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Evaluate the renal system damage caused by zoledronic acid: a comprehensive analysis of adverse events from FAERS

Zhaojun Wang[1†], Xin Su[2†], Donglei Shi[1] and Li Wei[1*]

Abstract

Background Zoledronic acid (ZA) is widely used for the treatment of osteolytic bone metastases in malignancies and osteoporosis, but it has been associated with renal impairment. In this study, we investigated adverse events (AEs) related to renal and urinary system diseases associated with ZA using the U. S. FDA's Adverse Event Reporting System.

Methods We collected FAERS data from Q1 2004 to Q1 2024 and used the reporting odds ratio to detect AEs related to renal and urinary system diseases associated with ZA. Additionally, we applied multiple algorithms, including ROR, proportional reporting ratio, bayesian confidence propagation neural network, and multi-item gamma poisson shrinker, to quantify renal and urinary AEs under different indications.

Results A total of 52,495 AE reports involving ZA as the primary suspect drug were identified. Among renal and urinary system diseases, 25 distinct AEs were recognized, with renal tubular necrosis being the most frequently reported. For different indications, renal tubular necrosis was the most reported AE in breast cancer and osteoporosis; nephrogenic diabetes insipidus was both the most frequent and strongest signal in lung cancer; proteinuria was most common in multiple myeloma, and polyuria in prostate cancer. Furthermore, most AEs occurred in patients who had been on ZA for more than 360 days, followed by those within the first 30 days of use.

Conclusion Based on pharmacovigilance data from FAERS, different renal and urinary system AEs should be closely monitored and addressed according to the specific indications for which ZA is used.

Keywords Zoledronic acid, FDA adverse event reporting system, Adverse events

Background

Zoledronic acid (ZA) is a third-generation bisphosphonate compound that was approved by the U. S. Food and Drug Administration (FDA) in 2001 for the treatment of hypercalcemia of malignancy and bone metastases in patients with solid tumors [1], with a dose of 4 mg. A 5 mg dose later became available for the treatment of postmenopausal osteoporosis and Paget's disease. The pharmacological action of ZA primarily involves inhibiting bone resorption by suppressing osteoclast activity and inducing osteoclast apoptosis [2]. Additionally, ZA can inhibit the enhanced osteoclast activity and

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bone calcium release caused by various factors released by tumors, thereby reducing tumor-induced osteolytic lesions, bone resorption, pain, and hypercalcemia due to bone metastasis [3]. However, during its use, several adverse reactions are commonly observed, such as fever, myalgia, gastrointestinal reactions, and renal function impairment.

Although ZA is generally well-tolerated in clinical treatment of osteoporosis, preclinical studies found similar renal function effects between the experimental and control groups [4]. However, in January 2011, the FDA issued a drug safety communication highlighting new contraindications and updated warnings for Reclast (zoledronic acid) due to cases of acute renal failure, some with fatal outcomes, following its use [5]. ZA is primarily excreted intact through the kidneys, and studies have shown that it increases the risk of nephrotoxicity. The risk of renal function deterioration appears to be time-dependent, with renal impairment or progression to renal failure occurring even in patients with normal baseline renal function [4]. Nevertheless, comprehensive studies assessing the renal damage associated with the use of ZA are still lacking.

Real-world data on drug use serves as a powerful tool for evaluating drug safety [6]. Recently, Su et al. published a study using FDA adverse event reporting system (FAERS) data to investigate the indications and adverse event (AE) characteristics of denosumab and ZA. They compared the signal strength of AEs between denosumab and ZA and studied off-label use [7]. However, their study did not specifically focus on AEs related to renal and urinary system diseases. Therefore, this study also utilizes the FAERS database, with a specific focus on AEs related to renal and urinary system diseases associated with ZA, as well as the AEs in these systems across different indications. This research serves as a valuable complement to the study by Su et al. By conducting this study, we aim to provide more comprehensive insights into the safe clinical use of ZA, particularly regarding AEs related to renal and urinary system diseases.

Methods

Data source and collection

The FAERS database is used to support FDA's post-marketing safety surveillance of drugs and therapeutic biologics. It contains reports of AEs, medication errors, and product quality complaints [8]. ZA was first approved by the FDA for clinical use in 2001. Therefore, this study utilized FAERS data from the second quarter of 2004 to the second quarter of 2024. The FAERS database consists of seven sub-datasets: demographics (DEMO), reactions (REAC), drugs (DRUG), indications (INDI), outcomes (OUTC), therapy start and end dates (THER), and report sources (RPSR). AEs in FAERS are coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs), which are classified into 27 System Organ Classes (SOC). Drugs in FAERS are classified into four categories based on their involvement in the reported AEs: primary suspect, secondary suspect, concomitant, and interacting drugs [9]. To ensure accuracy, this study only included reports where ZA was the primary suspect drug.

