Use of Recombinant Human Bone Morphogenetic Protein 2 for Mandible Reconstruction

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Background: Microvascular osseous free tissue transfer is the standard of care for reconstructing significant mandibulectomy defects; however, this procedure can carry a significant rate of morbidity.

Objectives: To describe the use of recombinant human bone morphogenetic protein 2 (rhBMP-2) as an option for segmental or near-complete rim mandibulectomy defects in a select group of patients, precluding the need for free tissue transfer.

Methods: A retrospective review was performed of 6 patients who had undergone repair of a mandible defect using rhBMP-2 with beta-tricalcium phosphate matrix or a cadaveric bone graft at a single tertiary care institution. The defects resulted from resection of benign neoplasms or from previous trauma. Reconstruction success was defined as no hardware problems, healing without infection, no need for further surgical procedures, and imaging evidence of healing and union without resorption. The median follow-up period was 37.5 months (range, 12-51 months).

Results: Five of 6 patients underwent successful restoration of the mandibulectomy defect. One patient with a compromised immune system developed a significant postoperative wound infection requiring further reconstructive surgery.

Conclusion: The use of an rhBMP-2–based reconstructive approach is a feasible option for segmental or near-complete rim mandibulectomy defects in a select group of patients.

Level of Evidence: 4.


Mandible defects represent a unique challenge to the reconstructive surgeon, although numerous advances have been made in recent years. The early 1990s saw a paradigm shift for a wide acceptance of the reconstruction of segmental mandibular defects with osseous microvascular free tissue transfer. The use of vascularized bone-containing free flaps (eg, the radial forearm, fibula, iliac crest, and scapula) has gained widespread popularity and has become the standard of care for reconstructing oromandibular defects. However, microvascular free tissue transfer is associated with donor-site morbidity, as well as a major and minor complication rate of up to 60%.1,2

The limitations afforded by microvascular free tissue transfer include significant complication rates, lengthy operative times, limited donor-site availability, and prolonged hospital stays. These issues, coupled with recent basic science advances and clinical exposure to growth factor therapies in orthopedics, have led to increased interest in a possible tissue engineering approach to reconstruct mandible defects. Potential advantages of a tissue engineering approach include preclusion of donor-site morbidity, leading to quicker recovery and shorter operative times with decreased surgical complexity, while ideally creating a more customized reconstruction. One such tissue engineering approach uses growth factors and scaffolds to support osteogenesis. In particular, recombinant human bone morphogenetic protein 2 (rhBMP-2) has recently gained favor as a potential growth factor for de novo bone formation in mandible reconstruction because of its osteo-
inductive activity. Clinical experience with rhBMP-2 is well established in other fields, with Food and Drug Administration approval in 2002 for its use in anterior lumbar spinal fusion, as well as approval in 2007 for maxillary sinus floor augmentation and localized alveolar ridge defects.6-8 The successful use of rhBMP-2 for mandibular defects has been well described using several animal models; however, descriptions of its use in humans have been limited.9-11

At our institution, we began using rhBMP-2 for segmental or near-complete rim mandibulectomy defects in patients with limited associated soft-tissue defects who were not candidates for osseous free tissue transfer or who refused the use of an autologous bone donor site after extensive counseling. Patients who were diagnosed as having a malignant neoplasm or who had previous exposure to irradiation were excluded because of safety and efficacy concerns.12-14 Herein, we describe the use of rhBMP-2 in 6 patients with significant mandibular defects secondary to traumatic injury or benign neoplasms.

### METHODS

#### STUDY DESIGN

After obtaining approval from our Human Subjects and Research Protections Office, a retrospective review was performed of patients who had undergone repair of a mandible defect using rhBMP-2 with beta-tricalcium phosphate matrix or a cadaveric bone graft of cases at the Washington University Medical Center between January 2004 and December 2009. A total of 6 patients (age range, 45-59 years) underwent reconstruction with the off-label use of rhBMP-2 for segmental or near-complete rim mandibulectomy defects (Table). The defect lengths ranged from 5 to 12 cm. The near-complete rim mandibulectomy defects all had a remaining mandible height of less than 8 mm. Five pa-

