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A Multicenter, Retrospective, Case Series of Patients With Charcot Neuroarthropathy Deformities Undergoing Arthrodesis Utilizing Recombinant Human Platelet-derived Growth Factor With Beta-Tricalcium Phosphate

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ABSTRACT

Charcot neuroarthropathy has traditionally been treated using both nonsurgical and surgical strategies. Recently, orthobiologics have been used to promote arthrodesis in Charcot reconstructions, obviating the need for bone graft in some cases. Recombinant human platelet-derived growth factor BB homodimer (rhPDGF-BB) in combination with beta-tricalcium phosphate scaffold (β-TCP) is a bone graft substitute shown to have comparable efficacy to autograft in incidence of foot and ankle fusion. This multicenter, consecutive case series analyzed patients undergoing Charcot reconstructions utilizing rhPDGF-BB/β-TCP for joint fusion. In this cohort, 98 patients (62.24% male) with a mean age of 62.82 $\pm$ 10.28 years (range 40-87) had a fusion incidence of 217 of 223 joints (97.31%) with a mean time to fusion of 13.09 $\pm$ 4.87 weeks (range 6-30). There were 6 nonunions in the patient population. Fusion was defined as $\geq$50% osseous bridging based on computed tomography and/or radiographic consolidation, in addition to clinical findings. With an overall complication rate of 26.53% (26/98), adverse events occurring in more than 1 patient limb included hardware failures (n = 7, 7.14%), infection (n = 4, 4.08%), wound dehiscence (n = 4, 4.08%), amputation (n = 3, 3.06%), and death (n = 2, 2.04%). There were no adverse events related to the grafting material. From this review, we found rhPDGF-BB/β-TCP to be a safe and effective graft material that can be considered a viable alternative to autograft, even in high-risk patients such as those with Charcot neuroarthropathy.

The increased utility of operative intervention for complex limb salvage in conditions such as Charcot neuroarthropathy has resulted in an awareness of the intricacies of bone consolidation, despite the availability and use of improved fixation constructs. The foot and ankle literature report nonunion rates in arthrodesis as high as 41% in high-risk populations, including those with Charcot neuroarthropathy (1,2). As such, construct augmentation with grafting material is an area of research that warrants attention.

Although generally successful, current allo- and auto-grafting procedures do have inherent risks. The ideal grafting material to overcome these drawbacks would eliminate complications from autograft harvesting and the potential for transmission for disease associated with allograft. The material would also be osteoinductive and osteoconductive to facilitate faster healing of high-risk joint fusions (3).

Platelet-derived growth factor (PDGF) is a graft material that has many of these desirable qualities including stimulation of both fibroblastic activity and the healing cascade (4). Recombinant PDGF, and specifically recombinant human PDGF BB homodimer (rhPDGF-BB), is even more promising in its ability to stimulate bone growth, conferring osteoinductive properties (3). In combination with the osteoconductive properties of a beta-tricalcium phosphate scaffold (β-TCP), a powerful bone graft substitute is created which has shown comparable efficacy and non-inferiority to autograft in incidence of foot and ankle fusion in a prospective, randomized, controlled trial (5).

In this study, we sought to explore an orthobiologic alternative to traditional bone grafting techniques in patients with Charcot

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neuroarthropathy deformities. We hypothesized that the utilization of rhPDGF-BB/β-TCP would lead to union in the majority of Charcot reconstruction cases with no major or minor complications associated with the use of the grafting material. Since patients with Charcot neuroarthropathy were excluded from the Pivotal trials for this compound, the primary aim for this multicenter review was to assess the safety and efficacy of rhPDGF-BB/β-TCP bone grafting for arthrodesis in patients requiring Charcot reconstruction (5).

