Editorial

Use of OP-1 (rhBMP-7) in posterolateral lumbar arthrodesis

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Posterolateral fusion is a common treatment for lumbar spondylolisthesis (1). Most often, autologous bone from the iliac crest is used for arthrodesis. However, failure of fusion remains a common complication following this procedure (2-4). In addition to pseudoarthrosis, another concern is donor site morbidity related to iliac bone graft harvest, which may complicate as many as 25% of cases (5-7). There has hence been interest in the development and use of bioactive molecules capable of inducing bone regeneration in hopes of achieving higher fusion rates, while also avoiding the morbidity of autograft harvest. Marshall Urist in 1965 identified proteins from bone matrix responsible for ectopic bone formation, later termed bone morphogenetic proteins (BMPs) (8). BMPs exert an osteoinductive effect by stimulating differentiation of mesenchymal stem cells into mineral-depositing osteoblasts (9,10). Further efforts led to cloning of BMP-2 and BMP-7 (OP-1), members of the transforming growth factor-beta (TGF-beta) superfamily, and expression of recombinant human forms of these proteins (11,12). Both rhBMP-2 and rhOP-1 demonstrated efficacy in inducing bone formation in preclinical animal studies, which has spurred clinical investigation of their efficacy as bone graft substitute (13-16). Moreover, other investigators have suggested that BMPs, including OP-1, may show promise in promoting fusion in patients with high-risk adverse medical conditions (17).

However, to date, high-quality data regarding the effectiveness of OP-1 versus iliac crest bone graft in promoting fusion in lumbar surgery is lacking. To fill this knowledge gap, Delawi *et al*. (2016) recently published the results of a multicenter randomized controlled trial comparing osteogenic protein-1 (OP-1) to iliac crest autograft in instrumented posterolateral lumbar fusion (18).

The trial followed a non-inferiority design. There were nine participating centers from four European countries (the Netherlands, France, Italy, and Spain). Eligible patients were those undergoing single-level instrumented posterolateral lumbar fusion for degenerative or isthmic spondylolisthesis with symptoms of neurological compression caused by central or foraminal stenosis. Patients were randomized in a 1:1 ratio to receive either OP-1 (Osigraft; Stryker) combined with local bone (OP-1 group) or autologous iliac crest bone graft combined with local bone (autograft group). The primary outcome of 'overall success' was evaluated at 1 year and defined as evidence of bony fusion on CT, improvement in Oswestry Disability Index (ODI) ≥20% from baseline, no deterioration in neurological status, no additional surgical intervention to promote fusion, and no serious product-related adverse event.

A total of 119 patients were randomized; 60 patients were allocated to the OP-1 group and 59 to the autograft group. Data on the primary outcome were available for 113 patients. The rate of overall success was lower in the OP-1 group (40%) than the autograft group (54%), for a risk difference of –13.3% (90% CI, –28.6% to +2.1%). The lower confidence limit fell below the predefined 15% non-inferiority margin, indicating OP-1 was inferior to iliac crest autograft. This was driven by a significantly lower fusion rate in the OP-1 group: 54% versus 74% (P=0.03). There were no differences in blood loss, operative time, or hospital length of stay between study groups. There were no adverse events that could be directly related to the use of OP-1.

