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Renal toxicity in patients with multiple myeloma receiving zoledronic acid vs. ibandronate: A retrospective medical records review

ABSTRACT

Aims: This retrospective study investigated the rates of renal impairment in patients with multiple myeloma treated with zoledronic acid and ibandronate.

Materials and Methods: We retrospectively reviewed medical records in a German oncology clinic, from May 2001 to December 2005. Creatinine measurements were analyzed from baseline (before zoledronic acid or ibandronate treatment) to last evaluation for each patient. A total of 84 patients were included.

Results: Zoledronic acid increased the risk of renal impairment by approximately 3-fold compared with ibandronate (renal impairment rates: zoledronic acid 37.7% vs. ibandronate 10.5%, relative risk [RR] = 3.6, $P = 0.0029$ serum creatinine [SCr]; 62.3% vs. 23.7%, RR = 2.6, $P = 0.0001$ glomerular filtration rate [GFR]). Ibandronate-treated patients switched from zoledronic acid had a significantly higher risk of renal impairment than patients receiving ibandronate monotherapy (zoledronic acid over ibandronate 39.1% vs. ibandronate monotherapy 6.7%, RR = 5.9, $P = 0.028$ [SCr]; 65.2% vs 26.7%, RR = 2.4, $P = 0.022$ [GFR]). Multivariate analysis found significantly higher hazard ratios for zoledronic acid over ibandronate (SCr: Cox = 4.38, $P = 0.01$; Andersen-Gill = 8.22, $P < 0.01$; GFR: Cox = 4.31, $P < 0.01$; Andersen-Gill = 3.71, $P < 0.01$).

Conclusions: Overall, this retrospective study suggests that multiple myeloma patients are more likely to experience renal impairment with zoledronic acid than with ibandronate. The risk of renal impairment increased if patients had received prior therapy with zoledronic acid.

KEY WORDS: Ibandronate, multiple myeloma, renal impairment, zoledronic acid

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DOI: 10.4103/0973-1482.63570

INTRODUCTION

Multiple myeloma is an incurable malignant disease with a median survival of approximately three years.[1-4] Bone lesions are common during disease progression, affecting up to 95% of patients.[5] The resulting bone complications, such as bone pain and fractures, are a significant cause of morbidity and mortality.[6] Palliation of symptoms and maintenance of quality of life is therefore an essential goal of treatment. Bisphosphonates are currently a standard therapy for malignant bone disease in multiple myeloma as well as other malignancies including breast and prostate cancer. Ibandronate and zoledronic acid are two newer aminobisphosphonates that have demonstrated similar efficacy in preventing skeletal events in patients with advanced breast cancer in phase III trials.[7-10]

An alternative to zoledronic acid therapy for patients with multiple myeloma is particularly important for renal safety reasons. Renal impairment is a common feature in patients with multiple myeloma and renal failure is a long-term complication of this disease. As with all cancer patients, multiple myeloma patients may also be taking multiple concomitant medications that can affect renal health. Preservation of adequate renal function is also important if multiple myeloma patients are to proceed to more aggressive treatment options, such as autologous or allogeneic blood stem-cell transplantation.

The development of renal toxicity during zoledronic acid therapy is well documented.[11-15] This is supported by changes to product labeling for zoledronic acid, which includes renal toxicity warnings, mandatory kidney function tests, and dose adjustments for patients with mild or moderate renal impairment.[16,17] In patients with solid tumors, these limitations on zoledronic acid may result in increased inconvenience and resource use. However, in multiple myeloma, these concerns

are of greater clinical relevance because renal impairment is a characteristic feature of the disease itself.

The renal safety profile of ibandronate appears to be quite different to that of zoledronic acid. In phase III trials in patients with advanced breast cancer, the renal safety profile of intravenous (IV) ibandronate was comparable with placebo, both in the short- and long-term.[7,18] The favorable renal safety profile of ibandronate is reflected in its product labeling; there is no requirement for dose reductions due to mild-to-moderate renal impairment or mandatory kidney function tests.[19] Preliminary studies indicate that ibandronate has a similarly good renal safety profile in multiple myeloma. In an open-label study of 40 patients with normal renal function or pre-existing renal insufficiency intravenously administered ibandronate did not result in significant changes in serum creatinine or other markers of renal damage.[20]

Thus far, no formal studies have compared the renal safety profile of zoledronic acid and ibandronate. We conducted a retrospective review of medical charts of patients with multiple myeloma receiving either of these two agents in a real-life practice setting.