Patients and Methods

Patients

In order to evaluate the safety and efficacy of rhPDGF-BB/β-TCP (Augment® Bone Graft, Wright Medical Group, N.V., Franklin, TN) in patients with Charcot neuroarthropathy, we reviewed consecutive Charcot reconstructions (ICD-10 M14.671 or M14.672, International Classification of Diseases, Tenth Revision, Clinical Modification) that utilized rhPDGF-BB/β-TCP for joint fusion from September 2015 to August 2018. All patients were treated at the St. Thomas Highlands Medical Center and Central Tennessee Foot and Ankle Center, Sparta, TN (J.L.); Allegheny Health Network, Pittsburgh, PA (R.M.); or Mercy Hospital, Coconut Grove, FL. Inclusion criteria were patients who (1) underwent Charcot neuroarthropathy reconstruction that utilized rhPDGF-BB/β-TCP for joint fusion, and (2) had a minimum of 12 months follow up available. Exclusion criterion was patients with less than 12 months of follow-up.

The primary outcomes of this multicenter consecutive case analysis included (1) incidence of fusion for the population, (2) mean time to fusion, (3) complications (specifically hardware failure, wound healing issues, infection, and amputation), and (4) adverse events specifically related to the grafting material. Fusion of the joints was defined as ≥50% osseous bridging based on computed tomography (CT) and/or radiographic consolidation (evidence of healing/fusion of at least 3 of the 4 cortices), in addition to clinical findings. Statistical significance was defined at the 5% level ($p \leq .05$).

This multicenter consecutive case analysis was designed and implemented by J.L., R.M., and M.C. Each site obtained written informed consent from all patients to allow their clinical data and images to be used for research. All authors (J.L., R.M., M.C.) examined all patients, collected all data for the study, and performed all surgical procedures. All chart and radiographic reviews were also performed by J.L., R.M., and M.C. Each author contributed to the outcome assessment and manuscript. The study was conducted in accordance with good clinical practice and the 1964 Declaration of Helsinki.

Operative Technique

Patients underwent deformity correction along with arthrodesis of the joints using standard joint preparation and use of internal fixation and/or external fixation techniques. The individual components of the graft material (rhPDGF-BB liquid and β-TCP matrix) were mixed and allowed to sit for at least 10 minutes to maximize saturation prior to insertion at the attempted fusion site. The rhPDGF-BB/β-TCP was applied according to the package insert instructions (Fig. 1). A variety of hardware was used for fixation due to the complex nature of Charcot cases (Table 1). Patients received external fixation alone in 41 cases, internal fixation alone in 34 cases, and a combination of internal and external fixation in 23 cases. A regional block using 0.5% bupivacaine and 1% lidocaine was administered perioperatively to all subjects, and standard postoperative analgesia was directed by the surgeon as necessary for pain management.

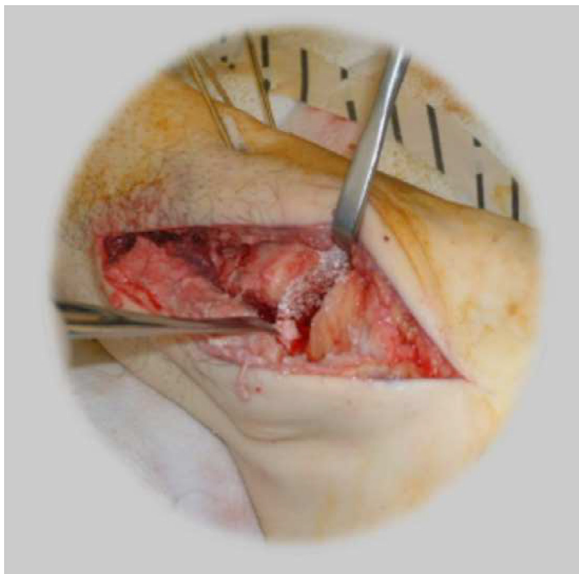

Fig. 1. Insertion of the rhPDGF-BB/β-TCP bone grafting material.