Compared with rhOP-1, rhBMP-2 has been more extensively evaluated in clinical studies of spinal arthrodesis, including anterior lumbar interbody fusion (ALIF), posterior lumbar interbody fusion (PLIF), anterior cervical discectomy and fusion (ACDF), and posterolateral lumbar fusion. In 2002, the U.S. Food and Drug Administration (FDA) approved rhBMP-2 for ALIF with a specific cage (19). The safety profile of rhBMP-2 was initially felt to be a point of concern on theoretical grounds, given the apparent involvement of the osteogenic protein in several physiological and pathological pathways, such as the inflammatory response (20). Hypothesized adverse events included, "bony overgrowth, interaction with exposed dura, cancer risk, systemic toxicity, reproductive toxicity, immunogenicity, local toxicity, osteoclastic activation, and effects on distal organs" (21). Nonetheless, the initial clinical studies of rhBMP-2 reported superior fusion rates with essentially no adverse events (20,22-25). This, together with the ability to avoid the morbidity of iliac crest bone graft harvest, made rhBMP-2 a highly popular choice among spine surgeons, including for off-label indications (26). The use of BMP in the U.S. increased from only 0.7% of all spinal fusions in 2002 to 25% of all fusions in 2006 (27). However, safety issues soon became apparent. In 2008, the FDA issued a Public Health Notification regarding life-threatening complications associated with rhBMP-2 use secondary to neck swelling and airway compression (28). Moreover, concerns began to emerge surrounding financial ties of clinicians and researchers with the manufacturer of rhBMP-2 amidst retraction of a study on rhBMP-2 from the *Journal of Bone and Joint Surgery* (29,30). Carragee *et al*. compared the conclusions regarding the safety and efficacy of rhBMP-2 from original industry-sponsored trials with those derived from subsequently available FDA data summaries, follow-up publications, and administrative and organizational databases (20). The authors found the risk of adverse events with rhBMP-2 to be 10 to 50 times greater than the original estimates reported in the industry-sponsored publications (20). The Yale University Open Data Access (YODA) Project team sought full data from industry sponsors and investigators of published randomized trials of rhBMP-2 versus iliac crest bone graft for spinal arthrodesis to permit independent reanalysis. In an independent patient data meta-analysis, the authors found rhBMP-2 to be associated with 12% higher fusion rate and reduced pain (3.5% lower ODI scores) at 24 months. There were no differences in hospital length of stay, return to work or usual activity, or analgesic use. Use of rhBMP-2 shortened operative time by 21 minutes. The risk of arthritis/bursitis, hardware failure, retrograde ejaculation, back and leg pain, other pain, wound complications, neurologic events (i.e., numbness/tingling), and vascular events increased by at least 50% in the rhBMP-2 group. Cancer was nearly twice as common among recipients of rhBMP-2 (RR 1.98), though this did not reach statistical significance (31).

There are fewer clinical studies using rhOP-1 in spinal arthrodesis, and the data on union rates has been less consistent. rhOP-1 has only a Humanitarian Device Exemption approval from the U.S. FDA for use in compromised patients undergoing revision posterolateral fusion, which was granted in 2004 (32). The earliest clinical investigations were non-controlled pilot studies, and these demonstrated mixed results. Laursen *et al*. reported disappointing fusion rates in five patients with unstable thoracolumbar spine fractures treated with transpedicular rhOP-1 transplantation in the context of short segment posterolateral instrumented fusion (33). None of the cases healed, and in fact, in one case there was significant bone resorption. Similarly, Jeppsson *et al*. observed bony bridging at the fusion site in only one of four rheumatoid patients treated with wire fixation and rhOP-1 for atlantoaxial instability (34). On the other hand, Fehlings and coworkers have demonstrated fusion rates exceeding 80% using rhOP-1 in patients at high risk for pseudoarthrosis undergoing cervical or lumbar fusion (17,35). The initial randomized controlled trials of rhOP-1 compared use of rhOP-1 to autograft in a small number of patients (<40) undergoing posterolateral lumbar fusion (36-39). Two of these found lower fusion rates in patients treated with rhOP-1, whereas one trial found a superior union rate; none of these differences were statistically significant (36-38). A fourth trial, the pilot study to the current trial by Delawi *et al*., found comparable fusion rates (39). Vaccaro and associates reported the results of the largest randomized trial of rhOP-1 for spinal fusion in 2008 (40). This study compared the safety and efficacy of OP-1 Putty to iliac crest bone autograft in 295 patients undergoing uninstrumented, single-level posterolateral fusion for degenerative lumbar spondylolisthesis and symptomatic spinal stenosis. The primary outcome of 'overall success' was evaluated at 24 months; the definition was essentially the same as that used by Delawi *et al*. in the present study. However, at 24 months, fusion was assessed using AP and flexion-extension radiographs and defined as new

