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Foot Ankle Int 2010 31: 473
DOI: 10.3113/FAI.2010.0473

FOOT & ANKLE INTERNATIONAL

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ABSTRACT

Background: **Augment™ Bone Graft, a fully synthetic bone graft material composed of recombinant human PDGF and a calcium phosphate matrix (rhPDGF/TCP), has been considered as a possible alternative to autogenous bone graft. Before proceeding with randomized control studies comparing rhPDGF/TCP to autograft bone, a human trial to assess efficacy and safety was required.** ***Materials and Methods:*** **The current study was a prospective, open-label, multi-center trial designed to evaluate rhPDGF in a calcium phosphate matrix (Augment™ Bone Graft). Sixty patients requiring hindfoot or midfoot fusion were prospectively followed for 36 weeks. All patients received 0.9 to 2.7 mg of rhPDGF at the fusion sites and returned for clinical and radiographic review at Day 7 to 14 and Weeks 6, 9, 12, 16, 24, and 36. Computerized tomography (CT) scans of the fusion site were obtained at the 6- and 12-week postoperative appointment, with an additional CT scan at 16 weeks if required.** ***Results:*** **No patients suffered a serious adverse event caused by rhPDGF. CT scan evaluation at 12- to 16-week time periods revealed moderate or complete osseous bridging of 75% (44/59) at 36 weeks.** ***Conclusion:*** **These results indicate that rhPDGF is a safe product and provides clinical/radiographic outcomes that justify the pursuit of randomized controlled studies comparing rhPDGF/TCP to autograft.**

Level of Evidence: IV, Case Series

Key Words: Autogenous bone graft; Arthrodesis; Augment Bone Graft; Bone Regeneration

Funds were received from Biomimetics in support of the research and/or clinical study presented in this article.

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INTRODUCTION

Fusions failing to heal result in morbidity and disability.[8] Approximately 200,000 bone grafts are harvested in the United States annually to assist in bone healing.[15] Bone autograft is the only graft material previously available that has osteogenic, osteoinductive, and osteoconductive properties.[14] Complications of autograft harvest include blood loss, postoperative pain, risk of infection, heterotopic bone formation, hernia, and nerve injury.[4,7,9,13,16] Viable substitutes to autograft are therefore an attractive alternative to help avoid the co-morbidities associated with a second surgical site. Equivalent outcomes to autograft would have significant implications for foot and ankle fusions. Currently, there remains an unmet clinical need to provide a cost-effective, synthetic, osteogenic bone graft substitute without the morbidity associated with harvesting autograft. In foot and ankle surgery, fusions are often required and for some fusion sites the nonunion rates remain significant.[3,5,6]

Augment Bone Graft (BioMimetic Therapeutics, Inc., Franklin, TN), a bone regeneration device, is composed of beta tricalcium phosphate (β-TCP) and 0.3 mg/ml recombinant human platelet derived growth factor-BB (becaplermin) (rhPDGF) in a sodium acetate buffer. In the present study, rhPDGF (in the form of Augment Bone Graft) was applied in foot and ankle fusions to evaluate the impact on osseous healing and assess any complications associated with the graft material.

MATERIALS AND METHODS

Study design

A prospective, open-label, multi-center clinical trial was performed in patients undergoing midfoot, hindfoot, or ankle fusions. Patients were enrolled at three institutions following approval by the local Research Ethics Board (REB) and Health Canada. The null hypothesis for radiographic fusion was that the rhPDGF non-union rate at 9 months is

comparable to (±10%) the non-union rate reported in the literature and that it is a safe product for human use.

Sixty eligible patients who met the inclusion and exclusion criteria underwent at least one fusion procedure using rhPDGF applied to the fusion site. The fusion site was prepared with removal of all cartilage and preparation of the subchondral bone using standardized technique. The key exclusion criteria are listed below:

- Fusion site requiring plate fixation; more than four screws at each fusion site.
- If rigid fixation was unable to be achieved (none was encountered in this study).
- Fusion site requiring more than 9 cc (or three Augment Bone Graft kits) of bone graft to fill voids or surface defects or requiring structural graft.
- Infection at proposed fusion site.
- Neuromuscular or musculoskeletal deficiency.

