Characterization of and Risk Factors for the Acute-Phase Response after Zoledronic Acid

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Context: Intravenous aminobisphosphonates often cause an acute-phase response (APR), but the precise components of this, its frequency, and the risk factors for its development have not been systematically studied.

Objective: The objective of the study was to characterize the APR and determine its frequency and the risk factors for its development.

Design: The study was an analysis of adverse events from a large randomized trial.

Setting: This was a multicenter international trial.

Patients: Patients included 7765 postmenopausal women with osteoporosis.

Intervention: Zoledronic acid 5 mg annually or placebo was the intervention.

Main Outcome Measure: Adverse events occurring within 3 d of zoledronic acid infusion were measured.

Results: More than 30 adverse events were significantly more common in the zoledronic acid group and were regarded collectively as constituting an APR. These were clustered into five groups: fever; musculoskeletal (pain and joint swelling); gastrointestinal (abdominal pain, vomiting, diarrhea); eye inflammation; and general (including fatigue, nasopharyngitis, edema). A total of 42.4% of the zoledronic acid group had an APR after the first infusion, compared with 11.7% of the placebo group. All APR components had their peak onset within 1 d, the median duration of the APR was 3 d, and severity was rated as mild or moderate in 90%. Stepwise regression showed that APR was more common in non-Japanese Asians, younger subjects, and nonsteroidal antiinflammatory drug users and was less common in smokers, patients with diabetes, previous users of oral bisphosphonates, and Latin Americans ($P < 0.05$ for all).

Conclusion: This analysis identifies new components of the APR and provides the first assessment of risk factors for it. Despite its frequency, APR rarely resulted in treatment discontinuation in this study. **(*J Clin Endocrinol Metab* 95: 4380–4387, 2010)**

Infusions of aminobisphosphonates are now established therapies in osteoporosis, Paget's disease, and the prevention of skeletal-related events in cancer (1–3). Their use is associated with fever and musculoskeletal pain in some subjects, referred to as the acute phase response (APR). The APR has been alluded to in passing in a number of papers describing the use of iv aminobisphosphonates but has not been the subject of a systematic analysis. Thus, there are anecdotes and opinions regarding precipitating and relieving factors [*e.g.* prior use of oral aminobisphos-

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Abbreviations: APR, Acute-phase response; NSAID, nonsteroidal antiinflammatory drug.

phonates, nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, body size and renal function] but scant documentation to support them.

Aminobisphosphonates inhibit bone resorption by blocking farnesyl pyrophosphate synthase, an enzyme in the mevalonate pathway that leads to the synthesis of cholesterol. Recent work suggested that this action may underlie the development of the APR because intermediates in this pathway, isopentenyl diphosphate and dimethylallyl diphosphate, accumulate in monocytes when this enzyme is blocked and result in the activation of adjacent γδT cells with the release of interferon-γ and TNF (4). The mevalonate pathway is also blocked proximally by statins, which are widely used in the management of hyperlipidemia. Therefore, it has been hypothesized that concomitant use of these drugs might reduce the frequency or severity of the APR in bisphosphonate-treated subjects (5).

The HORIZON-Pivotal Fracture Trial was the largest trial in the phase 3 osteoporosis program for zoledronic acid (1). Although adverse events from the study have been reported (1), this has provided only a cursory assessment of the APR. The substantial safety database from this study provides a unique opportunity to systematically characterize the APR and determine its frequency and the risk factors for its development. This information is necessary if patients considering the use of these valuable therapeutic agents are to be appropriately advised.

Patients and Methods

Study design

The HORIZON-Pivotal Fracture Trial was a multicenter, randomized, double-blind, placebo-controlled trial involving postmenopausal women with osteoporosis. Patients were randomly assigned to receive either zoledronic acid (5 mg as an iv infusion over 15 min) or a placebo infusion at baseline, 1 yr, and 2 yr. Patients were monitored for 3 yr with quarterly telephone interviews and clinic visits at months 6, 12, 24, and 36. The trial protocol has been described in detail previously (1).

