J Surg Med. 2022;6(8):772-777.
DOI: 10.28982/josam.1036910

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Evaluation of intravenous zoledronic acid-induced acute-phase response in the emergency department

Dilek Ozge Zincir Ercin [1], Dogan Ercin [2]

[1] Kocaeli State Hospital, Department of Physical Medicine and Rehabilitation, Kocaeli, Turkey
[2] Kocaeli State Hospital, Depertment of Emergency Medicine, Kocaeli, Turkey

ORCID ID of the author(s)
DOZE: 0000-0002-0430-6299
DE: 0000-0002-7274-0775

Corresponding Author
Dilek Özge Zincir Erçin
Kocaeli State Hospital, Department of Physical Medicine and Rehabilitation, Kocaeli, 41100, Turkey
E-mail: dr.dilekozge@gmail.com

Ethics Committee Approval
The ethical approval was obtained from Derince Training and Research Hospital Clinical Research Ethics Committee (date: 10/10/2019, decision number: 2019-89).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2022 August 27

Abstract

Background/Aim: A temporary influenza-like condition, called acute-phase reaction (APR), is commonly observed with intravenous (IV) administration of nitrogen-containing amino bisphosphonates, such as zoledronic acid (ZOL). This single-center study aimed to evaluate the incidence of APR symptoms after intravenous (IV) ZOL administration in patients with postmenopausal osteoporosis who were admitted to emergency department (ED).

Methods: In this cross-sectional study, 107 osteoporotic patients who were diagnosed with post-menopausal osteoporosis (bone mineral density T-score equal to or below −2.5 with/without prevalent fractures) and who had an ED admission in the first 72 h after intravenous injection of ZOL were included in the study. The patient's pre-treatment blood sample measurements, presenting symptoms (such as fever, fatigue, hyperpyrexia, headache), family history, previous medical treatment, and adverse effects caused by osteoporosis drugs, in addition to information on co-morbidities and comedications were obtained from clinical records.

Results: One-hundred seven osteoporotic patients (19.56%) patients experienced APR and were admitted to the ED after IV-ZOL administration. The mean age was 64.58 (11.15) years (n = 107). The three most commonly reported symptoms were diffuse musculoskeletal symptoms, influenza-like illness, and gastrointestinal symptoms (34.5%, 21.5%, and 18.5%, respectively). Seventy percent of the patients who presented to the ED with APR symptoms were prescribed drugs only, and 30% of the patients received treatment specific for their symptoms in the ED. Most of the diffuse musculoskeletal symptoms consisted of myalgia (22.4%). A positive correlation between the onset time of APR symptoms and the number of IV bisphosphonate (BP) doses was found ($r = 0.597$; $P = 0.032$).

Conclusion: Our study indicates that as the number of IV-ZOL administrations increase yearly in patients with osteoporosis, symptom onset time occurs later. A linear relationship was found between the number of drug applications and the duration of symptoms. Also, the incidence of APR following IV-ZOL administration was 19% in the osteoporotic patient population who presented to the ED or to other clinics according to the symptoms.

Keywords: Zoledronic acid, Acute-phase response, Postmenopausal osteoporosis, Emergency department

How to cite: Zincir Ercin DO, Ercin D. Evaluation of intravenous zoledronic acid-induced acute-phase response in the emergency department. J Surg Med. 2022;6(8):772-777.

Introduction

Osteoporosis is a common bone disease that represents vertebral and hip fragility fractures associated with an increase in morbidity and mortality [1, 2]. Over a lifetime, it is considered that 30% of women and 15% of men will be exposed to a fracture associated with osteoporosis [3, 4]. Thus, early diagnosis of patients at risk and suitable treatment in affected patients is compulsory [2, 3].

Bisphosphonates (BP), synthetic analogues of bone mineralization, and regulator pyrophosphates have been associated with remarkable clinical increases in bone mineral density, suppression of bone-turnover markers, and reduction of vertebral fractures [5–7]. Both types of compounds both effective, well-tolerated drugs that are considered as a standard treatment choice for osteoporosis, and available in both oral and intravenous (IV) formulations [8]. Amino-bisphosphonates (alendronate, ibandronate, risedronate, and zoledronate), which contain nitrogen in their structure, inhibit farnesyl diphosphate synthase. This inhibition results in impedance of cell signaling [9] and rapid production of pro-inflammatory cytokines, such as tumor necrosis factor and interleukin 6 (TNF-α and IL-6) [10].

