PRODUCT APPROVAL INFORMATION PACKET

AUGMENT® Bone Graft

THE FIRST AND ONLY PROVEN ALTERNATIVE TO AUTOGRAFT IN ANKLE AND HINDFOOT ARTHRODESIS

rhPDGF-BB/β-TCP

WRIGHT. FOCUSED EXCELLENCE
The Time Has Come to Augment Your Fusion.

AUGMENT® Bone Graft is the first and only proven alternative to autograft in ankle and hindfoot arthrodesis.

Proven
Level 1 evidence of safety and effectiveness as a replacement to autograft in the largest F&A clinical trial ever conducted

Unique
The only biologic product specifically engineered, proven, and approved for ankle and hindfoot fusions

Labeled
Class III combination product specifically proven in, and labeled for, ankle and hindfoot arthrodesis via a rigorous PMA regulatory pathway

Safe
Proven safe through multiple clinical trials and successful commercial use since 2009 in Canada and 2011 in Australia and New Zealand, while eliminating the proven risks, morbidities, and costs associated with autograft harvest
AUGMENT® Bone Graft Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-6002

Biomimetic Therapeutics, LLC
Russ Pagano, Ph.D.
Vice President, Clinical and Regulatory Affairs
389 Nichol Mill Lane
Franklin, Tennessee 37067

September 1, 2015

Re: P100006
Trade/Device Name: Augment® Bone Graft
Filed: May 7, 2010
Amended: May 7, May 13, November 19, 2010; April 15, August 5, 2011; June 15, July 2,
September 13, 2012; September 3, September 5, 2013; February 7, March 31,
April 29, June 24, October 31, November 4, November 19, 2014; February 18,
and April 9, 2015
Procode: NOX

Dear Dr. Pagano:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for Augment® Bone Graft. This device is indicated for use as an alternative to autograft in arthrodesis (i.e., surgical fusion procedures) of the ankle (tibiotalar joint) and/or hindfoot (including subtalar, talonavicular, and calcaneocuboid joints, alone or in combination), due to osteoarthritis, post-traumatic arthritis, rheumatoid arthritis, psoriatic arthritis, avascular necrosis, joint instability, joint deformity, congenital defect, or joint arthropathy in patients with preoperative or intraoperative evidence indicating the need for supplemental graft material. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

CONFIDENTIAL INFORMATION REDACTED
If you have any questions concerning this approval order, please contact Sarah Brittain at 240-402-3141 or Sarah.Brittain@fda.hhs.gov.

Sincerely yours,

Mark N. Melkerson -S

Mark N. Melkerson
Director
Division of Orthopedic Devices
Office of Device Evaluation
Center for Devices and
Radiological Health
Choosing an Appropriate Graft for Hindfoot and Ankle Fusion Surgery

With the myriad of bone graft options available and continuing to grow, it has become increasingly difficult for surgeons and hospitals to avoid confusion and maintain a clear understanding of the clinical value, specific features, benefits, and appropriate uses of available graft choices.

<table>
<thead>
<tr>
<th>Categorization</th>
<th>Characteristics</th>
<th>Regulatory Pathway and Clinical Burden of Proof</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Recombinant Growth Factors</td>
<td>Proven alternative to Autograft</td>
<td>True biologic: Combination products with consistent, highly active signal proteins that drive bone regeneration</td>
<td>Pre-Market Approval (PMA) Safety and Efficacy in large pivotal clinical trial</td>
</tr>
<tr>
<td>Allograft Tissue</td>
<td>Bone Void Fillers</td>
<td>Osteoconductive and weakly osteoinductive putties with variable handling</td>
<td>Human tissue products (361 HCT/Ps) – No proof needed</td>
</tr>
<tr>
<td>Synthetic Scaffolds</td>
<td>Bone Void Fillers</td>
<td>Passive osteoconduction and fills space</td>
<td>Synthetics – 510(k)</td>
</tr>
</tbody>
</table>

1. Combination Growth Factor products composed of biologically active signals that promote chemotaxis, mitogenesis, angiogenesis, and/or osteoinductivity, rigorously reviewed by FDA and proven to be non-inferior to the Gold Standard, autograft in specific approved indications (see back page).
2. Void fillers with mineralized or demineralized bone, with or without cryopreserved cells from same donor intended for treatment of musculoskeletal defects.
3. Physical scaffolds composed of synthetic materials (e.g. calcium phosphate) intended to be used to fill bone voids.
4. Platelet-derived growth factor (rhPDGF-BB) and bone morphogenetic protein-2 (rhBMP-2) have been tested, reviewed and established as alternatives to autograft in multiple clinical studies for specific indications in foot & ankle (rhPDGF-BB only), spine/orthopaedic trauma (rhBMP-2 only) and dental (rhPDGF-BB & rhBMP-2).
5. Multiple clinical trials culminating in a large pivotal trial are typically required to prove that the combination device is both safe and efficacious in the specified indications.
6. Human tissues designated as 361 HCT/Ps are not regulated as medical devices and do not require a submission and/or review for commercialization. Tissue processors are required to register with FDA and follow Good Tissue Practices (GTP) per 21 CFR 1271.
7. A 510(k) clearance demonstrates that the device is substantially equivalent to a legally marketed device.
What Is the Evidence?

AUGMENT® Bone Graft is the first and only proven alternative to autograft in hindfoot and ankle arthrodesis.

- The role of PDGF in bone repair and regeneration is documented in at least ten peer-reviewed publications including two large-scale randomized, controlled clinical trials involving rhPDGF-BB/β-TCP.
- This Level-I clinical data is considered the most reliable quality of data based upon standards for peer-reviewed evidence.
2 How Was It Approved?

AUGMENT® Bone Graft was approved via the rigorous PMA pathway by the U.S. FDA as a Class III combination medical device/drug product.

- The PMA application was supported by two pilot clinical trials, the largest prospective, randomized controlled clinical trial in foot and ankle history, and numerous preclinical studies.

3 How Should It Be Used?

Among the criteria for which patients undergoing hindfoot and ankle arthrodesis should receive AUGMENT® Bone Graft, the following factors should be considered:

- In the Randomized, controlled pivotal trial conducted to support U.S. FDA approval of AUGMENT® Bone Graft, 75% of the treated patients had one or more risk-factors for non-union. AUGMENT® Bone Graft treated patients were found to have equivalent clinical and radiographic outcomes and a better overall safety profile versus autograft (due to the elimination of harvest site pain and morbidity).¹

- A natural deficiency in PDGF-BB has been found to be correlated with non-union and poor bone formation in clinical and preclinical studies involving subjects with diabetes, osteoporosis and smokers.² ³ ⁴

- Unlike growth factors such as the bone morphogenetic proteins (BMPs), which lead solely to osteoblastic differentiation of cells at the implantation site, there are no reported incidences of ectopic bone formation.⁵

¹ DiGiovanni CW, et al., JBJS (2013)
² Verma, et al., Curr Orthop Pract (2011)
³ Hollinger, et al., JOR (2008)
⁵ Carragee EJ, et al., Spine J (2011)
AUGMENT® Bone Graft works in a unique way to stimulate the **key active processes** of early bone healing, as well as provide a scaffold to support new bone formation.

### ACTIVE EARLY HEALING SIGNALS

**Chemotaxis**

rhPDGF-BB attracts Mesenchymal Stem Cells (MSCs) to the local fusion site. | **FIGURE 1**

**Mitogenesis**

MSCs are stimulated to divide and proliferate in the presence of the higher concentration of rhPDGF-BB within the graft site. | **FIGURE 2**

**Angiogenesis**

rhPDGF-BB promotes the formation of new blood vessels at the site of healing by increasing vascular endothelial cell, pericyte, and smooth muscle responses.  
- PDGF-BB has been shown to upregulate VEGF production, leading to neoangiogenesis.

### ACTIVE LATE HEALING SIGNALS

**Osteoinduction**

Native endogenous factors, such as Bone Morphogenic Proteins (BMPs) are secreted from the local bony environment and induce the MSCs to mature into osteoblasts. These mature, bone forming cells will then lay down new bone to create a continuous scaffold, fusing the bone surfaces.

**Osteoconductivity**

The β-TCP component fills the surgical defect, reliably delivers the rhPDGF-BB over time, and provides a physical scaffold for new bone formation.

**Rigid Fixation**

In order to allow for proper healing, rigid fixation is used to stabilize the fusion site and allow the biologically active and passive processes to take place.

