Editorial

Bio-augmented spinal fusion—the best is yet to come

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It is a pleasure to write an Editorial for the *Journal of Spine Surgery* on the recently published study "OP-1 compared with Iliac Crest Autograft in Instrumented Posterolateral Fusion: A Randomized, Multicenter Non-Inferiority Trial" by Delawi *et al*. 2016 (1).

In recent years, the use of biological augmentation of spine fusion received a great deal of interest. Main reasons are to improve union rate and to avoid donor site-morbidity—ranging from 7.4% to 49% in the literature (2,3). rhBMP has been used with success in fracture treatment and was considered a plausible candidate. Delawi *et al*. performed a randomized, controlled, multicenter trial on 113 patients. It was investigator-initiated and conducted with an unconditional grant from the manufacturer of osteogenic protein-1 (OP-1) (Stryker). It examined non-inferiority of OP-1 in comparison with iliac crest bone graft (ICBG) in single-level instrumented posterolateral fusion of the lumbar spine. Primary outcome was the success rate, defined as a combined measure of clinical success [Oswestry disability index (ODI)] and radiographic union rate. An interesting and noteworthy point for those not trained in study methodology is the design. A non-inferiority study aims at proofing the effect of a new treatment to be no worse—within a margin—than a gold standard. This has been referred to as "me too drugs". In this case it is expected that OP-1 is simply no worse than ICBG. Non-inferiority testing, which requires much larger sample sizes than the conventional a *vs*. b testing by means of significant differences, is usually done when a new treatment offers other advantages in secondary outcomes, such as lower cost, less complications, etc. It is difficult to see any of these as being the case for OP-1. Non-inferiority, however, is accepted by the FDA for drug approval purposes (4).

At the one-year follow-up, Delawi *et al*. were not able to show non-inferiority of OP-1, i.e., it was not at least as "successful" as ICBG. Although there was no difference in the ODI, the significantly lower fusion rate in the OP-1 influenced the overall outcome (P=0.03). Adverse events were described, but none were related to OP-1 use. The authors recommend not to use OP-1 instead of ICBG in instrumented posterolateral fusion, but suggest to initiate further research into its safety profile and efficacy.

In point of fact, such research exists, and for a good reason. While rhBMP is—at least to orthopedic surgeons and spine surgeons—known almost exclusively for its eponymous effect on bone, it has a wide range of systemic functions. It is being investigated for a potential role in kidney disease, infertility, and obesity. Such wide-ranging effects suggest the potential for severe adverse events. However, a recent meta-analysis of the available controlled trials on the use of OP-1 showed no difference in complication rate between OP-1 and ICBG. It showed no benefit of union rate compared with ICBG either (5). On the other hand, in 2004, the FDA reported on seven patients who were diagnosed with new onset of cancer after the treatment with OP-1. Six of these seven cases were non-osseous cancers in elderly patients, and the other one was recurrence of a chondrosarcoma in a patient with a history of suffering from this tumor (6).

This is reminiscent of the recent literature on the other rhBMP—rhBMP-2. A considerable amount on literature exists discussing the role of rhBMP-2. It is known to have a great osteoinductive potential achieving high union rates in spine fusion but has come under scrutiny because of reporting bias as well as its high rate of

(severe) adverse events. Further, it is its off-label use that is primary examined. Complications like delayed wound-healing, perioperative infections, hematomas, ectopic bone formation, radiculitis, local swelling causing dysphagia, vertebral osteolysis, pseudarthrosis, retrograde ejaculation, and even the new onset of cancer are discussed (7-13). A recently published meta-analysis of 26 controlled trials showed that the general risk of complications in spine fusion increases by about 80% with the use of rhBMP-2 (13). Of particular interest are also the results from the Yale Open Data Access (YODA) project. Medtronic provided individual patient data for assessment by two independent academic institutions in the USA and the UK. Their reports state that rhBMP-2 "provided little or no benefit compared with bone graft and may be associated with more harms, possibly including cancer" (14).

This recent study adds to a body of evidence that dissuades the use of either of the rhBMPs as a substitute for ICBG in spine fusion. Unsurprisingly, attention was shifted towards other biological stimulants. Platelet-rich plasma (PRP) has been used with considerable success in various fields ranging from fracture care to sports medicine and chronic wound-healing (15,16). In spine, high-level evidence shows significantly decreased union rate with the use of platelet concentrate compared with ICBG. At least, it was not associated with increased complication or revision rates (17).

Even if overall union rate is high, nonunion in spine fusion is a real problem, causing individual suffering and considerable socioeconomic cost. The recent findings, however, beg the question if the old gold standard is still the current gold standard. ICBG is—even if not abundantly—readily available, and, compared a potentially increased cancer risk, donor site pain pales as an adverse event. The use of donor bone from the tissue bank is popular in many parts of Europe, but not as alluring to physicians in countries with limited availability or restrictive legislation, nor to industry. This is not to say that there is no need for ways to improve union rate, but as it seems this remains an unanswered question.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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