INTRODUCTION

Surgeons can now control osteogenesis through local application of BMP-2. BMP’s are osteoinductive proteins that are located in bone matrix and are responsible for embryonic skeletal formation and bone healing. Marshal Urist first coined the term “bone morphogenic protein” over 40 years ago. Recombinant human BMP-2 is an osteoinductive growth factor that has the potential to make autogenous bone grafting unnecessary. By demonstrating the capabilities of demineralized bone matrix to induce ectopic bone formation in a rat muscle pouch, Urist introduced the concept that growth factors can induce bone formation independent of a bone tissue environment.

Recombinant human bone morphogenic proteins (rhBMPs) are cytokines belonging to the growth factor-B superfamily (TGF-B). There are over 20 types of bone morphogenic proteins (BMPs) with varying osteoinductive potential. rhBMP-2 is a genetically engineered version of BMP-2, a naturally occurring protein which is active in normal bone repair. The two most frequently studied include rhBMP-2 and rhBMP-7 (OP 1). These cytokines have the ability to bind to mesenchymal cells triggering differentiation into osteoblasts.

The availability of recombinant BMPs has allowed definitive tests of their osteoinductive activity in a variety of situations, including animal models of clinically relevant bone defects. Cheng et al, demonstrated the relative osteoinductivity of different BMPs at various stages of differentiation in mesenchymal progenitor and osteoblastic cells infected by adenovirus-mediated gene transfer of BMPs. Recombinant BMP-2, 6, and 9 play an important role in the early phase of differentiation of the stem cells to preosteoblasts, while most BMPs promote the terminal differentiation of these preosteoblasts to osteoblasts.

The identification of the gene responsible for the production of rhBMP-2 led to its being cloned through recombinant technology. Oligonucleotide probes are used to create the human cDNA sequence that is then inserted into a viral vector (plasmid) which, in turn, is transfected into a carrier cell (recombination). These cells have the ability to produce large quantities of
The emergence of rhBMP-2 as a viable alternative to traditional bone grafting is based on two important clinical challenges. The first is to eliminate the need to harvest bone from the iliac crest or other sites when performing maxillofacial reconstruction because increased morbidity is associated with these procedures. The second reason is to try to enhance the degree of new bone formation for placement of dental implants into an ideal location. Clinical application of BMP’s now includes defects of the facial skeleton, such as alveolar reconstruction, sinus augmentation, segmental defects and alveolar ridge preservation.


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REFERENCES


MECHANISM OF ACTION

The osteoinductive cytokine rhBMP-2 induces the differentiation of pluripotential precursor cells into new bone tissue at the site of implantation. Through signaling, it promotes the recruitment of the patient’s own adult mesenchymal stem cells (AMS) to the surgical site, and proliferation of the recruited cells, and the differentiation of these cells into bone cell precursors. (Fig. 3) The bone induced by rhBMP-2/ACS remodels and assumes the structure appropriate to its location and function as would be expected from host bone. Although the number of AMS decreases with age, studies have shown that bone formation and repair with BMP-2 is as effective in old animals and in elderly human patients as in young children with cleft palates.\textsuperscript{8,9}

rhBMP-2 binds to specific receptors on the stem cell surface causing them to differentiate into bone-forming osteoblasts. (Fig. 4) Not all BMPs are capable of this binding. There are two types of transmembrane serine/threonine kinase receptors, BRI and BRII, which form heteromeric complexes prior to and after ligand binding. Within a BMP-bound receptor complex, BRII associates with a BRI molecule to form a signaling receptor complex. BRI and BRII receptors signaling begin through Smad proteins, Smad binding proteins, mediator Smads (Co-Smad 4 for BMPs), inhibitory Smads (I-Smads 6 and 7), Smad binding proteins,
Growth and differentiation factors such as BMP-2 play an essential role in cellular functioning but require a tempering of their signal for coordinated bone formation and remodeling. This is achieved by feedback mechanisms, extracellular antagonists (i.e., noggin, gremlin, DAN and cerberus) and intracellularly by inhibition and modulation of the Smad-signalling pathway.

**COMPARISON TO AUTOGRAFTS**

Probably the greatest potential advantage for rhBMP-2 use is eliminating the need for graft harvest and its associated morbidity. Prospective studies have shown that rhBMP-2 is superior to autografts in obtaining successful lumbar fusion. Although it remains to be seen whether this will be true for maxillofacial reconstructions, studies thus far are promising. Cleft palate patients and patients undergoing a sinusal lift procedure who received rhBMP-2 performed as well as patients receiving iliac crest autografts.

Complications with harvest of iliac crest bone graft may occur in as many as 15% to 25% of patients. Harvesting iliac crest bone is associated with pain and carries the risk of significant morbidity. Harvest complications from an additional operative site include chronic donor site pain, increased operative time, and additional cost. For larger defects the quantity of bone available to harvest may be insufficient for large defects or in patients with previous graft harvests.