Patients were followed for 9 months. A total of seven followup visits were scheduled: Day 7 to 14, Weeks 6, 9, 12, 16, 24, and 36. Patients were followed by the investigators beyond the study period when necessary. At these visits, the site investigator assessed clinical and functional outcomes and plain radiographs were taken. CT scans were obtained for supplemental and confirmatory information at Weeks 6, 12, and 16 (if necessary). The radiographs (CT scans and plain radiographs) were assessed by a central independent fellowship trained musculoskeletal radiologist for evidence of union and other radiographic parameters at the fusion site.

Operative procedure

All surgeries were performed by orthopedic surgeons who were fellowship-trained in foot and ankle reconstruction. Standard surgical technique was employed to gain access to each fusion site and to ensure rigid fixation of the fusion site. The entire joint was exposed and denuded to subchondral bone, and the subchondral plate was perforated to augment the subsequent fusion. The opposing surfaces of the joints to be fused were prepared with the use of standard instrumentation. Sound surgical technique, including thorough debridement, rigid fixation of the fusion site(s), and solid bony apposition of the surfaces intended for fusion was employed. The importance of patient compliance with immobilization and weightbearing was made aware to the patients. Patients underwent a midfoot, hindfoot, or ankle fusion procedure or a combination of these procedures. Standard postoperative protocols were followed. Patients were placed supine with a tourniquet around the thigh. Perioperative prophylactic antibiotics were administered before surgical incision. The opposing surfaces of the joints to be fused were prepared in standard fashion. The joints were then coapted and fused with screws (3.5 to 7.3 mm, depending upon the size of the patient's foot). No more than four screws were used across a given fusion space to ensure adequate visualization of it during followup imaging. Plate fixation was excluded due to hardware scatter on radiography and to ensure hardware standardization. Supplemental pins, wires, and/or staples were permitted. The Augment Bone Graft was packed into the fusion site at the time of rigid fixation, such that the graft material was in contact with the entire surface area of the joints. The amount of graft inserted was at the surgeons discretion based on the number of joints to be fused and the surface area of fusion, but was not to exceed 9 cc of total graft volume. Following final fixation, additional graft material was placed around the fusion site. A layered closure was performed prior to deflating the tourniquet in order to optimize containment of the graft material within the fusion site. The patient was then placed in a sterile compressive dressing and posterior splint. Sutures were removed at 2 weeks and patients transferred to a walker boot or cast. Patients were nonweightbearing for 2 weeks postoperatively, after which partial weightbearing (PWB) was initiated. After 6 weeks physical therapy was performed including edema control, range of motion of unfused joints and scar mobilization. Patients were transitioned into a regular walking shoe (between 8 to 12 weeks) and gait training commenced at 6 to 12 weeks.

Clinical/Radiographic assessment

The primary efficacy endpoint was radiographic healing (union), as assessed by an independent radiologist assessing plain film radiographs and CT scans. Union was felt to have occurred on radiographs if bridging and/or disappearance of the joint space of subchondral bone (on at least two of the four radiologic aspects) was detected.[2]

The secondary radiographic endpoints included the overall assessment of osseous bridging (absent, minimal, moderate, or complete) from CT scans at Weeks 6, 12, and 16 only, and presence of abnormal bone formation at the fusion site.

The secondary clinical and functional endpoints included the following:

- Time to radiographic union.
- Clinical outcomes (range of motion, weightbearing, lack of significant pain and edema, etc).
- Quality of Life (QOL) and functional assessments consisting of questionnaires for Foot Function Index (FFI), and American Orthopaedic Foot and Ankle Society (AOFAS) scores.
- Safety (e.g. complications, adverse events).

The clinical and radiographic endpoint data were combined to provide an overall assessment of treatment success.

Safety

Overall patient safety was evaluated by tabulating reports of adverse events. Adverse events were also reviewed for complications associated with reduction, fixation or immobilization related to the primary device or fixation hardware. Complications associated with the surgical procedure were also identified.

Statistics

Categorical data are displayed as percents, and continuous data are displayed using descriptive statistics (N, mean, standard deviation), with exact binomial confidence intervals computed for revision rates. Time to event data is displayed using life tables. For time to event analyses, the start date was Visit 2, the date of surgery. For all other measures, the earliest visit date prior to surgery served as the baseline.

