Bone Morphogenic Proteins: Applications in Spinal Surgery

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Abstract The prospect of predictable and reliable osseogenesis without the need for secondary bone grafting to treat a wide spectrum of spinal disorders is tremendously appealing. Recombinant human bone morphogenic proteins (rhBMP) have been the subject of extensive basic science, animal, and clinical research as a potential therapeutic modality to promote bony fusion. Animal studies and prospective, randomized clinical trials have demonstrated the efficacy of rhBMPs as an adjunct or substitute to autogenous bone graft in the specific treatment of certain spinal conditions. The future role of rhBMPs in spinal surgery applications remains to be determined and will be dependent upon future investigations evaluating 1) the efficacy in a variety of spinal conditions and environments, 2) the optimal dose and delivery system, 3) the long-term safety profile (immunogenicity, antibody formation), and 4) the cost effectiveness of these therapeutic growth factors.

Key words bone morphogenic protein · arthrodesis · spinal fusion · growth factor · osteogenic protein-1 · recombinant human bone morphogenic protein-2

Introduction

Arthrodesis remains among the most common treatments for various acquired and degenerative conditions of the spine. The “gold standard” technique for achieving spinal fusion involves the placement of an autogenous iliac crest bone graft (ICBG) between decorticated spinal surfaces. Autogenous ICBG remains the preferred substrate because of its unique properties of osteoinduction, osteoconduction, and supply of osteoprogenitor cells. Despite these osteogenic properties, autologous ICBG typically requires a separate surgical procedure, which may prolong operative times and increase blood loss, and is associated with a pseudarthrosis rate approaching 26% [1]. Furthermore, the incidence of donor site morbidity associated with ICBG

harvesting was reported to be from 6% to 25% and include chronic pain, hypersensitivity, surrounding anesthesia, neurovascular injury (lateral femoral cutaneous nerve, cluneal nerves, and superior gluteal artery), hematoma, infection, fracture, and possible postoperative gait disturbances [2–4]. Since autograft donor site morbidity can compromise the clinical results after spinal fusion surgery, the development of autograft alternatives and/or substitutes containing both osteoconductive and osteoinductive properties to limit the need for harvesting autologous bone has been a major goal of orthopedic research.

Allograft bone has been used as an autograft alternative and can serve osteoconductive and/or osteoinductive roles depending on its method of preservation. However, in most applications, allograft serves limited to no demonstrable osteoconductive potential and, as a result, has yielded inferior fusion results and higher rates of graft resorption compared with autograft [5, 6].

More potent osteoinductive agents have been investigated as potential autograft alternatives. The initial results using demineralized bone matrix (DBM) in animal models had been encouraging [7, 8]. DBM provides a suitable osteoconductive framework for osteogenesis while maintaining some noncollagenous osteoinductive proteins. However, the osteoinductive potential of DBM is greatly influenced by its demineralizing processing, and the content of these commercially available preparations has been poorly defined and has not always been reproducible. As a result, rigorous prospective, randomized clinical trials have never demonstrated the efficacy of DBM to be equivalent or superior to that of autologous bone [9].

It has been nearly 40 Years since Marshall R. Urist made the seminal discovery that a specific protein, later named bone morphogenic protein (BMP), found in the extracellular matrix of demineralized bone could induce new bone formation when implanted in extraosseous tissues in a host [10]. Since Urist’s initial discovery, BMPs have been the subject of extensive basic science and animal and clinical research as a potential therapeutic modality to induce fracture healing and to promote bone fusion. As a result of the initial preclinical, proof-of-concept studies and the subsequent prospective, randomized clinical trials,

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BMPs 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 spinal conditions. The preclinical studies, clinical trials, and the current and future applications of BMP in the clinical arena of spinal surgery will be the focus of discussion in this review.

Principles of bone graft biology

A comprehensive discussion on the molecular biology of osteogenesis is beyond the scope of this review. However, to understand the role of BMP in bone graft applications, a basic understanding of the principles of bone graft biology is needed. Bone grafts serve a combined mechanical and biologic function; depending on the desired clinical outcome, one function may be more important than the other. Autogenous cancellous ICBG for posterolateral spine fusion provides a biologic stimulus for new bone formation, with little mechanical function, whereas autogenous tricortical ICBG harvested for an interbody fusion serves as much of a mechanical function as a biological stimulus.