Table 1
Hardware used in included cases (N = 98)

Hardware*,†	Frequency
Bolts	30
Beams	28
Plating system	25
Hindfoot fusion nail	18
External fixation system	64
Ankle fusion plates	3
Fibular plates	1

* Patients received external fixation alone in 41 cases, internal fixation alone in 34 cases, and a combination of internal and external fixation in 23 cases.

† All hardware used was from Wright Medical Group, N.V., Memphis, TN, USA.

Follow Up

Patients were admitted to the hospital for surgery and typically discharged 1 to 3 days later, either to home with home health nursing or to a skilled nursing facility for further care. Initial follow-up was performed in-office 10 to 12 days postoperatively and then every 2 weeks after that.

At these follow-up visits, patients had serial radiographs of the foot or ankle (anterior-posterior, oblique, and lateral views) to assess healing along with cast changes or checking the external fixator for anything loose on the device. When approved by patients' insurance carriers, CT scans were obtained in 37 of 98 (37.76%) patients between 12 and 16 weeks postoperatively to assess healing at the fusion sites. Patients with an external fixator typically had it removed 3 to 4 months following surgery and were placed into a Charcot Restraint Orthotic Walker (CROW) walking boot for up to a year following the original surgery. In patients without use of an external fixator, casts were changed, again progressing into a CROW walking boot when appropriate. The ultimate goal for patients was to progress into an extra-depth shoe or double upright brace, depending on the type of deformity that was corrected.

Results

Ninety-eight patients (62.24% male) with a mean age of 62.82 ± 10.28 years (range 40-87) were included in this case review. Of note, 76 (77.55%) of these patients had neuropathy secondary to diabetes, and 22 (22.45%) had neuropathy due to non-diabetic causes. Overall, 79 (80.61%) patients had at least one comorbidity with Charcot neuroarthropathy. A statistical description of the consecutive case series is presented in Table 2.

Table 2
Patient demographics (N = 98 patients)

Characteristic		Value
Sex (n, %)		
	Male	61 (62.24)
	Female	37 (37.76)
Age (y)		
	Mean ± standard deviation	62.82 ± 10.28
	Median	63
	Range	40.0 to 87.0
BMI (kg/m^2)		
	Mean ± standard deviation	33.8 ± 6.80
	Median	33.2
	Range	21.0 to 54.9
Comorbidities (n,%)		
	Smoking	25 (25.51)
	Ulceration (preoperatively)	19 (19.39)
	Diabetes	76 (77.55)
	Non-diabetic neuropathy	22 (22.45)
	At least 1 comorbidity + Charcot neuroarthropathy	79 (80.61)

Abbreviation: BMI, body mass index.

Table 3
Joints fused (N = 223 joints of 98 patients)

Joint	Frequency	%
Ankle	46	20.63
Subtalar	54	24.22
Talo-navicular	54	24.22
Calcaneo-cuboid	32	14.35
TTC	2	0.89
Medial column	34	15.25
Fibula	1	0.45
Total joints in which fusion was attempted	223	

Abbreviation: TTC, tibio-talo-calcaneal.

Table 4
Postsurgical outcomes and follow-up

Outcomes (n, %) N = 223 Joints of 96* Patients	
Incidence of fusion	
Yes	217/223 (97.31)
No† (all ankle joints)	6/223 (2.69)
Infection	
No	92 (95.83)
Yes‡	4 (4.17)
Follow-up (months) N = 96*	
Mean ± standard deviation	15.35 ± 6.57
Median	14
Range	2.0 to 36.0
Return to weightbearing (weeks) N = 94§	
Mean ± standard deviation	13.62 ± 4.98
Median	13
Range	0.0 to 30.0
Time to fusion(weeks) N = 92‖	
Mean ± standard deviation	13.09 ± 4.87
Median	13
Range	6.0 to 30.0

* Omits 2 patients who died.
† 3 of the 6 nonunions are also infections that resulted in below the knee amputation (BKA).
‡ All infections resulted in nonunions.
§ Omits 2 patients who died, 1 who had BKA prior to walking, and 1 with data missing.
‖ Omits 2 patients who died and 4 who did not achieve fusion.