Patients

Postmenopausal women aged 65–89 yr were eligible for inclusion if bone mineral density T-score at the femoral neck was less than −2.5 or T-score was less than −1.5 with at least two mild or one moderate vertebral fracture(s). Previous use of oral bisphosphonates was allowed, with the duration of the washout period dependent on previous use. Subjects were ineligible if there was any previous use of PTH, strontium, or sodium fluoride; use of anabolic steroids or GH within 6 months before trial entry; or systemic corticosteroids within 12 months. A calculated creatinine clearance greater than 30 ml/min was also required.

A total of 7765 women were randomized, 3876 to placebo and 3889 to zoledronic acid. Twenty-two patients who did not receive study drug (placebo, nine; zoledronic acid, 13) were excluded from the safety analyses as were 29 patients (placebo, 15; zoledronic acid, 14) because the participation of their clinical center was terminated owing to issues associated with data reliability. Thus, 3852 women randomized to placebo and 3862 randomized to zoledronic acid form the basis of the present report. Their baseline characteristics are shown in Table 1.

TABLE 1. Baseline characteristics of the study population of 7714 subjects

Variable	Placebo (n = 3852)	Zoledronic acid (n = 3862)
Age (yr)	73 (5)	73 (5)
Body mass index (kg/m^2)	25 (4)	25 (4)
Region		
Western Europe	1160 (30%)	1156 (30%)
Eastern Europe	770 (20%)	772 (20%)
North America/Oceania	763 (20%)	762 (20%)
Latin America	621 (16%)	623 (16%)
Asia	538 (14%)	549 (14%)
Femoral neck BMD T-score	−2.75 (0.55)	−2.75 (0.54)
Prevalent vertebral fracture	2470 (64%)	2408 (62%)
Prior medication use		
HRT	812 (21%)	824 (21%)
Bisphosphonates	556 (14%)	563 (15%)
Calcitonin	425 (11%)	443 (11%)
SERMs	411 (11%)	431 (11%)
Concomitant medications used by >5% of patients in stratum 2		
Women in stratum 2	821	827
Raloxifene	368 (45%)	374 (45%)
Calcitonin	175 (21%)	178 (22%)
Conjugated estrogens	118 (14%)	124 (15%)
Estradiol	85 (10%)	85 (10%)

Data are mean ± SD or n (%). BMD, Bone mineral density; HRT, hormone replacement therapy; SERM, selective estrogen receptor modulator.

Defining the APR

All adverse events were recorded and categorized according to individual preferred terms used in the *Medical Dictionary for Regulatory Activities* (6). To determine which of these events were part of the APR and characterize this symptom complex with greater precision, adverse events occurring within 3 d of the first administration of study drug were listed. The timing of an adverse event was determined by subtracting the date of the infusion from the date of the event. There was some redundancy in the terms used to describe adverse events, so items considered to be very similar were pooled (*e.g.* pyrexia and increased body temperature were pooled as fever; myalgia, arthralgia, bone pain, and musculoskeletal pain were pooled as diffuse musculoskeletal pain; anorexia and decreased appetite were pooled as anorexia; conjunctivitis, uveitis; episcleritis, eye inflammation, eye irritation, eye pruritus, and ocular hyperemia and panophthalmitis were pooled as eye inflammation). From the resulting list of terms, those that were significantly different between groups ($P < 0.05$, without correction for multiple comparisons) were tabulated. For convenience, they were grouped into five symptom clusters: fever; musculoskeletal (pain and joint swelling); gastrointestinal (abdominal pain, vomiting, diarrhea); eye inflammation; and other (including fatigue, nasopharyngitis, edema). The occurrence of any adverse event falling within these clusters within 3 d of study drug infusion was defined as constituting an APR.

Statistics

Data were analyzed on an intention-to-treat basis with the number of treated patients within each group experiencing at least one of the adverse event categories compared between zoledronic acid and placebo groups by Fisher's exact test. Stepwise logistic regression was performed to determine the significant independent predictors of experiencing at least one APR. Odds ratios and 95% confidence intervals are presented. All analyses were performed using SAS (version 9.1; SAS Institute Inc., Cary, NC). All tests were two tailed and $P < 0.05$ was considered significant.

Results

Within the first 3 d of the first study drug infusion, 1133 adverse events were reported in 801 subjects randomized to placebo, and 3854 adverse events were reported in 1901 subjects receiving zoledronic acid.

What constitutes the APR?

