendronate, risedronate, and ibandronate for postmenopausal osteoporosis showed no short-term or long-term effects on renal function. Transient postinfusion increases in serum creatinine have been reported in patients receiving intravenous ibandronate and zoledronic acid; however, studies showed that treatment with these agents did not result in long-term renal function deterioration in clinical trial patients with osteoporosis. 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. © 2013 American Society for Bone and Mineral Research.

KEY WORDS: BISPHOSPHONATES; RENAL IMPAIRMENT; OSTEOPOROSIS; ZOLEDRONIC ACID; RENAL SAFETY

Introduction

Osteoporosis is a major public health concern with rising prevalence resulting from the increasing longevity in many regions.⁽¹⁾ A number of pharmacological options are available for the management of osteoporosis. They include bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid), estrogens (estrogen and/or hormone therapy), estrogen agonist/antagonist (raloxifene), parathyroid hormone (PTH[1–34], teriparatide), and the receptor activator of NF- κ B (RANK) ligand inhibitor, denosumab.⁽²⁾ Available in both oral and parenteral preparations, bisphosphonates are widely regarded as the drug class of choice for the prevention of fractures in postmenopausal women.⁽¹⁾ This class of drug constitutes the focus of this review.

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 U.S. 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.⁽³⁾ 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.⁽⁴⁾ 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

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1 statement that zoledronic acid 5 mg is contraindicated in
2 patients with creatinine clearance (CrCl) <35 mL/min and in
3 those with evidence of acute renal impairment (the FDA
4 accepted eGFR calculated by the Cockcroft-Gault formula⁽⁵⁾ in
5 lieu of a 24-hour urine collection for calculation of GFR by
6 CrCl).^(4,6)

7 As a result of the mechanism of bisphosphonate excretion via
8 the kidney, and the lack of clinical trial data in patients with
9 osteoporosis and severe renal impairment (CrCl <30 mL/min),
10 the oral bisphosphonates alendronate, risedronate, and ibandronate
11 and the intravenous (IV) bisphosphonates ibandronate
12 and zoledronic acid all carry warnings regarding their use in
13 patients with CrCl <30 mL/min (risedronate, oral and IV
14 ibandronate) or <35 mL/min (alendronate) and recently for
15 zoledronic acid, a "contraindication" for CrCl^{O1} <35 mL/min.⁽⁶⁻⁹⁾

16 As both osteoporosis and renal insufficiency become more
17 prevalent with age⁽¹⁰⁾ and bisphosphonates are the most widely
18 prescribed treatment for osteoporosis, it is important for
19 physicians to understand the impact of bisphosphonate
20 therapies in osteoporotic patients with different levels of renal
21 function. The aim of this review is to examine clinical data
22 regarding renal safety in patients with osteoporosis treated with
23 bisphosphonates and to discuss considerations for bisphosphonate
24 use in patients who have osteoporosis and chronic kidney
25 disease (CKD) (but who do not require renal dialysis). Data from
26 pivotal trials (including post hoc analyses) and their extension
27 studies of approved bisphosphonates were obtained via
28 PubMed, and were reviewed and discussed with support from
29 published literature available on PubMed. A comprehensive
30 search of postmarketing surveillance data was also performed
31 through the European Medicines Agency (EMA) and FDA
32 websites.

33 **Bisphosphonates and the Renal System**

34 Bisphosphonates are stable analogues of the inorganic com-
35 pound, pyrophosphate, in which the P-O-P backbone of the
36 molecule has been replaced by P-C-P.⁽¹¹⁾ The presence of a
37 carbon atom allows for the attachment of side chains, the
38 modification of which differentiates first-generation and second-
39 generation bisphosphonates (eg, clodronate and pamidronate,
40 respectively) from third-generation compounds (eg, zoledronic
41 acid).⁽¹¹⁾ Third-generation bisphosphonates typically contain a
42 heteroaromatic ring with at least one nitrogen atom as part of
43 their side chains and have improved antiresorptive effect
44 compared with early generations.⁽¹¹⁾ These nitrogen-containing
45 bisphosphonates have improved potency over early generations
46 because their antiresorptive effect is mediated via inhibition of
47 the mevalonate pathway, whereas the non-nitrogen-containing
48 bisphosphonates act by interfering with adenosine triphos-
49 phate-dependent intracellular pathways.⁽¹²⁾

