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Prospective Randomized Controlled Trial of Hindfoot and Ankle Fusions Treated With rhPDGF-BB in Combination With a β-TCP-Collagen Matrix

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Abstract

Background: Ankle and hindfoot arthrodesis is often supplemented with autograft to promote bony union. Autograft harvest can lead to increased perioperative morbidity. Purified recombinant human platelet-derived growth factor BB homodimer (rhPDGF-BB) has stimulated bone formation in mandibular defects and hindfoot fusion. This randomized controlled trial evaluated the efficacy and safety of rhPDGF-BB combined with an injectable, osteoconductive beta-tricalcium phosphate (β-TCP)–collagen matrix versus autograft in ankle and hindfoot fusions.

Methods: Seventy-five patients requiring ankle or hindfoot fusion were randomized 5:1 for rhPDGF-BB/β-TCP-collagen (treatment, n = 63) or autograft (control, n = 12). Prospective analysis included 142 autograft control subjects from another clinical trial with identical study protocols. Standardized operative and postoperative protocols were used. Patients underwent standard internal fixation augmented with autograft or 0.3 mg/mL rhPDGF-BB/β-TCP-collagen. Radiologic, clinical, and quality-of-life outcomes were assessed over 52 weeks. Primary outcome was joint fusion (50% or more osseous bridging on computed tomography) at 24 weeks. Secondary outcomes included radiographs, clinical healing status, visual analog scale pain score, American Orthopaedic Foot & Ankle Society Ankle-Hindfoot Scale score, Foot Function Index score, and Short Form-12 score. Noninferiority *P* values were calculated.

Results: Complete fusion of all involved joints at 24 weeks as indicated by computed tomography was achieved in 53 of 63 (84%) rhPDGF-BB/β-TCP-collagen-treated patients and 100 of 154 (65%) autograft-treated patients ($P < .001$). Mean time to fusion was 14.3 ± 8.9 weeks for rhPDGF-BB/β-TCP-collagen patients versus 19.7 ± 11.5 weeks for autograft patients ($P < .01$). Clinical success at 52 weeks was achieved in 57 of 63 (91%) rhPDGF-BB/β-TCP-collagen patients and 120 of 154 (78%) autograft patients ($P < .001$). Safety-related outcomes were equivalent. Autograft controls had 2 bone graft harvest infections.

Conclusions: Application of rhPDGF-BB/β-TCP-collagen was a safe, effective alternative to autograft for ankle and hindfoot fusions, eliminating the pain and morbidity associated with autograft harvesting.

Level of Evidence: Therapeutic Level I, prospective randomized study.

Keywords: ankle fusion, autogenous bone graft, collagen, hindfoot fusion, nonunion, platelet derived growth factor, randomized controlled trial, rhPDGF-BB

End-stage hindfoot and ankle arthritis causes musculoskeletal pain, limits function, and impairs quality of life.[12] Arthrodesis reduces the pain and corrects the bony deformity associated with end-stage hindfoot and ankle arthritis. However, a common and major complication of joint fusion is nonunion. A recent systematic review of 1262 ankle arthrodeses across 39 studies reported a 10% incidence of nonunion.[13] In high-risk patients, the incidence of nonunion following ankle fusion may reach 41%.[10]

Nonunion following hindfoot and ankle fusion results in increased morbidity and disability.[2] For this reason, arthrodesis surgery is often supplemented with autogenous bone graft (autograft) to promote bony union.[3,8,19] Until recently, bone autograft was the only available graft material with

osteogenic, osteoinductive, and osteoconductive properties. However, complications associated with harvesting autograft include blood loss, postoperative pain, risk of infection, heterotopic bone formation, hernia, and nerve injury.[8,10,13,14] Alternatives to autograft for ankle and hindfoot fusions that can eliminate such risks while promising favorable healing rates would presumably be well received. Currently, there is an unmet clinical need for a cost-effective, synthetic, osteogenic bone graft substitute that avoids the morbidity associated with harvesting autograft.

A suitable alternative to autograft is platelet-derived growth factor (PDGF), which stimulates blood vessel formation and is required for cell division of fibroblasts, thereby promoting tissue repair.[1] The angiogenic properties of PDGF, combined with its strong mitogenic and chemotactic effects on mesenchymal cells, play a central role in the early phases of the healing cascade.[18] Additionally, PDGF mobilizes mesenchymal stem cells and helps stabilize newly forming vessels.[9,15,20] Recombinant DNA technology has been used to purify the most active PDGF isoform in bone and other connective tissues, recombinant human PDGF BB homodimer (rhPDGF-BB). This homodimer was recently combined with beta-tricalcium phosphate (β-TCP), an osteoconductive scaffold, and has been shown to promote bone healing in foot and ankle arthrodesis.[4,5,16] A prospective, randomized clinical trial demonstrated that treatment with rhPDGF-BB combined with β-TCP resulted in fusion rates comparable to those achieved through treatment with autograft, with less pain and fewer side effects.[6]