MATERIALS AND METHODS

Data source

Patient medical records from May 2001 to December 2005 from a German oncology clinic were reviewed. All the patients included in the review met the following criteria: Age ≥18 years, treated actively at the clinic, a confirmed diagnosis of multiple myeloma, received at least one intravenous infusion of ibandronate or zoledronic acid, and at least one serum creatinine measurement available both before and after the first bisphosphonate infusion. The observation period began on the date of the first bisphosphonate infusion and ended on the last clinic visit date, last creatinine test date, or the defined study end date (December 28, 2005), whichever occurred later. Disease status (plateau phase, relapsed, etc.) relating to multiple myeloma was not recorded as part of this study.

Patients who sequentially received both zoledronic acid and ibandronate were included as separate observations for each bisphosphonate treatment period. A washout period of at least 28 days was imposed between the final infusion of the first bisphosphonate and the baseline creatinine measurement for the second bisphosphonate.

Assessment of renal impairment

All serum creatinine measurements, whether obtained at the clinic or from community physicians, were included in the analysis. Creatinine measurements were then used to calculate the glomerular filtration rate (GFR), using the abbreviated modification of diet in renal disease (MDRD) formula.[21] Changes in serum creatinine and GFR from baseline (defined as the last serum creatinine test prior to beginning bisphosphonate treatment) were used separately to assess renal impairment.

Patients were defined as having renal impairment using two different criteria to test the result robustness: 1) if they had any of the following abnormal serum creatinine elevations (an increase in serum creatinine after bisphosphonate treatment of ≥0.5 mg/dL from baseline values <1.4 mg/dL, or an increase of ≥1 mg/dL from baseline values ≥1.4 mg/dL); or 2) if they had a ≥25% decrease from baseline GFR. Serum creatinine and GFR were measured throughout each patient's observation period. As this is a retrospective analysis, these measures were not taken at pre-specified time points.

Statistics

Univariate analysis of serum creatinine and GFR changes was used to calculate the percentage of patients with renal impairment for each bisphosphonate and the relative risk of impairment, as well as the incidence of renal impairment (number of renal impairment events per patient-year) and the incidence rate ratio of renal impairment between the two agents.

Multivariate analysis was performed, adjusted for significant covariates selected through a stepwise procedure, by the Cox proportional hazards model for time to first event and the Andersen-Gill extension of the Cox model for multiple-event analysis.[22] Patients who did not experience any renal impairment events during their observation periods were included in the analysis as censored observations. Covariates controlled for included age, baseline serum creatinine or GFR, prior bisphosphonate use, renal-related comorbidities, and concomitant use of drugs associated with acute renal failure;[23] also controlled for were anti-myeloma therapy and any other concomitant therapy.

RESULTS

Patient characteristics

A total of 84 patients were included in the analysis. Of these, 46 received zoledronic acid, 15 received ibandronate, and 23 initially received zoledronic acid and were then switched to ibandronate. Thus, 69 records were evaluable for zoledronic acid and 38 records for ibandronate. As this study was a retrospective review looking at renal impairment in normal clinical practice, the bisphosphonate choice was the physician's decision. Typically, this was based on serum creatinine levels. Patients with serum creatinine >1.4 mg/dL received ibandronate; patients with serum creatinine <1.4 mg/dL received zoledronic acid. This difference in prescribing criteria would potentially account for imbalances in baseline renal function.

Patient demographics and baseline characteristics are shown in Table 1. The requirement for chemotherapy, including myeloma-specific therapy, was similar between the 2 groups. The zoledronic acid group had significantly better baseline renal function than the ibandronate group possibly reflecting the contraindications and warnings for

