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ORIGINAL ARTICLE

Factors associated with acute-phase response of bisphosphonate-naïve or pretreated women with osteoporosis receiving an intravenous first dose of zoledronate or ibandronate

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Abstract
Summary A first intravenous dose of bisphosphonates may be associated with an acute-phase response (APR). In bisphosphonate-naïve women with postmenopausal osteoporosis, the characteristics and frequency of APR may differ by compound. Prior bisphosphonate exposure was predictive of APR risk and severity.
Introduction Intravenous (IV) administration of bisphosphonates (BP), such as zoledronate (ZOL) and ibandronate (IBN), may be associated with an APR. The characteristics of APR may differ by compound. The aim of the present study was to evaluate the characteristics of APR (rates, signs and symptoms, severity), in the absence of any preventive measure, after a first IV application of ZOL or IBN in patients naïve or previously exposed to BP in a real-world clinical setting.
Methods This is an open-label prospective exploratory study with two cohorts of consecutive postmenopausal women with osteoporosis treated with either IV ZOL or IBN at the Department of Osteoporosis of the University Hospital of Berne, Switzerland.
Results Intravenous BP was administered to 725 women (411 ZOL and 314 IBN). Prior oral or IV BP use was less frequent in the ZOL group (61.8 vs. 71.7%, $p = 0.005$). In total, 301 women (41.5%) reported the presence of one or more signs or symptoms of APR with rates for ZOL and IBN of 47.7 and 33.4%, respectively ($p < 0.001$). Corresponding APR rates in the subgroup of BP-naïve patients were 55.6 and 32.4%, respectively ($p < 0.001$). The leading APR clinical sign was the presence of post-dose myalgia or arthralgia (68.1%). Prior BP exposure was predictive of both APR risk and severity, and lower serum 25-hydroxy vitamin D (25(OH)D) levels were possibly predictive of severity.
Conclusions In a real-world setting, APR rates with ZOL and IBN may be higher than reported in randomised controlled trials and may differ by compound, prior BP exposure, and serum 25(OH)D levels.

Keywords Acute-phase response · Ibandronate · Postmenopausal osteoporosis · Zoledronate

Introduction

Bisphosphonates (BP) administered intravenously (IV), such as zoledronate (ZOL) 5 mg once yearly and ibandronate (IBN) 3 mg every 3 months, are first-line therapies for postmenopausal osteoporosis [1, 2]. Bisphosphonates are chemically stable analogues of inorganic pyrophosphate (P–O–P) resistant to enzymatic hydrolysis, which bind strongly to hydroxyapatite crystals, sharing a high affinity for bone mineral related to their sole common characteristic, the P–C–P moiety [3–5]. The individual efficacy and safety profile of each BP is highly dependent upon its specific chemical structure, i.e. the side chain attached to the P–C–P moiety [3]. In addition, the side chain is essential with regard to the potency of the individual compounds with nitrogen-containing BP, such as IBN and ZOL, belonging to the most potent compounds [5]. As such, each bisphosphonate must be considered as a unique compound in terms of not only potency but also efficacy and safety

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[3]. While their biological effects were originally ascribed to their physico-chemical effects on hydroxyapatite crystals, their effects on cells are key to their clinical efficacy when used as antiresorptives for treating metabolic bone diseases [3, 5]. After having been internalised by bone-resorbing osteoclasts, nitrogen-containing BP inhibit the farnesyl pyrophosphate synthase in the mevalonate pathway, resulting in the loss of function of that pathway and in osteoclast apoptosis [6]. It has been suggested that intermediate metabolites, namely isopentenyl diphosphate and dimethylallyl diphosphate, may then accumulate intracellularly and lead to gamma/delta T cell activation and cytokine release, the latter resulting in characteristic post-dose symptoms known as the acute-phase response (APR) to bisphosphonate treatment in humans [7, 8].

