Adverse effects of posterior lumbar interbody fusion using rhBMP-2

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To the Editor

We read with great interest the recent article on the use of recombinant human bone morphogenetic protein 2 soaked into an absorbable collagen sponge (rhBMP-2/ACS) in the posterior lumbar interbody fusion (PLIF) written by Meisel et al. [13]. However, a few corrections and clarifications are required to update this otherwise exceptionally significant article.

Meisel et al. [13] mentioned a sheep distal femur model in which transient peri-implant osteolysis with regard to BMP overfilling and hyper-concentration has been observed [1], but several examples are present in the literature that clarify the pathophysiology and the relevance of the vertebral osteolysis much better. For instance, Seeherman and Wozney [15] have shown that a collagen sponge soaked with rhBMP-2 and placed in contact with trabecular bone of the distal femoral core defect in non-human primates resulted in significant transient bone resorption at 2 weeks after the surgery. This was not the case when they used a carrier with slower release of rhBMP (calcium phosphate matrix). The rapid release of rhBMPs at the bone surface which is in contact with the collagen sponge creates favorable conditions for significant osteoclastic reaction prior to the bone formation phase. According to a review of the interaction of BMPs with osteoclast lineage cells, BMPs in most of the reports had a stimulatory effect that up-regulated formation of osteoclasts, their bone resorptive capacity, or both of these phenomena [5].

As Meisel et al. [13] emphasized the note of Boden et al. [1] that parity between the distal femur and the central region of the vertebra may not be fully warranted as a clinically relevant spine model, we would like to emphasize a very significant article published by Laursen et al. [10] in this very Journal 10 years ago which definitively presents a relevant spinal model. It was the first report of trabecular bone resorptions after a clinical application of rhBMPs/ACS in proximity of vertebral bodies. The first report of trabecular bone resorptions after a clinical application of rhBMPs to our best knowledge was identified in a manuscript of Howell et al. [8]. The loss of bone volume in some of the cases after the rhBMP-2/ACS local alveolar ridge preservation or augmentation was noted between the 4- and 8-week time points. Anyway, Laursen et al. [10] treated five patients with single-level unstable burst fracture and no neurological impairment with intracorporal rhBMP-7 transplantation, posterior fixation and posterolateral fusion. Radiographic and computed tomography (CT) evaluation after 3 and 6 months showed severe resorption of the whole anterior column at the site of transplantation, but after a year, new bone had started to fill in at the area of resorption. In all cases, there was a loss of correction with regard to anterior and middle column height and sagittal balance at the latest follow-up. Based on the obtained data, the authors by ethical obligation discontinued and redesigned the study. At this moment, we are interested in whether or not Meisel et al. [13] considered discontinuing and redesigning their study after they faced such vertebral resorptions in their patients at 3 months postoperatively (enrollment of the patients lasted from January until June of 2004). We had to emphasize that back in 2004 only a few researchers had some information about the resorptions and their clinical impacts, but that information for some reason has not been presented to

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the wider medical community at the time (T. Smoljanovic et al. unpublished data, 2008).

The authors stated that ethical approval for the study was not required based on separate approved status of both the TelamonTM poly-ethyl-ether-ketone (PEEK) cage (Medtronic Sofamor Danek, Memphis, TN) and rhBMP-2/ACS (InductOs[®] 12 mg Kit for implant; Wyeth Europa Ltd, Taplow, UK) [13]. However, we are not aware that the use of rhBMP2/ACS has been allowed for the PLIF. On the contrary, the United States Food and Drug Administration (FDA) halted the trial of Haid et al. [6], after the ectopic bone formation into the spinal canal was observed in 75% patients (24 of 32) who received rhBMP-2/ACS. Although Haid et al. [6] claimed that no statistical correlation between increased leg pain and corresponding ectopic bone formation extending outside the disc space and into the spinal canal or neuroforamina after PLIF assisted with rhBMP-2/ACS was found, their findings were seriously challenged by later findings [25]. A case report of Wong et al. [25] presented five patients whose ectopic bone formation in the spinal canal after either PLIF or transforaminal interbody fusions (TLIF) assisted with rhBMP-2/ACS was associated with neural complaints, which resulted in demanding revision surgeries in three of their five patients. The remaining two underwent chronic pain management in the workers compensation system. Reoperated patients had partial improvement in their corresponding radicular pain postoperatively, suggesting that at least a portion of their root pain was associated with the extrinsic pressure or tethering of the root. Fortunately, in the study of Meisel et al. [13] only one patient has demonstrated intracanal bone formation that could be attributed to rhBMP-2 demonstration and that patient remained asymptomatic.