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Competitive Summary

<table>
<thead>
<tr>
<th>Feature</th>
<th>AUGMENT® Bone Graft</th>
<th>INFUSE® Bone Graft</th>
<th>Platelet-Rich Plasma (PRP)</th>
<th>DBM Putties</th>
<th>DBM w/ Allogenic Stem Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I Evidence Demonstrating safe &amp; effective use as alternative to autograft</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FDA approved for hindfoot and ankle fusions</td>
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<tr>
<td>Biologic specifically engineered and proven in hindfoot and ankle fusions</td>
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<td></td>
<td></td>
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<tr>
<td>Consistent &amp; reliable concentration, composition and activity</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td></td>
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<tr>
<td>Easy to administer/apply to surgical site</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Off-the-shelf (minimal preparation required)</td>
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<tr>
<td>Regulatory Classification</td>
<td>Class III – PMA Required (Safety &amp; Efficacy Evidence Required)</td>
<td>Class III – PMA Required (Safety &amp; Efficacy Evidence Required)</td>
<td>510k Clearance on disposables (no safety or effectiveness data on PRP)</td>
<td>510k Clearance (no clinical trials demonstrating safety and effectiveness) or HCT/P (Human Tissue) for homologous use – No Safety or Efficacy Evidence</td>
<td>HCT/P (Human Tissue) for homologous use – No Safety or Efficacy Evidence</td>
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</table>

AUGMENT® Price List

<table>
<thead>
<tr>
<th>Catalog #</th>
<th>Product</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>K20001510</td>
<td>AUGMENT Bone Graft 1.5cc</td>
<td>$1,895</td>
</tr>
<tr>
<td>K20003010</td>
<td>AUGMENT Bone Graft 3.0cc</td>
<td>$3,495</td>
</tr>
<tr>
<td>CK20004510</td>
<td>AUGMENT Bone Graft 4.5cc*</td>
<td>$4,995</td>
</tr>
</tbody>
</table>

*4.5cc AUGMENT® Bone Graft Convenience Kit consists of (1) 3cc AUGMENT® Bone Graft Kit and (1) 1.5cc AUGMENT® Bone Graft Kit
Peer-Reviewed Clinical Evidence


*FDA did not base its approval of AUGMENT® Bone Graft on radiologic findings from the pivotal study, but instead relied on clinical outcomes.


5. Glazebrook, Mark; Daniels, Timothy R.; Abidi, Nicholas A.; Younger, Alastair; DiGiovanni, Christopher W. Role of Platelet-derived Growth Factor in Hindfoot Fusion. Techniques in Foot & Ankle Surgery. 11(1):34-38, March 2012. doi: 10.1097/BTF.0b013e3182469626


* AUGMENT® Bone Graft is only approved for ankle and hindfoot fusions. This list was compiled in 2016. It includes references cited by Wright Medical Technology, Inc. scientists in their protocols, reports, and papers. These documents focus on the rhPDGF-BB platform technology and other topics of relevance to the product pipeline at Wright. This list is updated regularly.


Peer-Reviewed Pre-Clinical Evidence


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**Supplemental Evidence**


The Importance of Sufficient Graft Material in Achieving Foot or Ankle Fusion.

DiGiovanni CW1, Lin SS2, Daniels TR3, Glazebrook M4, Evangelista P5, Donahue R6, Beasley W6, Baumhauer JF7.

Abstract

BACKGROUND:
Nonunion, an important complication following foot and ankle arthrodesis, causes substantial morbidity and disability. In patients undergoing hindfoot and ankle arthrodesis, autogenous bone graft (autograft) or a suitable alternative is often used to promote osseous fusion across the joint. This study assessed the importance of adequate graft material in the fusion space to achieve joint fusion during ankle and hindfoot arthrodesis.

METHODS:
This study used data from a previously published clinical trial of grafting material (recombinant human platelet-derived growth factor-BB with beta-tricalcium phosphate [rhPDGF-BB/β-TCP] or autograft) for healing in hindfoot and ankle arthrodesis to correlate the amount of graft fill at 9 weeks with ultimate healing. Patients who received supplemental graft material for ankle or hindfoot arthrodesis for end-stage ankle or hindfoot arthritis were stratified according to nonunion risk factors and surgical fusion site. Patients underwent arthrodesis using standard rigid internal fixation. Graft fill was defined as “adequate” if the material occupied ≥50% of the cross-sectional area of the fusion space on a computed tomography (CT) scan made at 9 weeks. Fusion was defined as osseous bridging of ≥50% of each articulation on a CT scan made at 24 weeks. Three hundred and seventy-nine patients with 573 joints (383 managed with rhPDGF-BB/β-TCP and 190 managed with autograft) that underwent arthrodesis had complete follow-up with 9-week and 24-week CT scans available.

RESULTS:
Overall, 472 (82%) of 573 joints had adequate graft fill; of those, 383 (81%) were successfully fused at 24 weeks compared with 21 (21%) of 101 joints without adequate graft fill (p < 0.0001). Absolute fusion rate differences (joints with adequate fill minus those without adequate fill) were consistent across joints (61% to 63%) and for graft materials. The overall odds ratio (OR) of successful fusion in joints with adequate graft fill compared with those without adequate graft fill was 16.4 (95% confidence interval, 9.6 to 27.9).

CONCLUSIONS:
This study demonstrates an association between the amount of graft material and successful hindfoot and ankle arthrodesis. Graft material filling of ≥50% of the fusion space at 9 weeks, regardless of type or origin, was associated with significantly higher fusion rates at 24 weeks.

LEVEL OF EVIDENCE:
Therapeutic Level II. See Instructions for Authors for a complete description of levels of evidence.

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PMID: 27489316 DOI: 10.2106/JBJS.15.00879


Collaborators (41)


Author Information

1Department of Orthopaedic Surgery, The Warren Alpert School of Medicine at Brown University, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903, USA. christopher_DiGiovanni@brown.edu

Abstract

Background

Joint arthrodesis employing autogenous bone graft (autograft) remains a mainstay in the treatment of many foot and ankle problems. However, graft harvest can lead to perioperative morbidity and increased cost. We tested the hypothesis that purified recombinant human platelet-derived growth factor-BB (rhPDGF-BB) homodimer combined with an osteoconductive matrix (beta-tricalcium phosphate [β-TCP]) would be a safe and effective alternative to autograft.

Methods

A total of 434 patients were enrolled in thirty-seven clinical sites across North America in a prospective, randomized (2:1), controlled, non-inferiority clinical trial to compare the safety and efficacy of the combination rhPDGF-BB and β-TCP with those of autograft in patients requiring hindfoot or ankle arthrodesis. Radiographic, clinical, functional, and quality-of-life end points were assessed through fifty-two weeks postoperatively.

Results

Two hundred and sixty patients (394 joints) underwent arthrodesis with use of rhPDGF-BB/β-TCP. One hundred and thirty-seven patients (203 joints) underwent arthrodesis with use of autograft. With regard to the primary end point, 159 patients (61.2% [262 joints (66.5%)]) in the rhPDGF-BB/β-TCP group and eighty-five patients (62.0% [127 joints (62.6%)]) in the autograft group were fused as determined by computed tomography at six months (p < 0.05). Clinically, 224 patients (86.2%) [348 joints (88.3%)]) in the rhPDGF-BB/β-TCP group were considered healed at fifty-two weeks, compared with 120 patients (87.6% [177 joints (87.2%)]) in the autograft group (p = 0.008). Overall, fourteen of sixteen secondary end points at twenty-four weeks and fifteen of sixteen secondary end points at fifty-two weeks demonstrated statistical non-inferiority between the groups, and patients in the rhPDGF-BB/β-TCP group were found to have less pain and an improved safety profile.

Conclusions

In patients requiring hindfoot or ankle arthrodesis, treatment with rhPDGF-BB/β-TCP resulted in comparable fusion rates, less pain, and fewer side effects as compared with treatment with autograft.

Comment In


PMID: 23824386 [PubMed - indexed for MEDLINE]

Note: FDA did not base its approval of AUGMENT® Bone Graft on radiologic findings from the pivotal study, but instead relied on clinical outcomes.

* AUGMENT® Bone Graft is only approved for ankle and hindfoot fusions. This list was compiled in 2016. It includes references cited by Wright Medical Technology, Inc. scientists in their protocols, reports, and papers. These documents focus on the rhPDGF-BB platform technology and other topics of relevance to the product pipeline at Wright. This list is updated regularly.

The role of recombinant human platelet-derived growth factor-BB (rhPDGF-BB) in orthopaedic bone repair and regeneration.

Friedlaender GE*, Lin S, Solchaga LA, Snel LB, Lynch SE.

AUTHOR INFORMATION

1Department of Orthopaedics and Rehabilitation, Yale University School of Medicine, New Haven, CT 06520-8071, USA. gary.friedlaender@yale.edu

ABSTRACT

Recombinant human PDGF BB homodimer (rhPDGF-BB) is a potent recruiter of, and strong mitogenic factor for, cells crucial to musculoskeletal tissue repair, including mesenchymal stem cells (MSCs), osteogenic cells and tenocytes. rhPDGF-BB also upregulates angiogenesis. These properties allow rhPDGF-BB to trigger the cascade of bone and adjoining soft tissue repair and regeneration. This mechanism of action has been established in numerous preclinical and clinical studies. Demonstration of the safety and efficacy of rhPDGF-BB in the healing of chronic foot ulcers in diabetic patients and regeneration of alveolar (jaw) bone lost due to chronic infection from periodontal disease has resulted in two FDA-approved products based on this molecule. A third product is in late stages of clinical development, with pilot and pivotal clinical studies of rhPDGF-BB mixed with an osteoconductive bone matrix (Augment® Bone Graft) in foot and ankle fusions demonstrating that this product is at least as effective as bone autograft, and has an improved safety profile. Additional combinations of rhPDGF-BB with tissue-specific matrices are also being studied clinically in additional musculoskeletal indications.

