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ORIGINAL ARTICLE

Safety and effectiveness of once-yearly zoledronic acid in Japanese osteoporosis patients: three-year post-marketing surveillance

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Abstract

Introduction Zoledronic acid (5 mg; ZOL), a once-yearly bisphosphonate, reduces osteoporotic fractures and increases bone mineral density (BMD). This 3-year post-marketing surveillance examined its real-world safety and effectiveness.

Materials and methods This prospective, observational study included patients who started ZOL for osteoporosis. Data were assessed at baseline, 12, 24, and 36 months for safety and effectiveness. Treatment persistence, potentially related factors, and persistence before and after the COVID-19 pandemic started were also investigated.

Results The safety analysis and effectiveness analysis sets included 1406 and 1387 patients, respectively, with mean age of 76.5 years. Adverse reactions (ARs) occurred in 19.35% of patients, with an acute-phase reaction in 10.31, 1.01, and 0.55% after the first, second, and third ZOL infusions. Renal function-related ARs, hypocalcaemia, jaw osteonecrosis, and atypical femoral fracture occurred in 1.71, 0.43, 0.43, and 0.07% of patients, respectively. Three-year cumulative fracture incidences were 4.44% for vertebral, 5.64% for non-vertebral, and 9.56% for clinical fractures. BMD increased by 6.79, 3.14, and 1.78% at the lumbar spine, femoral neck, and total hip, respectively, after 3-year treatment. Bone turnover markers remained within reference ranges. Treatment persistence was 70.34% over 2 years and 51.71% over 3 years. Male, age ≥ 75 years, no previous medicines for osteoporosis, no concomitant medicines for osteoporosis, and inpatient at the first infusion were related to discontinuation. There was no significant difference in the persistence rate between before and after the COVID-19 pandemic (74.7% vs. 69.9%; $p = 0.141$).

Conclusion This 3-year post-marketing surveillance confirmed the real-world safety and effectiveness of ZOL.

Keywords Zoledronic acid · Osteoporosis · Safety · Effectiveness · Post-marketing surveillance

Introduction

Fragility fractures may occur and restrict normal daily life in patients with osteoporosis. Japan is a rapidly aging nation with a growing population of osteoporotic patients, estimated at over 12 million, and hip fractures occur in approximately 200,000 patients annually [1, 2]. Osteoporosis and associated bone fractures are, therefore, among the major societal concerns.

Bisphosphonates are frequently used as a first-line medication for the treatment of osteoporosis. Zoledronic acid (ZOL; Reclast®) is a bisphosphonate, administered once yearly at a dose of 5 mg via intravenous (iv) infusion. A randomized, placebo-controlled, double-blind study (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial; HORIZON-PFT) involved 7736 post-menopausal women and showed that the drug significantly reduced the incidence of new

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morphometric vertebral fractures by 70%, non-vertebral fractures by 25%, and hip fractures by 41% during 3-year treatment [3]. Another randomized, placebo-controlled, double-blind study (HORIZON-Recurrent Fracture Trial; HORIZON-RFT) conducted in patients who were first administered ZOL within 90 days after surgical repair of a hip fracture showed that it significantly reduced the risk of any clinical fractures by 35%, clinical non-vertebral fractures by 27%, and clinical vertebral fractures by 46% [4]. ZOL also reduced mortality by 28% in the same study. Such risk reduction by ZOL was also applicable to glucocorticoid-induced osteoporosis and osteoporosis in men [5, 6].

A phase 3, randomized, placebo-controlled, double-blind study (ZOledroNate treatment in Efficacy to osteoporosis; ZONE study) was conducted in Japan with the same dosage and regimen as used in the studies conducted worldwide. After 2-year follow-up of 665 patients with primary osteoporosis, ZOL significantly reduced the incidence of new morphometric vertebral fractures by 65.8% compared to placebo. The incidence of any clinical fractures, clinical vertebral fractures, and clinical non-vertebral fractures was also significantly reduced by 54, 70, and 45%, respectively [7]. This was the first report showing the efficacy of bisphosphonates to reduce the incidence of non-vertebral fractures in Japan.

Although ZOL was shown to have excellent effectiveness, it must be mentioned that these phase 3 studies were generally conducted in a strictly controlled manner with specific patient inclusion and exclusion criteria. In other words, it is important to verify the usefulness of ZOL in the real-world setting. The aims of this study were to examine the long-term safety, effectiveness, and treatment persistence of ZOL in the real-world setting, which differs from a strictly controlled clinical trial, focusing particularly on (i) the occurrence of adverse reactions (ARs) and comparison of the AR profile with that observed in the previous clinical studies, (ii) effectiveness in reference to the incidence of osteoporotic fractures and changes in bone mineral density (BMD) and bone turnover markers (BTMs), and (iii) treatment persistence and factors that potentially affected persistence over a 3-year period.