A novel bone regeneration device was recently developed consisting of an injectable formulation of β-TCP/type I bovine collagen matrix combined with rhPDGF-BB that can be applied through a cannula for ease of access to joints intended for fusion. An initial independent, open-label pilot study with 10 study subjects resulted in 10 of 10 (100%) clinical unions and no unexpected serious adverse device effects. We conducted a prospective, randomized controlled, multicenter trial of rhPDGF-BB/β-TCP-collagen treatment in foot and ankle fusions to evaluate its impact on osseous healing and assess any complications associated with this graft material.

Methods

Study Design

A prospective, randomized controlled, blinded, noninferiority, pivotal clinical trial was undertaken at 5 clinical sites across Canada between September 2009 and June 2011 to evaluate the safety and effectiveness of rhPDGF-BB/β-TCP-collagen (Augment Injectable Bone Graft, BioMimetic Therapeutics, Inc, now Wright Medical Technologies, Franklin, TN). Health Canada and the local hospital research ethics boards provided approval for this trial, which was prospectively registered at clinicaltrials.gov (NCT01008891). Patients who required ankle or hindfoot fusion were enrolled in accordance with good clinical practice guidelines. Eligible subjects who met the inclusion criteria (Table 1) and provided informed consent were randomized in a 5:1 ratio of rhPDGF-BB/β-TCP-collagen to autograft, to allow for a greater number of patients to be treated with rhPDGF-BB/β-TCP-collagen and for collection of more long-term safety data on rhPDGF-BB/β-TCP-collagen. Randomization was performed via computer modeling by an independent contractor within 2 days of the fusion procedure, and the result was forwarded to the surgeon shortly before the procedure.

Patients were treated with ankle or hindfoot fusion using standard rigid internal fixation techniques and either autograft or rhPDGF-BB/β-TCP-collagen. Any patient who had bone loss and/or deformity requiring structural graft insertion or more than 9 cc of bone graft was excluded. Routine graft harvest for patients randomized to receive autograft was performed through a separate exposure. For patients randomized to receive the synthetic graft material, the individual components (rhPDGF-BB 0.3 mg/mL liquid and β-TCP-collagen matrix) were mixed and allowed to sit for at least 10 minutes to maximize saturation prior to insertion via cannula at the fusion site.

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Table 1. Study Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
The patient signed Research Ethics Board–approved informed consent form.	The patient had undergone previous surgery of the proposed fusion site or required revision of a failed total ankle arthroplasty.
The patient had a bone defect in the ankle or hindfoot requiring fusion with supplemental bone graft or synthetic substitute, requiring one of the following procedures: • Ankle joint fusion • Subtalar fusion • Talonavicular fusion • Calcaneocuboid fusion • Triple arthrodesis (subtalar, talonavicular, and calcaneocuboid joints) • Double fusion (combination of any 2 of subtalar, calcaneocuboid, and talonavicular joints)	The patient required a pantalar fusion (ie, fusion of the ankle plus all hindfoot joints [talonavicular, subtalar, and calcaneocuboid]) or a tibiotalocalcaneal fusion (ie, fusion of ankle and subtalar joints).
The fusion site was able to be rigidly stabilized with no more than 3 screws across the fusion site. Supplemental pins and staples may have been used. Supplemental screws external to the fusion site(s) were also allowed.	The fusion site required plate fixation or more than 3 screws to achieve rigid fixation, more than 3 kits of rhPDGF-BB 0.3 mg/mL liquid and β-TCP-collagen matrix, or more than 9 cc of autograft material.
The patient was independent and ambulatory and could comply with all postoperative assessments.	The fusion site required structural bone graft, allograft, bone graft substitute, platelet-rich plasma, or bone marrow aspirate for completion of the fusion procedure.
The patient was at least 18 years of age and was considered to be skeletally mature.	There was radiographic evidence of bone cysts, segmental defects, or growth plate fractures around the fusion site that might negatively affect bony fusion.
	The patient had untreated malignant neoplasm(s), was undergoing radiation or chemotherapy, or was diagnosed with hypercalcemia.
	The patient had a preexisting sensory impairment (eg, diabetes with baseline sensory impairment) that limited his or her ability to perform objective functional measurements and/or might place the patient at risk for complications. Diabetic patients who were not sensitive to the 5.07 monofilament (Semmes-Weinstein) were excluded.
	The patient had a metabolic disorder known to adversely affect the skeleton, other than primary osteoporosis or diabetes (eg, renal osteodystrophy or hyperglycemia).
	The patient had chronically used medications known to affect the skeleton (eg, glucocorticoid use of more than 10 mg/d).
	The patient had a prefracture neuromuscular deficiency that limited the ability to perform objective functional measurements.
	The patient was physically or mentally compromised (eg, currently being treated for a psychiatric disorder, senile dementia, Alzheimer's disease, etc) to the extent that the investigator judged the patient to be unable or unlikely to remain compliant.
	The patient had an allergy to yeast-derived products or an allergy to bovine collagen and/or other bovine source medications, supplements, or products.
	The patient had a history of anaphylaxis or multiple nonenvironmental allergies that had precipitated an anaphylactic reaction.
	The patient had received an investigational therapy or approved therapy for investigational use within 30 days of surgery or during the follow-up phase of this study.