PMID: 23432673 [PubMed - indexed for MEDLINE]


Effect of implantation of AUGMENT® Bone Graft on serum concentrations of platelet-derived growth factors: a pharmacokinetic study.

Solchaga LA*, Daniels T, Roach S, Beasley W, Snel LB.

AUTHOR INFORMATION

BioMimetic Therapeutics Inc., 389 Nichol Mill Lane, Franklin, TN 37067, USA. lsolchaga@biomimetics.com

ABSTRACT

BACKGROUND

AUGMENT® Bone Graft is a bone graft substitute intended to be used as an alternative to autologous bone graft in the fusion of hindfoot and ankle joints. AUGMENT® Bone Graft is a combination device comprised of beta-tricalcium phosphate (β-TCP) and recombinant human platelet-derived growth factor BB homodimer (rhPDGF-BB).

OBJECTIVE

This human pharmacokinetic study was undertaken to assess the effect of AUGMENT® Bone Graft implantation on the serum concentration of platelet-derived growth factors (PDGFs).

METHODS

Under the terms of a Research Ethics Board-approved protocol, AUGMENT® Bone Graft was implanted in patients (n = 7) undergoing hindfoot and ankle arthrodesis procedures requiring graft material. The control cohort of the study (n = 4) received autologous bone graft. The serum concentrations of PDGF isoforms AA, AB and BB in blood samples, obtained prior to and at ten time points (up to 7 days) after surgery, were measured using enzyme-linked immunosorbent assays (ELISA).

RESULTS

The serum concentration of PDGF-BB did not vary significantly from baseline (median of the combined cohorts 3.89 ng/mL) throughout the course of the study. The serum concentrations of PDGF-AA, PDGF-AB and total PDGF did not deviate from their baseline values (medians of the combined cohorts were 2.87, 14.95 and 20.19 ng/mL for PDGF-AA, PDGF-AB and total PDGF, respectively) except for the last time point in which they were increased (medians for the combined cohorts were CONTINUED ON NEXT PAGE

* AUGMENT® Bone Graft is only approved for ankle and hindfoot fusions. This list was compiled in 2016. It includes references cited by Wright Medical Technology, Inc. scientists in their protocols, reports, and papers. These documents focus on the rhPDGF-BB platform technology and other topics of relevance to the product pipeline at Wright. This list is updated regularly.
Abstracts

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Techniques in Foot & Ankle Surgery:
March 2012 - Volume 11 - Issue 1 - p 34–38
doi: 10.1097/BTF.0b013e3182469626

**Role of Platelet-derived Growth Factor in Hindfoot Fusion**

Glazebrook, Mark MSC, PhD, MD, FRCS(C), Dip Sports Med.; Daniels, Timothy R. MD, FRCS(C)†; Abidi, Nicholas A. MD‡; Younger, Alastair MSc MD, FRCSC§; DiGiovanni, Christopher W. MD

**ABSTRACT**

Bone healing that is orchestrated by osteoblasts and osteoclasts is regulated by a complex interaction between biochemical factors such as cytokines and growth factors. One of the critical early growth factors that have an influence on healing is platelet-derived growth factor (PDGF). PDGF is a family of polypeptides that has the ability to attract and stimulate the metabolic activity of mesenchymal cells, stimulating a repair process that includes increased bone formation. Recently, a fully synthetic bone graft material composed of recombinant human platelet-derived growth factor and a β-tricalcium phosphate matrix under the name AUGMENT® Bone Graft was shown to be a safe alternative to autogenous bone graft for hindfoot fusion operations. This review provides an overview of the role of PDGF in the biology of bone healing and examines the clinical utility and most recent literature regarding efficacy of the use of PDGF as a safe alternative to autogenous bone graft for hindfoot fusion operations. Finally, the surgical procedure of ankle arthrodesis is described as an example of how PDGF may be used for surgical treatment of end-stage hindfoot arthritis.

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**Recombinant human PDGF-BB in foot and ankle fusion.**

DiGiovanni CW1, Lin S, Pinzur M.

**AUTHOR INFORMATION**

Department of Orthopedic Surgery, The Warren Alpert School of Medicine at Brown University, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903, USA. christopher_DiGiovanni@brown.edu

**ABSTRACT**

Autogenous bone graft (autograft) is currently the gold standard for augmenting bone repair and fusion procedures of the foot and ankle. The time, cost and morbidity involved in obtaining autograft, however, are well documented and legitimate concerns remain surrounding this intervention. Endogenous human PDGF is chemotactic and mitogenic for osteoblasts and undifferentiated osteoprogenitor cells, and upregulates expression of cytokines necessary for osseous and soft tissue healing and regeneration. The BB isoform of PDGF, and the biosynthetic replica recombinant human PDGF-BB, is a key regulatory molecule in bone homeostasis, repair and regeneration. When combined with a β-tricalcium phosphate osteoconductive matrix, recombinant human PDGF-BB mitigates a number of problems associated with the use of autograft and, based on its preclinical performance and early clinical success, appears to be an equally effective and perhaps an even safer alternative to autograft for foot and ankle fusion (arthrodesis) procedures.

PMID: 22404772 [PubMed - indexed for MEDLINE]
Prospective, randomized, multi-center feasibility trial of rhPDGF-BB versus autologous bone graft in a foot and ankle fusion model.


AUTHOR INFORMATION
University Orthopaedics, Inc., 100 Butler Dr., Providence, RI 02906, USA. Christopher_DiGiovanni@brown.edu

ABSTRACT
BACKGROUND
The increased morbidity and surgical time associated with harvesting autologous bone graft (ABG) have encouraged surgeons to develop synthetic orthobiologic alternatives. The recombinant form of platelet-derived growth factor (rhPDGF-BB), an angiogenic, mitogenic, and chemotactic cytokine, has been shown to significantly enhance bone formation in human periodontal osseous defects when combined with a tricalcium phosphate carrier (β-TCP). The purpose of this prospective, controlled, randomized, multi-center feasibility clinical trial was to compare the safety and efficacy of this biosynthetic bone graft substitute (AUGMENT® Bone Graft) to ABG during ankle and hindfoot fusion.

MATERIALS AND METHODS
Twenty adult subjects requiring ankle or hindfoot fusion from three U.S. centers were enrolled and randomized in a 2:1 ratio to receive AUGMENT® or ABG, respectively. Surgical approach and fixation techniques were standardized, and minimum followup was 9 months. The primary endpoint was radiographic osseous union, evaluated by a blinded independent radiologist. Secondary endpoints included assessment of clinical success, union rate by serial computed tomography (CT) examination, time to full weightbearing, AOFAS Ankle-Hindfoot Score (AOFAS), Foot Function Index (FFI), Short Form-12 (SF-12), and Visual Analog pain assessment Scale (Pain VAS).

RESULTS
At 36 weeks, 77% (10/13) of the AUGMENT® and 50% (3/6) of the ABG patients were fused based on radiographic criteria. There were two nonunions in theAUGMENT® group (9%, 2/14). Healing rates based on 12 week CT scanning (50% osseous bridging) were 69% (9/13) in the AUGMENT® and 60% (3/5) in the ABG groups, respectively. All functional outcome measures (FFI, AOFAS, SF-12), as well as the VAS pain scores, improved in both groups over time. Surgical procedure times lasted an average 26 minutes longer for the ABG as compared to the AUGMENT® populations. There were no device related serious adverse events in this study.

CONCLUSION
Based on the available data, the rate of radiographic union, time to full weightbearing, and outcomes scores between the AUGMENT® and ABG subjects appear comparable. AUGMENT® may represent a safe and efficacious treatment alternative to ABG during foot and ankle arthrodesis.

PMID: 21733435 [PubMed - indexed for MEDLINE]
Abstracts

The evolution of rhPDGF-BB in musculoskeletal repair and its role in foot and ankle fusion surgery.
DiGiovanni CW*, Petricek JM.

AUTHOR INFORMATION
Division of Foot and Ankle Surgery, Department of Orthopaedic Surgery, The Warren Alpert School of Medicine at Brown University, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02904, USA. christopher_DiGiovanni@brown.edu

ABSTRACT
Platelet-derived growth factor (PDGF) is one of the most thoroughly studied proteins in the body. Research has progressively highlighted the role of PDGF during wound healing and in the bone repair cascade. This research has resulted in FDA approval of 2 products containing a recombinant version of the protein, rhPDGF-BB, for treating chronic diabetic foot ulcers and periodontal bone defects. This article reviews the applicable basic science and mechanisms of action of PDGF, with attention to the increasingly defined role of rhPDGF-BB in initiating bone regeneration. The most recent data from prospective clinical trials evaluating the use of rhPDGF-BB in combination with beta tricalcium phosphate as a substitute for autogenous bone graft in hindfoot and ankle arthrodesis are also summarized.

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PMID: 21056861 [PubMed - indexed for MEDLINE]

Prospective clinical pilot trial in a single cohort group of rhPDGF in foot arthrodeses.
Daniels T*, DiGiovanni C, Lau JT, Wing K, Younger A.

