

Recombinant Human Platelet-Derived Growth Factor-BB and Beta-Tricalcium Phosphate (rhPDGF-BB/ β -TCP): An Alternative to Autogenous Bone Graft

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Investigation performed at thirty-seven clinical sites in North America

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

continued

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A commentary by Zbigniew Gugala, MD, PhD, is linked to the online version of this article at jbsj.org.

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.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Approximately 110,000 foot and ankle arthrodeses were performed in the United States in 2009¹, and this number is expected to increase annually because of both an aging population and the continued prevalence of contributory comorbidities. Arthrodesis is designed to ameliorate severe disability often associated with the numerous maladies that cause joint destruction, including trauma, diabetes, inflammatory arthritides, seronegative arthropathy, instability, malalignment, and congenital deformity²⁻⁷. The common manifestation of these conditions in the ankle and hindfoot is end-stage arthritis, often culminating in marked pain, limitation in function, and impaired quality of life⁸. Although arthrodesis has long been the mainstay of surgical treatment for these conditions, one of its most common complications has been nonunion. Thus, arthrodesis has frequently been supplemented with autogenous bone graft (autograft)^{5,9}. It has been suggested in the literature that nonunion rates can reach over 40% in certain populations, with an overall rate of approximately 10%^{5,9,10}. Frey et al.¹⁰ reported a nonunion rate of 41% in high-risk ankle arthrodeses, and Easley et al.⁹ found a 14% nonunion rate after primary subtalar arthrodesis, a 29% nonunion rate after revision subtalar arthrodesis, and a 27% nonunion rate in smokers. In a more recent meta-analysis of the ankle arthrodesis literature, Haddad et al.¹¹ reported an overall nonunion rate of 10%. Thus, it remains clear that nonunion is an important complication of hindfoot and ankle arthrodesis⁹⁻¹².

Surgeons use autograft to promote fusion across osseous surfaces, particularly in higher-risk surgical sites and patient populations¹³⁻¹⁶, but its use comes with certain tradeoffs. Important clinical complications have been documented at the autograft donor site, including blood loss, chronic pain, fracture, seroma, scarring, infection, heterotopic ossification, hernia, and nerve injury^{15,17-20}. Furthermore, the quality and quantity of autograft are known to vary with patient age, body mass index, sex, and overall health status²¹. Equally importantly, harvesting autograft also requires additional operative time or personnel, and, ultimately, cost^{15,22-24}.

As a result of these limitations, suitable alternatives to autograft that are capable of providing its benefits while avoiding its limitations have been sought. One such family of alternatives is the bone and tissue growth factors. These proteins can be categorized into osteoinductive bone morphogenetic proteins and broader-acting stimulatory growth factors that regulate the wound-healing and bone formation cascades, such as platelet-derived growth factor (PDGF). Bone morphogenetic proteins can induce bone wherever applied (or inadvertently migrated), and PDGF stimulates tissue repair by promoting growth of the vasculature and healing cells without changing the cellular

phenotype. Although the bone morphogenetic proteins have been shown to be safe and effective in indications approved by the U.S. Food and Drug Administration (FDA), their widespread use has recently come under criticism because of safety concerns and cost²⁵⁻²⁸.

PDGF should not be confused with platelet-rich plasma. Platelet-rich plasma is a variable mixture of proteins and cellular components with diverse and sometimes conflicting bioactivities, whereas purified PDGF is prepared with use of recombinant DNA technology under highly controlled, reproducible conditions. Recently, the recombinant human PDGF BB (rhPDGF-BB) homodimer, the most active PDGF isoform in bone and other connective tissues, has been combined with an osteoconductive scaffold (beta-tricalcium phosphate [β -TCP]) to promote bone healing in foot and ankle arthrodesis and alveolar bone defects²⁹⁻³³. We report here, in the largest foot and ankle investigation of its kind to date (to our knowledge), prospective, controlled, randomized, multicenter data regarding the safety and efficacy of rhPDGF-BB/ β -TCP compared with autograft in foot and ankle arthrodesis.