50 Bisphosphonates are not metabolized. Between 27% and 62%
51 of the drug binds to bone mineral and the rest is excreted via the
52 kidneys, predominantly within hours after administration.^(13,14)
53 Renal excretion occurs by both passive glomerular filtration and
54 active transport in renal proximal tubular cells.^(15,16)

55 In humans, early use of bisphosphonates to treat hypercalce-
56 mia due to malignancy highlighted three cases of renal failure

57 following IV administration of high doses of etidronate and
58 clodronate.⁽¹⁷⁾ Such cases of nephrotoxicity may occur secondary
to the formation of aggregates within the blood.^(18,19) Renal
impairment such as toxic acute tubular necrosis, tubulointer-
stitial damage, or focal segmental glomerulosclerosis have
also been reported following IV administration of the third-
generation bisphosphonate, zoledronic acid, every 3 to 4 weeks
in patients with multiple myeloma or Paget's disease
(Table 1).⁽²⁰⁻²³⁾ In contrast to the mechanism by which first-
generation bisphosphonates lead to renal failure, it is believed
that the nephrotoxicity that may occur secondary to administra-
tion of third-generation bisphosphonates is caused—at least in
part—by inhibition of the mevalonate pathway.^(10,24) All
reported cases of zoledronic acid-associated renal impairment
involved the dosing regimen of zoledronic acid 4 mg once every
3 to 4 weeks, which is higher than the 5 mg once-per-year dosing
for patients with osteoporosis.⁽²⁵⁾ Moreover, cancer patients (eg,
patients with multiple myeloma or some advanced solid tumors)
are known to be at risk of renal failure from compromised kidney
function and hypercalcemia.⁽²⁶⁻²⁹⁾

Clinical data suggest that any potential renal damage
associated with IV bisphosphonates may be infusion time-
related 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.⁽³⁰⁾ This change was made because
of the high incidence of increased serum creatinine (SCr) levels
among patients receiving zoledronic acid via a 5-minute
infusion.⁽³¹⁾ 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.⁽³⁰⁾ A prostate cancer
prevention trial also showed that a slower zoledronic acid
infusion rate (15 minutes) may improve renal safety compared
with a rapid (5-minute) infusion.⁽³¹⁾

Concerns about the potential impact on renal function of
bisphosphonates led to exclusion of patients above a predefined
SCr threshold in earlier studies: SCr >1.27 mg/dL for the Fracture
Intervention Trial (FIT) of alendronate⁽³²⁾; SCr >1.1 times the
upper limit of normal for the Vertebral Efficacy with Risedronate
Therapy MultiNational (VERT-MN) and VERT-North America (VERT-
NA) studies of risedronate⁽³³⁾; and SCr >2.4 mg/dL for the Oral
Ibandronate Osteoporosis Vertebral Fracture Trial in North
America and Europe (BONE),⁽³⁴⁾ the Monthly Oral Ibandronate
in Ladies (MOBILE) trial,⁽³⁵⁾ and the Dosing IntraVenous
Administration (DIVA) study of IV ibandronate.⁽³⁶⁾ These early
bisphosphonate trials excluded patients on the basis of SCr rather
than GFR because, at the time, it was not appreciated that SCr—
which is derived from skeletal muscle—is an inadequate means
of estimating GFR. More recent clinical trials have used eGFR or
actual GFR in the study inclusion/exclusion criteria. For example,
patients with an estimated CrCl <30 mL/min were excluded from
the Health Outcomes and Reduced Incidence with Zoledronic
Acid Once Yearly (HORIZON) clinical trial program of zoledronic
acid⁽³⁷⁻³⁹⁾ and those with an actual GFR <35 mL/min were
excluded from the Designed for Intravenous (IV) Ibandronate
Renal Safety Evaluation (DIVINE) study.⁽⁴⁰⁾

Table 1. Case Reports of Renal Events in Patients Receiving Zoledronic Acid^(20–23)

