The Efficacy of Platelet-Derived Growth Factor as a Bone-Stimulating Agent

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KEYWORDS

• Bone graft substitute • Foot and ankle arthrodesis • Fusion
• Platelet-derived growth factor • rhPDGF-BB

KEY POINTS

- The use of recombinant human platelet-derived growth factor (PDGF)-BB/β-tricalcium phosphate has been approved in 2015 by the Food and Drug Administration (FDA) as an alternative to autograft during ankle and hindfoot fusion surgery.
- Augment Bone Graft upregulates osteoblast and blood vessel formation, which promotes chondrogenesis/osteogenesis at the fusion area of interest.
- In a phase III randomized, controlled trial, 66.5% of PDGF-treated joints and 62.6% of autograft-treated joints demonstrated fusion on computed tomography scanning at 24 weeks postoperatively.
- Clinical success was deemed directly dependent on good surgical technique, ensuring that bony contact between any joint surfaces intended for fusion was maximized while not impairing direct host bone apposition.

INTRODUCTION

Since the latter one-half of the 20th century, foot and ankle surgeons have focused on achieving rigid fixation to achieve successful arthrodesis. Alarmingly, however, more recent investigations have identified numerous risk factors capable of impairing osseous healing (diabetes, osteoporosis, tobacco use, age, corticosteroid therapy, and various pharmaceutical agents) and threatening the capacity to achieve uneventful fusion across diseased articular surfaces—even in the presence of a stable

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mechanical environment. Reported delayed and nonunion rates within these high-risk populations have averaged approximately 10%, but ranged as high as 40%.[1–3] In response to these findings, the past decade has ushered in a new era of orthobiologic research aimed at optimizing the healing environment during fusion surgery: focus has shifted from looking not just at the mechanical but also at the biological nature of these procedures. Specifically, recent advances in cellular and protein technology have led to the development of cutting edge growth factors and related biologic agents, which can serve as useful adjuncts to conventional therapies by promoting an elevated level of bone and soft tissue healing in this higher risk patient population. Platelet-derived growth factor (PDGF) represents a particular bone-stimulating agent of recent clinical interest that has proven effective for foot and ankle surgical patients through well-controlled, level I clinical evidence. It is likely that this protein technology will have a major positive impact on the future care of patients requiring hindfoot or ankle fusion procedures.

PDGF refers to a family of proteins that are released from platelets and macrophages in response to tissue injury and bone fracture.[4,5] The PDGF-BB dimer has been found to be the most potent form of the growth factor, and is both chemotactic and mitogenic for osteoblast progenitor cells as well as osteoblasts (the key bone-forming cell).[6,7] In addition, PDGF-BB has the capacity to promote new blood vessel formation (angiogenesis) even in the proximity of compromised host tissues, which allows for an influx of proinflammatory and chondrogenic/osteogenic agents to the fusion area of interest.[8] Based on more than a decade of rigorous basic science, animal, and human clinical research, the use of recombinant human PDGF-BB (rhPDGF-BB) in conjunction with a β-tricalcium phosphate (β-TCP) carrier (Augment Bone Graft, Wright Medical Technology, Inc., Memphis, TN) was approved in 2015 by the Food and Drug Administration (FDA) as a viable alternative to autograft in ankle and hindfoot fusion surgery. This therapy has already been available for commercial use and used quite successfully in Canada since 2009, Australia (2011), and New Zealand (2011). Alternative applications of rhPDGF-BB for bone defects in dental patients as well as for wound healing in neuropathic ulceration are also FDA approved. We aim to review the key preclinical and clinical trials leading to the approval of rhPDGF-BB for use in the foot and ankle surgical population.

PRECLINICAL INVESTIGATION

Between 1989 and 2009, several animal studies demonstrated the usefulness of rhPDGF-BB in potentiating bone healing. Al-Zube and colleagues,[9] examined the effect of intramedullary rhPDGF-BB treatment on femoral fracture healing in diabetic rats. An increase in early cellular proliferation was noted within the fracture callus of experimental rats as compared with controls. Further, rhPDGF-BB treatment increased the maximum torque to failure at 8 weeks after fracture and resulted in a greater callus bone area at 12 weeks after fracture. Similarly, Hollinger and colleagues[10] found a significant increase in torsional strength of fractured tibiae 5 weeks after rhPDGF-BB administration in geriatric, osteoporotic rats. The healed fractures and contralateral (nonfractured) tibiae had equivalent biomechanical properties at the 5-week time point. Additionally, local rhPDGF-BB treatment accelerated bone growth in a rabbit osteotomy model,[11] increased lumbar bone mineral density in baboons,[12] and enhanced bone healing in a rat model of distraction osteogenesis.[13] Local rhPDGF-BB, in combination with insulinlike growth factor-1, has also been shown to increase osseointegration of dental implants in a beagle dog model as well as promote bone regeneration of periodontal osseous defects in humans.[14–16]