Acute-phase response is the most common transient side effect occurring within 24 to 72 h after the IV administration of BP, with highest incidences seen after the first IV administration [9]. The term APR includes influenza-like symptoms, such as fatigue, malaise, headache, myalgia, arthralgia, bone pain, increasing body temperature and, rarely, chills. In the DIVA-study, a randomised controlled pivotal trial conducted with IBN, the APR rate was 5% after exclusion of women with a history of any previous use of IV BP or of oral BP use during the 6 months prior to inclusion [10]. In the HORIZON-study, a randomised controlled pivotal trial conducted with ZOL, the APR rate was 32% after a BP washout period of variable duration depending on the previously used BP [11]. This rate rose to 42% when clusters of adverse events within the first 3 days after study drug infusion were applied for defining an APR [12]. Finally, in a retrospective evaluation of APR after IV administration of ZOL under conditions of daily practice, APR rates exceeded 50% [13]. In these studies, the degree of severity of the clinical symptoms characterising an APR ranged from mild to severe. Risk factors associated with an increased risk of APR after the first application of ZOL have been identified, including but not limited to the following: younger age, non-Japanese Asian ethnicity and current use of nonsteroidal anti-inflammatory drugs [12]. Furthermore, factors associated with a reduced risk of APR such as current smoking and previous use of oral bisphosphonates were reported [12].

Outside of clinical trials, data on the incidence, the degree of severity and risk factors of APR in large patient populations are scarce. The aim of the present study was to further explore characteristics of APR with IV ZOL and IBN in the daily practice setting.

Materials and methods

This study was conducted at the Department of Osteoporosis of the University Hospital of Bern, Switzerland, as an open-label exploratory prospective study comparing APR in two cohorts of consecutive postmenopausal women with osteoporosis treated for the first time with either ZOL or IBN between January 2007 and December 2010. The study was approved by the institutional review board of the University Hospital of Bern, Switzerland.

Subjects and clinical evaluation

All included women had osteoporosis or severe osteoporosis in accordance with the operational disease definition suggested by the World Health Organization, i.e. an areal bone mineral density (BMD) T-score at or below −2.5 assessed by dual energy X-ray absorptiometry (DXA), with or without prevalent fractures [14, 15]. All women received a first dose of either ZOL 5 mg or IBN 3 mg administered as a short IV infusion over 15 to 20 min at the Department of Osteoporosis of the University Hospital of Bern, Switzerland. All patients were adequately supplied with calcium and vitamin D prior to the infusion and all were informed about the possible occurrence of flu-like symptoms during the days following the IV infusion. In accordance with the Swiss prescribing information of ZOL and IBN at the time of the study, no preventive treatment was prescribed and no preventive or symptom-alleviating measures were recommended.

At baseline, patient demographics and history were collected by face-to-face interviews conducted by staff physicians, including personal and familial medical and fracture history; age at menopause; previous or current use of any drugs influencing bone health, such as hormone replacement therapy (HRT) and corticosteroids; drinking habits (three or more units of alcohol daily) and current smoking status; and prior ever use of bisphosphonates (prior BP exposure) or not (BP naïve). Measured lab parameters included the following: fasting serum calcium, phosphate and creatinine, serum alkaline phosphatase (ALP), serum osteocalcin (OC), urinary deoxypyridinoline/creatinine ratio (DPD/Crea), serum β-isomerised C-terminal crosslinking telopeptide of type I collagen (CTX), serum 25-hydroxyvitamin D (25(OH)D), serum parathyroid hormone (PTH) and serum protein electrophoresis. Patients with secondary osteoporosis were ruled out by our clinical and laboratory standard protocol and were not included. Areal BMD was assessed by DXA and results expressed as T-scores defined as the number of standard deviations from the mean of a healthy young female population. The National Health and Nutrition Examination Survey III (NHANES III) database [16, 17] served as a reference for all hip sites, and the manufacturer's normative database was used as a reference for the lumbar spine after analysis according to rules of the International Society of Clinical Densitometry [18, 19]. For tibial BMD measurements, the local normative database derived from healthy Caucasian women living in the area of Bern, Switzerland, served as a reference [20]. The presence

of vertebral fractures was assessed by conventional radiography of the thoracic and lumbar spine.

In accordance with the department's standard operating procedures, all patients had their first control visit 3 months after their first IV BP infusion. At this point in time, a predefined standardised questionnaire was administered to all participants for the purpose of the study. The occurrence of one or more of the following symptoms during the first 3 days after IV BP administration was considered an APR: pyrexia (patient-reported as increased temperature/chills), headache, fatigue, nausea and musculoskeletal pain (myalgia or arthralgia). The degree of severity of each symptom defining APR was classified into one of the three following categories: mild, moderate or severe in accordance with the definitions of the Common Terminology Criteria for Adverse Events (www. http://evs.nci.nih.gov/ftp1/CTCAE/About.html). In addition, the duration of the APR was also recorded by the staff physician in charge.