The temporary influenza-like condition caused by a transient increase of proinflammatory cytokines is called acute-phase reaction (APR), which is rarely observed with oral administration, but commonly observed after intravenous (IV) administration of nitrogen-containing amino bisphosphonates, such as zoledronic acid (ZOL) or ibandronic acid [11]. APR appears to be caused by the rapid and transient release of proinflammatory cytokines from circulating T-cells [11]. It frequently occurs in the first dose of treatment within 24 to 72 h after IV administration, and its intensity gradually decreases after subsequent doses of IV BP treatment [12–14]. APR manifests with fatigue, malaise, low-grade fever, myalgia, and arthralgia symptoms, which resolve within 3 to 14 days [8, 15–17]. Symptoms disappear usually without treatment or sometimes with the use of anti-inflammatory or antipyretic drugs [18].

ZOL is a potent, novel bisphosphonate that is administered via a IV route once per year [19]. It was approved in August 2007 for the treatment of postmenopausal osteoporosis [10]. APR symptoms, such as fever and a flu-like syndrome, are frequently observed after IV administration of ZOL [20]. Based on safety data from clinical trials performed in different countries, the incidence of APR varies between 46.8% and 54.3% after a patient receives an IV injection of ZOL [17, 21]. It is thought that race may be a significant factor in the development of APR. Non-Japanese Asians and Pacific Islanders have the highest risk [13]. In a postmenopausal osteoporosis study performed with a small patient population in Turkey, APR was observed in 2 of 38 (5.2%) patients who received IV ZOL [22].

When the literature was analyzed, a few studies were found addressing APR from different countries and populations. Although growing awareness of post-treatment IV BP-associated APR in postmenopausal osteoporosis among the general public around the world is ongoing, we have little knowledge about the incidence of APR in the Turkish osteoporotic patient population.

Therefore, this present single-center study aimed to evaluate the incidence of APR symptoms after IV ZOL treatment in patients with postmenopausal osteoporosis. The second aim was to determine the awareness, knowledge, and treatment skills of emergency department (ED) physicians in terms of APR symptoms.

Materials and methods

Study design and population

In this cross-sectional, single-center study, we analyzed data from patients who were admitted to the ED of State Hospital between September 1, 2019, and September 1, 2020 due to symptoms of APR after IV administration of ZOL. The records of patients who were diagnosed with postmenopausal osteoporosis from internal medicine, physical therapy, and orthopedic clinics and prescribed IV ZOL were obtained from the hospital program named “SARUS”. Also, the patient’s pre-treatment blood sample measurements, presenting symptoms (such as fever, fatigue, hyperpyrexia, headache), family history, previous medical treatment and adverse effects caused by osteoporosis drugs, in addition to information on co-morbidities and comedications were available from clinical records of the SARUS hospital program. Health records and drug reports for the last six months were obtained by examining the ‘Med-eczane’ and ‘E-nabız’ systems.

The measured laboratory parameters included several indicators: (1) serum calcium, phosphate, and creatinine; (2) serum alkaline phosphatase (ALP); (3) serum 25-hydroxyvitamin D (25[OH]D); (4) serum parathyroid hormone (PTH); (5) C-reactive protein (CRP); (6) white blood count (WBC); and neutrophil and lymphocyte counts and neutrophil/lymphocyte ratio (NLR). Patients with a baseline level of 25(OH)D above 30 ng/mL were considered as vitamin D normal, those with a level between 20 and 29 ng/mL were considered as vitamin D insufficient, and patients with levels below 20 ng/mL were deemed to be deficient [23].

Acute-phase response is defined as the presence of fever (body temperature > 38°C) or the presence of at least one other APR symptom. Also, symptoms considered to be very similar were grouped (for example, pyrexia and raised body temperature were pooled as fever, myalgia, cramps, arthralgia, bone and musculoskeletal pain were pooled as diffuse musculoskeletal pain, nausea, vomiting, dyspepsia, anorexia and decreased appetite were pooled as gastrointestinal issues, headache, dizziness, fatigue, vertigo, nasopharyngitis and malaise were grouped as a flu-like syndrome, and uveitis, episcleritis, conjunctivitis, eye inflammation, eye irritation, eye pruritus and ocular hyperemia were pooled as eye inflammation).

Patients who were diagnosed with postmenopausal osteoporosis as defined by the available disease definition suggested by the World Health Organization as an aerial bone mineral density (BMD) T-score at or below −2.5 that was assessed using dual-energy X-ray absorptiometry (DXA) with/without prevalent fractures and who had an ED admission in the first 72 h after IV injection of ZOL were included in the study.