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 immunocompatibility between the donor and the host, (5) preservation techniques, and (6) local (cytokines, growth 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 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. *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 (PDGFs), fibroblast growth factors (FGFs), insulin-like growth factors (IGFs), vascular endothelial-derived growth factors (VEGFs), and various interleukins (ILs). *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. Most commercially available bone graft extenders (DBM, allograft, calcium salts, coral, hydroxyapatites, etc) serve as osteoconductive agents with limited to no osteoinductive potential.

Bone morphogenic proteins

Since Urist's landmark study, which articulated the concept of specific BMPs, at least 7 structurally related BMPs have been isolated, purified, and characterized using recombinant DNA techniques [11–15]. 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 [16, 17]. Animal studies have demonstrated that BMPs are capable of up-regulating other BMPs (BMP-4, BMP-6) and growth factors (PDGF, VEGF, IGF, EGF, FGF) in their naturally occurring sequence [18–20].

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 Sofamor Danek	INFUSE	RhBMP-2 protein with absorbable collagen sponge	Bioresorbable sponge Osteoinduction	Lower animal studies Nonhuman primate studies Prospective, randomized clinical trials	July 2002 Received premarket approval (PMA)	Anterior lumbar interbody fusion (L4-S1) for degenerative disc disease 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 an HDE	Revision posterolateral (intertransverse) fusion

At the time of this writing, there are only two BMPs that have received FDA approval for clinical use (Table 1). Recombinant human bone morphogenic protein-2 (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, Medtronic) 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, USA) is FDA approved as a humanitarian device exemption (HDE) for revision posterolateral lumbar spinal fusion.

Recombinant human bone morphogenic protein-2

rhBMP-2 (INFUSE) is one of the earliest and most investigated BMPs in preclinical studies and clinical trials. INFUSE, a combination of rhBMP-2 on an absorbable collagen sponge, delivered in an LT-CAGE, was FDA approved in July 2002 as the first complete bone graft substitute in spinal fusion [21]. Its use is currently approved for one-level anterior lumbar interbody fusion with an LT-CAGE in patients with symptomatic degenerative disc disease (DDD) from L4 to S1 via an anterior open or an anterior laparoscopic approach.

Animal studies (interbody fusion)

Sandhu et al [22, 23] reported the first preclinical study of the use of an interbody cage augmented with BMP-2 in a sheep model. 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 autograft group had histological evidence of fusion at 6 months compared with 100% in the rhBMP-2 group. It was also noted histologically that there was less fibrous tissue ingrowth in the fenestrations of the cage in the rhBMP-2 group compared with that in the autograft group. Zdeblick et al [24] reported similar findings using titanium BAK fusion cages (Sulzer Spine-Tech, Minneapolis, MN, USA) in a goat model.

Boden et al then demonstrated the efficacy of rhBMP-2 in nonhuman primate model [25]. They used two different concentrations (0.75 or 1.50 mg/mL) of rhBMP-2 with the same collagen carrier packed in a titanium lumbar interbody fusion cage in rhesus monkeys. They observed a dose-response phenomenon with the higher concentration producing faster and thicker interbody fusion mass. Because of these findings, the 1.50-mg/mL dose was used for the interbody fusion implants in subsequent clinical trials.

Hecht et al [26] also demonstrated similar findings in rhesus monkeys using BMP-2 packed in threaded cortical allograft interbody dowels. Interestingly, they noted at 6 months complete resorption and remodeling of the cortical allograft within the fusion mass, suggesting that rhBMP-2

may accelerate not only osteoblastic bone formation, but also osteoclastic remodeling. This finding was in sharp contrast to that observed in the control autograft group in which no remodeling was observed.