AUTHOR INFORMATION
1St. Michael’s Hospital, University of Toronto, 55 Queen Street East, Suite 800, Toronto, Ontario MSC 1R6, Canada. danielst@smh.toronto.on.ca

ABSTRACT
BACKGROUND
AUGMENT® Bone Graft, a fully synthetic bone graft material composed of recombinant human PDGF and a calcium phosphate matrix (rhPDGF/TCP), has been considered as a possible alternative to autogenous bone graft. Before proceeding with randomized control studies comparing rhPDGF/TCP to autograft bone, a human trial to assess efficacy and safety was required.

MATERIALS AND METHODS
The current study was a prospective, open-label, multi-center trial designed to evaluate rhPDGF in a calcium phosphate matrix (AUGMENT® Bone Graft). Sixty patients requiring hindfoot or midfoot fusion were prospectively followed for 36 weeks. All patients received 0.9 to 2.7 mg of rhPDGF at the fusion sites and returned for clinical and radiographic review at Day 7 to 14 and Weeks 6, 9, 12, 16, 24, and 36. Computerized tomography (CT) scans of the fusion site were obtained at the 6- and 12-week postoperative appointment, with an additional CT scan at 16 weeks if required.

RESULTS
No patients suffered a serious adverse event caused by rhPDGF. CT scan evaluation at 12- to 16-week time periods revealed moderate or complete osseous bridging of 75% (44/59) at 36 weeks.

CONCLUSION
These results indicate that rhPDGF is a safe product and provides clinical/radiographic outcomes that justify the pursuit of randomized controlled studies comparing rhPDGF/TCP to autograft.

PMID: 20557811 [PubMed - indexed for MEDLINE]

* AUGMENT® Bone Graft is only approved for ankle and hindfoot fusions. This list was compiled in 2016. It includes references cited by Wright Medical Technology, Inc. scientists in their protocols, reports, and papers. These documents focus on the rhPDGF-BB platform technology and other topics of relevance to the product pipeline at Wright. This list is updated regularly.
Abstracts


**Recombinant human platelet-derived growth factor: biology and clinical applications.**

Hollinger JO, Hart CE, Hirsch SN, Lynch S, Friedlaender GE.

**AUTHOR INFORMATION**

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**ABSTRACT**

The abilities of bone to remodel, fractures to repair, and bone grafts to incorporate are all fundamental reflections of the bone remodeling cycle. This process is characterized by the recruitment and differentiation of osteoblastic and osteoclastic cell populations, whose cellular activities are coordinated and regulated by an elaborate system of growth factors and cytokines. One of the crucial biological factors responsible for reparative osseous activity is platelet-derived growth factor (PDGF). The potent stimulatory effects of PDGF as a chemoattractant and mitogen for mesenchymal cells (including osteogenic cells), along with its ability to promote angiogenesis, have been demonstrated in a variety of preclinical models predicting maxillofacial, spine and appendicular skeletal, and soft-tissue applications. The biological profile of PDGF, including its ability to recruit osteoprogenitor cells, makes it particularly suited to address the skeletal defects that are seen with comorbid conditions such as osteoporosis, diabetes, and the effects of smoking. The clinical success and safety that have been demonstrated with use of recombinant human PDGF (rhPDGF) in the repair of periodontal defects have led to U.S. Food and Drug Administration (FDA) approval of rhPDGF for this indication. Ongoing pilot and pivotal trials in the United States and internationally will continue to clarify the promising role of PDGF in the treatment of challenging skeletal disorders.

PMID: 18292357 [PubMed - indexed for MEDLINE]


**Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: results of a large multicenter randomized controlled trial.**

Nevins M, Giannobile WV, McGuire MK, Kao RT, Mellonig JT, Hinrichs JE, McAllister BS, Murphy KS, McClain PK, Nevins ML, Paquette DW, Han TJ, Reddy MS, Lavin PT, Genco RJ, Lynch SE.

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**ABSTRACT**

**BACKGROUND**

Growth factors are generally accepted to be essential mediators of tissue repair via well-established mechanisms of action that include stimulatory effects on angiogenesis and cellular proliferation, ingrowth, differentiation, and matrix biosynthesis. The aim of this study was to evaluate in a large-scale, prospective, blinded, and randomized controlled clinical trial the safety and effectiveness of purified recombinant human platelet-derived growth factor (rhPDGF-BB) mixed with a synthetic beta-tricalcium phosphate (beta-TCP) matrix for the treatment of advanced periodontal osseous defects at 6 months of healing.

**METHODS**

Eleven clinical centers enrolled 180 subjects, each requiring surgical treatment of a 4 mm or greater intrabony periodontal defect and meeting all inclusion and exclusion criteria. Subjects were randomized into one of three treatment groups: 1) beta-TCP + 0.3 mg/ml rhPDGF-BB in buffer; 2) beta-TCP + 1.0 mg/ml rhPDGF-BB in buffer; and 3) beta-TCP + buffer (active control). Safety data were assessed by the frequency and severity of adverse events. Effectiveness measurements included clinical attachment levels (CAL) and gingival recession (GR) measured clinically and linear bone growth (LBG) and percent bone fill (% BF) as assessed radiographically by an independent centralized radiology review center. The area under the curve (AUC), an assessment of the rate of healing, was also calculated for CAL measurements. The surgeons, clinical and radiographic evaluators, patients, and study sponsor were all masked with respect to treatment groups.

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Abstracts

RESULTS
CAL gain was significantly greater at 3 months for group 1 (rhPDGF 0.3 mg/ml) compared to group 3 (beta-TCP + buffer) (3.8 versus 3.3 mm; P = 0.032), although by 6 months, this finding was not statistically significant (P = 0.11). This early acceleration of CAL gain led to group 1 exhibiting a significantly greater rate of CAL gain between baseline and 6 months than group 3 as assessed by the AUC (68.4- versus 60.1-mm weeks; P = 0.033). rhPDGF (0.3 mg/ml)-treated sites also had significantly greater linear bone gain (2.6 versus 0.9 mm, respectively; P < 0.001) and percent defect fill (57% versus 18%, respectively; P < 0.001) than the sites receiving the bone substitute with buffer at 6 months. There was less GR at 3 months in group 1 compared to group 3 (P = 0.04); at 6 months, GR for group 1 remained unchanged, whereas there was a slight gain in gingival height for group 3 resulting in comparable GR. There were no serious adverse events attributable to any of the treatments.

CONCLUSIONS
To our knowledge, this study is the largest prospective, randomized, triple-blinded, and controlled pivotal clinical trial reported to date assessing a putative periodontal regenerative and wound healing therapy. The study demonstrated that the use of rhPDGF-BB was safe and effective in the treatment of periodontal osseous defects. Treatment with rhPDGF-BB stimulated a significant increase in the rate of CAL gain, reduced gingival recession at 3 months post-surgery, and improved bone fill as compared to a beta-TCP bone substitute at 6 months.

COMMENT IN
The era of biologics and reparative medicine: a pivotal clinical trial of platelet-derived growth factor for periodontal regeneration. [J Periodontol. 2005]
Synthetic platelet-derived growth factor (rhPDGF) may improve bone fill over beta-tricalcium phosphate (beta-TCP) alone. [J Evid Based Dent Pract. 2007]
PMID: 16332231 [PubMed - indexed for MEDLINE]

Peer-Reviewed Pre-Clinical Evidence

Safety of recombinant human platelet-derived growth factor-BB in AUGMENT® Bone Graft.

Solchaga LA1, Hee CK, Roach S, Snel LB.

AUTHOR INFORMATION
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ABSTRACT
This article discusses nonclinical and clinical data regarding the safety of recombinant human platelet-derived growth factor-BB as a component of the AUGMENT® Bone Graft. AUGMENT® is a bone graft substitute intended to be used as an alternative to autologous bone graft in the fusion of hindfoot and ankle joints. Nonclinical studies included assessment of the pharmacokinetic profile of intravenously administered recombinant human platelet-derived growth factor-BB in rat and dog, effects of intravenous administration of recombinant human platelet-derived growth factor-BB in a reproductive and development toxicity study in rats, and chronic toxicity and carcinogenicity of Augment in a 12-month implantation model. These studies showed that systemic exposure was brief and clearance was rapid. No signs of toxicity, carcinogenicity, or tumor promotion were observed even with doses far exceeding the maximum clinical dose. Results of clinical trials (605 participants) and commercial use of recombinant human platelet-derived growth factor-BB containing products indicate that these products are not associated with increased incidence of adverse events or cancer. The safety data presented provide evidence that recombinant human platelet-derived growth factor-BB is a safe therapeutic when used in combination products as a single administration during surgical procedures for bone repair and fusion. There is no evidence associating use of recombinant human platelet-derived growth factor-BB in Augment with chronic toxicity, carcinogenicity, or tumor promotion.