Materials and Methods

Study Design

Between April 2007 and January 2010, a prospective, randomized, controlled, multicenter, non-inferiority, pivotal clinical trial was performed at thirty-seven clinical sites across the United States and Canada. The trial was prospectively registered at clinicaltrials.gov (NCT00583375). Patients requiring either hindfoot or ankle arthrodesis were enrolled in accordance with the FDA good clinical practice guidelines. Only patients who required supplemental bone graft as determined by the surgeon on the basis of a number of clinical risk factors, including obesity, diabetes, prior surgery, smoking, and severe deformity, and radiographic risk factors, including peri-articular erosion and bone voids not requiring structural graft, were enrolled prospectively. Following approval by applicable regulatory bodies including the FDA and Health Canada, individual institutional review boards, and research ethics boards, eligible subjects satisfying the inclusion criteria (see Appendix) provided informed consent, were randomized (with use of a 2:1 ratio of rhPDGF-BB/ β -TCP to autograft), and were managed with arthrodesis with use of standard rigid internal fixation plus either autograft or a combination of rhPDGF-BB (0.3 mg/mL) and β -TCP (Augment Bone Graft; BioMimetic Therapeutics, Franklin, Tennessee). All patients undergoing arthrodesis who met the enrollment criteria had articular surface or deformity irregularities as part of the disease state that required up to 9 cc of graft to maximize fusion, and did not have any defect that, in the opinion of the surgeon, would be treated best by structural graft augmentation. Prior to any graft insertion at the fusion site(s), patients randomized to receive autograft underwent a routine graft harvest through a separate exposure and those randomized to receive Augment had its components (rhPDGF-BB liquid and β -TCP matrix) mixed and the mixture was allowed to sit for at least ten minutes to maximize saturation prior to application.

A regional block with use of 0.5% Marcaine (bupivacaine) and 1% lidocaine was administered to aid in postoperative pain control. Postoperative pain was assessed with use of numerical pain assessment, and pain management was directed by the investigator as necessary with use of standard postoperative

TABLE I Radiographic Results Summary

| | Full-Complement Analysis (N = 397) | | | All-Joints Analysis (N = 597) | | |
|--|------------------------------------|--|----------|----------------------------------|--|----------|
| | rhPDGF-BB/β-TCP Group* (N = 260) | Autologous Bone Graft Group* (N = 137) | P Value† | rhPDGF-BB/β-TCP Group‡ (N = 394) | Autologous Bone Graft Group‡ (N = 203) | P Value† |
| At twenty-four weeks | | | | | | |
| Primary end point | | | | | | |
| CT fusion rates | 159 (61.2%) | 85 (62.0%) | 0.038 | 262 (66.5%) | 127 (62.6%) | <0.001 |
| Secondary end points | | | | | | |
| Radiographic union rates (three aspects) | 80 (30.8%) | 45 (32.8%) | 0.054 | 151 (38.3%) | 77 (37.9%) | 0.007 |
| Radiographic union rates (two aspects) | 158 (60.8%) | 91 (66.4%) | 0.194 | 266 (67.5%) | 144 (70.9%) | 0.049 |
| At fifty-two weeks | | | | | | |
| Secondary end points | | | | | | |
| Radiographic union rates (three aspects) | 96 (36.9%) | 50 (36.5%) | 0.020 | 191 (48.5%) | 90 (44.3%) | <0.001 |
| Radiographic union rates (two aspects) | 184 (70.8%) | 103 (75.2%) | 0.115 | 304 (77.2%) | 158 (77.8%) | 0.005 |

*The values are given as the number of patients, with the percentage in parentheses. †All p values are for non-inferiority. ‡The values are given as the number of joints, with the percentage in parentheses.

analgesia. All medications taken by the subject were monitored and were recorded on the postoperative medication case report form.

A total of eight postoperative visits were performed at one to three, six, nine, twelve, sixteen, twenty-four, thirty-six, and fifty-two weeks. All follow-up procedures were performed by the investigator according to protocol. During each visit, investigators recorded the patient's clinical and functional healing status and made radiographs.

In accordance with the FDA-approved protocol, and specifically for the purpose of assessing patient outcomes in this trial, computed tomography (CT) was performed at nine, sixteen, twenty-four, and thirty-six weeks. In addition to being viewed by each clinician as a part of routine follow-up care, these images were independently assessed by a blinded, fellowship-trained, board-certified, musculoskeletal radiologist (P.E.) responsible for determining all radiographic end points. Percent osseous bridging was assessed by the independent radiologist to determine fusion on the basis of benchmarks of 0% to 24%, 25% to 49%, 50% to 74%, and 75% to 100% bridging bone across each joint intended for fusion. Intrarater reliability was examined by having the radiologist (P.E.) reread a subset of fifty-three CT scans at least three months after his original reading of these scans. The kappa value was found to be 0.67 (95% confidence interval [95% CI], 0.46 to 0.87), with 85% concordance and 92% tetrachoric correlation. In addition, radiographs were assessed by the independent radiologist (P.E.) and the investigator at all time points. Only the radiologist was specifically blinded to treatment in this study.

