Pediatric Mandibular Defect Rehabilitation by Human Transforming Growth Factor-β3 with an Implant-Supported Prosthesis

Carlo Ferretti, BDS, Mdent1,2/Ugo Ripamonti, MD, PhD1

Large mandibular defects in children are an uncommon but challenging problem for surgeons to solve. The time-honored options of autologous bone grafts are seldom a viable option, as suitable donor sites are unavailable. Osteoinductive morphogens may yet provide a solution in these cases. A large mandibular tumor in a child 10 years of age necessitated the resection of the entire dentate portion of the mandible. The defect was reconstructed at a second stage with a composite graft of human transforming growth factor-β3 (hTGF-β3), human demineralized bone matrix, and 12 g of autologous bone harvested from the posterior iliac crest. A mature ossicle suitable for the placement of osseointegrated implants developed in the erstwhile defect, and an implant-supported dental prosthesis was placed. The patient has been followed up into adulthood. Facial growth has proceeded unhindered, and the patient has maintained full oral and dental function. This case reports the long-term result of an uncommon condition treated with a novel method. The long-term follow-up of this patient provides evidence to dispel some of the concerns for the use of osteoinductive proteins in children. A composite graft of osteogenic morphogens, osteocompetent autologous cells, and mineralized and demineralized matrices—as opposed to osteogenic morphogens used solo—may improve clinical bone regeneration.


Keywords: tissue engineering, human, mandible, transforming growth factor-β3, osseointegrated implants

Reconstructing a large mandibular defect in a pediatric patient poses a dilemma for surgeons. While some mandibular defects can be repaired without the restoration of the dentition and can thus be reconstructed with only a metal plate, defects of hemimandible size and larger significantly detract from patient quality of life if rehabilitation does not include a dental prosthesis supported with osseointegrated implants. A reconstructed ossicle in a mandibular defect is only useful if its volume is adequate to place sufficient osseointegrated implants. In children, this precludes both a vascular flap (typically a free fibula flap) and a particulate corticocancellous bone graft for osseous reconstruction, as the former is too narrow to reconstruct a mandible and the latter will not provide enough particulate graft volume to obtain a suitable ossicle. Bone tissue engineering would be ideal for situations like these, where patients and surgeons require a suitable substitute for autologous bone.

For several decades, osteogenic proteins have been used in human patients to repair defects of the appendicular and axial skeleton. Recombinant human bone morphogenetic protein-2 (hBMP-2; Infuse Bone Graft, Medtronic) received FDA approval for clinical use in anterior lumbar interbody spinal fusion in 2002, open tibial fractures in 2004, and finally for limited use in the maxillofacial skeleton (sinus grafting and socket augmentation) in 2007.1 Off-label use of hBMP-2 and naturally derived BMP in mandibular segmental defects has been reported in several case series.2–5 Originally, hBMP-2 used per manufacturer instructions, ie, lyophilized hBMP-2 reconstituted by the manufacturer in a liquid vehicle, was loaded at the time of surgery onto an absorbable Type I collagen sponge and implanted into the defect. Using this protocol, adequate ossicle regeneration in a mandibular defect has been a hit-or-miss occurrence, seldom yielding an ossicle suitable for the placement of osseointegrated dental implants. While avoiding a frank discussion of these obvious failings, some surgeons have indirectly acknowledged this failure by modifying the protocol for the use of hBMP-2 by combining hBMP-2 loaded on a Type I collagen sponge with either autologous bone graft6 or a composite of bone marrow stem cell aspirates and different matrices.7,8 The results for this protocol modification have been encouraging thus far.

1Bone Research Laboratory, Department of Internal Medicine, School of Clinical Medicine, University of the Witwatersrand, Johannesburg, South Africa.
2Department of Maxillofacial and Oral Surgery, School of Oral Health Sciences, University of the Witwatersrand, Johannesburg South Africa.

Correspondence to: Dr Ugo Ripamonti, Bone Research Laboratory, School of Clinical Medicine, Faculty of Health Sciences, 7 York Road, Parktown 2193, South Africa. Email: ugo.ripamonti@wits.ac.za

Submitted December 5, 2021; accepted April 16, 2022.
©2022 by Quintessence Publishing Co Inc.
Preclinical studies of TGF-β have unequivocally established its osteoinductive activity. The mammalian TGF-β3 isoform acts upstream as an initiator of osteoinduction, since implantation of hTGF-β3 results in BMP gene expression and secretion of BMP gene products, ultimately initiating the induction of bone formation.

A previous study reported the use of hTGF-β3 in a pilot trial of pediatric patients with mandibular defects, and the rationale for arriving at a protocol that combines hTGF-β3 and an autologous particulate graft has been previously described. The present study reports the treatment of a pediatric patient with a large mandibular tumor through resection, reconstruction, placement of osseointegrated implants and an implant-supported prosthesis, and follow-up into adulthood.

**CASE REPORT**

**First Stage**
A female patient 10 years of age presented a progressively enlarging swelling of the mandible for assessment (Fig 1a). Clinical examination revealed a diffuse, nontender, hard swelling of the mandible extending from the left to the right angle. Radiographic and CT examinations further revealed a well-circumscribed radiolucent lesion that had eroded and expanded the dentate portion of the mandible from the right angle to the left angle (Fig 1b). Incisional biopsy confirmed the diagnosis of ameloblastoma. Definitive treatment mandated resection of the dentate portion of the mandible from the left angle to the right angle (Fig 2). The resection and intermediate reconstruction were planned and effected as previously described. Briefly, the tumor was resected in a supraperiosteal plane via an intraoral approach, and a patient-matched plate was secured to the extant mandible. A silicone spacer was secured to the plate, primary mucosal closure was obtained, and the patient was discharged following post surgery recovery.

