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Recombinant Human Platelet–Derived Growth Factor BB in Combination With a Beta-Tricalcium Phosphate (rhPDGF-BB/β-TCP)-Collagen Matrix as an Alternative to Autograft

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Abstract

Background: Joint arthrodesis often employs autograft to promote union; graft harvesting can lead to perioperative morbidity. A Canadian randomized controlled trial (RCT) demonstrated that recombinant human platelet–derived growth factor BB homodimer (rhPDGF-BB) combined with beta-tricalcium phosphate (β-TCP)-collagen was a safe, effective alternative to autograft. This multicenter North American RCT compared the safety and efficacy of rhPDGF-BB/β-TCP-collagen with autograft for ankle and hindfoot fusion. Subclassification using propensity scores (PS) incorporated patients from previous trials for enhanced statistical power for noninferiority testing and broader review of treatments.

Methods: Patients requiring ankle or hindfoot arthrodesis and supplemental bone graft were treated with rhPDGF-BB/β-TCP-collagen ($n = 69$) or autograft ($n = 35$). Outcomes included joint fusion on computed tomography (24 weeks), clinical healing status, visual analog scale (VAS) pain, Short-Form 12 (SF-12), American Orthopaedic Foot & Ankle Society (AOFAS) Ankle-Hindfoot Scale, and Foot Function Index (FFI) scores over 52 weeks. PS methodology addressed potential selection bias arising from pooling data among these patients and 2 previous RCTs with similar inclusion criteria, surgical techniques, graft harvest techniques, and outcomes. All 132 rhPDGF-BB/β-TCP-collagen–treated patients and 167 of 189 candidate autograft-treated controls were selected for comparison by an independent statistician blinded to outcomes.

Results: In the PS subclassification, 68.1% treatment patients and 68.4% controls achieved >50% osseous bridging at fusion sites. Clinical healing status was achieved in 84.8% of treated patients and 90.7% of controls at 52 weeks. Clinical, functional, and quality of life results demonstrated noninferiority of rhPDGF-BB/β-TCP-collagen to autograft. Safety-related outcomes were equivalent.

Conclusion: PS subclassification analysis of 3 RCTs demonstrated that rhPDGF-BB/β-TCP-collagen was as effective as autograft for ankle and hindfoot fusions, with less pain and morbidity than treatment with autograft.

Level of Evidence: Level I, prospective randomized study.

Keywords: ankle fusion, autogeneous bone graft, collagen, hindfoot fusion, nonunion, platelet-derived growth factor, rhPDGF-BB, randomized controlled trial, propensity score cohort analysis

Introduction

End-stage ankle and hindfoot arthritis culminates in marked musculoskeletal pain, limited function, and impaired quality of life equivalent to that observed with end-stage hip arthritis.[19] Ankle and hindfoot arthrodesis reduces pain, improves function, and corrects bony deformity. The most common complication following ankle arthrodesis is nonunion. A meta-analysis of 39 studies of ankle arthrodesis in 1262 patients reported an overall nonunion rate of 10%,[21]

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which may reach 41% in high-risk patients.[14] Nonunion causes substantial morbidity and disability.[28]

Surgeons often use autogenous bone graft (autograft) to promote osseous fusion, particularly in higher-risk patients.[5,12,31] Complications associated with harvesting autograft include blood loss, chronic pain at the donor site, scarring, infection, heterotopic bone formation, nerve injury, and increased operating time and cost.[2,8,12,14,15,21,26] Moreover, the quality and quantity of available autograft vary with patient age, body mass index (BMI), gender, and overall health status.[4]

Suitable synthetic alternatives to autograft for ankle and hindfoot arthrodesis that eliminate the risks of autograft but provide the benefit of favorable healing rates have been sought. Platelet-derived growth factor (PDGF) stimulates blood vessel formation, stabilizes newly forming vessels, mobilizes mesechymal stem cells, and plays a key role in early phases of the healing cascade, thereby promoting tissue repair.[1,13,22,29] The purified, most active isoform of PDGF, recombinant human PDGF BB homodimer (rhPDGF-BB) combined with beta-tricalcium phosphate (β-TCP), an osteoconductive scaffold, has been shown to promote bone healing in ankle and hindfoot arthrodesis.[6,9,23] In a multicenter randomized clinical trial (RCT) of 397 patients (597 joints) requiring ankle or hindfoot arthrodesis, treatment with rhPDGF-BB/β-TCP demonstrated comparable fusion rates, less pain, and fewer side effects to those observed with treatment with autograft.[10]

More recently, an injectable formulation of rhPDGF-BB combined with β-TCP/type I bovine collagen matrix was developed to enable application through a cannula and facilitate access to the joints intended for fusion. A recent multicenter RCT of rhPDGF-BB/β-TCP-collagen treatment of 75 patients requiring ankle or hindfoot arthrodesis conducted at 5 Canadian sites demonstrated equivalent rates of joint fusion, radiologic outcomes, clinical success, and functional improvement compared to those of autograft.[7]

We report here the results of a second multicenter, noninferiority RCT in the United States and Canada to compare the safety and efficacy of rhPDGF-BB/β-TCP-collagen with autograft in ankle or hindfoot arthrodesis using a propensity score (PS) subclassification cohort study design. This type of analysis incorporates patients from previous trials to enhance statistical power for testing the primary hypothesis of noninferiority of rhPDGF-BB/β-TCP-collagen to autograft and provides a broader review of the 2 treatments.