Table 1: Patient demographics

	Zoledronic acid	Ibandronate	*P* value
Patients treated, n	69	38	
Age at baseline (years), Mean (range)	67.8 (38-86)	71.2 (51-94)	0.09
Male, n (%)	34 (49.3)	16 (42.1)	0.48
Baseline SCr (mg/dL), Mean (range)	1.01 (0.5-3.0)	1.33 (0.5-3.5)	0.006
Baseline GFR (mL/min/1.73 m^2), Mean (range)	75.9 (21.9-150.0)	57.3 (13.6-124.6)	0.0002
Observation duration (days), Mean (range)	558.4 (28-1625)	389.9 (22-1005)	0.008
Total bisphosphonate infusions, Mean (range)	17.6 (1-57)	13.5 (1-33)	0.056
Days between bisphosphonate infusions, Mean (range)	30.6 (26-91)	30.6 (27.6-62.5)	0.97
Prior pamidronate use, n (%)	25 (36.2)	8 (21.1)	0.04
Concomitant use of drugs associated with acute renal failure, n (%)	64 (92.8)	35 (92.1)	0.90
Chemotherapy treatment, n (%)	50 (72.5)	26 (68.4)	0.66
Baseline comorbidities			
Renal disease, n (%)	3 (4.3)	3 (7.9)	0.44
Hypertension, n (%)	24 (34.8)	10 (26.3)	0.37

SCr - Serum creatinine; GFR - Glomerular filtration rate

this bisphosphonate in patients with pre-existing renal impairment. Patients in the zoledronic acid group also had a significantly longer duration of observation, reflecting the earlier market entry date, and a higher mean number of bisphosphonate infusions.

Univariate analysis of renal impairment

Patients in the ibandronate group had a significantly lower risk of renal impairment than those in the zoledronic acid group, whether assessed by change in serum creatinine or GFR [Figure 1]. Compared with ibandronate, zoledronic acid increased the relative risk of renal impairment by approximately 3-fold (relative risk: Serum creatinine, 3.6; GFR, 2.6; $P = 0.0029$ and $P = 0.0001$, respectively). Similarly, the renal impairment incidence rate was significantly lower in the ibandronate group (incidence rate ratio: Serum creatinine, 6.1; GFR, 3.4; both $P < 0.0001$) [Figure 2].

Effect of prior zoledronic acid on renal function in patients receiving ibandronate

Of the 38 patients treated with ibandronate, 23 were switched from previous treatment with zoledronic acid. Of these 23 patients, 15 (65%) were switched due to renal related problems as noted by the treating physician (including, light-chain proteinuria, serum creatinine increases, or renal insufficiency), five (22%) were switched due to patient discomfort (such as, fever, nausea, arthralgia, or myalgia), and three (13%) were switched due to inflammation or osteonecrosis of the jaw.

According to increases in serum creatinine, nine of these 23 patients (39.1%) experienced renal impairment during the ibandronate phase compared with only one of 15 patients (6.7%) who did not receive zoledronic acid before their ibandronate therapy (relative risk = 5.9, $P = 0.0284$). Based on GFR declines, 15 out of 23 patients (65.2%) in the switched group and four out of 15 (26.7%) in the ibandronate monotherapy group had renal impairment (relative risk = 2.4, $P = 0.0219$). The patients who were switched from zoledronic acid to ibandronate therapy experienced an overall deterioration in renal function (upward trend in mean serum creatinine) during zoledronic acid therapy, followed by an overall improvement in renal function (downward trend in mean serum creatinine) during ibandronate therapy [Figure 3].

Multivariate analysis

Multivariate analyses using the Cox proportional hazards

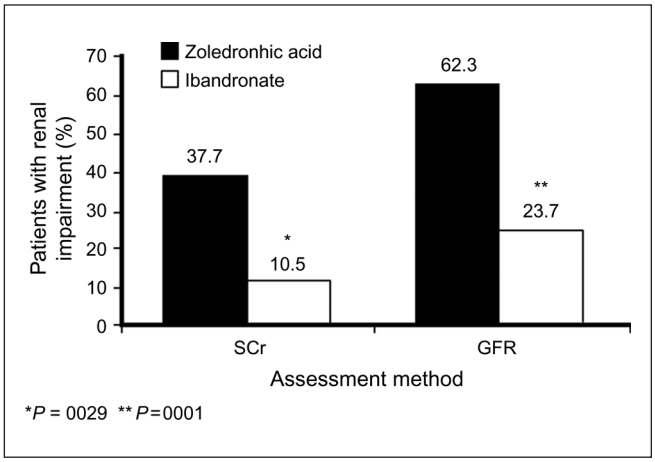

Figure 1: Percentage of patients experiencing renal impairment with zoledronic acid or ibandronate