Revision rates were compared to those observed in the literature. A revision rate of 9% reported in a meta-analysis encompassing 1,262 ankle arthrodesis patients was used for hypothesis testing.[6]

RESULTS

Surgery

Of the 60 enrolled patients, 59 completed the study. One patient withdrew due to difficulty traveling to the study site after the Week 12 visit; however, the radiographs for Week 24 and Week 36 were taken at another location and were assessed by the independent radiologist.

Forty-eight patients (80%) had general anesthesia for all procedures. Regional nerve block with sedation was used in six patients (10%), and spinal anesthesia was used for 11 patients (18%). Five subjects received combinations of the above noted anesthesia. Thirty-one (52%) patients had a hindfoot/ankle fusion performed, including nine ankle fusions, seven isolated subtalar fusions, one combined ankle/subtalar procedure, 11 triple arthrodeses, and four calcaneocuboid (CC) and/or talonavicular (TN) joints. Twenty-six (43%) patients had a midfoot fusion performed at the naviculocuneiform (NC) or tarsometatarsal (TMT) joints. Three patients had a combination of midfoot and hindfoot/ankle procedures; all received a triple arthrodesis with a naviculocuneiform, tarsometatarsal, and/or interphalangeal joint fusions. Screws were used for fixation in all procedures, with seven procedures for which Kirschner wires or pins were used as well. The mean procedure time was 104.9 minutes (±32.9), with a median of 100 minutes. The maximum procedure time was 178 minutes.

Patient demographics

A total of 130 joints were treated with rhPDGF on 60 patients between January 2006 and September 2007. A summary of patient demographics and clinical characteristics are presented in Table 1. Thirty-seven patients (62%) treated in this study had at least one risk factor for nonunion and/or surgical complication, including recent smoking history, diabetes, and revision surgery.

Patient followup

One patient withdrew from clinical followup due to difficulty traveling to the study site after Week 12 visit, but 24 and 36 week radiographs were obtained. This study subject underwent a triple artrhodesis for pes planus deformity and was noted as 75% to 100% osseous bridging at Week 12. The patient has not had revision surgery and independent radiographic and clinical review suggests no adverse events or complications.

Table 1: Demographics and Clinical Characteristics at Baseline—ITT Population

Gender	$n = 60$
Male	20 (33%)
Female	40 (67%)
Race*	
Caucasian	57 (95%)
African American	1 (2%)
Other	2 (3%)
Age (years)	
Mean (SD)	53.4 (14.56)
Median	54.5
Min, Max	19.0, 78.0
BMI (kg/m^2)	
Mean (SD)	29.0 (6.68)
Median	27.3
Min, Max	19.7, 49.6
Foot/Ankle to be treated	
Right	32 (53%)
Left	28 (47%)
Age of Injury/Deformity at Baseline (Weeks) ($n = 41$)	
Mean (SD)	152.9 (229.48)
Median	99.3
Min, Max	21.9, 1156.6
Description of Injury/Deformity*	
Primary arthritis	21 (35%)
Rheumatoid arthritis	7 (12%)
Post-traumatic injury/deformity	20 (33%)
Other**	21 (35%)
Risk Factors*	
Smoking history within last 5 years***	12 (20%)
Previous revision history	20 (33%)
Diabetes history (Type 1 or 2)	6 (10%)
None	21 (35%)
Patients with multiple risk factors	21 (35%)

Note: Percents are based on the number of patients in the ITT population. *, Patients may check more than one. **, The other deformities including hallux valgus deformity, ankle instability, pes planus deformity, calcaneonavicular coalitions, and congenital clubbed feet (charcot arthropathy was an exclusion criterion). ***, Mean age of patients who smoked previously is 60.5 years.

Radiographic assessment

Overall, 52 of 59 patients (88%) had radiographic union during the study. Table 2 presents the radiographic union rate

Table 2: Radiographic Union (2 Aspects) by Visit

	Whole Population $n = 60$	At Risk Population $n = 39$
Visit 3 (Day 7–14)	0/45 (0%)	0/28 (0%)
Visit 4 (Week 6)	13/42 (31%)	18/27 (33%)
Visit 5 (Week 9)	24/43 (56%)	15/29 (52%)
Visit 6 (Week 12)	34/46 (74%)	21/29 (72%)
Visit 7 (Week 16)	44/55 (80%)	28/34 (82%)
Visit 8 (Week 24)	46/54 (85%)	29/35 (83%)
Visit 9 (Week 36)	52/59 (88%)	32/38 (84%)

Note: Missing Week 36 data is imputed with Week 24 data, if available. No other data are imputed.