End Points

Clinical, functional, and radiographic end points were assessed to monitor safety, clinical healing status, and progression of fusion. Tracked metrics included recording adverse events, complications, protocol deviations, and revision surgeries.

The primary effectiveness end point was fusion as assessed by means of CT at twenty-four weeks. A joint was considered fused if ≥50% osseous bridging across the articulation was identified. In cases in which multiple joints were concomitantly addressed, assessment was made on the basis of the full complement of treated joints (all treated joints had to be fused for the arthrodesis to be a success) as well as on an individual joint basis (fusion across each treated joint was assessed independently), termed "all joints." As the individual joints within a patient

cannot be assumed to be independent, we also examined logistic regression models to estimate the differences between the two treatments while still accounting for the correlation between joints within a patient. The results from these models were consistent with the findings in the simpler all-joints success rate analyses.

Secondary end points were chosen to incorporate patient, surgeon, and independent radiologist-reported data. These included clinical, functional, quality-of-life, and additional radiographic assessments. The clinical healing status was based on the caregiver's global assessment of patient progress at both the full joint level (taking into account the full complement of fusion sites) and the individual joint level (considering every joint independently). The clinical healing status was also extrapolated from the clinical and composite success rates as well as the therapeutic failure rate (defined as any symptomatic nonunion or delayed union requiring secondary therapeutic intervention). Secondary outcomes also included visual analog scale (VAS) pain measurements at the surgical site with weight-bearing and at the graft harvest site, as well as quality-of-life and functional assessments using the following instruments: the Short Form-12 (SF-12), the American Orthopaedic Foot & Ankle Society (AOFAS) hindfoot and ankle outcomes score, and the Foot Function Index. Secondary efficacy radiographic end points included an assessment of osseous bridging based on both CT and radiographs at additional time points, including a final fifty-two-week assessment.

Analysis of safety-related data included adverse event frequency, severity, and potential relationship to the rhPDGF-BB/β-TCP; surgical site complications, including nonunion; and patient dropout due to death or other important adverse events. Treatment emergent adverse events are adverse events reported during or following treatment through completion of the study. Events were classified as serious if they met any of the following criteria: death, life-threatening event, event that required or prolonged in-patient hospitalization, event that resulted in persistent or important disability or incapacity, other medically important events that in the opinion of the investigator may have required intervention to prevent one of the other outcomes listed above, or any serious problem associated with the device that related to the rights, safety, or welfare of the patients in the study. The presence of anti-rhPDGF-BB antibodies was evaluated with use of a tiered approach according to FDA guidance. This evaluation consisted of screening for rhPDGF-BB-specific antibodies with use of an enzyme-linked immunosorbent assay (ELISA) followed by the detection of neutralization potential by both a

receptor-binding radioimmunoassay and a cell-based receptor phosphorylation assay. Safety radiographic parameters included heterotopic bone formation, β-TCP migration, and fixation complications.

Statistical Methods

The goal of the trial was to establish non-inferiority of rhPDGF-BB/β-TCP relative to autograft. As such, contrary to tests for determining differences or superiority, significant non-inferiority *p* values ($p \leq 0.05$) denote outcomes for which rhPDGF-BB/β-TCP is essentially equivalent to autograft.

For binary end points (including the primary end point of fusion), non-inferiority tests were carried out by fitting a one-sided lower confidence bound for the rhPDGF-BB/β-TCP fusion rate minus the autograft fusion rate and requiring documented evidence of success (patients without a data point could not be declared a success for that data point); this lower confidence bound was compared with a ten percentage point margin. The *p* values and confidence intervals were based on asymptotic, normal theory computations. Because of large sample sizes, exact tests were seen to be consistent with asymptotic results. Binary end-point data were reported as counts and percentages, with corresponding non-inferiority *p* values, with the exception of the percent of patients with graft harvest site pain and adverse events, which report difference test *p* values rather than non-inferiority *p* values.

The study was powered under the assumptions fulfilling the primary analysis in conjunction with a 2:1 randomization, 80% power to declare non-inferiority, and an assumed overall success rate of 85%. This power calculation resulted in a desire to produce 357 subjects for analysis. This total was scaled up to account for an anticipated approximate 10% dropout rate, producing a final desired sample size of 396 patients, with 264 receiving rhPDGF-BB/β-TCP and 132 receiving autograft. Thus, the power of this non-inferiority study represents the chance that the study will demonstrate sameness between the two treatments, as opposed to a superiority study, in which power represents the chance that the study will demonstrate a difference between the two treatments.