Animal studies (posterolateral fusion)

The initial preclinical investigations of rhBMP-2 for posterolateral spinal fusion demonstrated consistently larger, thicker, and stiffer fusion masses compared with autograft controls. These studies used rhBMP-2 on a collagen sponge carrier in rabbit and canine models [27–31]. However, success with rhBMP-2 for posterolateral fusion in lower animals did not directly translate to nonhuman primates. Martin et al [32] found that the rhBMP-2 concentrations effective in lower animals were not effective in higher species and was the result of mechanical compression of the overlying paraspinal muscles on the collagen sponge carrier, thereby impeding new bone formation. Consequently, a porous polyethylene shield was developed and placed over the rhBMP-2 soaked collagen sponge to protect the carrier from overlying muscle compression. This intervention led to successful fusion with an even lower rhBMP-2 concentration and thicker, more compact fusion masses compared with those achieved without the shield.

It thus became evident that the delivery of rhBMP-2 in posterolateral fusion applications would need to be different from that found in the interbody fusion model because of the different anatomic characteristics in each environment. Boden et al [33] first demonstrated the preclinical efficacy of rhBMP-2 for posterolateral fusion in a nonhuman primate model. The investigators developed a highly porous biphasic calcium phosphate compression-resistant matrix consisting of 60% hydroxyapatite and 40% tricalcium phosphate to be used in a primate posterolateral fusion model. This specific carrier resulted in solid fusion masses when used with any of 3 different concentrations of rhBMP-2.

Different delivery systems in the posterolateral fusion model continue to be investigated. Suh et al [34] demonstrated the efficacy of a newer, easily moldable, compression-resistant, biphasic calcium phosphate ceramic composite as a carrier for rhBMP-2 in primates. Bulking agents consisting of allograft chips or ceramic granules to provide the collagen sponge some compression resistance have also been introduced and demonstrated promising results [35, 36].

Animal studies (inhibitory effects)

The ability of rhBMP-2 to overcome inhibitory effects of nonsteroidal anti-inflammatory drugs and nicotine were also demonstrated in animal studies. Martin et al [37] established the adverse effects of ketorolac on posterolateral spinal fusion and then tested the ability of rhBMP-2 to overcome such inhibition. The investigators demonstrated an autograft fusion rate of 35% with an intravenous (IV) ketorolac pump infusion when compared with a 75% fusion rate with an IV saline pump.

Clinical studies

The first clinical study examining the use of BMP-2 in spinal fusion applications was conducted in 1996 as a pilot Investigational Device Exemption study to evaluate the safety and feasibility of INFUSE for anterior lumbar interbody fusion [38]. This prospective, randomized, controlled multicenter trial enrolled 14 patients for a one-level anterior interbody fusion using an lumbar tapered titanium interbody fusion cage (LT-CAGE) with either INFUSE or iliac crest autograft. All 11 patients in the rhBMP-2 cohort achieved a successful fusion as determined by plain radiographs and fine-cut computed tomography scans interpreted by blinded, independent radiologists, whereas only 2 of 3 patients in the iliac crest autograft control group had a successful fusion. The one patient in the pseudarthrosis group required additional posterolateral fusion and instrumentation approximately 18 months after the index procedure. Although the results from this study were too small to achieve significant values, the rhBMP-2 group also had achieved a better clinical outcome as determined by the Oswestry Disability Index (ODI) scores at each follow-up.

The safety and efficacy data from this initial pilot study initiated a larger pivotal trial [39, 40]. The study design, interventions, and outcome measurements were nearly identical to the original pilot study. Approximately 280 patients in 16 investigational centers were enrolled in the study. Both operative time and blood loss were significantly less in the experimental rhBMP-2 group compared with the iliac crest autograft control group. Radiographic fusion rates were slightly greater in the rhBMP-2 cohort at 2-Year follow-up (Table 2). There were no differences in (1) clinical outcomes, measured by the ODI; (2) presence of back pain, measured by a pain analog scale; and (3) in the number of patients returning to employment between the 2 cohorts. However, over one third of the patients in the autograft group still experienced some type of donor-site pain 2 Years after surgery.