Data analysis

Four commonly used disproportionality analysis methods were employed in this study: reporting odds ratio (ROR), proportional reporting ratio (PRR), bayesian confidence propagation neural network (BCPNN), and multi-item gamma poisson shrinker (MGPS) algorithms [10]. ROR and PRR represent the ratio between the observed reporting rate and the expected reporting rate, with higher values indicating a stronger association between the drug and a specific adverse event (AE). Both BCPNN and MGPS utilize Bayesian methods for calculation. MGPS provides more stable values compared to ROR, thereby reducing potential false positives, while the Information Component (IC) calculated by BCPNN reflects the strength of the association between the drug and AE signals [11]. Therefore, the use of all four methods in this study helps minimize false positives and provides a more reliable assessment of the association between the drug and AE signals. The specific formulas and criteria for positive signals for these four algorithms are provided in Supplementary Table 1. For this study, at the SOC level, we used the ROR positive signal criterion (95% CI>1 and $N \geq 3$) as the screening standard. At the PT level, we continued to use the ROR positive signal criterion to screen signals, with a primary focus on AEs under the SOC of renal and urinary system diseases. Additionally, we further analyzed the onset time of ZA-related AEs, calculated as the time interval in days between the EVENT_DT (adverse event date) and START_DT (drug start date). Finally, we conducted a subgroup analysis, focusing on renal and urinary system disease-related AEs in cases where ZA was used for indications such as breast cancer, lung cancer, osteoporosis, plasma cell myeloma, and prostate cancer. For these cases, an event was only considered a positive signal if it met the criteria of all four algorithms. The higher the score in the ROR algorithm, the more disproportionate the event is, indicating a stronger association between the drug and the AE [12].

All data processing and statistical analyses were conducted using R software, version 4.2.3, and data visualization was performed using the "ggplot2" package.

Results

Descriptive analysis

Figure 1 shows the flowchart of the data selection process in this study. The FAERS database contains a total of 21,433,114 records. After removing duplicate entries based on the FDA's recommended method, 18,182,912 records were retained. Ultimately, 52,495 AE reports involving ZA as the primary suspect drug were identified. Table 1 presents the overall and subgroup-specific clinical characteristics of patients with ZA-induced AEs. The majority of cases involved females in the overall cohort (69.2%), breast cancer (94.9%), and osteoporosis (85.7%) groups, whereas males were predominant in lung cancer (57.4%), multiple myeloma (51.1%), and prostate cancer (96.9%) groups. In terms of reporting sources, consumers reported the highest percentage of cases in the total cohort (35.6%) and osteoporosis (47.2%) groups, while physicians were the primary reporters for breast cancer (32.8%), and other health professionals for lung cancer (33.1%), multiple myeloma (34.1%), and prostate cancer (30.1%) groups. Geographically, the United States had the highest number of reports. Among reported outcomes, the "other serious" category was the most common, while lung cancer had the highest mortality rate (31.5%), followed by prostate cancer (24.3%). The number of reports over the past five years showed minimal variation.

Signal of system organ class

Figure 2 displays the signal strength of ZA-related AEs categorized by system organ class (SOC). A total of eight organ systems were affected by ZA-related AEs: musculoskeletal and connective tissue disorders, infections and infestations, neoplasms (benign, malignant, and unspecified), surgical and medical procedures, metabolism and nutrition disorders, eye disorders, renal and urinary disorders, ear and labyrinth disorders, and endocrine disorders. The musculoskeletal and connective tissue disorders category had both the highest number of reports (n=46,560) and the strongest signal [ROR 4.21 (95% CI: 4.17–4.25)].

Signal of preferred terms

Table 2 presents the related AEs at the PT level under the SOC of kidney and urinary system diseases. A total of 25 AEs were identified. The most reported was renal tubular necrosis (n=166), while the strongest signal was