Materials and methods

Study design

The study was scheduled from December 2016 through May 2022. Patients with osteoporosis received once-yearly infusion of ZOL (5 mg) for 3 years in the real-world setting. Patients' background information and any other data were collected at baseline and 12, 24, and 36 months after the first infusion via an Electronic Data Capture system. The present survey was performed according to Good Post-marketing Study Practice (GPSP; Ordinance of the Ministry of Health, Labour and Welfare of Japan) and related laws and regulations.

Safety assessment

Information on any ARs, laboratory tests, and other measurements, especially of renal function and serum calcium, was collected. In association with the use of ZOL, the following conditions were included as the known, important risks: predefined acute-phase reaction (APR: pyrexia, malaise, arthralgia, myalgia, nausea, vomiting, influenza-like illness, headache, diarrhea, bone pain, pain in an extremity, and acute-phase reaction as reported by the attending physician), renal function-related ARs, hypocalcaemia, osteonecrosis of the jaw, and atypical femoral fracture. Any events were classified according to MedDRA ver. 23.0.

Effectiveness assessment

The effectiveness of ZOL was assessed based on the occurrence of new osteoporotic fractures (vertebral, non-vertebral, and clinical), changes in BMD of the lumbar spine, femoral neck, and total hip, and BTMs (type I procollagen N-propeptide, P1NP, and tartrate-resistant acid phosphatase 5b, TRACP-5b). BMD was assessed using % of young adult mean (YAM), since this index was likely to vary due to different devices. BTM was assessed as the changes of absolute values, but not % changes, because previous drugs were likely to affect this index.

Treatment persistence

Treatment persistence was evaluated over 3 years, and treatment compliance was followed up for the second and third infusions. In addition, the persistence rate for 3 years and the factors potentially affecting persistence were examined.

During the study period, the COVID-19 pandemic became prevalent, and thus the effect of COVID-19 on treatment persistence was investigated. The start of the pandemic was set as of March 1, 2020, based on the following: (i) the Provision for anti-COVID-19 measures was fixed by governmental Novel Coronavirus Response Headquarters as of February 25, 2020; and (ii) the Act on Special Measures against COVID-19 pandemic was enacted as of March 14, 2020. In this study, all patients received the second infusion before the COVID-19 pandemic. Therefore, patients who received the second infusion were divided into two groups based on the third infusion scheduled either by the end of February 2020 or after March 1, 2020 to examine treatment persistence.

Ethical approval

This study was conducted in accordance with the Japanese GPSP guidelines. Under these guidelines, the requirement for written, informed consent is waived because treatment is in accordance with clinical practice.

Statistical analysis

Demographic data are presented as numbers of patients (n) and %. BMD and serum levels of BTMs are presented as median, 25th percentile, and 75th percentile values. The χ^2 test was used to analyze the AR profile including APR by patient background characteristics and drug use. The incidence rate of bone fractures was analyzed by the Kaplan–Meier method. Factors affecting treatment persistence were also analyzed by the χ^2 test. The p values were nominal. Software packages used for statistical analysis were SAS ver.9.4 and Python ver.3.7.4.

Results

Patients' background characteristics

A total of 1540 patients were enrolled. The individual patients received ZOL infusions once yearly and were then followed up for 3 years after the infusion started. The safety analysis set and effectiveness analysis set included 1406 and 1387 patients, respectively (Online Resource 1).

The baseline characteristics of the 1406 patients are shown in Table 1. The patients were mostly women (86.49%), and their mean age at baseline was 76.5 years (77.1 years in men and 76.4 years in women). More than half of the patients (52.77%) had prevalent osteoporotic fractures. Complications were observed in 69.42% of patients at baseline. Medicines for osteoporosis were previously used in 46.94% of patients, whereas more than half of patients were naïve to anti-osteoporosis medicines at baseline. Other medicines for osteoporosis were used in 46.37% of patients concomitantly, and the active form of vitamin D was the most frequent (44.87%).