Patient	Renal-related comorbidities	Bisphosphonate treatment	Clinical presentation and histology ^a
59-year-old male with multiple myeloma ⁽²⁰⁾	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: SCr increased from 1.9 to 4.0 mg/dL; 24-hour urine protein, 1.08 g/d; biopsy revealed toxic ATN
73-year-old female with Paget's disease ⁽²⁰⁾	Acute renal failure	Pamidronate 90 mg monthly for 21 months then switch to zoledronic acid 4 mg monthly	After 4 doses of zoledronic acid: SCr increased from ~1.5 to 3.8 mg/dL; 24-hour urine protein, 2 g/d; biopsy revealed toxic ATN
57-year-old female with multiple myeloma ⁽²⁰⁾	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: SCr increased from 1.3 to 2.5 mg/dL; 24-hour urine protein, 194 mg/d to 1.3 g/d; biopsy revealed toxic ATN
75-year-old male with multiple myeloma ⁽²⁰⁾	NR	Pamidronate 90 mg monthly for 22 months then switch to zoledronic acid 4 mg monthly	By the fourth dose of zoledronic acid: 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 ⁽²⁰⁾	NR	Pamidronate 90 mg for 2 doses then switch to zoledronic acid 4 mg monthly	After 3 doses of zoledronic acid: SCr increased from 1.6 to 3.8 mg/dL; biopsy revealed toxic ATN; 1 month after zoledronic acid discontinuation: SCr reached 5.5 mg/dL; 24-hour urine protein, 1.7 g/d
66-year-old male with multiple myeloma ⁽²⁰⁾	NR	Pamidronate 90 mg monthly for 4 months then switch to zoledronic acid 4 mg monthly	After 4 doses of zoledronic acid: SCr increased from 1.0 to 2.0 mg/dL; 24-hour urine protein, 2.6 g/d; biopsy revealed toxic ATN
65-year-old male with multiple myeloma ⁽²¹⁾	NR	Zoledronic acid 4 mg (9 doses), 3.3 mg (1 dose)	After 9 doses of zoledronic acid, SCr levels were 2.39 mg/dL. Shortly after the 10th dose: 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 ⁽²²⁾	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
72-year-old female with multiple myeloma ⁽²³⁾	NR	Zoledronic acid 4 mg monthly	After fifth 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 ⁽²³⁾	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

SCr = serum creatinine; ATN = acute tubular necrosis; NR = not reported; CrCl = creatinine clearance.

^aConversion factor for SCr from mg/dL to μmol/L is 88.4.

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.^(41–44) However, a post hoc analysis of the FIT study of alendronate in women with postmenopausal osteoporosis showed that alendronate (5 mg/d for 2 years and 10 mg/d for the third year) had no negative effect on renal function, even in patients with eGFR as low as 15 mL/min (Table 2^(45–48)).⁽³²⁾ No differences were found in bone mineral density (BMD) increases and antifracture efficacy for vertebral and all clinical fractures by renal function.⁽³²⁾ The odds ratio (OR) for clinical fracture after alendronate therapy was 0.84 (95% confidence interval [CI], 0.45–1.54) in patients with eGFR <45 mL/min compared with 0.74 (95% CI, 0.61–0.91) in those with moderately reduced or normal eGFR (≥ 45 mL/min) (interaction $p = 0.72$). For spinal fractures, the OR was 1.01 (95% CI, 0.29–3.6) for those with eGFR <45 mL/min and 0.62 (95% CI, 0.36–1.10) for those with moderately reduced or normal eGFR (interaction $p = 0.19$).⁽⁴³⁾

For risedronate, renal safety results were not discussed specifically in the VERT-NA study publication,⁽⁴⁹⁾ 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 (Fig. 1).⁽³³⁾ The overall incidence of renal function-related adverse events did not differ statistically or clinically either within or between treatment groups in those patients with severe (CrCl <30 mL/min; risedronate versus placebo 3% versus 3%; relative risk [RR], 0.80; 95% CI, 0.31–2.04), moderate (CrCl ≥ 30 –<50 mL/min; 1% versus 2%; RR, 0.88; 95% CI, 0.53–1.45), or mild (CrCl ≥ 50 –<80 mL/min; 1% versus 2%; RR, 0.63; 95% CI, 0.37–1.07) renal impairment. The incidence of new vertebral fractures in risedronate-treated patients was also similar ($p = 0.124$) across subgroups of patients with different levels of renal impairment (eGFR using the Cockcroft-Gault formula).^(5,33) These data demonstrate that the vertebral antifracture efficacy of risedronate was not affected by these degrees of renal impairment.⁽³³⁾ Additionally, a prospective, randomized trial in women with osteoporosis or osteopenia found no significant differences in blood urea nitrogen (BUN), SCr, and eGFR between baseline and 12 months for patients receiving risedronate, alendronate, or raloxifene.⁽⁴⁵⁾ Moreover, between baseline and 12 months, the mean value of SCr remained unchanged and mean eGFR increased in all three treatments groups. These results suggest that use of these agents in patients with osteoporosis did not cause a change in renal function.⁽⁴⁵⁾