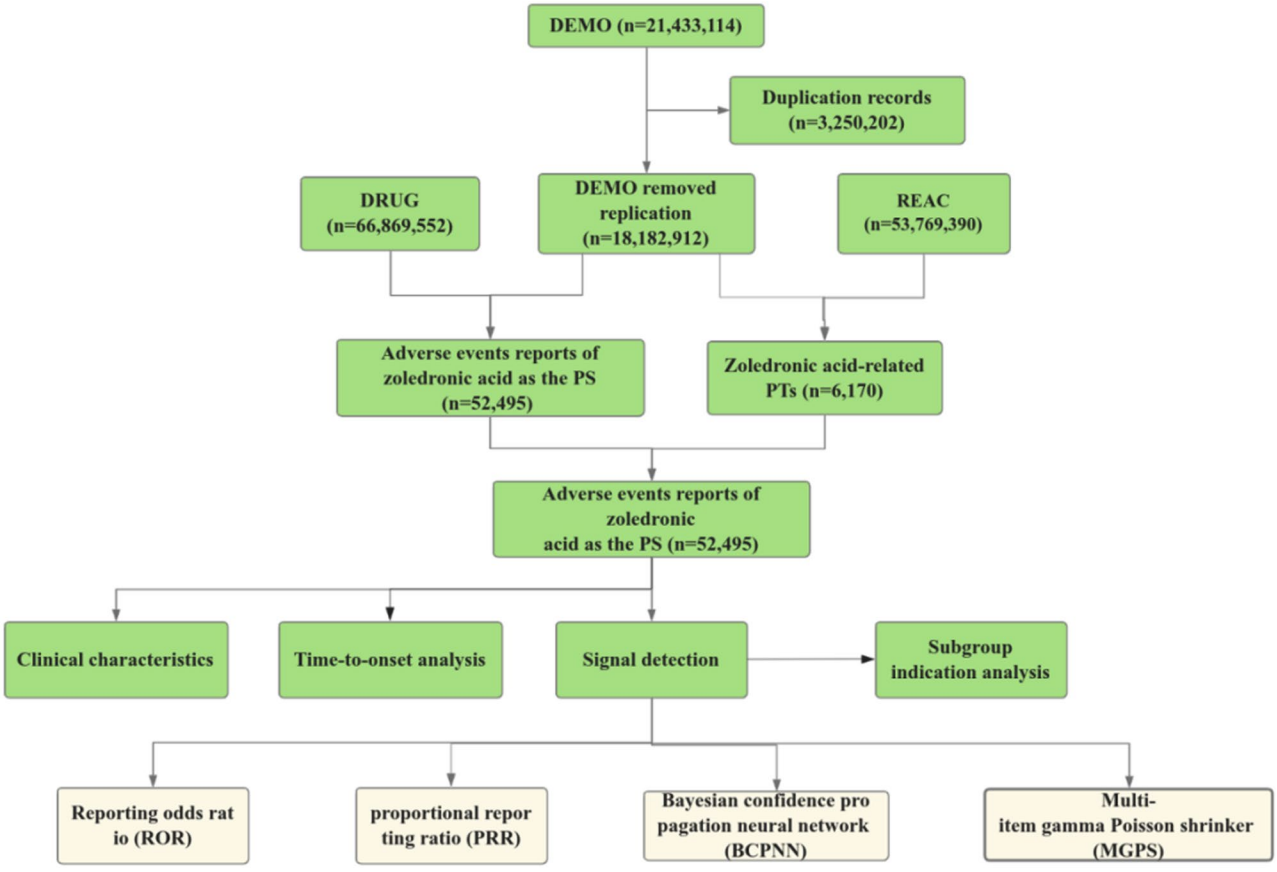

Fig. 1 The flowchart of identifying zoledronic acid AEs in the FAERS database. *Abbreviations* FAERS, United States Food and Drug Administration Adverse Event Reporting System; DEMO, demographic and administrative information file; DRUG, drug information file; REAC, adverse events file; PS, Primary Suspect; PT, preferred term

Table 1 Clinical characteristics of reports with zoledronic acid from the FAERS database

Factors	Number of events (%)					
	Total	Breast cancer	Lung cancer	Osteoporosis	Multiple myeloma	Prostate cancer
Gender						
Female	36,289 (69.2)	4,740 (94.9)	215 (38.7)	14,898 (85.7)	1,442 (43.5)	14 (0.5)
Male	13,374 (25.5)	46 (0.9)	319 (57.4)	2,055 (11.8)	1,694 (51.1)	2,675 (96.9)
Unknown	2,810 (5.4)	211 (4.2)	22 (4)	423 (2.4)	176 (5.3)	72 (2.6)
Age						
< 18	379 (0.7)	2 (0)	1 (0.2)	90 (0.5)	-	4 (0.1)
18-64.9	11,608 (22.1)	2,024 (40.5)	206 (37.1)	3,119 (18)	876 (26.4)	379 (13.7)
65–85	17,167 (32.7)	1,359 (27.2)	199 (35.8)	6,543 (37.7)	1,468 (44.3)	1,350 (48.9)
> 85	2,030 (3.9)	42 (0.8)	-	1,012 (5.8)	56 (1.7)	91 (3.3)
Unknown	21,289 (40.6)	1,570 (31.4)	150 (27)	6,612 (38.1)	912 (27.5)	937 (33.9)
Reporter						
Consumer	18,670 (35.6)	1,027 (20.6)	106 (19.1)	8,201 (47.2)	444 (13.4)	790 (28.6)
Physician	14,472 (27.6)	1,641 (32.8)	148 (26.6)	4,394 (25.3)	1,035 (31.3)	680 (24.6)
Other health-professional	11,038 (21)	1,461 (29.2)	184 (33.1)	2,334 (13.4)	1,130 (34.1)	830 (30.1)
Health Professional	2,842 (5.4)	373 (7.5)	66 (11.9)	995 (5.7)	213 (6.4)	181 (6.6)
Pharmacist	1,572 (3.0)	120 (2.4)	19 (3.4)	432 (2.5)	79 (2.4)	63 (2.3)
Reported countries						
United States	13,538 (25.8)	848 (16.9)	82 (15)	4,011 (23.1)	907 (27.4)	346 (12.5)
Japan	3,343 (6.4)	407 (8.1)	59 (10.7)	293 (1.7)	190 (5.7)	215 (7.8)
Canada	3,285 (6.3)	201 (4)	40 (7.2)	1,847 (10.7)	61 (1.9)	129 (4.7)
Italy	2,425 (4.6)	483 (9.6)	46 (8.3)	124 (0.7)	437 (13.2)	204 (7.4)
United Kingdom	2,330 (4.5)	214 (4.3)	10 (1.8)	744 (4.3)	128 (3.9)	125 (4.5)
Outcome						
Other Serious	24,837 (47.3)	2,755 (55.1)	250 (45)	7,203 (41.5)	1,943 (58.7)	1,328 (48.1)
Death	10,409 (19.8)	664 (13.3)	175 (31.5)	3,681 (21.2)	293 (8.8)	671 (24.3)
Hospitalization	10,122 (19.3)	1,052 (21.1)	102 (18.3)	3,973 (22.9)	654 (19.7)	551 (20)
Disability	2,416 (4.6)	266 (5.3)	8 (1.4)	898 (5.2)	226 (6.8)	107 (3.9)
Life-Threatening	1,282 (2.4)	75 (1.5)	8 (1.4)	638 (3.7)	57 (1.7)	34 (1.2)
Year (The last five years)						
2020	2,192 (4.2)	283 (5.7)	30 (5.4)	657 (3.8)	118 (3.6)	122 (4.4)
2021	1,922 (3.7)	214 (4.3)	27 (4.9)	610 (3.5)	85 (2.6)	84 (3)
2022	1,566 (3)	198 (4)	15 (2.7)	583 (3.4)	67 (2)	53 (1.9)
2023	2,037 (3.9)	247 (4.9)	20 (3.6)	784 (4.5)	70 (2.1)	59 (2.1)
2024	1,143 (2.2)	144 (2.9)	22 (4)	409 (2.4)	31 (0.9)	40 (1.4)

