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Applications of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) in Spinal Surgery

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Animal studies and clinical trials have demonstrated the efficacy of rhBMP-2 as an adjunct or substitute to autogenous bone graft in anterior lumbar interbody fusion, posterolateral fusion, and in overcoming inhibitory effects (ketolorac and nicotine) on fusion. Importantly, no serious adverse events or systemic side effects have been observed in clinical trials. Before widespread application of rhBMP-2 can be accepted, future investigations are needed to evaluate its efficacy in various spinal disorders, optimal dose and delivery system, long-term safety profile (immunogenicity, antibody formation), cost-effectiveness of therapeutic growth factors, and non-fusion application in altering the progression of degenerative disc disease.
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It has been nearly 40 years since Marshall R. Urist made the seminal discovery that a specific protein, later named bone morphogenetic protein (BMP), found in the extracellular matrix of demineralized bone could induce new bone formation when implanted in extraosseous tissues in a host.[1] Since Urist's initial discovery, BMPs have been the subject of extensive basic science, animal, and clinical research as a potential therapeutic modality to induce fracture healing and to promote bone fusion. Numerous structurally related BMPs have been isolated, purified, and characterized using recombinant DNA techniques.[2-6] These factors in combination with a number of cytokines and matrix components have been shown to induce a cascade of events resulting in the recruitment and differentiation of osteoprogenitor cells during bone formation and remodeling.[7,8] Animal studies have demonstrated that BMPs are capable of upregulating other BMPs (BMP-4, -6) and growth factors (PDGF, VEGF, IGF, EGF, FGF) in their naturally occurring sequence.[9-11]

As a result of the initial preclinical, proof-of-concept studies and the subsequent prospective, randomized clinical trials, recombinant human bone morphogenetic proteins (rhBMP) have now become commercially available as they have been shown to demonstrate equivalent or superior efficacy to autogenous ICBG in the specific treatment of certain orthopedic trauma (ie, open tibia fractures) and spinal conditions.

At the time of this writing, there are only two rhBMPs that are commercially available for clinical spinal applications (Table 1). rhBMP-2 carried on an absorbable collagen sponge, trademarked as INFUSE Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is commercially available and FDA-approved when used with a lumbar tapered fusion cage (LT-CAGE™) for one-level anterior lumbar interbody fusion for degenerative disc disease. rhBMP-7, trademarked as Osteogenic Protein-1 (OP-1 Putty; Stryker Biotech, Inc., Hopkinton, MA), is FDA-approved as a humanitarian device exemption (HDE) for revision posterolateral lumbar spinal fusion.

The preclinical studies, clinical trials, and the current and future applications of rhBMP-2 in the clinical arena of spinal surgery will be the focus of discussion in this review.

Principles of Bone Graft Biology

Several factors dictate the successful incorporation of grafted bone and include (1) the type of bone graft; (2) the host site; (3) the vascularity of the graft and host–graft interface; (4) the immunocompatability between the donor and the host; (5) preservation techniques; and (6) local (cytokines, growth

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Table 1 Commercially Available rhBMPs Approved for Spinal Applications

RhBMP	Company	Product	Composition	Reported Mechanism of Action	Burden of Proof	FDA-Approval	Indication
RhBMP-2	Medtronic	INFUSE	RhBMP-2 protein with absorbable collagen sponge	Bioresorbable sponge	Lower animal studies	July 2002	Anterior lumbar interbody fusion (L.4-S1) for degenerative disc disease
	Sofamor Danek			Osteoinduction	Nonhuman primate studies Prospective, randomized clinical trials	Received Premarket Approval (PMA)	Delivered in LT-Cage via open or laparoscopic anterior approach
RhBMP-7	Stryker Biotech	OP-1 Putty	RhBMP-7 protein on type 1 collagen carrier with CMC additive	Resorbable collagen scaffold Osteoinduction	Lower animal studies Nonhuman primate studies Prospective, randomized clinical trials	April 2004 Approved as a Humanitarian Device Exemption (HDE)	Revision posterolateral (intertransverse) fusion

factors, etc) and systemic factors (smoking, steroids, etc). In the posterolateral spine, autogenous bone fusion matures through a series of steps including inflammation, fibrocartilage formation, enchondral ossification, and final remodeling.

Osteogenesis is the synthesis of new bone by cells derived from either the graft or the host and refers to the ability of graft or host cells to directly form bone. Only autogenous bone marrow elements possess osteogenic properties with osteoinductive proteins, osteoprogenitor cells, and a local blood supply. *Osteoconduction* refers to the process by which an organized, microarchitectural framework is established that acts as a scaffold to support the formation of new host bone. *Osteoinduction* is the process by which mesenchymal stem cells at and around the host site are recruited as osteoprogenitor cells to differentiate into mature osteoblasts. Recruitment and differentiation are the two characteristic processes of osteoinduction and are tightly modulated by various graft matrix-derived growth factors and cytokines. These growth factors include BMP, platelet-derived growth factors (PDGF), fibroblast growth factors (FGF), insulin-like growth factors (IGF), vascular endothelial-derived growth factors (VEDGF), and various interleukins (IL). The majority of commercially available bone graft extenders (DBM, allograft, calcium salts, coral, hydroxyapatites, etc) serve as osteoconductive agents with limited to no osteoinductive potential.

Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2)

rhBMP-2 (INFUSE) is one of the earliest and most investigated rhBMPs in preclinical studies and clinical trials. INFUSE, a combination of rhBMP-2 on an absorbable collagen sponge, delivered in a lumbar tapered fusion cage (LT-CAGE™), was FDA-approved in July 2002 as the first complete bone-graft substitute in spinal fusion.[12] Its use is currently approved for one-level anterior lumbar interbody fusion in patients with symptomatic degenerative disc disease (DDD) from L4-S1 via an anterior open or an anterior laparoscopic approach. Animal studies and human clinical trials, which have demonstrated the efficacy of rhBMP-2 in interbody fusion and in overcoming inhibitory effects of fusion, have formed the basis for the current and future applications of rhBMP-2 as a viable bone graft substitute in spinal surgery. The exact role of rhBMP-2 in the posterolateral fusion environment remains to be determined and continues to be the subject of further investigation.

Animal Studies (Interbody Fusion)

Sandhu and coworkers reported the first preclinical study of the use of an interbody cage augmented with rhBMP-2 in a sheep model.[13,14] In this study, cylindrical, threaded fusion cages were filled with either autogenous ICBG or rhBMP-2 on an absorbable collagen sponge carrier. All animals in both treatments appeared to have achieved radiographic evidence of fusion at 6 months. However, only 37% of the sheep in the