(at least two aspects) by visit. Figure 1 presents the time to radiographic union using Kaplan-Meier survival curves. The median time to radiographic union was 87 days.

There were no observations of heterotopic bone formation, as rhPDGF does not result in cell differentiation through the osteoblast lineage. Two patients had abnormal bone resorption at or around the fusion site reported at both the Week 24 and Week 36 visits. There was one radiographic observation of possible infection at Week 36, although this was not confirmed clinically. One patient had pre-existing osteolysis of the distal tibia, resulting from a previous fracture and surgery. It was not noted at the Week 36 assessment.

CT scans

At Week 6, 43% (22/51) of patients demonstrated moderate (51 to 75%) or complete (76 to 100%) osseous bridging, while during the Weeks 12 to 16 time period, 75% (44/59) had moderate or complete osseous bridging (Table 3).

Clinical success

Of the 60 treated patients, 54 (90%) did not require or were not recommended for revision surgery within 12 months of the index surgery (Table 4). In the hindfoot/ankle population (including isolated ankle and subtalar fusions, as well as triple arthrodeses and other combination fusions), 97% (33/34) of patients did not require revision.

A total of 130 joints of 60 patients were treated with rhPDGF, a clinical success rate of 95.4% (124/130) was observed for the treated joints in this study.

Six patients (10%) assessed as clinical failures required or were recommended for revision surgery within 12 months of the index surgery. Five of these six patients had their procedure performed on a midfoot joint. The other patient had a history of previous triple arthrodesis, and reported a baseline body mass index of 32.0 and had a history of smoking within the last 5 years, both of these being reported as risk factors for failure of fusion.[3] The revision rates were

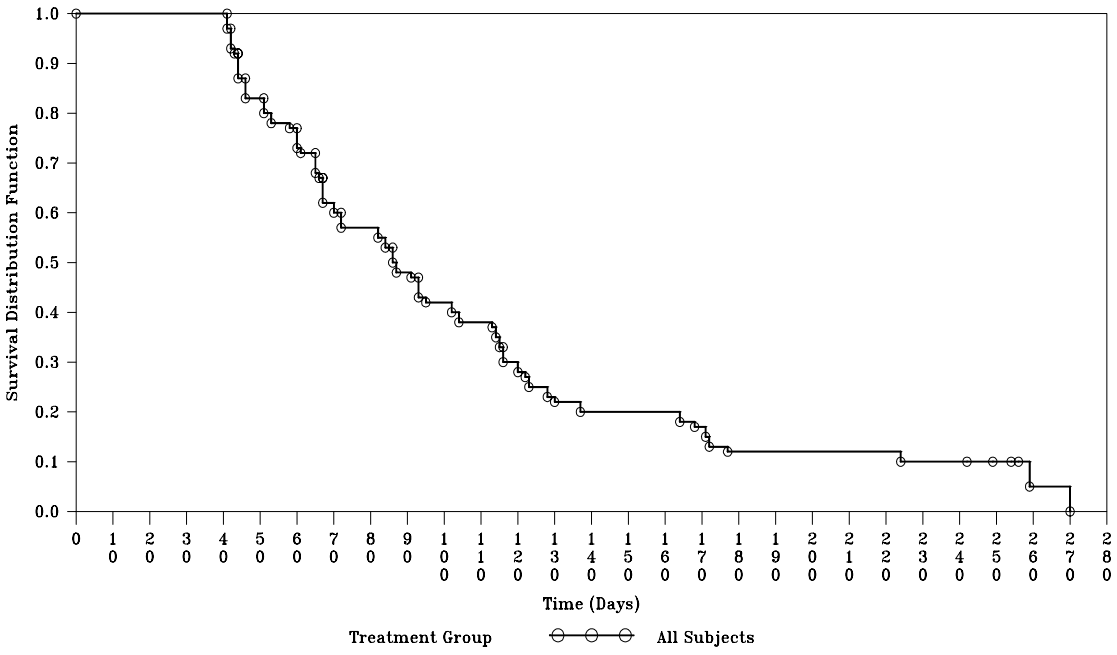

Fig. 1: Kaplan-Meier Survival Curve of Time to Radiographic Union—ITT Population. Time to radiographic union was determined using Kaplan-Meier survival curve. The x-axis represents the days since surgery. The y-axis represents the survival function, distribution of patients who have not achieved radiographic union (1-[Radiographic Union rate]), which indicates increased rates of radiographic union over time.