bone formation bridging across the transverse processes, angulation ≤5°, and ≤3 mm of translation. CT scan was obtained at 36+ month follow-up. Analogous to the findings reported by Delawi *et al.*, the authors failed to demonstrate non-inferiority of OP-1 Putty versus autograft based on overall success (38.7% *vs.* 49.4%, respectively). This was driven by a lower fusion rate with OP-1 Putty as compared to iliac crest autograft (61.7% *vs.* 83.1%, respectively). At the 36+ month mark, CT demonstrated comparable rates of new bone growth in OP-1 Putty and autograft patients (74.8% *vs.* 77.4%, respectively). Nonetheless, bridging bone was seen in only 56% of patients in the OP-1 Putty group versus 83% of the iliac crest autograft group (P=0.001). Reported complications of using rhOP-1 have included, most notably, ectopic bone formation and cancer (17,39,41). The FDA reported seven patients developing cancer with use of rhOP-1 (32). Six of the seven were non-osseous malignancies occurring in elderly patients, and the last was a chondrosarcoma in a patient with a history of chondrosarcoma. Another concern is the immunogenicity of rhOP-1. Hwang *et al.* detected anti-OP-1 antibodies in 26% of patients treated with OP-1 Putty (42). Antibody production peaked between 6 weeks and 3 months and diminished thereafter; anti-OP-1 antibodies were not detected in any patient beyond 24 months. Moreover, the authors found no correlation between anti-OP-1 antibody status and safety or efficacy of treatment. A meta-analysis including the previously discussed randomized trials found no difference in fusion (RR =0.97) or complication (RR =0.92) rates with rhOP-1 compared to iliac crest bone graft, local bone, or tricalcium phosphate (43).

The study by Delawi *et al.* is the first large randomized trial comparing rhOP-1 to iliac crest bone graft in instrumented posterolateral lumbar fusion. The authors conclude, "OP-1 with a collagen carrier was not as effective as autologous iliac crest bone for achieving fusion". Broadly speaking, there are two possibilities: (I) this is untrue; that is, rhOP-1 is as effective as iliac crest autograft for producing fusion, but the present study failed to detect this difference (type II error); or (II) this is true; that is, rhOP-1 indeed is not as effective as iliac crest autograft for achieving fusion.

To comment on point 1 above requires us to a closer look at the methodology of the present study in order to provide an assessment of the validity of the results. The experimental design is strong. This was a multicenter randomized controlled trial performed according to appropriate guidelines. The authors appropriately selected a non-inferiority design and defined an inferiority margin a priori based on data pertaining to complication rates of autologous bone harvesting. Randomization followed a computer-generated scheme produced by an independent researcher and followed a permuted block design to ensure equal number of patients per treatment group. Outcome assessors were blinded. Surgeons were blinded until decompression and instrumentation were complete. Allocation was concealed and randomization codes were sealed in opaque envelopes. The surgical procedure was standardized and included decortication of the transverse processes and facets to promote fusion. The same pedicle screw-rod system was used in all patients. The rhOP-1 (Osigraft) was also prepared and implanted in a standard fashion. Fusion was assessed on CT in all patients. This is an important point. Previous studies have found that rhOP-1 may lead to preferential bone growth medially along the transverse processes and along the lateral border of the facet joints (14,40). On plain X-rays, this may be obscured by the lateral border of the vertebral body and hypertrophied facet joints, and hence X-rays may be less reliable than CT in assessing bony fusion when rhOP-1 is used. Fusion was graded by a spine surgeon and radiologist, with conflicting findings adjudicated by a third reviewer, according to a standardized system based on the Christensen score (44). The authors included a prior sample size calculation. This suggested 65 patients were required in each group. While the initial number of patients included (N=134) exceeded the minimum estimated sample size, 15 patients had to be excluded, most due to poor quality CT scans at a single center. It is unclear exactly at what stage of the study these patients had to be excluded; "inadequate CT quality" would seem to imply these patients were excluded at the stage of radiological outcome assessment. If so, this could be a source of bias. Otherwise, losses to follow-up were minimal and similar between the two treatment groups. The groups did differ at baseline in the percentage of reported smokers—48% in the rhOP-1 group and 31% in the autograft group. Given that smoking is an important risk factor for nonunion, this could have biased the results toward a lower fusion rate in patients treated with rhOP-1 (45). The authors did perform a multivariate logistic regression analysis including smoking status and treatment group, and did not find smoking to impact overall success or rate of fusion. However, ideally, randomization would have been stratified by smoking status and/or other potential confounding variables to ensure balance in important prognostic factors between the two groups. The trial was

partially funded by Stryker, but initiated by the investigators and monitored by an independent trial monitor. All things considered, this was a robust study with a low risk of bias.