(continued)

Table 1. (continued)

Inclusion Criteria	Exclusion Criteria
	The patient was a prisoner, was known or suspected to be transient, or had a history of drug and/or alcohol abuse within the 12 months prior to screening for study entry.
	The patient was pregnant or was a female intending to become pregnant during the study period. A urine pregnancy test was administered within 21 days of the operative visit to any female unless she was postmenopausal, had been sterilized, or was practicing a medically accepted method of contraception.
	The patient was deemed morbidly obese (body mass index >45 kg/m^2).
	The patient had an acute infection at the operative site at the time of study enrollment.

Investigators estimated the amount of autograft used with sterile graduated surgical cups. A volume of 1 to 3 cc of graft material was used in 50.8% of rhPDGF-BB/β-TCP-collagen patients and 29.2% of autograft patients; 4 to 6 cc was used in 47.6% of rhPDGF-BB/β-TCP-collagen and 47.4% of autograft patients; and 7 to 9 cc was used in 1.6% of rhPDGF-BB/β-TCP-collagen and 22.7% of autograft patients. The rhPDGF-BB/β-TCP-collagen is more compressible than autograft, which may account for the difference in volume used compared with autograft. Autograft was harvested from the iliac crest graft in 12.3% of control group patients, distal tibia in 18.2%, proximal tibia in 47.4%, calcaneus in 13.6%, and an alternative lower extremity site in 8.4%.

Patients

A total of 217 patients were included in this study (Figure 1). Seventy-five patients were randomized and treated with either rhPDGF-BB/β-TCP-collagen (treatment group; n = 63) or autograft (12 patients). An additional control group of 142 patients randomized to autograft in another study with identical inclusion, exclusion, and outcome criteria collected by the same study group[6] were included in this analysis, for a total of 154 control patients. Four (6.3%) rhPDGF-BB/β-TCP-collagen treated patients and 6 (3.9%) autograft-treated patients were discontinued prior to study completion: 3 treatment patients and 1 control patient were discontinued upon investigator request; 1 treatment patient and 3 control patients declined to continue participation; 1 control patient was lost to follow-up, and 1 control patient required revision surgery. Missing data were excluded from analysis for all continuous endpoints and were treated as failures for all binary endpoints. The patient who required revision surgery was considered a failure for all binary outcome measures.

Baseline Characteristics

Mean age was 55.5 years (range, 18-81 years) in the rhPDGF-BB/β-TCP-collagen treatment group and 57.5 years (range, 20-82 years) in the autograft control group. The treatment group consisted of 58.7% males and the control group consisted of 56.5% males. The most common primary diagnoses for the 217 patients were posttraumatic arthritis or deformity (47.5%), primary osteoarthritis (36.4%), and rheumatoid arthritis (5.5%). Body mass index, operated side, and risk factors for nonunion (ie, smoking, obesity, previous revision surgery, diabetes) were comparable between the groups.

A numerical scale was used to assess postoperative pain; standard postoperative analgesia was directed by the investigator as needed for pain management. All postoperative medications taken by the subject were recorded.

Eight postoperative clinical evaluations were conducted by the investigator according to protocol, at weeks 1-3, 6, 9, 12, 16, 24, 36, and 52. The patient's clinical and functional healing status was recorded at each visit. Plain film radiographs were collected at weeks 1-3, 6, 12, 24, and 52. Computed tomography (CT) was performed at weeks 9, 16, 24, and 36, specifically to assess patient outcomes for this clinical trial. These images were viewed by each clinician as part of routine follow-up care and were also independently assessed by a blinded, fellowship-trained, board-certified musculoskeletal radiologist responsible for determining all radiologic endpoints. Benchmarks of 0%-24%, 25%-49%, 50%-74%, and 75%-100% were used to assess percentage of osseous bridging across each joint intended for fusion.[8] Radiographs were also assessed by the independent radiologist and investigator at each time point. Only the radiologist was blinded to the assigned treatment for each patient.