Methods

Study Design

Between April 2011 and March 2014, a blinded, noninferiority RCT was undertaken at 20 clinical sites across the United States and Canada to evaluate the safety and effectiveness of rhPDGF-BB/β-TCP-collagen (Augment Injectable Bone Graft; Wright Medical Technologies, Franklin, TN) compared with autograft. The trial was approved by individual institutional review boards and research ethics boards and was prospectively registered at clinicaltrials.gov (NCT01305356). Patients who required hindfoot fusion and supplemental bone graft, as determined by the surgeon based on the presence of bone voids and clinical risk factors,[35] were enrolled in accordance with good clinical practice guidelines. Patients who met inclusion criteria (Appendix I) and provided informed consent were randomized in a 2:1 ratio of rhPDGF-BB/β-TCP-collagen to autograft via computer modeling by an independent contractor within 2 days of the procedure, with the result forwarded to the surgeon shortly before the procedure.

Hindfoot fusion procedures used standard rigid internal fixation techniques. Patients randomized to receive autograft underwent routine graft harvest at the proximal tibia (51.4%), distal tibia (34.3%), calcaneus (8.6%), or iliac crest (5.7%) through a separate exposure. The autograft harvest site was chosen based on the bone volume required, surgical site, and surgeon preference. For patients receiving synthetic graft material, its components (rhPDGF-BB 0.3 mg/mL liquid and β-TCP-collagen matrix) were mixed and allowed to sit for ≥10 minutes to maximize saturation prior to insertion at the fusion site with a cannula.

Eight postoperative evaluations were performed by the investigator at weeks 1 to 3, 6, 9, 12, 16, 24, 36, and 52, according to protocol. The patient's clinical and functional status were recorded and radiographs made. Computed tomography (CT) images performed at weeks 9, 16, 24, and 52 were viewed by the clinician as part of follow-up care. CT images were also independently assessed by a blinded, fellowship-trained, board-certified musculoskeletal radiologist to evaluate radiographic endpoints. Benchmarks of 0% to 24%, 25% to 49%, 50% to 74%, and 75% to 100% were used to assess percentage of osseous bridging across each joint intended for fusion.[10]

Patients: Randomized Controlled Trial

One hundred six patients were randomized (Figure 1). Two patients did not receive treatment: one withdrew consent prior to treatment; the other was deemed unfit for surgery due to vascular insufficiency. Thus, 69 patients were managed with rhPDGF-BB/β-TCP-collagen (ie, treatment) and 35 patients were managed with autograft (ie, control). Three patients (2 treatment, 1 control) were lost to follow-up, and 3 patients (1 treatment, 2 control) requested discontinuation from the study prior to 52-week completion.

The mean age was 51.7 ± 5.1 years in the rhPDGF-BB/β-TCP-collagen cohort and 51.8 ± 16.2 years in the