Table 3: Moderate to Complete Osseous Bridging

	Whole Population $n = 60$	Hindfoot/Ankle Population $n = 34$	At Risk Population $n = 39$
Visit 4 (Week 6)	22/51 (43%)	13/30 (43%)	15/34 (44%)
Visit 6 (Week 12)	39/57 (68%)	22/32 (69%)	24/38 (63%)
Visit 7 (Week 12–16)	44/59 (75%)	24/33 (73%)	25/38 (66%)

Note: Patients that did not require Week 16 CT are represented with their Week 12 data imputed, if available. No other data are imputed. There were 33 patients with Week 16 data.

Table 4: Clinical Success Rate

ITT Population ($n = 60$)	
Clinical Success* Achieved	
Yes	54 (90.0%)
No	6 (10.0%)
90% CI for Revision Rate	(4.4%, 18.8%)
Hindfoot/Ankle Population ($n = 34$)	
Clinical Success* Achieved	
Yes	33 (97.1%)
No	1 (2.9%))
90% CI for Revision Rate	(0.2%, 13.2%)
At Risk Population ($n = 39$)	
Clinical Success* Achieved	
Yes	37 (94.9%)
No	2 (5.1%)
90% CI for Revision Rate	(0.9%, 15.2%)

*, Lack of recommendation for revision surgery within 12 months of initial procedure.

10% (6/60) for the whole population (90% CI 4.4 to 18.8%), 3% (1/34) for the hindfoot/ankle population (90% CI 0.2 to 13.2%), and 5% (2/39) for the at risk population (90% CI 0.9 to 15.2%). Within the nonunion group post-operative radiographic analysis suggested that an excess amount of TCP had been introduced into the fusion area resulting in what was referred to 'over-packing of the joint.'

Quality of Life (QOL) and functional assessments

The AOFAS Ankle-Hindfoot mean total score improved by 19 points at Week 12 (60.7 ± 18.0; Median, 65.0) from baseline (41.7 ± 16.7; median, 40.0), and continued to show improvement at Week 36 (64.1 ± 23.4; median, 73.5). A similar improvement was observed in the AOFAS Midfoot score. The results of the FFI score for self-assessed pain and disability also showed continued improvement in foot function throughout the study. The FFI mean total score improved by 3 points at Week 12 (35.5 ± 19.5; Median, 34.7) from baseline (38.5 ± 19.5; Median, 36.9), and continued to show improvement at Week 36 (24.2 ± 21.7; Median, 17.1).

Postoperative clinical utility assessment

Overall satisfaction of the treatment outcomes was rated "Excellent" for 69% of the procedures and "Good" for 17% at the 6-month utility assessments. All other clinical utility categories assessed were also favorable for this assessment which was provided by the treating orthopedic surgeon.

The mean time of surgery in the study was 104.9 minutes; for comparison, this value may be compared to a mean time of 143.7 minutes for patients requiring autogenous bone graft in a controlled rhPDGF pilot study, and a range of 133 to 183 minutes seen in a published hindfoot fusion study using

Table 5: Summary of Key Effectiveness Endpoints at 9 Months

Effectiveness Endpoint	Study Population			Hypothesis Testing Assumption	Literature Reported Rates
	ITT	Hindfoot/ankle	At Risk**		
Radiographic Union Rate	88%	88%	84%	—	90%,[6] 84%,[3] 59%[5]
Radiographic Non-union Rate	12%	12%	16%	15%	10%,[6] 16%,[3] 41%[5]
Revision Rate	10%	3%	5%	9%	9%[5]
Aggregate Success Rate	83%	91%	87%	82.5%	n/a
Mean Time to Full Weightbearing (days)	84	90	87	—	n/a
AOFAS Hindfoot/Ankle Overall Score	—		—	—	70,[3]
Mean					75.6[5]
Median		64.1			
		73.5			
AOFAS Midfoot Overall Score		—	—	—	n/a
Mean	72.5*				
Median	77*				

*, This parameter for midfoot population only. **, High risk patients include patients who possess at least one of the following risk factors: diabetic, smoker within the last 5 years, obese, previous surgery at the fusion site.

either iliac crest or demineralized bone matrix as grafting material.[10]

Effectiveness summary

The data from the study effectiveness endpoints at nine months are summarized in Table 5. The table includes the rates used for the non-inferiority hypothesis testing, and equivalent rates from the literature on foot and ankle fusions. The study data are compatible with the non-inferiority hypothesis and literature reported rates for all three study populations.