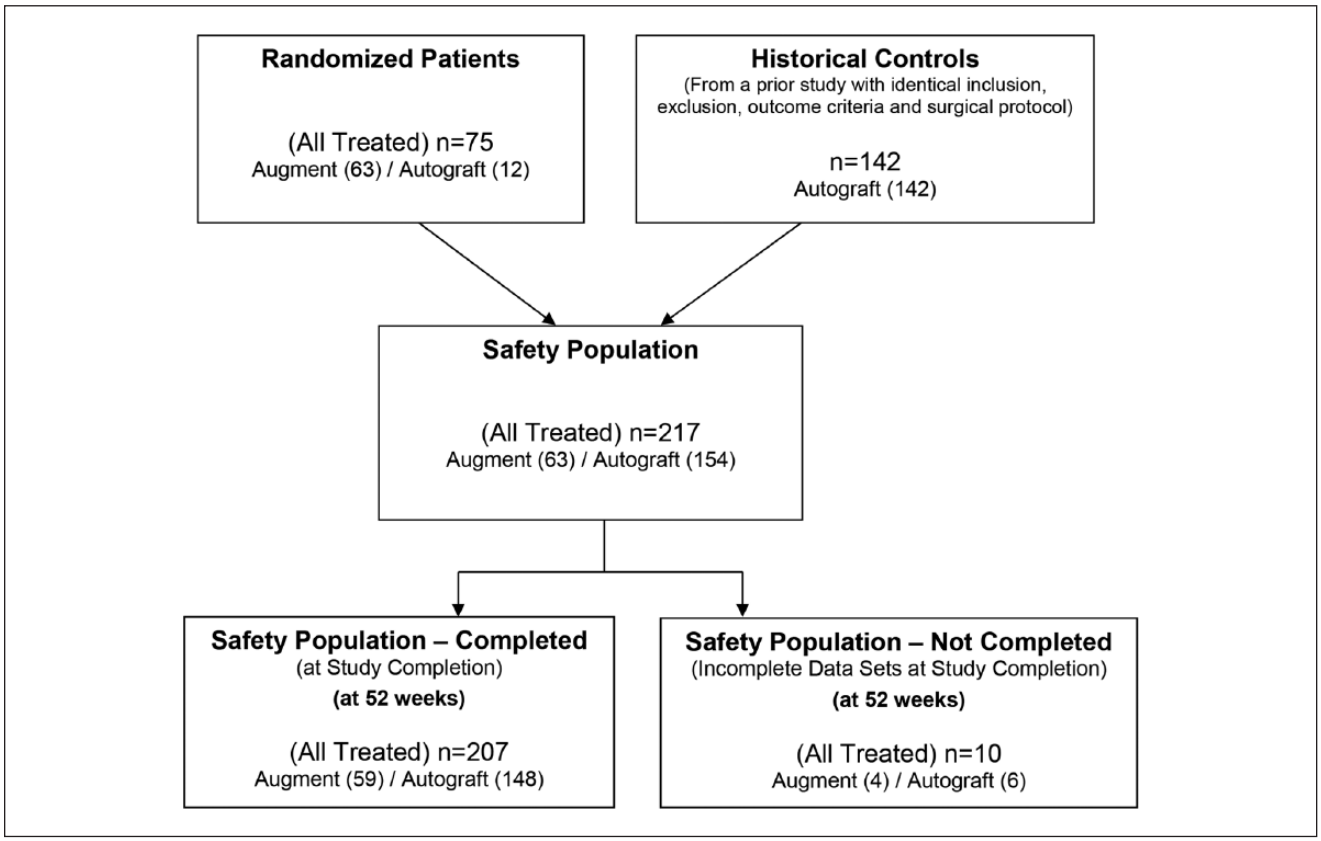

Figure 1. Patient disposition flowchart. Seventy-five patients were randomized and treated. A control group of 142 patients randomized to autograft in a previous study with identical inclusion, exclusion, and outcome criteria and treated in an identical surgical protocol[6] were included in the analysis, resulting in a safety study population of 217 patients. Ten patients were discontinued prior to study completion.

Study Outcomes

Clinical, functional, and radiologic outcomes were assessed to monitor safety, clinical healing, and progression of fusion. Adverse events, complications, protocol deviations, and revision surgeries were recorded.

The primary outcome was joint fusion, as assessed by CT at 24 weeks, where osseous bridging of 50% or more across the articulation was considered a success (ie, fusion). When multiple joints were being fused, the full complement of treated joints was assessed (ie, all treated joints had to be fused for the procedure to be deemed a success), and each individual joint was independently assessed, termed "all joints." Logistic regression models were used to estimate the differences between the 2 treatments while accounting for the correlation between individual joints within a patient, since the joints cannot be assumed to be independent. The logistic regression model results were consistent with the results of the all-joints analyses of fusion success rates.