Randomization was performed by an independent contract research organization via a computer model in a 2:1 ratio within two days of the arthrodesis, with the result being thereafter forwarded to the surgeon just before the beginning of the operation. A 2:1 randomization scheme was selected to allow a greater number of patients to be managed with rhPDGF-BB/β-TCP so as to produce more long-term safety data on rhPDGF-BB/β-TCP.

Continuous end points were likewise examined for non-inferiority with use of a similar one-sided confidence interval approach and are presented as means and standard deviations and corresponding non-inferiority *p* values. All scales used 10-point non-inferiority margins except for the SF-12, which used a margin of 5 points.

Because of the complicated nature and unresolved statistical methodology of multiplicity adjustment for correlated non-inferiority end points, no formal adjustments were made for multiplicity.

Source of Funding

The study was sponsored by BioMimetic Therapeutics. Funds were used for salaries, supplies, imaging studies, laboratory procedures, data management activities, and other administrative fees.

Results

Patients

Four hundred and thirty-four patients were initially randomized. Twenty of these patients never received treatment in the study either because they had a preoperative medical finding or because they elected not to proceed with surgery (Fig. 1). Therefore, 414 randomized patients were managed with either rhPDGF-BB/β-TCP (272 patients) or autograft (142 patients) and comprised the population analyzed for

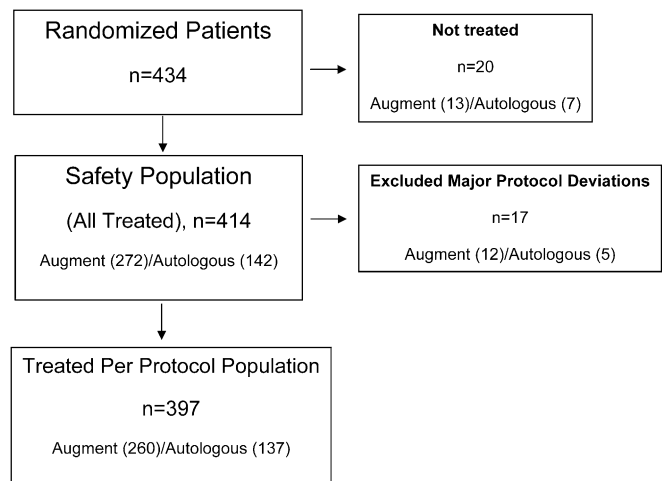


Fig. 1

Patient disposition flowchart. A total of 434 patients were randomized. Twenty patients who were randomized were intraoperative screening failures (e.g., it was discovered intraoperatively that the patient required another fusion procedure) or were otherwise not managed. These failures resulted in 414 patients being randomized and managed in the study; this population of patients is noted as the safety (all treated) population. Another seventeen patients were excluded following treatment because of major protocol violations (e.g., use of a bone stimulator), yielding the treated per protocol population ($n = 397$).

safety. However, for the purposes of effectiveness evaluation, seventeen patients were excluded because of major protocol violations such as having undergone procedures with use of plates instead of screws or those that included midfoot joints. Efficacy results were thus based on the remaining 397 evaluable patients (597 joints) who were eligible, were properly randomized, and received treatment in accordance with study protocol. Of these, 260 patients (394 joints) received rhPDGF-BB/β-TCP and 137 patients (203 joints) received autograft. Nineteen patients in the rhPDGF-BB/β-TCP group and five patients in the autograft group ($p = 0.187$) dropped out of the study prior to study completion, most commonly because of subject or investigator request (eight patients), required revision surgery (seven), or loss to follow-up (five). The seven patients for whom revision surgery was required were considered failures for all binary outcome measures. The patients were enrolled across all thirty-seven sites, with the distribution of patients ranging from one to thirty-six patients per site, and with multiple sites reaching the thirties, twenties, and teens in enrollment numbers.