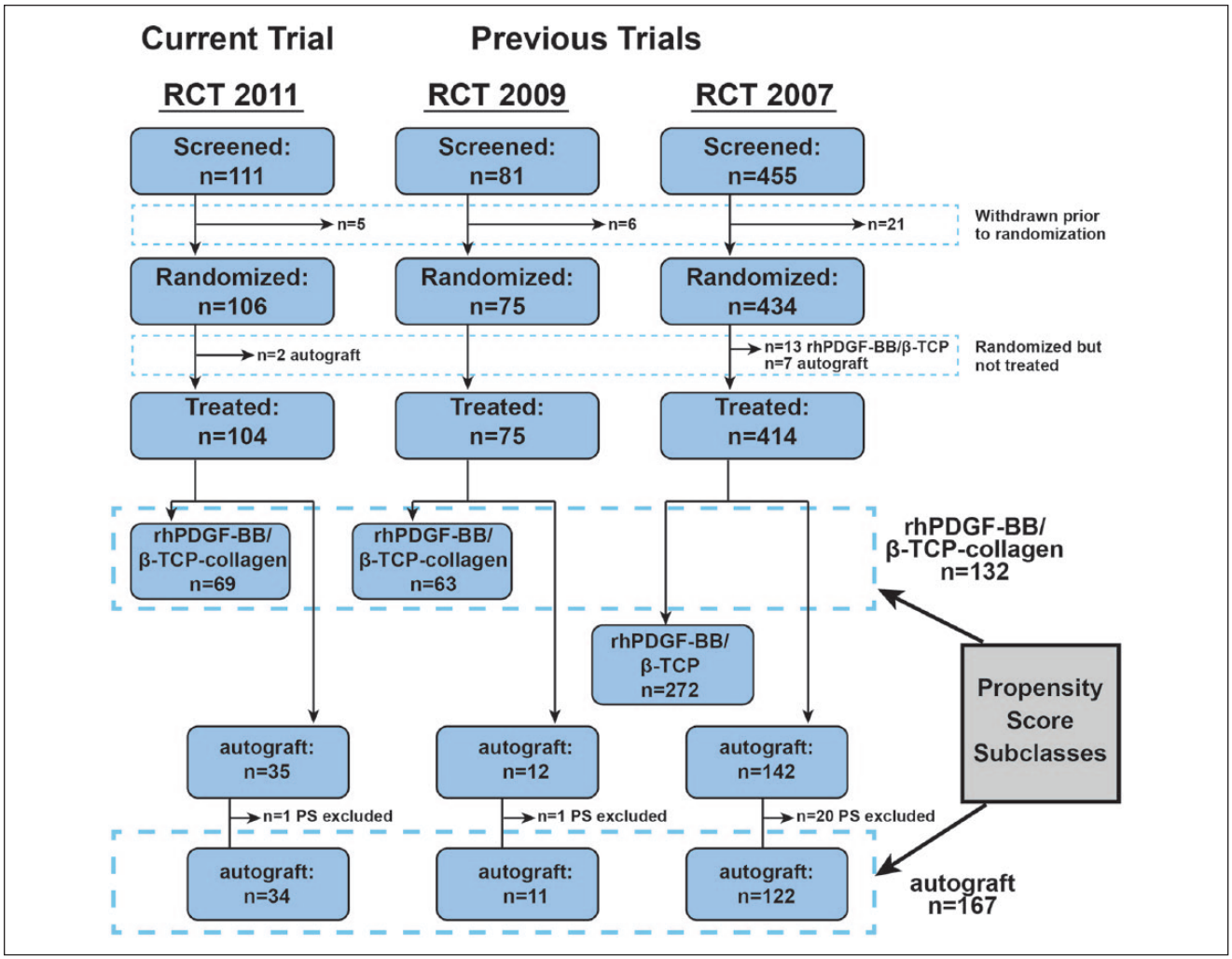

Figure 1. Patient accounting tree for 3 randomized controlled trials (RCTs) and the propensity score subclasses. The 2007 RCT and 2009 RCT included both ankle arthrodesis and hindfoot arthrodesis. The 2011 RCT included only hindfoot arthrodesis.

autograft cohort. The treatment group included 47.8% males; the control group included 34.3% males. The most common diagnoses for the 104 patients were primary osteoarthritis (52.9%) and posttraumatic arthritis or deformity (31.7%).

Subclassification Using Propensity Scores

Subclassification using PS quintiles[33] was used to address potential selection bias when combining patients treated with rhPDGF-BB/B-TCP-collagen with similar control patients treated with autograft, utilizing data from the current RCT and 2 previously published studies.[7,10] Experimental and autograft patients from the Canadian RCT of rhPDGF-BB/β-TCP-collagen treatment, conducted September 2009 to June 2011 (clinicaltrials.gov no. NCT01008891),[7] were included (Figure 1). Autograft patients from the initial RCT of rhPDGF-BB/β-TCP (Augment Bone Graft; Wright Medical Technologies, Franklin, TN), conducted across 37 clinical sites in North America from April 2007 to January 2010 (clinicaltrials.gov no. NCT00583375),[10] were also included. The experimental cohort in that trial received a slightly different formulation of synthetic graft material; thus their data were not included in the PS design. All 3 RCTs utilized similar surgical techniques, graft harvest techniques (for patients randomized to receive autograft), and clinical, functional, and radiologic outcomes. The 2 previous trials included both ankle fusion and hindfoot fusion as indications; the current trial included only hindfoot fusion. Other patient inclusion and exclusion criteria were similar for all trials, with only minor variations (Table 1).

The PS model included patient demographics such as sex, age, BMI, smoking status, type and number of joints treated; baseline AOFAS Ankle-Hindfoot Scale alignment subscore; baseline measurements of function and pain,

Table 1. Patient Inclusion and Exclusion Criteria Common Across All 3 Clinical Trials.

