Letters

Osteosarcoma risk in rats using PTH 1-34

We read with interest the recent research article 'Reconstructing the skeleton with intermittent parathyroid hormone' by Ego Seeman and Pierre Delmas, published in *Trends in Endocrinology & Metabolism*[1] and at http://www.HMS_Beagle.com. The article is a good review of the efficacy of the first parathyroid hormone to treat osteoporosis, PTH 1-34, including the limits of that efficacy.

We would like to bring attention to the fact that there is a primary safety issue (the induction of osteosarcomas in a rat carcinogenicity study) related to the use of PTH 1-34, which was discussed at some length in the article by Neer *et al.*[2] (http://www.fda.gov/ohrms/dockets/ac/01/briefing/376162_fda.htm).

In trials with rats, osteosarcomas occurred in rats treated from the age of six to seven weeks for two years with PTH 1-34 (representing near lifetime treatment) at frequencies of 0%, 5%, 35% and 52% (control, low, middle and high dose) in males and in 0%, 7%, 20% and 38% of females (http://www.fda.gov/ohrms/dockets/ac/01/briefing/3761b2_05_PharmTox.htm). No 'no-effect level' for osteosarcomas was established because tumors were present at even the lowest dose tested. There was also a statistically significant increase in osteoblastomas in both sexes.

As a result of these findings, the clinical trials were prematurely stopped in December 1998. Consequently, the median treatment duration was only 19 months for the main trial, rather than the three years that were originally planned (http://www.fda.gov/ohrms/dockets/ac/01/briefing/3761b2_04_Statistics.htm). The human significance of these osteosarcomas has been rationalized away by citing: (1) the lack of osteosarcomas in the clinical trial; (2) the absence of bone tumors in an 18-month monkey study; (3) the lack of genotoxicity; and (4) the lack of tumors in patients with hyperparathyroidism.

The absence of bone tumors in the clinical trial patients is not surprising given that osteosarcomas are rare and the time to appearance for chemically induced tumors, in general, ranges from ten to 20 years from the time of exposure. Similarly, the monkey study was much too short (not lifetime) and lacked statistical power, having only four monkeys per group rather than the 60 individuals per group in the rat study.

Because the formation of osteosarcomas is mechanism based (PTH stimulates proliferation of osteoblasts, thus increasing the likelihood of mutations), the absence of positive results in genotoxicity tests is not relevant. A probable mechanism for carcinogenicity is drug-induced cell division, increasing the chances for generating genetic errors and then magnifying them.

Finally, that osteosarcomas are not seen in patients with hyperparathyroidism is of limited relevance, because those patients are exposed to chronically elevated PTH levels, whereas patients being treated with PTH are on an intermittent dosing schedule, which can induce a differential effect on osteoblastic gene expression (http://www.fda.gov/ohrms/dockets/ac/01/briefing/3761b2_05_PharmTox.htm).

In summary, these data present a compelling case for the carcinogenicity of PTH 1-34. Moreover, the rat study might have actually underestimated the incidence of bone tumors. Tumors were detected by a clinical finding of a bone nodule and/or by microscopic evaluation, but only four bones per animal were routinely examined. The limits of clinical detection are illustrated by one bone tumor that was fatal yet was only detected upon microscopic examination. Patients could have microscopic tumors that could not yet be detected clinically.

For these reasons, we feel that if PTH 1-34 is approved to treat osteoporosis, (a) its use should be restricted to a second-line drug to minimize population exposure to this carcinogen; (b) there should be a black-box warning on the carcinogenicity findings; (c) patients should be given an FDA-approved Medguide each time a prescription is filled; and (d) the sponsor should be required to establish a registry in order to identify patients with PTH 1-34-associated osteosarcomas.

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References
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2 Neer, R.M. *et al.* (2001) Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *New. Engl. J. Med.* 344, 1434–1441

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Response from Seeman and Delmas

We thank Barbehenn and colleagues[1] for drawing attention to the induction of osteosarcomas in rats treated with parathyroid hormone PTH 1-34. We agree with the importance of highlighting such a safety issue and recommend that readers refer to the information and recommendations on the FDA website (http://www.fda.gov/ohrms/dockets/ac/01/briefing/3761b2_fda.htm), and to the Discussion section in the paper by Neer and colleagues[2].

As is the case in all complex matters such as the clinical significance to humans of toxicology in animals, detailed analyses, deliberation and timely recommendations are best made within the scientific community and by regulatory authorities, such as the FDA, following publication of all of the data in the peer-reviewed literature.

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References
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