Calcif Tissue Int (2014) 94:311–318
DOI 10.1007/s00223-013-9812-9

ORIGINAL RESEARCH

Remission Over 3 Years in Patients with Paget Disease of Bone Treated with a Single Intravenous Infusion of 5 mg Zoledronic Acid

Jean-Pierre Devogelaer · Piet Geusens · Evis Daci · Evelien Gielen · Kris Denhaerynck · Karen MacDonald · Christine Hermans · Stefaan Vancayzeele · Ivo Abraham · Steven Boonen

Received: 13 August 2012 / Accepted: 4 July 2013 / Published online: 24 November 2013

Abstract Using data from the Belgian Paget's Disease Registry of 142 patients treated with a 5 mg intravenous infusion of zoledronic acid, we examined disease remission over 3 years in 98 patients with Paget disease of bone (PDB) seen in routine practice. Median age was 76 years, most patients (60.2 %) were male, and all were Caucasian. Median time since PDB diagnosis was 11.5 years, few patients (5.1 %) had a family history of PDB, and 32.6 % had received prior bisphosphonate and/or other treatments. The most common pagetic locations were pelvis, spine, femur, tibia, and skull. The most common symptoms included pain, impaired mobility, bone deformities, and joint disease: 36.7 % of patients had comorbid osteoarthritis and 16.3 % comorbid osteoporosis. Response rates were 93.3 % at 1 year, 89.5 % at 2 years, and 91.6 % at 3 years, statistically similar to an extension study of the original zoledronic acid trials. Twenty-one patients experienced a relapse over the 3-year period at a median of 20.7 months posttreatment; of these, 13 regained remission by the end of the observation period. Relapse was not associated with osteoarthritis, osteoporosis, or other comorbidities. Safety data were similar to those reported elsewhere. In summary, in this somewhat frailer sample of patients with PDB, effectiveness and safety data were similar to those observed in the original trial populations. These findings, which are the first on the use of zoledronic acid for PDB in routine clinical practice, underscore the therapeutic benefits and relative safety of zoledronic acid in the management of PDB in "real-world" clinical settings.

Keywords Paget disease of bone · Bisphosphonate · Zoledronic acid · Treatment · Remission

Professor S. Boonen passed away unexpectedly on 20 May 2013. This article is dedicated to him in recognition of his many contributions to the science and practice of metabolic bone disease.

J.-P. Devogelaer has consultant/advisory role to Novartis and Amgen. E. Daci, S. Vancayzeele, and C. Hemans are employees of Novartis. S. Boonen had consultant/advisory role to Novartix. I. Abraham, K. Denhaerynck, and K. MacDonald are employees of Matrix45 and are prohibited from owning equity in client organizations or contracting independently with client organizations. All other authors have stated that they have no conflict of interest.

J.-P. Devogelaer
Department of Rheumatology, Saint-Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium

P. Geusens
Subdivision of Rheumatology, Department of Internal Medicine, Maastricht University Medical Centre and CAPHRI School of Public Health and Primary Care Research, Maastricht University, Maastricht, The Netherlands

P. Geusens
Biomedical Research Centre, Hasselt University, Hasselt, Belgium

E. Daci · C. Hermans · S. Vancayzeele
Novartis Pharma, Vilvoorde, Belgium

E. Gielen · S. Boonen
Division of Gerontology and Geriatrics, Department of Clinical and Experimental Medicine, Katholieke Universiteit Leuven, Leuven, Belgium

K. Denhaerynck
Matrix45; Institute of Nursing Science, Universität Basel, Basel, Switzerland

K. MacDonald
Matrix45, Tucson, AZ, USA

I. Abraham (✉)
Matrix45; Center for Health Outcomes and Pharmacoeconomic Research; Department of Pharmacy Practice and Science, College of Pharmacy, University of Arizona, 1295 N Martin

