Original Article

Evaluation of musculoskeletal adverse effects of once weekly oral bisphosphonates in osteoarthritis

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Abstract

Background: Commonly used oral once weekly (ow) bisphosphonate therapy for bone diseases is accompanied by various adverse effects. However, information regarding the musculoskeletal adverse effects (MAEs) is scarce.

Objectives: To evaluate whether alendronate (ALN) or risedronate (RSN) given orally ow could produce MAEs and which among ALN / RSN had a greater propensity to cause MAEs?

Methods: One hundred and twelve osteoarthritic patients on ow oral ALN 35 mg or RSN 35 mg from orthopaedic clinics were examined and followed up for MAEs, using Short Form McGill Pain Questionnaire (SFMPQ).

Results: Eighteen (16.07%) patients reported MAEs after ALN / RSN treatment. Of the patients experiencing MAEs, 72.72% experienced MAEs after first dose in the RSN group while 71.42% experienced after the second dose in ALN group (p=0.927).

Conclusions: Oral ow ALN / RSN induced MAEs in 16.07% patients, any time between the first to fourth doses equally in both genders which rarely recurred after repeating the dose in the same patient.

Key words: Alendronate; adverse effects; osteoarthritis; risedronate.

Introduction

Bisphosphonates are of proven benefit in treatment of bone diseases with increased bone resorption viz. osteoporosis, paget's disease of bone, multiple myeloma etc. [1]. Various adverse effects have been documented depending on their chemical nature, dose, frequency and route of administration, among which renal toxicity, acute phase reactions (APR) and gastrointestinal (GI) disorders are the commonest [2]. Transient flu-like symptoms, termed APR similar to musculoskeletal adverse effects (MAEs), are well documented to occur following intravenous nitrogen containing bisphosphonates [3, 4].

The U.S. Food and Drug Administration (US FDA) alert letter, highlighting the possibility of severe and sometimes incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates, has been issued to healthcare professionals to remind them, that these symptoms might go unrecognised by healthcare providers, thereby delaying the diagnosis, prolonging the symptoms, and necessitating the use of analgesics [3]. Also, the US FDA made it clear that it was describing symptoms different from the mild and transient symptoms of APR [4]. Despite these reports, once weekly (ow) dosing regimens of alendronate (ALN) / risedronate (RSN) which have better patient compliance due to less incidence of upper GI adverse effects are currently the preferred regimes for treatment of osteoarthritic patients. However, information regarding these oral bisphosphonates causing the MAEs is still scanty, with only a few reports about

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their skeletal adverse effects [5,6], hence this study was planned to evaluate whether oral ALN 35 mg and RSN 35 mg given ow orally induced MAEs. Out of the two, ALN or RSN, which has a greater propensity to cause MAEs was also studied?

Methods

This prospective study was carried out by acquiring the data from a cohort of 112 osteoarthritic patients treated with ow oral ALN 35 mg or RSN 35 mg at orthopaedic clinics of a tertiary care hospital and private nursing homes of two cities over a period of six months. Patients diagnosed with osteoarthritis between the ages of 40-70 years, of either sex, and initiated on bisphosphonate therapy for the first time with either ALN 35 mg or RSN 35 mg ow were included in the study after obtaining an informed written consent. Patients having musculoskeletal pain because of use of any other drug, preexisting chronic neurological disease or diabetes mellitus were excluded.

The study protocol was approved by the Institutional Ethics Committee and it followed the ethical standards of the committee on human experimentation as well as the Helsinki Declaration of 1975, as revised in 2000.

The patients were enquired for development of MAEs any time after the first dose of ow ALN 35 mg or RSN 35 mg given per oral, using the widely accepted Short Form McGill Pain Questionnaire (SFMPQ) in English language [7]. The main components of the SFMPQ are 15 descriptors (11 sensory, 4 affective) which are rated on an intensity scale of 0 = none, 1 = mild, 2 = moderate and 3 = severe. The major pain score is a total score derived from the sum of the intensity values of words chosen. Although the SFMPQ also yields two one-dimensional pain indices, present pain intensity (PPI) and visual analogue scale (VAS) score, this study used the combined sensory and affective total pain score as a pain index because it was considered important to measure the quality as well as the intensity of pain due to MAEs. The patients were followed up till the sixth dose of ALN/RSN treatment.The questionnaire was translated to the local language for the patients who were unable to follow the English format. Onset and duration of MAEs in one of the following forms- (i) Muscular pain, (ii) Joint pain, (iii) Back pain, (iv) Generalized body ache, (v) Exacerbation of already existing pain, or (vi) any other MAEs due to ALN /RSN use; were accounted for analysis.

To ascertain regular follow up and to avoid drop outs, patients were contacted telephonically or by self addressed reply paid envelops provided to the participants at the first meeting. Statistical analysis was carried out using Chi-square and Mann-Whitney U tests, $p < 0.05$ was considered significant.

Results

A total of 112 consecutive osteoarthritic patients (mean age 54.91 years; 101 females, 11 males) receiving ALN or RSN treatment were included in the study [Table 1]. The number of male patients in this study group was less compared to females due to the fact that male patients attending the orthopaedics clinics being diagnosed with osteoarthritis were less compared to the females.