Therefore, we are probably dealing with the second scenario—that is, rhOP-1, as used in the present study, truly is less effective than iliac crest autograft for producing bony fusion. But, why is it less effective? This could be because rhOP-1 is a poor inducer of bone formation, period. It is more likely, though, that this therapy needs further optimization. The dose and biomaterial carrier of BMPs are important considerations, and these two are closely linked, as the effective dose depends on the properties of the carrier system (46). The clinical trials of rhOP-1, including the present study, have used 3.5 mg of rhOP-1 in a type 1 collagen-based matrix carrier. The carrier is a key factor influencing the efficacy of BMP in regenerating bone, and it likely does so through several mechanisms. Firstly, it may provide an attachment substrate for target cells and influence cellular differentiation into an osteogenic phenotype. Moreover, the carrier may bind BMPs and potentiate their activity by providing an increased local concentration of BMPs sequestered in a carrier, by presenting BMPs to target cells in "bound" form, or by allowing slow release of BMPs and thereby providing a physiologic concentration of free BMP locally over an extended period of time (47,48). Although a number of carriers have been found to support the osteoinductive effects of rhBMPs in preclinical animal studies, only collagen-based carriers are being used clinically, partly because collagen is a natural component of bone and hence its degradation can be mediated by normal physiological processes (48). Several properties of the biomaterial carrier may influence the osteoinductive activity of rhBMPs, including the strength of rhBMP binding, degree of rhBMP retention, degradability of the carrier, and compressibility of the implant. Uludag *et al.* demonstrated that rhBMPs exhibiting higher implant retention elicited more bone formation, lending credence to the hypothesis that slow release of rhBMPs over a prolonged period of time may potentiate greater bone growth (48). Collagen crosslinking with formaldehyde and sterilization with ethylene oxide have been found to alter the physicochemical properties of absorbable collagen sponges (ACS) (49,50). During *in vivo* pharmacokinetics studies, Uludag *et al.* found unprocessed collage sponges had higher initial uptake of rhBMP-2, but crosslinked/sterilized sponges retained rhBMP-2 for longer (48). The high initial retention of untreated collagen sponges suggested better binding of rhBMP-2 by native collagen than crosslinked/sterilized sponges, but the rapid loss thereafter suggested rapid degradation of native collagen *in vivo*. The authors surmised crosslinking techniques that preserve the native collagen rhBMP-2 binding motif while enhancing the *in vivo* resiliency of the sponge may be desirable. This group has also engineered thermoreversible polymers which demonstrate enhanced local rhBMP retention and are compatible with the osteoinductive activity of rhBMP (48,51). Preclinical studies using ceramics of hydroxyapatite (HA) and beta-tricalcium phosphate (beta-TCP) as carriers for rhBMP have similarly found a positive association between rhBMP retention and osteoinductive effect (52,53). These variables are further influenced by pore size and geometry, and various film coatings have also demonstrated potential for improving rhBMP binding and retention and osteogenesis (54-58). A distinct advantage of bioceramic carriers is their resistance to compression, which has proven to be a problem with collagen sponges because of compression from the paraspinal musculature and soft tissues. A few animal studies have found greater bone growth using beta-TCP compared to ACS and hypothesized this to be due to the lack of space-maintaining capacity of ACS (59,60). One thought is to reduce the compressibility and improve the handling characteristics of ACS by adding HA and/or TCP. In fact, several animal studies have demonstrated good results using a compression resistant matrix consisting of biphasic ceramic phosphate impregnated collagen sponges for delivery of rhBMP-2, with lower doses of rhBMP-2 being needed as compared to plain ACS (61-63). Various synthetic polymers have also been developed and used as carriers for rhBMP in preclinical studies, but have yet to reach clinical application (64,65).

In summary, the authors are to be congratulated for their timely contribution to the literature. The negative results should not be taken as discouraging. There may still be a role for OP-1 in cases where the quality or amount of autologous iliac crest bone graft is limited, or in the setting of multiple non-unions. In addition, more research to optimize the biomaterial carrier and concentration of rhOP-1 may be needed. Further efforts will help improve fusion rates and functional outcomes and reduce morbidity for patients undergoing spinal arthrodesis.

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Footnote

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