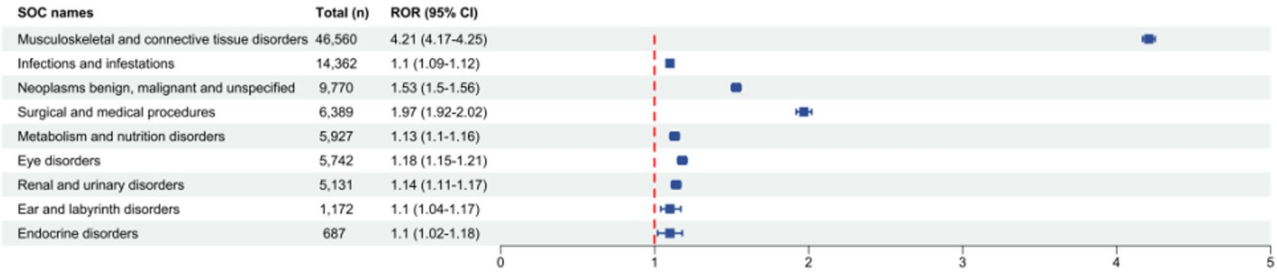

Fig. 2 Analysis of gender-differentiated risk signals in zoledronic acid. PT, preferred term; SOC, system organ class; Reporting odds ratios (ROR) with 95% CI for all positive gender-related adverse drug events; CI, confidence intervals. lower limit of 95% CI>1

for globulinuria [ROR 327.91 (95% CI: 54.79–1962.48)], followed by hyperuricosuria [ROR 32.15 (95% CI: 12.57–82.2)].

Table 3 outlines the AE signals within the SOC of renal and urinary system diseases in the ZA-related subgroups. In the breast cancer group, renal tubular necrosis was the most reported AE (n=13), and urinary tract inflammation had the strongest signal [ROR 25.35 (95% CI: 10.01–64.24)]. In the lung cancer group, nephrogenic diabetes insipidus had both the highest number of

Table 2 Related AE signals of zoledronic acid based on SOC in FAERS for renal and urinary system diseases