<table>
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<th>Defect Length, cm</th>
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<td>1/F/55 Segmental mandibulectomy body</td>
<td>5</td>
<td>Extraoral</td>
<td>rhBMP-2 (4.2 mg) on bovine type I collagen sponge, allogenic cadaveric fibula, locking reconstruction plate</td>
<td>Untreated mandibular fracture, resulting in infected nonunion</td>
<td>4 d/150 mL/5 h</td>
<td>Well healed, no complications</td>
<td>12 (Died of unrelated cause)</td>
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<td>2/M/57 Segmental mandibulectomy body, parasymphysis, symphysis</td>
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<td>4/F/45 Near-complete rim mandibulectomy defect in ramus and parasymphysis involving the entire medial cortex</td>
<td>10</td>
<td>Intraoral</td>
<td>rhBMP-2 (18 mg), beta-tricalcium phosphate matrix</td>
<td>Odontogenic keratocyst</td>
<td>1 d/30 mL/1.5 h (Resection included)</td>
<td>Well healed, small wound dehiscence that healed primarily (1.5 cm intraoral)</td>
<td>50^4</td>
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<tr>
<td>5/M/46 Near-complete rim mandibulectomy defect from the ramus to body</td>
<td>6</td>
<td>Extraoral</td>
<td>rhBMP-2 (12 mg), beta-tricalcium phosphate matrix, locking reconstruction plate</td>
<td>Odontogenic keratocyst</td>
<td>2 d/150 mL/4.5 h (Resection included)</td>
<td>Well healed, no complications</td>
<td>51^4</td>
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<tr>
<td>6/F/54 Near-complete rim mandibulectomy defect body</td>
<td>3.5</td>
<td>Intraoral and extraoral</td>
<td>rhBMP-2 (6 mg), beta-tricalcium phosphate matrix, locking reconstruction plate, platysma flap</td>
<td>Giant cell reparative granuloma</td>
<td>4 d/50 mL/4 h (Resection included)</td>
<td>Well healed, no complications</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviations: EBL, estimated blood loss; rhBMP-2, recombinant human bone morphogenetic protein 2.

^4 Last follow-up visit was by telephone interview.

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Patients had benign neoplasms, and 1 patient had chronic malunion secondary to trauma. All patients had extensive preoperative counseling for the off-label use of rhBMP-2. The 3 patients who underwent reconstruction for a near-complete rim mandibulectomy defect did not want to proceed with a segmental resection that was initially recommended. For the segmental mandibulectomy defects, 2 patients refused osseous free tissue transfer, and 1 patient was not a candidate for a free flap because of extensive comorbidities.

**SURGICAL TECHNIQUE**

An extraoral approach was used whenever possible. For the segmental mandibulectomy defects, rhBMP-2 (INFUSE Bone Graft; Medtronics) was reconstituted using sterile water. The amount of protein used (range, 4.2-18 mg) was calculated based on maintaining a minimum concentration of 1.5 mg/mL throughout the defect. This rhBMP-2 concentration is known to have osteoinductive activity in humans.9,10 The reconstituted protein was then placed on bovine type I collagen sponges. After waiting a minimum of 15 minutes to allow for adherence of the protein to the collagen sponge, the sponges were molded in a jelly roll manner and were placed into the drilled-out medullary space of allograft cadaveric fibula bone. All 3 patients who had segmental mandibulectomy defects had an interposition cadaveric allograft bone (1651010; AlloSource) placed that was loaded with rhBMP-2 collagen sponges to act as an osteoconductive scaffold for supporting osteogenesis. Small gaps between the interfaces of the bone grafts were filled with demineralized bone matrix. The graft was fixated into position using monocortical screws into the bridging 2.5-mm mandibular reconstruction plate (Mandible Locking Plate; Synthes).

For patients with near-complete rim mandibulectomy defects, rhBMP-2 was combined with beta-tricalcium phosphate matrix (Vitoss Bone Graft; Orthovita). The resultant putty was shaped to the defect by layering it on top of the thin inferior bone that remained, maintaining continuity of the mandible. A 2.5-mm mandible reconstruction plate was used to add strength to the mandible given the thin nature of the inferior bone that remained.

All patients received perioperative dexamethasone sodium phosphate (10 mg intravenously every 8 hours for 48 hours), as well as a 1-week course of amoxicillin with clavulanate potassium (875 mg by mouth twice daily) or clindamycin (300 mg by mouth 3 times daily) depending on their allergy status. Successful healing and union were determined by clinical and radiographic criteria. From a clinical standpoint, patients were followed up for complications related to the graft or the hardware. Imaging criteria included serial postoperative radiographic evaluations (Panorex CDRPANX; Schick) for the near-complete rim mandibulectomy defects. The patients with segmental mandibulectomy defects underwent yearly computed tomography for up to 3 years after surgery, with bone scintigraphy at 8 months. Reconstruction success was defined as no hardware problems, healing without infection, no need for further surgical procedures, and imaging evidence of healing and union without resorption.

**REPORT OF CASES**

**CASE 1**

A 57-year-old man was seen for evaluation of an 11-cm segmental anterolateral mandibulectomy defect (Figure 1 and patient 2 in the Table). The patient had originally undergone resection of an ameloblastoma, followed by reconstruction with a fibula free tissue transfer; however, the free flap became nonviable secondary to venous congestion and was unable to salvaged. The patient had an 11-cm defect extending...
from the distal left mandibular ramus to the right parasymphysis. The patient refused another autogenous free tissue transfer, so the option of rhBMP-2 was discussed and offered to him.