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).⁽³⁴⁾ Renal safety results were not included in the publication of the MOBILE study.⁽⁵⁰⁾ 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.

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.^(56,46) At baseline, CrCl values (estimated using the Cockcroft-Gault formula⁽⁵⁾) were <90 mL/min in 95.0% of patients and <60 mL/min in 50.5% of patients.⁽⁴⁶⁾ The proportion of patients with a decline in CrCl at any time point was similar between the three treatment groups (daily oral ibandronate 2.5 mg, 14.1%; 2 mg every 2 months, 14.1%; 3 mg every 3 months, 17.3%) and the overall incidence of renal adverse events was low and similar across the treatment groups (daily oral ibandronate 2.5 mg, 2%; 2 mg every 2 months, 3%; 3 mg every 3 months, 2%). 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.⁽⁴⁶⁾ The effect of IV ibandronate on renal function has also been compared with that of oral alendronate. In the prospective, randomized open-label DIVINE study, 801 postmenopausal women considered to be at increased risk for renal disease received IV ibandronate (3 mg every 3 months) given by bolus injection or 15-minute infusion, or oral alendronate (70 mg/week). The effects of the three therapies on renal function were similar (percentage change from baseline in GFR at month 9: ibandronate bolus, $-1.3\% \pm 7.14\%$ [SD]; ibandronate infusion, $-0.5\% \pm 7.86\%$; oral alendronate, $-1.6\% \pm 5.89\%$), suggesting that injection and slow infusion of ibandronate had similar renal safety profiles.⁽⁴⁰⁾

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).⁽³⁷⁾ Patients were excluded from the trial if they had an estimated CrCl <30 mL/min by the Cockcroft-Gault formula^(5,47) 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, and a similar frequency of long-term (3-year) changes from baseline in renal adverse events, impairments and function in the zoledronic acid-treated and placebo-treated groups (increase in serum creatinine >0.5 mg/100 mL: zoledronic acid, 36/3022 [1.19%]; placebo, 38/3066 [1.24%]; $p = 0.907$; estimated CrCl <30 mL/min: zoledronic acid, 97/2994 [3.24%]; placebo, 96/3035 [3.16%]; $p = 0.884$).⁽⁴⁷⁾ 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 ($n = 5035$).⁽³⁷⁾ 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 ($p < 0.002$; Fig. 2A). The proportion of patients

Table 2. Clinical Evidence of the Effect of on Renal Function^(32–34,36–39,45–46)