Statistics

Exploratory descriptive statistical analyses were performed using the Predictive Analysis SoftWare (PASW) statistical software (version 18.0; SPSS™, Chicago, IL). Normality of distribution was assessed by using the Kolmogorov-Smirnov test. Results were expressed as means ± standard deviation (SD) or median values, as appropriate. Exploratory significance testing used Student's t tests, chi-square tests or Mann Whitney U tests, as appropriate. All tests were two-tailed, and $p < 0.05$ was considered to indicate a statistically significant difference.

Results

Baseline characteristics

Between January 2007 and December 2010, 725 women with postmenopausal osteoporosis were administered a first dose of IV BP (411 ZOL and 314 IBN), regardless of previous BP exposure. Mean age (± SD) was 67.1 ± 6.7 years. Two thirds of the women had been previously treated with a BP, the majority of them orally. The groups did not significantly differ with regard to mean age, BMI, BMD or number of prevalent fractures. However, women in the ZOL group were significantly less likely to have received prior BP therapy (61.8 vs. 71.7%, $p = 0.005$) or prior HRT (4.6 vs. 9.6%, $p = 0.009$). Mean baseline levels of bone turnover markers were significantly higher in the ZOL group. Only few patients were current users of nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids in both groups. Comprehensive baseline characteristics by treatment group are shown in Table 1.

Characteristics of APR

In the absence of any preventive measures (consistent with the Swiss prescribing information at the time the study was performed), 301 patients reported 467 signs or symptoms of APR, corresponding to mean 1.6 symptoms per episode. The mean number of symptoms per APR episode was significantly higher with ZOL than with IBN (1.7 vs. 1.3, $p = 0.02$). The mean duration of an APR episode was significantly longer with ZOL (100 vs. 73 h, $p < 0.001$). The proportion of patients experiencing one or more APR symptoms lasting for at least 3, 7 or 10 days was significantly higher with ZOL than with IBN: 45.2 vs. 10.2, 19.2 vs. 3.8 and 8.0 vs. 1.6%, respectively ($p < 0.001$ for all).

As shown in Fig. 1, APR episodes were significantly more frequent in BP-naïve patients than in BP-experienced patients who received a first infusion of ZOL (69.4 vs. 34.3%, $p < 0.001$), which was not the case with IBN (38.2 vs. 31.6%, n.s.). In addition, APR episodes were significantly more frequent with ZOL than with IBN in BP-naïve patients (69.4 vs. 38.2%, $p < 0.001$) but not in women with prior BP exposure (34.3% vs. 31.6%, n.s.).

As shown in Table 2, the incidence of APR was significantly higher in patients treated with ZOL than in those treated with IBN (47.7 vs. 33.4%, $p < 0.001$). Of these, significantly more women who experienced an APR episode were BP naïve in the ZOL group compared to the IBN group (55.6 vs. 32.4%, $p < 0.001$) and significantly less had a history of earlier treatment with either an IV BP alone (3.6 vs. 19.0%, $p < 0.001$) or an oral and IV BP (6.6 vs. 22.9%, $p < 0.001$).

With regard to individual APR signs and symptoms (Table 3), the leading characteristic sign of APR was the presence of myalgia or arthralgia reported by 68.1% of all patients with APR symptoms and numerically more frequent in patients treated with ZOL. Significantly more patients who developed an APR reported pyrexia or nausea with ZOL compared to IBN (23.5 vs. 4.8%, $p < 0.001$, and 22.4 vs. 9.5%, $p = 0.005$), respectively. Fatigue and/or headache were reported by 39.2 and 13.0% of the patients having experienced an APR, respectively, with no significant difference between ZOL and IBN.

Finally, more than one third (36.2%) of all APR episodes were of moderate (15.6%) or severe (20.6%) intensity with no significant difference between ZOL and IBN (23.0 vs. 16.2% and 12.8 vs. 21.0%, respectively).