A physician blinded to the study telephoned the patients who met the criteria for inclusion in the study and questioned

whether or not they had been admitted to the emergency department after IV-zol treatment. If the patients replied "yes", the physician inquired about the types of symptoms on admission in the first 72 h after a ZOL injection. Another physician blinded to the study entered the data and clinical data assessments for the diagnosis of APR.

Patients who were not admitted to the ED after IV injection and received supportive treatment at home or patients who admitted after 72 h after the injection were excluded from the study. Patients were also excluded if they had one more of several conditions: (1) any bone and mineral disorders other than osteoporosis (such as osteogenesis imperfecta, multiple myeloma, hyperparathyroidism, Paget's disease, fibrous dysplasia, metastatic bone tumors), (2) if they were regularly using anti-inflammatory medicines, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunosuppressives for rheumatologic disorders; (3) if they had previously used parathyroid hormone, strontium, or sodium fluoride; (4) if they used or were using anabolic steroids for the last six months; and (5) if they were diagnosed as having any other organic pathology that could explain their symptoms. Also, patients with repeated ED or symptom-associated outpatient admissions within three days and patients who did not want to answer APR questions, and/or patients whose data cannot be obtained from "E- nabız" or 'Med-eczane' systems were excluded from the study.

Ethical approval

The local Ethics Board approval was taken from the study Derince Training and Research Hospital Clinical Research Ethics Committee (date: 10/10/2019, decision number: 2019-89) and The study was performed in accordance with principles of the Declaration of Helsinki.

Outcomes

In this study, our primary outcome was to determine the frequency and variety of symptoms of patients who were diagnosed with osteoporosis who were admitted to the ED with APR syndrome after IV ZOL administration. The second outcome of our study was to investigate knowledge, awareness, and treatment skills concerning ZOL-induced APR of ED physicians.

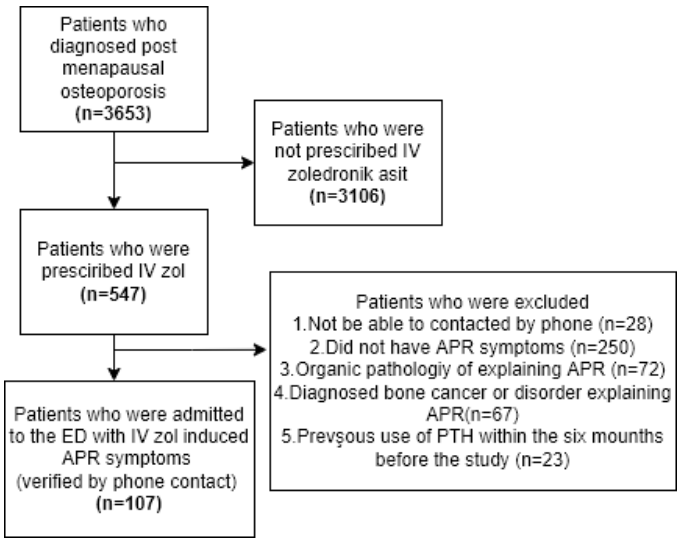
Statistical analysis

Statistical analysis was mainly performed using the Predictive Analysis Software (PASW) statistical software (version 18.0; SPSS™, Chicago, IL). Data for quantitative variables were described as mean (standard) error of the mean. Data for categorical variables were described as numbers and/or percentages. Correlations between variables were evaluated using Spearman's correlation test. All tests were two-tailed, and $P < 0.05$ was considered significant. The sample size of the study was calculated using the G*Power 3.1 program. Reaching 80% power and adding a 20% patient loss, 100 patients had been planned to be included in the study with data obtained from the previous study [13].

Results

A total of 3653 patients who were diagnosed as having postmenopausal osteoporosis in the Internal Medicine, Physical Therapy, or Orthopedic clinics of the state hospital between September 1, 2019, and September 1, 2020, were included in the study. Five-hundred forty-seven (14.97%) out of 3653 patients were prescribed IV ZOL. Four-hundred forty patients were excluded because they could not fulfil the inclusion criteria; thus, 107 patients were included in the final analysis (Figure 1).