The adverse events that were significantly different between groups in the 3 d after the first infusion of study drug are shown in Table 2. The most common event was fever, which, together with associated symptoms such as chills and flushes, occurred in 20% of zoledronic acid-treated subjects, in comparison with less than 3% of the placebo group. Approximately the same proportion of patients had acute musculoskeletal symptoms, principally pain, which was most commonly experienced as a generalized discomfort, although some reported only local complaints involving the back, neck, chest, or shoulders. About 1% of

TABLE 2. Adverse events occurring within 3 d of the first study drug infusion

	Placebo (n)	Placebo (%)	Zoledronic acid (n)	Zoledronic acid (%)	*P*[a]
Fever					
Fever	70	1.8	663	17.2	<0.0001
Chills	23	0.6	171	4.4	<0.0001
Hot flush	10	0.3	27	0.7	0.0075
Any of the above group	96	**2.5**	785	**20.3**	<0.0001
Musculoskeletal					
Joint swelling	0	0.0	14	0.4	<0.0001
Regional musculoskeletal pain	73	1.9	190	4.9	<0.0001
Musculoskeletal stiffness	5	0.1	37	1.0	<0.0001
Diffuse musculoskeletal pain	114	3.0	606	15.7	<0.0001
Any of the above group	180	**4.7**	770	**19.9**	<0.0001
Gastrointestinal					
Abdominal pain	17	0.4	40	1.0	0.0031
Anorexia	7	0.2	45	1.2	<0.0001
Diarrhea	23	0.6	55	1.4	0.00035
Nausea	37	1.0	158	4.1	<0.0001
Vomiting	6	0.2	73	1.9	<0.0001
Any of the above group	80	**2.1**	300	**7.8**	<0.0001
Eye					
Eye inflammation	2	0.1	14	0.4	0.0041
Eye pain	0	0.0	9	0.2	0.0039
Any of the above group	2	**0.1**	22	**0.6**	<0.0001
General					
Fatigue	63	1.6	205	5.3	<0.0001
Dizziness/vertigo	40	1.0	75	1.9	0.0013
Edema peripheral	4	0.1	18	0.5	0.0043
Influenza like illness	49	1.3	303	7.8	<0.0001
Headache	59	1.5	225	5.8	<0.0001
Syncope	0	0.0	7	0.2	0.0156
Pain	11	0.3	74	1.9	<0.0001
Malaise	16	0.4	45	1.2	<0.0001
Nasopharyngitis	5	0.1	17	0.4	0.017
Thirst	0	0.0	11	0.3	0.00097
Insomnia	1	0.0	8	0.2	0.039
Tremor	2	0.1	11	0.3	0.022
Any of the above group	226	**5.9**	847	**21.9**	<0.0001
APR (any of the above symptom clusters)	450	**11.7**	1636	**42.4**	<0.0001

Data are the number or percent of subjects in each group that experienced that adverse event. Only those events that were significantly different in frequency between groups are shown. Percentages for each symptom cluster are shown in *bold*.

[a] Fisher's exact test.

the zoledronic acid group also reported stiffness of the muscles or joints, and about half this proportion complained of joint swelling. The latter symptom suggests an inflammatory reaction within the joints, rather than just altered pain perception.

The third most common specific cluster of symptoms affected the gastrointestinal system. This was reported by about 8% of zoledronic acid-treated subjects and in 2% of the placebo-treated women. Nausea, vomiting, and diarrhea were the major components of this. One percent complained of abdominal pain, which could be related to intraabdominal inflammation (*e.g.* gastroenteritis) or might reflect musculoskeletal pain, as reported for most other parts of the body.

Inflammatory changes in the eyes have been associated previously with bisphosphonate use, particularly with iv infusions of pamidronate. They have not usually been considered to be part of the APR, but their occurrence (albeit rare) within the same time frame as the other inflammatory symptoms, suggests that they may have a similar pathogenesis. A variety of different diagnostic labels were attached to these symptoms (conjunctivitis, episcleritis, panophthalmitis, uveitis), but in the absence of detailed ophthalmological examination, it is likely that these all represent a similar syndrome, so they are grouped together as eye inflammation in Table 2. Twenty-two women treated with zoledronic acid had these symptoms after the first infusion, seven of whom did not complete the study. Two placebo-treated subjects complained of eye problems (conjunctivitis in one and eye pruritus in another) in the 3 d after injection, but this was less than a tenth of the total incidence of eye complaints seen in the zoledronic acid group, suggesting that eye symptoms are indeed part of the APR. Therefore, they have been included as a fourth cluster within the definition of the APR.