Introduction

Paget disease of bone (PDB) is a chronic, progressive metabolic skeletal disorder characterized by focal abnormal increases in bone resorption and formation leading to weakened bone strength and abnormal bone architecture [1–4]. Antiresorptive therapy with bisphosphonates is the first-choice treatment for PDB [1]. Of the six agents in clinical use, zoledronic acid has the highest affinity for bone mineral, resulting in a long half-life, and is the most potent inhibitor of farnesyl diphosphate synthase in vitro and bone resorption in vivo [3, 5–7]. The 6-month efficacy and safety of a single dose of 5 mg zoledronic acid administered intravenously over 15 min versus daily oral treatment with risedronate for 60 days were documented in the pooled analysis of two identical randomized, double-blind, controlled phase 3 trials [8]. At 6 months, 96.0 % of patients in the zoledronic acid arm had a therapeutic response, defined as normalization of serum alkaline phosphatase (ALP) levels or a reduction of ≥75 % in serum alkaline phosphatase (sALP) excess, compared to 74.3 % of patients in the risedronate arm ($p < 0.001$). ALP normalized in 88.6 vs. 57.9 % of patients in the respective arms ($p < 0.001$). Median time to first therapeutic response was 64 vs. 89 days, respectively ($p < 0.001$).

The effects of zoledronic acid may extend beyond 6 months. Patients who showed therapeutic response in the registration trials [8] were eligible to enter an open extension observational study. At 2 years, 98 % of patients on zoledronic acid were still in remission versus only 57 % for those on risedronate ($p < 0.0001$) [9]. A recent analysis compared a residual of 44 % of the original responders in the zoledronic acid arm and a residual of 18 % of those randomized to the risedronate arm up to 6.5 years following treatment. At 3 years, 88 % of patients treated with zoledronic acid had normalized ALP levels versus 43 % for those who received risedronate; at 6.5 years, these rates were 84 and 43 %, respectively [10].

Using data from the Belgian Paget's Disease Registry, we report on the remission rates and remission duration observed over 3 years in 98 evaluable PDB patients treated with a single 5 mg infusion of zoledronic acid. We also report on determinants of and retreatment following relapse, as well as serum creatinine and calcium levels over the same time period.

Ave., Tucson, AZ, USA
e-mail: iabraham@matrix45.com;
abraham@pharmacy.arizona.edu

I. Abraham
Department of Family and Community Medicine, College of Medicine, University of Arizona, Tucson, AZ, USA

Methods

Registry

The Belgian Paget's Disease Registry is a multicenter disease and product registry of patients with PDB treated with a single IV infusion of 5 mg zoledronic acid. Patients were recruited into the registry at the time of their zoledronic acid treatment and followed for a minimum of 36 months on a schedule determined by their physician to monitor treatment outcomes and disease remission. There were no fixed time points for visits and data collection and no required data to be collected; only data available from routine clinical practice were recorded. The data model included patient demographics, clinical parameters of PDB, relevant laboratory and imaging tests, treatment and retreatment decisions, concomitant medications, and remission. Twenty-two Belgian sites participated in the registry, mainly rheumatology centers ($n = 16$) but also rehabilitation ($n = 3$) and internal medicine, geriatrics, and endocrinology centers ($n = 1$ each). Seven were academic medical centers.

The registry includes male and female adults (age ≥18 years) diagnosed with PDB and being treated de novo with a single IV infusion of 5 mg zoledronic acid over 15 min per their treating physician's best clinical judgment and in accordance with treatment guidelines, a scientific leaflet, and Belgian reimbursement criteria. Both newly diagnosed patients and patients previously treated for PDB but for whom a new treatment was indicated were eligible for inclusion. Excluded were patients previously treated with zoledronic acid or with a treatment indication other than PDB. All patients (or their legal guardians) provided written informed consent to be included in the registry.

Time Points

The 1- and 2-year time points were calculated, respectively, as 12 ± 4 and 24 ± 4 months following infusion with zoledronic acid. The 3-year time point was calculated as any visit at least 32 months following infusion.

Effectiveness and Safety Outcomes

The primary outcome of interest was disease remission versus relapse as rated by the patients' treating physician. Physicians were instructed to consider ALP normalization or a reduction of 75 % or more in excess phosphatase as indicators of therapeutic response, but this was not verified independently. The study protocol also specified that treatment should conform to the approved label and reimbursement criteria. In Belgium, zoledronic acid is reimbursed for PDB upon written certification by the treating

physician that the patient (1) has either clinical active symptoms of Paget disease (e.g., pain, osteolytic lesions, fractures, bone deformities, nerve compressions) and that the ALP levels exceed the upper normal limit or (2) is clinically asymptomatic but has radiological signs of Paget disease and (2.1), for patients less than 50 years old, ALP levels exceed the upper normal limit or (2.2), for patients 50 years or older, ALP levels exceed more than twice the upper normal limit.