A concurrent pilot study investigating the safety and efficacy of rhBMP-2 in anterior lumbar interbody fusion using machined cortical allograft dowels was also conducted [41]. This prospective, randomized multicenter trial enrolled 47 patients for a one-level anterior interbody fusion using an allograft bone dowel packed with either INFUSE or iliac crest autograft. The investigators reported significantly less blood loss and greater improvement in

Oswestry scores at 3- and 6-month follow-up in the INFUSE group. They also reported higher fusion rates at 6- and 12-month follow up in the INFUSE group. At 1 Year, all (100%) patients in the experimental group had fused compared with 90% (17/19) of patients in the control group. At 2 Years, 67% of the INFUSE group compared with 35% of the control group were able to return to employment. Furthermore, 39% (7/18) of the patients in the control group continued to report of persistent donor-site pain, whereas no adverse effects were reported in the rhBMP-2 group.

Clinical studies have also examined the use of rhBMP-2 in lumbar posterolateral fusion. Boden et al [42] reported the early results of a pilot study investigating the use of rhBMP-2 in single-level posterolateral fusion. Based on nonhuman primate studies, dose and carrier modifications were made to accommodate the differences between the posterolateral and interbody fusion environments. Experimental groups were given a higher dose (20 mg) of rhBMP-2 and a different carrier [biphasic calcium phosphate (BCP) carrier acting as a bulking agent] compared with experimental groups in the interbody fusion studies. In this prospective multicenter trial, 25 patients were randomized to receive 1 of 3 different interventions. Patients in the control group received an instrumented fusion with autograft. Patients in the 2 experimental groups received either an instrumented fusion with rhBMP-2 with a BCP carrier or uninstrumented fusion with rhBMP-2 with a BCP carrier. At 17 months, the radiographic fusion rate was 40% (2/5) in the control group and 100% (20/20) in the two experimental groups ($p=0.004$). The investigators also found a significantly greater and faster improvement in patient-derived clinical outcome measurements in the two experimental rhBMP-2 groups.

A concurrent pilot, prospective, randomized clinical study evaluating the use of rhBMP-2 with a BCP carrier was conducted [43]. The control group was treated with a unilateral intertransverse process fusion with iliac crest autograft and a contralateral fusion with the rhBMP-2 implant. The experimental group was treated with bilateral intertransverse process fusions with the rhBMP-2 implant. Luque [43] found superior clinical outcomes and higher fusion rates in the experimental group. Radiographic evidence of fusion was found on 22 (96%) of 23 sides treated with rhBMP-2, compared with only 4 (57%) of 7 treated with autograft 12 months after surgery.

Table 2. Clinical and radiographic results of rhBMP-2 vs iliac crest autograft in anterior lumbar interbody fusion using a lumbar tapered titanium cage

	RhBMP-2	Iliac crest autograft
Fusion rate at 2-y follow-up (%)	100	95.6
FDA criteria for successful result (%)	94.5	88.7
20% Improvement in Oswestry Disability Index (%)	79	79

Osteogenic Protein-1: rhBMP-7

In October 2001, Osteogenic Protein-1 (OP-1 Implant), which is rhBMP-7 on a bovine type 1 collagen carrier, received FDA approval as an HDE for recalcitrant long-bone nonunions in which alternative treatments have failed or in which autograft would not be feasible [44]. The use of rhBMP-7 in specific spinal applications has only recently been approved in April 2004. rhBMP-7 (OP-1 Putty) received FDA approval as an HDE for use as “an alternative to autograft in compromised patients requiring revision

posterolateral lumbar fusion, for whom autologous bone and bone marrow harvesting would not be feasible or would not be expected to promote fusion” [45]. Compromising risk factors include osteoporosis, smoking, or diabetes. OP-1 Putty, which is a derivative of OP-1 Implant, contains rhBMP-7 on the same collagen carrier in addition to the food additive carboxymethylcellulose (CMC). CMC acts as a thickening agent creating a puttylike characteristic that improves the implant’s handling and molding characteristics and allowing the protein to remain in place during the beginning of the bone-formation process. FDA approval as an HDE for this specific indication was received on the basis of extensive animal testing and clinical trials.