Inclusion Criteria	Exclusion Criteria
Signed research ethics board–approved informed consent form	Previous surgery of the proposed fusion site, or requires revision of a failed ankle fusion or total ankle arthroplasty
Requires hindfoot fusion (all 3 trials) or ankle fusion (in the 2007 and 2009 trials only) with supplemental bone graft or synthetic substitute, requiring one of the following procedures: • Subtalar fusion • Talonavicular fusion • Calcaneocuboid fusion • Triple arthrodesis (subtalar, talonavicular, and calcaneocuboid joints) • Double fusion (combination of any two of subtalar, calcaneocuboid, and talonavicular joints)	Requires 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 requires plate fixation, intramedullary rods or nails, or more than 3 screws to achieve rigid fixation, or more than 9 cc of autograft material
The patient was independent, ambulatory, and could comply with all postoperative assessments	Radiographic evidence of bone cysts, segmental defects, or growth plate fractures around the fusion site that may negatively impact bony fusion
The patient was adult and considered to be skeletally mature	A preexisting sensory impairment (eg, diabetes with baseline sensory impairment) that limited the ability to perform objective functional measurements and/or may place the patient at risk for complications; diabetic patients who were not sensitive to the 5.07 monofilament (Semmes-Weinstein) were excluded
	Metabolic disorder known to adversely affect the skeleton, other than primary osteoporosis or diabetes (eg, renal osteodystrophy or hyperglycemia)
	Use of chronic medications known to affect the skeleton (eg, glucocorticoid usage of more than 10 mg/day)
	A prefracture neuromuscular deficiency that limited the ability to perform objective functional measurements
	The patient has a diagnosis or history of bipolar disorder, schizophrenia, suicidal ideation, posttraumatic stress disorder, senile dementia, or Alzheimer's disease 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
	Receipt of an investigational therapy or approved therapy for investigational use within 30 days of surgery or during the follow-up phase of this study
	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 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

including FFI activity limitation, disability, and pain subscales, fusion site pain, weightbearing pain, and Short-Form 12 (SF-12) Physical Component Summary (PCS) score; and important pair-wise interactions. PS subclassification was done via quintiles.[32] The PS model was evaluated according to rigorous criteria[24,33] using a published

heuristic.[30] This procedure is designed to reduce systemic bias in treatment-control comparisons.[34] PS subclasses were identified by an independent statistician with no access to outcome data. A PS design was identified such that within each subclass, subjects in the 2 treatment groups had approximately the same multivariate covariate distribution. Consequently, analyses could proceed as if the patients within each subclass had been randomly allocated to their treatment. The analysis of the outcome variables was then carried out in a stratified manner when estimating the difference between treatment groups.

Patients: Propensity Score Model

All 132 patients treated with rhPDGF-BB/β-TCP-collagen were assigned to a PS subclass. In contrast, 167 of 189 patients treated with autograft were assigned to a PS subclass (Figure 1). The 22 excluded controls had combinations of baseline covariates not observed in the 132 patients treated with rhPDGF-BB/β-TCP-collagen. After subclassification and controlling for PS subclass, there were no important differences between the 2 groups for any of the baseline covariates considered (all $P \geq .725$).

Demographic data and outcome measure scores at baseline for the 132 rhPDGF-BB/β-TCP-collagen–treated patients and 167 autograft-treated patients selected by the PS model are summarized in Table 2. The mean age for the rhPDGF-BB/β-TCP-collagen cohort was 53.5 ± 14.7 years and for the autograft cohort was 56.2±14.0 years. The treatment and control groups consisted of 53% and 51.5% males, respectively. The most common primary diagnoses were posttraumatic osteoarthritis (126/299, 42.1%), primary arthritis (125/299, 41.8%), and rheumatoid arthritis (20/299, 6.7%). BMI and relative risk factors for nonunion (ie, smoking and obesity) were comparable between the groups. All preoperative clinical outcome measures were similar for both groups.

Study Outcomes

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

The primary outcome for the RCT was joint fusion, assessed by CT using a robust definition of ≥50% osseous bridging across the articulation for successful fusion. After this protocol was finalized, a study demonstrated that clinical success is obtained with ≥25% osseous bridging.[18] If 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 successful). The primary outcome for the PS model was pain at the fusion site with weightbearing, assessed by 0- to 100-mm visual analog scale (VAS) pain scores; a difference <10 mm between the groups indicated noninferiority.

Secondary outcomes incorporated patient-, surgeon-, and independent radiologist-reported data. "Clinical healing status" was determined by the surgeon based on a global assessment of the patient's progress at the level of the full joint (if more than 1 joint was fused) and at the level of the individual joints. Therapeutic failure was defined as any nonunion or delayed union that required secondary therapeutic intervention. VAS pain was assessed at the surgical site with weightbearing, at the fusion site, and at the graft harvest site. "Clinical success" was defined as reduced VAS pain on weightbearing and lack of revision surgery. Other secondary outcomes included the SF-12 PCS score version 2,[16,36] American Orthopaedic Foot & Ankle Society (AOFAS) Ankle-Hindfoot Scale,[27] and Foot Function Index (FFI).[3] Decreases in VAS pain and FFI scores represented improvement, whereas increases in AOFAS and SF-12 scores represented improvement. 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 event frequency, severity and potential relationship to the study device, surgical site complications including nonunion, and patient dropout due to death or serious adverse events.