Baseline Characteristics

The mean patient age was 56.6 years: 56.2 years (range, 19.8 to 86.2 years) in the rhPDGF-BB/β-TCP group and 57.5 years (range, 20.3 to 82.2 years) in the autograft group. The three main diagnoses included primary osteoarthritis (34.3%), post-traumatic arthritis or deformity (48.2%), and rheumatoid arthritis (6.7%). There were 52.6% female patients and 47.4% male

TABLE II Secondary Clinical Outcomes Results Summary

| | At Twenty-four Weeks | | | At Fifty-two Weeks | | |
|--|------------------------------|------------------------------------|----------|------------------------------|------------------------------------|----------|
| | rhPDGF-BB/β-TCP (N = 260) | Autologous Bone Graft (N = 137) | P Value* | rhPDGF-BB/β-TCP (N = 260) | Autologous Bone Graft (N = 137) | P Value* |
| Clinical healing status† (patient level) | 216 (83.1%) | 115 (83.9%) | 0.010 | 228 (87.7%) | 121 (88.3%) | 0.003 |
| Clinical healing status | | | | | | |
| Full complement of joints† | 214 (82.3%) | 114 (83.2%) | 0.011 | 224 (86.2%) | 120 (87.6%) | 0.008 |
| All joints‡ (assessed individually) (n = 597) | 329 (83.5%) | 169 (83.3%) | <0.001 | 348 (88.3%) | 177 (87.2%) | <0.001 |
| Other clinical outcomes | | | | | | |
| Composite success rate†§ | 184 (70.8%) | 95 (69.3%) | 0.009 | N/A | N/A | N/A |
| Clinical success rate† | 194 (74.6%) | 107 (78.1%) | 0.071 | 200 (76.9%) | 107 (78.1%) | 0.022 |
| Therapeutic failure rate†# | 24 (9.2%) | 15 (10.9%) | <0.001 | 19 (7.3%) | 11 (8.0%) | <0.001 |
| SF-12 Physical Component Score** | 39.9 ± 9.5 | 41.4 ± 9.3 | <0.001 | 42.4 ± 10.3 | 45.0 ± 9.9 | 0.015 |
| Foot Function Index total score** | 27.4 ± 21.3 | 22.3 ± 19.7 | 0.012 | 20.1 ± 19.0 | 17.5 ± 20.4 | <0.001 |
| AOFAS total score** | 71.7 ± 15.8 | 73.9 ± 15.8 | <0.001 | 77.8 ± 14.4 | 78.2 ± 17.7 | <0.001 |
| Fusion site pain** | 18.9 ± 23.2 | 16.5 ± 22.9 | 0.001 | 13.2 ± 21.4 | 12.9 ± 23.4 | <0.001 |
| Weight-bearing pain** | 23.5 ± 25.8 | 19.3 ± 24.3 | 0.016 | 15.6 ± 22.4 | 15.8 ± 25.2 | <0.001 |
| Patients with graft harvest site pain††† (≥20 mm on VAS) | N/A | 17 (12.4%) | <0.001 | N/A | 12 (8.8%) | <0.001 |

*The p value for pain in the bone graft harvest site is for superiority. All other p values are for non-inferiority. †The values are given as the number of patients, with the percentage in parentheses. ‡The values are given as the number of joints (n = 394 for the rhPDGF-BB/β-TCP group and n = 203 for the autograft group), with the percentage in parentheses. §The composite success rate was not determined at fifty-two weeks because it included a CT scan component, which was not performed at fifty-two weeks. #Therapeutic failures are patients who were assessed as having nonunion or delayed union, or required secondary therapeutic intervention for nonunion or delayed union. **The values are given as the mean and the standard deviation, in points. ††Patients in the rhPDGF-BB/β-TCP group did not experience graft harvest site pain because there was no need for graft harvest.

patients who underwent treatment in the rhPDGF-BB/β-TCP group compared with 43.0% female patients and 57.0% male patients who underwent treatment in the autograft group. Body mass index, affected extremity (laterality), and relative risk factors (body mass index of >30 kg/m², smoking habit, diabetes, and previous surgery other than arthrodesis at the site) were comparable between groups.

Investigators were provided with sterile graduated surgical cups to estimate the amount of autograft used. There were no significant differences between groups in the volume of the graft materials employed in this study: 1 to 3 cc of graft material were used in 28.8% of the rhPDGF-BB/β-TCP group compared with 29.2% of the autograft group; 4 to 6 cc were used in 51.9% of the rhPDGF-BB/β-TCP group compared with 48.2% of the autograft group; and 7 to 9 cc were used in 19.2% of the rhPDGF-BB/β-TCP group compared with 22.6% of the autograft group. For the autograft group, iliac crest graft was harvested in 11.7%, distal tibia in 16.1%, proximal tibia in 50.4%, calcaneus in 13.9%, and another lower-extremity

site in 8.0%. Although this study employed autograft techniques as well as harvest sites considered to be the most common standards for orthopaedic foot and ankle surgeons, there have been biological differences reported among autograft harvest sites²¹. In comparison, rhPDGF-BB is produced in a quality-controlled environment that guarantees consistency.