Table 1- Demographic characteristics of osteoarthritic patients

	ALN	RSN	N
No. of patients	46	66	112
Mean age (years)	53.76	56.06	-
Male patients (%)	7(15.22 %)	4(6.07 %)	11
Female patients (%)	39 (84.78%)	62 (93.93%)	101

MAEs were reported in 18 (16.07%) patients. The MAEs occurred in two male patients who were treated with ALN while, among the 16 females complaining of bisphosphonate induced MAEs, 11 were treated with RSN and 5 with ALN. There was no statistically significant gender difference in development of bisphosphonate induced MAEs (χ^2 = 0.040, df = 1, p = 0.840) as analyzed by Chi square test.

The reported MAEs were acute back pain 9 (50%), acute arthralgia 6 (33.33%), generalised body aches 2 (11.11%) and acute severe chest pain 1 (5.56%).

These MAEs persisted for two to three days after onset and subsided without treatment except in one case where the patient developed severe chest pain with difficulty in breathing leading to stoppage of treatment with bisphosphonates and the patient being hospitalised for evaluation and treatment. The chest pain resolved completely after treatment with analgesic drugs and the patient was discharged from the hospital.

To analyse whether both the drugs have an equal propensity to produce the adverse effect, Mann Whitney U test was done on the VAS data of the SFMPQ. There was no statistically significant difference ($p = 0.927$) between frequency of MAEs in ALN and RSN treated groups, which indicates that there exists no statistical difference between the two drugs in the propensity to cause MAEs.

Out of 16 female patients, in the RSN group, a total of 11 patients developed MAEs, out of which 8 (72.72%) developed MAEs after the first dose and 3 (27.28%) developed after two doses. While the remaining five patients developed MAEs due to ALN treatment, out of which 1 (20%) patient developed MAEs after the first dose, 3 (60%) after two doses and 1 (20%) developed after three doses. No MAEs were reported after the fourth dose. The two male patients developed ALN induced MAEs after two doses.

This indicates that the bisphosphonate induced MAEs were more common after one dose in RSN 35 mg group but more common after two doses in ALN 35 mg group ($\chi^2 = 4.898$, df = 1, $p = 0.026$) [Table 2].

However, in all 18 patients, MAEs occurred only once, there was no recurrence of the MAEs in these patients after a repeat dose was administered, except in the case of the patient who developed severe chest pain and in whom the bisphosphonate was not repeated.

Two patients could not be followed up due to their non-attendance to the clinic as well as loss of contact and hence were not included for statistical analysis.

Discussion

The results of this prospective study indicate that in a cohort of osteoarthritic patients (n=112) treated with ALN 35 mg or RSN 35 mg ow, the frequency of appearance of MAEs is 16.07%, with no statistical difference in propensities of ALN and RSN in producing these MAEs. It is also clear that there is no statistically significant gender difference in occurrence of MAEs. However, this finding could be less accurate as the number of male patients enrolled in this study was less compared to the female patients.

Bock et al [5], in their study reported that MAEs occurred mainly after first dose of therapy but in contrast, the findings of the present study state that MAEs with ALN 35 mg can also occur after second/ third dose of starting therapy while RSN 35 mg did produce maximum MAEs after the first dose only. However, this could have been due to the fact that in the present study, the patients were followed up to six doses while, the other study considered MAEs only in the first 48 hours of treatment. Also, a difference in the dosing of ALN 35 mg in the present study as compared to 70 mg of the other study could

Table 2- Appearance of MAEs at various doses

Dose of ALN/RSN	RSN 35 mg (ow oral)		ALN 35 mg (ow oral)	
	No. of patients	% of patients	No. of patients	% of patients
I st	8*	72.72*	1	14.29
II nd	3	27.28	5*	71.42*
III rd	Nil	Nil	1	14.29
IV th	Nil	Nil	Nil	Nil
Total No. of patients with MAEs	11	100	7	100

* $\chi^2 = 4.898$ with 1 d.f., the two-tailed $p = 0.0269$

have been an influencing factor. With this data, it is clear that the low dose of ALN 35 mg can also lead to MAEs though delayed, indicating that MAEs by bisphosphonates could be dose dependent. Both the studies found that MAEs are more common in patients exposed to bisphosphonates for the first time and their recurrence is rare.

The mechanisms for development of APR have been partly elucidated but that of MAEs is still obscure. As these adverse effects are related in nature to each other, the same mechanisms could play a role. The APR is linked to the release of TNF-α and interleukins (IL-6, IL-10, IL-11) and interference in the mevalonate pathway [8, 9]. Nitrogen containing bisphosphonates are known to inhibit farnesyl pyrophosphate (FPP) synthase leading to inhibition of the mevalonate pathway and accumulation of metabolic intermediates including isopentenyl pyrophosphate (IPP) [10]. IPP itself is a potent activator of human peripheral blood γδ T cells which in turn releases IL-6 and TNF-α [11, 12]. As the acute phase response has not been observed with the non-nitrogen containing bisphosphonates (such as etidronate, clodronate, tiludronate) and is thus a specific feature of the nitrogen containing bisphosphonates, it seems possible that this phenomenon is mediated through γδ T cell activation [2].

