Becaplermin gel in the treatment of pressure ulcers: a phase II randomized, double-blind, placebo-controlled study

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Pressure ulcers are associated with significant rates of morbidity and mortality, particularly in the geriatric and spinal cord–injured populations. Newer pharmacologically active therapies include the use of topically applied recombinant human platelet-derived growth factor-BB (becaplermin), the active ingredient in REGRANEX® (becaplermin) Gel 0.01%, which has been approved in the United States for treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. In this study, the efficacy of becaplermin gel in the treatment of chronic full thickness pressure ulcers was compared with that of placebo gel. A total of 124 adults (≥ 18 years of age) with pressure ulcers were assigned randomly to receive topical treatment with becaplermin gel 100 μg/g (n = 31) or 300 μg/g (n = 32) once daily alternated with placebo gel every 12 hours, becaplermin gel 100 μg/g twice daily (n = 30), or placebo (sodium carboxymethylcellulose) gel (n = 31) twice daily until complete healing was achieved or for 16 weeks. All treatment groups received a standardized regimen of good wound care throughout the study period. Study endpoints were the incidence of complete healing, the incidence of ≥ 90% healing, and the relative ulcer volume at endpoint (endpoint/baseline). Once-daily treatment of chronic pressure ulcers with becaplermin gel 100 μg/g or 300 μg/g significantly increased the incidences of complete and ≥ 90% healing and significantly reduced the median relative ulcer volume at endpoint compared with that of placebo gel ($p < 0.025$ for all comparisons). Becaplermin gel 300 μg/g did not result in a significantly greater incidence of healing than that observed with 100 μg/g. Treatment with becaplermin gel was generally well tolerated and the incidence of adverse events was similar among treatment groups. In conclusion, once-daily application of becaplermin gel is efficacious in the treatment of chronic full thickness pressure ulcers. **(WOUND REP REG 1999;7:141–147)**

Pressure ulcers are a prevalent clinical problem. Conservative estimates indicate that in the United States alone, over 2 million people in hospitals and nursing homes are afflicted with these wounds annually.[1] Pressure ulcers are associated with significant rates of morbidity and mortality, particularly in the geriatric and spinal cord–injured populations.[2,3] Patients who develop pressure ulcers suffer pain and discomfort, often have an increased length of stay in hospitals and longer rehabilitation time, and use considerably more resources than patients who do not develop pressure ulcers.[4,5]

Pressure ulcers have a great impact on morbidity and mortality. As a result, patients with pressure

AE	Adverse event
PDGF	Platelet-derived growth factor
rhPDGF	Recombinant human PDGF
SAE	Serious AE

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**The members of the Pressure Ulcer Study Group are listed in the Appendix.*

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ulcers often have prolonged and expensive hospitalizations. The mean length of stay for a patient with a primary diagnosis of pressure ulcer was nearly 5 times greater than that of patients without pressure ulcers in one cross sectional study.[4,6] The increased length of stay and higher resource utilization in patients with pressure ulcers translates into significant costs: the mean hospital charge for patients with a primary diagnosis of pressure ulcer was nearly $22,000 in 1992.[7] The same study found that patients with a secondary diagnosis of pressure ulcer incurred an average of $11,000 in additional hospital charges.

Platelet-derived growth factor (PDGF) is a dimeric protein of approximately 25 kDa, composed of 2 disulfide-linked polypeptide chains.[8] It exists in 3 different isoforms, the heterodimer PDGF-AB (consisting of an A and B chain), and 2 homodimers, consisting of 2 A or 2 B chains (PDGF-AA and PDGF-BB, respectively). The homodimer PDGF-BB has been shown in preclinical and clinical studies to promote the formation of granulation tissue at the wound site and to stimulate wound healing.[9–12]

Becaplermin (recombinant human PDGF-BB [rhPDGF-BB]) is produced using recombinant DNA technology by insertion of the gene for the B chain of PDGF into the yeast *Saccharomyces cerevisiae*. The biological activity of becaplermin has been shown to be similar to that of naturally-occurring PDGF.

Becaplermin is formulated in a preserved, sodium carboxymethylcellulose-based gel for topical administration. This aqueous gel may provide the additional benefit of a moist wound healing environment.[12,13] Becaplermin gel has been approved in the United States as an adjunct to good wound care for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. Pressure ulcers are another type of chronic full thickness wound, similar to diabetic foot ulcers, and represent a potential application for becaplermin gel treatment.