Type of bisphosphonate	Study details	Dosage	Renal function effects ^a
Oral bisphosphonates	FIT subanalysis in women with postmenopausal osteoporosis (<i>n</i> = 6438) ⁽³²⁾	Alendronate versus placebo; 3-year follow-up	Small significant increase in SCr from baseline to 3 years in both groups
	Risedronate pooled analysis of Phase III studies (<i>n</i> = 9883) in women with osteoporosis (91% renal impairment at baseline, subdivided into severe, moderate, and mild) ⁽³³⁾	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 (<i>n</i> = 2946) ⁽³⁴⁾	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
	Postmenopausal women with osteoporosis or osteopenia (<i>n</i> = 127) ⁽⁴⁵⁾	Alendronate 70 mg weekly, risedronate 35 mg weekly or raloxifene 60 mg daily for 12 months	No significant differences in blood urea nitrogen, creatinine, and eGFR seen between baseline and 12 months
IV bisphosphonates	DIVA study in women with postmenopausal osteoporosis (<i>n</i> = 1395) ^(36,46)	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 (<i>n</i> = 7765) ^(37,47)	Zoledronic acid 5 mg once yearly (IV infusion 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 (<i>n</i> = 2127) ⁽³⁸⁾	Zoledronic acid 5 mg once yearly (IV infusion 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 (<i>n</i> = 833); Prevention/treatment cohorts ⁽³⁹⁾	Once-yearly zoledronic acid 5 mg (IV infusion 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; three cases acute renal failure related to underlying disease
	Study in men with osteoporosis (<i>n</i> = 1199) ⁽⁴⁸⁾	Once-yearly zoledronic acid 5 mg (IV infusion over 15–30 minutes)	Increased in SCr >0.5 mg/dL occurred in 2.4% (14/584) patients receiving zoledronic acid, and 3.0% (18/610) patients receiving placebo; CrCl < 30 mL/min at any time during the study was reported in 0.5% (3/557) zoledronic acid-treated patients, and 1.6% (9/577) placebo-treated patients; CrCl was calculated using the Cockcroft-Gault formula ⁽⁵⁾

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

^aConversion factor for SCr from mg/dL to μmol/L is 88.4.

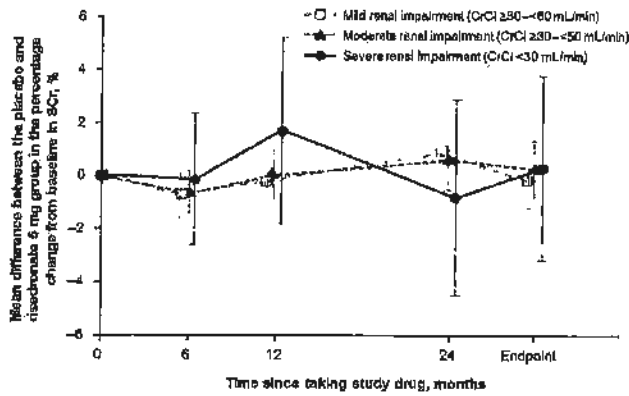


Fig. 1. Mean (95% confidence interval) difference between the placebo and risedronate 5-mg treatment groups in the percentage change from baseline in serum creatinine at 6, 12, and 24 months and at the endpoint (last postbaseline visit).⁽³³⁾ Results were based on the analysis of nine randomized, double-blind, placebo-controlled, parallel-group, phase III trials of risedronate 5 mg daily treatment. Mean differences are shown for the severe (CrCl, <30 mL/min), moderate (CrCl, ≥30–<50 mL/min), and mild (CrCl, ≥50–<80 mL/min) renal impairment subgroups. Negative values imply that decreases from baseline in serum creatinine were greater in the risedronate group than in the placebo group. Figure reprinted from Miller and colleagues,⁽³³⁾ with permission from John Wiley and Sons. CrCl was calculated using the Cockcroft-Gault method.⁽⁴⁵⁾ CrCl = creatinine clearance; SCr = serum creatinine.

experiencing an increase >0.5 mg/100 mL from the preinfusion value in the zoledronic acid group was greatest in those with baseline estimated CrCl between 30 and 34 mL/min. Follow-up of these patients showed that SCr returned to within 0.5 mg/100 mL of preinfusion values within 12 months.⁽⁴⁷⁾ There was also no significant difference between the zoledronic acid and placebo groups after the first or third infusions (13 versus 6, 8 versus 13, respectively), in the subsequent extension study, significantly more patients experienced short-term rises in SCr 9 to 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 ($n=18$ versus $n=4$; $p=0.002$); however, these increases were transient and resolved with no overall long-term impact on renal function (Fig. 2B).^(48,51) These data demonstrated that three annual infusions of zoledronic acid have no significant effect on eGFR⁽³⁷⁾ and that any effect on SCr—even in patients who have received six annual zoledronic acid infusions—is transient.^(37,51)

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).⁽³⁹⁾ 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