While we did not verify during the course of the study whether patients indeed showed the above-specified reduction of 75 % or more in excess phosphatase, we did so post hoc. We also applied post hoc the Russell et al. [11] historical definition of positive treatment response as a 30 % or greater fall in ALP compared to pretreatment values.

Secondary outcomes included duration of remission (in months) and, alternately, time to first relapse (in months), with early relapse possibly indicating non- or poor response to treatment. Time to first relapse was modeled as a function of comorbidities. Safety outcomes included adverse events (AEs) suspected to be related to zoledronic acid, as well as serum creatinine and calcemia.

Statistical Analysis

The analysis population consisted of the 98 patients for whom data were available at the 3-year time point. The safety population included the 142 patients who received an infusion of zoledronic acid.

Descriptive statistics included measures of frequency, central tendency, and dispersion under consideration of the level of measurement of the variables. Comparison with literature data was done using Fisher's exact test for discrete data and the *t* test for independent samples for continuous variables. The latter test was also applied to compare the duration of remission between comorbid conditions. Proportional hazards regression analysis was performed to model the time between baseline and first visit in which the patient showed relapse, taking into account that the majority of patients remained in remission. Testing for trends over time in serum creatinine and calcemia employed mixed effects regression using time as a fixed-effects and patient as a random-effects variable. Creatinine was logarithmized to meet the assumption of normal distribution of the residuals.

Results

Patient Disposition

In total 142 patients were enrolled between February 10, 2006, and the census date for analysis of October 27, 2010. Of these, 98 (69.0 %) had follow-up data at 32 or more months compared to 44 (31.0 %) patients who were discontinued for various reasons and/or had no visit at 32+ months (Fig. 1). At the time of census patients had been followed for a mean of 37.3 ± 2.6 months and had been seen between two and nine times following treatment. Most patients (58.2 %) were followed by the physician who prescribed zoledronic acid versus external follow-up by general practitioners (18.4 %), rheumatologists (13.3 %), orthopedic surgeons or internists (3.1 % each), and endocrinologists (1.0 %). Three (3.1 %) patients were followed by other clinicians.

Demographics and Clinical Status at Enrollment

Evaluable patients had a mean age of 74.2 years, and the majority (84.7 %) were age 65 or older (Table 1). Most (60.2 %) were male, and all were Caucasian. Median body mass index was 25.8 kg/m^2. In 67.4 % of patients PDB had been diagnosed 5 or more years prior to zoledronic acid treatment (median = 11.5 years). Pagetic sites were most frequently located in the spine (82.6 % of patients), pelvis (63.3 %), femur (40.8 %), tibia (31.6 %), and skull (22.5 %). The most common complaints at enrollment were pain (82.7 % of patients), impaired mobility (51.0 %), bone deformities (34.7 %), joint disease (24.5 %), and pathological fractures (15.3 %). Some patients presented with comorbid osteoarthritis (36.7 %) or osteoporosis (16.3 %). About one-third (32.6 %) of patients had been treated previously with various other bisphosphonates and calcitonin and/or had received supportive therapy with calcium, vitamin D, and anti-inflammatory or analgesic agents.

Compared to patients randomized to the zoledronic acid arm in the original trials [8] and in the extended observational study [9, 10], in our registry subjects were older ($p = 0.006$ and 0.002, respectively) and fewer of them had been treated previously with other bisphosphonates ($p = 0.011$ and 0.018, respectively). There were no significant differences in mean sALP at the time of infusion between the three samples. Compared to the original trial subjects [8], patients in our registry tended to weigh less ($p = 0.031$) but gender distributions between the two were statistically similar.

Bisphosphonate Exposure and Concomitant Treatment

All evaluable patients received one dose of 5 mg zoledronic acid administered intravenously over 15 min according to their treating physician's decision. The most common reasons to treat with zoledronic acid were elevated ALP (82.7 % of patients), pain (78.6 %), and/or findings from imaging studies (52.0 %) (Table 2). In the