Figure 1: Flow chart



First, these 107 patients (19.56%) patients experienced APR symptoms and were admitted to the ED after IV-ZOL administration. All patients were women, and their mean age was 64.58 (11.15) years. BMD t-score of the lumbar spine was lower than the femur neck t-score (−2.5 [0.62] versus 1.96 [0.75]). In 33.3% of the patients, symptoms of APR started on the first day of IV administration. Ninety-nine patients (92.5%) had no previous history of oral bisphosphonate use. APR symptoms were observed in 69 (64.5%) patients after the first dose of IV ZOL.

The patient's data of prior IV BP therapy, age, BMD t-scores, laboratory parameters in serum, and white blood cell (WBC) counts, and percentage of patients previous IV or oral BP use are presented in Table 1. Except for 25(OH)D values, counts of serum parameters and WBCs were determined to be within normal limits. 25(OH)D levels were found to be 29.23 (16.54) ng/mL and within the insufficiency range of 20 to 29.9 ng/mL.

Table 1: Baseline characteristics of the study population of 107 patients

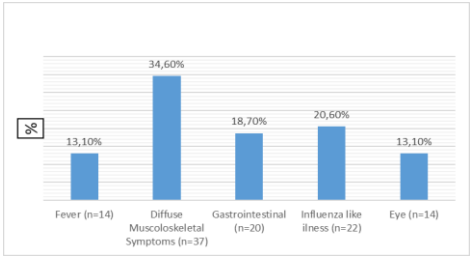
	Mean (SD)	Median	Min–Max
Age(years)	64.58 (11.15)	63	45–90
Bone Mineral Density			
Lumber vertebrae L1-L4 (t-score)	-2.5 (0.62)	2.6	0.3–4.2
Femur neck (t-score)	-1.96 (0.75)	2.1	0.1–3.5
Lab parameters in serum			
25OH-D ng/mL	29.23 (16.54)	25	4.7–85.8
Calcium mg/dL	9.32 (0.49)	9.3	8–10.4
PTH pg/mL	67.02 (36.23)	62	29.5–342
ALP U/L	68.95 (18.04)	69	27–105
Phosphate mg/dL	3.42 (0.55)	3.42	1.7–4.63
Creatinine mg/dL	0.77 (0.19)	0.75	0.02–1.58
CRP mg/dL	0.72 (1.03)	0.46	0.08–9.4
Lab parameters in white blood cell counts			
WBC µL	6519.31 (1621.82)	6500	1930–9940
Neutrophil µL	3875.04 (1424.81)	3590	1150–8570
Lymphocyte µL	1997.67 (794.10)	1900	340–4100
N/L ratio	1012.20 (6060.33)	1.94	0.68–44075
	n (%)		
The onset time of APR symptoms			
First day	36 (33.3)		
Second Day	35 (32.4)		
Third Day	36 (33.3)		
Previous history of BP use (oral)			
Yes	8 (7.5)		
No	99 (92.5)		
The number of IV BP administration			
1st	69 (64.5)		
2nd	30 (28)		
3rd	8 (7.5)		

*Normal range of 25(OH)D: 14-60 ng/mL, Calcium (Ca) 8.8-10.6 mg/dL, PTH: 12-88 pg/mL, ALP: 30-120 U/L, Phosphate (P): 2.3-4.7 mg/dL, Creatinine (Cr): 0.6-1.1 mg/dL, CRP: 0-0.5 mg/dL, WBC: 4-10 $x10^3$/µL, Neutrophils: 2-7 $x10^3$/µL, Lymphocyte: 0.8-4 $x10^3$/µL. h: hours, WBC: white blood count; CRP: C-reactive protein, ALP: alkaline phosphatase, PTH: parathyroid hormone, 25(OH)D:25-hydroxyvitamin D3, N/R ratio: Neutrophil/Lymphocyte ratio; Min: minimum, Max: Maximum

Seventy-eight (72.9%) patients had no fractures, but 22 (20.6%) patients had one, and seven (6.5%) patients had more than one fracture associated with osteoporosis. NSAIID drugs had been prescribed together with IV-ZOL in 99 (89.7%) of the women's treatment regimens.

The three most frequently reported symptoms were diffuse musculoskeletal symptoms, influenza-like illness, and gastrointestinal symptoms (34.5%, 21.5%, and 18.5.%, respectively). Eye symptoms and fever were seen in equal ratios. They were the two least common symptoms (13.1%) as shown in Figure 2.

Figure 2: Distribution of the main acute-phase response (APR) symptoms



Most of the diffuse musculoskeletal symptoms consisted of myalgia, and most of the influenza-like illness symptoms consisted of nasopharyngitis (22.4% and 13.1%, respectively) as shown in Table 2.