The joints fused in this series varied based upon individual clinical characteristics of each patient. A total of 223 joint fusions were attempted in this patient population. The most frequently involved joints were the subtalar (n = 54, 24.22%), talonavicular (n = 54, 24.22%), and ankle (n = 46, 20.63%). The full list of joint fusions is presented in Table 3.

Charcot reconstruction with arthrodesis utilizing rhPDGF-BB/β-TCP was performed on all patients. The majority of patients (94.88%) received 3 cc of rhPDGF-BB/β-TCP, while the remaining patients received either 4.5 or 6 cc.

The mean patient follow-up was 15.35 ± 6.57 months. Overall there was an incidence of fusion in 217 of 223 joints (97.31%) in the series with a mean time to fusion of 13.09 ± 4.87 weeks (range 6-30) (Table 4). The mean time to return to weightbearing was 12.3 ± 5.82 weeks. There were 6 nonunions (2.69%) in the study that all occurred at the ankle joint, 3 of which developed at the ankle joint and required below the knee amputations (Table 4). Two representative patient cases are described in Figs. 2 and 3.

The overall complication rate in the study was 26.53%. The most common adverse event was exchanged broken wires on external fixation (7 patients; 7.14%). Four (4.08%) patients experienced either infection or wound healing issues but went on to heal following appropriate treatment. An additional 4 (4.08%) patients were noted to have been noncompliant (failure to be non-weightbearing, unstable blood glucose levels, missed appointments, etc.). Three (3.06%) patients required below the knee amputation. Of these 3 patients, 1 had an intramedullary (IM) nail along with external fixation, and 2 had external fixation alone. There were no adverse reactions attributable to the grafting material itself. Two patients died following the original surgery, one from myocardial infarction and one from heart failure. The complete list of adverse events is presented in Table 5.

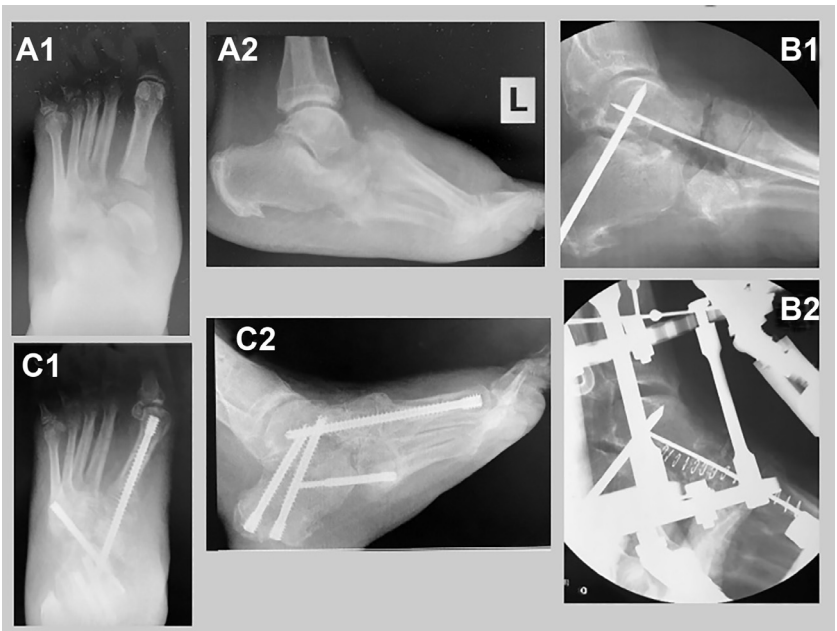

Fig. 2. A 50-year-old white female with unstable Charcot deformity of the right foot for several months prior underwent a midfoot osteotomy with application of an external fixator and beaming of the foot for a panpedal fusion with rhPDGF-BB/β-TCP augmentation. Successful fusion was achieved at 16 weeks. (*A1* and *A2*) Preoperative radiographs (anteroposterior [AP] and lateral views), (*B1* and *B2*) Intraoperative radiographs showing midfoot osteotomy with deformity correction and application of external fixator (lateral views), (*C1* and *C2*) Postoperative radiographs showing intermedullary beaming of foot (AP and lateral views).

