

## Bisphosphonate Related Osteonecrosis of the Jaws

To the Editor:

As a rheumatologist who has seen and managed bisphosphonate related osteonecrosis of the jaws (Fung E, Medwatch case reports; Harper and Fung<sup>1</sup>), I wish to comment and raise questions on the recent editorial by Kahn<sup>2</sup> and article by Etminan, *et al*<sup>3</sup>.

Osteonecrosis of jaws (ONJ) might be old, dating back a century in the form of "phossy jaw"; but bisphosphonate related ONJ is rather new, first reported in 2003<sup>4</sup>. By the current, mostly accepted, definition, it is certainly not equal to osteoradionecrosis and we should not confuse the 2 conditions.

The incidence of bisphosphonate related ONJ in oral therapy was estimated as 0.7 or < 1 per 100,000 patient-years<sup>5</sup>; it is not the < 1 per 100,000 patients that has been so frequently misquoted<sup>2</sup>. The importance of getting it straight is, as rightfully pointed out by Dr. Kahn<sup>2</sup>, that the duration of therapy might be a very important factor, particularly in view of the very long bone half-life of aminobisphosphonates<sup>6</sup>.

In the editorial<sup>2</sup>, the work by Mavrokokki, *et al* from Australia in 2007<sup>7</sup> is not mentioned. I remind readers that that work cannot be taken lightly, in view of the country-wide design of the survey, which was supported by the national healthcare service and also by the centralized electronic records for dental care used in South Australia. The results for bisphosphonate related ONJ, as published, for osteoporosis treated with oral bisphosphonate were as high as 1/2260 cases without and 1/296 cases with dental extraction. While these findings seemingly are at odds with the North American experience<sup>5</sup> (except the recently reported prevalence of bisphosphonate related ONJ of 1/1424 cases from Northern California<sup>8</sup>), the incidence for malignancy treated with bisphosphonate of 1.15% without and 9.1% with dental extraction is in agreement with data reported in North America<sup>9,10</sup>.

The article by Etminan, *et al*<sup>3</sup> shows a 3-fold increase of aseptic osteonecrosis with bisphosphonate, but the site of the aseptic osteonecrosis cannot be verified. In fact it might be at sites other than the jaw, since there was no International Classification of Disease code for it prior to November 2007, and Etminan, *et al* felt these findings might be corticosteroid related in view of the imbalance of the percentages of corticosteroid use. However, within their Methods section, Etminan, *et al* stated that potential confounders including oral corticosteroids were adjusted for by conditional logistic regression. Did Dr. Etminan actually adjust or not adjust for the corticosteroids in this study? This might fall short compared to the Australian report, in which cases of ONJ were confirmed, although not adjudicated, by experienced clinicians.

Finally, the only bisphosphonate clinical study that has included ONJ in the protocol is the zoledronic acid Horizon trial<sup>11</sup>. If indeed the incidence is as high as the Australian survey indicates, we could have seen some signals of it; on the other hand, if it is anywhere close to the finding of < 1 per 100,000 patient-years, then, as Etminan and colleagues commented, none of the bisphosphonate trials to date has the statistical power to reveal this one way or the other.

Bisphosphonate related ONJ does not discredit bisphosphonates as an effective osteoporosis therapy, but our patients deserve more than having their treating physicians look the other way from this new development, or entity. Adding to the laborious Australian survey<sup>7</sup> and the thoughtful American Society of Oral and Maxillofacial Surgeons 2007 position statement<sup>12</sup>, we should welcome the results of the Canadian survey<sup>3</sup> as well as the authors' position in this important issue.

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## REFERENCES

1. Harper RP, Fung E. Resolution of bisphosphonate-associated osteonecrosis of the mandible: possible Application for intermittent low-dose parathyroid hormone [rhPTH(1-34)]. *J Oral Maxillofac Surg* 2007;65:573-80. Erratum in: *J Oral Maxillofac Surg* 2007;65:1059.
2. Khan AA. Osteonecrosis of the jaw: new developments in an old disease [editorial]. *J Rheumatol* 2008;35:547-9.
3. Etminan M, Aminzadeh K, Matthew IR, Brophy JM. Use of oral bisphosphonates and the risk of aseptic osteonecrosis: a nested case-control study. *J Rheumatol* 2008;35:691-5.
4. Marx RE. Pamidronate and zoledronate induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;61:1115-8.
5. Merck & Co. correspondence.
6. Fosamax prescription information.
7. Mavrokokki T, Cheng A, Stein B, Goss A. Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. *J Oral Maxillofac Surg* 2007;65:415-23.
8. Lo JC, O'Ryan FS, Gordon NP, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure: the Kaiser-Permanente PROBE Study [abstract]. Proceedings of the Endocrine Society, June 15, 2008, San Francisco, CA, USA:OR14-1.
9. Hoff AO, Toth BB, Altundag K, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res* 2008;23:6:826-36.
10. Krueger CD, West PM, Sargent M, et al. Bisphosphonate-induced osteonecrosis of the jaw. *Ann Pharmacother* 2007;41:2:276-84.
11. Ringe JD, Nitschmann S. Zoledronic acid for preventing fractures. HORIZON trial (Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly). *Internist Berlin* 2008;49:502-4.
12. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2007;65:369-76.

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