Statistical Analysis

A power analysis was performed before conducting the PS subclassification analysis with the primary outcome of weightbearing VAS pain at the fusion site. The original pivotal trial demonstrated a change of approximately 50 points in weightbearing VAS pain from baseline to 1-year follow-up. Noninferiority was declared if the upper confidence bound of a 2-sample confidence interval for the difference between the treatments was less than the predetermined 10-point margin. Employing a type 1 error rate of 5% and assuming equal responses for the 2 treatment arms, a sample size of 132 rhPDGF-BB/β-TCP-collagen subjects and 167 autograft subjects produced at least 88% power to declare noninferiority of rhPDGF-BB/β-TCP-collagen relative to autograft.

Binary data are presented as counts and rates. The treatments were compared using a logistic regression model to allow for PS quintile as a stratification variable. Odds ratios (OR) were calculated as the odds of significant improvement for rhPDGF-BB/β-TCP-collagen divided by odds of significant improvement for autograft, where OR >1.0 favors rhPDGF-BB/β-TCP-collagen and OR <1.0 favors autograft. Noninferiority was declared when the 95% confidence bound of the OR exceeded 0.50.[17] Continuous data are presented as means and standard deviations. Comparisons between treatment groups were carried out

Table 2. Demographic and Clinical Factors for the Treatment Cohorts After Subclassification Using Propensity Scores.[a]

Variable	rhPDGF-BB/β-TCP-Collagen ($n = 132$)	Autograft ($n = 167$)	*P* Value[b]
Gender			.816
Male	70 (53.0)	86 (51.5)	
Female	62 (47.0)	81 (48.5)	
Age, y[c]	53.5 ± 14.7	56.2 ± 14.0	
≥65 years	35 (26.5)	58 (34.7)	.133
<65 years	97 (73.5)	109 (65.3)	
Primary diagnosis			
Posttraumatic arthritis or deformity	58 (43.9)	68 (40.7)	.103
Primary/osteoarthritis	60 (45.5)	65 (38.9)	
Rheumatoid arthritis	8 (6.1)	12 (7.2)	
Ankylosing spondylitis	0	1 (0.6)	
Congenital or acquired deformity	4 (3.0)	6 (3.6)	
Other	2 (1.5)	15 (9.0)	
Joints treated			.131
Ankle fusion	31 (23.5)	46 (27.5)	
Subtalar fusion	52 (39.4)	59 (35.3)	
Calcaneocuboid fusion	3 (2.3)	0	
Talonavicular fusion	6 (4.6)	9 (5.4)	
Double fusion[d]	21 (15.9)	17 (10.2)	
Triple arthrodesis[e]	19 (14.4)	36 (21.6)	
BMI, kg/m^2 [c,f]	31.2 ± 6.1	31.4 ± 5.7	
≥30	63 (47.7)	99 (59.3)	.061
<30	68 (51.5)	68 (40.7)	
Ever smoked			.562
Yes	71 (53.8)	84 (50.3)	
No	61 (46.2)	83 (49.7)	
Preoperative clinical outcome measures			
VAS pain weightbearing, >40[g]	120 (90.9)	145 (86.8)	.569
VAS pain weightbearing, ≤40[g]	12 (9.1)	19 (11.4)	
VAS pain weightbearing[c,g]	72.0 ± 22.3	69.9 ± 22.0	
VAS pain at fusion site[c]	49.8 ± 26.3	51.7 ± 26.4	
AOFAS Ankle-Hindfoot Scale total score[c]	43.3 ± 17.2	43.6 ± 16.8	
FFI total score[c]	50.6 ± 18.4	50.0 ± 15.1	
SF-12 PCS[c]	30.8 ± 8.4	31.2 ± 8.3	

Abbreviations: AOFAS, American Orthopaedic Foot & Ankle Society; BMI, body mass index; FFI, Foot Function Index; rhPDGF-BB/β-TCP, recombinant human platelet–derived growth factor BB homodimer; SF-12 PCS, Short-Form 12 Physical Component Summary Score; VAS, visual analogue scale.

[a]The PS matching technique is designed to match the treatment groups such that *P* values for between-group comparisons of covariates are large. Comparisons of covariates that were not part of the PS matching technique or comparisons using different methodologies than what were used in the PS matching (eg, using binary versions of covariates in place of continuous data) may result in *P* values that are smaller than those found in the final PS matching. Nevertheless, this table shows that all preoperative clinical outcome measures examined were similar for both groups. All values are presented as *n* (%) or mean ± SD.

[b]Fisher's exact test for categorical variables; 2-sample *t* test for continuous variables.

[c]Results are based on generalized linear model with the following factors: treatment (rhPDGF-BB/β-TCP-collagen vs autograft) and propensity score quintiles.

[d]Combination of any two of the following joints: subtalar, talonavicular, and calcaneocuboid.

[e]Subtalar, talonavicular, and calcaneocuboid joints.

[f]Data missing for 1 patient in the rhPDGF-BB/β-TCP-collagen treatment group.