Table 2: Occurrence of acute-phase response symptoms within three days of IV-ZOL treatment

	n (%)
Fever	14 (13.1)
Diffuse Musculoskeletal Symptoms	37
Myalgia	24 (22.4)
Arthralgia	13 (12.1)
Gastrointestinal	20
Dyspepsia	13 (12.1)
Gastroenteritis	6 (5.6)
Nausea	1 (0.9)
Influenza-like Illness	22
Headache	3 (2.8)
Malaise	2 (1.9)
Vertigo	4 (3.7)
Nasopharyngitis	13 (13.1)
Eye	14
Eye inflamation	6 (5.6)
Allergic conjunctivitis	8 (7.5)

Seventy percent of the patients who presented to the ED with APR symptoms were prescribed drugs only, and 30% of the patients received treatment specific to their symptoms in the ED (Table 3).

Table 3: Treatment skills of emergency department physicians

	n (%)
Prescribed drugs only	70 (65.4)
Antipyretic drugs	11 (10.3)
Paracetamol tablets	3 (2.8)
Pseudoephedrine tablets	6 (5.6)
Paracetamol+Codeine phosphate	2 (1.9)
NSAIDs	26 (24.3)
Ibuprofen tablet	6 (5.6)
Dexketoprofen trometamol tablet	8 (7.5)
Diclofenac sodium tablet	3 (2.8)
Ibuprofen gel	2 (1.9)
Diclofenac sodium gel	6 (5.6)
Dexketoprofen trometamol gel	1 (0.9)
Steroids	3 (2.8)
PPI	10 (9.3)
Antivertigo drugs	2 (1.9)
Antispasmotic drugs	4 (3.7)
Intraocular treatments (droplets, creams)	14 (13.1)
Symptomatic treatment in the ED	37 (34.6)
IM injection	11 (10.3)
Diclofenac ampule	8 (7.5)
Prednisolone ampule	3 (2.8)
IV injection	24 (22.4)
Paracetamol vial	5 (4.7)
Metoclopramide ampule	11 (10.3)
Metamizole sodium	8 (7.5)
Nasal treatments	2 (1.9)

ED: Emergency Department, NSAIDs: non-steroidal anti-inflammatory drugs, PPI: Proton pump inhibitors, IM: intramuscular injection, IV: intravenous injection

The three most frequently prescribed drug types were NSAIDs, proton pump inhibitors (PPIs), and antipyretics (24.3%, 10.3%, and 9.3%, respectively).

We found a positive correlation between the onset time of APR symptoms and the number of IV BP doses (P = 0.032) and a negative weak correlation between serum 25(OH)D levels and the onset time of APR. No correlation between BMD scores of lumbar vertebrae and femur, age, lymphocytes, and N/R ratio (P = 0.78) was found (Table 4).

Table 4: Correlation analysis between BMD scores, age, the number of IV BP dose, lymphocytes, NLR, and APR and serum 25(OH)D levels

	The onset time of APR r*	Serum 25OH-D levels r*
The onset time of APR	N/A	-0.223**
Serum 25(OH)D levels	-0.223**	N/A
Lomber vertebrae L1-L4 (t-score)	0.045	-0.038
Femur neck (t-score)	0.106	-0.231
Age	0.01	-0.145
The number of IV BP dose	0.597**	-0.077
Lymphocyte	-0.102	0.042
N/R ratio	-0.054	-0.071

* r Spearman's correlation coefficient, ** P = 0.032 (statistically significant), N/A: Not applicable

Discussion

In this study, we first aimed to investigate the characteristics of patients with osteoporotic symptoms who presented to the ED with APR after IV-ZOL administration and which treatments were administered to these patients by the physicians in the ED. An important finding of study was that the number of IV-ZOL administrations increased yearly in patients with osteoporosis in this Turkish study population, and the time of the appearance of APR symptoms emerged in later. Also, as the second result of our study, we found that the rate of patients who presented to the ED with symptoms of APR after IV-ZOL administration in the osteoporotic patient population was 19%.