KEYWORDS:
Platelet-derived growth factor; arthrodesis rhPDGF-BB.; bone graft substitute; bone repair; safety
PMID: 22511993 [PubMed] PMCID: PMC3324841
Abstracts


**PDGF in bone formation and regeneration: new insights into a novel mechanism involving MSCs.**

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**ABSTRACT**

With the identification of mesenchymal stem cells (MSCs) as pericytes, the details of bone formation, regeneration, and repair take on new meaning. Growth factors and other signaling molecules together with MSCs play important roles in these bone fabrication processes. However, the interaction of these cellular healing components is not completely understood. The formation of new vasculature is critical to regeneration and repair as both the driver and orientor of new bone formation. In this context, MSCs are proposed to be largely derived from pericytes associated with the vasculature. A comprehensive perspective is presented in which signaling molecules such as PDGF take on new significance in the vasculature-pericyte-MSC-osteoblast dynamics. Current data suggest that PDGF could function as a central connector between the cellular components and contributors of the osteoblast differentiation program. The inference is that PDGF could function at sites of injury to mobilize the pericytes from their abluminal location, stimulate mitotic expansion of these cells and help organize them. In this way, PDGF both contributes to the osteogenic lineage and helps to stabilize newly forming vessels that act to drive the multistep, multicomponent cascade of new bone formation. This thesis explains how PDGF functions as a powerful therapeutic agent for bone formation and repair.

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**Correlation of growth factor levels at the fusion site of diabetic patients undergoing hindfoot arthrodesis and clinical outcome**

Current Orthopaedic Practice 04/2011; 22(3):251–256. DOI: 10.1097/BCO.0b013e318212584c

**AUTHOR**

Ravi Verma, John D. Koerner, Eric A. Breitbart, David Pagila, Swaroopa Vaidya, Michael S. Pnnzur

**ABSTRACT BACKGROUND:**

The purpose of this study was to quantify the levels of growth factors (platelet-derived growth factor [PDGF] AB, vascular endothelial growth factor [VEGF], insulin-like growth factor [IGF] 1, and transforming growth factor [TGF]-β1) within bone samples at the fusion site of diabetic patients undergoing hindfoot arthrodesis to determine any correlation with successful fusion.

**METHODS**

The study included 10 adult diabetic patients from one US center, with an average age of 57.9 years (range 49–71 years). Interventions included hindfoot arthrodeses with a fixator (n=8) and pantalar arthrodeses with fixator (n=2). During each procedure, a bony bed sample was taken from the fusion site and frozen. This local bone bed was analyzed for growth factors using ELISA kits. A platelet-rich plasma (PRP) concentration was applied to each fusion site during the procedure.

**RESULTS**

Three of the ten patients had a nonunion. After normalizing to bicinchoninic acid assay (BCA) total protein levels, a 70% decrease in PDGF-AB (0.044 pg/μg non-union to 0.149 pg/μg union; P=0.016) and a 44% decrease in VEGF (0.522 pg/μg non-union to 0.924 pg/μg union; P=0.031) were observed in the three nonunion bone samples compared with the arthrodesis group. No difference existed in the levels of IGF-1 between the groups. Insignificantly higher levels of TGF-β1 were detected in the nonunion group (0.199 ng/μg non-union to 0.142 ng/μg union; P=0.544). Conclusions: Significant differences in local growth factor (PDGF, VEGF) levels exist between diabetic patients who achieve union and non-union. Potentially, growth factor levels, PDGF-AB and VEGF, in bone may affect the outcome of successful fusion.

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arthrodens in diabetic patients. This study supports the concept that growth factor levels within the fusion site of a diabetic patient may affect the outcome of a successful hindfoot arthrodesis.


The effect of bone morphogenetic protein-2, bone morphogenetic protein-7, parathyroid hormone, and platelet-derived growth factor on the proliferation and osteogenic differentiation of mesenchymal stem cells derived from osteoporotic bone.

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ABSTRACT

INTRODUCTION

It has been previously shown that in patients with osteoporosis, mesenchymal stem cell (MSC) growth rate and osteogenic potential is decreased contributing to inferior fracture consolidation. The aim of this study was to investigate the effect of bone morphogenetic protein-2 (BMP-2), BMP-7, parathyroid hormone (PTH), and platelet-derived growth factor (PDGF) on proliferation and osteogenic differentiation of MSCs derived from patients with osteoporosis.

MATERIALS AND METHODS

Trabecular bone was obtained from 10 patients (four males, mean age 76 years) with lower extremity osteoporotic fractures. MSCs were isolated by enzymatic digestion. Functional assays of proliferation and osteogenic differentiation were performed under the influence of a wide range of concentrations of BMP-2, BMP-7, PTH, and PDGF-BB. Proliferation was assessed using CFU-F and XTT assays. Osteogenic differentiation was assessed by alkaline phosphatase activity and total calcium production.

RESULTS

MSC proliferation was found to be stimulated by supplementation with BMP-7 and PDGF-BB, whereas BMP-2 and PTH had little effect. The largest increase in proliferation rate was observed after administration 100 ng/mL of BMP-7. All four molecules induced alkaline phosphatase activity and calcium production in growing osteoblasts with a dose-dependent effect noted. BMP-2 and BMP-7 at their highest studied concentration (100 ng/mL) produced a threefold increase in the osteogenic potential of MSCs.

CONCLUSION

BMP-7, BMP-2, PTH, and PDGF-BB were observed to have a positive effect on osteogenic differentiation of MSCs. BMP-7 and PDGF-BB (in high doses) could be considered most potentially advantageous because they enhance both proliferation and osteogenic differentiation of MSCs derived from elderly osteoporotic bone.

PMID: 20736793 [PubMed - indexed for MEDLINE]
Abstracts

Recombinant human platelet-derived growth factor-BB augmentation of new-bone formation in a rat model of distraction osteogenesis.


AUTHOR INFORMATION
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ABSTRACT

BACKGROUND
Distraction osteogenesis creates a challenging bone-healing environment with protracted demand for cells of the osteoblast lineage. Platelet-derived growth factor-BB (PDGF-BB) is an osteoblast mitogen and chemotaxin that has been shown to accelerate and/or enhance bone-healing in several preclinical studies. The purpose of the present study was to determine whether recombinant human platelet-derived growth factor-BB (rhPDGF-BB) would have a similar effect on regenerate healing after distraction osteogenesis.

METHODS
Unilateral 7-mm mid-diaphyseal femoral lengthening procedures were performed in eighty-three male Sprague-Dawley rats that were separated into five experimental groups. During the distraction period (Days 7 to 28), each animal received a weekly 50-microL injection of either sodium acetate buffer, bovine collagen dissolved in sodium acetate buffer, or one of three concentrations of rhPDGF-BB (100, 300, or 1000 microg/mL) into the distraction site. Animals from each group were killed on Days 35, 42, 49, 56, and 63. Healing was assessed with biweekly serial radiographs, micro-computed tomography of the explanted bones, and histologic analysis.

RESULTS
rhPDGF-BB treatment significantly increased new-bone formation at the midconsolidation time points (Days 42, 49, and 56) as well as the union rate. On Day 49 regenerate bone volume was significantly greater in each of the three rhPDGF-BB-treated groups than in the controls (p < 0.05, p = 0.0002, and p < 0.05 for the 100, 300, and 1000 microg/mL rhPDGF-BB groups, respectively), whereas on Day 42 regenerate bone volume was significantly greater in the 300 and 1000 microg/mL rhPDGF-BB groups than in the controls (p = 0.0002 and p < 0.05, respectively) and on Day 56 regenerate bone volume was significantly greater in the 100 and 300 microg/mL rhPDGF-BB groups than in the controls (p < 0.05 and p < 0.0001, respectively). The overall union rate was 40.4% (nineteen of forty-seven) in the rhPDGF-BB-treated animals, compared with 4.5% (one of twenty-two) in the controls (p = 0.01). The radiographic and histologic results were consistent with new-bone formation as quantified by micro-computed tomography, although they were less definitive.

CONCLUSIONS
The administration of exogenous rhPDGF-BB into the distraction site during diaphyseal distraction enhanced bone-healing in a rat model of distraction osteogenesis as evidenced by both increased regenerate new-bone formation and a higher union rate.

PMID: 19651957 [PubMed - indexed for MEDLINE]
Recombinant human platelet-derived growth factor BB (rhPDGF-BB) and beta-tricalcium phosphate/collagen matrix enhance fracture healing in a diabetic rat model.


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ABSTRACT
Diabetes mellitus is a common systemic disease that has been associated with poor fracture healing outcomes. The mechanism through which diabetes impairs bone regeneration is unknown. One possible mechanism may be related to either decreased or uncoordinated release of local growth factors at the fracture site. Indeed, previous studies have found reduced platelet-derived growth factor (PDGF) levels in the fracture callus of diabetic rats, suggesting that local application of PDGF may overcome the negative effects of diabetes and promote fracture healing. To test this hypothesis, low (22 microg) and high (75 ug) doses of recombinant human PDGF-BB (rhPDGF-BB) were applied directly to femur fracture sites in BB Wistar diabetic rats that were then compared to untreated or vehicle-treated animals. rhPDGF-BB treatment significantly increased early callus cell proliferation compared to that in control specimens. Low dose rhPDGF-BB treatment significantly increased callus peak torque values (p < 0.05) at 8 weeks after fracture as compared to controls. High dose rhPDGF-BB treatment increased callus bone area at 12 weeks postfracture. These data indicate that rhPDGF-BB treatment ameliorates the effects of diabetes on fracture healing by promoting early cellular proliferation that ultimately leads to more bone formation. Local application of rhPDGF-BB may be a new therapeutic approach to treat diabetes-impaired fracture healing.