[g]Data missing for 3 patients in the autograft control group.

via analysis of covariance, adjusted for PS strata. Noninferiority was determined by comparing the appropriate upper or lower confidence limit to the desired noninferiority threshold. For radiographic outcome rates, AOFAS scores, and SF-12 scores, comparisons were made to a lower confidence limit, while for VAS pain and FFI

Table 3. Clinical Results Summary at 24 and 52 Weeks Postoperative for Propensity Score Subclassification Cohorts.[a]

	24 Weeks				52 Weeks					
Outcome Measure	*N*	rhPDGF-BB/β-TCP-Collagen	*N*	Autograft	*N*	rhPDGF-BB/β-TCP-Collagen	*N*	Autograft	Difference/ OR[b]	95% UB/LB[c]
VAS pain, weightbearing[d]	128	25.1 ± 2.4	160	18.3 ± 2.1	124	16.6 ± 2.4	157	15.9 ± 2.1	0.7	6.2
VAS pain, fusion site[d]	129	20.9 ± 2.2	164	15.3 ± 1.9	125	15.8 ± 2.2	160	12.6 ± 1.9	3.2	8.3
VAS pain ≥20 mm, graft harvest site	130	0%	161	13.0%	129	0%	158	10.1%	—	—
FFI total score[d]	129	26.3 ± 1.8	164	19.8 ± 1.6	123	19.6 ± 1.9	160	16.9 ± 1.6	2.7	7.1
AOFAS total score[d]	129	73.4 ± 1.5	164	75.5 ± 1.3	125	79.5 ± 1.6	160	79.3 ± 1.4	−3.4	0.2
SF-12 PCS[d]	129	40.3 ± 0.9	164	42.2 ± 0.7	123	42.9 ± 0.9	160	45.5 ± 0.8	−4.6	−2.5
Clinical healing status, patient level[e]	132	82.9%	167	88.5%	132	84.8%	167	90.7%	0.57	0.29
Clinical healing status, full complement of joints[e]	132	83.4%	167	87.0%	132	82.8%	167	89.7%	0.55	0.30
Clinical success rate[e]	132	89.0%	167	81.8%	132	88.9%	167	79.5%	2.07	1.13

Abbreviations: AOFAS, American Orthopaedic Foot & Ankle Society; FFI, Foot Function Index; LB, lower boundary; OR, odds ratio; rhPDGF-BB/β-TCP, recombinant human platelet–derived growth factor BB homodimer; SF-12 PCS, Short-Form 12 Physical Component Summary Score; UB, upper boundary; VAS, visual analog scale.

[a]Propensity score subclassification cohort analysis based on logistic regression with the following factors: treatment (rhPDGF-BB/β-TCP-collagen vs autograft) and propensity score quintiles. All mean comparisons employed a generalized linear model with the following factors: baseline value, treatment (rhPDGF-BB/β-TCP-collagen vs autograft), and propensity score quintiles.

[b]Estimate of the difference of rhPDGF-BB/β-TCP-collagen minus autograft, based on the logistic model.

[c]95% upper boundary or lower boundary at 52 weeks. The upper boundary is reported for VAS pain weightbearing, VAS pain fusion site, and FFI total score. The lower boundary is reported for AOFAS total score and SF-12 PCS.

[d]The values are given as the mean ± standard error, in points.

[e]The values are given as rates and lower bound of propensity score subclassification cohort analysis on the OR based on logistic regression with the following factors: treatment (rhPDGF-BB/β-TCP-collagen vs autograft) and propensity score quintiles.

scores, comparisons were made to an upper confidence limit. Patients who required revision surgery were considered failures for all binary outcome measures. All statistical analyses were performed using statistical software (SAS version 9.4, SAS Inc, Cary, NC).

Results

Noninferiority Randomized Controlled Trial

For the primary outcome of joint fusion, CT analysis at 52 weeks demonstrated noninferiority of rhPDGF-BB/β-TCP-collagen to autograft for all joints ($P = .011$; Appendix II), a rigorous CT endpoint that may not be necessary for a clinically successful outcome.[18] The full complement fusion rate for rhPDGF-BB/β-TCP-collagen (64%) was comparable to that for autograft (66%), although the test of noninferiority was not statistically significant. The AOFAS total score also demonstrated noninferiority of rhPDGF-BB/β-TCP-collagen to autograft at 52 weeks ($P = .05$; Appendix III).

Key safety-related outcomes were equivalent in both groups (Appendix IV). Patients treated with rhPDGF-BB/β-TCP-collagen did not have donor site pain, in contrast to patients treated with autograft.

Propensity Score Model: Clinical and Radiographic Results

The primary outcome of VAS pain on weightbearing and all other clinical, functional, and quality of life results demonstrated noninferiority of rhPDGF-BB/β-TCP-collagen to autograft at 24 and 52 weeks postoperative (Table 3). Clinical healing status was achieved in 84.8% of rhPDGF-BB/β-TCP-collagen–treated patients and 90.7% of autograft-treated patients (range, 82.9%-95.7% depending on graft harvest site; Appendix V) at 52 weeks. Clinical success, FFI, AOFAS Ankle-Hindfoot Scale, SF-12, and VAS pain scores all demonstrated noninferiority at 52 weeks. Changes in pain and clinical outcome scores from baseline to 52 weeks also demonstrated noninferiority of rhPDGF-BB/β-TCP-collagen to autograft (Table 4).