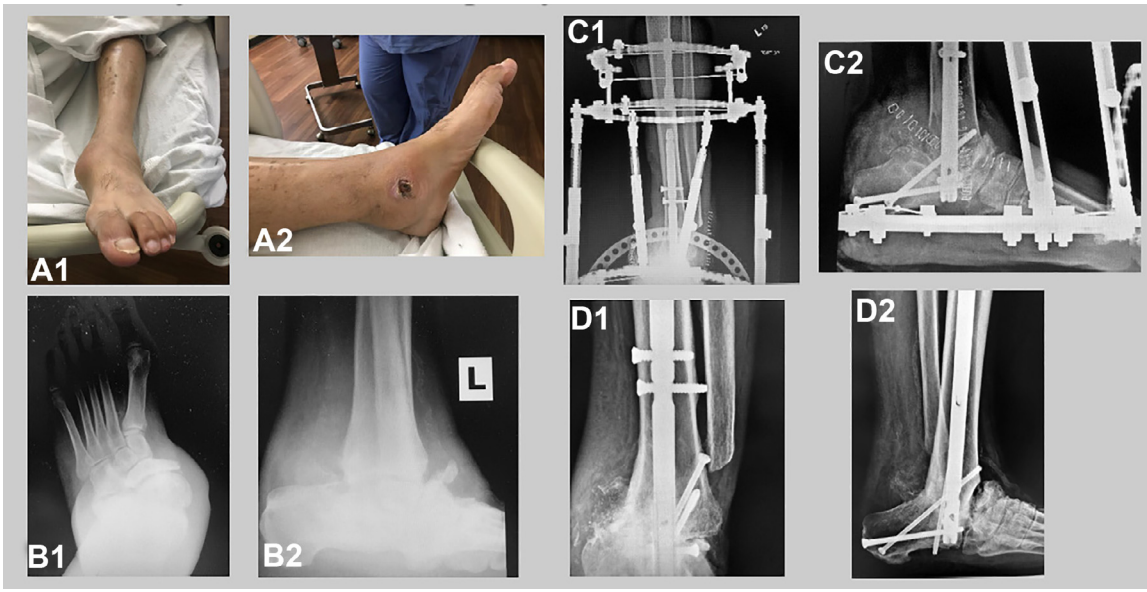

Fig. 3. A 47-year-old Hispanic male developed a Charcot deformity in his left ankle that caused a wound of several months' duration along the medial aspect of the ankle. He underwent a talectomy with tibiocalcaneal fusion via intramedullary nail and external fixator with rhPDGF-BB/β-TCP augmentation. He achieved a successful fusion at 20 weeks. (*A1* and *A2*) Clinical photographs of Charcot deformity with ulceration on foot, (*B1* and *B2*) Preoperative radiographs showing Charcot deformity (AP and lateral views), (*C1* and *C2*) Immediate postoperative radiographs showing talectomy with tibiocalcaneal fusion and placement of intermedullary nail and external fixator with bone graft (AP and lateral views), (*D1* and *D2*) Radiographs showing fusion following removal of external fixator (AP and lateral views).

There were no statistically significant differences in nonunion rates, mean time to fusion, mean time to return to weight bearing, and rates of adverse events between the 3 surgeons performing this series of fusions.

Discussion

Charcot neuroarthropathy is a progressive joint disease of the foot and ankle that can lead to fracture, deformity, and even amputation. While most commonly found in patients with diabetes mellitus, Charcot may also be seen in patients experiencing neuropathy secondary to infection, toxic exposure (including alcoholism, chemotherapy, and radiation), rheumatoid arthritis, multiple sclerosis, traumatic injury, and metabolic abnormalities (6).

