HYPERSEDIVE LEG ULCERS (HLUs), first described in the 1940s, were renamed Martorell HLUs or necrotic angiodermatitis by American and European dermatologists. Hypertensive leg ulcers are extremely painful, superficial, rapidly spreading, necrotic wounds on the dorsolateral part of the leg and have red purpuric margins. Several case series have confirmed the highly characteristic and almost invariable clinical presentation. Skin biopsy specimens of the wound border extending from healthy surrounding skin to the area of necrosis show subcutaneous arteriosclerosis and should be taken to distinguish the diagnosis of HLU from atypical differential diagnoses. Patients with long-standing hypertension and/or diabetes (usually patients older than 60 years) without peripheral arterial occlusive disease develop HLUs. The pathophysiologic characteristics of HLUs include dermal and subdermal vessel arteriosclerosis, inappropriate local vasoconstriction, but no significant involvement of the large deeper vessels. They may represent up to 15% of all treated skin ulcers in specialized departments. Medical management of HLU is currently symptomatic: controlling hypertension and diabetes, wound debridement, and application of the usual dressings. Surgical management with grafts may achieve rapid pain relief and healing, possibly by releasing growth factors into the wound. However, because only case series have been published, the evidence level of any HLU treatment is limited.
Becaplermin is a recombinant human platelet-derived growth factor (rhPDGF-BB), which plays a pivotal role in wound healing and is the only growth factor now approved by American and European authorities to heal chronic wounds such as diabetic ulcers while allowing for adequate peripheral circulation. The present study was designed to determine the effect of topical becaplermin gel on HLU healing.

METHODS

DESIGN OVERVIEW

This multicenter, randomized controlled trial was conducted in 17 French centers from March 2004 to June 2009 and performed in accordance with the Declaration of Helsinki. Informed written consent was obtained from each patient before study inclusion. The ethics committee of the Pitie´-Salpeˆtriere Hospital, Assistance Publique–Hˆpitaux de Paris (AP-HP), and regulatory authorities approved the study protocol (No. 3403), registered in clinicaltrials.gov (NCT00970697).

SETTING AND PARTICIPANTS

We enrolled consecutive ambulatory or hospitalized patients with 1 or more HLUs. Eligibility criteria were age 18 years or older, ability to give informed consent and follow the treatment procedure, and presence of 1 or more HLUs of 1 to 30 cm² in total area. Inclusion criteria were presence of an HLU defined by clinical criteria alone (typical location, superficial or deep skin necrosis surrounded by a characteristic purpuric margin, peripheral progression, and intractable pain) in (1) a patient who met the World Health Organization criteria for hypertension, treated arterial occlusive disease, defined as the presence of peripheral pulses; and/or (2) a patient with diabetes treated with an oral hypoglycemic agent, insulin, or diet without clinical signs of severe chronic venous insufficiency (eg, skin hyperpigmentation, lipodermatosclerosis); and (3) a patient without significant peripheral arterial occlusive disease, defined as the presence of peripheral pulses or an ankle brachial index of 0.8 or higher.

Exclusion criteria were concomitant cutaneous vasculitis (eg, palpable or necrotic purpura); ongoing systemic disease known to be associated with pyoderma gangrenosum or necrotizing vasculitis (such as rheumatoid arthritis), other autoimmune diseases, or cryoglobulinemia; known allergy to hydrogel or becaplermin gel; prior or evolving cancer; evolving systemic disease (eg, cardiac or renal failure, hepatic insufficiency, thrombotic disease, connective tissue disorder); serum creatinine above 2.26 mg/dL (above 200 mg/dL in diabetic patients); serum creatinine level >2.26 mg/dL; high doses of corticosteroids, immunosuppressive or cytotoxic drugs, and/or joint exposure in the wound; and concomitant treatment with corticosteroids, immunosuppressive or cytotoxic drugs, and/or iloprost during the 3 months preceding the study. To convert creatinine to micromoles per liter, multiply by 88.4; to convert glucose to millimoles per liter, multiply by 0.0555.

RANDOMIZATION AND INTERVENTIONS

Eligible participants were randomly assigned by facsimile though a central automated system designed by the Clinical Research Regional Department (AP-HP) to receive either topical becaplermin gel (rhPDGF-BB, 0.01%) (Regranex gel; Ethicon Division of Johnson & Johnson Wound Management, Issy-les-Moulineaux, France) or hydrogel (Duoderm Hydrogel; Convatec, Rueil-Malmaison, France). A computer engineer not involved in the study center by a nurse not involved in the trial and completely blinded to patient assignment. The patient or his/her caregiver was instructed on proper wound care, gel application, and wound dressing, which was continued until complete healing or for a maximum of 8 weeks, shorter than that recommended for diabetic ulcers but comparable to the time required for complete HLU healing reported in retrospective studies using cutaneous autografts.

When the study treatment was stopped at week 8, each investigator selected the replacement local wound care, depending on the wound stage and, if the ulcer was not healed, decided if a pinch graft was appropriate. All patients were observed through week 12.

OUTCOMES AND MEASUREMENTS

The primary outcome was the complete wound closure rate at treatment week 8. The secondary outcomes were (1) percentages of patients with complete wound closure at week 12; (2) changed ulcer area after treatment week 8 vs baseline; (3) changed ulcer-related pain assessed with a pain visual analog scale (VAS; range, 0-100 mm); (4) health-related quality of life under treatment, evaluated with the Skindex scale; and (5) adverse events. To calculate ulcer area, we used simple wound measurements previously described as being highly correlated with planimetric wound measurements. An investigator blinded to patient assignments and not applying the gel collected outcome measures at baseline and at every subsequent study visit (weeks 0, 2, 4, 8, and 12).