Autogenous bone has long been considered the “gold standard”, but transplanted autogenous bone may need to be resorbed or remodeled before fusing. BMP has a role in the regulation of bone turnover via coupled osteoblastic and osteoclastic activity. Itoh et al. described how BMP mediated signals are involved in osteoclastic resorption.

Therefore, rhBMP-2 may accelerate the creeping substitution of an allograft by stimulating an osteoclastic response in concert with an osteoblastic response. Because rhBMP-2 is osteoinductive and allografts are osteoconductive, it appears logical to combine the two in an effort to enhance the amount and rate of bone formation.

**CLINICAL USE OF rhBMP-2**

Reports of clinical use of extracts of human BMP from allograft bone matrix began in the late 1980’s. In 1988 the DNA sequence for BMP was isolated from a purified extract, leading to the production of recombinant BMP. This recombinant process allows for the production of large quantities of highly purified BMP at a known concentration.

In 2007, the FDA granted approval of rhBMP-2 (INFUSE Bone Graft®, Medtronic, Memphis, TN) as an alternative to autogenous bone grafts for sinus augmentations, and for localized alveolar ridge augmentation of defects associated with extraction sockets. This approval was based on data from 312 patients enrolled in a total of 5 clinical studies. However, rhBMP-2 is contraindicated for patients with a known hypersensitivity to rhBMP-2 or bovine type I collagen. It should not be used in the vicinity of a resected recognition for his research, much of which was completed in cooperation with Dr. Philip Boyne. Several of his research endeavors are related to growth factors and their use in facial reconstruction. Last May, 2008, Dr. Herford was named the inaugural Philip Boyne-Peter Geistlich Professor of Oral and Maxillofacial Surgery. He also recently was inducted into the American College of Surgeons.

Dr. Jeffrey S. Dean received his D.D.S. from Creighton University School of Dentistry and his M.D. from the University of Texas Southwestern Medical School in Dallas. Dr. Dean completed his training in oral and maxillofacial surgery at Parkland Memorial Hospital at the University of Texas Southwestern Medical Center in Dallas. Currently he is in private practice with Facial and Oral Surgery Associates in Pocatello, Idaho and Assistant Professor in the Department of Oral and Maxillofacial Surgery at Loma Linda University. He has been involved in research and has multiple articles and book chapters. He is a fellow of the American College of Surgeons. Dr. Dean practices full-scope oral and maxillofacial surgery with interests in facial flaps, facial reconstruction, cleft and craniofacial surgery.
reoperation were all improved with rhBMP-2 in their large series of patients. 

Despite the extent of bone formation, there has been no evidence of bone formation extending beyond the boundaries of the defect. The process of induced bone formation appears to be a controlled response to highly concentrated levels of rhBMP-2. Because this bone-inducing protein is normally present endogenously in the body it is likely that normal growth regulating genes control the growth process and prevent overgrowth.

QUESTIONS FOR THE FUTURE

Still unanswered are questions such as:

- What is the ideal grafting material to combine with BMP to enhance bone formation in a specific defect?
- Does the addition of BMP to autogenous bone improve the “gold standard”?
- Will alloplastic, allogenic, or xenogenic graft material in combination with rBMP-2 prove to be superior than rhBMP-2/ACS alone?
- Are there other cytokines that will enhance the activity of BMP-2?
- Future studies will help us continue to shed light on these questions and many more as we strive to improve our understanding of bone healing.

CONCLUSIONS

The published literature suggests that rhBMP-2 is clinically effective in treatment of critical-size defects in both extremities as well as in the maxillofacial region by predictably inducing new bone formation at the site of implantation. Further study will be needed to support this conclusion and offer definitive proof that rhBMP-2/ACS can be as safe an alternative to the harvest of autografts in maxillofacial trauma as it has proved to be in orthopedic applications. The advantages of rhBMP-2 repair to the patient include a shorter hospital stay, avoidance of gait and sensory disturbance, as well as decreased sites for scar formation and possible infection. Surgical time is reduced because the surgeon does not have to harvest autogenous bone from a secondary site. In the future, the use of exogenous cytokines, particularly those in the BMP series will become common and the regeneration of osseous defects will likely be brought about through a clinical outpatient procedure.

Dr. Alan Herford received his Doctor of Dental Surgery from Loma Linda University School of Dentistry in 1994. He then moved to Dallas where he attended the University of Texas Southwestern Medical Center, earning his MD degree in 1997 and completing the Advanced Education Program in Oral and Maxillofacial Surgery at Parkland Hospital. Following his return to LLU in 2000, he was appointed chair of the OMFS Department and advanced program director in 2002. During his tenure at Loma Linda the residency program has tripled in size and has integrated with the Loma Linda University School of Medicine. Dr. Herford has achieved distinction as a leader in surgery, receiving tumor, in patients with any active malignancy, in infected sites or in pregnant women.

