Efficacy and Safety of a Topical Gel Formulation of Recombinant Human Platelet-Derived Growth Factor-BB (Becaplermin) in Patients With Chronic Neuropathic Diabetic Ulcers

A phase III randomized placebo-controlled double-blind study

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OBJECTIVE — To compare the efficacy and safety of topically applied recombinant human platelet–derived growth factor-BB (rhPDGF-BB) (becaplermin) with placebo gel in patients with chronic diabetic neuropathic ulcers of the lower extremities.

RESEARCH DESIGN AND METHODS — This multicenter double-blind placebo-controlled phase III trial included 382 patients with type 1 or type 2 diabetes and chronic ulcers of at least 8 weeks' duration. After sharp debridement of the ulcer, patients were randomized to receive becaplermin gel 30 μg/g, becaplermin gel 100 μg/g, or placebo gel, in conjunction with a standardized regimen of good wound care until complete wound closure was achieved or for a maximum of 20 weeks. Moist saline-soaked gauze dressings were changed twice daily with study medication applied by patients or caregivers at the evening dressing change. Safety was assessed by monitoring adverse events (AEs) and by clinical laboratory evaluations.

RESULTS — Compared with placebo gel, becaplermin gel 100 μg/g significantly increased the incidence of complete wound closure by 43% (50 vs. 35%, $P = 0.007$) and decreased the time to achieve complete wound closure by 32% (86 vs. 127 days; estimated 35th percentile, $P = 0.013$). AEs reported during treatment or during a 3-month follow-up period were similar in nature and incidence across all treatment groups.

CONCLUSIONS — Becaplermin gel 100 μg/g, in conjunction with good wound care, significantly increased the incidence of complete wound closure and significantly reduced the time to complete closure of chronic diabetic neuropathic ulcers. The safety profile of becaplermin gel was similar to that of placebo gel.

Lower-extremity ulcers are a serious complication of diabetes (1). Multiple factors associated with diabetes, including peripheral vascular disease, neuropathy, and immunopathy, contribute to the development and persistence of lower-extremity ulcers in patients with diabetes (2). These factors, combined with the mechanical stress normally associated with weight bearing, make the lower extremities particularly vulnerable to the development of ulcers. At least 15% of individuals with diabetes will develop foot ulcers during their lifetime (3,4). Diabetic neuropathic ulcers of the lower extremities are noted for their slow healing rate and resistance to traditional methods of treatment (2). If not properly treated, these ulcers can develop complications, such as infection and gangrene, and, in some cases, amputation of the affected limb may be required. It is estimated that there are ~67,000 amputations in people with diabetes annually in the U.S. (5), with a 5-year mortality rate of 50–60% for people with diabetes who have undergone lower-limb amputation (4). In patients who manage to avoid lower-limb amputation, lower-extremity ulcers represent a significant social and economic burden, stemming from severe functional debilitation, loss of income, and an overall reduction in quality of life (1,6). Thus, the potential long-term benefits associated with rapid and complete ulcer healing may be substantial.

In the last 2 decades, our understanding of the wound repair process and the role that growth factors, including platelet-derived growth factor (PDGF) and transforming growth factor-β, play in this process has greatly increased, offering the potential for improved treatment of chronic wounds. In phase II studies, recombinant human PDGF-BB (rhPDGF-BB) was shown to have a positive effect on healing pressure ulcers (7,8) and lower-extremity ulcers in patients with diabetes (9), suggesting that rhPDGF-BB may have clinical applications for promoting wound healing. Nevertheless, there has been a dearth of well-designed placebo-controlled clinical studies in the area of wound healing, making comparison of different therapeutic regimens difficult.

This study was conducted to compare the efficacy and safety of two concentra-

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Abbreviations: AE, adverse event; IAET, International Association of Enterostomal Therapy; PDGF, platelet-derived growth factor; rhPDGF-BB, recombinant human platelet–derived growth factor-BB; SAE, serious adverse event; $TcPO_2$, transcutaneous oxygen tension.

tions of becaplermin gel (30 and 100 μg/g) with that of placebo gel when applied for up to 20 weeks in patients with chronic diabetic neuropathic ulcers of the lower extremities. Topical application of becaplermin gel or placebo gel was combined with a standardized regimen of good wound care, which included initial and ongoing sharp debridement of the ulcer, twice-daily moist saline dressing changes, off-loading of pressure from the affected area, and control of infection, if present.