But let us return to the resorptions. The incidence of the resorptions in the study of Burkus et al. [2] was higher than the 14% reported by Meisel et al. [13]. The resorptions were observed in 14 patients, but as there was a total of 79 patients in the rhBMP-2 group in the second report of two sequential phases of a prospective, randomized, multicenter, FDA-approved investigational device exemption study conducted to determine the safety and efficacy of the use of rhBMP-2/ACS in anterior lumbar interbody fusion (ALIF) with threaded cortical allograft dowels, the incidence was 17.7% [2, 3]. An analysis of vertebral resorption reports has confirmed our previous findings [18] that transient vertebral resorptions occur regardless of the doses of rhBMP-2 which have been used clinically per level of interbody fusion in published reports until now, but depending on the size of the contact area between the rhBMP-2/ACS and vertebral trabecular bone [16, 17] (T. Smoljanovic et al. unpublished data, 2008). The larger contact area in the studies, which reported occurrence of the resorptions, was created due to

the design of the interbody spacers (larger apertures like in case of PEEK cages [13, 22, 23], or femoral ring allografts (FRA) [7, 14]) or with additional rhBMP-2/ACS which were placed outside the interbody spacers within the interbody space [2, 3, 9, 11, 12, 19, 24]. As Burkus et al. [2–4] placed an additional rhBMP-2/ACS between allograft dowels in their two-phase Level I study under FDA control; we were not surprised when unreported vertebral resorptions were discovered [19] in Fig. 10 of the first phase where Burkus et al. [4] stated that because of the early incorporation of the allograft to the vertebral endplates in the rhBMP-2 group, a radiolucent line around the implants was not seen after surgery in the rhBMP-2 group. Although Burkus et al. [2, 3] claimed that study protocols were identical for both phases, the dose of rhBMP-2 used per level of fusion was decreased from 12–18 mg in the first phase, to 8.4–12 mg in the second phase [21]. One might speculate that Burkus et al. [2–4] shared the opinion of Meisel et al. [13] that the dose of rhBMP-2 used might have been higher than generally indicated for use in single-level lumbar fusion in adults with degenerative disc disease, and that they tried to avoid the occurrence of the resorptions with a 30% lower dose of rhBMP-2. However, we do not know whether Burkus et al. [3] succeeded to decrease the incidence of the resorptions with the lower dose of rhBMP-2 in the second phase, but we kept wondering why Burkus et al. [4] presented a CT scan with such obvious resorptions [19] especially if they wanted to ignore them, i.e. why they did not present a patient without the resorptions?! Until now it has not been possible to raise the speculations that Burkus et al. [2–4] simply had no patient without resorptions. The results of Meisel et al. [13] finally provide a firm argument that it is possible that rhBMP-2/ACS, because of carrier imperfection [15], causes the resorptions in each case when it is placed in close contact with human trabecular bone, and that is, by our modest opinion, the most significant contribution of Meisel et al.'s work [13]. However, there are previous reports in which the resorptions were found in each case where CT scanning was performed within early follow-up in patients who underwent lumbar interbody fusions assisted with rhBMP-2/ACS [11, 24], but as only some patients were scanned (usually those who were symptomatic [11]; and all patients in the study of Meisel et al. [13] were asymptomatic), it was not possible to outline the suspicions so categorically before the results of Meisel et al. [13] became available. We have to mention that Vaidya et al. [22, 23] have already reported the incidence of the resorptions to be 100%, but it was within the cervical spine which is more easily visualized by plain radiographs. Also, we have to mention that there are several additional reports about rhBMP-2/ACS use in interbody fusions in which no resorption was reported although CT scans were performed within early follow-up (T. Smoljanovic et al. unpublished

data, 2008), but possible explanations for these are far beyond the scopes of this Letter.

Finally, we are a bit confused by the contradictory statements of Meisel et al. [13] regarding the consequences of the resorptions. The authors stated in the abstract that the resorptions of bone surrounding the PEEK cage did not result in subsidence, pain or complications in their 17 patients who underwent PLIF assisted with PEEK cages filled with rhBMP/ACS and posterior screw fixation. Later, at the end of the discussion, they stated that although migration was seen in some patients, the rigid posterior fixation prevented sufficient slip to become symptomatic. After the large resorptions evident in CT scans in the article of Meisel et al. [13] have been carefully examined, would the authors be able to explain to us how they defined subsidence and did they consider loss of correction as one of the complications of the resorptions in their patients? Maybe Meisel et al. [13] have also placed the PEEK cages slightly too deep and angulated as Slosar et al. [20] did with FRA filled with rhBMP-2/ACS in their study. Anyway, Vaidya et al. [23] have shown in their patients who underwent either ALIF (12 levels in 10 patients), or TLIF (36 levels in 24 patients) or PLIF (2 levels in 2 patients) assisted with rhBMP-2/ACS (2 mg of rhBMP-2 per level) and posterior screw fixation that PEEK cage migration occurred maximally in patients with TLIF (33%) and PLIF (50%). Furthermore, revision surgery was required in all these cases except in one because of neurologic symptoms. The subsidence was observed in 11 of 50 (22%) lumbar levels with an average disc space subsidence of 17.8%. However, the study of Meisel et al. [13] is the first study after a long time, i.e. after the studies of Burkus et al. [2, 3] and Kuklo et al. [9], in which the resorptions caused no clinical impact for the patients. In all other, more recent studies [7, 11, 12, 14, 22–24], regardless of the presence of additional stabilizations, clinical effects of the resorptions were identified [16, 17] (T. Smoljanovic et al. unpublished data, 2008). To make matters easier for Meisel et al. [13], the patients in the studies of Burkus et al. [2, 3] and Kuklo et al. [9], contrary to Meisel et al.'s patients, did not have any additional stabilization.

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