Results of previous studies of rhPDGF-BB treatment of chronic stage III or IV pressure ulcers have shown that doses of less than 100 μg/ml have little effect on healing compared with placebo.[14,15] However, a phase II study involving 41 patients showed that, when expressed as a percentage of initial ulcer volume, once-daily application of rhPDGF-BB 100 μg/ml or 300 μg/ml resulted in a decrease in ulcer volume at endpoint, a trend that approached significance when compared with placebo ($p = 0.056$).[16] The results of these and other unpublished studies suggested a need for further dose-ranging studies of rhPDGF-BB for the treatment of pressure ulcers. Therefore, this dose-ranging study evaluated the efficacy and safety of becaplermin gel in the treatment of nonhealing full thickness pressure ulcers compared with that of placebo gel in patients receiving a standardized regimen of good wound care.

MATERIALS AND METHODS

This study was a prospective, multicenter, double-blind, parallel group, placebo-controlled trial involving a total of 124 patients (20 women and 104 men) ≥ 18 years of age. Patients had at least 1 but no more than 3 chronic full thickness (stage III or IV as defined by the National Pressure Ulcer Advisory Panel)[1] pressure ulcers (primary or recurrent) without involvement of bone tissue. To be eligible for the study, the patient had to have a target ulcer with a volume between 10 ml and 150 ml, inclusive, following debridement at the baseline visit. If more than 1 full thickness ulcer was present, the investigator designated the ulcer that would presumably take the longest time to heal as the target ulcer. Target ulcers had to be present for at least 4 weeks despite previous treatment, and had to be anatomically located where pressure could be off-loaded for the duration of the study. Prior to study entry, patients were required to have albumin concentrations > 2.5 g/dl, total lymphocyte count > 1,000, and concentrations of vitamins A and C within the normal range.

Before randomization, the target ulcer was debrided to remove all nonviable tissue. Quantitative bacteriology was performed on tissue biopsy specimens obtained from the center of the base of the ulcer. Before debridement, any infection (defined from tissue culture as the presence of $>10^5$ organisms per gram of tissue) was treated followed by another tissue culture until $< 10^5$ bacteria per gram of tissue were present. Patients were excluded if: 1) osteomyelitis affecting the area of the target ulcer was present; 2) after debridement, the target ulcer volume (measured by Jeltrate mold)[17] was < 10 ml or > 150 ml; or 3) topical antibiotics, antiseptics, enzymatic debriding agents, or other agents that would interfere with study evaluations had been used within the 7 days preceding randomization. Patients with ulcers resulting from 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, chemo-

therapy, or immunosuppressive agents) that would deleteriously affect healing, or interfere with evaluation of the study medication. Women who were pregnant, nursing, or of childbearing potential and not using an acceptable method of birth control were excluded. The protocol was approved by the institutional review boards and ethics committees at all sites, and all patients gave written informed consent before enrolling in the study.

Study Design

Patients were randomly assigned to 1 of 4 parallel treatment groups: 1) becaplermin gel 100 μg/g of sodium carboxymethylcellulose vehicle gel (REGRANEX® Gel 0.01%) (n = 31) once daily alternated with placebo gel every 12 hours; 2) becaplermin gel 300 μg/g (n = 32) once daily alternated with placebo gel every 12 hours; 3) becaplermin gel 100 μg/g twice daily (n = 30); or 4) placebo gel (n = 31) twice daily. A thin layer of study drug (becaplermin gel or placebo gel) was placed on the entire exposed wound surface, and the wound was then packed with saline-moistened gauze. All study sites received dressing supplies to ensure a uniform regimen. The second daily dressing was applied in a similar fashion after gently rinsing the wound surface with saline or water. Study medication was administered in conjunction with a standardized regimen of good wound care for 16 weeks or until the target ulcer was completely healed, whichever came first.

Debridement of ulcers to remove 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 included culture of tissue biopsy specimens to rule out infection, systemic treatment of wound infections, off-loading of pressure from the affected area, maintenance of a moist wound environment, and nutritional support as needed. Efficacy and safety evaluations were performed at each visit.

Efficacy Evaluations

Efficacy evaluations were based on functional assessment of the ulcer (completely healed or < completely healed, scored as 1 or 2, respectively), ulcer volume measurements (determined by Jeltrate mold) and ulcer area measurements (determined by planimetric analyses of acetate tracings). The primary efficacy endpoint was the incidence of complete healing. Additional efficacy endpoints included incidence of ≥ 90% healing and relative ulcer volume at endpoint (endpoint volume/baseline volume).

Safety Evaluations

Safety was evaluated by monitoring adverse events (AEs), serious adverse events (SAEs), deaths, discontinuations, clinical laboratory measurements, and vital signs. Serum samples were collected at baseline and upon completion of the study for the evaluation of antibecaplermin antibody formation. Adverse events 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. Serious adverse events were AEs 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.