Joint fusion demonstrated noninferiority of rhPDGF-BB/β-TCP-collagen to autograft on both CT and radiographs (Table 5) for the PS subclassification cohorts. Fusion rates on CT at 24 weeks were 68.1% for the rhPDGF-BB/β-TCP-collagen cohort and 68.4% for the autograft cohort (OR, 0.99; lower bound, 0.62, which is greater than the OR noninferiority threshold of 0.50). Similarly, radiographic fusion across 3 aspects at 24 weeks on radiographs demonstrated success rates of 35.1% for the rhPDGF-BB/β-TCP-collagen

Table 4. Changes in Clinical Outcome Measures From Baseline to 52 Weeks Postoperative for Propensity Score Subclassification Cohorts.[a]

Outcome Measure	*N*	rhPDGF-BB/β-TCP-Collagen (*n* = 132)	*N*	Autograft (*n* = 167)	Difference[b]	95% UB/LB[c]
VAS pain, weightbearing, mm	124	−54.3 ± 2.4	157	−55.0 ± 2.1	0.7	6.2
VAS pain, fusion site	125	−34.4 ± 2.2	160	−37.6 ± 1.9	3.2	8.3
FFI	123	−30.5 ± 1.9	160	−33.3 ± 1.6	2.7	7.1
AOFAS total score	125	35.9 ± 1.6	160	35.7 ± 1.4	−3.4	0.2
SF-12 PCS	123	12.0 ± 0.9	160	14.6 ± 0.8	−4.6	−2.5

Abbreviations: AOFAS, American Orthopaedic Foot & Ankle Society; FFI, Foot Function Index; LB, lower boundary; rhPDGF-BB/β-TCP, recombinant human platelet–derived growth factor BB homodimer; SF-12 PCS, Short-Form 12 Physical Component Summary Score; UB, upper boundary; VAS, visual analog scale.

[a]All mean comparisons employed a generalized linear model with the following factors: baseline value, treatment (rhPDGF-BB/β-TCP-collagen vs autograft), and propensity score quintiles.

[b]Difference in score at 52 weeks, rhPDGF-BB/beta-TCP-collagen minus autograft.

[c]95% Upper Boundary or Lower Boundary at 52 weeks. Upper boundary is reported for VAS Pain Weightbearing, VAS Pain fusion site, and FFI. Lower boundary is reported for AOFAS total score and SF-12 PCS.

Table 5. Summary of Radiologic Results Based on CT Scans and Radiography, at 24 and 52 Weeks Postoperative, for Propensity Score Subclassification Cohorts.[a]

	Full Complement of Joints (*n* = 299)			
	rhPDGF-BB/β-TCP-Collagen (*n* = 132)	Autograft (*n* = 167)	LB	OR
24 weeks				
CT fusion	68.1%	68.4%	0.62	0.99
Radiographic union rate (3 aspects)	35.1%	30.3%	0.78	1.24
Radiographic union rate (2 aspects)	72.9%	72.2%	0.64	1.03
52 weeks				
CT fusion at 36+ weeks[b]	71.0%	73.1%	0.55	0.90
Radiographic union rate (3 aspects)	35.0%	33.7%	0.67	1.06
Radiographic union rate (2 aspects)	75.9%	78.9%	0.50	0.84

Abbreviations: CT, computed tomography; LB, lower boundary at 52 weeks; OR, odds ratio at 52 weeks; rhPDGF-BB/β-TCP, recombinant human platelet–derived growth factor BB homodimer.

[a]Propensity score subclassification cohort analysis based on logistic regression with the following factors: treatment (rhPDGF-BB/β-TCP-collagen vs autograft) and propensity score quintiles.

[b]Based on the final CT reading for each study: week 36 for DiGiovanni et al[10] and Daniels et al[7] and week 52 for the current randomized clinical trial.

cohort and 30.3% for the autograft cohort (OR, 1.24; lower bound, 0.78).

Therapeutic failures, defined as nonunion or delayed union requiring surgery or further therapeutic intervention, occurred in 15 of 132 (11.4%) rhPDGF-BB/β-TCP-collagen–treated patients and in 13 of 167 (7.8%) autograft-treated patients in the PS model cohorts ($P = .322$).

Propensity Score Model: Safety-Related Outcomes

Safety results for the PS model cohorts are summarized in Table 6. Equivalent rates of serious treatment-emergent adverse events (TEAEs), device-related TEAEs, complications associated with surgery, serious operative complications, and infections were observed in the treatment and control groups. Clinically meaningful graft harvest site pain (ie, ≥20 mm) was reported in 16 of 158 (10.1%) autograft patients at 52 weeks.