Data from clinical trials indicate that the incidence of APR varies between 4.9% and 54.9% [24, 28]. A lower APR incidence was found in patients using IV-IBN and oral BP (4.9% and 5.6%, respectively) [24, 25]. The incidence of APR symptoms was greater in patients with osteoporosis treated with IV-ZOL (41.5%,42.4%, 46.8%, 54.3%, and 54.9% respectively) [13, 17, 21, 26–28]. Due to the lack of a precise definition of APR, the authors based their definitions on a different variety of symptoms when these studies were analyzed [28]. Also, it is easy to follow-up symptoms in studies designed prospectively. Symptom inquiries via phone and informing patients about the symptoms that may be experienced after IV administration by clinicians may contribute to a higher reported incidence of APR in these studies [13, 17, 28]. The relatively low rate in our study may be attributed to reasons. In addition, in a study of 87 patients with similar race, the incidence of APR was found as 5.2% [22]. We are of the opinion that the 19% incidence of APR in the Turkish population should be supported by further prospective studies.

It is confirmed that APR incidence showed a dramatic decline after the second and third infusions [13]. Additionally, previous BP use is known to be one of the protective factors against APR [27]. The present study, whose results parallel the above studies, indicates that as the number of IV-ZOL doses administered increases, the onset of time APR symptoms gradually increases. In other words, a correlation between an increased number of IV doses and the onset time of symptoms

can be found. This situation can also be interpreted as the increase in the number of IV-ZOL doses leads to an increase on patient awareness of APR symptoms, and those whose symptoms do not decrease even after using symptomatic treatment at home may present to the ED.

The present study indicates another relationship between the APR symptom onset time and serum 25OH-D levels. Although we found a weak correlation between these two parameters, the onset time of APR symptoms was earlier in patients with lower serum 25OH-D levels. Amino bisphosphonates, IV-ZOL in particular, can produce an APR by stimulating a transient release of pro-inflammatory cytokines from activated monocytes, macrophages, and γδ-T-cells [18]. It was revealed that IV ZOL treatment induced γδ-T cells to mature toward an interferon (IFN)-γ-producing cell type, which may induce release of more acute-phase proteins, such as CRP and elastase. [18, 29]. Furthermore, 25(OH)D is a potent immunomodulator that plays a role in the inhibitory action on adaptive immunity through inhibiting T cell proliferation, mainly the γδ-T cells that produce IFN-γ and interleukin (IL)-2 and activate macrophages [30, 31].

We are of the opinion that with the decrease in serum 25(OH)D levels, the inhibitory effect on T-cells may be eliminated, and also the positive impact on the increase of T cells of IV-ZOL may be supported. From this point of view, we conclude that in patients with low serum 25(OH)D levels, early and severe APR symptoms resulting in an increase in pro-inflammatory cytokine release may occur after IV-ZOL treatment. The findings of our study did not verify a strong relationship between 25(OH)D levels and the onset time of APR. Further randomized, controlled trials are needed to clarify this relationship based on a strong rationale.

In the present study, we defined APR as a rise in body temperature to > 38 °C or the presence of at least one other APR symptom. Using these conservative criteria, we found that the leading sign of APR was diffuse musculoskeletal symptoms consisting of myalgia and arthralgia, which were reported by 34.5% of the entire patient population with APR symptoms. Consistent with our results, an open-label prospective study found that musculoskeletal symptoms were the most common group among APR symptoms (68.1%) [27].

In contrast to our results, previous trials performed with IV-ZOL have determined the leading sign of APR was fever, ranging from 17.2% to 54.9% [13, 17, 28]. The lack of a clear definition of APR may have created this difference between studies. Additionally, we believe that symptoms of fever may have been detected relatively less in our study population due to deficiencies in vital sign records during the outpatient admission process into the ED.

The APR treatment strategy is another issue to be addressed; in a randomized-controlled study, treatment with acetaminophen or ibuprofen safely and effectively relieved the symptoms of postmenopausal women with osteopenia after a single dose of IV-ZOL [32]. The probability of having APR after IV-ZOL administration may be decreased by using a combination of acetaminophen an another anti-inflammatory agent (commonly paracetamol or ibuprofen) after dosing and continuing for the next three days [13, 15, 33].

We found that paracetamol was prescribed in 9.4% and ibuprofen in 5.6% of patients when all patients admitted to the outpatient or treated in the ED were examined, and our results are in agreement with these studies [13, 17, 32, 33]. We found that pseudoephedrine tablets and metamizole sodium ampules were given more in the antipyretic drugs group, and dexketoprofen trometamol tablets and diclofenac ampules were administered more in the NSAID group.

We suppose that the reason why wide variety of NSAIDs and antipyretic drugs are preferred instead of paracetamol or ibuprofen in the treatment of APR may be due to a number of factors: (1) ED physicians do not consider patients' symptoms as APR, (2) they do not have sufficient awareness about the symptoms and treatment of APR, and (3) patients are not treated by the same physicians.