Statistical Methods

All statistical analyses were based on the intent-to-treat population. The primary endpoint, incidence of complete healing, was analyzed using the Cochran-Mantel Haenszel test, which evaluated the association between the response variable and treatments, while adjusting for the effects of study center. Because the incidence of complete healing in the control group was 0, the incidence of and time to 90% ulcer closure were also analyzed. The incidence of 90% closure was analyzed using the Cochran-Mantel Haenszel test, and the significance of differences in time to 90% closure was assessed using the Cox proportional hazards model with baseline ulcer volume as a covariate.

The relative ulcer volume, defined as the ulcer volume at the end of the study divided by the ulcer volume at baseline, was analyzed using an analysis of covariance model with terms for treatment effect, center effect, and baseline ulcer volume effect, with tests for the relevant interactions. All hypotheses regarding interactions were tested at a significance level of 0.10.

All hypotheses regarding comparisons of the active treatment to the vehicle control were 2-sided, performed at the 0.05 level of significance. To ascertain the dose–response relationship, the Cochran-Armitage trend test was used for complete and 90% wound closure parameters. The trend test was one-sided at the 0.025 level against the alternative of a linearly increasing dose–response.

RESULTS

A total of 124 patients from 14 study sites were assigned randomly to the various treatment groups. No

Table 1. Patient demographic and clinical characteristics at study inclusion

Characteristic	Placebo gel	Becaplermin gel		
		100 μg/g	300 μg/g	100 μg/g BID
Gender				
Male	25 (81)[a]	26 (84)	27 (84)	26 (87)
Female	6 (19)	5 (16)	5 (16)	4 (13)
Age (years)[*]	50 ± 13.6	48 ± 13.1	49 ± 12.5	51 ± 18.3
Target ulcer volume (ml)[†]	19.6 ± 21.9	16.6 ± 15.1	17.2 ± 19.7	17.6 ± 33.8
Duration of ulcer (weeks)[†]	30 ± 43	22 ± 32	33 ± 40	22 ± 52

[a]Values indicate number and percent of total in parentheses

[*]Mean ± standard deviation
[†]Median ± interquartile range.

clinically important differences between treatment groups were observed for any of the demographic or baseline efficacy variables (Table 1).

Efficacy Results

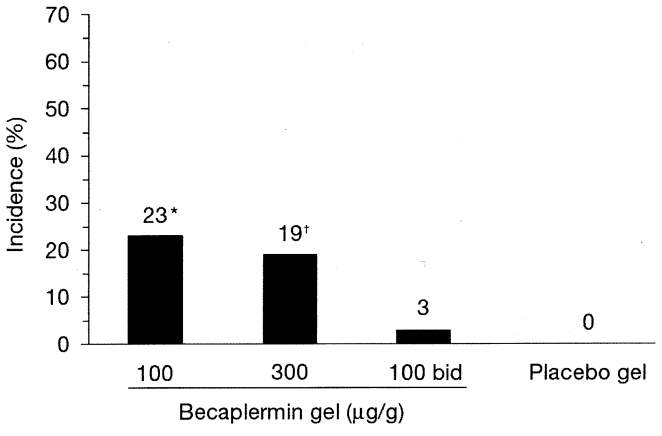
In the groups treated with either dose of becaplermin gel once daily (100 μg/g or 300 μg/g), the incidence of complete healing was significantly greater compared with that of placebo gel (23% and 19% for the 100 μg/g and 300 μg/g becaplermin gel treatment groups, respectively, vs. 0% for the placebo gel treatment group, $p = 0.005$ and $p = 0.008$, respectively; Figure 1). A similar difference was observed in the incidence of ≥ 90% healing: 58% and 59% for the 100 μg/g and 300 μg/g becaplermin gel treatment groups, respectively, vs. 29% for the placebo gel treatment group, $p = 0.021$ and $p = 0.014$, respectively, (Figure 2). The incidences of complete and ≥ 90% healing were 3% and 40%, respectively, in patients receiving becaplermin gel 100 μg/g twice daily.

The median relative ulcer volume at endpoint was 0.07 and 0.05 in the becaplermin gel 100 μg/g and 300 μg/g treatment groups, respectively, compared with 0.27 in the placebo gel group ($p = 0.013$ and $p = 0.011$, respectively, Figure 3). Median relative ulcer volume at endpoint was 0.15 in the group receiving becaplermin gel 100 μg/g twice daily.