RESEARCH DESIGN AND METHODS

Study population

This study was a multicenter (23 sites in the U.S.) double-blind parallel-group placebo-controlled trial involving a total of 382 patients (127 women and 255 men) ≥19 years of age with type 1 or type 2 diabetes. Patients had at least one full thickness (stage III or IV, as defined in the International Association of Enterostomal Therapy [IAET] guide to chronic wound staging [10,11]) chronic ulcer of the lower extremities. If more than one lower-extremity ulcer was present, the one that would, in the opinion of the investigator, take the longest time to heal with good wound care practice was designated as the target ulcer. Target ulcers had to be present for at least 8 weeks despite previous treatment. To ensure that arterial circulation was adequate, transcutaneous oxygen tension ($TcPo_2$) on the limb with the target ulcer had to be ≥30 mmHg.

Before randomization, the target ulcer was sharply debrided to remove all nonviable tissue and callus. Any infection or cellulitis present before debridement had to be well controlled before randomization. Patients were excluded if *1*) osteomyelitis affecting the area of the target ulcer was present, 2) after debridement, the target ulcer area (estimated by multiplying length by width) was <1 cm^2 or >40 cm^2, or 3) the sum of the areas of all ulcers present exceeded 100 cm^2. Patients with ulcers resulting from any cause other than diabetes (e.g., electrical, chemical, or radiation insult) and patients with cancer were excluded. Additional exclusion criteria included concomitant diseases (e.g., connective tissue disease), treatment (e.g., radiation therapy), or medication (e.g., corticosteroids, chemotherapy, or immunosuppressive agents) that would present safety hazards or interfere with evaluation of the study medication.

Table 1—*Patient demographics and target ulcer characteristics*

Characteristic	Placebo gel	Becaplermin gel (μg/g) 30	100	Total
n	127	132	123	382
Sex				
Male	91 (72)	82 (62)	82 (67)	255 (67)
Female	36 (28)	50 (38)	41 (33)	127 (33)
Race				
White	100 (79)	108 (82)	101 (81)	309 (81)
Black	18 (14)	15 (11)	14 (11)	47 (12)
Asian	1 (0.8)	0 (0)	0 (0)	1 (0.3)
Hispanic	7 (5.5)	9 (6.8)	8 (6.5)	24 (6.3)
Other	1 (0.8)	0 (0)	0 (0)	1 (0.3)
Age (years)	58 ± 11.8	58 ± 11.3	57 ± 11.5	58 ± 11.5
Target ulcer				
Area (cm^2)	2.8 ± 4.14	2.6 ± 2.69	2.6 ± 3.41	2.7 ± 3.45
*n**	127	132	123	382
Depth (cm)	0.5 ± 0.54	0.5 ± 0.48	0.4 ± 0.46	0.5 ± 0.49
*n**	122	129	117	368
Duration (weeks)	46 ± 52.1	56 ± 80.3	46 ± 54.7	49 ± 64.0
*n**	119	123	113	355
$TcPo_2$ (mmHg)				
Foot dorsum	55.5 ± 19.61	54.1 ± 20.94	55.0 ± 22.60	54.9 ± 21.02
*n**	127	132	123	382

Data are *n*, *n* (%), or means ± SD. *Reduced *n* values reflect the number of patients with missing baseline data.

Women who were pregnant, nursing, or of childbearing potential and not using either an intrauterine device or oral contraception were excluded. All patients gave their written informed consent before study entry.

Study design

Eligibility for randomization was determined at a screening visit (visit 1), during which a full medical history and lower-extremity radiographs were obtained, and a complete physical examination was given. At visit 2, eligibility criteria were confirmed, the target ulcer was surgically debrided if necessary, and the area of the target ulcer was determined by measuring length multiplied by width. Study visits were scheduled weekly for visits 2–6 and every other week after visit 6. Patients who healed were asked to complete a poststudy questionnaire 3 months after healing to determine the rate of ulcer recurrence.