We indicate that prospective, multicenter, and controlled studies involving data from a large cohort of patients are needed to confirm our findings concerning the relationship between APR onset time, IV-BP dose, and 25(OH)D.

To the best of our knowledge, the present study is one of the first studies to reveal the incidence of APR in a Turkish osteoporotic population. Also, we consider that this study is the first of several steps toward conducting more extensive studies to address the relationship between the onset of APR symptoms and the dose of IV BP and 25(OH)D, and to examine the treatment patterns of physicians in the ED.

Strengths and limitations

This present study's results should be considered within the bounds of its strengths and limitations. First, errors may arise from the incomplete recording of the clinical data, which might not have been eliminated because our retrospective findings are based on data collected from clinical reports. Second, due to the lack of a control group, the exact incidence of APR is uncertain. Third, because our study was not multicenter, it may have been biased in determining the incidence of APR. Finally, in our study, we included the pre-treatment blood samples of the patients. Blood samples could not be obtained from all patients at the time of onset of APR and the first month post-treatment, so this information could not be included. Collecting blood samples from before treatment, at APR onset time, and first-month post-treatment may help in clarifying the relationship between 25(OH)D, IV BP dose, and APR onset time of symptoms.

Conclusion

Our study indicates that as the number of IV-ZOL administrations increases yearly in patients with osteoporosis, symptom onset time occurs later. A linear relationship was found between the number of drug applications and symptom duration. Also, the incidence APR following IV-ZOL administration was 19% in the osteoporotic patient population who presented to the ED or other clinics according to the symptoms. The mechanisms underlying the IV-ZOL dose number and the onset time of APR warrants further investigation.

References

1. Pisani P, Renna MD, Conversano F, Casciaro E, Di Paola M, Quarta E, et al. Major osteoporotic fragility fractures: Risk factor updates and societal impact. World J Ortop. 2016;7(3):171-2.
2. Miller AN, Lake AF, Emory CL. Establishing a fracture liaison service: an orthopedic approach. J Bone Joint Surg Am. 2015;97(8):675-8.
3. Kanis JA, Johnell O, Oden A, Sernbo I, Redlund JI, Dawson A et al. Long-term risk of osteoporotic fracture in Malmö. Osteoporos Int. 2000;11(8):669-74.