Having identified these system-specific symptom clusters, there remained a number of other adverse event reports, which are shown in Table 2 as general. In total, these affected about 20% of the study population. Two novel findings within this group are nasopharyngitis (in 17 zoledronic acid patients compared with five subjects in the placebo group) and peripheral edema. The excess of cases of nasopharyngitis implies that the generalized inflammatory response of the APR sometimes affects the upper airway as well as the other regions already discussed. Edema could represent swelling of the ankle joints related to local arthritis, although this was probably not the impression of the patients' physicians or it would not have been reported in this way. Many of the symptoms in this cluster are nonspecific (fatigue, dizziness, malaise, and headache) all being consistent with a generalized inflammatory response, and some of the reports of pain might have been classified elsewhere had more details been provided. The largest nonspecific group is influenza-like illness, which overlaps with most of the other categories in this table.

The above categories of adverse events are not mutually exclusive, so the total number of subjects affected cannot be arrived at by simply summing the individual event frequencies. Accordingly, we determined the number of subjects with any one of these events, which together we have taken as comprising the APR. As Table 2 shows, an APR defined in this way occurred in 42% of the zoledronic acid group and 12% of placebo, the difference between groups representing about one third of study subjects. Thus defined, the APR represents a syndrome involving inflammatory changes in the eyes, musculoskeletal, gastrointestinal, or respiratory systems, with associated nonspecific symptoms.

Time course

To determine whether limiting the definition of the APR to events occurring within 3 d of study drug infusion was appropriate, the time of onset of adverse events within each cluster of the APR out to 15 d is shown in Fig. 1. All components had their highest onset rate in the first 2 d after the infusion, with a rapid decrease in incidence after 3 d. Whereas symptom onset was much rarer from 4 to 15 d, there were statistically significant excesses of musculoskeletal pain, fever and chills, nausea, diarrhea, and peripheral edema in the zoledronic acid group during this time, although because of the small number of events, this is not obvious from Fig. 1. If we consider all events occurring out to 15 d that otherwise meet the definition of

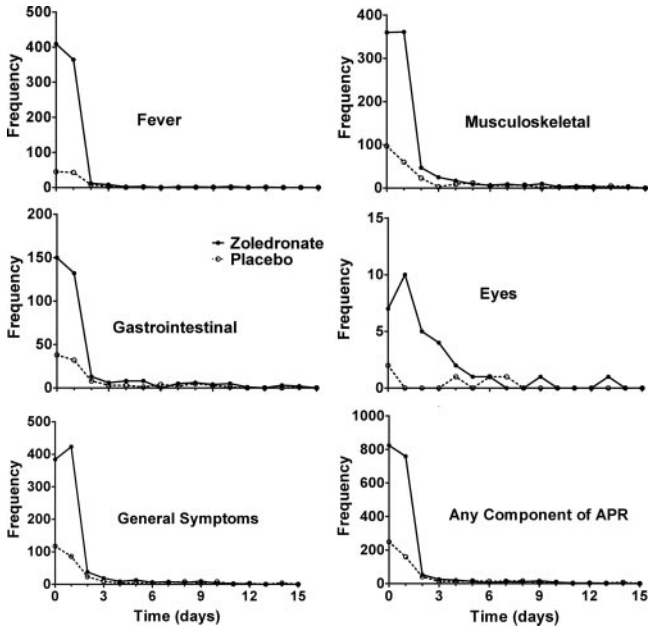

FIG. 1. Time from first infusion of study drug to onset of each adverse event cluster. The y-axes are number of subjects first reporting that event cluster each day.

TABLE 3. Severity of APR and its components after first study drug infusion

	Placebo				Zoledronic acid				
	n	Mild (%)	Moderate (%)	Severe (%)	n	Mild (%)	Moderate (%)	Severe (%)	*P*
Fever	96	64	34	2	785	51	43	6	0.044
Musculoskeletal	180	60	36	4	770	40	48	12	<0.0001
Gastrointestinal	80	76	21	3	300	62	33	5	0.05
Eye	2	100	0	0	22	59	36	5	0.52
General	226	73	24	3	847	51	43	7	<0.0001
APR	450	67	30	4	1636	46	45	10	<0.0001

n is the number of subjects with that component of the APR. *P* value is for comparison of the overall distribution of mild, moderate, and severe between placebo and zoledronic acid, using the χ^2 test. Numbers are too few for eye events in the placebo group for statistical testing across severity categories to be meaningful.