Factors associated with APR

As shown in Table 4, comparing women having experienced an APR after IV administration of either ZOL or IBN with those who had not, these were significantly younger (64.9 vs. 68.6 years, $p = 0.001$), taller (160.8 vs. 157.9 cm, $p = 0.001$), and less likely to have been

Table 1 Patient demographics and baseline characteristics (mean ± SD or percent of total). Shown exploratory *p* values were limited to significant findings of potential clinical relevance

	ZOL	IBN	*p* value
N (total)	411	314	
Age (years)	66.8 ± 10.6	67.4 ± 10.2	
Height (cm)	159.3 ± 7.1	158.9 ± 6.6	
Weight (kg)	61.5 ± 12.1	60.6 ± 11.0	
BMI (kg/m^2)	24.3 ± 4.7	24.1 ± 4.4	
Lumbar spine T-score	−2.4 ± 1.0	−2.4 ± 1.0	
Femoral neck T-score	−2.2 ± 0.9	−2.3 ± 0.8	
Tibial diaphysis T-score	−1.6 ± 1.3	−1.6 ± 1.2	
Tibial epiphysis T-score	−2.6 ± 1.1	−2.6 ± 1.0	
Prevalent vertebral fracture (%)	50.1	50.6	
History of non-vertebral fracture (%)	40.6	45.2	
Current smoker (%)	12.2	12.7	
≥3 alcohol units/day (%)	2.2	1.9	
Prior BP use, *n* (%)	254 (61.8%)	225 (71.7%)	0.005
Intravenous, *n* (%)	74 (18.0%)	143 (45.5%)	<0.001
Oral, *n* (%)	223 (54.3%)	146 (46.5%)	0.038
Both, *n* (%)	43 (10.5%)	64 (20.3%)	<0.001
Current use of			
HRT, *n* (%)	19 (4.6%)	30 (9.6%)	0.009
Corticosteroids, *n* (%)	18 (4.4%)	8 (2.5%)	
NSAIDs, *n* (%)	15 (3.6%)	8 (2.5%)	
Serum calcium (mmol/L)	2.3 ± 0.1	2.3 ± 0.1	
Serum phosphate (mmol/L)	1.08 ± 0.1	1.13 ± 0.2	
Serum creatinine (μmol/L)	67.5 ± 15.0	70.0 ± 17.0	
Serum alkaline phosphatase (IU/L)	79.0 ± 53.5	70.0 ± 23.0	0.001
Serum osteocalcin (mmol/L)	28.5 ± 15.8	24.3 ± 16.1	<0.001
Serum deoxypyridinoline/creatinine ratio (nmol/mmol)	9.1 ± 3.7	8.1 ± 4.0	<0.001
Serum C-terminal telopeptide (mmol/L)	477 ± 246	521 ± 342	
Serum 25(OH)D (nmol/L)	60.3 ± 27.0	62.7 ± 26.0	
Serum PTH (ng/L)	44.7 ± 24.0	43.0 ± 26.0	
Serum total protein (g/L)	71.3 ± 0.5	71.7 ± 0.6	
Albumin fraction (%)	60.5 ± 0.3	61.0 ± 0.4	
Serum alpha-1 globulins (g/L)	4.6 ± 0.2	4.1 ± 0.1	0.007
Serum alpha-2 globulins (g/L)	10.4 ± 0.1	10.1 ± 0.1	
Serum beta globulins (g/L)	10.5 ± 0.1	10.3 ± 0.1	
Serum gamma globulins (g/L)	14.2 ± 0.2	14.2 ± 0.3	

previously exposed to BP therapy (52.5 vs. 75.7%, $p < 0.001$). With the exception of serum osteocalcin (higher in women with APR) and serum calcium and alpha1-globulin levels (both lower in women with APR), no significant difference in laboratory parameters between groups was detected, including with regard to other markers of bone turnover, serum PTH and serum 25(OH)D levels.

Because severe APR has the greatest clinical relevance, the subgroup of women with severe APR was compared to that of women who had experienced no APR after a first administration of IV ZOL or IBN. Women with severe APR were significantly younger (63.5 vs. 68.6 years, $p < 0.001$), taller (160.7 vs. 157.9 cm, $p = 0.007$) and less likely to have been previously exposed to BP therapy (33.9 vs. 75.7%, $p < 0.001$), and had significantly lower serum 25(OH)D levels (52.5 vs. 62.6 nmol/L, $p = 0.008$). When compared to women who had experienced a mild or moderate APR, only prior BP exposure and lower serum 25(OH)D levels remained significant predictors of APR severity. Thus, of all clinical and laboratory parameters examined as potential predictors of an APR, prior BP exposure appears predictive of APR risk and severity and lower serum 25(OH)D levels may be predictive of more severe APRs.