The osteoinductive capabilities of rhBMP-2 have been widely studied in different bone healing environments. Preclinical and clinical research has demonstrated that rhBMP-2 combined with an absorbable collagen sponge (ACS) can induce new bone formation. Dose-dependent clinical studies have determined 1.5mg/cc as a safe and predictable dose for bone formation. rhBMP-2 has been shown to heal critical-size bone defects both in animal models and clinically.

Using extracts of BMP, Johnson, et al, reported on a dozen nonunion patients. Union was obtained in 11 out of 12 nonunions, at an average time of 4.7 months. This was followed by a report of BMP implanted along with autograft in six patients with traumatic 3 cm to 17 cm tibial defects. The tibia were stabilized with external fixation and all six patients regained function.

Because the half-life of rhBMP-2 is only minutes in the bloodstream, it must be administered locally to the bleeding bone over a period of time to stimulate with new bone formation. The absorbable collagen sponge (ACS) carrier matrix provides a means of delivering and retaining rhBMP-2 at the surgical site.

It also helps prevent soft tissue prolapse into the defect, enabling bony vascular growth to occur during rhBMP-2 induced bone formation. The ACS is type I collagen derived from highly purified bovine tendon. Because the ACS lacks structural stability the soft-tissue walls of the defect can compress it. Development of future carriers with greater structural stability will better maintain the space for optimal bone formation.

The delivery of rhBMP-2 to a surgical site on an absorbable collagen sponge has been investigated in preclinical and clinical studies of localized alveolar grafting as well as sinus floor augmentations prior to implants. A pivotal study indicated that rhBMP-2 provides clinical and radiographic outcomes that are equivalent to those after autogenous grafting.

Localized Alveolar Defects

rhBMP-2 can be used for localized ridge augmentation procedures. A randomized prospective study evaluating the use of rhBMP-2 for extraction socket augmentation showed that rhBMP-2 could predictably form de novo bone. Eighty patients requiring local alveolar augmentation for bucal wall defects in the anterior maxilla were evaluated. Patients who received 1.5 mg/cc rhBMP-2/ACS had significantly greater bone augmentation compared to controls (p<0.05). The adequacy of bone for placement of a dental implant was approximately twice as great in the rhBMP-2/ACS group.(Fig. 5)

Maxillary Sinus Lift

The maxillary sinus lift can reliably provide sufficient bone for placement of dental implants. Boyne, et al, reported the results of bone induction by rhBMP-2/ACS in maxillary sinus floor augmentation. They found that rhBMP-2 in Maxillofacial Surgery

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MP-2 predictably and safely induced adequate loading of endosseous dental implants in patients requiring staged maxillary floor augmentation. The proportion of patients who received dental implants that were functionally loaded and remained functional at 36 months post-functional loading was 62% and 76% in the bone graft and 1.5 mg/ml rhBMP-2/ACS treatment groups, respectively.

The technique is similar to the standard maxillary sinus lift procedure described by Boyne and James. After elevating the Schneiderian membrane, the rhBMP-2 soaked collagen sponges are placed. Care is taken to effectively pack the floor of the sinus.

**OFF-LABEL USE OF rhBMP-2**

rhBMP-2 has been used successfully in non-human primates and humans to restore large critical-sized defects including continuity defects, alveolar clefts, and extensive vertical bone defects (preprosthetic defects). Continuity Defects

**Poor Bone Healing Environments**

Radiation and bisphosphonates are examples of factors that have the potential to impair bone and soft tissue healing. Chronic osteomyelitis is another example of a site associated with impaired healing. Because of the angiogenic response to the BMP, this factor may have a role in poor bone healing environments such as those with inhibited healing due to radiation or bisphosphonates.

**RISKS OF USING BMPs**

Both rhBMP-2 and rhBMP-7 have been studied in thousands of patients and tens of thousands of animals with a high safety profile. It is estimated that over 500,000 patients have been treated with rhBMP-2. A low risk, similar to that in clinical trials leading to approval, can be expected with “on-label” use. Transient increases in antibodies to BMP develop in 5% to 10% of patients, but this does not affect bone healing on first exposure. However, less is known about the effects of multiple exposures.

Carreon, et al., studied patients who were re-exposed to rhBMP for spine surgery. They found no significant difference in the number of complications between first and second spine surgeries of the 96 patients using rhBMP-2. There were no wound problems or allergic reactions among the twelve patients who had a third surgery with rhBMP-2. They concluded that multiple exposures to rhBMP-2 does not increase the risk of wound infections or other problems and does not result in clinically detectable allergic reactions.