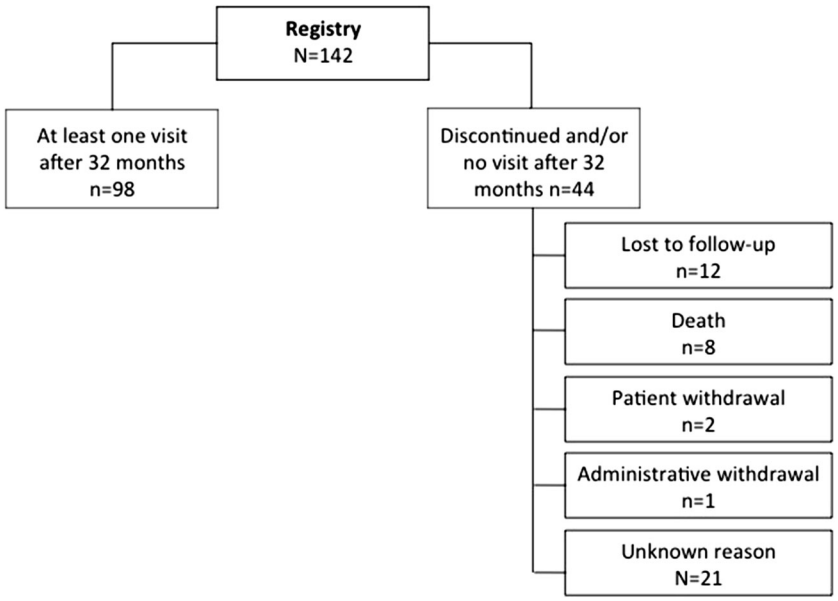

Fig. 1 Patient disposition at census date

first year following initial treatment with zoledronic acid, one patient was retreated with zoledronic acid and one with pamidronate. By the end of year 3, 11 patients had been retreated, including nine with zoledronic acid, one with pamidronate, and one with zoledronic acid complemented with pamidronate.

Nearly all patients were prescribed calcium (95.9 %) and vitamin D (96.9 %) for at least 10 days after zoledronic acid treatment. One patient was taking NSAIDs, and one was taking analgesics at inclusion and continued thereafter.

Remission

Per treating physicians' reports, 93.3 % of patients were in remission at 1 year, 89.5 % at 2 years, and 91.6 % at 3 years, rates similar to those reported for the same time points in the extended observation study (all p values nonsignificant) [10]. Of the 87 patients in remission at 3 years, 20 were newly diagnosed patients, whereas 67 had been diagnosed at an earlier time point. One of the eight patients not in remission at 3 years was newly diagnosed. There was no association between the 3-year remission rate and being newly diagnosed with PDB at the time of infusion or with previous bisphosphonate treatment.

Relapse and Retreatment Outcomes

As shown in the time plot in Fig. 2 and the flowchart in Fig. 3, 21 patients (21.4 %) showed a relapse at some point during the follow-up period. Of these, 13 (1.26, 10.8, 14.1, 15.2, 16.1, 16.4, 25.5, 25.6, 3.12, 4.1, 5.12, 6.3, 9.1) regained their remission status by the 3-year time point, including five patients (10.8, 14.1, 16.1, 25.5, 25.6) who evidenced a slow treatment response. Eight of the 21 relapsing patients (1.15, 25.1, 3.13, 3.16, 3.18, 3.27, 3.8, 9.2) did not show treatment response at the end of the observation period. Of these, 5 patients showed a treatment response during the observation period but not at the 3-year time point (1.15, 25.1, 3.13, 3.18, 3.8), whereas three patients (3.16, 3.27, 9.2) showed (virtually) no response to treatment with zoledronic acid over the study period. Five of the eight patients who did not show a treatment response at study end had been treated with other bisphosphonates prior to the zoledronic acid infusion.

We examined the reported sALP recordings for the three patients who did not respond to zoledronic acid treatment (all data as available). Patient 3.16 had sALP values of 105 U/L at enrollment, 123 U/L at 114 days, 123 U/L at 218 days, 108 U/L at 521 days, and 98 at 703 days. Patient 3.27 showed sALP values of 175 U/L at enrollment, 231 U/L at 338 days, 161 U/L at 422 days, 190 U/L at 800 days, and 219 U/L at 1,164 days. Patient 9.2 had sALP values of 112 U/L at enrollment, 80 U/L at 376 days, 73 U/L at 558 days, 76 U/L at 649 days, and 98 at 703 days. All three patients reported pain at one or more time points.

We also assessed the sALP results for the 18 patients with an initial response that was not sustained at the 3-year time point. Their sALP values were not statistically different at visits with relapse compared to visits in remission ($p = 0.10$).