Secondary outcomes included clinical, functional, quality of life, and additional radiologic assessments, reported by the patient, surgeon, and independent radiologist. "Clinical healing status" was based on the surgeon's global assessment of the patient's progress at the level of the individual joint (ie, considering every joint independently) and at the level of the full joint (if more than 1 joint was fused). Therapeutic failure was defined as any nonunion or delayed union requiring secondary therapeutic intervention. Outcomes were assessed using 0- to 100-mm visual analog scale (VAS) pain scores at the operative site, with weight bearing, and at the graft harvest site, as well as Short Form (SF)-12, American Orthopaedic Foot & Ankle Society (AOFAS) Ankle-Hindfoot Scale, and Foot Function Index (FFI). "Clinical success" was based on more than 20-mm improvement in VAS pain with weight bearing and lack of any secondary procedure (revision) requirement. "Subject performance composite success" was achieved when all of the following were met: full complement CT fusion, improvement more than 20 mm in weight-bearing VAS pain, more than 10-points reduction in FFI score, harvest site VAS pain less than 20 mm, and no serious adverse events or secondary procedures to enhance healing. Secondary efficacy radiologic endpoints included time to fusion and extent of osseous bridging based on both CT and

plain radiographs. Radiographic fusion was determined by the presence of osseous bridging across at least 3 of 4 predefined aspects (anterior, posterior, medial, and lateral).

Safety-related outcomes analyzed included frequency and severity of adverse events and their potential relationship to the study device, complications at the operative site including nonunion, and discontinued patients due to death or important adverse events. Safety radiologic parameters included heterotopic bone formation, β-TCP migration, and fixation complications. Patients were screened for anti-rhPDGF-BB-specific antibodies using enzyme-linked immunosorbent assay, followed by receptor binding radioimmunoassay to detect neutralization potential.

Statistical Analysis

The purpose of the trial was to establish noninferiority of rhPDGF-BB/β-TCP-collagen relative to autograft. Thus, statistically significant noninferiority *P* values (ie, when $P \leq .05$) represent outcomes for which rhPDGF-BB/β-TCP is essentially equivalent to autograft.

A total of 217 study subjects were analyzed (63 rhPDGF-BB/β-TCP-collagen-treated patients and 154 autograft-treated controls). The combined autograft groups were examined for homogeneity with respect to the primary endpoint, to assess the validity of the combined autograft data set as a comparator to the rhPDGF-BB/β-TCP-collagen-treated cohort.

Treatment groups were examined for noninferiority of the primary and secondary outcomes. Noninferiority tests of binary endpoints were carried out by fitting a 1-sided lower confidence interval for the odds ratio, defined as the odds of fusion with rhPDGF-BB/β-TCP-collagen over the odds of fusion with autograft, where an odds ratio of 1.0 indicates that the fusion rates for the 2 treatment groups are equal. The odds ratio statistic possesses high power for rates near 50% and lower power for rates near 0% or 100%. Noninferiority *P* values were computed using Fisher's exact test and a 95% confidence interval. Binary endpoints are reported as counts and percentages, with corresponding noninferiority *P* values. Fusion success required documented evidence of success. Continuous endpoints are reported as means and standard deviations and corresponding noninferiority *P* values based on 2-sample *t* tests. All binary endpoints used an odds ratio of 0.5 noninferiority margins, and all continuous scales used 10-point noninferiority margins, except the SF-12, which used a 5-point noninferiority margin.

The proportion of patients with clinically important graft harvest site pain (ie, 20 mm or more) was calculated. Treatment adverse event rates were compared using 2-sided Fisher's exact test, where statistically significant *P* values (ie, $P \leq .05$) represent outcomes for which rhPDGF-BB/β-TCP is different from autograft.

Results

Radiologic Effectiveness

Radiologic effectiveness results are summarized in Table 2. For the primary outcome of joint fusion, CT analysis at 24 weeks demonstrated noninferiority of rhPDGF-BB/TCP-collagen compared with autograft. In the full complement analysis, the rhPDGF-BB/TCP-collagen patients had a fusion rate of 84.1%, and autograft patients had a fusion rate of 64.9% ($P < .001$); for the all-joints analysis, 86.4% of rhPDGF-BB/β-TCP-collagen-treated joints were fused compared with 67.0% of autograft-treated joints ($P < .001$).

Radiographic union rates at 52 weeks also demonstrated noninferiority of rhPDGF-BB/β-TCP-collagen compared with autograft in both the full complement analysis and all-joints analysis (Table 2).

Mean time to fusion in rhPDGF-BB/TCP-collagen patients was 14.3 ± 8.9 weeks compared with 19.7 ± 11.5 weeks for autograft ($P < .001$).