Animal studies

Posterolateral fusion

Cook et al [46] demonstrated lumbar facet fusions in a dog model using rhBMP-7 with a collagen-based carrier. They demonstrated that animals implanted with rhBMP-7 demonstrated a faster, more mature fusion mass than those with autograft. All animals with rhBMP-7 achieved a stable facet fusion by 12 weeks, whereas those with autograft did not do so until 26 weeks postoperatively. They also created performed testing under sham conditions in which the collagen carrier was implanted alone or in which no implant was used; under these conditions, there were no facet fusions.

Grauer et al [47] compared rhBMP-7 with autograft and collagen carrier alone in a rabbit intertransverse fusion model and found that 100% (8/8) of the animals implanted with rhBMP-7 achieved a solid fusion. Sixty-three percent (5/8) of the rabbits with autograft achieved fusion, whereas none (0/8) of the rabbits with collagen carrier alone achieved fusion. They also demonstrated that the fusion mass in the rhBMP-7 group was significantly stiffer biomechanically and more mature histologically than those obtained with autograft. The fusion mass obtained through autograft was predominantly fibrocartilage histologically, whereas that obtained through rhBMP-7 was maturing trabecular bone surrounded by a cortical shell.

Cunningham et al [48] also demonstrated an accelerated rate of fusion and a stiffer, more mature posterolateral fusion mass in a dog model. They studied the animals after treatments with (1) autograft alone, (2) autograft plus OP-1, and (3) OP-1 alone. They found that by 8 weeks fusion occurred in 88% of the autograft/OP-1 group, 66% of the OP-1-alone group, and only 22% of the autograft-alone group. By 24 weeks, only 50% of the autograft-alone group achieved radiographic evidence of fusion. They also demonstrated a stiffer fusion mass in the OP-1-treated groups. They also found histologically a more rapid process of osteointegration in the OP-1-treated groups than in the autograft group, although these differences were no longer evident by 24 weeks. They concluded that in contrast to the enchondral ossification process that occurs in autograft fusion, bone induction and formation in the OP-1 groups was the result of intramembranous ossification. Consequently, bone formation with OP-1 is accelerated and

maturation earlier because the intermediate cartilage model found in enchondral ossification is bypassed.

Interbody fusion

Animal studies have also demonstrated the efficacy of OP-1 in lumbar interbody fusion. Magin and Delling [49] found a higher fusion rate, greater size of fusion mass, and stiffer and more mature fusion mass using OP-1 compared to autograft and to a hydroxyapatite bone extender in a sheep interbody fusion model. Cunningham et al [50] used a skip-level sheep interbody thoracic fusion model to compare (1) BAK cages with autograft, (2) BAK cages with OP-1, and (3) an autograft dowel. They found a higher fusion rate using a BAK with OP-1 (75%) when compared with the BAK with autograft (62.5%) and autograft dowel (50%). Chirossel et al [51] demonstrated similar efficacious results with OP-1 using polyetheretherketone cages and titanium cages.

Inhibitory agents

OP-1 has also been shown to overcome the inhibitory effects of nicotine in a rabbit posterolateral fusion model. Patel et al studied rabbits undergoing a one-level posterolateral fusion using either iliac crest autograft or OP-1 with a collagen/carboxymethylcellulose (CMC) carrier [52]. Nicotine was then administered to all animals using a subcutaneous mini-osmotic pump. At 5 weeks, they found a 100% (7/7) rate of fusion at by manual palpation and histological analysis in the OP-1 group and only 25% (2/8) in the autograft group. Histological analysis also demonstrated very immature bone in the autograft fusion sites, whereas predominantly mature bone was found in the OP-1 fusion masses.

Clinical studies

All clinical trials using OP-1 have involved uninstrumented intertransverse fusion in the setting of lumbar spinal stenosis and degenerative spondylolisthesis. The preliminary results from these trials have been promising.