4. Lippuner K, Johansson H, Kanis JA, Rizzoli R. Remaining lifetime and absolute 10-year probabilities of osteoporotic fracture in Swiss men and women. Osteoporos Int. 2009;20(7):1131-40.
5. Russell RGG, Bisaz S, Fleisch H, Dietz A, Fallet G. Inorganic pyrophosphate in plasma, urine, and synovial fluid of patients with pyrophosphate arthropathy (chondrocalcinosis or pseudogout). Lancet. 1970;296(7679):899-902.
6. Bone HG, Hosking D, Devogelaer JP, Emkey RD, Tonino RP, Liberman UA. Ten years experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med. 2004;350(12):1189-99.
7. Harris ST, Watts NB, Genant HK, Clark D, Mckeever MD, Thomas HD, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. JAMA. 1999;282(14):1344-52.
8. Silverman SL, Maricic M. Recent developments in bisphosphonate therapy. Sem In Arthritis and Rheum. 2007;37(1):1-12.
9. Roelofs AJ, Thompson K, Gordon S, Rogers MJ. Molecular mechanisms of action of bisphosphonates: current status. Clin Cancer Res. 2006;12(20):6222-30.
10. Strampel W, Emkey R, Civitelli R. Safety considerations with bisphosphonates for the treatment of osteoporosis. Drug safety. 2007;30(9):755-63.
11. Hewitt RE, Lissina A, Green AE, Price DA, Sewell AK. The bisphosphonate acute phase response: rapid and copious production of proinflammatory cytokines by peripheral blood gd T cells in response to aminobisphosphonates is inhibited by statins. Clin Exp Immunol. 2005;139(1):101-11.
12. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M el al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Jama.1999;282(14):1344-52.
13. Reid, IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM, Characterization of and risk factors for the acute-phase response after zoledronic acid. J Clin Endocrinol Metab. 2010;95(9):4380-7.
14. Lin JH, Chen IW, Deluna FA, Hichens M. Renal handling of alendronate in rats. An uncharacterized renal transport system. D Metab Disposit. 1992;20(14):608-13.
15. Recker RR, Lewiecki EM, Miller PD, Reiffel J. Safety of bisphosphonates in the treatment of osteoporosis. Am J Med. 2009;122(2):22-32.
16. Reginster JY, Adami S, Lakatos P, Stepan JJ, Silverman SL, Greenwald M, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis. 2006;65(5):654-61.
17. Sieber P, Lardelli P, Kraenzlin CA, Kraenzlin ME, Meier C. Intravenous bisphosphonates for postmenopausal osteoporosis: safety profiles of zoledronic acid and ibandronate in clinical practice. Clin Drug Invest. 2013;33(2):117-22.
18. Dalle Carbonare L, Zanatta M, Gasparetto A, Valenti MT. Safety and tolerability of zoledronic acid and other bisphosphonates in osteoporosis management. Drug Healthc Patient Saf. 2010;2(1):121-37.
19. Russell RGG, Rogers MJ, Frith JC, Benforth HL, Fleisch HA. et al. The pharmacology of bisphosphonates and new insights into their mechanisms of action. J Bone Min Res. 1999;14(2):53-65.
20. Van Poznak CH. Catherine H. The use of bisphosphonates in patients with breast cancer. Cancer Control. 2002;9(6):480-9.
21. Black DM, Delmas PD, Eastell R, Boonene S, Cauley JA, Felicia C, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809-22.
22. Aslan A, Özmeriç A, Bilal Ö, Fatih D, Zubeyde O. Comparative evaluation of clinical effectivity and side effects of two different parenteral agents used in the treatment of osteoporosis. J Rheumatol Orthop.2014;1:1-6.
23. Rosen CJ. Vitamin D deficiency. N Engl J Med. 2007;364(3):248-54.
24. Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Price R, et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. J Rheumatol. 2008;35(3):488-97.
25. Bock O, Boerst H, Thomasius FE, Degner M, Stephen M, Valnetine SM, et al. Common musculoskeletal adverse effects of oral treatment with once weekly alendronate and risedronate in patients with osteoporosis and ways for their prevention. J Musculoskelet Neuronal Interact. 2007;7(2):144-8.
26. Tuzun S, Eskiyurt N, Akarirmak U, Sarigöl M, Senocak M, Johanson H, et al. Incidence of hip fracture and prevalence of osteoporosis in Turkey: the FRACTURK study. Osteoporos Int. 2012;23(3):949-55.
27. Popp AW, Senn R, Curkovic I, Senn C, Buffot H, et al. Factors associated with acute-phase response of bisphosphonate-naïve or pretreated women with osteoporosis receiving an intravenous first dose of zoledronate or ibandronate. Osteoporos Int. 2017;28(6):1995-2002.
28. Anastasilakis AD, Polyzos SA, Makras P, Sakellarious GT, Bisbinas I, Gkiomisi A, et al. Acute phase response following intravenous zoledronate in postmenopausal women with low bone mass. Bone. 2012;50(5):1130-4.
29. Dieli F, Gebbia N, Poccia F, Caccamon N, Montesanoo C, Fulfaro F, et al. Induction of γδ T-lymphocyte effector functions by bisphosphonate zoledronic acid in cancer patients in vivo. Blood. 2003;102(6):2310-1.
30. Penna G, Roncari A, Amuchastegui S, Daniel KC, Berti E, Colonna M, et al. Expression of the inhibitory receptor ILT3 on dendritic cells is dispensable for induction of CD4+ Foxp3+ regulatory T cells by 1, 25-dihydroxyvitamin D3. Blood 2005;106(10):3490-7.
31. Pasco JA, Henry MJ, Nicholson GC, Brennan SL, Kotowicz MA. Behavioural and physical characteristics associated with vitamin D status in women. Bone. 2009; 44(6):1085-91.
32. Wark JD, Bensen W, Recknor C, Ryabitseva O, Chiodo J, Mesenbrink P, et al. Treatment with acetaminophen/paracetamol or ibuprofen alleviates post-dose symptoms related to intravenous infusion with zoledronic acid 5 mg. Osteoporos Int.2012;23:503-12.
33. Silverman SL, Kriegman A, Goncalves J, Kianifard F, Carlson T, Leary E, et al. Effect of acetaminophen and fluvastatin on post-dose symptoms following infusion of zoledronic acid. Osteoporos Int. 2011;22(8):2337-45.

The National Library of Medicine (NLM) citation style guide has been used in this paper.