Radiographic and Clinical Results

Radiographic effectiveness results are shown in Table I. Non-inferiority was observed for the primary end point of fusion. For the full-complement analysis, the fusion rate was 61.2% for patients in the rhPDGF-BB/β-TCP group compared with 62.0% for patients in the autograft group (p = 0.038); for the all-joints analysis, the fusion rate was 66.5% for joints in the rhPDGF-BB/β-TCP group compared with 62.6% for joints in the autograft group (p < 0.001). The fusion rates stratified by volume of graft were similar across treatment groups: for 1 to 3 cc, the fusion rate was 75% for the rhPDGF-BB/β-TCP

TABLE III Safety Results Summary

| | rhPDGF-BB/β-TCP Group (N = 272) | | Autograft Group (N = 142) | | P Value* |
|--|---------------------------------|---------------|---------------------------|---------------|----------|
| | No. of Subjects | No. of Events | No. of Subjects | No. of Events | |
| Serious treatment emergent adverse events | 28 (10.3%) | 45 | 21 (14.8%) | 29 | 0.201 |
| Device-related treatment emergent adverse events | 6 (2.2%) | 9 | 6 (4.2%) | 10 | 0.354 |
| Complications associated with surgical procedure | 65 (23.9%) | 92 | 43 (30.3%) | 56 | 0.194 |
| Serious complications | 14 (5.1%) | 18 | 9 (6.3%) | 10 | 0.654 |
| Surgical complications or infection | 23 (8.5%) | 28 | 16 (11.3%) | 18† | 0.378 |
| Chronic pain at autograft donor site (≥20 mm on VAS) | | | | | |
| At six months | 0 (0%) | 0 | 18 (12.7%) | 18 | <0.001 |
| At twelve months | 0 (0%) | 0 | 13 (9.2%) | 13 | <0.001 |

*The p value was determined by means of a two-sided Fisher exact test for a treatment difference based on subject counts. †There was one serious surgical infection at the site of the bone graft harvest.

group compared with 73% for the autograft group; for 4 to 6 cc, it was 59% for the rhPDGF-BB/β-TCP group compared with 62% for the autograft group; and for 7 to 9 cc, it was 48% for the rhPDGF-BB/β-TCP group compared with 48% for the autograft group.

Clinical, functional, and quality-of-life results are shown in Table II. Non-inferiority of rhPDGF-BB/β-TCP was established for fourteen of the sixteen secondary end points at twenty-four weeks and fifteen of the sixteen secondary end points at fifty-two weeks. At twenty-four weeks, the achievement of clinical union in the full complement of treated joints was 82.3% for patients in the rhPDGF-BB/β-TCP group compared with 83.2% for patients in the autograft group ($p = 0.011$), and the achievement of clinical union in all joints was 83.5% for patients in the rhPDGF-BB/β-TCP group compared with 83.3% for patients in the autograft group ($p < 0.001$). Clinical healing rates improved modestly between six and twelve months. At one year, the success rates as determined by the full-complement analysis were 86.2% for patients in the rhPDGF-BB/β-TCP group and 87.6% for patients in the autograft group ($p = 0.008$), and the success rates as determined by the all-joints analysis were 88.3% in the rhPDGF-BB/β-TCP group and 87.2% in the autograft group ($p < 0.001$).

At the conclusion of this study, the radiographic union rates, as determined by the presence of osseous bridging across at least three of the four predefined aspects (anterior, posterior, medial, and lateral, with supplemental radiographic views [superior and inferior] assessed for subtalar arthrodesis) of each joint, were 36.9% for patients in the rhPDGF-BB/β-TCP group and 36.5% for those in the autograft group with use of the full-complement analysis ($p = 0.020$),

and 48.5% for the rhPDGF-BB/β-TCP group and 44.3% for the autograft group with use of the all-joints analysis ($p < 0.001$).

Quality-of-Life and Functional Outcomes

The SF-12, Foot Function Index, and AOFAS Ankle-Hindfoot questionnaires demonstrated improvement from baseline in both groups for all outcome measures (Table II). All quality-of-life and functional outcome data supported non-inferiority of rhPDGF-BB/β-TCP compared with autograft.

Therapeutic failure rates, defined as delayed union or nonunion requiring surgery or further therapeutic intervention, were 7.3% for patients in the rhPDGF-BB/β-TCP group and 8.0% for patients in the autograft group ($p < 0.01$).