Speck [53] performed a study in 5 patients, in whom OP-1 putty was placed between the transverse processes on one side while autograft was placed on the contralateral side. The preliminary results of this Australian study demonstrated that bone formation was equal or greater on the OP-1 side when compared with the autograft side using computed tomography scan assessment. However, the clinical efficacy and functional outcomes between the two treatments cannot be interpreted from this study design.

Patel et al [54] performed a pilot study to investigate the safety and efficacy of OP-1 as an *adjunct* to iliac crest autograft. Sixteen patients undergoing an uninstrumented posterolateral fusion were prospectively randomized to autograft alone or autograft with OP-1. Although the number of patients enrolled were too small to reach any statistical significance, they found a higher rate of radiographic evidence of fusion in the OP-1 group (75%)

compared with the autograft group (50%) and a greater clinical improvement as measured by the Oswestry score at preliminary follow-up of 6 months.

Vaccaro et al [55] reported the 2-Year results of the same series of patients with OP-1 as an adjunct to iliac crest autograft and compared their results to historical controls of patient with uninstrumented fusions with iliac crest autograft alone. They found approximately 89% of the patients with OP-1 and autograft having substantial clinical improvement, defined as greater than 20% improvement in their preoperative Oswestry score. Using apparently more stringent radiographic criteria for assessment of fusion, they found only 50% of the series achieved a solid fusion although 70% (7/10) had radiographic evidence of bridging bone formation. They found the combination of autograft and OP-1 did not demonstrate superior rates of fusion compared with historical controls. However, there were no adverse events related to the use of the OP-1 putty in the series.

An additional pilot study is currently investigating the safety and efficacy of OP-1 as a *substitute* for autograft [56]. The study design is nearly identical to the previous prospective, randomized, multicenter trial that studied OP-1 as an adjunct to autograft. The preliminary results of the 36 enrolled patients demonstrated a 13% higher clinical success rate as measured using the Oswestry score in the OP-1 group than in the autograft group at 12 months. They found that 74% (14/18) of the OP-1 patients achieved successful posterolateral fusion fulfilling all criteria, whereas only 60% (6/10) of the autograft patients had successful fusion. They concluded that the successful posterolateral fusion was achieved with OP-1 putty at a rate similar but not necessarily superior to that of autograft given the sample size. Although the results of the pilot study were not statistically significant because of the relatively small sample size, no adverse events related to OP-1 were demonstrated in this clinical trial, which supports the findings in animal studies suggesting the safety of BMP-7 in spinal surgery.

The pivotal study investigating OP-1 as a *substitute* for autograft in patients with a noninstrumented posterolateral spinal fusion for lumbar spinal stenosis and degenerative spondylolisthesis is currently ongoing.

Current and future applications of BMP

OP-1 Putty is currently approved as an HDE for use in revision posterolateral fusion. INFUSE is currently approved for primary anterior lumbar interbody fusion. The early results from several completed prospective, randomized clinical trials have demonstrated rhBMP-2 and -7 to be equivalent or superior to autologous iliac bone graft in both fusion rate and clinical outcome [40–42, 55–57]. Furthermore, no adverse effects related to the use of rhBMPs have been reported in contrast to the 30% to 40% incidence of persistent donor-site pain related to ICBG. At longer-term 10-Year follow-up, Sandhu et al have reported that no patients experienced adverse sequelae related to the rhBMP-2 implant [58].

The future role of BMPs in spinal surgery applications remains to be determined. Questions of BMP with regard to (1) carrier/dose combination, (2) immunogenicity, (3) cost-effectiveness, and (4) its role in nonfusion spinal applications will be the subject of future investigation. Further work is necessary to determine the optimal dosing in the interbody and posterolateral environment to improve on the preliminary results reported thus far. Preclinical studies have also demonstrated that the ideal delivery system for BMP depends on the anatomic location where the treatment is needed. Carriers for rhBMP are used to increase the retention of these growth factors at the fusion site while at the same time providing an osteoconductive matrix on which bone formation can occur. The study of different compression-resistant carriers, bulking agents, and easy-handling substrates in the posterolateral fusion environment are under current investigation. Moreover, percutaneous, injectable strategies to deliver BMP without direct exposure of the operative site are being studied. These injectable delivery systems could complement the minimally invasive approaches, techniques, and instrumentation that have now become commercially available in spinal surgery.