Safety

ARs that occurred at a rate greater than 0.3% are shown in Table 2. Overall, ARs were observed in 19.35% (272/1406) of patients following each of the 3 yearly infusions of ZOL, whereas the incidence rate decreased after repeated infusions, 15.22, 5.06, and 2.75%, respectively. Frequently

Table 1 Patients' baseline characteristics

Total	*n* (%)
	1406
Sex	
Male	190 (13.51)
Female	1216 (86.49)
Menopause (women only)	
No	8 (0.66)
Yes	1038 (85.36)
Unknown	170 (13.98)
Age (y)	
Mean ± SD	76.5 ± 9.9
Age category (y)	
< 75	497 (35.35)
≥ 75	909 (64.65)
Weight (kg) (n = 1286)	
Mean ± SD	50.33 ± 9.61
Height (cm) (n = 1192)	
Mean ± SD	150.5 ± 8.53
BMI (kg/m^2) (n = 1188)	
Mean ± SD	22.2 ± 3.74
Disease classification[a]	
Primary	1233 (87.70)
Secondary	184 (13.09)
Steroid (glucocorticoids) use	114 (8.11)
Other	70 (4.98)
Duration of osteoporosis (y)	
< 0.5	344 (24.47)
≥ 0.5 to < 3	309 (21.98)
≥ 3	400 (28.45)
Unknown	353 (25.11)
Prevalent osteoporotic fracture	
No	625 (44.45)
Yes	742 (52.77)
Unknown	39 (2.77)
BMD (%YAM)	
Lumbar (n = 1018; mean ± SD)	75.75 ± 16.88
Femoral neck (n = 929; mean ± SD)	65.85 ± 12.61
Total hip (n = 445; mean ± SD)	68.08 ± 13.66
Comorbidities	
No	430 (30.58)
Yes	976 (69.42)
Hypertension	423 (43.34)
Osteoarthritis	202 (20.70)
Hyperlipidemia	196 (20.08)
Diabetes mellitus	142 (14.55)
Heart disease	120 (12.30)
Rheumatoid arthritis	113 (11.58)
Prostate cancer	30 (3.07)
Breast cancer	8 (0.82)
Hyperthyroidism	4 (0.41)
CrCl (mL/min) (Cockcroft–Gault estimation)	

Table 1 (continued)

Total	*n* (%)
	1406
< 35 (severe)	92 (7.42)
≥ 35 to < 60 (moderate)	592 (47.74)
≥ 60 to < 90 (mild)	451 (36.37)
≥ 90 (normal)	105 (8.47)
Previous medicines for osteoporosis	
No	746 (53.06)
Yes	660 (46.94)
Concomitant medicines for osteoporosis	
No	754 (53.63)
Yes[a]	652 (46.37)
Active Vitamin D	631 (44.87)
Calcium Preparations	36 (2.56)
Vitamin K	31 (2.20)
SERM	14 (1.00)
Anti-RANKL antibody	7 (0.50)
Bisphosphonate	6 (0.43)
Calcitonin	5 (0.36)
PTH	4 (0.28)
Others	3 (0.21)

[a]Multiple choices were accepted according to patients' status

SD standard deviation, *BMI* body mass index, *BMD* bone mineral density, *YAM* young adult mean, *CrCl* creatinine clearance, *SERM* selective estrogen receptor modulator, *RANKL* receptor activator of nuclear factor-kappa B ligand, *PTH* parathyroid hormone

observed ARs and their incidence rates, as well as APR incidence, are shown below.

Acute-phase reaction

APRs were observed in 10.81% (152/1406) overall. The incidence rate of APR was 10.31, 1.01, and 0.55% after the first, second, and third infusions, respectively (Online Resource 2). Most APRs occurred after the first infusion, and the incidence decreased after the second and third infusions. Pyrexia (5.48%), malaise (1.78%), and headache (1.71%) were the most frequently observed APRs. An analysis by patient background showed that age < 65 years, no previous bisphosphonate use, and no concomitant use of active vitamin D were the risk factors for APR (Online Resource 3).

Renal function-related ARs

ARs related to renal function were observed in 1.71% (24/1406) of patients (Online Resource 4). The rate of patients whose renal function was tested prior to the first infusion was 94.03% (1322/1406), whereas ZOL was contraindicated for patients with severe renal impairment (creatinine clearance < 35 mL/min), 7.42% (92/1240), 8.41% (62/737), and 6.87% (36/524) received ZOL at the first, second, and third infusions. Renal function appeared not to deteriorate further after the drug, even in patients for whom it was contraindicated.

Hypocalcaemia

Six patients (0.43%) developed hypocalcaemia-related ARs, including hypocalcaemia in five patients and blood calcium decreased in one patient. In five patients, ARs were observed after the first infusion. All six cases were non-serious and resolved or improved (Online Resource 5).

Osteomyelitis and osteonecrosis of the jaw

Osteomyelitis and osteonecrosis of the jaw were observed in one patient (0.07%) and five patients (0.36%), respectively (Online Resource 6). Four patients received prior treatments with bisphosphonates. Five patients experienced the events within 24 months after the first infusion.