APR as determined above, then the frequency of an APR after the first zoledronic acid infusion is 1766 of 3862 in the zoledronic acid group (46%) and 571 of 3852 on the placebo group (15%), although the between groups difference is little changed (31%) from that found in the first 3 d.

Most APR components were short lived, the median (interquartile range) time from onset to resolution in the zoledronic acid-treated women being fever, 2 (2–3) d; musculoskeletal symptoms, 3 (2–6) d; gastrointestinal symptoms, 3 (2–5) d; eyes, 5 (2–11) d; general symptoms, 3 (2–4) d; and for any APR component (defined as time from onset of initial component to offset of last component for those with more than one symptom type) 3, (2–5) d.

Cataract was the only adverse event that was more common in the zoledronic acid group in d 4–15 (zoledronic acid, 5; placebo, 0) that had not shown an increased frequency in d 1–3 (zoledronic acid, 5; placebo, 6). Bisphosphonates have not previously been linked with the development of cataract, and it is biologically implausible that a cataract could develop so rapidly. Therefore, it is more likely that these cataracts were diagnosed incidentally during an eye examination that was triggered by inflammatory eye symptoms.

Severity

Table 3 sets out the distribution of severity of each APR component. The global APR rating represents the greatest severity of any component of the APR. In 90% of subjects, investigators rated their APR as being either mild or moderate. Of the 1636 people with an APR after the first zoledronic acid infusion, 87% received the second infusion and 82% the third. In those allocated to zoledronic acid who did not report an APR after the first infusion, 88 and 79% received second and third infusions, respectively.

Risk factors for APR

Knowing which individuals are more at risk of an APR is important in advising patients considering taking an iv bisphosphonate and might also give insight into the pathogenesis and amelioration of the APR. Therefore, we set out to determine the baseline characteristics that influence a subject's likelihood of having an APR by performing stepwise logistic regression. Variables considered included history of previous bisphosphonate use, age, race, body mass index, calculated creatinine clearance, country/geographic region of residence, baseline comorbidities, and baseline concomitant medications, with particular reference to NSAIDs, cyclooxygenase-2 inhibitors, and statins. The results of this analysis (Table 4) show that APRs were more common in younger subjects, NSAID users, and those having back pain and less common in smokers, diabetics, calcitonin users, and previous bisphosphonate users. Statin use was not protective. Race was a significant predictor of APR. The racial group with the highest risk was non-Japanese Asians and Pacific Islanders, with an univariate odds ratio of 2.20 and 3.39 after adjustment for

TABLE 4. Determinants of occurrence of an APR after first study drug infusion

Characteristic	Odds ratio	95% CI		*P*
Zoledronic acid	6.19	5.48	7.00	<0.0001
Region				<0.0001
Race				0.0068
Quintile of Age				<0.0001
64–67y *vs.* 78–89y	1.72	1.43	2.06	
68–71y *vs.* 78–89y	1.67	1.41	1.97	
72–74y *vs.* 78–89y	1.19	1.00	1.43	
75–77y *vs.* 78–89y	1.28	1.06	1.54	
Current smoker	0.73	0.59	0.90	0.0033
NSAID use at baseline	1.35	1.20	1.51	<0.0001
Prior bisphosphonate usage	0.78	0.66	0.92	0.0005
Active back pain	1.30	1.12	1.49	0.0023
Active diabetes	0.73	0.58	0.92	0.0084
Calcitonin use at baseline	0.66	0.51	0.86	0.0017

Other variables assessed but that were not found to be significant in the model were: calculated creatinine clearance; other baseline comorbidities; and other baseline concomitant medications, including cyclooxygenase-2 inhibitors and statins. CI, Confidence interval.