Patients were randomized to one of three parallel treatment groups: becaplermin gel 100 μg/g (Regranex Gel 0.01%) (*n* = 124), becaplermin gel 30 μg/g (*n* = 132), or placebo gel (*n* = 127). (One patient in the group treated with becaplermin gel 100 μg/g was lost to follow-up and had no post-baseline data.) Becaplermin (rhPDGF-BB) is a homodimer produced by recombinant DNA technology by insertion of the human gene for the B chain of PDGF into the yeast *Saccharomyces cerevisiae*. Becaplermin gel consisted of 100 or 30 μg of becaplermin per gram of vehicle gel (sodium carboxymethylcellulose aqueous-based gel containing parabens, m-cresol, and L-lysine). The placebo gel was identical to the vehicle component of the gel formulation containing the active drug. Moist saline dressings were changed twice daily, once in the morning and once in the evening. Patients were instructed to apply a continuous thin layer of gel to the entire ulcer area once daily, preferably when the dressing was changed in the evening. The amount of study medication to be applied was determined based on ulcer area at that visit. Study medication was administered in conjunction with a standardized regimen of good wound care for 20 weeks or until the target ulcer was completely healed. Complete sharp debridement of ulcers to remove callus, fibrin, and necrotic tissue was an important component of good wound care and was performed by investigators during clinic visits if necessary. Good wound care also consisted of twice-daily dressing changes (moist saline), off-loading of pressure from the affected area, and adequate control of infection if present. Effi-

Table 2—*Discontinuations from the study*

	Placebo gel	Becaplermin gel (μg/g) 30	100	Total
n	127	132	123	382
Reason for discontinuation				
Lost to follow-up	2 (1.6)	1 (0.8)	1 (0.8)	4 (1.0)
AE	13 (10)	17 (13)	13 (11)	43 (11)
Noncompliance	3 (2.4)	4 (3.0)	3 (2.4)	10 (2.6)
Protocol violation	3 (2.4)	2 (1.5)	2 (1.6)	7 (1.8)
Other	3 (2.4)	4 (3.0)	2 (1.6)	9 (2.4)
Total discontinuations	24 (19)	28 (21)	21 (17)	73 (19)
Patients completing study*	103 (81)	104 (79)	102 (83)	309 (81)
Treatment failures	7 (5.5)	17 (13)	10 (8.1)	34 (8.9)

Data are *n* or *n* (%). *Patients whose target ulcer decreased by <20% at week 10 were considered treatment failures and discontinued; however, they were considered to have completed the study.

cacy and safety evaluations were performed at each visit as described below.

Efficacy evaluations

At each visit, the area of the target ulcer was measured (length multiplied by width), and the target ulcer was assigned a functional assessment score based on whether the wound was completely closed without drainage or need of dressing (scored as 1) or <100% closed with drainage and requiring a dressing (scored as 2). For statistical analyses, the area of the target ulcer was determined by planimetry from acetate tracings made at each visit. For cases in which debridement of the target ulcer was performed, efficacy measurements (measurements of length and width and acetate tracings) were made after debridement. The primary efficacy criterion was the percentage of patients that achieved complete healing (i.e., functional assessment score = 1) within the 20-week study period. A secondary efficacy criterion was time required to achieve complete healing.

Safety evaluations

Safety was evaluated by monitoring adverse events (AEs), serious adverse events (SAEs), deaths, discontinuations, clinical laboratory measurements, and vital signs. AEs were monitored by open-ended questioning of patients by investigators. A treatment-emergent AE was defined as an AE that was either not present at baseline or, if present at baseline, increased in severity as the study progressed. SAEs were those that were either immediately life threatening, permanently or significantly disabling, required a prolonged hospitalization, resulted in long-term outpatient treatment, or resulted in a congenital anomaly, cancer, or death. The presence of serum antibodies to PDGF-BB was also assessed before and after the study.

Statistical methods

Efficacy analysis was based on the intent-to-treat population, which included all patients who were randomized to treatment, received at least one application of study medication, and had any postbaseline data. Patients whose target ulcer area had decreased by <20% (determined by multiplying length by width) at week 10 were discontinued from study treatment. However, for statistical evaluations, these patients were assigned a study duration of 20 weeks regardless of when treatment was discontinued.