After making a cervical neck incision, special attention was made to avoid violating the healed intraoral mucosa. A total of 10 mg of rhBMP-2 was used. The cadaveric fibula bone graft was split into 2 pieces and then loaded with the rhBMP-2–soaked sponges into the medullary cavity, which had been previously enlarged to provide a wide hollow shaft throughout the entire length of the graft. Small gaps at the interfaces were filled with rhBMP-2–soaked sponges coated on the external surface with demineralized bone matrix. The 2 grafts were then fixated to the preexisting reconstruction plate for stability. After surgery, the patient had moderate facial swelling that lasted for 2 weeks. No complications occurred. He developed complete union and has been tolerating an oral diet, with no complaints or reconstructive-related problems at the last follow-up visit at 39 months.

CASE 2

A 46-year-old man was seen with a long history of a right mandible mass; a previous biopsy had revealed it to be an odontogenic keratocyst (Figure 2 and patient 5 in the Table). The patient underwent transcervical excision, with careful attention paid to avoid violating the intraoral mucosa. The mass was 5 × 4 cm, resulting in a 6-cm-long defect involving the ramus and posterior body. The vertical height of the remaining inferior mandible maintaining anatomical bone continuity was 5 mm, resulting in the need for reconstruction.

A locking reconstruction plate was placed for stabilization. Afterward, 12 mg of rhBMP-2 was reconstituted and then saturated onto beta-tricalcium phosphate matrix. The graft was then molded into the shape of the defect. Next, the masseter muscle was reapproximated to itself to provide vascularized soft-tissue coverage overlying the graft and to create a pocket for stabilization. The patient developed moderate facial swelling that resolved within 2 weeks. No postoperative complications occurred, and the patient was found to have complete healing of the defect at the 9-month follow-up visit.

RESULTS

Three men and 3 women (mean age, 52.7 years; age range, 45-59 years) underwent reconstruction with rhBMP-2 (Table). Three patients had segmental mandibulectomy defects, and 3 patients had near-complete rim mandibulectomy defects. For reconstruction, 1 patient had solely an intraoral approach, 3 patients had solely an extraoral approach, and 2 patients had a combined intraoral and extraoral approach. Two patients had a staged reconstructive procedure, while 4 patients had the resection and reconstruction performed the same day. Origins of the mandibulectomy defect included benign tumors in 5 patients and a history of trauma in 1 patient.

Five of 6 patients underwent successful restoration of the mandibulectomy defect, requiring no further sur-

Figure 2. Patient 5, a 46-year-old man having a near-complete rim mandibulectomy defect treated with recombinant human bone morphogenetic protein 2 (rhBMP-2) with a beta-tricalcium phosphate onlay graft. A, Preoperative radiographic evaluation (Panorex CDRPANX; Schick) showing odontogenic keratocyst with a thin inferior rim of bone. B, Intraoperative view of the near-complete rim mandibulectomy defect with the reconstructive plate already in place. C, Intraoperative view after placement of the onlay rhBMP-2 graft. D, Nine-month postoperative radiogram (Panorex) showing complete osteogenesis and healing.
surgery. One patient with a compromised immune system developed a postoperative wound infection that required removal of the graft. All 6 patients experienced moderate facial swelling after surgery that resolved within 2 weeks. No patient required any airway intervention for his or her postoperative swelling. The mean length of hospital stay was 3 days (range, 1-5 days), with step-down unit stays ranging from 0 to 2 days. No patient required intensive care unit admission. Five of 6 patients had an estimated blood loss of 150 mL or less; however, 1 patient lost 800 mL, with most of the blood loss occurring during the resection portion of the procedure. The median operative time was 4.3 hours (range, 1.5-6 hours). None of the patients in this series underwent subsequent dental restoration. One patient with a near-complete rim mandibulectomy defect underwent a platysma flap placement to assist with creating a pocket for the rhBMP-2 graft, with the mucosa being primarily closed over the defect. No patient required a soft-tissue flap for local closure. The median follow-up period was 37.5 months (range, 12-51 months).

**COMMENT**

Urist, in 1965, was first to hypothesize the existence of a molecule with osteoinductive activity in the demineralized bone matrix. In the 1980s, these osteoinductive molecules (BMPs) were isolated and purified, and their genes were cloned, with each protein being numbered in the order in which they were isolated. Today, 20 BMPs have been identified, representing a large subgroup of the transforming growth factor β family of growth and differentiation proteins. The use of rhBMP-2 has recently gained attention as a potential alternative reconstructive option for mandibular defects. In 2001, Moghadam et al described the first human application of rhBMP in the mandible of a patient. This was followed by 3 subsequent studies in the oral maxillofacial surgery literature, with segmental mandibulectomy defects in 14, 5, and 10 patients by Herford and Boyne, Carter et al, and Clokie and Sándor, respectively. Herford and Boyne and Clokie and Sándor reported complete clinical and radiographic union in their series, while 2 of 5 patients in the series by Carter et al had inadequate bone formation. Carter et al and Clokie and Sándor adjunctionally used BMP-2 and BMP-7, respectively, in combination with demineralized bone matrix or allogenic bone chip and bone marrow cells. Herford and Boyne used rhBMP-2 alone for segmental mandibulectomy defects at 1.5 mg/mL; however, the other 2 studies did not mention the concentration or dose used. This differs from our methods because we believed that allogenic cadaveric bone was necessary to provide a scaffold for reconstruction in large segmental mandibulectomy defects based on our experience.