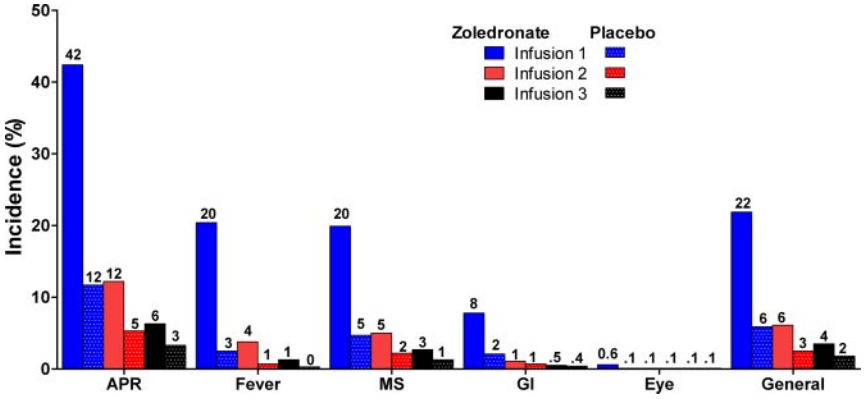

FIG. 2. Incidence of any component of the APR and of its five specific symptom clusters in the 3 d after each infusion of study drug. For each symptom cluster, the *bars from left to right* show the frequency for zoledronic acid and then placebo for the first to third infusions. There was no between-group difference in the frequency of eye and gastrointestinal reactions after the second and third infusions, but overall APR and the other categories of reactions did remain more common in the zoledronic acid group ($P < 0.0001$). In the zoledronic acid group, 3862 received the first infusion, 3409 the second, and 3107 the third. In the placebo group, the numbers were 3852, 3517, and 3190, respectively. MS, Musculoskeletal; GI, gastrointestinal.

the other variables in the model. This group constituted 14% of the cohort and were predominantly people from China, Hong Kong, Korea, Taiwan, and Thailand. Region was also a significant determinant, with Latin America having a lower risk than other regions (univariate odds ratio 0.36 compared with western Europe, 0.26 in the multivariate model). Repetition of this analysis for each symptom cluster produced essentially similar results, although previous cancer and osteoarthritis increased risk, and current use of raloxifene and higher body mass index were protective for some clusters. Results were similar when the analysis was repeated for severe or moderate APRs. Changes in total hip bone mineral density over 3 yr were not different in zoledronic acid patients reporting or not reporting an APR ($P = 0.30$, data not shown).

Redosing

Figure 2 shows the percent of subjects with any and each component of the APR after the first and subsequent infusions. As anecdotal experience has shown, all aspects of this problem are infrequent after second and third infusions, the net rates (zoledronic acid minus placebo) being 30, 7, and 3% after infusions 1–3, respectively. The frequency of APR symptoms also decreased in the placebo group over time. It is possible that this results from those who have APRs after the first infusion declining to receive further study medication. To assess this possibility, we repeated the analysis, restricted to those who received all three study drug infusions. The temporal patterns of each of the APR components are indistinguishable from those shown in Fig. 2.

Discussion

Since the first use of aminobisphosphonates iv, there have been reports of transient elevations of body temperature in the days immediately after administration (7, 8), and this has also been reported after high-dose oral bisphosphonate therapy (9). It appears not to be related to bisphosphonate dose (10, 11). The fever was noted to be associated with a fall in circulating lymphocyte number (7, 12) and increases in circulating IL-6 (12) and TNF-α (12–14) but not IL-1 (14). More recently, similar changes have been documented after zoledronic acid administration (15). The detailed cellular events that result in this cytokine release have now been delineated by workers in Aberdeen, who have shown that aminobisphosphonates indirectly activate $\gamma\delta$T cells through inhibition of farnesyl pyrophosphate synthase, which leads to intracellular accumulation of isopentenyl diphosphate and dimethylallyl diphosphate (5). They have shown that treatment of human peripheral blood mononuclear cells with zoledronic acid induces selective accumulation of these intermediates in monocytes, which correlates with the efficient uptake of bisphosphonates by these cells. Furthermore, zoledronic acid-pulsed monocytes trigger activation of $\gamma\delta$T cells in a cell contact-dependent manner (4). Nonaminobisphosphonates, such as clodronate, do not block this metabolic pathway and do not produce an APR, even when administered in high doses iv (13).