PT	Case reports	ROR (95% CI)	PRR(χ2)	EBGM (EBGM05)	IC (IC025)
Renal tubular necrosis	166	4.28 (3.67–4.99)	4.28 (408.75)	4.21 (3.71)	2.07 (0.41)
Fanconi syndrome acquired	37	4.99 (3.6–6.91)	4.99 (115.4)	4.9 (3.73)	2.29 (0.63)
Renal tubular acidosis	34	4.12 (2.94–5.79)	4.12 (78.92)	4.06 (3.06)	2.02 (0.36)
Myoglobinuria	33	15.19 (10.67–21.62)	15.19 (408.94)	14.27 (10.62)	3.83 (2.16)
Renal atrophy	27	5.27 (3.59–7.71)	5.27 (91.1)	5.16 (3.75)	2.37 (0.7)
Renal tubular dysfunction	18	7.98 (4.99–12.78)	7.98 (106.05)	7.74 (5.22)	2.95 (1.28)
Stress urinary incontinence	15	3.26 (1.96–5.43)	3.26 (23.19)	3.23 (2.11)	1.69 (0.02)
Renal tubular atrophy	15	4.22 (2.53–7.03)	4.22 (36.16)	4.16 (2.71)	2.06 (0.39)
Urinary tract inflammation	12	8.83 (4.96–15.73)	8.83 (80.11)	8.53 (5.26)	3.09 (1.42)
Bladder outlet obstruction	11	16.58 (8.98–30.61)	16.58 (149.73)	15.48 (9.27)	3.95 (2.27)
Urethral obstruction	8	4.73 (2.35–9.52)	4.73 (23.01)	4.65 (2.59)	2.22 (0.54)
Renal glycosuria	8	29.64 (14.16–62.03)	29.64 (194.96)	26.22 (14.14)	4.71 (3.01)
Hydroureter	8	5.79 (2.87–11.69)	5.79 (30.89)	5.67 (3.15)	2.5 (0.83)
Postrenalfailure	8	4.21 (2.09–8.48)	4.21 (19.24)	4.15 (2.31)	2.05 (0.38)
Ureteric dilatation	7	6.32 (2.98–13.41)	6.32 (30.49)	6.17 (3.29)	2.63 (0.95)
Bladder hypertrophy	7	4.31 (2.04–9.11)	4.31 (17.45)	4.25 (2.27)	2.09 (0.41)
Hyperphosphaturia	7	15.15 (7.04–32.59)	15.15 (86.52)	14.23 (7.5)	3.83 (2.14)
Hyperuricosuria	5	32.15 (12.57–82.2)	32.15 (131.55)	28.15 (12.84)	4.82 (3.09)
Urethral dilatation	5	20.24 (8.1–50.6)	20.24 (83.7)	18.61 (8.65)	4.22 (2.51)
Bence jones proteinuria	4	30.15 (10.6-85.77)	30.15 (99.08)	26.62 (11.1)	4.73 (3)
Mesangioproliferative Glomerulonephritis	4	6.83 (2.53–18.48)	6.83 (19.31)	6.65 (2.89)	2.73 (1.05)
Renal hypertrophy	4	4.94 (1.83–13.31)	4.94 (12.29)	4.85 (2.12)	2.28 (0.6)
Hyperkaliuria	3	13.38 (4.17–42.94)	13.38 (32.39)	12.67 (4.78)	3.66 (1.95)
Pneumaturia	3	7.81 (2.47–24.7)	7.81 (17.19)	7.57 (2.89)	2.92 (1.23)
Globulinuria	3	327.91 (54.79-1962.48)	327.9 (391.09)	131.76 (29.49)	7.04 (5)

Abbreviations: PT, preferred term; ROR, reporting odds ratios; PRR, proportional reporting ratios; χ2, chi-squared; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% CI of EBGM; IC, information component; IC025, the lower limit of the 95% CI of the IC; CI, confidence interval

reports (n=7) and the strongest signal [ROR 57.44 (95% CI: 23.8–138.59)]. In the osteoporosis group, renal tubular necrosis had the most reports (n=81), while haemoglobinuria had the strongest signal [ROR 22.85 (95% CI: 5.71–91.35)]. In the multiple myeloma group, proteinuria had the highest number of reports (n=24), while glycosuria had the strongest signal [ROR 76.85 (95% CI: 18.37–321.61)]. In the prostate cancer group, polyuria was the most frequently reported AE (n=11), and renal tubular acidosis had the strongest signal [ROR 31.47 (95% CI: 7.87–125.83)].

Onset time of events

The most common onset of AEs occurred in patients more than 360 days after starting ZA (38.84%), followed by those within 30 days (32.4%). The proportion of events between 30 and 180 days was small and showed a gradual decline. However, a clear upward trend emerged after 180 days (Fig. 3).

Discussion

The FAERS database is an important tool for post-marketing surveillance, collecting reports of adverse drug reactions that may not be evident under the controlled conditions of clinical trials [13]. This is crucial for ensuring medication safety. In this study, we comprehensively analyzed post-marketing reports of renal and urinary system AEs associated with ZA use from the FAERS database. We found that the most frequently reported renal and urinary system AE associated with ZA was renal tubular necrosis. Specifically, renal tubular necrosis was the most reported AE in patients treated for breast cancer and osteoporosis, while nephrogenic diabetes insipidus was most frequently reported in lung cancer, proteinuria in multiple myeloma, and polyuria in prostate cancer.

The baseline distribution of AEs associated with ZA suggests that the majority of reports, especially for breast cancer and osteoporosis, came from female patients, which may be related to the drug's use in postmenopausal osteoporosis. Additionally, a higher percentage of AEs was reported in patients aged 65–85, likely due to age-related decline in renal function and the consequent reduction in renal drug excretion. Regarding outcomes, "Other Serious" events were the most common, while death was frequently reported in lung and prostate cancer patients, signaling a need to monitor for serious outcomes in these populations.