Five of 6 patients developed clinical and radiographic union. Patient 3 required further surgery to remove the graft; several hypotheses as to why the graft failed include a large intraoral mucosal incision, with significant oral contamination of the surgical site. The wound characteristics, including an associated dead space, coupled with an already immunocompromised state associated with human immunodeficiency virus diagnosis were likely predictive factors for the graft failure.

An expected adverse effect of the surgical procedures described herein is postoperative facial edema, which for this application is self-limiting and caused no complications. Edema is a well-described adverse effect of rhBMP-2 use and can lead to severe dysphagia and airway compromise when used for cervical spine fusion. In 2008, the Food and Drug Administration released a public health notification of life-threatening risks associated with the use of rhBMP-2 in cervical spine surgery. The cause of swelling could be related to larger clinical doses, with less containment of the rhBMP in the reconstructed field. In our series, we observed no significant airway swelling in any of our patients; rather, the edema was superficial because of the location of the graft placement. All our patients were prescribed perioperative corticosteroids in anticipation of this adverse effect. Other studies of the use of rhBMP-2 in mandibular reconstruction reported no airway swelling requiring intervention.

The package insert for rhBMP-2 describes contraindications for its use, including active infection at the operative site, pregnant women or those planning to become pregnant within 1 year, patients with a known hypersensitivity to rhBMP-2 or bovine type I collagen, and any patient with an active malignant neoplasm or a history of malignant neoplasm in the vicinity of the proposed surgery. This important oncologic contraindication stems from concerns about the unknown effects of this growth factor on cancer cells. Recent studies showed increased pathogenicity of oral cancer cell lines after transient exposure to rhBMP-2. In addition, Zhou et al performed gene microarray analysis with quantitative polymerase chain reaction in 25 oral tongue squamous cell carcinomas and found that increased BMP2 gene expression was associated with regional lymph node metastasis and with extracapsular spread. Based on available data, we believe that rhBMP-2 should not be used for reconstruction of mandibular defects originating from oral cancers.

The use of rhBMP-2 is a novel and exciting alternative for mandibular reconstruction in a select group of patients. However, given the relative lack of published clinical experience, future studies must focus on several practical issues before its use becomes more common. Such issues include the dose of rhBMP-2 needed to achieve osteoinduction per the size of the defect, as well as the most optimal surgical technique. Other concerns include the significant cost of the product and the potential for future dental restoration. For various reasons, none of the patients in our series had dental restoration performed; however, this was proven feasible in another series. In terms of cost, significant savings would likely offset the cost of the rhBMP-2 given the shorter operative times and hospital stays and less use of intensive care units, as well as the decreased need for postoperative physical therapy; however, a formal cost analysis has yet to be performed. Further limitations of our pilot study include the small clinical sample size and the lack of a control group. We did not believe that a control group using cadaveric bone without rhBMP-2 was ethically fea-
sible based on significant anecdotal experience, as well as the published literature using nonvascularized autografts in similar large-sized defects.\textsuperscript{12, 23} Finally, the population in our study did not include patients who required soft-tissue reconstruction. The usefulness of this approach for these patients with more complicated composite defects is unknown.

In conclusion, among a select group of patients with mandible defects caused by benign neoplasms or traumatic injury, rhBMP-2 can be a feasible alternative for reconstruction. However, the use of rhBMP is not the current standard of care for the reconstruction of these defects but rather represents a potential alternative for patients who refuse or are not candidates for osseous free tissue transfer. Potential patients should have no history of malignant neoplasm and should have no history of or planned need for radiation therapy.\textsuperscript{12-14} Surgical technique should involve an extraradial approach whenever possible. From our experience, the use of rhBMP-2 avoids donor-site morbidity, decreases surgical complexity, and allows for quicker recovery and shorter hospital stays. Future studies are needed to determine practical issues such as the need for a scaffold, the exact dose per defect size, the potential for dental restoration, and the most optimal approach and insertion technique, as well as to provide a comparative cost analysis.

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Author Contributions: The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Desai and Nussenbaum.

Drafting of the manuscript: Desai, Sclaroff, and Nussenbaum.

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