Relapses occurred anywhere from 1.0 to 38.2 months postinfusion, with a median of 20.7 months (Table 3). The mean and median relapse times for patients with and without osteoarthritis, osteoporosis, or other comorbidities were not

Table 1 Patient demographics and clinical status at enrollment

	Range	Median	Mean ± SD
Demographics			
Age (years)	47–90	76	74.2 ± 9.8
Weight (kg)	40–179	71	73.4 ± 16.4
Height (cm)	75–188	166	164.5 ± 13.3
		n	%
Gender			
Male		59	60.2
Female		39	39.8
	Range	Median	Mean ± SD
Paget disease of bone			
Duration (years)	0–41	11.5	12.5 ± 10.9
ALP (U/L)	82–2,370	347	469 ± 404
		n	%
Family history		5	5.1
Past treatment		32	32.6
Pamidronate		30	30.6
Tiludronate		32	32.6
Risedronate		13	13.3
Other bisphosphonates		20	20.4
Calcitonin		22	22.5
Calcium		20	20.4
Vitamin D		20	20.4
NSAIDs		7	7.1
Analgesics		6	6.1
Other		1	1.0

	Left		Right	
	n	%	*n*	%
Localization of pagetic lesions				
Femur	16	16.3	24	24.5
Tibia	15	15.3	16	16.3
Fibula	2	2.0	3	3.1
Humerus	7	7.1	6	6.1
	n	%		
Spine				
Cervical	1	1.0		
Thoracic	16	16.3		
Lumbar	34	34.7		
Sacral	28	28.6		
Coccyx	2	2.0		
Pelvis	62	63.3		
Skull	22	22.5		
Other	17	17.3		

Table 1 continued

	n	%
Symptoms		
Pain	81	82.7
Bone deformities	34	34.7
Mobility impairment	50	51.0
Fractures	15	15.3
Increased skull size	7	7.1
Hearing loss	11	11.2
Local skin warming	8	8.2
Joint disease	24	24.5
Nerve compression syndromes	3	3.1
Cardiovascular complications	4	4.1
Neoplastic disease	2	2.0
Comorbidities		
Osteoarthritis	36	36.7
Osteoporosis	16	16.3
Rheumatoid arthritis	0	0.0
Other	10	10.2

Categories are not mutually exclusive; hence, totals may exceed 100 %

ALP serum alkaline phosphatase, *NSAID* nonsteroidal anti-inflammatory drug

statistically significant (all p values nonsignificant). Proportional hazards regression modeling did not retain these conditions as independent predictors of time to first relapse.

Safety

A total of 180 AEs were reported in 79 of the 142 (55.6 %) patients treated with zoledronic acid, for an AE rate per patient year of observation of 0.06. In 23 (29.1 %) of these patients at least one AE was suspected to be related to zoledronic acid. Treatment with zoledronic acid was the suspected cause of 3 of the 38 musculoskeletal and connective tissue AEs, 0 of the 23 cardiovascular AEs, and 12 of the 19 flu-like symptoms and fever AEs. Eight patients experienced fractures, but only one case was assumed to be associated with treatment. Three cases of atrial fibrillation and two cases each of arrhythmia and palpitations were reported, none suspected of being related to zoledronic acid. No cases of osteonecrosis of the jaw were reported.

In total 38 serious AEs (SAEs), including 9 fatal, were reported in 31 patients, for an SAE rate per patient year of observation of 0.02. None of the fatal and only two of the nonfatal SAEs were suspected of being treatment-related. The first patient was an 85-year-old male diagnosed with PDB 2 years prior and admitted to the hospital the day following treatment with zoledronic acid. The most

Table 2 Physicians' reported reasons to treat patients with 5 mg zoledronic acid

	n	%
Pain	77	78.6
Bone deformities and complications	16	16.3
Neurological complications	4	4.1
Location with potential for complications	7	7.1
Elevated ALP	81	82.7
Increased bone markers	16	16.3
X-ray findings	31	31.6
Bone scintigraphic findings	20	20.4
Preoperative treatment prior to orthopedic surgery	1	1.0
Other	5	5.1