Functional assessment score was analyzed using a logistic regression model adjusted for baseline target ulcer area. The time to complete healing, defined as the number of days until the patient achieved a functional assessment score of 1, was analyzed using Cox's proportional hazards model, with treatment group and baseline wound area as covariates.

RESULTS

Demographic and baseline characteristics

A total of 382 patients were randomized to treatment. No clinically important differences between treatment groups were observed for any of the demographic or baseline efficacy variables (Table 1). Of the 382 patients randomized to treatment, 309 (81%) completed the study. The reasons for discontinuations are shown in Table 2.

Initial and ongoing sharp debridement was part of the standardized regimen of good wound care that all patients received. The percentage of visits at which debridement was performed was similar among groups (85% in the group treated with placebo gel, 86% in the group treated with becaplermin gel 30 μg/g, and 85% in the group treated with becaplermin gel 100 μg/g). Almost all patients (95%) had target ulcers with areas ≤10 cm² as determined by planimetry.

Efficacy results

Treatment with becaplermin gel 100 μg/g significantly increased the incidence of complete healing by 43% compared with placebo gel (50 vs. 35%, $P = 0.007$) (Fig. 1). A total of 61 of 123 (50%) patients randomized to receive becaplermin gel 100 μg/g achieved complete wound healing (i.e., functional assessment score = 1) at end point. In the groups treated with placebo gel and becaplermin gel 30 μg/g, the number of patients who achieved complete wound healing was 44 of 127 (35%) and 48 of 132

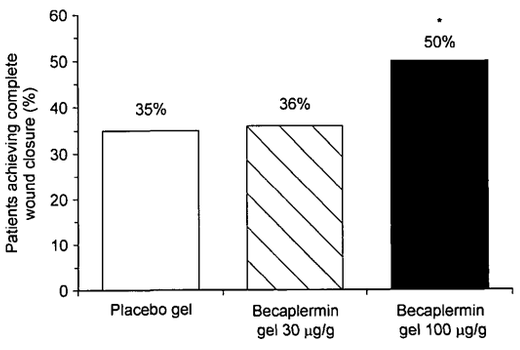

Figure 1—*Effect of becaplermin gel on complete wound closure in patients receiving becaplermin gel 100 μg/g* (n = *123), becaplermin gel 30 μg/g* (n = *132), and placebo gel* (n = *127).* *P = *0.007 vs. placebo gel.*

Table 3—*Effects of age, baseline HbA_{1c}, and non–weight-bearing compliance on ulcer healing by treatment group*

	Placebo gel		Becaplermin gel (μg/g) 30		100	
	Healed	Not healed	Healed	Not healed	Healed	Not healed
Age (years)	59 ± 13.8 (35)	58 ± 10.7 (65)	57 ± 12.6 (36)	58 ± 10.6 (64)	57 ± 11.0 (50)	58 ± 12.1 (50)
Baseline HbA_{1c}	6.5 ± 1.1 (35)	6.7 ± 1.5 (65)	7.2 ± 1.2 (35)	6.9 ± 1.7 (65)	7.0 ± 1.3 (50)	7.1 ± 1.4 (50)
Compliance*	35.7	64.3	39.6	60.4	52.3	47.7
Noncompliance	26.7	73.3	20.8	79.2	25.0	75.0

Data are means ± SD (%) or %. *Compliance with non–weight-bearing measures and use of appropriate off-loading device.

(36%), respectively. There was no statistically significant difference in the incidence of complete wound healing in patients receiving becaplermin gel 30 μg/g and those receiving placebo gel. No interactions were observed between age or baseline HbA_{1c} and complete healing, whereas compliance with a nonweightbearing regimen was positively associated with complete healing (Table 3).

Becaplermin gel 100 μg/g significantly decreased the time to achieve complete healing by 32% (86 days for becaplermin gel vs. 127 days for placebo gel; estimated 35th percentile, $P = 0.013$). Figure 2 shows the percentage of patients achieving complete healing over time.

Safety results

Most AEs reported during the study were related to the ulcers, underlying conditions, or age of the patient. The incidences of the most common treatment-emergent AEs in all treatment groups are shown in Table 4. The incidence of treatment-emergent AEs, particularly infection such as osteomyelitis and cellulitis, was similar across all treatment groups.