Historically, the primary nonsurgical treatment for Charcot has been immobilization and offloading, including splints, braces, orthosis, or casts, often non-weightbearing (7). Other nonsurgical modalities of treatment, successful to varying degrees, include pharmacologic antiresorptive therapy (e.g., bisphosphates, calcitonin) and bone growth stimulation utilizing ultrasonic, magnetic field, or direct current electrical bone growth stimulators (6-8).

Surgical management for Charcot neuroarthropathy may include external and/or internal fixation, reconstruction/realignment, arthrodesis, plantar exostectomy, bone grafting, or some combination of these procedures (7,9,10). Amputation is also a surgical option, albeit a procedure of last resort.

Bone grafting plays an important role in surgical reconstruction to promote bone formation, replacement, and repair. Autograft is the gold standard of bone graft procedures because complete histocompatibility is ensured and transmission of disease from donor tissue is eliminated (11). Autograft, most commonly harvested from the iliac crest, also has the advantages of providing osteogenic cells, osteoinductive growth factors, and osteoconductive scaffolding (12,13). However, it brings with it potential complications such as donor site morbidity, limited availability, increased surgical time, bleeding, infection, loss of sensation, and persistent pain (11-13).

Allografts may be more readily available; however, the drawbacks of allografts include the risk of disease transmission, potential antigenic response, nonuniform preservation practices, potential structural weaknesses, cost, and possible increased risk of nonunion or failure (13-15).

Other graft alternatives such as bovine and porcine xenografts as well as coral grafts have been studied, however, autograft remains the standard of care (13). Most recently, advances in graft alternatives have been seen in three-dimensional (3-D) printing of bone grafts, often designed based on an intact contralateral bone. Bone grafts have been printed out of titanium and ceramic, as well as compounds containing bioactive nanoparticles that can stimulate bone tissue formation (16-20).

In addition to these surgical and nonsurgical interventions for Charcot neuroarthropathy, recent advances in orthobiologics have added another option for patients. Orthobiologics may not only reduce the

Table 5
Adverse events (N = 98 patients)

Adverse Events	Frequency	%
Exchanged broken wires on external fixation	7	7.14
Infection (1 infected hematoma)	4	4.08
Wound dehiscence	4	4.08
Below the knee amputation	3	3.06
Death*	2	2.04
Ankle Valgus	1	1.02
Chronic pain	1	1.02
Lateral ankle wound	1	1.02
Lumbar pain	1	1.02
Needed incision & drainage and IV antibiotics	1	1.02
Small plantar wound remained	1	1.02
Adverse reaction to grafting material	0	0.00
Overall adverse event rate	26 patients	26.53%

* One patient died from heart failure 4 months following surgery (was schedule to have external fixation removed the week he died); One patient died from myocardial infarction 4 weeks postoperatively.

need for surgery in treating musculoskeletal injuries, but also enhance the effectiveness of existing surgical techniques (21).

The synthetic graft substitute used in this study, rhPDGF-BB/β-TCP, is composed of beta-tricalcium phosphate granules, which provide scaffolding properties, and recombinant human platelet-derived growth factor BB homodimer, which provides the stimulation for proliferation of osteoblasts as well as revascularization (22,23). It can be used as an alternative to autograft in arthrodesis of the foot and ankle. In 2 multicenter clinical trials of rhPDGF-BB/β-TCP, no serious adverse events were attributable to the product. There are, however, reports in the literature of adverse events with the use of autograft or other bone graft substitute products including swelling, pain, bleeding, hematoma, superficial or deep wound infection, cellulitis, wound dehiscence, incomplete or lack of osseous ingrowth, transient hypercalcemia, neuralgia and loss of sensation locally and peripherally, and anaphylaxis (23), so these events were specifically tracked.