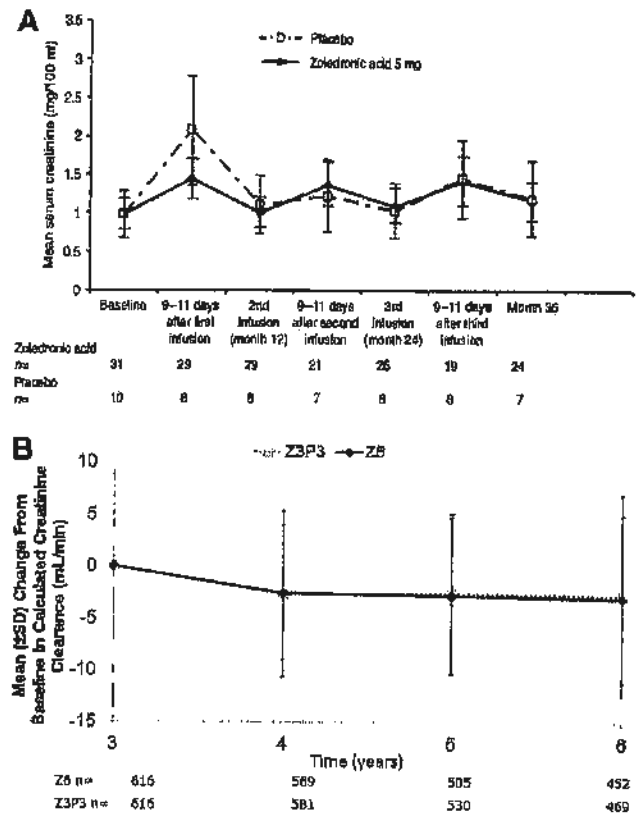


Fig. 2. (A) Mean serum creatinine levels in patients with preinfusion to postinfusion change of >0.5 mg/100 mL from baseline to 36 months in the HORIZON-PFT.⁽⁴⁷⁾ For each infusion, the patients treated with 5 mg of zoledronic acid showed similar mean serum creatinine levels at 9 to 11 days postinfusion and also at 12 months postinfusion. Figure reprinted from Boonen and colleagues,⁽⁴⁷⁾ with permission from the International Society of Nephrology. (B) 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 versus placebo (safety population).⁽⁴⁸⁾ Figure reprinted from Miller and colleagues⁽⁵²⁾ with permission from Springer. Conversion factor for SCr from mg/dL to $\mu\text{mol/L}$ is 88.4. 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.

similar across the zoledronic acid-treated and placebo-treated groups (increase in SCr >0.5 mg/dL, 6.2% versus 5.6%; calculated CrCl <30 mL/min, 8.2% versus 7.3%).⁽³⁸⁾

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).⁽³⁹⁾ Renal function was assessed by monitoring serum creatinine and calculated CrCl before treatment, 9 to 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 numbers of patients with an SCr increase of >44 $\mu\text{mol/L}$ (zoledronic acid, $n=8$; placebo, $n=6$) or CrCl <30 mL/min (zoledronic acid, $n=4$; placebo, $n=4$) after drug administration

were comparable between the two groups ($p = 1.000$ for both). 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.⁽³⁹⁾

Adding to data from the HORIZON-PFT, HORIZON-RFT, and HORIZON-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 2).⁽⁵²⁾ As in the HORIZON clinical trial program, patients with a baseline eGFR <30 mL/min were excluded from this study.

Postmarketing Evidence of the Effect of Bisphosphonates on Renal Function

Clinical trials have the advantage that all safety outcomes are recorded, follow-up is good, and the risks of particular adverse events can be calculated. Postmarketing surveillance reports, on the other hand, may reflect the real-world situation in clinical practice, in which patients may have more comorbidities than subjects randomized into clinical trials. 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 postmarketing cases of renal impairment and acute renal failure associated with zoledronic acid 5 mg.^(3,4) Details of these cases have been reported in full in the FDA reports and are detailed below. More than one-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 (eg, 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 to death due to acute renal failure.⁽³⁾ These data led to the revision of the prescribing information for zoledronic acid 5 mg in the United States.⁽⁴⁾ A similar process led to updating of the Summary of Product Characteristics in Europe in response to postmarketing reports.⁽⁵³⁾