Atypical femoral fracture

One patient (0.07%) developed an atypical femoral fracture 25 months after the first infusion. The patient had received bisphosphonates for over 10 years, with concomitant use of bisphosphonates and steroids. Therefore, the relationship of the event to ZOL was unclear.

Effectiveness

The effectiveness of ZOL was evaluated in an effectiveness analysis set (1387 patients).

Fractures

The cumulative incidence rate of new vertebral fracture was 1.56%, 3.06%, and 4.44% at months 12, 24, and 36 post-first infusion, respectively (Fig. 1a). Similarly, the cumulative incidence of non-vertebral fracture was 2.23%, 3.40%, and 5.64% (Fig. 1b), and that of clinical fracture was 3.86%, 6.52%, and 9.56%, respectively (Fig. 1c).

BMD

BMDs of the lumbar spine, femoral neck, and total hip were plotted against time post-first infusion as % of YAM (Fig. 2a–c). Percent change (median) from baseline of lumbar spine BMD was 3.38%, 5.67% and 6.79%, respectively. Similarly, % changes of BMD at the femoral neck and total hip were 1.20%, 2.00%, and 3.14%, and 1.49%, 1.37%, and 1.78% at months 12, 24, and 36, respectively.

Table 2 Summary of adverse reactions

	Total[a]	First infusion[b]	Second infusion[b]	Third infusion[b]	Onset time unknown[b]
Patients analyzed	1406	1406	989	727	1406
Patients with AR	272 (19.35)	214 (15.22)	50 (5.06)	20 (2.75)	15 (1.07)
Pyrexia	77 (5.48)	73 (5.19)	4 (0.40)	1 (0.14)	–
Malaise	25 (1.78)	20 (1.42)	4 (0.40)	2 (0.28)	–
Headache	24 (1.71)	22 (1.56)	3 (0.30)	–	–
Renal impairment	20 (1.42)	12 (0.85)	6 (0.61)	2 (0.28)	–
Arthralgia	17 (1.21)	17 (1.21)	1 (0.10)	1 (0.14)	–
Nausea	15 (1.07)	15 (1.07)	–	–	–
Acute-phase reaction	13 (0.92)	13 (0.92)	–	–	–
Back pain	10 (0.71)	8 (0.57)	–	2 (0.28)	–
Hepatic function abnormal	7 (0.50)	4 (0.28)	2 (0.20)	1 (0.14)	–
Osteonecrosis of jaw	5 (0.36)	–	3 (0.30)	–	2 (0.14)
Hypocalcaemia	5 (0.36)	4 (0.28)	1 (0.10)	–	–
Decreased appetite	5 (0.36)	5 (0.36)	–	–	–
Rash	5 (0.36)	4 (0.28)	–	1 (0.14)	–
Feeling abnormal	5 (0.36)	3 (0.21)	2 (0.20)	–	–

[a]When the same AR with the specific preferred term was observed multiple times in a patient, the patient was counted only once

[b]When the same AR with the specific preferred term was observed multiple times in a patient, the patient was counted on the basis of frequency of the event

Values are presented as numbers (%). ARs with incidence rate at ≥ 0.3% were listed in the table. Terms refer to MedDRA version 23.0

'– 'means 0 (0%), *AR* adverse reaction

The waterfall plots of % changes of BMD (36 months after the start of ZOL) are shown in Fig. 2d–f. Of 199 patients, 177 (88.9%) showed increased BMD of the lumbar spine, including 0% change, and more than a 3% increase was observed in 70.9% over the 3-year period. Similarly, BMDs increased in 70.0% and 67.1% of patients at the femoral neck and total hip, and more than a 3% increase was observed in 51.6% and 38.2%, respectively.

BTM

Median values of total P1NP and TRACP-5b reached their nadirs within 6 months after the first infusion and then maintained nearly steady levels up to month 36 (Fig. 3a and b). The median levels of the markers were within their reference ranges [8] throughout the survey period.

Treatment persistence

Of 1406 patients given the first infusion of ZOL, 70.34% (989/1406) and 51.71% (727/1406) received the second and third infusions, respectively. Of the patients who received the second infusion, 73.51% (727/989) received the third infusion. The major reason for treatment discontinuation was no visit (34.07%). In addition, treatment compliance was examined by comparing the scheduled dates and actual dates of the second and third infusions. The percentages of the patients receiving the next infusion within 52 ± 4 weeks from the previous infusion date were 89.8% (888/989; 888 = 411 + 477) and 88.2% (641/727; 641 = 321 + 320), as shown in Online Resource 7.