Categories are not mutually exclusive; hence, totals may exceed 100 %

ALP serum alkaline phosphatase

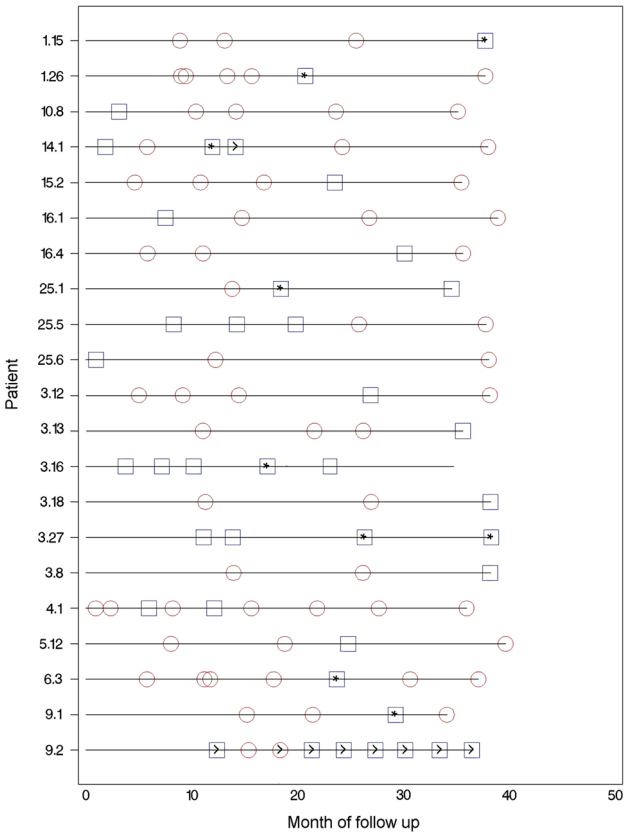

Fig. 2 Management of patients with no treatment response and/or relapse. The *x*-axis represents month of follow-up after treatment with zoledronic acid. The time line for each of the 21 patients who showed relapse at some point during follow-up is presented *horizontally*. *Circle* visit on which patient was in remission, *square* visit on which patient was not in remission, *asterick* visit on which patient was retreated with zoledronic acid, *greater than* visit on which patient was retreated with pamidronate. Patients 3.16, 3.27, and 9.2 may be considered nonresponders and patients 10.8, 14.1, 16.1, 25.5, and 25.6 slow responders to treatment with zoledronic acid

common AEs included general malaise, fever, fatigue, abdominal pain, and dyspnea. Laboratory assessments showed increased levels of creatinine kinase, C-reactive protein, and lactate dehydrogenase, as well as hypocalcemia and hypophosphatemia. Hypocalcemia was associated with subobstruction (abdominal pain), which resolved spontaneously. The second patient was a 65-year-old female with PDB diagnosed 12 years prior, known osteoporosis, a family history of PDB, and prior treatment with pamidronate. She was hospitalized about 3 months following treatment with zoledronic acid with a spontaneous right hip fracture. Though PDB was a possible etiology, the fracture was suspected to be related to treatment with zoledronic acid because of its nontraumatic character, its unusual subtrochanteric transversal (horizontal) shape, and, per the surgeon's report, the unusually hard fractured bone. Both patients remained in remission.

Serum creatinine levels declined by 1 % per year ($p = 0.02$). Calcemia values remained stable over the observation period ($p = 0.64$).

Discussion

Prior to the advent of long-acting intravenous zoledronic acid, oral bisphosphonates taken daily for 2–6 months were the standard of care for PDB. However, gastrointestinal side effects, poor absorption, potentially impaired bioavailability, and the need to fast before and after intake have been associated with poor adherence and subsequent AEs among patients with osteoporosis [12–14], findings that, arguably, can be extended to patients with PDB. Further, pamidronate requires multiple serial infusions, each lasting several hours. Zoledronic acid represents a marked advance in therapeutic benefit and patient convenience owing to a convenient single 15-min IV administration every 12 months; the drug's high affinity for bone mineral and its potent inhibition of the enzyme farnesyl diphosphate synthase [5, 6]; the qualitative difference in terms of stability of biochemical markers of bone turnover [10]; and, as now documented in two previous reports [9, 10] and our findings, long-term remission of PDB.

