

Common musculoskeletal adverse effects of oral treatment with once weekly alendronate and risedronate in patients with osteoporosis and ways for their prevention

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Abstract

Objective: To examine in a major cohort of patients whether or not musculoskeletal adverse effects (MAEs), similar to those seen in intravenous bisphosphonates (BP), might occur also in high dosage oral treatment regimens with alendronate (ALN) and risedronate (RSN). **Patients and methods:** 612 consecutive patients treated in the osteoporosis outpatient clinic at Charité, Campus Benjamin Franklin, between July 2002 and October 2003 with oral ALN or RSN (mean age 68.2+/-9.7 years; 527 females, 85 males), were examined and followed up for MAEs. **Results:** The overall frequency of any severe MAEs in our patients was low (5.6%). All severe MAEs occurred in primarily once weekly treated patients: 27 in ALN 70 mg once weekly (27/134=20.1%) and 7 in RSN 35 mg once weekly (7/28=25.0%), with no significant difference between those groups. The most frequently reported MAE was acute arthralgia in 12.6%, followed by acute back pain in 9.1% of all primarily once weekly treated cases. None of the 302 patients initially treated with daily BP reported any MAEs when later switching to once weekly administration (218 patients to ALN 70 mg once weekly and 84 patients to RSN 35 mg once weekly). With reference to recently published data, the phenomenon is probably related to dose dependent $\gamma\delta$ T cell activation by accumulation of isopen-tenyl pyrophosphate (IPP) due to inhibition of the mevalonate pathway by nitrogen containing bisphosphonates (nBP). **Conclusions:** MAEs in oral BP are, in general, less common and severe than in intravenous BP. They are observed exclusively in patients starting ALN or RSN treatment with once weekly dosage regimens. In order to avoid this phenomenon, it is suggested to start ALN or RSN treatment with the lower daily dosages of ALN 10 mg daily or RSN 5 mg daily for about two weeks before switching to the overall, more convenient, once weekly dose regimen.

Keywords: Osteoporosis, Bisphosphonates, Adverse Effects, Musculoskeletal

Introduction

Bisphosphonates (BP) are the current standard of care for numerous bone diseases associated with increased bone resorption. They effectively reduce symptoms and skeletal complications in patients with osteoporosis, Paget's disease of bone, multiple myeloma, hypercalcaemia of malignancy

and bone metastases¹.

Despite recent reports on osteonecroses of the jaw associated with BP use, mostly in cancer patients treated with intravenous nitrogen containing bisphosphonates (nBP)², these substances showed an overall beneficial safety and tolerability profile^{3,4}. In general, systemic adverse effects (AEs) are more common in intravenous than in oral applications of BP and are considered to be application specific. Intravenous nBP (e.g., pamidronate, ibandronate, zoledronate) are often associated with myalgia, arthralgia and bone pain, with or without systemic acute phase reactions including fever and general fatigue, described as flu-like symptoms or influenza-like illness (ILI) and accompanied by a number of well-defined biochemical changes in C-reactive protein, lymphocyte count and serum zinc⁴. The occurrence of these side effects within 24 hours after first application,

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Abbreviations
AE, adverse effect
ALN, alendronate
ALN 10 d, alendronate 10 mg daily
ALN 70 ow, alendronate 70 mg once weekly
BP, bisphosphonates
EBM, evidence based medicine
ILI, influenza-like illness
MAE, musculoskeletal adverse effect
nBP, nitrogen containing bisphosphonates
RSN, risedronate
RSN 5 d, risedronate 5 mg daily
RSN 35 ow, risedronate 35 mg once weekly

	BP and dose regimen given initially			
	ALN 10 d	ALN 70 ow	RSN 5 d	RSN 35 ow
No. of patients	273	134	177	28
Age (years), mean±SD	67.6±10.2	68.9±9.8	66.4±10.1	67.6±9.2
Men, no. (%)	51 (18.7)	18 (13.4)	16 (9.0)	0 (0)
Women, no. (%)	222 (81.3)	116 (86.6)	161 (91.0)	28 (100)
No significant difference in age. Differences in no. of patients per group are mainly caused by different dates of approval for both BPs. Differences in gender distribution are due to ALN (10 d), being the only BP approved for male osteoporosis.				

Table 1. Patient characteristics.

persistence for a couple of days, dose dependency, and very rare re-occurrence after repeated applications belong to their characteristics. Otherwise, oral nBP (e.g., alendronate (ALN), risedronate (RSN), ibandronate) are sometimes associated with upper gastrointestinal side effects⁵, but the latter are not considered in this paper. In recently published data from major clinical studies with oral ALN and RSN (in accordance to actual EBM based guidelines most widely used in osteoporosis treatment), there is no indication for the occurrence of musculoskeletal adverse effects (MAEs) as seen frequently with intravenous BP^{6,7}.

Since once weekly dosing regimens have been shown to reduce the incidence of upper gastrointestinal AEs^{5,6} and to improve overall patients' convenience, compliance, and adherence to oral BP^{4,6}, a majority of osteoporosis patients is currently being treated with ALN 70 ow or RSN 35 ow⁷.