Clinical Outcomes

Evaluation of clinical union established noninferiority of rhPDGF-BB/β-TCP-collagen compared with autograft (ie, $P < .001$) for the majority of secondary outcomes at 24 and 52 weeks (Table 3). Clinical outcome measures, including the SF-12, FFI, and AOFAS Ankle-Hindfoot Scale, all showed improvement from 24 weeks to 52 weeks postoperatively in both groups and demonstrated noninferiority (Table 3). The 52-week mean FFI score was 15.0 ± 17.5 in the rhPDGF-BB/β-TCP-collagen group and 17.4 ± 20.4 in the autograft group ($P < .001$), where a lower score indicates a better result.

Mean VAS pain scores for the fusion site and with weight bearing also demonstrated noninferiority of rhPDGF-BB/β-TCP-collagen treatment compared with autograft at 1 year postoperatively (Table 3). Furthermore, patients treated with autograft required a graft harvest procedure, and 13.6% and 9.1% reported clinically important graft harvest site pain (20 mm or more on VAS) at weeks 24 and 52, respectively.

The clinical success rate was 88.9% in the rhPDGF-BB/β-TCP-collagen group and 77.9% in the autograft group at 24 weeks, and 90.5% and 77.9%, respectively, at 52 weeks, demonstrating noninferiority ($P < .001$). At 24 weeks, rhPDGF-BB/β-TCP-collagen-treated patients achieved 82.5% clinical union for the full complement and 85.2% for all joints, compared with 83.1% and 83.5%, respectively, in autograft-treated patients. Although noninferiority of rhPDGF-BB/β-TCP-collagen was not established based on the odds ratio ($P = .07$ for full complement of joints; $P = .12$ for all joints), the rates of clinical union between the 2 groups were not more than 5% apart, and clinical union for all joints using rhPDGF-BB/β-TCP-collagen

Table 2. Summary of Radiologic Results Based on CT Scans and Radiography, at 24 and 52 Weeks.

	Full Complement of Joints (n = 217)				Individual Joints [All Joints] (n = 311 Joints)			
	rhPDGF-BB/β-TCP-Collagen (n = 63 Joints)	Autologous Bone Graft (n = 154 Joints)	Odds Ratio[a]	*P* Value[b]	rhPDGF-BB/β-TCP-Collagen (n = 81 Joints)	Autologous Bone Graft (n = 230 Joints)	Odds Ratio[a]	*P* Value[b]
24 weeks								
Primary endpoint								
CT full complement of fusion rates	84.1%	64.94%	2.06	<.001	86.4%	67.0%	3.08	<.001
Secondary endpoints								
Time to full complement CT fusion, wk, mean ± SD	14.3 ± 8.9	19.7 ± 11.5		<.001				
Radiographic union rate (3 aspects)	42.9%	33.8%	1.47	<.001	45.7%	39.1%	1.07	.051
Radiographic union rate (2 aspects)	84.1%	69.5%	2.33	<.001	86.4%	72.2%	1.84	.001
52 weeks								
Secondary endpoints								
Radiographic union rate (3 aspects)	46.0%	37.0%	1.45	<.001	54.3%	45.7%	1.76	.009
Radiographic union rate (2 aspects)	84.1%	76.6%	1.62	.001	84.0%	79.6%	1.30	.016

Abbreviations: CT, computed tomography; β-TCP, beta-tricalcium phosphate; rhPDGF-BB, recombinant human platelet-derived growth factor BB homodimer.
[a]Odds of rhPDGF-BB/β-TCP-collagen over autograft.
[b]All *P* values are for noninferiority.

was higher. Clinical healing improved modestly between 6 and 12 months. Clinical union at 1 year was observed in 87.3% of rhPDGF-BB/β-TCP-collagen patients and 87.7% of autograft patients by full complement analysis ($P = .099$) and in 86.4% of rhPDGF-BB/β-TCP-collagen patients and 87.8% of autograft patients by the all-joints analysis ($P < .363$).

Therapeutic failures, defined as nonunion or delayed union requiring surgery or further therapeutic intervention, occurred in 7 of 63 (11.1%) rhPDGF-BB/β-TCP-collagen patients and 13/154 (8.4%) autograft patients ($P = .65$).

Safety-Related Outcomes

Safety results are summarized in Table 4. Equivalent rates of device-related treatment emergent adverse events (TEAEs), serious TEAEs, complications associated with surgery, and infections were observed in the treatment and control groups. No device-related serious TEAEs were reported in either group (Table 4).

Two patients in the autograft group required treatment for complications at the autograft harvest site: 1 patient required hospitalization for irrigation and debridement of a wound infection, and the other developed cellulitis that required oral antibiotics.

There were no cancer-related adverse events in the rhPDGF-BB/β-TCP group and 2 events (renal carcinoma and endometrial cancer) in the autograft group.

Nonneutralizing antibody titers were observed in 13.9% of rhPDGF-BB/β-TCP-collagen-treated patients and 3.6% of autograft-treated patients at 24 weeks. Neutralizing antibodies to PDGF-BB were detected in 6 (9.5%) subjects in the rhPDGF-BB/β-TCP-collagen group and 2 (1.3%) subjects in the autograft group. Immune responses were transient; notably, any patients with neutralizing antibodies returned to baseline by 52 weeks.

