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 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. (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 patients is not surprising given the limits of that efficacy; (2) the absence of bone tumors in an 18-month monkey study; (3) the lack of tumors in order to identify patients with osteosarcoma risk in rats using PTH 1-34.

We thank Barbehenn and colleagues 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.

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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1 Barbehenn, E. et al. (2001) Osteosarcoma risk in rats using PTH 1-34. Trends Endocrinol. Metab. 12, 383

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Response from Seeman and Delmas

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