Approximately 39–45% of ZA is excreted unchanged by the kidneys [14]. Previous studies have reported

Table 3 AE signal of zoledronic acid related subgroups, SOC level for renal and urinary system diseases

Subgroup	PT	Case reports	ROR (95% CI)	PRR (χ2)	EBGM (EBGM05)	IC (IC025)
Breast cancer	Renal tubular necrosis	13	4 (2.25–7.12)	4 (25.96)	3.66 (2.26)	1.87 (0.19)
	Urinary tract inflammation	8	25.35 (10.01–64.24)	25.35 (103.94)	14.53 (6.67)	3.86 (2.07)
	Renal atrophy	5	7.92 (2.97–21.11)	7.92 (24.19)	6.54 (2.88)	2.71 (0.95)
	Fanconi syndrome acquired	3	8.64 (2.41–30.98)	8.64 (15.93)	7 (2.41)	2.81 (0.98)
	Diabetic nephropathy	3	19.01 (4.54–79.56)	19.01 (31.99)	12.26 (3.7)	3.62 (1.69)
	Bladder hypertrophy	3	7.31 (2.08–25.66)	7.31 (13.28)	6.13 (2.14)	2.62 (0.81)
	Renal tubular acidosis	3	13.58 (3.51–52.52)	13.58 (24.47)	9.8 (3.16)	3.29 (1.41)
Lung cancer	Nephrogenic diabetes insipidus	7	57.44 (23.8-138.59)	57.33 (274.45)	40.9 (19.57)	5.35 (3.59)
	Renal tubular acidosis	7	46.5 (19.75-109.44)	46.41 (233.29)	35.06 (17.13)	5.13 (3.38)
Osteoporosis	Renal tubular necrosis	81	19.7 (13.75–28.23)	19.69 (527.58)	7.86 (5.82)	2.97 (1.29)
	Nephropathy toxic	24	6.53 (3.95–10.78)	6.53 (71.48)	4.52 (2.97)	2.18 (0.47)
	Anuria	19	4.34 (2.56–7.36)	4.34 (35.4)	3.42 (2.2)	1.77 (0.07)
	Oliguria	16	6.09 (3.32–11.18)	6.09 (44.41)	4.32 (2.6)	2.11 (0.39)
	Haemoglobinuria	6	22.85 (5.71–91.35)	22.84 (41.78)	8.28 (2.6)	3.05 (1.15)
Multiple myeloma	Proteinuria	24	6.84 (4.45–10.5)	6.83 (104.04)	6.08 (4.25)	2.6 (0.92)
	Tubulointerstitial nephritis	14	6.59 (3.76–11.54)	6.59 (58.05)	5.89 (3.68)	2.56 (0.87)
	Renal tubular necrosis	14	5.57 (3.2–9.69)	5.56 (46.77)	5.07 (3.19)	2.34 (0.66)
	Hydronephrosis	8	10.25 (4.76–22.05)	10.24 (54.61)	8.56 (4.51)	3.1 (1.38)
	Polyuria	7	4.97 (2.28–10.83)	4.96 (20.01)	4.58 (2.38)	2.2 (0.5)
	Azotaemia	7	4.82 (2.21–10.5)	4.82 (19.17)	4.46 (2.32)	2.16 (0.46)
	Fanconi syndrome acquired	6	27.67 (10.06–76.14)	27.66 (96.37)	17.66 (7.57)	4.14 (2.34)
	Urinary tract obstruction	6	5.53 (2.37–12.91)	5.53 (19.89)	5.05 (2.48)	2.34 (0.63)
	Glycosuria	5	76.85 (18.37-321.61)	76.84 (140.35)	29.44 (8.89)	4.88 (2.96)
	Renal atrophy	5	16.47 (5.93–45.73)	16.47 (53.52)	12.4 (5.27)	3.63 (1.85)
	Stress urinary incontinence	4	18.44 (5.78–58.81)	18.44 (47.13)	13.46 (5.1)	3.75 (1.93)
	Renal colic	4	26.35 (7.71–90.02)	26.34 (62.06)	17.13 (6.13)	4.1 (2.24)
	Renal tubular atrophy	4	16.77 (5.34–52.66)	16.76 (43.48)	12.56 (4.82)	3.65 (1.84)
	Kidney fibrosis	3	19.76 (5.11–76.42)	19.76 (37.4)	14.13 (4.56)	3.82 (1.94)
	Renal tubular disorder	3	9.88 (2.84–34.38)	9.88 (19.72)	8.31 (2.93)	3.06 (1.26)
	Renal tubular dysfunction	3	27.67 (6.61-115.77)	27.66 (48.18)	17.66 (5.33)	4.14 (2.22)
	Pneumaturia	3	23.05 (5.77–92.19)	23.05 (42.19)	15.7 (4.92)	3.97 (2.07)
Prostate cancer	Polyuria	11	6.79 (3.54–13.03)	6.78 (44.64)	5.76 (3.34)	2.53 (0.82)
	Renal tubular necrosis	8	11.45 (5.09–25.71)	11.44 (55.89)	8.66 (4.4)	3.11 (1.37)
	Renal tubular disorder	6	12.59 (4.88–32.45)	12.58 (45.7)	9.27 (4.2)	3.21 (1.44)
	Nephropathy	6	12.59 (4.88–32.45)	12.58 (45.7)	9.27 (4.2)	3.21 (1.44)
	Fanconi syndrome acquired	6	18.88 (6.86–51.96)	18.87 (63.48)	12.17 (5.22)	3.61 (1.8)
	Nephropathy Toxic	5	9.83 (3.6-26.85)	9.83 (30.22)	7.73 (3.34)	2.95 (1.17)
	Renal tubular acidosis	4	31.47 (7.87-125.83)	31.46 (58.98)	16.23 (5.09)	4.02 (2.1)
	Cystitis noninfective	4	6.29 (2.15–18.41)	6.29 (14.84)	5.41 (2.2)	2.44 (0.67)
	Hyperphosphaturia	3	31.46 (6.35-155.91)	31.46 (44.23)	16.23 (4.25)	4.02 (2.03)
	Neurogenic bladder	3	15.73 (3.93–62.91)	15.73 (27.59)	10.82 (3.39)	3.44 (1.54)