Treatment persistence was analyzed in detail (Table 3). The risk factors that significantly lowered the persistence rate were male, age ≥ 75 years, no previous medicines for osteoporosis, no concomitant medicines for osteoporosis, and inpatient at the first infusion.

After the start of this study, the COVID-19 pandemic became prevalent, and the effect of the pandemic on treatment persistence for the third ZOL infusion was examined as described above. The cohort scheduled before the pandemic start (February 2020) received the third infusion at a rate of 74.7% (555/743 patients), and the post-pandemic start cohort received it at a rate of 69.9% (172/245; $p = 0.141$, Table 4).

Discussion

In the present post-marketing surveillance, the safety and effectiveness of ZOL were assessed in the real-world setting over a 3-year period. The incidence rate of ARs did not exceed that observed in the ZONE study (19.35% vs

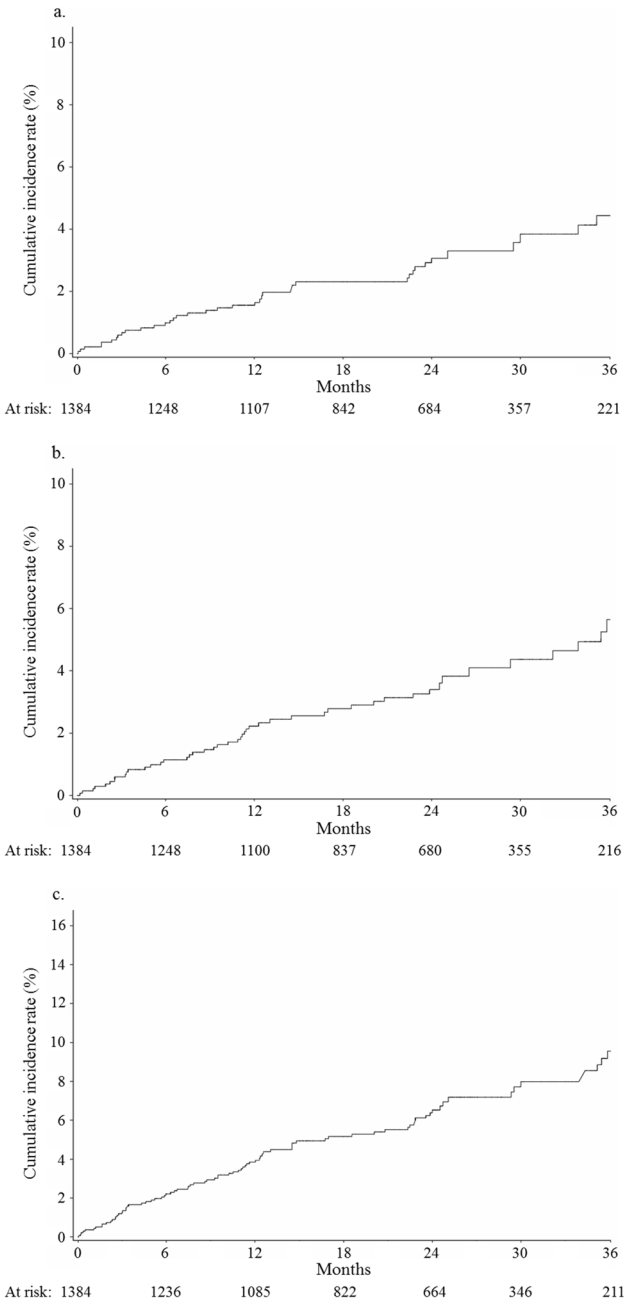

Fig. 1 Cumulative incidence rates of new fractures. **a**: Vertebral, **b**: Non-vertebral, **c**: Clinical

59.2%). The cumulative incidences of osteoporotic fractures and changes in BMDs and BTMs did not exceed or showed no obvious differences from those observed in the ZONE study [7]. These results confirm the safety and effectiveness of ZOL in the real-world setting in Japan.

The mean age of patients was 76.5 years in the present study, higher than the 74.0 years in the ZONE study. In addition, 38.3% of the patients had a history of prior bisphosphonate use for osteoporosis treatment, clearly differing from the previous treatment mode in the ZONE study, in which the patients were bisphosphonate-naive or experienced a 2-year or longer washout procedure before study start [7]. In addition, patients who appeared APR may have dropped out without having received a second or third infusion. Thus, the incidence of APR in this study was likely lower than in the ZONE study. The APR incidence rate was lower after the repeated infusion. The risk factors for APR were no previous bisphosphonate use, no concomitant use of active vitamin D, and age < 65 years (Online Resource 3). Such factors were generally consistent with those reported in previous studies [9–12]. Furthermore, there have been reports that 33.0% to 33.5% of patients had a temperature ≥ 37.5 °C, but were asymptomatic [10, 12]. Temperature measurements were not mandatory in this survey, likely allowing cases of such asymptomatic fever to escape safety assessment.