A total of seven patients (three in the placebo gel group, three in the becaplermin gel 30 μg/g group, and one in the becaplermin gel 100 μg/g group) died during the study or during the 3-month follow-up period. No deaths were considered to be related to the study medication.

Discontinuations because of AEs, as well as the incidences of SAEs, target ulcer–related AEs, and wound infection–related AEs were similar across all treatment groups (Table 5). There was a 2% incidence of application-site disorders in each treatment group.

There were no clinically meaningful changes from baseline in clinical laboratory parameters (including serum chemistry, hematology, and urinalysis) or vital signs in any of the treatment groups.

Of the 315 patients who were assessed for anti-PDGF-BB antibodies at both baseline and poststudy, 2 patients (both in the 30 μg/g group) had a positive antibody response at the end of the study compared with baseline. In both cases, binding was not inhibited by the addition of excess PDGF-BB, suggesting that the antibodies were either of very low affinity or represented a nonspecific response in the assay.

In a 3-month follow-up period during which no standardized regimen of preventive care was used, the incidence of ulcer recurrence was ~30% in all treatment groups, demonstrating that the durability of ulcer closure was comparable in all treatment groups.

CONCLUSIONS — In this study, the effect of a single growth factor, rhPDGF-BB (becaplermin), was evaluated in promoting wound healing in patients with chronic diabetic neuropathic ulcers of the lower extremities. Although several growth factors have been or are currently being explored as potential wound healing agents (12–14), becaplermin is the first and only growth factor to date to demonstrate a statistically significant effect in a phase III clinical trial. Phase II studies have also demonstrated the clinical efficacy of rhPDGF-BB in the treatment of pressure ulcers; both Robson et al. (8) and Mustoe et al. (7) have shown that treatment with rhPDGF-BB for 4 weeks reduces the size of chronic pressure ulcers.

The results of this study demonstrated that treatment with becaplermin gel 100 μg/g significantly increased the percentage of patients achieving complete healing by 43% compared with that of patients treated with placebo gel. In a previous study that included 118 patients with diabetes and chronic ulcers of the lower extremities, Steed et al. (9) reported that the incidence of complete healing with becaplermin gel 30 μg/g was significantly greater than that with placebo gel (48 vs. 25%, respectively, $P < 0.01$). In the present study, the incidence of complete healing with becaplermin 30 μg/g was not significantly different from that with placebo. Several factors may have con-

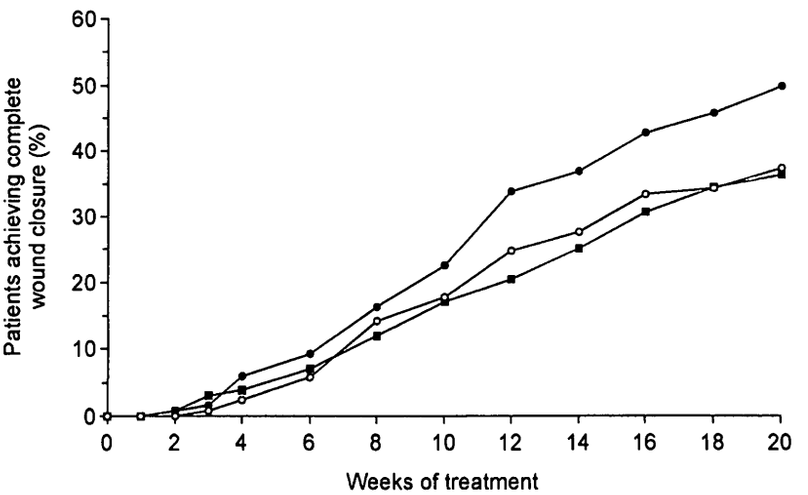

Figure 2—*Incidence of complete wound closure at each time point for patients receiving becaplermin gel 100 μg/g (●, n = 123), becaplermin gel 30 μg/g (■, n = 132), and placebo gel (○, n = 127).*