The immunogenicity of these substrates and antibody formation to BMPs and collagen is a safety concern regarding the use of BMPs. Serological testing from the previously mentioned clinical trials have demonstrated that patients do develop antibodies to rhBMP and/or to their collagen carrier; these studies have shown that more patients develop antibodies to the collagen carrier rather than the BMP itself [24, 38, 39]. Although no adverse clinical sequelae associated with BMP implants have been reported, the theoretical concerns regarding antibody formation and its interactions with fetal development, autoimmune disorders, and malignancies remain. The effect of maternal BMP antibodies on an unborn fetus or a nursing child has not been studied. Studies in genetically altered mice indicate that BMP is critical for fetal development and that lack of OP-1 activity, as might be induced by antibody, may cause neonatal death or birth defects [59–61]. Studies in rats injected with high doses of OP-1 have also shown that small amounts of OP-1 will cross the placental barrier [62]. Furthermore, the interaction of anti-BMP or anticollagen antibodies in patients with autoimmune disorders, collagen vascular disorders, or a history of malignancy is unknown. Because of these potential safety concerns, rhBMP-7 is contraindicated in pregnant women, skeletally immature patients, patients with a history of malignancy, and patients with a known hypersensitivity to BMPs or collagen.

Critics argue that the high cost of rhBMPs preclude their routine use. The economic feasibility and allocation of health care resources to these emerging technologies will become the subject of future cost-analysis studies. Polly et al [63] developed an economic model based on clinical trial data, peer-reviewed literature, and clinical expert opinion to perform a cost analysis of rhBMP vs autogenous ICBG in a single-level anterior lumbar interbody fusion. They concluded that the front-end costs of BMP (approximately \$3400) would be offset to a significant extent by reductions

in the use of other medical resources, particularly if costs incurred during the 2-Year period after the index hospitalization are taken into account. Further study will be necessary to determine the cost effectiveness of these implants.

The role of rhBMPs in the treatment of degenerative disc disease will also be the topic of future investigation. Immunohistochemical studies have demonstrated that BMPs and their receptors may play roles in the development of degenerative disc disease [64, 65]. BMP-2 was shown to increase aggrecan and type II collagen mRNA expression, which would both be beneficial in maintaining an extracellular matrix of a healthy disc [64, 65]. BMP expression was also shown to be down-regulated in degenerative discs [66]. Furthermore, BMP and its receptors were shown to move from the hyaline cartilage of the vertebral endplate in healthy discs to the calcified cartilage at the site of entheses in degenerative discs [67]. Future studies will continue to investigate the exact role of BMP expression in degenerative disc disease and may begin to explore techniques such as gene therapy to augment BMP production with the hope of possible altering the progressive course of disc degeneration.

Conclusion

Animal studies and clinical trials have demonstrated the efficacy of rhBMPs as an adjunct or substitute to autogenous bone graft in (1) posterolateral fusion, (2) anterior lumbar interbody fusion, and (3) overcoming inhibitory effects (nicotine, ketolorac) of fusion. More importantly, no serious adverse events or systemic side effects have been observed in these trials. The current FDA-approved applications of rhBMPs are limited to one-level anterior lumbar interbody fusions (rhBMP-2) and revision posterolateral fusions (rhBMP-7).

The future role of BMPs in spinal surgery applications remains to be determined. The prospect of predictable and reliable osteogenesis without the need for secondary bone grafting to treat a wide spectrum of spinal disorders is tremendously appealing. However, the dose and delivery of rhBMP was shown to be site specific and species specific. Results for a specific condition or a specific region cannot necessarily be extrapolated to another condition or another region. Before there can be widespread acceptance of BMP in spinal applications, future investigations are needed to evaluate (1) the efficacy in a variety of spinal conditions, (2) the optimal dose and delivery system, (3) the long-term safety profile (immunogenicity, antibody formation), and (4) the cost effectiveness of these therapeutic growth factors.

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