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Platelet-derived growth factor stimulates osteoprotegerin production in osteoblastic cells.

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ABSTRACT
Osteoprotegerin (OPG) is a major regulator of osteoclastogenesis, bone resorption and vascular calcification. OPG is produced by various cell types including mesenchymally derived cells, in particular, osteoblastic cells. Here we show OPG production by osteoblastic cells was stimulated by platelet-derived growth factor (PDGF) in two human osteosarcoma cell lines (MG63, Saos-2), a mouse pre-osteoblastic cell line (MC3T3-E1) and human bone marrow stromal cells (hMSC) by 152%, 197%, 113% and 45% respectively over 24 h. OPG was measured in the cell culture medium by immunoassay. PDGF isoforms AA, BB and AB show similar stimulation of OPG production. Message for OPG was also increased similarly to the increased secretion into the culture medium. Using specific inhibitors of cell signalling we demonstrate that PDGF acts through the PDGF receptor, PKC, PI3K, ERK and P38 and not via NF-kB or JNK. The importance of PDGF in fracture healing suggests a role for OPG production in countering bone resorption during the early phase of this process.

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PMID: 18814141 [PubMed - indexed for MEDLINE]
Abstracts


PDGF receptor beta is a potent regulator of mesenchymal stromal cell function.


AUTHOR INFORMATION
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ABSTRACT
Mesenchymal stromal cells (MSCs) in bone marrow are important for bone homeostasis. Although platelet-derived growth factor (PDGF) has been reported to be involved in osteogenic differentiation of MSCs, the role remains controversial and the network of PDGF signaling for MSCs has not been clarified. To clarify the underlying regulatory mechanism of MSC functions mediated by PDGF, we deleted the PDGF receptor (PDGFR)beta gene by Cre-loxP strategy and examined the role of PDGF in osteogenic differentiation of MSCs and fracture repair. In cultured MSCs, the mRNA expression of PDGF-A, -B, -C, and -D as well as PDGFRalpha and beta was detected. Depletion of PDGFRbeta in MSCs decreased the mitogenic and migratory responses and enhanced osteogenic differentiation as evaluated by increased alkaline phosphatase (ALP) activity and mRNA levels of ALP, osteocalcin (OCN), bone morphogenetic protein (BMP) 2, Runx2, and osterix in quantitative RT-PCR. PDGF-BB, but not PDGF-AA, inhibited osteogenic differentiation accompanied by decreased ALP activity and mRNA levels, except for BMP2. These effects of PDGF-BB were eliminated by depletion of PDGFRbeta in MSCs except that PDGF-BB still suppressed osterix expression in PDGFRbeta-depleted MSCs. Depletion of PDGFbeta significantly increased the ratio of woven bone to callus after fracture. From the combined analyses of PDGF stimulation and specific PDGFRbeta gene deletion, we showed that PDGFRbeta signaling distinctively induces proliferative and migratory responses but strongly inhibits osteogenic differentiation of MSCs. The effects of PDGFRalpha on the osteogenic differentiation were very subtle. PDGFRbeta could represent an important target for guided tissue regeneration or tissue engineering of bone.

PMID: 18410236 [PubMed - indexed for MEDLINE]


Osteoclasts control osteoblast chemotaxis via PDGF-BB/PDGFR receptor beta signaling.

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ABSTRACT
BACKGROUND
Bone remodeling relies on the tightly regulated interplay between bone forming osteoblasts and bone digesting osteoclasts. Several studies have now described the molecular mechanisms by which osteoblasts control osteoclastogenesis and bone degradation. It is currently unclear whether osteoclasts can influence bone rebuilding.

METHODOLOGY/PRINCIPAL FINDINGS
Using in vitro cell systems, we show here that mature osteoclasts, but not their precursors, secrete chemotactic factors recognized by both mature osteoblasts and their precursors. Several growth factors whose expression is upregulated during osteoclastogenesis were identified by DNA microarrays as candidates mediating osteoblast chemotaxis. Our subsequent functional analyses demonstrate that mature osteoclasts, whose platelet-derived growth factor bb (PDGF-bb) expression is reduced by siRNAs, exhibit a reduced capability of attracting osteoblasts. Conversely, osteoblasts whose platelet-derived growth factor receptor beta (PDGFR-beta) expression is reduced by siRNAs exhibit a lower capability of responding to chemotactic factors secreted by osteoclasts.

CONCLUSIONS/SIGNIFICANCE
We conclude that, in vitro mature osteoclasts control osteoblast chemotaxis via PDGF-bb/PDGFR-beta signaling. This may provide one key mechanism by which osteoclasts control bone formation in vivo.

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**Accelerated fracture healing in the geriatric, osteoporotic rat with recombinant human platelet-derived growth factor-BB and an injectable beta-tricalcium phosphate/collagen matrix.**

Hollinger JO¹, Onikepe AO, MacKrell J, Einhorn T, Bradica G, Lynch S, Hart CE.

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**ABSTRACT**

Aging and osteoporosis contribute to decreased bone mass and bone mineral density as well as compromised fracture healing rates and bone repair quality. Consequently, the purpose of this study was to determine if recombinant human platelet-derived growth factor-BB (rhPDGF-BB) delivered in an injectable beta-tricalcium phosphate/collagen matrix would enhance tibial fracture healing in geriatric (>2 years of age), osteoporotic rats. A total of 80 rats were divided equally among four groups: Fracture alone; Fracture plus matrix; Fracture plus matrix and either 0.3 mg/mL or 1.0 mg/mL rhPDGF-BB. At 3 and 5 weeks, rats were euthanized and treatment outcome was assessed histologically, radiographically, biomechanically, and by micro-CT. Results indicated rhPDGF-BB-treated fractures in osteoporotic, geriatric rats caused a statistically significant time-dependent increase in torsional strength 5 weeks after treatment. The healed fractures were equivalent in torsional strength to the contralateral, unoperated tibiae. Data from the study are the first, to our knowledge, to underscore rhPDGF-BB efficacy in an injectable beta-tricalcium phosphate/collagen matrix accelerated fracture repair in a geriatric, osteoporotic rat model.

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PMID: 17676626 [PubMed - indexed for MEDLINE]


**Comprehensive analysis of chemotactic factors for bone marrow mesenchymal stem cells.**

Ozaki Y¹, Nishimura M, Sekiya K, Suehiro F, Kanawa M, Nikawa H, Hamada T, Kato Y.

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**ABSTRACT**

To understand which growth factors/cytokines can affect migration of mesenchymal stem cells (MSCs) to injured tissues, we compared the effects of many (26) growth factors/cytokines on the migration activity of rabbit and human MSCs using a microchemotaxis chamber. Among them, platelet-derived growth factor (PDGF)-BB, PDGF-AB, epidermal growth factor (EGF), HB-EGF, transforming growth factor (TGF-alpha), insulin growth factor (IGF-I), hepatocyte growth factor (HGF), fibroblast growth factor (FGF-2), and thrombin consistently enhanced the migration of rabbit and human MSCs at appropriate concentrations. PDGF-BB showed the greatest effect on migration. Various combinations of these factors further enhanced the migration of MSCs, whereas combinations of factors that shared common cell-surface receptors did not induce the additive stimulation. On the other hand, some combinations, including that of FGF-2 or thrombin with PDGF-BB, suppressed the migration activity of MSCs. These findings suggest that combinations of growth factors are important to eliciting the maximal chemotactic effect. The factors that induced the migration of MSCs also enhanced their proliferation, suggesting that migration and proliferation can take place simultaneously. The above factors were also effective in stimulating the migration of fibroblasts, but thrombin alone selectively enhanced the migration of MSCs, suggesting that thrombin is useful to stimulate migration of MSCs without migration of fibroblasts.

PMID: 17348810 [PubMed - indexed for MEDLINE]

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Abstracts


New blood vessel formation and expression of VEGF receptors after implantation of platelet growth factor-enriched biodegradable nanocrystalline hydroxyapatite.

Kilian O1, Alt V, Heiss C, Jonuleit T, Dingeldein E, Flesch I, Fidorra U, Wenisch S, Schnettler R.

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ABSTRACT
Vascular endothelial growth factor (VEGF) plays a key role for the interaction of osteoblasts and endothelial cells and, therefore, is an important factor for the osteointegration of bone substitutes. The aim of the current work was to study the effects of platelet growth factors (PLF) on new blood vessel formation and VEGF-receptors expression pattern in bone defects filled with nanocrystalline hydroxyapatite (HA) paste in miniature-pigs. Conventional histology, RT-PCR for VEGF and receptors mRNA, Western blot analysis, immunohistochemical staining and quantitative assessment of newly formed vessels was performed. HA enriched with platelet growth factor (HA/PLF+) led to an up-regulation of VEGF-R1 synthesis, a slightly enhanced number of newly formed vessels with higher sprouting activity compared with HA without PLF (HA/PLF-) filling defects. These observation are most likely attributable to a stimulating effect of TGF-ss from the platelet factor on VEGF expression in osteoblasts.