The present study analyses the largest database available in which to assess the APR. Its incidence is comparable with that reported previously, with figures of 10–50% being cited in the early literature. Whereas early reports focused on fever as the defining characteristic of the syndrome, the present study makes clear that the clinical presentation is much more diverse and can be manifest as inflammatory changes in most body systems. This is presumably a reflection of the pleiomorphic actions of the two cytokines thought to mediate the APR. The symptoms reported in the present study suggest the development of inflammatory changes in the joints, gastrointestinal tract, eyes, upper respiratory tract, and possibly skin. In addition, patients reported a number of nonspecific symptoms, such as headache, malaise, and fatigue, which are probably a reflection of the fever and widespread inflammatory changes. With the addition of these diverse symptoms to the definition of the APR, 42% of subjects treated with

zoledronic acid manifested some aspect of the syndrome, in comparison with 12% treated with placebo. This produces a between-group difference of about 30%, which is the figure that patients should be made aware of when considering infusions of an aminobisphosphonate.

When counseling prospective patients, it is also important to make them aware of the spectrum of severity and time course of the APR so that their decisions regarding treatment can be fully informed. In only 10% of those subjects having an APR was any component of it rated by the investigator as severe. This is 164 subjects from the 3862 that were randomized to zoledronic acid, representing 4% of that group. Discontinuation rates from the study were not higher in subjects reporting an APR, indicating that in most individuals the APR is not a deterrent to continuation of bisphosphonate therapy. A further reason that the APR has so little impact on long-term treatment adherence might be because of the transience of the symptoms, the median duration being 3 d. It is the anecdotal experience of physicians using these drugs frequently that when patients present for redosing a year later, most have no recollection of adverse events at the time of their initial treatment. Having said this, some women did have severe responses, and these are sometimes prolonged. Rarely patients will have symptoms that persist for more than a week, particularly musculoskeletal pain.

Patient decision making and the management of the APR would be greatly facilitated if there were clear-cut risk factors for its development. The present analysis is somewhat disappointing in that respect. It does confirm that previous bisphosphonate use (almost always oral) is protective but only partly so. Thus, subjects randomized to zoledronic acid who have previously used these drugs still experience an APR in 32% of cases, as opposed to 44% of those who were bisphosphonate naive. It is difficult to gauge to what extent the other risk factors identified have a firm pathophysiological basis, as opposed to reflecting different thresholds on the part of the patient or doctor for recording an adverse event. It is possible that patients already suffering from chronic pain (*e.g.* those recording back pain at baseline or concomitant NSAID use) are more sensitive to the effects of superadded inflammatory changes.

The regional and racial differences in APR incidence could represent different thresholds for the reporting and recording of adverse events or could reflect racial differences in cytokine production or action. Comparisons of postdose cytokine levels between Asian, European, and Latin American subjects would be of great interest. The absence of a protective effect associated with long-term NSAID use is surprising because there is clinical trial evidence that acute administration of these drugs diminishes both the change in body temperature and the subjective perception of APR symptoms after zoledronic acid treatment (16). Presumably long-term NSAID users have other medical problems associated with chronic pain and/or inflammation, which may be complicating the situation. The failure of statins to influence APR incidence is perhaps less surprising because this lack of effect has also been reported from a small clinical trial (17) and probably reflects the substantial first-pass liver metabolism of those statins in widespread clinical use. The protective effect of concomitant use of calcitonin might be related to its analgesic effect (18) or to the fact that procalcitonin is itself secreted in many inflammatory conditions (19). Possibly prior calcitonin use desensitizes the inflammatory response.

The present data provide the first systematic confirmation that the incidence of APR is greatly reduced on redosing. The analysis of individuals who had all three doses still shows this dramatic fall-off in APR incidence, confirming that this is a real finding and not merely an artifact produced by subject dropout. This is an important message to communicate to patients because it indicates that redosing is appropriate in those who have experienced an APR and that long-term drug use without significant APR side effects can be expected.

In conclusion, the APR is by far the most common adverse effect from the use of iv aminobisphosphonates, and all prospective patients should be counseled about it. Despite its frequency, it is of mild to moderate severity in most individuals and lasts only a few days. Probably for these reasons, it has minimal impact on long-term adherence to therapy. It is less common in subjects who have previously used bisphosphonates. There is trial evidence that its severity can be reduced by more than half with coadministration of paracetamol/acetaminophen, so the short-term use of these drugs to lessen the APR is advisable in patients receiving their first iv dose of an aminobisphosphonate.

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