In 2013, DiGiovanni et al published a prospective, randomized, controlled clinical trial on the use of rhPDGF-BB/β-TCP in hindfoot and ankle fusions. In that study, 434 patients requiring hindfoot or ankle arthrodesis were randomized 2:1 into autograft or rhPDGF-BB/β-TCP groups. They reported fusion in 262 of 394 (66.5%) and 127 of 203 (62.6%) joints for the 2 groups, respectively, with fusion defined as >50% osseous bridging confirmed using CT scans. Of the patients in the rhPDGF-BB/β-TCP group, 224 patients (86.2%) were considered clinically healed at 52 weeks compared with 120 (87.6%) in the autograft group. While the 2 groups achieved comparable incidence of fusion, the rhPDGF-BB/β-TCP group had fewer side effects and less pain (5).

In another prospective randomized controlled trial of hindfoot and ankle fusions treated with rhPDGF-BB/β-TCP, Daniels et al enrolled 75 patients, randomizing them 5:1 to rhPDGF-BB/β-TCP (n = 63) or autograft (n = 12). Results from an additional 142 autograft patients from another study with identical study protocols were also analyzed. The primary outcome was joint fusion, defined as 50% or more osseous bridging on CT, at 24 weeks. Complete fusion was achieved in 53 of 63 (84%) of the rhPDGF-BB/β-TCP-treated patients and 100 of 154 (65%) of the autograft-treated patients ($p < .001$). The mean time to fusion was 14.3 $\pm$ 8.9 weeks for rhPDGF-BB/β-TCP patients versus 19.7 $\pm$ 11.5 weeks for autograft patients ($p < .01$) (3).

In Charcot reconstruction, fusion is critically important in achieving the end goal of successful limb salvage. The fusion results of our consecutive case series compare favorably to these prior studies, particularly considering our high-risk Charcot patient population. The 217 of 223 patient (97.31%) incidence of joint fusion and 13.09 $\pm$ 4.87 weeks (range 6-30 weeks) to fusion also fare well when compared to historical autograft controls (2).

With respect to safety, we saw no complications specifically associated with the use of rhPDGF-BB/β-TCP, in contrast to potential complications seen with autograft or allograft (12-14). This suggests that the recombinant human platelet-derived growth factor is a safe and effective way to achieve high rates of fusion in a population with multiple high-risk factors for developing nonunions.

Of the 6 nonunions, all patients were diabetics and all involved the ankle joint. Three were male, and 3 were female, ranging from 57 to 87 years of age. Two of the 6 were smokers, and 1 used recreational drugs. With respect to fixation hardware, 2 of these patients had IM nails, 1 had IM nail along with external fixation, and 3 had external fixation alone. Of the 4 patients in whom external fixation was used, all experienced broken wires, which required exchange of wires during their treatment. It is difficult to draw conclusions with such small numbers, however it stood out that all of the nonunions were diabetic patients along with an element of noncompliance.

There were several limitations to this study, including its retrospective design, no comparison group, and variable follow-up. Additionally, there could have been some variability in results, depending on which bones were targeted for arthrodesis. In spite of these limitations, our results were encouraging. This series is, to our knowledge, one of the largest samples described in the literature, and we had patients with follow up as long as 3 years, in spite of the comorbidities that accompanied this Charcot population. Further trials of rhPDGF-BB/β-TCP for arthrodesis in this Charcot neuroarthropathy population are warranted, and our findings could be used to help estimate sample size for a prospective cohort study or a randomized controlled clinical trial.

This case series review of rhPDGF-BB/β-TCP for arthrodesis in patients requiring Charcot reconstruction demonstrated both efficacy and safety. Based on the rate of fusion, reasonably short time to fusion, complication rates comparable to other interventions, and no adverse events deemed to be related to the graft material itself, rhPDGF-BB/β-TCP is a safe and effective graft material and should be considered a suitable alternative to autograft, even in high-risk patients with Charcot neuroarthropathy.

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