PMID: 16019434 [PubMed - indexed for MEDLINE]


To go or not to go: Migration of human mesenchymal progenitor cells stimulated by isoforms of PDGF.

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ABSTRACT
The recruitment of mesenchymal progenitor cells (MPCs) and their subsequent differentiation to osteoblasts is mandatory for bone development, remodeling, and repair. To study the possible involvement of platelet-derived growth factor (PDGF) isoforms, primary human MPCs and osteogenic differentiated progenitor cells (dOB) were examined for chemotaxic response to homodimeric human platelet-derived growth factor AA, -BB, and heterodimeric PDGF-AB. The role of PDGF receptors was addressed by preincubation with PDGF receptor alpha and beta chain specific antibodies. Migration of MPCs, dOB, and primary osteoblasts (OB) was stimulated by the addition of rhPDGF-AA, rhPDGF-BB, and rhPDGF-AB. The effect was highest in MPCs and for rhPDGF-BB, and declining with osteogenic differentiation. Preincubation with the receptor alpha specific antibody decreased the CI to borderline values while pretreatment with the receptor beta specific antibody led to a complete loss of chemotactic response to PDGF isoforms. In control experiments, basal migration values and rhBMP-2 as well as rxBMP-4 induced chemotaxis of MPC were not influenced by the addition of receptor alpha or beta antibodies. Interestingly, without preincubation the parallel exposure of MPC to rhTGF-beta1 instantaneously leads to a selective loss of migratory stimulation by rhPDGF-AA. The chemotactic effect of PDGF isoforms for primary human MPCs and the influence of osteogenic differentiation suggest a functional role for recruitment of MPCs during bone development and remodeling. Moreover, these observations may be useful for novel approaches towards guided tissue regeneration or tissue engineering of bone.

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PMID: 15389881 [PubMed - indexed for MEDLINE]

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Abstracts


Differential regulation of platelet-derived growth factor stimulated migration and proliferation in osteoblastic cells.

Mehrotra M, Krane SM, Walters K, Pilbeam C.

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ABSTRACT
Osteoblastic migration and proliferation in response to growth factors are essential for skeletal development, bone remodeling, and fracture repair, as well as pathologic processes, such as metastasis. We studied migration in response to platelet-derived growth factor (PDGF, 10 ng/ml) in a wounding model. PDGF stimulated a twofold increase in migration of osteoblastic MC3T3-E1 cells and murine calvarial osteoblasts over 24-48 h. PDGF also stimulated a tenfold increase in 3H-thymidine (3H-TdR) incorporation in MC3T3-E1 cells. Migration and DNA replication, as measured by BrdU incorporation, could be stimulated in the same cell. Blocking DNA replication with aphidicolin did not reduce the distance migrated. To examine the role of mitogen-activated protein (MAP) kinases in migration and proliferation, we used specific inhibitors of p38 MAP kinase, extracellular signal regulated kinase (ERK), and c-Jun N-terminal kinase (JNK). For these signaling studies, proliferation was measured by carboxyfluorescein diacetate succinimidyl ester (CFSE) using flow cytometry. Inhibition of the p38 MAP kinase pathway by SB203580 and SB202190 blocked PDGF-stimulated migration but had no effect on proliferation. Inhibition of the ERK pathway by PD98059 and U0126 inhibited proliferation but did not inhibit migration. Inhibition of JNK activity by SP600125 inhibited both migration and proliferation. Hence, the stimulation of migration and proliferation by PDGF occurred by both overlapping and independent pathways. The JNK pathway was involved in both migration and proliferation, whereas the p38 pathway was predominantly involved in migration and the ERK pathway predominantly involved in proliferation.

PMID: 15660418 [PubMed - indexed for MEDLINE]


Effects of platelet growth factors on human mesenchymal stem cells and human endothelial cells in vitro.


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ABSTRACT
The aim of the present in vitro study has been to investigate the effects of an enriched platelet derived growth factors on proliferation and migration of human endothelial and mesenchymal stem cells and on osteogenic differentiation of stem cells. Platelet rich plasma has been produced, yielding a four time higher number of thrombocytes than normal plasma. Degranulation of platelets has been performed by means of calcium and thrombin. Plasma has served as a control, whereas plasma in combination with calcium and thrombin was used to distinguish the difference between calcium and/or thrombin mediated effects and growth factor induced effects on the cells. The observed enhanced proliferation and migration of endothelial cells towards the platelet derived growth factors was driven by the plasma component of these preparations. However PDGF solely stimulated the migration and proliferation of mesenchymal stem cells. The increased osteogenic differentiation of growth factor treated mesenchymal stem cells was mostly driven by the high level of calcium used for the platelets degranulation. In summery, the different components of platelet derived growth factors work together to influence human endothelial and mesenchymal stem cells. This is of special clinically interest regarding the stimulation of bone healing in orthopaedic and traumatic surgery.

PMID: 15337634 [PubMed - indexed for MEDLINE]
Abstracts

Factors in the fracture microenvironment induce primary osteoblast angiogenic cytokine production.

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ABSTRACT
Neoangiogenesis is essential for successful wound repair. Platelets are among the earliest cells recruited to a site of skeletal injury and are thought to provide numerous factors critical to successful repair. The release of platelet-derived growth factor (PDGF) after skeletal injury increases osteoblast proliferation, chemotaxis, and collagen synthesis; however, its angiogenic effect on osteoblast biology remains unknown. The purpose of this study was to investigate the effect of recombinant human (rh)PDGF-BB on the synthesis of vascular endothelial growth factor (VEGF) by primary neonatal rat calvarial osteoblasts. Furthermore, the authors investigated whether PDGF works in concert with hypoxia, another component of the fracture microenvironment, to additively or synergistically induce VEGF production. Osteoblast cultures were stimulated with varying concentrations of rhPDGF-BB (1, 10, 50, and 100 ng/ml) in normoxic and hypoxic (<1% oxygen) conditions for 0, 3, 6, 12, and 24 hours, and VEGF gene expression was analyzed by Northern blot analysis. To determine whether rhPDGF-BB-induced VEGF messenger RNA (mRNA) expression was transcriptionally mediated or required de novo protein synthesis, transcription, and translation, studies were performed using actinomycin D and cycloheximide, respectively. Treatment with 50 ng/ml rhPDGF-BB resulted in a 2.4-fold increase in VEGF mRNA expression after 3 hours. Interestingly, rhPDGF-BB and hypoxia seemed to have an additive effect, resulting in a 3.7-fold increase in VEGF mRNA expression after 6 hours in primary neonatal rat calvarial osteoblasts. Furthermore, by using actinomycin D and cycloheximide, the authors demonstrated that the rhPDGF-BB-induced VEGF mRNA expression was transcriptionally mediated and not dependent on de novo protein synthesis. These data demonstrate that rhPDGF-BB transcriptionally increases osteoblasts VEGF mRNA expression in vitro. Furthermore, the semiquantitative results suggest that rhPDGF-BB and hypoxia act additively to increase VEGF mRNA expression. It is postulated that similar mechanisms may occur in vivo, at a site of skeletal injury, to induce neoangiogenesis and promote fracture repair.

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BMP-2, BMP-4, and PDGF-bb stimulate chemotactic migration of primary human mesenchymal progenitor cells.
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Abstract: For bone development, remodeling, and repair; the recruitment of mesenchymal progenitor cells (MPC) and their differentiation to osteoblasts is mandatory. The process of migration is believed to be regulated in part by growth factors stored within the bone matrix and released by bone resorption. In this study, primary human MPCs and to osteoblasts differentiated progenitor cells were examined for chemotaxis in response to human basic fibroblast growth factor (rhbFGF), human transforming growth factor beta 1 (rhTGF-beta1), human platelet derived growth factor bb (rhPDGF-bb), human bone morphogenetic protein-2 (rhBMP-2), and recombinant bone morphogenetic protein-4 of Xenopus laevis (rxBMP-4) from 0.001 to 1.0 ng/ml each. The results of migration were expressed as a chemotactic index (CI). Migration of primary human progenitor cells was stimulated by rhBMP-2, rxBMP-4, and rhPDGF-bb in a dose-dependent manner. The increase of CI was up to 3.5-fold for rhBMP-2, 3.6-fold for rxBMP-4, and up to 22-fold for rhPDGF-bb, whereas rhTGF-beta1 and rhbFGF did not stimulate cell migration in the concentration range tested. In contrast differentiated progenitor cells behave similar to primary human osteoblasts. rxBMP-2, rhPDGF-bb, and rhTGF-beta1 stimulated the migration from 2.2 to 2.4-fold each, while rxBMP-4 and rhbFGF reached only a CI of 1.7-1.6. The effect of rhBMP-2, rxBMP-4, and rhPDGF-bb as chemoattractive proteins for primary human MPC, including the change in response to growth factors after differentiation suggests a functional role for recruitment of MPCs during bone development and remodeling, as well as fracture healing.

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PMID: 12397612 [PubMed - indexed for MEDLINE]
Abstracts

* AUGMENT® Bone Graft is only approved for ankle and hindfoot fusions. This list was compiled in 2016. It includes references cited by Wright Medical Technology, Inc. scientists in their protocols, reports, and papers. These documents focus on the rhPDGF-BB platform technology and other topics of relevance to the product pipeline at Wright. This list is updated regularly.