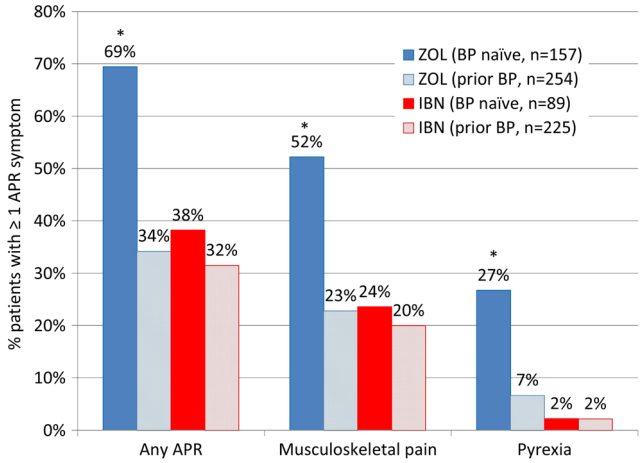

Fig. 1 Incidence of APR by symptoms (any, musculoskeletal pain, pyrexia) in BP-naïve and previously BP-exposed women after a first infusion of either ZOL or IBN. * $p < 0.001$ vs. ZOL prior BP and IBN

Discussion

In the present study in a large population of women treated with first IV BP infusion (ZOL or IBN) in the context of daily practice, APR rates observed in the absence of any preventive measures in accordance with the Swiss label at the time the study was performed were at the higher end of (ZOL) or exceeded (IBN) those reported in randomised controlled trials. In BP-naïve patients, APR rates differed between ZOL and IBN, with episodes generally being of higher clinical intensity and longer duration in patients treated with ZOL in the present study. Among all potential predictors of APR, prior IV BP exposure was the most robust factor associated with a lower APR incidence of less severe intensity and lower serum 25(OH)D levels may be associated with more severe APR.

In the pivotal trials with IV administration of either ZOL or IBN, APR episodes were described as mild transient adverse drug reactions. In a daily practice setting, patients might have different characteristics from those in clinical trials; in particular, patients may be younger. Another reason for the discrepancy in the incidences of APR between our study and previous studies may be subject recall or reporting bias. Acute-phase responses may have been less frequently reported by patients who were not specifically informed about the possibility of an APR before the administration of the drug or if patients were not specifically queried about the occurrence of post-dose symptoms occurring during the few days following IV administration of a BP. Furthermore, recall bias may have resulted in underreporting of mild APR. In the present study, the observed APR rates after a first IV BP administration were generally as high as (ZOL) or higher (IBN) than those previously reported in pivotal randomised controlled trials (RCTs) [10, 11]. However, based on indirect comparison, the observed associations are consistent with the APR rates reported in these trials [10, 11].

The present findings suggest that taller height may be associated with an increased risk for APR—all RCTs of ZOL reported BMI as the only risk factor for APR [11, 12, 21]. This finding should be considered with caution as body height may not be an independent predictor. As an example, younger age has also been previously identified as a risk factor for APR after ZOL administration [12] and younger subjects will expectedly be taller than older patients. In the present study, women with severe APR—regardless of whether they were treated with ZOL or IBN—had lower 25(OH)D serum levels than women with mild or moderate APR and women without any APR. The relationship between serum 25(OH)D levels and the development of APR, especially pyrexia, after the first infusion of ZOL was first described in 2010 [22]. It was hypothesised that APR may be caused by an acute increase in PTH following BP administration, which strongly activates the conversion of 25(OH)D into its less immunomodulating active metabolite 1, 25 dihydroxy-vitamin D and depletes serum 25(OH)D stocks. Serum levels of 25(OH)D remaining above 40 ng/mL (100 nmol/L) were deemed necessary to prevent APR [22]. Whether or not the significantly higher serum alpha1-globulins levels (including vitamin D-binding protein) observed in the ZOL group has directly or indirectly contributed to the higher APR rates seen with ZOL remains speculative.