Another issue was that more elderly patients were enrolled in the present survey, raising concerns about the effect of ZOL on renal function. However, the incidence rate of renal function-related ARs was 1.71% (24/1406), not higher than the 3.0% seen in the ZONE study [13]. One of 24 patients was diagnosed with sequelae because the serum creatinine level at 64 days after ZOL infusion was as high as that at the onset of renal impairment. The relationship with ZOL was unclear because of the possible influence of concomitant medications.

Two-year incidence rates of new fractures, vertebral, non-vertebral, and clinical, were 3.06%, 3.40%, and 6.52%, respectively, in the present survey, compared to 3.0%, 6.9%, and 8.2% in the ZONE study [7]. Although the differences in patient characteristics prevent a direct comparison, the incidence rates of fractures in the present survey did not exceed those in the ZONE study. Prior treatments for osteoporosis were taken by 47.47% (657/1384, the effectiveness analysis set) of patients, and active vitamin D was concomitantly used by 45.08% (624/1384) in the present survey. These may have led to a positive impact on fractures. BMDs were considerably elevated at the lumbar spine (median: 6.79%), femoral neck (3.14%), and total hip (1.78%) during 3-year treatment with ZOL. Most patients showed increased BMD. The levels of both TRACP-5b and P1NP were within their reference ranges throughout the survey period. This suggests no excessive changes in BTMs during the treatment period, though it was difficult to measure these markers frequently, not as in the ZONE study, due to restrictions set by the health insurance system.

It should be mentioned that a decrease of treatment persistence is an issue with managing osteoporosis in the real-world setting. A database analysis by Nakatoh et al. showed that the persistence rate of patients aged 70 to 79 years decreased to 58.2% after 1 year and 48.0% after 2 years [14]. The rate of 1-year persistence to oral bisphosphonate treatment was 42.5% (alendronate) and 44.6%