Pain Assessments

The mean VAS score (and standard deviation) of overall arthrodesis site pain was 13.2 ± 21.4 mm for the rhPDGF-BB/β-TCP group compared with 12.9 ± 23.4 mm for the autograft group at fifty-two weeks ($p < 0.001$). The pain score (and standard deviation) for weight-bearing pain was 15.6 ± 22.4 mm for the rhPDGF-BB/β-TCP group compared with 15.8 ± 25.2 mm for the autograft group ($p < 0.001$).

Of the patients in the autograft group (for whom a graft harvest procedure was required), 12.4% reported clinically significant graft harvest site pain (≥20 mm on the VAS) at twenty-four weeks and 8.8% did at fifty-two weeks.

Safety Summary

Fewer device-related treatment emergent adverse events were observed in the rhPDGF-BB/β-TCP group (2.2%) compared with the autograft group (4.2%). Additionally, a smaller number of serious treatment emergent adverse events occurred in the

TABLE IV Diagnosis and History for Reported Cancers

| Diagnosis | Treatment Group | Subject Cancer History |
|--------------------------------|-------------------------|--|
| Prostate cancer | rhPDGF-BB/ β -TCP | Prostate cancer (1996) |
| Prostate cancer | rhPDGF-BB/ β -TCP | None reported |
| Infiltrating lobular carcinoma | rhPDGF-BB/ β -TCP | Basal cell carcinoma (2008) |
| Renal carcinoma | Autograft | Prostate cancer (2004) and basal cell carcinoma (2003) |
| Endometrial cancer | Autograft | None reported |

rhPDGF-BB/ β -TCP group (10.3%) compared with the autograft group (14.8%) and fewer serious complications occurred in the rhPDGF-BB/ β -TCP group (5.1%) compared with the autograft group (6.3%). There were also no device-related serious treatment emergent adverse events reported in the rhPDGF-BB/ β -TCP group and fewer serious surgical wound infections as compared with the autograft group (Table III). However, none of these differences reached significance.

One patient in the autograft group required hospitalization for the treatment of a serious infection at the autograft harvest site. Another patient in the autograft group developed cellulitis at the graft harvest site requiring additional treatment. Obviously, no patients in the rhPDGF-BB/ β -TCP group experienced any autograft harvest site pain or other such complications, as no bone graft harvest was required.

There were five reported cancer-related serious adverse events (Table IV). The overall cancer incidence was 1.1% in the rhPDGF-BB/ β -TCP group and 1.4% in the autograft group. There were two events coded as neoplasms, but neither were cancers. One event was defined as colonic polyps, considered an ongoing issue in a patient with a history of polyps. The other was a plantar fibromatosis. There were no trends noted in either the occurrence or recurrence of cancers.

No neutralizing antibodies to rhPDGF-BB were detected in either group at any time with use of the receptor-binding radioimmunoassay. Seven patients (2.6%) had transient neutralizing antibodies to rhPDGF-BB at a single time point with use of the cell-based receptor phosphorylation assay, but all of these values normalized with subsequent assessment. Approximately 13.9% of patients in the rhPDGF-BB/ β -TCP group and 3.6% of the patients in the autograft group had positive, non-neutralizing antibody titers during the study. These immune responses were transient and all titers returned to baseline by the end of the study. There was no obvious clinical consequence for these transient antibodies on any safety or efficacy assessment.

Discussion

This multicenter, randomized, controlled trial provides Level I evidence that equivalent outcomes in hindfoot and ankle arthrodesis can be obtained with fully synthetic rhPDGF-BB combined with an osteoconductive matrix when compared with an autograft gold standard, without incurring the additional morbidity associated with harvesting the graft. Most

importantly, the primary effectiveness end point was met: twenty-four-week fusion rates for rhPDGF-BB/ β -TCP as assessed by means of CT were found to be non-inferior (equivalent) to those for autograft. Furthermore, the criteria of at least 50% bridging seen on CT and at least three of four aspects of the joint being fused on radiographs represent rigorous benchmarks when assessing fusion in the foot and ankle³⁴.

This study was designed to demonstrate that Augment rhPDGF-BB/ β -TCP is at least as effective as autograft, because prior data have suggested that it offers the advantages of being safer and less painful for the patient as a result of eliminating the bone graft harvest site^{30,31}. In fact, the results demonstrate that the two treatment groups had highly similar radiographic, clinical, functional, and quality-of-life outcomes, but that the patients in the rhPDGF-BB/ β -TCP group had fewer serious treatment emergent adverse events and complications. Patients in the rhPDGF-BB/ β -TCP group obviously also had no donor-site pain when compared with patients in the autograft group.