In a recent review by Papapetrou PD [13], a hypothetical mechanism for severe bone pain has been put forth which highlights towards bisphosphonate-induced secondary hyperparathyroidism leading to relatively higher bone uptake and higher concentration of the bisphosphonate in the bone microenvironment. This in turn may result in a localised, relatively increased bisphosphonate-induced production of interleukin-6 with other proinflammatory cytokines [11, 12], and an inflammatory reaction confined to bones. Moreover, the high level of parathyroid hormone (PTH) in secondary hyperparathyroidism is also known to cause elevated interleukin-6 levels [14]. Thus, higher bisphosphonate concentration in the bone and high PTH may have a synergistic effect in increased production of interleukin-6 which finally results in severe bony pain in the patients.

Though these mechanisms could probably explain the occurrence of MAEs, but the precise mechanism by which the body gets adapted to the bisphosphonates and results in non-recurrence of these MAEs after repeated doses, is yet to be elucidated.

This study clearly states that bisphosphonate-induced MAEs can occur less intensely with oral ow bisphosphonate administration, equally in both genders, any time after the start of therapy but are more frequent after the first dose and may persist for two to three days but rarely recur after continuing the dose. Also, there is no difference in the propensity of producing MAEs between ALN/RSN. Thus, this study paves a way for further studies to elucidate and recommend if once daily dose of bisphosphonates could be used to initiate therapy, as the patient would be free from MAEs after two to three days of starting once daily dosing and then switch to more convenient ow regimens to abate the MAEs.

Key Points

- Alendronate (ALN)/ risedronate (RSN) administered once weekly (ow) orally are the preferred drugs for the treatment of osteoarthritis.
- Among the various adverse effects noted, musculoskeletal adverse effects (MAEs) described to be different from the well known acute phase reactions (APR) also occur with ALN/RSN with their oral use.
- It is noteworthy that these MAEs with both oral bisphosphonates given ow, occur less intensely, equally in both genders, any time after the start of therapy but are more frequent after the first dose and may persist for two to three days but rarely recur after repeating the dose.
- A careful dose titration would be prudent during the initiation of oral ow bisphosphonate therapy for the treatment of osteoarthritis.

References

1. Compston JE. The therapeutic use of bisphosphonates. BMJ 1994;309:711-5.
2. Diel IJ, Bergner R, Grötz KA. Adverse effects of bisphosphonates: current issues. J Support Oncol 2007;5:475–82.

3. U.S. Food and Drug Administration. www.fda.gov. Updated september 30, 2009. Accessed on September 13, 2010. http://www.fda.gov/Drugs/Drugsafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124165.htm
4. Recker RR, Lewiecki EM, Miller PD, Reiffel J. Safety of bisphosphonates in the treatment of osteoporosis. Am J Med 2009;122(2 Suppl):S22–32.
5. Bock O, Boerst H, Thomasius FE, Degner C, Stephan-Oelkers M, Valentine 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;7:144-8.
6. Wysowski DK, Chang JT. Alendronate and risedronate: Reports of severe bone, joint and muscle pain. Arch Intern Med 2005;165:346-7.
7. Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30:191-7.
8. Sauty A, Pecherstorfer M, Zimmer-Roth I, Fioroni P, Juillerat L, Markert M, et al. Interleukin-6 and tumor necrosis factor alpha levels after bisphosphonates treatment in vitro and in patients with malignancy. Bone 1996;18:133-9.
9. Thiébaud D, Sauty A, Burckhardt P, Leuenberger P, Sitzler L, Green JR et al. An in vitro and in vivo study of cytokines in the acute-phase response associated with bisphosphonates. Calcif Tissue Int 1997;61:386–92.
10. Van Beek E, Pieterman E, Cohen L, Lowik C, Papapoulos S. Nitrogen-containing bisphosphonates inhibit isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase activity with relative potencies corresponding to their antiresorptive potencies in vitro and in vivo. Biochem Biophys Res Commun 1999;255:491-4.
11. Gober HJ, Kistowska M, Angman L, Jeno P, Mori L, De Libero G. Human T cell receptor gammadelta cells recognize endogenous mevalonate metabolites in tumor cells. J Exp Med 2003;197:163-8.
12. Tanaka Y, Morita CT, Tanaka Y, Nieves E, Brenner MB, Bloom BR. Natural and synthetic non-peptide antigens recognized by human gamma delta T cells. Nature 1995; 375:155-8.
13. Papapetrou PD. Bisphosphonate- associated adverse events. Hormones 2009;8(2):96-110.
14. Nakchbandi IA, Grey A, Masiukewicz U, Mitnick M, Insogna K. Cytokines in primary hyperparathyroidism. In: Bilezikian JP, Marcus R, Levine M, editors. The Parathyroids, Basic and Clinical Concepts. Academic Press, San Diego, 2001, 2nd ed, pages 411-21.