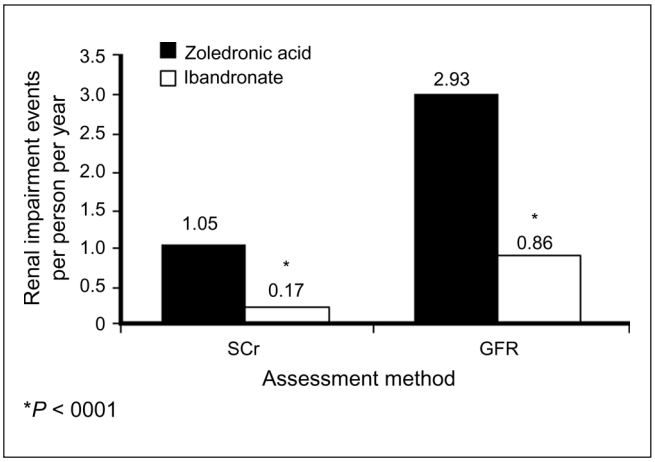

Figure 2: Incidence of renal impairment in patients treated with zoledronic acid or ibandronate

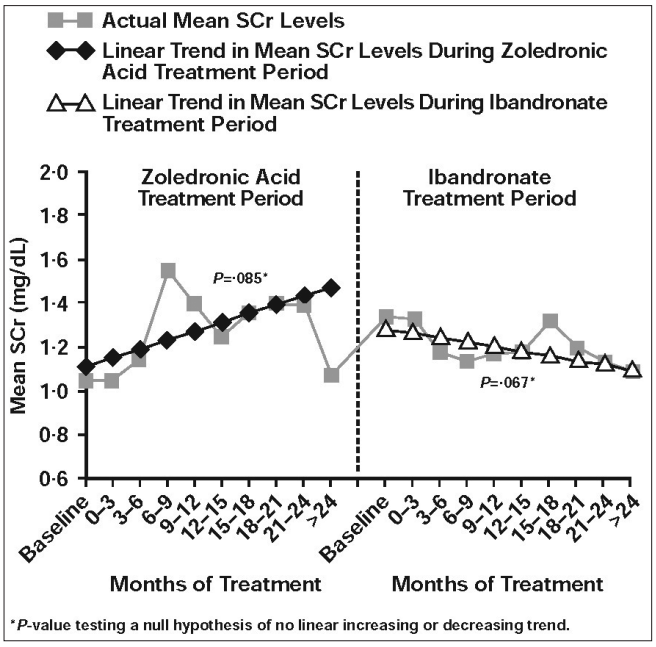

Figure 3: Trends in mean serum creatinine levels in patients switched from zoledronic acid to ibandronate

and Andersen-Gill models adjusted for differences in group characteristics found zoledronic acid to be a significant independent risk factor for renal impairment compared with ibandronate, with a four- to eight-fold increased risk, depending on the assessment and model used [Table 2]. Other risk factors for renal impairment included elevated serum creatinine/lower GFR at baseline, age, prior pamidronate use, chemotherapy use, and history of renal disease.

DISCUSSION

Our data confirm existing clinical evidence that the renal safety profiles of bisphosphonates, particularly zoledronic acid and ibandronate, differ. The analysis presented allowed us to assess trends in renal function over time and relate this to bisphosphonate use. In patients with multiple myeloma, zoledronic acid significantly increased the risk and incidence of renal impairment compared with ibandronate. Furthermore, analysis of serum creatinine over time in patients who received both bisphosphonates showed that prior use of zoledronic acid significantly contributed to renal impairment observed in the ibandronate group.

The renal toxicity of zoledronic acid is well recognized. The largest report was provided by the Food and Drug Administration (FDA) Adverse Event Reporting System.[11] Seventy-two patients with renal failure associated with zoledronic acid treatment were identified, including 42 with multiple myeloma. Twenty-seven of these patients required dialysis and 18 died. Renal function testing is mandatory before and during treatment with zoledronic acid and doses higher than the standard 4 mg every three to four weeks are prohibited for renal safety reasons. For patients with creatinine clearance between 30 mL/min to 60 mL/min, dose reductions are required.[16,17] The mechanism of renal toxicity of zoledronic acid is not known, but renal toxicity appears to be associated with high doses and short infusion times. Ibandronate, on the other hand, has an excellent renal safety profile, with the incidence of renal impairment similar to placebo for both the intravenous and oral formulations in randomized phase III trials.

