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Letters

To the Editor:

Re: Toth JM, Boden SD, Burkus JK, et al. Short-term osteoclastic activity induced by locally high concentrations of recombinant human bone morphogenetic protein-2 in a cancellous bone environment. Spine 2009;34:539–50.

Toth *et al*[1] mentioned the study of Meisel *et al*,[2] who reported 100% incidence of the resorptions in 17 patients treated with 12 mg (8 cm^3) of rhBMP-2 following posterior lumbar interbody fusion (PLIF) performed with 2 polyetheretherketone (PEEK) vertebral body spacers per level of fusion. As the internal volume of each interbody construct was 1.3 cm^3, overfilling the constructs in this manner produced a local rhBMP-2 concentration of approximately 4.6 mg/cm^3 (6 mg rhBMP-2/1.3 cm^3 volume), which was more than 3 times the 1.5 mg/cm^3 used in the article cited Investigational Device Exemption clinical trials involving interbody constructs. The local high rhBMP-2 concentration was suspected by Toth *et al*[1] as the reason for such high incidence of the resorptions.[2]

However, 1 of those 17 patients underwent PLIF at 2-levels at the same time.[3] The patient received a split dose for his 2-level intervention (6 mg [4 cm^3] of rhBMP-2 divided within 2 PEEK cages per level). The patient had a common outcome in that the resorptions of the vertebral bodies at both fused levels occurred despite the twofold lower dose of rhBMP-2. Meisel *et al*[3] stated that the potential for the response to be more general must be considered. In response to our comment, Meisel stated that our observation that transient vertebral resorption occurs regardless of the doses of BMP-2 which have been used clinically is correct, which further demonstrates that the available doses are still too high for intervertebral use.[4] This is in concordance with the opinion of Vaidya *et al* that endplate resorption occurs in all patients that undergo rhBMP assisted spinal interbody fusion.[5] It should be emphasized that only 2 mg of rhBMP-2 within PEEK spacer were used per level of LIF (1 mg for cervical spine) in commented study of Vaidya *et al*.[6] Therefore, is the overfilling of different intervertebral constructs with rhBMP-2 really the main cause of high incidence of the resorptions in the cancellous bone environment?[4]

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The legal regulatory status of the device(s)/drug(s) that is/are the subject of this manuscript is not applicable in my country.
No funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

In Response:

Thank you for your comment on our article.[1] As we mentioned in the introduction of our article, Meisel *et al*[2] reported in 2005 "reduced mineral density" and "transient regional osteopenia" at 3 months in 17 patients treated with 12 mg of rhBMP-2 in polyetheretherketone cages for lumbar interbody fusion. This corresponded to 6 mg of rhBMP-2 in each cage. Meisel *et al*[2] further indicated that these areas of "transient regional osteopenia" were resolved by 6 months. Since our manuscript was accepted on November 13, 2008, we did not have access to the subsequent publication by Meisel *et al*[3] which was published in *Spine* in December of 2008. In the 2008 article, Meisel *et al*[3] point out that 16 of the 17 patients had 12 mg of rhBMP-2 placed at each level, and as you noted, one (1) of the 17 patients were operated on at 2 levels with a "divided allotment" of 6 mg of rhBMP-2 placed at each of the 2 levels. If we look at a majority (16/17) of the patients, 12 mg of rhBMP-2 divided by the internal volume of 2 large PEEK Telamon cages (1.3 $cm^3 \times 2 = 2.6$ cm^3) results in a concentration of 4.62 mg/mL of rhBMP-2, well above the 1.5

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mg/mL of rhBMP-2 in INFUSE. Even if we consider the one patient you refer to in the Meisel *et al*[3] full publication, 6 mg of rhBMP-2 divided by the internal volume of the PEEK Telamon cage (1.3 $cm^3 \times 2 = 2.6\ cm^3$), results in a dose concentration of 2.31 mg/mL, still above the 1.5 mg/mL of rhBMP-2 in INFUSE. It should be pointed out that Meisel *et al*[3] describes the use of 3 different cage sizes in these patients: 10 × 26 mm (1.3 cm^3 internal volume), 8 × 26 mm (1.05 cm^3 internal volume), and 8 × 22 mm (0.75 cm^3 internal volume). Therefore, the concentrations calculated above (based on the largest cage size) are at least 4.62 mg/mL (16 patients) and 2.31 mg/mL, but could be even higher as hyperconcentration of the morphogen increases with a decrease in internal cage volume.

Our ovine corticocancellous study was performed to examine the effects of increasing local rhBMP-2 concentration on osteoclastic activity in a contained cancellous defect. Quantitative histomorphometry and QCT measurements from our study clearly showed that increasing the local rhBMP-2 concentration by overfilling the defect with rhBMP-2/ACS or hyperconcentrating the rhBMP-2 solution on the absorbable collagen sponge led to a concentration-dependent increase in peri-implant cancellous bone resorption at 1 week. This model might simulate the worst-case scenario in the spine in which significant exposure to a cancellous bone environment occurs due to extensive decortication of the endplates. Although we feel that the incidence and extent of transient resorption is related, in part, to the exposure to a cancellous bone environment, we note again that we observed and reported transient bone resorption in the ovine corticocancellous defect model with the lowest dose of rhBMP-2 (0.43 mg/mL). This finding would seem to be consistent with the 2002 publication of Poynton and Lane[4] who published a safety profile related to the safety and use of BMPs in spinal fusion. They state, ". . . BMPs have a role in the regulation of bone turnover *via* coupled osteoblastic and osteoclastic activity. As with fracture healing, the osteoclastic resorption occurs before bone formation by osteoblasts. The exact effect of this in spinal fusion is not completely understood. However, large doses of BMP may lead to localized areas of resorption."

The assertion that cancellous bone resorption occurs in all cases in which rhBMP-2/ACS is used in the interbody space is not evidence-based. In fact, there were very few instances of resorption in the series of patients with the titanium trapezoidal fusion cages used to gain the original Food and Drug Administration approval. In that series, the interbody device was an endplate-sparing device with minimal violation of the cortical endplates and therefore minimal exposure to cancellous bone, resulting in little or no resorption.[5] In contrast, a series published by Burkus *et al* demonstrated transient resorption when cortical allograft bone dowels were used for lumbar interbody fusion.[6] Insertion of the allograft bone dowel resulted in more aggressive endplate decortication/violation and consequently a higher incidence of transient resorption.[6] Thus, based on clinical evidence it is clear that access and proximity to cancellous bone is one important factor that can increase the risk of transient bone resorption. Our study showed that hyperconcentrating and/or overfilling the morphogen, which led to accelerated release kinetics, is yet another factor that can influence the likelihood of bone resorption.[1]

Using the Food and Drug Administration-approved rhBMP-2 concentration and matching the volume of rhBMP-2/ACS with the volume of the bony defect or internal cavity of the device may limit the occurrence of transient bone resorption. Using a more clinically relevant ovine model of lumbar interbody fusion, we are continuing to examine: (1) bone and endplate resorption due to increased local concentrations of rhBMP-2 on the ACS carrier, (2) the effects of bisphosphonates in inhibiting bone resorption, and (3) the influence of different carriers and release kinetics on the bone resorption.[7,8]

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The comment refers to a sheep study (not a clinical study). The device is FDA approved, but not for the use in metaphyseal defects as described in the initial manuscript.

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