Discussion

In a PS design using PS subclassification of 3 multicenter RCTs of patients who underwent ankle and hindfoot fusion for end-stage arthritis, rhPDGF-BB/β-TCP-collagen was as effective as autograft in achieving fusion and reducing pain, thus improving patients' clinical and functional outcomes. Treatment with rhPDGF-BB/β-TCP-collagen produced 24-week fusion rates, clinical success, functional outcomes, and reductions in pain equivalent to autograft, without the additional morbidity associated with harvesting of bone graft.

Table 6. Safety-Related Outcomes for the Propensity Score Subclassification Cohorts.

	rhPDGF-BB/β-TCP-Collagen (n = 132)		Autograft (n =167)		
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	P Value
Serious TEAEs	17 (12.7)	20	25 (15.0)	35	1.00
Device-related TEAEs	3 (2.3)	3	6 (3.6)	10	.741
Complications associated with surgical procedure	47 (35.6)	79	52 (31.1)	76	.141
Serious operative complications	8 (6.1)	8	10 (6.0)	11	.808
Infection—surgical or treatment emergent	27 (20.5)	36	26 (15.6)	32	.127
Chronic pain at autograft donor site (≥20 mm on VAS)					
At 6 months	0 (0)	0	21/161 (13.0)	21	<.01
At 12 months	0 (0)	0	16/158 (10.1)	16	<.001

Abbreviations: rhPDGF-BB/β-TCP, recombinant human platelet–derived growth factor BB homodimer; TEAE, treatment-emergent adverse event; VAS, visual analog scale.

Fusion in the ankle and hindfoot was evaluated by CT at 24 weeks and radiographs at 24 and 52 weeks using rigorous benchmarks of ≥50% osseous bridging on CT and at least 3 of 4 aspects fused on radiographs.[11] Using these criteria, fusion rates for rhPDGF-BB/β-TCP-collagen were statistically noninferior to autograft. The clinical healing status achieved in both groups was much higher than fusion by CT scan; Glazebrook et al recently demonstrated that clinical success is achieved if ≥25% osseous bridging is obtained.[18] Patient-reported outcomes, including FFI, AOFAS Ankle-Hindfoot Scale and SF-12 PCS scores, and VAS pain, were equivalent in both groups. Additionally, key safety-related outcomes were equivalent in both groups, with the benefit of no donor site pain in the rhPDGF-BB/β-TCP-collagen cohort. These results are consistent with an RCT of rhPDGF-BB/β-TCP-collagen conducted at 5 Canadian sites.[7]

The current study builds on earlier work by conducting an additional RCT across both the United States and Canada, and then using a PS subclassification technique for analysis to provide a robust observational design. Inferences regarding treatment group differences from combined studies may proceed as if patients within each cohort had been randomly allocated to a treatment arm within 5 subclasses, designed so treated and control subjects within each subclass share approximately the same multivariate covariate distribution. Control subjects with covariate combinations not observed in the treated group are trimmed, promoting covariate balance. The PS subclasses and trimming of controls was performed by an independent statistician without access to outcome data to avoid bias. PS modeling is preferred over a simple pooling of patient cohorts, as such pooling fails to account for potential differences in patient enrollment characteristics across studies. This methodology is especially valuable in orthopedic surgery, particularly ankle and hindfoot surgery, where it is difficult to conduct RCTs with large sample sizes. PS model cohort analyses were recently utilized to compare patient-reported functional outcomes, quality of life, and satisfaction following unicompartmental versus total knee arthroplasty.[20,25]

Patients included in this study required supplemental bone graft, as determined by the surgeons on the basis of accepted clinical risk factors for nonunion, such as smoking, diabetes, soft tissue injury, and interfragmentary gaps.[35] With the efficacy and safety of rhPDGF-BB/β-TCP-collagen now demonstrated in these patients, future studies could evaluate the use of rhPDGF-BB/β-TCP-collagen in patients at very high risk for nonunion, including patients with deformity, neuropathy, or metabolic disease; in more complicated cases requiring plate fixation or intramedullary rods or nails; and in patients requiring revision surgery.

Strengths of this study include the PS subclassification design, which allowed a valid analysis to compare, as if under randomization, the 2 treatment groups from multiple RCTs. Patients were enrolled at 37 sites in the United States and Canada for the 3 RCTs, allowing generalizability of the data. Another strength is the high rate of patient follow-up, with 121 of 132 (91.7%) patients treated with rhPDGF-BB/β-TCP-collagen having outcome data available at 1 year.

A limitation of this study is that the PS design could only control for differences on the observed covariates included in the model. A rich set of covariates were included to reduce this risk. Nonetheless, bias may result from covariates for which no data were collected in these cohorts, such as diabetes.

In conclusion, a PS subclassification model analysis of 3 RCTs demonstrated that rhPDGF-BB/β-TCP-collagen was at least as effective as autograft in achieving fusion in patients who underwent ankle and hindfoot arthrodesis for end-stage ankle arthritis, with less pain and fewer side effects compared with treatment with autograft.

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Declaration of Conflicting Interests

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