To our knowledge, apart from a small case series at one center extending 12–18 months postinfusion [15, 16], our registry offers the first adequately powered long-term multicenter data on remission and relapse in routine ("real-world") clinical practice. The findings confirm the remission rates at 1, 2, and 3 years reported by Reid and colleagues [10]. Further, patients in our registry were on average 3.4 and 4 years older compared to the samples of, respectively, the original trials [8] and the extended study subsample [10]. Combined with weighing on average 4.2 kg less at the time of zoledronic acid treatment [8], our

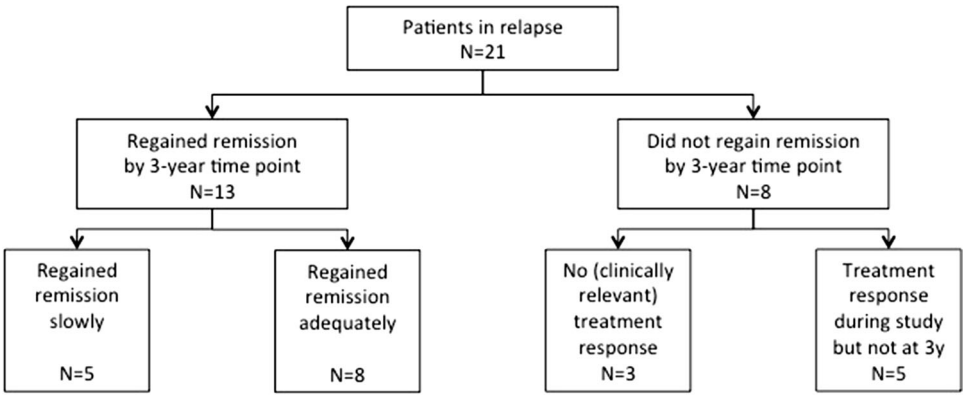

Fig. 3 Flowchart of the 21 patients experiencing relapse

Table 3 Time to first relapse (months) following treatment with 5 mg zoledronic acid

	Min	Max	Median	Mean ± SD	*p*
All patients	1.0	38.2	20.7	19.1 ± 13.0	
By comorbidity					
Osteoarthritis					
No	1.8	38.2	24.8	21.6 ± 14.4	ns
Yes	1.0	35.6	14.8	16.4 ± 11.4	
Osteoporosis					
No	1.0	38.2	18.4	17.4 ± 12.1	ns
Yes	3.8	38.2	32.4	26.7 ± 15.8	
Other					
No	1.8	38.2	23.7	21.5 ± 13.0	ns
Yes	1.0	18.4	8.5	9.1 ± 7.5	

ns Nonsignificant

sample represents a frailer population than those studied to date.

Being an observational study, there were no mandated tests or other assessments and only data from routine clinical practice were used. From a scientific point of view, asking physicians for their clinical evaluation of PDB remission and relapse may have made for a less rigorous assessment method compared to prior longitudinal reports but is consistent with routine clinical practice [9, 10]. In Belgium zoledronic acid treatment for PDB is reimbursed only if the prescribing physician provides written certification as to active clinical symptoms or radiological evidence, along with sALP levels. Hence, physicians have to consider objective data in their clinical evaluation and reimbursement certification. Most likely, this information was the basis for their data entries on the registry. Further, despite the potential for opportunistic ratings of treatment success, such assessments better reflect routine clinical practice.

Our findings confirm the relapse rates reported by Reid et al. [10] yet offer some new insights as well. Unlike Reid et al., we found no association between relapse and prior bisphosphonate use or being newly versus previously diagnosed. Comorbid osteoarthritis or osteoporosis was not predictive of relapse. That 13 of the patients experiencing relapse regained remission by the end of the observational period underscores the importance of retreatment with zoledronic acid, including in patients showing either no early treatment response or a relatively early relapse (see Fig. 2). Of the eight patients failing to show remission over the course of the study, five had been previously treated with bisphosphonates. Possible treatment failure, treatment resistance, or slow treatment response should be evaluated in future studies as has already been shown for pamidronate [17].

On the safety side, the AE and SAE rates per patient year of observation in our sample were statistically similar to those reported in the extended observation study [10]. Flu-like symptoms and fever are known side effects of zoledronic acid treatment. The frequency of musculoskeletal and connective tissue AEs may have been confounded by comorbid osteoarthritis. None of the cardiovascular AEs were attributed to treatment with zoledronic acid and may instead be due to the advanced age of patients. Only one fracture was suspected of being related to treatment. No cases of osteonecrosis of the jaw were reported. There was no evidence of toxicity to a major organ system.