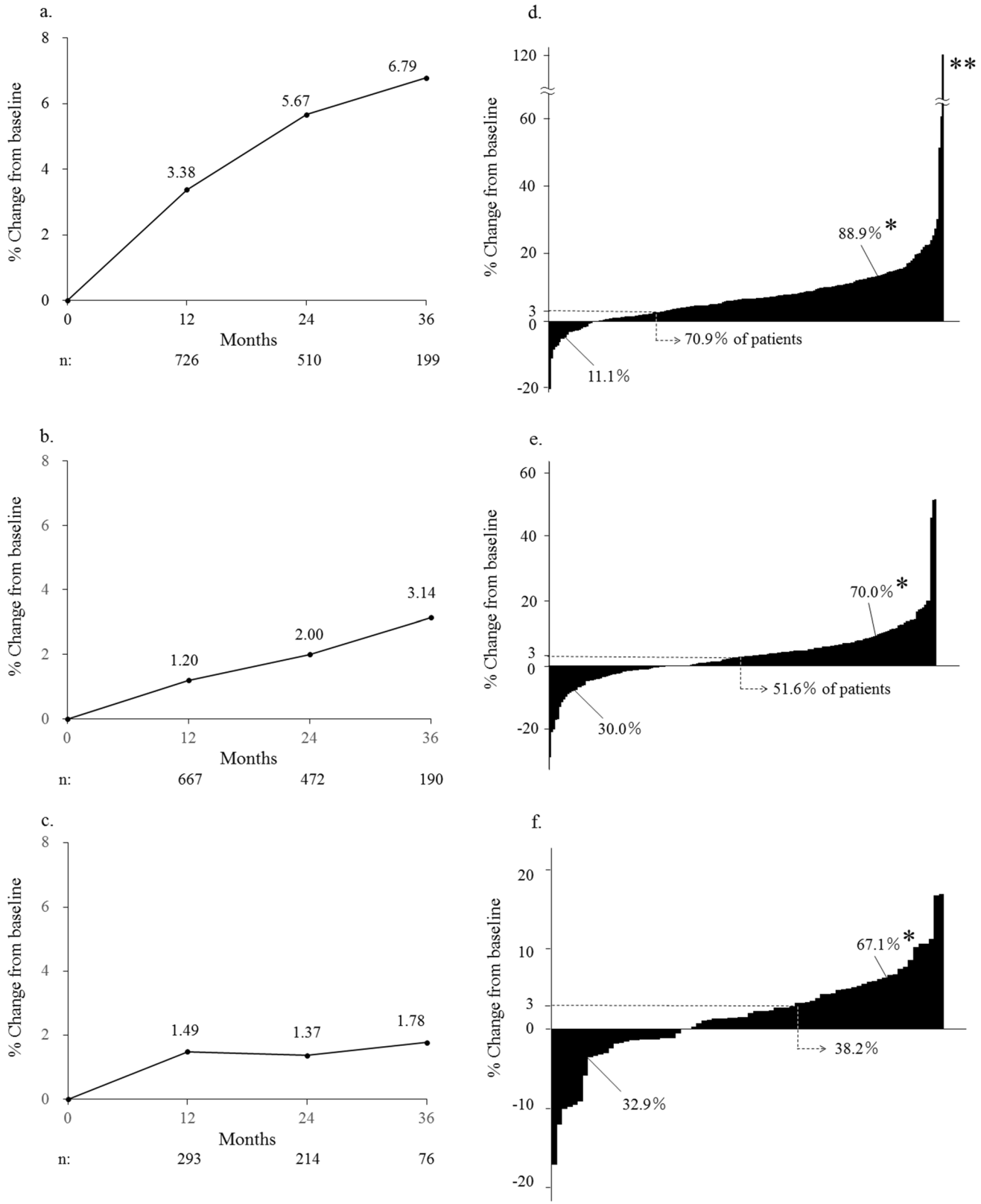

Fig. 2 Change of bone mineral density (BMD). BMD was calculated as % of YAM. Percent change (median) from baseline in BMD of the lumbar spine (**a**), femoral neck (**b**), and total hip (**c**). Waterfall plots of percent changes (median) of BMD at 36 months from baseline: lumbar spine (**d**), femoral neck (**e**), and total hip (**f**). YAM: Young adult mean. *Including patients with 0% change. **Only one patient increased lumbar spine BMD by 121.4%

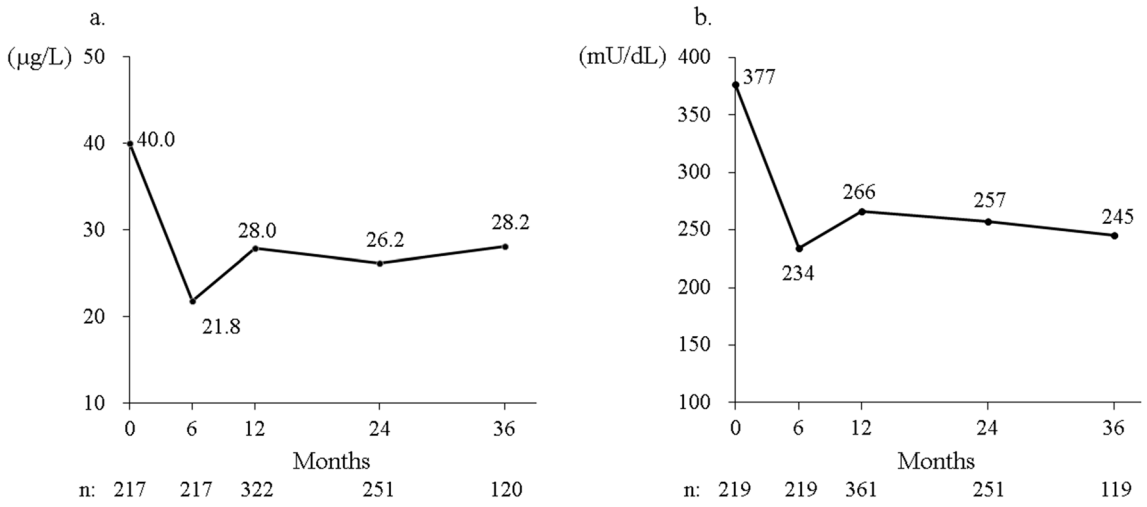

Fig. 3 Changes of bone turnover markers (BTMs). Percent changes (median) from baseline in P1NP (**a**) and TRACP-5b (**b**). Reference range of total P1NP: Men 18.1–74.1 μg/L, Premenopausal women 16.8–70.1 μg/L. Reference range of TRACP-5b: Men 170–590 mU/dL, Premenopausal women 120–420 mU/dL [8]. P1NP: type I procollagen-N-propeptide, TRACP-5b: tartrate-resistant acid phosphatase 5b