Discussion

Bisphosphonates, when used in accordance with the prescribing information, have demonstrated favorable renal safety results in clinical studies in patients with osteoporosis. Although cases of acute renal failure reported in postmarketing reports are important, 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: the reduction in GFR usually begins after 30 to 40 years of age and has the potential to decline at a faster rate after 50 to 60 years of age.⁽⁵⁴⁾ This decline is associated with structural and

functional changes in the kidneys.⁽⁵⁴⁾ 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.⁽⁵⁵⁾ Recent studies have indicated that combining proteinuria with eGFR may provide a better predictive model for progression of CKD than assessment of GFR alone.⁽⁵⁶⁾ In addition, the NKF classification of CKD categorizes eGFR >90 mL/min (up to 110 mL/min) as stage 1 and 90 to 60 mL/min as stage 2, only if the patient also has proteinuria.⁽⁵⁷⁾ 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) indicate 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.⁽⁵⁸⁻⁶⁰⁾ 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,⁽⁶¹⁾ and early phosphorus retention on bone might, in part, explain the increase in bone resorption or altered bone strength in these patients.⁽⁶²⁻⁶⁴⁾ 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.⁽⁶⁵⁻⁶⁷⁾ Hypothetically, these are interesting associations because fracture risk reduction as well as reduction in all-cause mortality has been observed with bisphosphonates even in an elderly and frail population.^(37,52)

In patients with severe CKD, clinicians should also be aware of the possibility of adynamic bone disease, a low bone turnover bone disease that shares many clinical features with osteoporosis such as low bone mass and increased risk of fractures, but is associated with low PTH and low bone turnover.⁽⁶⁹⁻⁷²⁾ In these cases, further suppression of bone turnover may not be recommended, because there is a hypothetical link between lowering bone turnover and increasing vascular calcification.^(62,73,74) Calcium and vitamin D treatment must also be used judiciously because they may enhance vascular calcification in these patients, who have very low capacity for calcium uptake in the bone compartment.⁽⁷⁵⁾ Given that BMD is poorly correlated with fracture risk in patients with stage 4 to 5 CKD,^(69,76) measurement of PTH and bone-specific alkaline phosphatase (BSAP) and/or histomorphometry assessment may be needed in selected patients with CKD stage 4 to 5 (eGFR <30 mL/min) in order to discriminate between osteoporosis and adynamic bone disease.^(62,77) A recent comprehensive review of quantitative histomorphometry and PTH/BSAP values suggests that combining PTH and BSAP may offer a higher positive predictive value for adynamic bone disease than measuring either PTH or low BSAP alone.⁽⁷⁷⁾

Potential management of adynamic bone disease includes reduction of calcium and vitamin D load to restore parathyroid activity, and prevention of other risk factors known to induce PTH oversuppression.^(69,75)

1 Data from the NHANES surveys suggest that the prevalence of
2 moderate renal impairment is underestimated when SCr is used
3 instead of eGFR to screen for CKD.⁽⁷⁸⁾ Use of eGFR may, therefore,
4 be of particular importance in older adults who are more likely to
5 have lower creatinine values due to lower muscle mass or poor
6 protein intake.^(78,79) Many commercial laboratory reports automati-
7 cally report eGFR using the Modification of Diet in Renal Disease
8 (MDRD) equation.^(80,81) Both the Cockcroft-Gault formula and the
9 MDRD are accurate, practical predictors of eGFR but neither has a
10 linear relationship to the most accurate eGFR measurements, inulin
11 clearance or iodothalamate determinations.⁽⁸²⁾ If either eGFR result
12 needs clinical confirmation, well-hydrated and carefully collected
13 24-hour urine for CrCl could be considered.⁽⁸³⁾ A recently
14 developed Chronic Kidney Disease Epidemiology Collaboration
15 eGFR equation has been shown to have improved precision,
16 accuracy, and mortality risk prediction compared with MDRD, and
17 is recommended for routine clinical use.^(84–86)

18 Given the prevalence of kidney impairment in patients
19 with osteoporosis, it is critical that clinicians know which
20 patients are suitable for treatment with specific bisphospho-
21 nates.⁽⁸⁷⁾ Although the oral bisphosphonates carry warnings on
22 their use in patients with severe renal impairment, renal function
23 did not change between treatment and placebo groups in clinical
24 studies on alendronate, risedronate, and oral ibandronate.^(32,33) A
25 recent retrospective cohort study in 122,727 patients aged ≥ 66
26 years with a fragility fracture also found that oral bisphosphonate
27 use was not associated with acute kidney injury.⁽⁸⁸⁾