Our analyses are limited to 98 patients from one country. Future observational studies might benefit from a multicenter and multicountry design to increase sample size, mirror regional variation in the epidemiology of PDB, and evaluate regional differences in remission. This will also enable further assessment of possible age differentials in remission; any role of elapsed time between PDB diagnosis and treatment with zoledronic acid; variation in patients and treatments and associated variations in treatment outcomes; possible treatment resistance to bisphosphonates; the effectiveness of supportive therapy with nonsteroidal anti-inflammatory or analgesic agents [18]; and, per data availability, formal validation for the accuracy of physician assessments of

remission and objective markers of response. Larger sample sizes will also increase the precision of AE and SAE rates and the adjudication of their relationship to zoledronic acid.

In conclusion, in this somewhat frailer sample of patients with PDB, effectiveness and safety data were similar to those observed in an open extended study of the original trial populations. These findings, which are the first on the long-term use of zoledronic acid for PDB in routine clinical practice, underscore the therapeutic benefits and relative safety of zoledronic acid in the management of PDB in "real-world" settings.

Acknowledgments The authors wish to thank the patients who volunteered to be part of the Belgian Paget's Disease Registry and the investigators and staff at participating centers. The authors also thank Hilde Capiau, Gail Tucker, An Hendrickx, Kathleen Piotrowski, and Evelyne Putman for their assistance in implementing the study. The Registry is supported by grants and contracts from Novartis Pharma.

References

1. Ralston SH, Langston AL, Reid IR (2008) Pathogenesis and management of Paget's disease of bone. Lancet 372:155–163
2. Michou L, Brown JP (2011) Emerging strategies and therapies for treatment of Paget's disease of bone. Drug Des Devel Ther 5:225–239
3. Reid IR, Hosking DJ (2011) Bisphosphonates in Paget's disease. Bone 49:89–94
4. Devogelaer JP, Nagant de Deuxchaisnes C (2003) Paget's disease of bone. In: Hochberg MC, Silman AJ, Smolen JS et al (eds) Rheumatology, vol 2, 3rd edn. Mosby, London, pp 2139–2147
5. Green JR, Rogers MJ (2002) Pharmacologic profile of zoledronic acid: a highly potent inhibitor of bone resorption. Drug Dev Res 55:210–224
6. Rogers MJ (2003) New insights into the molecular mechanisms of action of bisphosphonates. Curr Pharm Des 9:2643–2658
7. Dunford JE, Thompson K, Coxon FP et al (2001) Structure–activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. J Pharmacol Exp Ther 296:242–245
8. Reid IR, Miller P, Lyles K et al (2005) Comparison of single infusion of zoledronic acid with risedronate for Paget's disease. N Engl J Med 353:898–908
9. Hosking D, Lyles K, Brown JP et al (2007) Long-term control of bone turnover in Paget's disease with zoledronic acid and risedronate. J Bone Miner Res 22:142–148
10. Reid IR, Lyles K, Su G et al (2011) A single infusion of zoledronic acid produces sustained remissions in Paget's disease: data to 6.5 years. J Bone Miner Res 26:2261–2270
11. Russell RG, Smith R, Preston C et al (1974) Diphosphonates in Paget's disease. Lancet 303:894–898
12. Silverman SL, Schousboe JT, Gold DT (2011) Oral bisphosphonate compliance and persistence: a matter of choice? Osteoporos Int 22:21–26
13. Sampalis JS, Adachi JD, Rampakakis E et al (2012) Long-term impact of adherence to oral bisphosphonates on osteoporotic fracture incidence. J Bone Miner Res 27:202–210
14. Netelenbos JC, Geusens PP, Ypma G, Buijs SJ (2011) Adherence and profile of non-persistence in patients treated for osteoporosis: a large-scale, long-term retrospective study in the Netherlands. Osteoporos Int 22:1537–1546
15. Avramidis A, Polyzos SA, Moralidis E et al (2008) Scintigraphic, biochemical, and clinical response to zoledronic acid treatment in patients with Paget's disease of bone. J Bone Miner Metab 26:635–641
16. Polyzos SA, Anastasilakis AD, Efstathiadou Z et al (2009) The effect of zoledronic acid on serum dickkopf-1, osteoprotegerin and RANKL in patients with Paget's disease of bone. Horm Metab Res 41:846–850
17. Devogelaer JP (2002) Modern therapy for Paget's disease of bone. Focus on bisphosphonates. Treat Endocrinol 1:241–257
18. Langston AL, Campbell MK, Fraser WD et al (2009) Randomized trial of intensive bisphosphonate treatment versus symptomatic management in Paget's disease of bone. J Bone Miner Res 25:20–31