Discussion

This prospective, multicenter, randomized controlled, radiologically blinded trial demonstrated equivalent outcomes of synthetic rhPDGF-BB combined with a flowable, osteoconductive β-TCP-collagen matrix when compared with the gold standard of autograft in 217 patients undergoing ankle or hindfoot fusion. The rhPDGF-BB/β-TCP-collagen treatment produced equivalent rates of joint fusion, radiologic outcomes, clinical success, and functional patient improvement compared with autograft treatment, with the advantage of being better tolerated by the patient and safer by virtue of elimination of the need for harvesting of bone graft.

Fusion rates for rhPDGF-BB/β-TCP-collagen, as evaluated by CT scans at 24 weeks and radiographs at 52 weeks, were statistically noninferior (equivalent) to autograft. Fusion in the foot and ankle was assessed with rigorous benchmarks that required at least 50% osseous bridging on CT and a radiographic endpoint of at least 3 of 4 aspects to declare

Table 3. Clinical Results Summary at 24 and 52 Weeks.

	24 Weeks			52 Weeks		
	rhPDGF-BB/β-TCP-Collagen (n = 63)	Autologous Bone Graft (n = 154)	*P* Value[a]	rhPDGF-BB/β-TCP-Collagen (n = 63)	Autologous Bone Graft (n = 154)	*P* Value[a]
Clinical healing status (patient level)	82.5%	83.8%	.086	87.3%	88.3%	.130
Clinical healing status (by joint)						
Full complement of joints	82.5%	83.1%	.066	87.3%	87.7%	.099
All joints (assessed individually) (n = 311)	85.2%	83.5%	.116	86.4%	87.8%	.363
Subject performance composite success rate[b]	49.2%	40.9%	<.001	—	—	—
Clinical success rate[c]	88.9%	77.9%	<.001	90.5%	77.9%	<.001
Therapeutic failure rate[d]	15.9%	11.7%	.156	11.1%	8.4%	.150
Clinically important graft harvest site pain[e]	0%	13.6%	<.001	0%	9.1%	<.001
SF-12 PCS, mean ± SD	41.5 ± 8.7	41.2 ± 9.5	<.001	44.6 ± 8.5	45.0 ± 9.7	<.001
FFI total score, mean ± SD	21.4 ± 19.3	22.8 ± 20.4	<.001	15.0 ± 17.5	17.4 ± 20.4	<.001
AOFAS total score, mean ± SD	72.1 ± 16.1	73.4 ± 16.1	<.001	80.0 ± 13.9	78.5 ± 17.0	<.001
Fusion site pain, mean ± SD	18.6 ± 22.7	16.7 ± 23.0	.005	12.2 ± 19.4	13.0 ± 23.5	.001
Weight-bearing pain, mean ± SD	22.2 ± 25.3	20.1 ± 26.0	.014	13.0 ± 20.0	15.6 ± 25.4	<.001
Graft harvest site pain,[e] mean ± SD	0 ± 0	8.9 ± 17.9	<.001	0 ± 0	6.2 ± 16.6	<.001

Abbreviations: AOFAS, American Orthopaedic Foot & Ankle Society; β-TCP, beta-tricalcium phosphate; FFI, Foot Function Index; rhPDGF-BB, recombinant human platelet-derived growth factor BB homodimer; SF-12, Short Form-12; PCS, Physical Component Summary score.
[a]*P* values are for noninferiority, with the exception of graft harvest site pain, where *P* values are for superiority.
[b]Subject Performance Composite Success is achieved when all of the following conditions are met: full complement computed tomography (CT) fusion, 20 mm or more improvement in weight-bearing VAS pain score, 10-point or greater reduction in FFI score; graft harvest site VAS pain 20 mm or less, and no serious adverse events or secondary procedures during the study period. The rate was not determined at 52 weeks because the CT scan component was not performed at 52 weeks.
[c]Clinical success is defined as improved weight-bearing VAS pain score compared with baseline and no secondary procedures (ie, bone stimulator or revision surgery) needed.
[d]Therapeutic failures are patients who were assessed as having nonunion or delayed union or who required secondary therapeutic intervention for nonunion or delayed union.
[e]rhPDGT-BB/β-TCP-collagen patients did not experience graft harvest site pain because there was no graft harvest.