Table 3 Treatment persistence rate

	Total	Second infusion			Third infusion		
		N^a	%	χ^2 test	N^a	%	χ^2 test
Total	1406	989	70.3		727	51.7	
Sex							
Male	190	122	64.2		84	44.2	
Female	1216	867	71.3	$p=0.047$	643	52.9	$p=0.026$
Age (y)							
< 75	497	379	76.3		309	62.1	
≥ 75	909	610	67.1	$p<0.001$	418	46.0	$p<0.001$
Previous medicines for osteoporosis							
Yes	660	496	75.2		370	56.1	
No	746	493	66.1	$p<0.001$	357	47.9	$p=0.002$
Concomitant medicines for osteoporosis							
Yes	652	522	80.1		395	60.6	
No	754	467	61.9	$p<0.001$	332	44.0	$p<0.001$
Inpatient or outpatient at the first infusion							
Inpatient	138	52	37.7		32	23.2	
Outpatient	1265	935	73.9	$p<0.001^b$	695	54.9	$p<0.001^b$
Doctor's visit	3	2	66.7		0	0.0	

[a]Denotes the patient's status of survey persistence

[b]Inpatient vs Outpatient

(risedronate) [15]. A database analysis by Kishimoto and Maehara showed that the persistence rate tended to improve with a longer interval of bisphosphonate administration [16]. In the present survey, the persistence rate was 70.34% over 2 years and 51.71% over 3 years. Furthermore, 89.8% and 88.2% of the patients remaining on treatment received their second and third infusions, respectively, within 52 ± 4 weeks from the previous infusion date, suggesting good treatment compliance (Online Resource 7). Meanwhile, male, age ≥ 75 years, no previous medicines for osteoporosis, no concomitant medicines for osteoporosis, and inpatient at the first infusion were found to be the risk factors for treatment discontinuation (Table 3). Treatment persistence, especially of patients with such attributes, is an important factor to prevent secondary fractures. It will be necessary to construct a system

Table 4 Treatment persistence pre- vs. post-COVID-19 pandemic

Scheduled date for third infusion	Patients	Third infusion		Persistence rate (%)	χ^2 test
		Yes	No		
- February 29, 2020 (pre-pandemic start)	743	555	188	74.7	$p=0.141$
March 1, 2020 - (post-pandemic start)	246	172	74	69.9	
Total	989	727	262	73.5	

The start of the COVID-19 pandemic was set on March 1, 2020 (=post-pandemic) according to the following:

(i) Provision for anti-COVID-19 measures was fixed by governmental Novel Coronavirus Response Headquarters as of February 25, 2020) and (ii) Act on Special Measures against COVID-19 pandemic was enacted as of March 14, 2020. https://www.mhlw.go.jp/content/10900000/000599698.pdf

for inpatients that ensures cooperation among healthcare providers including an osteoporosis manager and communication with each patient even after hospital discharge.

Furthermore, the effects of the COVID-19 pandemic on patients' persistence with the infusions were investigated. The results showed no significant decrease in the persistence rate with the COVID-19 pandemic (74.7% vs. 69.9%, before vs after the pandemic start; $p=0.141$). In May 2020, the Japan Osteoporosis Society and the Japanese Society for Bone and Mineral Research announced that switching therapy to once-yearly ZOL infusion should be considered to maintain treatment persistence during the pandemic [17]. The result of this survey also suggests that once yearly infusion of ZOL is expected to continue osteoporosis treatment during the pandemic.

The present survey has a limitation of using no control drug, because it aimed to collect and confirm the safety and effectiveness of ZOL in daily clinical practice. Furthermore, this study was conducted in accordance with the GPSP Ministerial Ordinance (Ministerial Ordinance Concerning Standards for the Conduct of Post-marketing Surveillance and Testing of Pharmaceuticals: Ministry of Health, Labor and Welfare Ordinance No. 171, December 20, 2004), and no adjustment for confounding factors was made. Although this study has the bias of targeting medical institutions that were able to cooperate in the post-marketing survey, the participating medical institutions included special functioning hospitals, general hospitals, and clinics with/without beds nationwide, so the data are likely to accurately reflect actual clinical practice. Other limitations were that no central adjudication system was set for bone fracture imaging, and a limited number of BTM measurements were performed due to health insurance system restrictions.

In conclusion, the present post-marketing survey collected information from 1406 patients with osteoporosis and confirmed the safety and effectiveness of ZOL in the real-world setting, showing no obvious differences from the results obtained in the phase 3 ZONE study [7].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00774-023-01410-5.

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Declarations

Conflict of interest J. Takada received consulting fees and speaking fees from Asahi Kasei Pharma Corporation, (Tokyo, Japan). S. Sato, K. Arai, Y. Kito, Y. Oshita and K. Saito are employees of Asahi Kasei Pharma Corporation (Tokyo, Japan).

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