Adverse events and surgical complications

There were no unusual trends noted in the safety data. The majority of the reported events included expected outcomes from foot and ankle surgery, including local swelling (46.7%), and tenderness (41.7%) patients, but all events were collected as per the clinical protocol. No patient discontinued due to an adverse event.

A summary of adverse events experienced considered possibly or definitely related to study device (as per the assessment by the investigator) is presented in Table 6. All events were associated with either "broken screw" or "motion at the fusion site." These events were generally considered to be standard and expected complications in foot and ankle surgery, and there were no unexpected trends of complications related to the investigational device.

DISCUSSION

This study demonstrates acceptable safety and effectiveness of rhPDGF in foot and ankle fusion procedures. The rates of radiographic non-union observed in this study were consistent with those observed in the literature.[3,5,6] Historical union rates used for comparison observed a 10% nonunion rate in ankle arthrodesis.[6] The current study demonstrated a radiographic nonunion rate of 12%.

CT scans may provide the most sensitive, reliable, and accurate assessment of fusion.[2] Coughlin et al. suggested that achievement of 50% osseous bridging on CT scan closely correlates with successful fusion outcome. The authors also demonstrated that CT scans with bone bridging as low as 20% resulted in good clinical outcomes. The benchmark for fusion in this study is 50% osseous bridging; however, less extensive osseous bridging may be required to achieve clinical success. Subsequent studies may be warranted to further quantify the extent of osseous bridging needed to achieve a clinically successful outcome.

The study did illuminate some of the difficulties associated with midfoot fusions, as five of the six revisions required during the study were in the midfoot population. Generally, midfoot fusions have a higher nonunion rate than ankle fusions.[1,11] Healing in the midfoot is often impeded by the types and amount of stress applied to these joints during weightbearing, as well as the difficulty in obtaining reliable fixation during the procedure. The overall prognosis for midfoot fusion may be improving due to the recent availability of improved plates for fixation (plate fixation

Table 6: Device Related Adverse Events

	$n = 60$	
	Patients	**Events**
Any device related adverse event	4 (6.7%)	22
General disorders and administration site conditions	4 (6.7%)	15
Feeling hot	3 (5.0%)	3
Impaired healing	3 (5.0%)	4
Local swelling	3 (5.0%)	3
Tenderness	3 (5.0%)	5
Injury, poisoning, and procedural complications	4 (6.7%)	5
Medical device complication	4 (6.7%)	5
Musculoskeletal and connective tissue disorders	1 (1.7%)	2
Muscle spasms	1 (1.7%)	1
Pain in extremity	1 (1.7%)	1

Note: Percents are based on the number of patients in the population. Adverse events are coded using the MedDRA 8.0 dictionary or higher.

was excluded in this study). In addition, the nonunions observed in the midfoot may have been a result of a significant mass of TCP particles within the small joint spaces, perhaps preventing bony contact and resulting in movement of these joints prior to fusion. It is possible that, in cases where the joint space was overpacked with TCP particles, the particles may have resorbed over a period of months.

The biological activity of rhPDGF is relatively short term (most of rhPDGF is resorbed during the first 3 days); therefore, if TCP prevents bony apposition, the biologic activity of rhPDGF is not realized, and this could potentially result in a longer fusion time than in cases where the implanted material is not preventing bone to bone apposition. This effect applies to any bone graft material which resorbs over time, including autologous bone graft. Subsequent studies may result in higher fusion rates if care is taken to minimize the volume of TCP placed within the joint, particularly in midfoot and forefoot fusion procedures.

The current study demonstrated that rhPDGF is a safe product. Fusions rates obtained in this study were comparable to historical controls. The re-operation rate was higher than anticipated in the midfoot. After review of the cases it was considered that some of the smaller midfoot joints had been overpacked with the TCP and this may have been a contributing factor. The current study has demonstrated satisfactory outcomes that we believe justify the pursuit of randomized controlled studies comparing rhPDGF/TCP to autograft.

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