Table 4—*Incidence of treatment-emergent AEs*

	Placebo gel	Becaplermin gel (μg/g) 30	100
n	127	132	123
Disorders by body system or preferred term			
Application site (%)			
Cellulitis	15	10	16
General (%)			
Edema	4.7	5.3	5.7
Pain	1.6	6.1	5.7
Musculoskeletal system (%)			
Osteomyelitis	7.1	5.3	10
Resistance mechanism (%)			
Infection	20	20	20
Skin and appendage (%)			
Bullous eruption	3.1	5.3	4.9
Skin disorder	3.9	3.0	5.7
Skin ulceration	9.4	11	15

Treatment-emergent AEs are those that occurred in ≥5% of patients.

tributed to this difference. In the study by Steed et al., overall infection control, based on reports of infection-related events and clinical examination of the target ulcer, was better than that in the present study. This may have been due, in part, to the small number of investigators participating in their study, which limited variability in overall treatment. In addition, the study by Steed et al. was conducted with investigators who had considerable experience with difficult cases. In contrast, a large number of investigators from different specialties, many with less experience, participated in the present study. Also, the number of patients per investigator was smaller in more centers in this study compared with that of Steed et al., thus increasing the potential for variability of the results.

In this study, topical becaplermin gel or placebo gel was administered along with a standardized regimen of good wound care, which consisted of twice-daily dressing changes, sharp debridement of the ulcer when the investigator considered it necessary, systemic control of infection if present, and off-loading of pressure from the affected area. However, in actual clinical practice, wound care varies between clinics and even between physicians or primary caregivers, and no comprehensive standardized regimen for treating chronic wounds is universally practiced. The standardized regimen of wound care used in this study was chosen both to provide patients with what was considered the best possible wound care and to limit, as far as possible, the variability introduced by different methods of caring for chronic wounds. Some variability was inevitable because study medication was applied and wound dressings were changed by patients or caregivers outside a clinical setting, and the decision to perform debridement and the method of off-loading of pressure was left up to individual investigators. These conditions, however, are more representative of the kind of care patients are likely to receive in actual clinical practice.

Good wound care practice, including ongoing debridement to remove nonviable tissue, is an important factor in wound healing. In a retrospective study by Steed et al. (15), a trend was noted between healing rate and frequency of debridement, with higher healing rates occurring in centers where ulcers were debrided more frequently. Furthermore, the healing rate was approximately twice as high for patients treated with becaplermin gel compared with that for patients treated with placebo gel when the frequency of debridement was equivalent, indicating that treatment with becaplermin gel provides additional benefits over good wound care alone. The results of the present study are consistent with this finding; the frequency of debridement was similar for all groups, yet the incidence of healing was higher for patients treated with becaplermin gel 100 μg/g than for patients treated with placebo gel.

Becaplermin gel 100 μg/g also reduced the time to healing of these lower-extremity ulcers by 32% (nearly 6 weeks faster), when compared with that of patients receiving placebo gel (Kaplan-Meier 35th percentile, $P = 0.013$). The more rapid healing rate is likely to provide significant social and economic advantages for patients with chronic neuropathic diabetic ulcers and their caregivers, for example by reducing the numbers of office visits, hospital days, outpatient debridements, antibiotics, and serious wound complications, such as infection and gangrene, that can lead to amputations and by restoring patients to an ambulatory status sooner.

Overall, becaplermin gel was well tolerated, and there were no safety concerns associated with its administration. AEs experienced by patients during treatment or during the 3-month follow-up period were not unexpected for a population of middle-aged people with diabetes and were similar in nature and incidence across all treatment groups.

In conclusion, the results of this study suggest that within the setting of a comprehensive wound management program, becaplermin gel 100 μg/g increases the incidence of complete healing and reduces the time to complete healing of lower-extremity neuropathic ulcers in patients with diabetes. Moreover, becaplermin gel has an excellent safety profile and is easy to use by patients or by caregivers outside a clinical setting. Future studies are warranted to assess the efficacy and safety of topical becaplermin

Table 5—*Safety profile of becaplermin gel*

	Placebo gel	Becaplermin gel (μg/g) 30	100
n	127	132	123
Target ulcer–related AEs (%)	35	27	35
Wound-related infections (%)	31	23	29
SAEs (%)	24	25	30
Discontinuations because of AEs (%)	10	13	11

gel in other types of chronic wounds, such as pressure and venous ulcers, and to address issues such as the effect of becaplermin gel on health care resource utilization and patient quality of life.

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