The patients in the present study were recruited between January 2007 and December 2010 and were not

Table 2 Acute-phase response (APR) rates according to prior bisphosphonate (BP) use. Only statistically significant *p* values are shown

	All included	ZOL	IBN	*p* value ZOL vs. IBN
Total (*N*)	725	411	314	
Patients with ≥1 symptom of APR	301 (41.5%)	196 (47.7%)	105 (33.4%)	<0.001
Of which				
BP naïve	143 (47.5%)	109 (55.6%)	34 (32.4%)	<0.001
Prior use of IV BP	27 (9.0%)	7 (3.6%)	20 (19.0%)	<0.001
Prior use of oral BP	94 (31.2%)	67 (34.2%)	27 (25.7%)	
Prior use of IV and oral BP	37 (12.3%)	13 (6.6%)	24 (22.9%)	<0.001

Table 3 Acute-phase response (APR) and reported symptoms. More than one symptom may have been reported per episode. Only statistically significant *p*-values are shown

	All included	ZOL	IBN	*p* value ZOL vs. IBN
Total (*N*)	725	411	314	
Patients with ≥1 symptom of APR	301 (41.5%)	196 (47.7%)	105 (33.4%)	<0.001
Of which				
Pyrexia	51 (16.9%)	46 (23.5%)	5 (4.8%)	<0.001
Headache	39 (13.0%)	29 (14.8%)	10 (9.5%)	
Fatigue	118 (39.2%)	74 (37.8%)	44 (41.9%)	
Nausea	54 (17.9%)	44 (22.4%)	10 (9.5%)	0.005
Myalgia or arthralgia	205 (68.1%)	139 (70.9%)	66 (62.9%)	

preventively treated with paracetamol or a nonsteroidal anti-inflammatory drug, in accordance with the Swiss prescribing information at that time. Since then, oral acetaminophen/paracetamol or ibuprofen administered 4 h post-infusion was shown to alleviate post-dose influenza-like symptoms in bisphosphonate-naïve osteopenic (i.e. younger) postmenopausal women after a first IV infusion of ZOL [23]. These findings confirmed the results of an earlier trial which showed that acetaminophen 650 mg four times daily for 3 days, but not a single dose of fluvastatin, significantly reduced the incidence and severity of post-dose symptoms following ZOL infusion [24]. Thus, at the time of study closure, no recommendations with regard to APR prevention existed and none were implemented. The reported observed incidences reflect the spontaneous, unopposed APR rates when exposing patients to a first IV infusion of either ZOL or IBN.

This study has the limitations of many observational studies in a daily practice setting. By design, the study was not randomised and a treatment allocation bias cannot be excluded, as evidenced by higher bone turnover markers in the ZOL group (significantly higher serum

Table 4 Exploratory testing for significances between groups with and without APR symptoms, categorised by degree of APR severity (mild, moderate and severe). Only statistically significant *p* values are shown

