ABSTRACT:

Bone, cartilage, and tendon healing are clinically challenging processes. In order to address these concerns, orthobiologic research aims to enhance key steps involved in these processes using autologous and recombinant compounds, with the goal of achieving maximal clinical results. The potential for a quicker return to sport is appealing for athletes at all levels, and many high profile cases have driven continued orthobiologic research. In this chapter, we review the current clinical evidence regarding the use of biologic agents and scaffolds to improve healing following injury to the foot and ankle.

BONE ORTHOBIOLOGICS

Foot and ankle surgeons originally focused on mechanical stabilization to achieve successful arthrodesis when treating the various causes of joint destruction. However, numerous risk factors are now known to impair osseous healing (1) and nonunion rates range from 10% to as high as 40% within high-risk populations (2, 3). To address this concern, bone grafting techniques and adjunct therapies were developed to improve the local biologic environment.

Bone graft properties

Three important factors describe the biologic activity of bone grafts: osteoconduction (material serves as scaffold for existing bone to grow into), osteoinduction (material stimulates differentiation of existing osteoprogenitor cells), and osteogenesis (material contains osteoblasts that contribute to growth). Autologous bone graft (ABG) is the only graft possessing all three properties, and is considered the gold standard for managing bone defects and non-unions (4). However, ABG is associated with chronic donor site pain and is limited in quantity (5).

Allografts

Often, bulk allograft is needed for large defects to supplement the limited amounts of autograft. Heterologous bone grafts from cadavers can be fresh-frozen, freeze-dried, or demineralized bone matrix. Generally, these grafts must be irradiated to reduce immunogenic reactions, which in turn dramatically reduces their osteogenic and osteoinductive potential (6). Alternatively, synthetic grafts such as tricalcium phosphate
and calcium phosphate cement can be utilized, but have only osteoconductive capacity. Recent research has focused on orthobiologics (bone marrow aspirate, whole blood concentrates, recombinant proteins and growth factors) with osteoinductive properties, which can be either used alone or combined with osteoconductive grafting scaffolds. Specifically, recombinant human platelet-derived growth factor (rhPDGF) and bone morphogenetic proteins (BMPs) are common orthobiologics currently under investigation for use in foot and ankle surgery.

**Recombinant growth factors and proteins**

Platelet-derived growth factor (PDGF) refers to a family of growth factors that are released from platelets and macrophages following tissue damage. The PDGF-BB isoform has been shown to recruit inflammatory cells to the injury site, increase collagen deposition, and promote angiogenesis (7). DiGiovanni et al. (8) conducted a multicenter randomized controlled trial comparing the efficacy of rhPDGF-BB in a β-tricalcium phosphate scaffold (Augment Bone Graft; BioMimetic Therapeutics, Inc., Franklin, TN) to ABG in achieving arthrodesis. A total of 66.5% of PDGF-treated joints and 62.6% of ABG-treated joints demonstrated 50% or greater bone bridging on CT scan ($p<0.001$; statistically significant for equivalence). PDGF has been approved for ankle and hindfoot arthrodesis in Canada, Australia, and New Zealand and is currently under review in the United States and Europe.

Recombinant human bone morphogenetic proteins (rhBMPs) stimulate mesenchymal stem cells to develop into osteogenic and chondrogenic cells during bone healing (9). Currently, rhBMP-2 (INFUSE; Medtronic, Minneapolis, MN) and rhBMP-7 (OP-1; Olympus Biotech Corp., Hopkinton, MA) have demonstrated utility in foot and ankle surgery (**Table 1.14.1**) (10-14). However, the literature is limited to level III and IV case series at this time. Technically, BMPs are used off-label for foot and ankle applications and are not covered by many insurance policies.
SUMMARY

- According to level I clinical evidence (8), rhPDGF (Augment) is statistically equivalent to autologous bone graft for achieving arthrodesis in the foot and ankle. This product is currently under review for FDA approval.

- Several clinical studies (10-12) have reported higher union rates for hindfoot arthrodesis procedures augmented with rhBMP-2 (INFUSE), compared to non-supplemented controls.

REFERENCES

<table>
<thead>
<tr>
<th>Agent/Brand Name</th>
<th>Investigator</th>
<th>Level of Evidence</th>
<th>Procedure/Disease</th>
<th>Application</th>
<th>Combined Treatments</th>
<th>Comparison Group</th>
<th>Number of patients</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMP-2 (INFUSE)</td>
<td>Bibbo et al. (10)</td>
<td>Comparative study</td>
<td>Ankle or hindfoot arthrodesis</td>
<td>Surgical</td>
<td>No</td>
<td>Yes (historical controls)</td>
<td>69</td>
<td>3 months</td>
<td>Higher union rate (96%) than historical controls (48%)</td>
</tr>
<tr>
<td></td>
<td>DeVries et al. (11)</td>
<td>Comparative study</td>
<td>Revision tibiocalcaneal arthrodesis</td>
<td>Surgical</td>
<td>Yes (procedures were highly variable)</td>
<td>Yes (no BMP)</td>
<td>7 BMP vs. 16 no BMP</td>
<td>24 months</td>
<td>Higher union rate (71.4%) than controls (56.3%), but slower time to radiographic union (184 vs. 115 days)</td>
</tr>
<tr>
<td></td>
<td>Fourman et al. (12)</td>
<td>Comparative study</td>
<td>Ankle arthrodesis</td>
<td>Surgical</td>
<td>Ilizarov type frame</td>
<td>Yes (no BMP)</td>
<td>42 BMP vs. 40 control</td>
<td>3 months</td>
<td>Significantly higher union rate control (53%)</td>
</tr>
<tr>
<td>BMP-7 (OP-1)</td>
<td>Kanakaris et al. (13)</td>
<td>Case series</td>
<td>Ankle, subtalar, talonavicular, pubic or sacroiliac failed arthrodesis</td>
<td>Surgical</td>
<td>Bone graft (11 cases)</td>
<td>No</td>
<td>19 (7 in foot/ankle)</td>
<td>30 months</td>
<td>Clinical and radiographic improvement in 17 cases</td>
</tr>
<tr>
<td></td>
<td>Schubert et al. (14)</td>
<td>Case series</td>
<td>Forefoot procedures, tibiotalar or tibiotalocalcaneal arthrodesis, or distal tibial osteotomy</td>
<td>Surgical</td>
<td>Yes (procedures were highly variable)</td>
<td>No</td>
<td>38</td>
<td>10 months</td>
<td>Significant difference in union patients &lt;50 years of age (100%) vs patients &gt;50 (73%)</td>
</tr>
</tbody>
</table>