STATISTICAL ANALYSIS

We used a sequential method with a restricted procedure to allow early termination for a large size effect with a maximum of 30 patients per group; the main criterion was analyzed after every 4 consecutive patients to ensure that type I and II errors would be maintained at their desired values, despite multiple analyses during the trial (PEST software, version 3; University of Reading, Reading, England). The statistician gave no information to the clinicians about observed between-group differences. For secondary criteria, we used t tests for Gaussian variable comparisons and Mann-Whitney tests for non-Gaussian
RESULTS

Among the 64 consecutive patients enrolled, 59 received their allocated interventions, and findings were analyzed (Figure). At baseline, the treatment and control groups were comparable (Table): 95% (56 of 59) and 40% (23 of 59) of study patients, respectively, had hypertension and/or diabetes. Six patients, 2 assigned to becaplermin gel and 4 controls, had a history of cancer (1 breast, 1 cervix, 2 prostate, and 2 bladder), which was in complete remission at inclusion. Among the 59 patients without palpable peripheral pulses, 4 had an ankle brachial index higher than 1.3 (range, 1.38-1.73) related to age and/or diabetes medial calcinosis.

Complete wound closure rates for becaplermin hydrogel, respectively, were 18% (5 of 28 patients) and 10% (3 of 31 patients), respectively, at week 8 (an 8 percentage-point difference; 95% confidence interval [CI], −10.3 to 26.0) and 36% (10 of 28 patients) and 26% (8 of 31 patients) at week 12 (10 percentage-point difference; 95% CI, −13.6 to 33.4).

COMMENT

Topical becaplermin, compared with hydrogel dressing, did not improve the complete wound closure rate (primary outcome measure) after treatment week 8 and had no significant effect on quality of life, pain, or median wound area. A limitation of the study is the failure of the inclusion criteria to include a biopsy specimen with supportive histologic analysis. We included only typical HLUs, excluding patients with cutaneous vasculitis or the usual systemic diseases associated with necrotizing vasculitis or pyoderma gangrenosum. None of the included lesions evolved during follow-up into a vasculitis or pyoderma gangrenosum, making a misclassification bias improbable.

During the study, no significant becaplermin effect on health-related quality of life (P=.98) or pain (P=.71) was observed by analysis of variance for repeated measures. No cancer relapse was observed.
Complete HLU healing is more accurate than wound-area reduction because HLU-associated pain is known to be disproportionate to the lesion size, as supported by our findings. Indeed, even though the median wound area tended to be lower for the becaplermin group, no significant effect of becaplermin was observed on the health-related quality of life during the study, as evaluated with the Skindex Scale score, compared with the hydrogel dressing group. At the same time, mean VAS scores tended to decrease in both groups during the study, probably owing to the medical management of pain and local wound care by atraumatic gels beginning at baseline.

The severity of our inclusion criteria could account for the homogeneity of our enrolled patient characteristics and their small number. However, they are representative of the HLU population described by Graves et al and in the largest published case series, including in terms of healing time.

The becaplermin excipient has hydrogel properties and performs at least comparably to good wound practice alone to treat diabetic ulcers. Therefore, using a hydrogel dressing as the control was logical, even though a between-group difference may be more difficult to demonstrate.

Becaplermin biological activity includes chemotactic recruitment and proliferation of cells involved in cutaneous wound repair. Except for becaplermin treatment of diabetic ulcers, randomized controlled trial results using topical growth factors for chronic wounds have been disappointing, suggesting that growth factors might be rapidly degraded by wound proteases or that wound cells have decreased proliferative ability. To date, no medical management of HLU has emerged and surgical management by grafting, to achieve complete healing, remains the most promising treatment strategy but should be evaluated in a randomized controlled trial.

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REFERENCES

Punch Drunk

It was my freshman year at Yale. It was actually my second day at Yale. The overnight reading assignment for freshman English was to read *The Iliad* and *The Odyssey*. No problem! I’d read ’em in high school on my own time (yep! I was that kind of nerd). The teacher was droning on, I forget about what, when he uttered a word that made my heart freeze up and shrivel in my chest: genre. Now, I’d be willing to bet that I was the only person in my high school who even knew the word genre, but having seen it only in print, I’d assumed it was pronounced “jen-er,” like Bruce Jenner. When I heard the professor say “zhan-ra,” I realized what an ass I would have made of myself if I’d used that word with my dumb hill-billy pronunciation. I promptly dropped out of freshman English, and because that was a prerequisite to all higher courses, I never took any English classes at Yale. I tried to make up for this rather gigantic gap in my education by reading the entire *ouvre* (hey! That rhymes with genre!) of Kurt Vonnegut and Ian Fleming.

This little confession is my way of introducing my latest creations. Still working on the “Tools of the Trade” theme, I gathered a bunch of old biopsy punches to create the sub-genre, “Punch Drunk” series (Figure). Get it?

Mark Bernhardt, MD

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Figure. The “Punch Drunk” series: Hawaiian punch (A), 1-2 punch (B), sucker punch (C), fruit punch (D), rabbit punch (E), punch bowl (F), and Punch and Judy (G).

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