In addition to the risk-benefit assessment, the economic value of any novel technology must also be seriously considered today by surgeons, hospitals, payers, and patients. Studies have demonstrated notable resource utilization related to using autograft, including additional operating room time, supply and personnel costs, additional medications, added lengths of stay, donor site complications, and short and long-term side effects following graft harvest³⁵⁻³⁹. In the future, the costs of the use of bone grafts and rhPDGF-BB/ β -TCP should be compared and evaluated critically.

This study builds upon three earlier, phase-I/II clinical trials^{30,31} assessing the safety and benefit of rhPDGF-BB/ β -TCP in foot and ankle arthrodesis, as well as a series of clinical trials for alveolar bone applications²⁹. rhPDGF-BB/ β -TCP has been approved by the FDA and has been commercially available for alveolar bone regeneration since 2005 with no serious device-related adverse events reported. The cumulative clinical experience of this technology demonstrates a strong record of safety, which represents a substantial advantage over autograft and the commercially available bone morphogenetic proteins^{29,31}.

The clinical efficacy of rhPDGF-BB as an osteostimulatory protein was originally hypothesized because of its strong mitogenic and chemotactic effects on mesenchymal cells combined with its pro-angiogenic properties, all of which collectively play a central role in the early phases of the healing cascade^{40,41}.

Additionally, PDGF-BB mobilizes mesenchymal stem cells (pericytes) to contribute to the regenerative cell population and to help stabilize newly forming vessels⁴²⁻⁴⁶.

Considering the biology of PDGF-BB, it appears well suited for the challenges of joint arthrodesis in the distal extremity. Limited vascularity and diminished perfusion at these surgical sites represent obstacles to bone regeneration. Patients recognized as compromised healers (e.g., tobacco product users, the elderly, patients with diabetes, and those on anti-arthritis medications) could benefit from the pro-angiogenic properties of PDGF^{31,32,42}. In addition, the delivery of a precise therapeutic dose of rhPDGF-BB can yield a more predictable outcome when compared with treatment with quantitatively and qualitatively variable autogenous grafts or platelet gels.

Some apprehension has been voiced about the risk of cancer formation or potentiation with the use of growth factors. Although an isolated study comprising 414 treated patients cannot completely dispel all concerns, the data from this and previous studies provide no evidence of any increase in such risk for rhPDGF-BB. For example, the final analysis of a large study on patients managed with a topical gel containing rhPDGF-BB (Regranex, Healthpoint Biotherapeutics) found no relationship between the daily administration of rhPDGF-BB and cancer incidence or mortality⁴⁷. This result is reinforced by the data from this study in which there were no differences between the treatment groups (a cancer incidence of 1.1% for the rhPDGF-BB/ β -TCP group and 1.4% for the autograft group).


It is noteworthy that over the past decade the safety and efficacy of the rhPDGF-BB/ β -TCP combination have been assessed in at least three multicenter trials^{30,31} in foot and ankle arthrodesis (more than 500 patients), and in multiple clinical trials for alveolar bone applications²⁹, as well as in more than 200,000 patients following FDA approval in the latter applications, with no serious device-related adverse events, no increase in cancer incidence or mortality, and no serious complications related to the use of a single administration of rhPDGF-BB/ β -TCP.

As the largest study of its kind ever performed on foot and ankle surgery, to our knowledge, this prospective, randomized, controlled trial across thirty-seven sites in North America compared the safety and effectiveness of rhPDGF-BB combined with an osteoconductive scaffold β -TCP with those of autograft in 434 patients undergoing either hindfoot or ankle arthrodesis. The results demonstrated that rhPDGF-BB/ β -TCP treatment produced equivalent rates of joint fusion, clinical success, functional patient improvement, and radiographic outcomes compared with autograft treatment. In addition, patients in the rhPDGF-BB/ β -TCP group exhibited fewer therapeutic failures, less pain, and fewer serious treatment emergent adverse events, complications, and infections compared with patients in the autograft group.

Importantly, patients in the rhPDGF-BB/ β -TCP group were spared any autograft donor site pain and morbidity, which, in nearly 10% of patients in the autograft group, lasted for at least one year postoperatively. This study demonstrates

that this combination of a broad-acting, wound-healing, osteostimulatory growth factor and an osteoconductive scaffold is a viable alternative to the use of autograft in hindfoot and ankle arthrodesis.

Appendix

 A table showing study entry criteria is available with the online version of this article as a data supplement at jbjs.org. ■

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