Abbreviations PT, preferred term; ROR, reporting odds ratios; PRR, proportional reporting ratios; χ2, chi-squared; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% CI of EBGM; IC, information component; IC025, the lower limit of the 95% CI of the IC; CI, confidence interval

cases of acute kidney injury [15], including interstitial nephritis, acute tubular necrosis, and renal failure [16], following intravenous administration of ZA. In clinical studies of bisphosphonate treatment for multiple myeloma, bisphosphonates have been linked to nephrotoxicity and osteonecrosis of the jaw [17]. These findings are consistent with our study, which identified renal tubular necrosis as the most reported AE, particularly in osteoporosis patients. However, in clinical trials of ZA, adverse events predominantly presented as acute-phase reactions, which were likely unrelated to dosage and more associated with first-dose effects [18]. This differs significantly from our findings, which we attribute to the fact that our study is a post-marketing drug evaluation, providing a more accurate reflection of real-world clinical data. The nephrotoxic mechanism of ZA is thought to be similar to its pharmacological action in osteoclasts [19], likely involving inhibition of the mevalonate

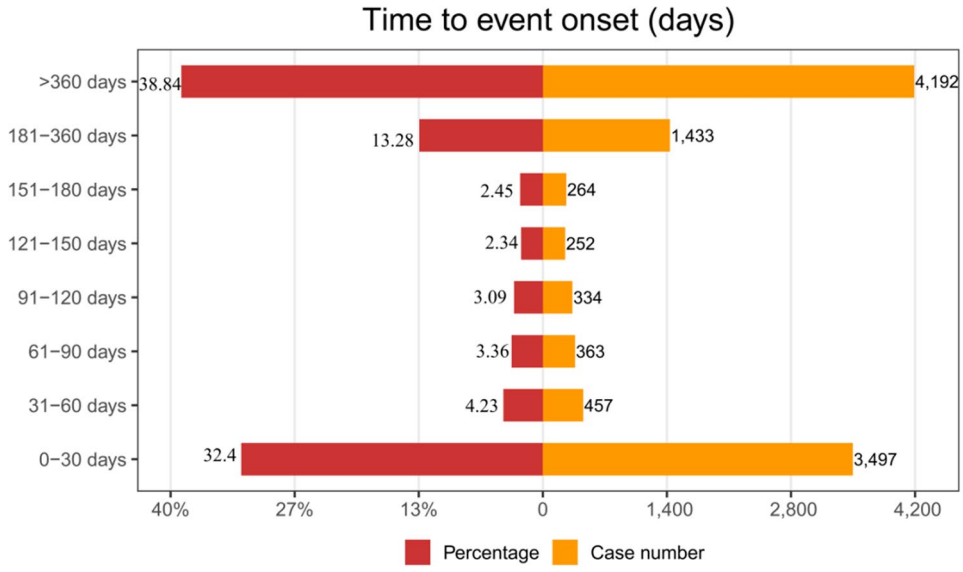

Fig. 3 Time to onset of zoledronic acid-related AEs

pathway [20]. ZA may also disrupt multiple pathways, including TGFβ/Smad3-mediated fibrosis, abnormal fatty acid metabolism, and small GTPase signaling [19]. Acute tubular necrosis and fibrosis are the primary pathological features observed in ZA-induced renal injury [21]. Thus, healthcare providers should exercise caution during intravenous administration, particularly in high-risk groups, to minimize renal injury.

The higher frequency of renal tubular necrosis in multiple myeloma patients compared to other cancers may be attributed to several factors. Multiple myeloma is commonly associated with renal complications such as light chain deposition and hypercalcemia, which predispose patients to renal tubular dysfunction [22]. In addition, multiple myeloma patients often receive higher or more frequent doses of ZA to manage bone disease, further increasing the risk of nephrotoxicity. Concomitant nephrotoxic medications, including chemotherapies and immunomodulatory drugs used in multiple myeloma treatment, likely amplify this risk [23]. This aligns with controlled trials that have shown cumulative nephrotoxicity in multiple myeloma patients undergoing ZA therapy [15]. However, the stronger signal for renal tubular necrosis in lung cancer patients from our study suggests potential differences in patient health status, treatment protocols, or ZA use patterns [24], which warrants further investigation. These findings underscore the importance of careful renal monitoring and individualized dosing of ZA, particularly in patients with multiple myeloma or other high-risk conditions.