Table 4. Safety Results Summary.

	rhPDGF-BB/β-TCP-Collagen (n = 63)		Autograft (n = 154)		
	Subjects, n (%)	Events, n	Subjects, n (%)	Events, n	*P* Value[a]
TEAEs	51 (81.0)	224	115 (74.7)	369	.3801
Serious TEAEs	9 (14.3)	9	23 (14.9)	31	>.999
Device-related TEAEs	2 (3.2)	2	6 (3.9)	10	>.999
Complications associated with operative procedure	27 (42.9)	48	49 (31.8)	71	.1579
Serious operative complications	5 (7.9)	5	11 (7.1)	12	.7826
Treatment emergent infections	10 (15.9)	10	20 (13)	22	.6651
Serious operative wound infections	2 (3.2)	2	6 (3.9)	6	.7979
Chronic pain at autograft donor site (20 mm or more on VAS) at 52 weeks[b]	0 (0)	0	14 (9.1)	14	<.001

Abbreviations: β-TCP, beta-tricalcium phosphate; rhPDGF-BB, recombinant human platelet-derived growth factor BB homodimer; TEAE, treatment emergent adverse event; VAS, visual analog scale.
[a]Two-sided Fisher exact test for a treatment difference (superiority) based on subject counts.
[b]rhPDGF-BB/β-TCP-collagen patients did not experience graft harvest site pain because there was no graft harvest.

union.[7] Patients treated with rhPDGF-BB/β-TCP-collagen had a notably shorter time to CT fusion (14.3 weeks) compared with the autograft control group (19.7 weeks). The key safety-related outcomes were equivalent in both groups. Additionally, patients treated with rhPDGF-BB/β-TCP had no donor-site pain, in contrast to autograft patients.

In the past decade, the safety and efficacy of rhPDGF-BB as an alternative to autograft have been demonstrated in several multicenter trials of foot and ankle arthrodesis.[4-6] Safety and efficacy have also been demonstrated in a series of clinical trials for alveolar bone applications[17]; rhPDGF-BB/β-TCP received FDA approval for this application in 2005 and has been used in more than 200,000 patients, with no serious device-related adverse events and no reported increase in cancer incidence or mortality. The rhPDGF-BB/β-TCP complex is also approved for use in orthopedic foot and ankle surgery as a bone graft substitute in Canada and Australia.

The current study builds on this earlier work by evaluating rhPDGF-BB in combination with an injectable formulation of β-TCP-collagen matrix, which can be applied through a cannula for easier access to joints in the ankle or hindfoot intended for fusion. The mitogenic, chemotactic, and angiogenic properties of PDGF-BB[15,16,18] make it well suited to promote joint fusion in the distal extremity, where diminished perfusion presents challenges to bone regeneration not seen in more proximal sites. Foot and ankle surgery patients considered at risk for nonunion due to compromised healing (eg, smokers, diabetic patients, the elderly, patients receiving anti-inflammatory medication) could benefit from the angiogenic properties of PDGF.[5,15,16] The rhPDGF-BB is produced in a quality-controlled environment that guarantees consistency. When it is combined with β-TCP, and particularly an injectable β-TCP-collagen matrix, this permits delivery of a precise therapeutic dose of rhPDGF-BB and yields a more predictable outcome compared with treatment with quantitatively and qualitatively variable autograft.

Patients who received rhPDGF-BB/β-TCP-collagen were obviously spared autograft donor-site pain and morbidity. This study used autograft techniques and harvest sites accepted as common standards by orthopedic foot and ankle surgeons, and yet 9% of patients treated with autograft still had pain at the harvest site 1 year after surgery. Serious complications at autograft harvest sites included infection requiring follow-up care and cellulitis requiring additional treatment.

This study has limitations. While the control cohort represents the largest and most comprehensive autograft comparator dataset in foot and ankle fusion surgery, it was drawn from both the current trial and an identical historical study. Although the study protocols included no differences in study parameters, care must be taken with regard to study claims. As such, we believe these data continue to support the equivalence of rhPDGF-BB to autograft, but we refrain from claiming superiority. Second, because of the utility of odds ratio analysis in modeling situations, all binary outcomes were tested using this type of analysis, which possesses high power for rates near 50% and lower power for rates near 0% and 100%. In contrast, comparison of rates based on the difference of 2 proportions provides greater power at the ends of the range versus in the middle. Thus, while success rates of 87.3% and 87.7% as observed for clinical healing status for the full complement of joints may appear to be identical, the *P* value from the odds ratio noninferiority test failed to produce significance ($P < .099$). Selective use of the difference of 2 proportions test in such cases may have yielded *P* values indicating significance. However, we felt it was more important to perform consistent tests of noninferiority across all study parameters, thereby sacrificing power to measure noninferiority at the ends of the ranges.

In conclusion, the combination of angiogenic and osteogenic rhPDGF-BB with a flowable, osteoconductive scaffold of β-TCP-collagen was a viable alternative to the use of autograft in hindfoot and ankle fusion surgery. Use of this synthetic bone graft material also eliminated the pain and morbidity associated with the autograft harvesting procedure.

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