Safety Results

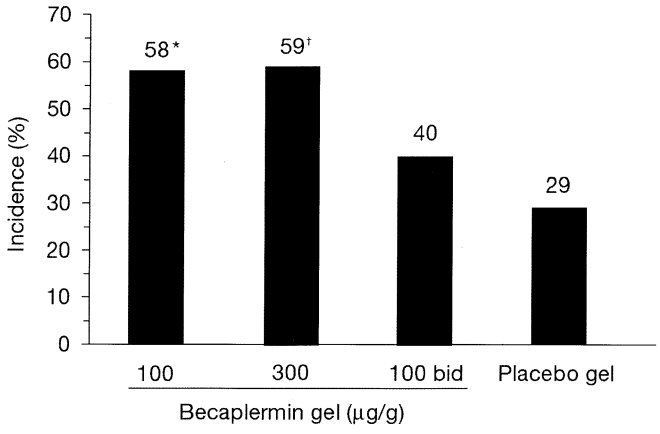
Safety evaluations were based on the intent-to-treat population of 124 patients. The overall incidence of treatment-emergent AEs was similar for all 4 treatment groups. The majority of these events were mild to moderate in severity and were generally consistent with the underlying disease state and age of the patient population. These included, but were not limited to, skin ulceration, urinary tract infection, skin disorder (e.g., rash, erythema), and fever. No deaths occurred during the treatment phase of the study.

A total of 21 patients (4 patients receiving placebo gel, 2 patients receiving becaplermin gel 100 μg/g once daily, 6 patients receiving becaplermin gel



* p = 0.005 vs placebo gel; Cochran-Mantel-Haenszel test.
† p = 0.008 vs placebo gel; Cochran-Mantel-Haenszel test.

Figure 1. Incidence of complete healing in all treatment groups. Individuals in the 100 and 300 μg/g groups received active gel once a day.



* p = 0.021 vs placebo gel; Cochran-Mantel-Haenszel test.
† p = 0.014 vs placebo gel; Cochran-Mantel-Haenszel test.

Figure 2. Incidence of ≥90% healing in the four treatment groups.

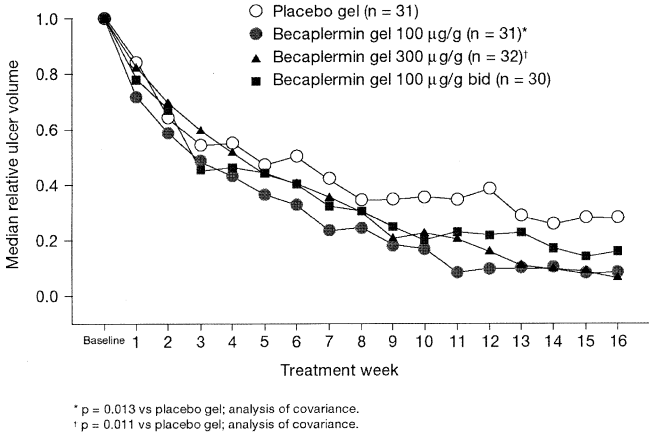


Figure 3. Median relative ulcer volume at each visit. Relative ulcer volume is the volume at an indicated week divided by the baseline volume.

300 μg/g once daily, and 9 patients receiving becaplermin gel 100 μg/g twice daily) experienced SAEs. All of these events were considered unrelated to study medication.

The incidence of wound-related, treatment-emergent AEs was similar among the 4 treatment groups: 2 patients in each of the placebo gel, becaplermin gel 100 μg/g once-daily and twice-daily treatment groups, and 3 patients in the becaplermin gel 300 μg/g group (Table 2). One patient treated with becaplermin gel 100 μg/g twice daily discontinued the study prematurely because of worsening condition of the ulcer; however, the patient reported placing pressure on the ulcer on multiple occasions between study visits, and the event was considered unlikely to be related to study medication.

Of the 103 patients who had pre- and post-study serum samples available for evaluation of anti-becaplermin serum antibodies, 6 tested positive. These included 2 patients from each of the 3 becaplermin gel treatment groups; none of the patients treated with placebo gel developed antibodies to becaplermin. Post-study sera from these patients inhibited the binding of excess free becaplermin in a competitive ELISA format by 18% to 78%. None of these sera, however, were able to inhibit becaplermin-induced proliferation in a fibroblast mitogenesis assay, indicating that the antibodies did not neutralize the biological activity of becaplermin

Changes in clinical laboratory values (levels of glucose, blood urea nitrogen, creatinine, aspartate transaminase, alanine transaminase, serum albumin, hemoglobin, and urine albumin) were comparable for the 4 treatment groups and were not related to study treatment. There were no clinically significant changes from baseline in vital signs in any patients in the 4 treatment groups.