Platelet-derived growth factor (PDGF)-BB stimulates osteoclastic bone resorption directly: the role of receptor beta.

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ABSTRACT

The growth-promoting activity of PDGF-BB was studied on the adult osteoclasts in the present study. The PDGF receptor beta was detected on the osteoclast membrane through immunohistochemistry (LSAB method) and immunomicroscopy. The PDGF-BB was exerted on the osteoclasts that adhered to the bone slice at concentrations of 0, 10, 20, 30, and 40 ng/ml. The volume of Howship's lacuna augmented significantly and the number of resorption pits also increased with its dose (p < 0.01). The activity of both total acid phosphatase (ACP) and tartrate-resistant acid phosphatase (TRAP) increased significantly. These results suggest that PDGF-BB promotes adult osteoclastic bone resorption directly through PDGF receptor beta and is believed to play important roles in the bone healing process and reconstruction.

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Establishing the relationship between clinical outcome and extent of osseous bridging between computed tomography assessment in isolated hindfoot and ankle fusions.

Glazebrook M, Beasley W, Daniels T, Evangelista PT, Donahue R, Younger A, Pinzur MS, Baumhauer JF, DiGiovanni CW.

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ABSTRACT
BACKGROUND
Determining the success of joint fusion operations is often a diagnostic dilemma, and many factors may be considered. Most would agree that the broad categories of clinical success and radiographic success are likely most useful to determine the overall success of a joint fusion operation. Very little evidence exists to assist the surgeon in determining what constitutes a successful radiographic fusion. The aim of this study was to determine the extent of osseous bridging as measured by computed tomography (CT) that was associated with a good clinical outcome as measured by the 12-Item Short Form (SF-12), Foot Function Index (FFI), and American Orthopaedic Foot & Ankle Society (AOFAS) clinical outcomes questionnaires at 24 weeks.

METHODS
Patients who had isolated joint fusions were evaluated (n = 275) to determine the correlation of extent of osseous bridging with clinical outcome. The extent of osseous bridging across the joint in question was categorized as absent (0%-24%), minimal (25%-49%) moderate (50%-74%), or complete (75%-100%). Clinical outcome scores included the SF-12, FFI, and AOFAS outcomes score.

RESULTS
Patients evaluated to have at least minimal osseous bridging at fusion sites (25%-49%) on CT reported a clinically important improvement in SF-12, FFI, and AOFAS, whereas those with "absent" osseous bridging (0%-24%) did not report a clinically important improvement in outcome scores.

CONCLUSION
This study suggests that osseous bridging of greater than 25% to 49% at the fusion site measured by CT may be necessary to consider a hindfoot or ankle fusion clinically successful.

LEVEL OF EVIDENCE
Level IV, case series.

KEYWORDS
arthritis; arthrodesis; computed tomography scan; fusion; outcome
PMID: 24043351 [PubMed - indexed for MEDLINE]
Survey on the need for bone graft in foot and ankle fusion surgery.

Baumhauer JF, Pinzur MS, Daniels TR, Lin SS, Beasley W, Donahue RM, DiGiovanni CW.

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Abstract
BACKGROUND
Generally, autologous bone graft is felt to be an important treatment adjunct in the presence of structural deformity, surface irregularities, defects (due to trauma, surgery, or degenerative changes), or underlying comorbidities that predispose the patient to healing challenges. This study assessed the prognostic and predictive factors used in the clinical decision making for bone graft supplementation in foot and ankle fusion surgery.

METHODS
Utilizing standard survey research methodology, key-informant interviews, pretesting, and pilot testing; a survey was constructed. The survey consisted of a web-based 5-point Likert-type scale (never, seldom, sometimes, almost always, always) listing 14 clinical and 11 radiologic criteria that may influence the use of autologous bone grafting or other biologic augmentation in foot and ankle surgery. This survey was sent to Orthopaedic Foot and Ankle Surgeons in North America and Canada.

RESULTS
A total of 48 foot and ankle surgeons completed the blinded survey (73% response rate). More than 70% of responders felt bone graft was almost always (AA) or always (A) indicated in prior nonunion of the indicated joint (96%). Fewer than 50% of respondents felt poor soft tissue integrity (20%), prior foot and ankle infection (20%), and current foot and ankle infection (4%) needed bone graft. Radiologic factors marked as AA or A in over 70% of responders include radiographic evidence of nonunion (96%), avascular necrosis (87%), and others. Factors chosen as AA or A by fewer than 50% of surgeons include prior adjacent joint fusions (47%), intra-articular deformity (31%), and extra-articular deformity (13%).

CONCLUSIONS
There was some uniformity of agreement on the number of both clinical and radiologic factors that prompt a surgeon to utilize autologous bone graft to try to avoid the complication of nonunion. Surgeons may wish to consider these factors when making a decision on the use of bone graft to supplement fusion.

KEYWORDS
arthrodesis; bone graft; fusion; indications; survey

PMID: 23986324 [PubMed - indexed for MEDLINE]
Site selection and pain outcome after autologous bone graft harvest.

Baumhauer J, Pinzur MS, Donahue R, Beasley W, DiGiovanni C.

Abstract

BACKGROUND:
In foot and ankle surgery, there are multiple sites used for autologous bone graft, including the proximal (PT) or distal tibia (DT), calcaneus (C), and iliac crest (ICBG). There has been no comparison between these anatomic areas and the potential for acute or persistent pain at 1 year. The purpose of this study was to prospectively compare patient-reported outcomes of acute and persistent pain at 1 year after surgery to determine if harvest site selection made a difference.

METHODS:
As part of a clinical trial examining ankle and hindfoot fusion rates with autograft compared with synthetic graft, the autologous bone graft harvest sites were assessed with visual analog pain outcome scores at 3, 24, 36, and 52 weeks after surgery. Patients with a score of 20+ defined clinically significant pain. Four harvest sites were compared: ICBG, PT, DT, and C. Fisher exact test was used to compare the graft site pain between locations.

RESULTS:
Twelve percent of subjects reported clinically significant pain at 24 weeks and 8.5% at 52 weeks postoperatively. Each lower extremity harvest site (C, DT, PT) showed higher rates of clinically significant graft harvest site pain than the ICBG at 52 weeks.

CONCLUSIONS:
Autologous bone graft harvest carried a risk of persistent pain at up to 1 year (weeks 24-52) in 18% of patients. Lower-extremity bone graft sites had the greatest risk for persistent pain at 1 year.

LEVEL OF EVIDENCE:
Level II, prospective comparative study.

KEYWORDS:
bone graft pain; foot and ankle autologous graft

PMID: 24227683 [PubMed - indexed for MEDLINE]
Brief Summary of Important Product Information

Indications for Use
AUGMENT Bone Graft is indicated for use as an alternative to autograft in arthrodesis (i.e., surgical fusion procedures) of the ankle (tibiotalar joint) and/or hindfoot (including subtalar, talonavicular, and calcaneocuboid joints, alone or in combination); due to osteoarthritis, post-traumatic arthritis, rheumatoid arthritis, psoriatic arthritis, avascular necrosis, joint instability, joint deformity, congenital defect, or joint arthropathy in patients with preoperative or intraoperative evidence indicating the need for supplemental graft material.

Contraindications
AUGMENT Bone Graft should not:

- be used in patients who have a known hypersensitivity to any of the components of the product or are allergic to yeast-derived products.
- be used in patients with active cancer.
- be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses).
- be used in pregnant women. The potential effects of rhPDGF-BB on the human fetus have not been evaluated.
- be implanted in patients with an active infection at the operative site.
- be used in situations where soft tissue coverage is not achievable.
- be used in patients with metabolic disorders known to adversely affect the skeleton (e.g. renal osteodystrophy or hypercalcemia), other than primary osteoporosis or diabetes.
- be used as a substitute for structural graft.

Warnings
As with all therapeutic recombinant proteins, there is a potential for immune responses to be generated to the rhPDGF-BB component of AUGMENT Bone Graft. The immune response to rhPDGF-BB was evaluated in two pilot and one pivotal studies for ankle and hindfoot arthrodesis procedures. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to AUGMENT Bone Graft with the incidence of antibodies to other products may be misleading. Women of childbearing potential should avoid becoming pregnant for one year following treatment with AUGMENT Bone Graft. The implantation of rhPDGF-BB in women and the influence of their development of anti-PDGF-BB antibodies, with or without neutralizing activity, on human fetal development are not known. The safety and effectiveness of AUGMENT Bone Graft in nursing mothers has not been established. It is not known if rhPDGF-BB is excreted in human milk.

Competitive Product Information

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The INFUSE® Bone Graft/Medtronic Interbody Fusion Device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L2-S1, who may also have up to Grade I spondylolisthesis or Grade 1 retrolisthesis at the involved level. The INFUSE® Bone Graft is indicated for treating acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. INFUSE® Bone Graft must be applied within 14 days after the initial fracture. Prospective controls should be skeletally mature. INFUSE® Bone Graft is indicated as an alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets.

*For more information please refer to the full package insert.