Zoledronic acid has been evaluated in several clinical trials in patients with bone metastases from various tumor types.[10,24-26] Some of these studies have not shown a particularly high incidence of renal adverse events with zoledronic acid, in contrast to the significant risk of renal impairment or failure indicated by other reports.[11,13] The reasons for this may be related to patient selection.

In clinical trials, patients with any evidence or suggestion of renal insufficiency may be under-represented because physicians are unwilling to enter such patients into these trials. In the retrospective analysis reported here, the baseline renal function of patients given zoledronic acid was significantly better than those given ibandronate, suggesting that in both community practice and in the clinical trial setting, patients with renal impairment at baseline are less likely to receive zoledronic acid. This may be due to precautions for this drug in this patient group.[16] While there was significantly less evidence of renal deterioration in the ibandronate group

Table 2: Multivariate analysis of hazards ratios of renal impairment for zoledronic acid vs. ibandronate after adjusting for significant covariates

Variable	SCr-based renal impairment				GFR-based renal impairment			
	Cox		Andersen-Gill		Cox		Andersen-Gill	
	HR	*P* value	HR	*P* value	HR	*P* value	HR	*P* value
Bisphosphonate treatment								
Zoledronic acid (reference group: Ibandronate)	4.38	0.01	8.22	<0.01	4.31	<0.01	3.71	<0.01
Covariates adjusted								
Baseline SCr*	5.92	<0.01	3.52	<0.01	NA	-	NA	-
Baseline GFR†	NA	-	NA	-	2.54	<0.01	1.87	<0.01
Age (per additional year)	-	NS	1.03	0.01	-	NS	1.02	<0.01
Prior pamidronate use	2.03	0.06	1.68	0.01	-	NS	-	NS
Chemotherapy treatment	-	NS	1.47	0.10	-	NS	-	NS
History of renal disease	-	NS	-	NS	2.74	0.05	-	NS

NS - Not significant (variable not included in model); SCr - Serum creatinine; GFR - Glomerular filtration rate; *Baseline SCr categorical variable: <1.4 mg/dL = 0; ≥1.4 mg/dL = 1; †Baseline GFR categorical variable: ≥60 mL/min/1.73 m² = 0; 30-60 mL/min/1.73 m² = 1; <30 mL/min/1.73 m² = 2

in this study compared with zoledronic acid, patients in the ibandronate group nevertheless had some degree of renal impairment. However, this would be expected in multiple myeloma where renal adverse events are part of the disease process. In phase III trials in breast cancer the renal safety profile of ibandronate was similar to placebo.[7,18]

A retrospective analysis was conducted to determine whether it would be valuable to conduct a prospective, randomized trial. Furthermore, this method allowed us to include a wide spectrum of patients in the clinical setting who may not normally meet the rigorous inclusion criteria for a prospective trial. This retrospective analysis highlights marked differences in renal safety between zoledronic acid and ibandronate. Because of the large numbers of cancer patients with pre-existing renal insufficiency,[27] in particular patients with multiple myeloma, physicians should consider the potential for drug-induced nephrotoxicity in devising a patient's treatment strategy. Whenever there is evidence of pre-existing renal insufficiency, less nephrotoxic bisphosphonates should be used. A prospective randomized study to confirm our findings is warranted.

ACKNOWLEDGMENTS

The authors would like to thank Gardiner-Caldwell US for assistance in drafting the manuscript.

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Source of Support: Nil, **Conflict of Interest:** None declared.

This study was sponsored by F. Hoffman-La Roche, Ltd., Basel, Switzerland. The funding from F. Hoffman-La Roche was not contingent upon the study results. RW and HK are employees of Praxisklinik für Hämatologie und Onkologie Koblenz, Koblenz, Germany, which has received research funds from Analysis Group, Inc. LA, MS, EC, and MSD are employees of Analysis Group, Inc., which has received research funds from F. Hoffman-La Roche, Ltd. JG and NW are employees of F. Hoffman-La Roche, Ltd. MPN was an employee of F. Hoffman-La Roche, Ltd. when this study was completed