DISCUSSION

Once-daily treatment of chronic pressure ulcers with becaplermin gel significantly increased the incidences of complete and ≥90% healing; in contrast, none of the patients treated with placebo gel achieved complete healing by the end of the study. Of note, patients treated with becaplermin gel 300 μg/g showed no additional clinical benefit beyond that observed in patients treated with becaplermin gel 100 μg/g once daily. It is unclear why the group receiving becaplermin gel 100 μg/g twice daily did not show a significant benefit compared with placebo gel. Analysis of baseline ulcer volume and ulcer duration did not show a pattern that would explain the reduced incidence of complete and ≥ 90% healing that was observed in the twice-daily treatment group.

The secondary endpoint, ≥ 90% healing, was chosen based on reports in the literature indicating that patients benefit substantially from achieving considerable but incomplete healing (i.e., 90% healing).[18–20] Healing to 90%, which largely reflects granulation tissue formation and contraction of the ulcer, is a relatively rapid process and is followed by a slower

Table 2. Wound infection-related adverse events associated with the target ulcer

		Becaplermin gel		
Adverse event	**Placebo gel**	**100 μg/g**	**300 μg/g**	**100 μg/g BID**
n	31	31	32	30
Condition aggravated	0 (0)[a]	0 (0)	1 (3)	1(3)
Osteomyelitis	1 (3)	2 (6)	1 (3)	0 (0)
Infection	1 (3)	0 (0)	0 (0)	1 (3)
Sepsis	0 (0)	0 (0)	1 (3)	0 (0)
Any adverse event	2 (6)	2 (6)	3 (9)	2 (7)

[a]Values indicate number of AEs with percent of total in parentheses

progression to epithelialization and complete resurfacing.[20] Further validation of 90% healing as a clinically relevant endpoint was provided by a study that investigated patterns of wound healing in people with diabetes. Results of this study showed that the rate of change in area was approximately linear during the first month of observation. The pattern of change in area, however, progressively decreased as the wound approached total closure.[18]

To investigate the effect of becaplermin gel treatment on the ease of surgical wound closure, a blinded retrospective evaluation based on photographs was also conducted in this study and reported by Robson and colleagues.[21] Although all 4 treatment groups showed a significant improvement compared with baseline evaluations, the results suggest that becaplermin gel treatment results in greater ease of wound closure, and may subsequently reduce the need for myocutaneous flap surgery, an expensive procedure associated with high morbidity, to a more simple procedure requiring a few sutures placed for approximation, a procedure that can be performed at bedside.

Consistent with results of clinical studies of becaplermin gel for treatment of lower extremity diabetic ulcers, treatment of patients with chronic pressure ulcers was well tolerated and there were no safety concerns associated with the use of becaplermin gel.[10–12] The majority of AEs were similar in incidence across treatment groups, were considered unlikely to be related to study medication, and were generally consistent with the underlying disease state and age of the patient population.

In conclusion, the results of this study suggest that within the setting of a comprehensive wound management program, becaplermin gel 100 μg/g once daily increases the incidence of complete healing and ≥90% healing in patients with full thickness pressure ulcers. Becaplermin gel also has an excellent safety profile. Moreover, the economic implications of the results of this and other studies using becaplermin gel may be significant. By increasing the incidence of healing, becaplermin gel may potentially reduce the costs associated with pressure ulcer treatment, which are estimated at 1.5 billion dollars annually across all treatment settings. Future studies are warranted to address issues such as the effect of becaplermin gel on healthcare resource utilization and patient quality of life.

APPENDIX

The members of the Pressure Ulcer Study Group are: J. J. Biundo, MD, Louisiana State University Medical Center, New Orleans, LA; A. E. Cram, MD, University of Iowa Hospitals and Clinics, Iowa City, IA; I. Eltorai, MD, Long Beach VA Medical Center, Long Beach, CA; R. H. K. Eng, MD, East Orange VA Medical Center, East Orange, NJ; S. Gupta, MD, MetroWest Medical Center, Framingham, MA; J. W. Harmon, MD, VA Medical Center, Washington, DC; A. Luterman, MD, University of South Alabama, Mobile, AL; B. A. Nemchausky, MD, The Edward J. Hines, Jr VA Hospital, Hines, IL; L. Phillips, MD, University of Texas Medical Branch, Galveston, TX; A. Pozez, MD, Medical College of Virginia, Richmond, VA; R. Read, MD, John L. McClellan Memorial Veterans Hospital, Little Rock, AR; E. E. Tredget, MD, MacKenzie Health Sciences Center, Edmonton, Alberta, Canada.

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