**Second Stage**
Following discussions with the Committee for Research on Human Subjects of the University of the Witwatersrand, Johannesburg, a humanitarian exemption was given for the use of the hTGF-β3 osteogenic device. Mucosal healing over the spacer was complete after 3 months (Fig 3), and the resultant 14-cm defect was reconstructed. The defect was exposed via a submandibular incision in the first neck crease with midline anterior relief. The spacer was removed, the recipient bed cleared of redundant scar tissue, and the mandibular stumps exposed. A bilateral posterior iliac crest harvest yielded 12 g of corticocancellous bone (the maximum mass of bone that could be safely harvested was removed bilaterally). Human demineralized bone matrix (DBM) was preloaded with rhTGF-β3 (250 µg rhTGF-β3 per gram of DBM) and lyophilized awaiting implantation. A total of 12 g of autologous bone graft was mixed with 15 g of DBM loaded with 3,750 µg of rhTGF-β3 (Fig 4a) and implanted into the recipient site (Fig 4b). The patient was fed via nasogastric tube for 4 days and discharged 1 week postoperatively.
The immediate postreconstruction radiograph revealed a speckled radiopacity throughout the length of the defect (Fig 5a).

**Third Stage**
The final stage began when the patient was 17 years of age, 6 years postreconstruction. Radiographic examination revealed that the composite graft had matured into a highly mineralized ossicle occupying the former mandibular resection site and that the ossicle was of adequate volume to place osseointegrated implants (Fig 5b). The ossicle was exposed via an intraoral approach, and five 5-mm–diameter implants with 5-mm transmucosal abutments (Southern Implants) were placed (Fig 6a). A fixed acrylic prosthesis was secured to the implants 3 months later (Figs 6b and 6c).

**Follow-up**
The patient is now 20 years of age and has functioned without complications with the fixed implant-supported dental prosthesis for 2 years. Facial symmetry and harmony have been maintained into adulthood (Fig 7a), and peri-implant bone levels have remained unchanged since implantation (Fig 7b).

**DISCUSSION**

The prospect of regenerating bone in a mandibular defect without resorting to the harvest of a bone graft is obviously attractive. Autologous bone grafts have been used with great success for many decades, making the justification for the use of tissue engineering less pressing. Therapeutic bone tissue engineering can only be justified if its use can guarantee results equivalent to those of autologous bone. However, in instances where an autologous bone graft will not suffice (eg, large defects in small patients), bone tissue engineering is no longer a useful option that reduces patient morbidity, but an essential strategy to attain a meaningful clinical result.

*Fig 4* (Right) (a) The prepared osteoinductive device was added to the autologous bone graft at the time of surgery. (b) The defect exposed and prepared via an extraoral approach was implanted with the composite graft.

*Fig 5* (Below) (a) Panoramic radiograph 2 weeks postimplantation reveals the speckled radiopacity of the matrix and particulate corticocancellous bone graft. (b) Panoramic radiograph 5 years postreconstruction. The graft has coalesced into a single ossicle with mature trabeculated bone and loss of radiographic interface between the graft mandibular remnants.

*Fig 6* (a) Osseointegrated implants placed into the ossicle of adequate volume. (b) Frontal and (c) occlusal views of implant-supported prosthesis 2 years postdelivery.
This case report provides further evidence that bone tissue engineering may yet help to solve some of the most challenging reconstructive cases: major skeletal defects in pediatric patients. The rationale for the use of a composite graft (autologous bone mixed with an osteogenic device) has been dealt with previously, but to summarize, based on the present authors’ experiences and the published data, it was concluded that the use of a morphogen combined with a delivery matrix was too unreliable for routine clinical use. To maximize the probability of achieving clinically significant osteoinduction, a composite of hTGF-β3, osteocompetent cells, and an appropriate demineralized and mineralized matrix was considered the avenue of choice.

It can be argued that mixing an autologous bone graft with an osteogenic device (or morphogen) creates ambiguities with regard to the therapeutic efficacy of the device. Typically, a 14-cm defect would require 70 to 98 g of autologous bone, an unobtainable mass for a child 10 years of age. The ossicle achieved in this patient using only 12 g of autologous bone can only be due to the synergy of the constituents of the composite graft.

The use of osteogenic morphogens in a growing patient has been a cause for concern, and the present authors’ previous pilot trial went some way to dispel some of the uneasiness. Reports of novel treatments for uncommon problems with long-term follow-up are rare. This report details the first patient rehabilitated to completion with hTGF-β3, an autologous bone composite graft, and an implant-supported prosthesis. The 10-year follow-up provides further valuable data supporting the use of growth factors for bone tissue engineering in children. Moreover, it appears that facial growth is not affected by the implantation of pleiotropic morphogens, and that a bone ossicle obtained in this manner does not preclude normal facial growth nor result in tumor recurrence.

CONCLUSIONS

Osteogenetic morphogen use in human patients is evolving, and although their use may not be as initially envisaged, it is clear that through incremental modification of the protocol for human tissue engineering, they will ultimately give surgeons and patients a viable, reliable alternative to autologous bone grafts.

ACKNOWLEDGMENTS

We thank the University of the Witwatersrand, Johannesburg, for continuously supporting the unit’s research on the recombinant human transforming growth factor-β since the 1990s. We gratefully acknowledge Novartis AG for the gift of the hTGF-β3. We thank Dr Selwyn Kabrun for the pro bono prosthodontic care he provided to this patient. The authors report no conflicts of interest.

REFERENCES