When ALN and RSN in their once weekly application were used in the clinical practice setting for the first time, patients reported MAEs more frequently than it had been expected and ever seen before in daily dosage regimens.

The aim of the study was to examine in a major cohort of patients whether musculoskeletal side effects similar to those seen in intravenous BP might also occur in oral treatment regimens with ALN and RSN, and, consequently, to draw conclusions for their reduction or prevention.

Patients and methods

This retrospective analysis is based on the data from 1,950 patients treated in the osteoporosis outpatient clinic at the Charité, University Medicine in Berlin - Campus Benjamin Franklin between July 2002 and October 2003.

Among them, 612 consecutive patients treated with oral ALN or RSN, given daily or once weekly, were examined and followed up.

Any MAEs occurring during the first month of treatment were registered and analysed according to possible causality, severity and impact on further drug intake. Only events starting within 48 hours after first BP application and without any

other evident causality were evaluated and accounted for this analysis.

MAEs were grouped for:

- myalgia / muscle pain
- arthralgia / joint pain
- back pain
- generalised bone pain.

Other related AEs of special interest we looked at were: fever, as a typical sign of ILI, and chest pain.

Statistical evaluation was carried out using SPSS Version 11.0. Descriptive statistics were used to describe and characterize the sample. Statistical analysis was performed using the χ^2 test for comparison of frequencies.

Results

612 patients (mean age 68.2+/-9.7 years; 527 females, 85 males) receiving ALN or RSN treatment were analyzed. Table 1 summarises the demographic baseline characteristics.

Major MAEs (resulting in treatment interruption or discontinuation) were reported in 34 patients. All cases occurred in patients whose treatment was commenced with ow BP: 27 in ALN 70 ow (27/134=20.1%) and 7 in RSN 35 ow (7/28=25.0%) as illustrated in Figure 1. There was no statistically significant difference between frequency of MAEs in ALN 70 ow and RSN 35 ow.

The most commonly reported MAEs were acute arthralgia in 12.6%, followed by acute back pain in 9.1% of cases. Figure 2 illustrates these and other MAEs in descending order of their frequency within the group of primarily once weekly treated patients (summarising ALN 70 ow and RSN 35 ow).

Chest pain was reported in 3 cases, 2 of them leading to further procedures in order to exclude myocardial infarction (due to the severity of the symptom combined with pain-induced shortness of breath).

Whereas arthralgia and back pain occurred mostly in patients already severely affected by advanced osteoporosis

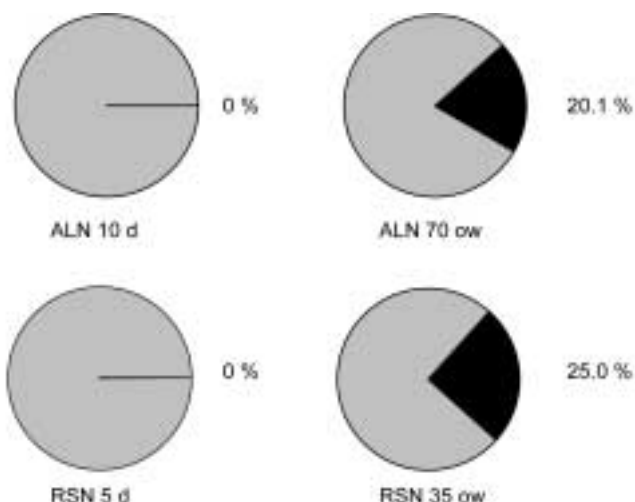


Figure 1. Percentage of patients experiencing significant MAEs in association with daily or once weekly dosing regimens of ALN and RSN.

with vertebral fractures (average number of vertebral fractures=2.3) or degenerative joint and/or spine changes, all other types of MAEs showed no correlation with any underlying condition.

No severe cases were reported for daily treatment regimens. Only in 3 cases (2 with ALN 10 d, 1 with RSN 5 d) mild to moderate symptoms were reported, but did not result in an interruption of the treatment due to these AEs.

None of the 302 patients initially treated with daily BP (302 of 450=67.1%) reported any MAEs when later switching to once weekly administration (218 patients to ALN 70 ow and 84 patients to RSN 35 ow).

Twenty-seven of the 34 patients (79.4%) with significant MAEs after newly given ow bisphosphonate agreed to re-exposure starting with daily dosage for 14 days and then switching back to the once weekly regimen. No reappearance of further major MAEs has been reported in those cases.

Discussion

In this retrospective study of a major cohort of osteoporotic patients in clinical practice, we obtain clear evidence of a comparatively common appearance of initial MAEs in oral BP as used widely in osteoporosis treatment according to EBM based guidelines. ALN as well as RSN were associated with the occurrence of MAEs, but only when therapy was commenced with the higher individual dosage as designated to be used in the once weekly dose regimens (ALN 70 ow or RSN 35 ow).