	No APR symptoms (none)		≥1 APR symptom (any)		Mild and moderate APR		Severe APR		None vs. any	Mild and moderate vs. severe	None vs. severe
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*p* value	*p* value	*p* value
Age (years)	424	68.6 ± 10.7	301	64.9 ± 9.7	239	65.3 ± 9.6	62	63.5 ± 10.0	0.001		<0.001
Weight (kg)	403	60.6 ± 11.8	288	61.9 ± 11.5	232	61.9 ± 11.7	56	61.6 ± 10.6			
Height (cm)	403	157.9 ± 7.0	288	160.8 ± 6.4	232	160.8 ± 6.4	56	160.7 ± 6.3	0.001		0.007
BMI (kg/m^2)	403	24.3 ± 4.6	288	24.0 ± 4.5	232	24.0 ± 4.6	56	23.9 ± 4.2			
Current smoker (%)	47	11.1	43	14.3	36	15.1	7	11.3			
Prior BP (%)	321	75.7	158	52.5	137	57.3	21	33.9	<0.001	0.001	<0.001
Calcium (mmol/L)	411	2.35 ± 0.1	287	2.32 ± 0.1	233	2.33 ± 0.1	54	2.31 ± 0.1	0.022		0.028
Phosphate (mmol/L)	405	1.10 ± 0.2	281	1.10 ± 0.2	228	1.10 ± 0.2	53	1.12 ± 0.1			
Creatinine (μmol/L)	405	68.4 ± 16.4	281	68.8 ± 15.0	227	69.1 ± 15.9	54	67.5 ± 10.1			
ALP (IU/L)	400	75.3 ± 37.2	281	74.2 ± 50.3	228	72.5 ± 27.5	53	81.9 ± 101.4			
OC (mmol/L)	409	26.1 ± 17.0	284	27.5 ± 14.7	229	27.8 ± 15.3	55	26.3 ± 11.8	0.008		
DPD/Crea	394	8.9 ± 4.3	278	8.3 ± 3.3	224	8.4 ± 3.4	54	7.9 ± 2.4			
CTX (mmol/L)	180	478.3 ± 292.0	160	495.8 ± 242.1	124	494.7 ± 245.2	36	499.7 ± 234.5			
25(OH)D (nmol/L)	399	62.6 ± 26.1	282	59.6 ± 26.8	228	61.3 ± 26.8	54	52.5 ± 25.8		0.028	0.008
PTH (ng/L)	359	43.2 ± 21.3	258	44.8 ± 28.9	204	45.6 ± 31.6	54	41.9 ± 15.3			
Protein total (g/L)	217	71.2 ± 9.1	183	71.8 ± 4.7	142	71.6 ± 4.6	41	72.3 ± 5.1			
Albumin (g/L)	238	42.1 ± 7.3	188	42.9 ± 6.3	146	43.0 ± 5.9	42	42.8 ± 7.5			
Alpha1 globulin (g/L)	217	4.7 ± 3.8	184	4.2 ± 0.9	143	4.2 ± 0.8	41	4.2 ± 1.1	0.030		
Alpha2 globulin (g/L)	217	10.4 ± 1.7	184	10.3 ± 1.7	143	10.3 ± 1.7	41	10.2 ± 1.5			
Beta globulin (g/L)	217	10.5 ± 1.5	184	10.4 ± 1.4	143	10.4 ± 1.5	41	10.3 ± 1.2			
Gamma globulin (g/L)	217	14.3 ± 3.7	184	14.1 ± 3.0	143	13.9 ± 2.9	41	14.7 ± 3.3			

alkaline phosphatase, osteocalcin and deoxypyridinoline/creatinine ratio at baseline in the ZOL group compared to the IBN group), suggesting that more severe patients might have been more likely to be treated with ZOL than with IBN based on the stronger published scientific evidence with regard to fracture risk reduction. On the other hand, all consecutive patients treated with either ZOL or IBN during the 4 years of observation were included in the analysis and both groups were balanced with regard to key predictors of fracture risk such as BMD T-scores and history of prior fractures. The individual patient sensitivity to APR signs and symptoms and the reporting of the results may have been influenced by the perceptions of the interviewing and recording physician. Furthermore, a recall bias (the questionnaires were administered 3 months after the first IV BP infusion) cannot be excluded, even more so for mild episodes. On the other hand, the information given was standardised in a single centre and APR symptoms were collected by using a single questionnaire. For future research, we would recommend adding functional items to the questionnaire, such as the ability to perform regular activities during the day or the use of rescue medication in order to capture the degree of severity more precisely. The significances revealed by the statistical analyses on multiple variables without a predefined hypothesis and without multiple adjustments should be considered purely explorative and a starting point for generating hypotheses to be tested in adequately designed randomised controlled trials. In the absence of a control group, the true incidence of APR remains uncertain. However, the incidences reported here correspond to those experienced by the patients in our real-world setting and strongly indicate the need for a preventive treatment aimed at lowering the occurrence and intensity of post-dose symptoms for daily practice. Finally, in patients previously exposed to a BP, neither the compound used nor the duration of prior exposure nor the duration of the washout period preceding the first IV BP administration at our site was collected, which may have resulted in a confounding bias. Beyond its real-world dimension, this study includes a large number of consecutive patients in a single centre, which increases its homogeneity and adds to its relevance for daily practice.

Conclusions

In conclusion, after a first IV BP administration, the observed real-world APR rates were at the upper end (ZOL) or higher (IBN) than those reported in previously published pivotal randomised controlled trials. In the absence of preventive measures, acute-phase response episodes might differ between ZOL and IBN in BP-naïve patients.

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Compliance with ethical standards

Conflicts of interest Kurt Lippuner is the primary investigator in clinical development programs in the field of metabolic bone diseases from Amgen and MSD.

Albrecht Popp and Christoph Senn are the sub-investigators in clinical development programs in the field of metabolic bone diseases from Amgen and MSD.

Renate Senn, Ivanka Curkovic and Helene Buffat declare that they have no conflict of interest.

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