When used “off-label”, there are possible adverse outcomes that must be balanced against the benefit of using rhBMP-2. Changing the recommended concentration of the BMP or the carrier material could risk inconsistent bone formation. If a higher concentration is used, local edema or fluid collection can occur; as has been reported after some cases of anterior cervical disectomy and fusion using BMP instead of autogenous bone. Adverse facial edema has also been noted when rhBMP-2 was used for cranial reconstruction to treat craniosynostosis. Because BMP can accelerate bone resorption in addition to bone formation, using more resorbable carriers, that have not been carefully tested with BMP, can result in accelerated resorption of the bone.

The absorbable collagen sponge is susceptible to compression from the overlying tissue. This compressibility problem has led to the consideration of ways to maintain space, including engineering an alternative carrier, addition of compressive resistant osteoconductive material, supporting the space with a membrane or mesh, or using screws or implants to “tent up” the tissue. Combining the rhBMP-2 with a graft extender may improve the economic feasibility of BMP-2 by reducing the required dose of the protein.

As with any new technology, concerns over additional costs of such interventions should be considered. As discussed by Kuklo, et al. there is a compelling argument for the continued use of such technologies, because the primary outcome measures of bone union, rate of infection, and
Mandibular continuity defects secondary to trauma or tumor resection are common and often present reconstruction challenges. Preclinical animal studies have demonstrated that rhBMP-2/ACS can induce bone formation and repair large, critical-size segmental defects in rat femora, rabbit radii and ulnae, dog radii, and nonhuman primate radii. Boyne, et al, showed that rhBMP-2 could heal critical-size oral and maxilla-facial defects in a nonhuman primate model. The first reported human application of BMP in the mandible was by Moghaden et al. in 2001. In 2004, Warnke et al. used BMP-7 and bone mineral blocks (xenografts) to create a custom vascularized bone graft. The engineered graft was allowed to heal in the trapezius muscle and was subsequently transplanted into the recipient site using microvascular anastomosis. Herford and Boyne used rhBMP-2 to treat mandibular continuity defects. All 14 patients demonstrated successful osseous restoration of the missing bone when rhBMP/ACS was used without concomitant bone grafting materials. The authors described the importance of maintaining the periosteal envelope. This can be accomplished with either a superiorly placed titanium miniplate or titanium mesh. (Fig. 7) This metallic tenting up of the mucosa and periosteum is thought to be necessary to maintain the space for osseous regeneration.

Carter et al. used either rhBMP-2 alone or in combination with bone marrow cells and allogenic bone. In 2 out of 5 patients their continuity defect failed to proceed to union. They suggested that the failures were due to
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Figure 7. A. Mandibular tumor involving the right mandible. B. Immediate reconstruction with rhBMP-2/ACS combined with demineralized bone. Note the mesh superiorly to provide for space maintenance. C. Implants placed 8 months later.

chronic infection or lack of space maintenance by the graft.

Clokie and Sandor recently used bioimplants containing BMP-7 for mandibular defects in a series of 10 patients. They reported successful restoration of critical size defects in 10 patients, with decreased operating room time and shorter hospital stays, thus saving health care system costs.

A recent study of 129 soldiers with type III open segmental tibia fractures and segmental cortical bone loss (2 cm to 10 cm) compared fixation with supplemental bone grafting (Group 1) or rhBMP-2/ACS and allograft bone (Group 2). There was a lower rate of infection in Group 2 (3.2%) compared to Group 1 (14.9%). Definitive union was observed in 76% of Group 1 patients and 92% for Group 2 patients.

Another study evaluated the use of rhBMP-2 with two different bone substitutes (calcium sulfate or calcium phosphate) to repair segmental bone defects involving the extremities. Defects averaged 4.75 cm (ranging from 1.5 to 8.0 cm). In this group of patients, rhBMP-2/ACS healed of 84% critical-size defects.

Alveolar Clefts

Growth factors have shown promise in congenital defects. (Fig. 8) In a non-human primate study using a simulated cleft model, Boyne, et al, found that rhBMP-2 could form bone in a cleft that was similar to that of autografts. Another study compared rhBMP-2 to anterior iliac crest bone graft for treatment of alveolar clefts. They found that rhBMP-2 was an effective alternative to conventional anterior iliac particulate cancellous grafts in that series of patients.

Preprosthetic Defects

Preprosthetic augmentation procedures using bone grafts, such as ridge augmentation, are commonplace. Jovanovic, et al, performed a histologic study of a canine ridge augmented with BMP. They found no significant differences between implants with rhBMP-2-induced bone and the resident bone. They concluded that rhBMP-2 allows installation, osseointegration, and long-term functional loading of dental implants. Titanium mesh is helpful in