This study provides a comprehensive PT-level analysis of AEs associated with ZA using the FAERS database. Our findings identified renal tubular necrosis as the most frequently reported AE across subgroups, consistent with existing knowledge of ZA-induced nephrotoxicity. However, we also identified less commonly reported or potentially undocumented AEs, such as nephrogenic diabetes insipidus and glycosuria, which were notably observed in lung cancer and multiple myeloma patients, respectively. These findings highlight the value of real-world data in uncovering signals that may not be apparent in controlled clinical trials. Fanconi syndrome is characterized by phosphate depletion, aminoaciduria, and glucosuria [25]. Although rarely reported as a complication of ZA therapy [26, 27], our study identified 35 cases of acquired Fanconi syndrome, including 3 cases in breast cancer, 6 in multiple myeloma, and 6 in prostate cancer. Some reports suggest that ZA may trigger new-onset Fanconi syndrome [28], possibly through uptake into renal tubular cells via fluid-phase endocytosis [29]. Given the severity of Fanconi syndrome, clinicians should be vigilant in recognizing and managing this complication, especially in patients with breast cancer, multiple myeloma, and prostate cancer. Immediate discontinuation of ZA and continuous electrolyte replacement should be initiated if Fanconi syndrome is suspected.

Regarding the time to onset, we found that these complications primarily occurred in patients who had used ZA for more than 360 days, followed by those who experienced AEs within the first 30 days of use. Some studies suggest that ZA-induced renal toxicity may be related to infusion time or dosage, with slower infusion rates potentially improving renal safety [30]. However, long-term studies have shown no significant differences in renal function between patients receiving ZA and control groups [31]. In a study of elderly patients with osteoporosis, only 1.4% developed acute kidney injury in the following year [32]. Therefore, further clinical studies are

needed to determine how soon renal impairment occurs following ZA administration.

These findings have significant clinical and pharmacological implications, emphasizing the importance of individualized ZA dosing and administration protocols, particularly for high-risk populations like those with multiple myeloma or pre-existing renal conditions. Therefore, we recommend regular monitoring of renal function, including serum creatinine and glomerular filtration rate, before and during ZA therapy, particularly in high-risk populations. Adjusting ZA infusion protocols, such as slowing the infusion rate and ensuring adequate hydration, can help reduce nephrotoxicity. Dose adjustments based on renal status are also advised, and alternative therapies, should be considered for patients exhibiting early signs of renal dysfunction. These measures aim to optimize patient safety and reduce the risk of ZA-associated renal complications in clinical practice.

This study has several limitations. First, the FAERS database is a spontaneous reporting system, with a proportion of reports submitted by consumers. The varying levels of expertise among reporters may result in data that is not entirely accurate. Additionally, underreporting or insufficient diagnosis is likely, which could affect the accuracy of this study's findings and lead to an underestimation of the true incidence of ZA-related adverse events. Second, we did not differentiate between the two available dosages of ZA (5 mg and 4 mg) or the indications for which they were used. For example, the dosage of ZA differs significantly between osteoporosis and oncology treatments, and it is important to distinguish the differences this may cause when understanding ZA's side effects. Third, the majority of reports came from the United States, which may introduce geographic bias into the data distribution. Fourth, we did not analyze concomitant medications, which may affect the consistency of drug safety assessments. Fourth, the adverse event onset times in this study should only be considered as a reference, as there may be significant variations among individuals. Finally, while disproportionality analysis methods are commonly used in pharmacovigilance research, establishing a causal relationship between ZA and AEs requires further clinical investigation. Despite these limitations, this study provides valuable insights into the renal and urinary system AEs associated with ZA in real-world clinical settings.

Conclusion

This study provides a comprehensive analysis of renal and urinary system AEs associated with ZA using the FAERS database. The findings highlight renal tubular necrosis as the most frequently reported AE across various indications, particularly in breast cancer and osteoporosis patients. Significant differences in the types of renal AEs were observed across different indications, such as nephrogenic diabetes insipidus in lung cancer and proteinuria in multiple myeloma. Additionally, prolonged use of ZA, especially beyond 360 days, appears to increase the risk of renal complications. Given the nephrotoxic potential of ZA, healthcare providers should be cautious during its administration, with particular attention to infusion rates and patient monitoring, especially in high-risk groups. Further clinical studies are needed to confirm these findings and guide safer use of ZA in clinical practice.

Abbreviations

ZA	Zoledronic acid
AEs	Adverse events
FDA	Food and Drug Administration
FAERS	FDA adverse event reporting system
PTs	Preferred terms
SOC	System organ classes
MedDRA	Medical Dictionary for Regulatory Activities
ROR	Reporting odds ratio
PRR	Proportional reporting ratio
BCPNN	Bayesian confidence propagation neural network
MGPS	Multi-item gamma poisson shrinker

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

Zhaojun Wang: Writing-original draft, Software, Methodology. Xin Su: Writing-original draft, Methodology, Formal analysis. Donglei Shi: Writing-review & editing, Validation, Data curation. Li Wei: Writing-review & editing, Data curation, Conceptualization.

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Data availability

The data that support the findings of this study are available upon from the corresponding author. All raw data for this study can be downloaded from the FAERS database.

Declarations

Ethics approval and consent to participate

Not applicable. Ethical approval was not required for this study because we used the FAERS database, which is a free open-access database.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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