The overall frequency of any MAEs in our setting of 612 patients was low (5.6%). However, since all 34 cases with MAEs occurred in the group of 162 patients initially treated with once weekly dosages of ALN or RSN, there was a fre-

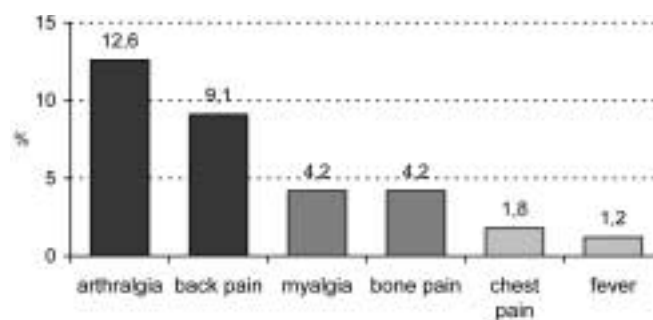


Figure 2. Frequency of MAEs in patients treated primarily with ALN 70 ow or RSN 35 ow.

quency of 21.0% in this sub-group of patients without significant differences between ALN 70 ow (20.1%) and RSN 35 ow (25.0%). However, due to a smaller number of patients treated with RSN 35 ow (resulting from the simple fact of later approval of RSN 35 ow), the frequency of MAS is less accurate than for that of ALN 70 ow. Apart from the retrospective study design, this was the major limitation of the study.

Nevertheless, our results give clear evidence not only of the appearance of initial MAEs in primarily once weekly treated ALN and RSN patients, but also show characteristics of these MAEs comparable to those seen in intravenous BP: 1. acute occurrence of musculoskeletal side effects within 24 hours after first application, 2. persistence for a couple of days, 3. very rare re-occurrence after repeated applications as long as the treatment interval allows patients to recover from their symptoms, and 4. a dose dependency since similar AEs^{3,4} were never seen in primarily ALN 10 d or RSN 5 d treated patients. The serum concentration of BPs after application of once weekly dosages is about seven times higher than with daily dose regimens, but still lower than after intravenous application of nBP with comparable anti-resorptive effect on osteoclasts.

The mechanism for acute phase reactions has been partly elucidated⁹ and appears to be associated with the release of TNF α and IL-6^{10,11}, although the effector cells that release these cytokines as well as the mechanisms of their action remain obscure. nBP are known to inhibit farnesyl pyrophosphate (FPP) synthase¹². It has been shown that this inhibition of the mevalonate pathway leads to an accumulation of metabolic intermediates including isopentenyl pyrophosphate (IPP). IPP itself is a potent activator of human peripheral blood $\gamma\delta$ T cells^{13,14}. As the acute phase response has not been observed with the non-nitrogen containing BP (such as etidronate, clodronate, tiludronate)^{3,4}, and is thus a specific feature of the nBP, it seems possible that this phenomenon is mediated through $\gamma\delta$ T cell activation. Recently, Hewitt et al. showed that nBP induce rapid and copious production of TNF α and IL-6 by peripheral blood $\gamma\delta$ T cells, that can be counteracted by β HMG-CoA reductase with statin pre-treatment¹⁵.

Despite these findings and our own clinical observations in oral BP, with an interesting analogy to acute phase reactions in patients treated with intravenous BP, acute MAEs in the initial treatment with once weekly ALN and RSN are less common and, first of all, much less severe than in intravenous BP. In single cases, however, a severe pain syndrome or classic acute phase reaction can occur. Gerster recently described a case of transient true polyarthritides with increased serum C-reactive protein levels in a patient with primary osteoporosis treated with ALN, symptoms starting twelve hours after the first intake of ALN 70 ow¹⁶. Some reports indicate that in monthly oral ibandronate the number of patients reporting ILI within three days of first intake was significantly higher compared with the daily regimen¹⁷.

Other reports on acute MAEs are rare, probably because of their transient and partly unspecific nature and difficulties to distinguish BP related AEs from symptoms of an underlying disease like symptomatic osteoporosis, severe degenerative spine or joint disorders or inflammatory rheumatic diseases.

Conclusions

The overall frequency of major MAEs in patients treated orally with ALN and RSN is low. Nevertheless, about one fifth of patients report acute MAEs if oral BP treatment was commenced using the higher once weekly dosage, either ALN 70 ow or RSN 35 ow. Although MAEs with this treatment regimen are, in general, less common and severe than in intravenous nBP, there seems to exist a dose-dependent effect similar to that reported after intravenous nBP application.

MAEs in oral ALN and RSN treatment are avoidable if treatment is commenced with lower daily dosages of ALN 10 d or RSN 5 d for about two weeks before switching to the overall, more convenient, once weekly dose regimen. According to our observation, patients having experienced MAEs after the first intake of ALN 70 ow or RSN 35 ow can be re-exposed, once the symptoms abate, since re-occurrence of major MAEs was not observed in our study.

Although the study was neither blind nor controlled, the authors, in full awareness of the limitations of a retrospective analysis of prospectively collected data, consider the data derived from a major patient cohort to be very relevant for the stepwise improvement of our understanding of osteoporosis treatment with oral nBP in a clinical setting.

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