Letter to the Editor

Response to letter of Vahle et al.

The letter of Dr. J. Vahle (Toxicol Pathol 35: 1045–1046, 2007) and colleagues at Lilly Research Laboratories concerning our recent report (Toxicol Pathol 34: 929–940, 2006) raises several important points that deserve comment. The primary objective of our paper was to report the results of a standard two-year rat carcinogenicity study conducted with recombinant full-length human PTH (1-84) to comply with international regulatory guidelines.

Dr. Vahle et al. are correct that our study did not directly compare the carcinogenic potential of PTH (1-84) and PTH (1-34), that is, teriparatide. Although scientifically intriguing, such a side-by-side comparison would be unprecedented in such studies. Additionally, interpretation of the results would remain problematic because we would have had to test a synthetic PTH (1-34) as comparator and not the recombinant peptide used by Vahle et al. (Toxicol Pathol 30: 312–321, 2002; Toxicol Pathol 32: 426–438, 2004).

As clearly described in our report, we designed the PTH (1-84) study to mirror as closely as possible that of teriparatide. However, one additional key element not used by Vahle et al. (Toxicol Pathol 30: 312–321, 2002; Toxicol Pathol 32: 426–438, 2004) was incorporated into the PTH (1-84) study. Whole-body radiographs allowed detection of bone tumors at sites not routinely sampled at necropsy because such tumors often originate in the endosteum and remain undetected unless they have breached the periosteum. This key element increased the sensitivity to detect bone tumors and increased confidence in the study results. Thus, despite the detection of additional tumors with this procedure, fewer tumors were still observed with PTH (1-84) than with teriparatide.

The initial report by Vahle et al. (Toxicol Pathol 30: 312–321, 2002) did an excellent job of establishing diagnostic criteria to categorize hyperplastic, benign, and malignant proliferative findings in bones and greatly facilitated the classification of skeletal changes induced by PTH (1-84). Thus, we are confident that very similar criteria were used for the bone tumors in our study. Importantly, this concept was supported by our pathology assessment validated by peer review, which noted a similar incidence, skeletal distribution, and histological appearance of other bone tumors (osteoblastoma and osteoma) with the mid and high doses of PTH (1-84) and teriparatide. We believe that our report contains sufficient information for the reader to understand that there exists the potential for differences in animals and pathological interpretation.

Vahle et al. (Toxicol Pathol 35: 1045–1046, 2007) noted that the pharmacodynamic effects on bone of the two peptides are critical in interpreting the results. In vivo studies that have directly compared the effects of PTH (1-84) and teriparatide in bone are unusual, but when they have been performed, teriparatide tends to be an equivalent or slightly more potent anabolic agent in rats. PTH (1-84) did not increase bone mineral content to the same extent quantitatively as teriparatide at approximately equimolar doses. Although direct comparisons have also not been performed, studies in postmenopausal women with osteoporosis have indicated that the increase in lumbar spine BMD is also greater with teriparatide than with PTH (1-84), although the vertebral antifracture efficacy of the two peptides appears similar (Neer et al., N Engl J Med 344: 1434–1441, 2001; Greenspan et al., Ann Intern Med 146: 326–339, 2007). The important point here is not that one peptide is a more potent anabolic agent, but that exposure to the two peptides at levels similar to those used clinically resulted in the induction of osteosarcoma with teriparatide, but not with PTH (1-84). Vahle et al. (Toxicol Pathol 35: 1045–1046, 2007) argue correctly that the differences at the low doses are numerically small, but it is important to point out that the difference between the peptides was maintained at the two higher doses when tumor induction was more frequent.

Although the mechanism underlying these apparent differences is poorly understood, we speculated that the C-terminal region of PTH (1-84), which is absent in teriparatide, may play a regulatory role, not only in the lesser anabolic response, but also in the lower carcinogenic potential of PTH (1-84). The biological actions of the C-terminal region of PTH (1-84) was the subject of a recent extensive review by Murray et al. (Endocr Rev 26: 78–113, 2005). However, confirmation of this hypothesis will require further scientific exploration.

Vahle et al. (Toxicol Pathol 35: 1045–1046, 2007) are correct that we did not make reference to their second carcinogenicity study with teriparatide (Toxicol Pathol 32: 426–438, 2004) when assessing a noncarcinogenic dose. The second teriparatide study was limited and would not meet established regulatory guidelines for a rat carcinogenicity bioassay. This study investigated only the low and mid doses used in the first study, namely 5 and
30 µg/kg/day; treatment was for a maximum of up to twenty and twenty-four months, respectively, and used only female rats. The incidence of osteosarcomas in both PTH (1-84) and teriparatide two-year carcinogenicity studies was lower in female than in male rats. Thus, the design of a female-only study with a delayed teriparatide treatment start and dosing at 5 µg/kg for up to twenty months increased the likelihood of a no-effect outcome.

The discussion of our report summarized the results of our rat carcinogenicity study and delineated similarities and differences between PTH (1-84) and teriparatide while providing detailed and plausible explanations for the observed differences. We agree with Vahle et al. (Toxicol Pathol 35: 1045–1046, 2007) that differences exist between human and rodent skeletal physiology, and we caution the reader regarding the application of the results of either study to humans. However, despite the difference in physiology, the results from two-year rodent carcinogenicity studies are used by regulatory agencies for labeling and to provide physicians and patients information regarding their risk with use of a product.

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