28 Clinical studies of IV bisphosphonates reported cases of acute
29 and transient increases in SCr following drug administration but
30 no long-term impact in kidney function has been reported. For
31 zoledronic acid, similar incidences of renal adverse events,
32 impairments, and function were reported for the zoledronic
33 acid–treated and placebo-treated groups over the duration of
34 the trials,⁽³⁷⁾ even in an older study population and in those who
35 had received IV zoledronic acid for up to 6 years.⁽⁴⁰⁾ Because
36 none of the patients in the zoledronic acid pivotal studies had
37 biochemical changes that could suggest CKD–mineral and bone
38 disorder (MBD), it is unknown whether the responses observed in
39 these trials would vary in patients with known intrinsic kidney
40 disease or unresolved secondary hyperparathyroidism.^(56,89,90)
41 Although the renal tissue half-life of ibandronate is shorter than
42 zoledronic acid (24 versus 150–200 days),⁽⁹¹⁾ no data comparing
43 the renal effects of IV ibandronate with IV zoledronic acid in a
44 randomized population have been published, and there is no
45 scientific evidence establishing any differences on renal effects
46 between these two bisphosphonates.

47 Clinicians wishing to prescribe bisphosphonates to patients
48 with osteoporosis are advised to check their patients' CrCl or
49 eGFR prior to initiating treatment and ensure that they adhere to
50 prescribing instructions. We recommend that in patients with
51 marginal eGFR values, a well-hydrated 24-hour CrCl should be
52 performed for GFR calculation before clinical management
53 decisions are made with regard to bisphosphonate use. For
54 zoledronic acid, IV administration should be over a period of no
55 less than 15 minutes and patients must be adequately hydrated
56 prior to the infusion. In addition, clinicians should make an
57 assessment of any concomitant medication that a patient may be
58 taking, with special regard to potentially nephrotoxic therapies.

Conclusion

Bisphosphonates—a class of drug that is available in both oral and parenteral preparations—have historically been associated with a low incidence of renal adverse events. This review of clinical trial and postmarketing surveillance data has shown that, if used with care and in accordance with the prescribing information, these agents can be administered to patients with various degrees of renal impairment, with no long-term decline in renal function. This applies to both oral and IV bisphosphonates. Clinical trials have shown little evidence of an association between oral bisphosphonate administration and renal impairment, and these medications are effective in reducing fracture risk and increasing BMD in patients (by post hoc analysis) with eGFR > 15 mL/min. Moreover, results from clinical trials of IV bisphosphonates have shown that, even in elderly osteoporotic 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.

Although bisphosphonates are generally well tolerated in clinical studies, the low incidence of renal adverse events has led to the inclusion of “warnings” on the prescribing information of all bisphosphonates regarding the use of these agents in patients with severe renal impairment (CrCl < 30 or < 35 mL/min). For IV zoledronic acid, this warning constitutes a “contraindication” in the registration labels for patients with eGFR < 35 mL/min.⁽⁴⁾ This contraindication—which does not alter the positive benefit-to-risk balance for the product⁽⁵³⁾—is primarily a result of the way bisphosphonates are excreted from the body, via glomerular filtration and tubular secretion. The parenteral formulations of therapies for postmenopausal osteoporosis are invaluable for patients intolerant to oral bisphosphonates, patients with preexisting esophageal disease, and those in whom there is uncertainty regarding gastrointestinal absorption. In view of their efficacy in preventing osteoporotic fractures, bisphosphonates are clearly beneficial in these patient groups. However, as with any drug, it is important that physicians follow the prescribing information for administration at all times, in order to maximize the benefit-to-risk ratio associated with administration.

This review has clearly shown that the benefit-to-risk ratio for all bisphosphonates is very favorable when they are used according to the label in the right patient populations for the right duration, and that IV bisphosphonates—which have an established renal safety profile when used according to prescribing information—can even be used in the majority of patients, including those who are elderly, as long as their eGFR is > 35 mL/min.^(92,93) These drugs therefore constitute an important and effective part of the physician's pharmacological armamentarium.

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