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Letter to the Editor

Intralesional Administration of Human Recombinant Epidermal Growth Factor Improves Healing and Reduces Amputations in Patients with Severe Diabetic Foot Ulcers

To the Editor:

Diabetic foot ulcer (DFU) is a major and devastating complication, affecting approximately 15% to 25% of all persons with diabetes during their lifetime.[1] Of those patients who develop DFU, 45% are not cured by standard therapy.[2]

In diabetes mellitus, failure in the repair process of distal peripheral soft tissues leads to the characteristic appearance of chronic wounds. Hyperglycemia is the trigger. A chronic wound is defined as a wound that has intrinsic impairment in the normal healing process. A biological definition would be documented intrinsic impairment to normal healing that is characterized by a prolonged inflammatory phase, slow-forming extracellular matrix, and decrease in the rate of epithelialization.

A DFU may be considered proinflammatory tissue that is sustained and/or exacerbated by the proinflammatory, pro-oxidant, and prodegradative phenotypes of the metabolically deregulated host, causing failure in peripheral soft tissue repair.[3] Preclinical studies suggest that diabetes-related wounds may not only represent a biochemically hostile environment due to the reduced growth factor availability but also due to changes in growth factor action.[4]

Evidence shows that patients with diabetes have decreased concentrations of growth factors in their tissues, notably epidermal growth factor (EGF). The primary effects of growth factors activate and direct every stage of wound healing, and, specifically, EGF induces mitogenic, motogenic, and cytoprotective actions that are essentials for healing events and could be summarized as stimulation of productive cells to migrate toward the injured area; stimulation of granulation tissue outgrowth, including extracellular matrix accumulation, maturation, and de novo angiogenesis; stimulation of wound contraction by myofibroblast activation and proliferation; and stimulation of the damaged area resurfacing by epithelial cell migration and proliferation. EGF is also endowed with angiogenic activity, promoting the growth of a vascular mesh within the wound bed. The mechanisms behind this angiogenic effect appear to be related to the chemotaxis of endothelial cells and enhancement of the expression of other angiogenic factors. In summary, it stimulates the proliferation of fibroblasts, keratinocytes, and vascular endothelial cells, contributing to the scar tissue formation property and playing a significant role in stimulating peripheral nerve regeneration. Its action is launched by the interaction with specific receptors located on the cellular membrane. The EGF receptor is a glycoprotein with an extracellular binding domain, transmembrane region, and cytoplasmic portion with tyrosine kinase activity. This receptor is expressed on most human cell types, including those that play critical roles for wound repair, such as fibroblasts, endothelial cells, and keratinocytes (undifferentiated, marginal, leading edge, hair follicles, sweat ducts, and sebaceous glands). Only hematopoietic cell lineages lack the EGF receptor.

The observation that diabetes-related wounds are enriched in proteases supports the premise that impaired growth factor availability may act as a rate-limiting factor in diabetes-related wound healing, which justifies appropriate wound bed preparation and growth factor replacement therapy. Why does EGF have to be injected within the lesion? The availability of the growth factor on the surface of the wound is limited because it can be degraded by proteases from the biofilm that covers the lesion and/or from its fluid. Responding granulation tissue develops from the deep layers of the wound. Granulation tissue biopsy cylinders (approximately 7 mm in length) from neuropathic patients were collected and paraffin-processed for different histochemical techniques and for incubation with anti-EGF receptor and anti-prohibitin antibodies. Fibroblasts populating the more superficial stratum expressed more prohibitin and lower EGF-receptor levels. Prohibitin is an inhibitor of cell cycle progression; therefore, it may contribute to the onset of the wound's chronic phenotype. This expression profile became progressively inverted through deeper cells layers. Advanced glycation end products and elastase also appeared more intensely labeled next to the wound surface than in the deeper cell strata.

This knowledge prompted the hypothesis that injecting EGF deep into the wound base and walls would allow for a greater pharmacodynamic response in terms of granulation tissue growth and wound closure.

The successful treatment of DFU depends on understanding the complex and dynamic interaction of the multiple factors that contribute to wound chronicity. In recent years, a better understanding of wound physiology has resulted in a more targeted approach to treating the feet of a person with diabetes. Therapeutic administration of growth factors reverts the suspended arrest of cells involved in the healing process.[5]

Based on the rationale that human recombinant EGF (hr-EGF) can enhance the healing of chronic wounds following repeated local infiltration, various clinical trials using human recombinant Epidermal Growth Factors in patients with DFU have been conducted, demonstrating its safety and efficacy. Infiltration with hr-EGF for healing of diabetes-related wounds does not replace standard procedures, but it should be incorporated into comprehensive wound care along with other interventions, such as metabolic control actions; appropriate management of the ischemia situation; control of the infection with antibiotic therapy according to local guidelines or surgical procedures, including minor amputation if necessary; offloading; and opportune wound bed preparation with 5 primary actions, including debridement, wound cleansing, advance or adjuvant therapies, wound coverage,

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and periwound treatment (according to tissue, inflammation/infection, moisture balance, edge concept). There could be a replacement therapy to guarantee granulation tissue formation and the closure of a DFU while reducing the risk of amputation.

A pilot study with a heterogeneous population of patients with severe DFU, which is defined as at an important risk of amputation with no further therapeutic choices, was conducted in 2001 and 2002. This study provided the first clinical evidence of the efficacy of intralesional hr-EGF infiltration. Enhanced healing and reduced diabetes-related lower limb amputations were reported in patients who received intralesional hr-EGF, and these findings paved the way for solid clinical development.[1] In subsequent years, hr-EGF local injection has been used to treat complex diabetes-related wounds in various clinical trials, demonstrating a favorable risk to benefit balance by speeding healing, reducing recurrences, and attenuating the amputation risk.[2]

Fernández-Montequín et al[3] performed a multicenter, double-blind, placebo-controlled trial to evaluate the intralesional infiltration of hr-EGF in Wagner's grade 3 or 4 DFUs. Patients (n = 149) were randomized to receive EGF (75 or 25 μg) or placebo 3 times per week for 8 weeks, with standard good wound care. The main end point was granulation tissue covering ≥50% of the ulcer at 2 weeks. It was achieved by 19 out of 48 control patients versus 44 out of 53 in the 75-μg group (odds ratio [OR] = 7.5; 95% confidence interval [CI], 2.9–18.9 and 34 out of 48 in the 25-μg group (OR = 3.7; 95% CI, 1.6–8.7). Secondary outcome variables, such as the end-of-treatment complete granulation response (28 out of 48 controls, 46 out of 53 with 75 μg and 34 out of 48 with 25 μg EGF), time to complete response (controls: 5 weeks and both EGF dose groups: 3 weeks), and wound closure after follow-up (25 out of 48 controls, 40 out of 53 with 75 μg EGF and 25 out of 48 with 25 μg EGF), were also treatment-dependent. Multivariate analyses demonstrated that they were significantly enhanced by 75-μg hr-EGF treatment and neuropathic versus ischemic ulcers. Most adverse events were mild and no drug-related severe adverse reactions were reported. It was concluded that hr-EGF local injections offer a favorable risk-to-benefit balance in patients with advanced DFU.

López-Saura et al[4] summarized the clinical information available from the intralesional use of rh-EGF for advanced DFU and showed that the postmarketing experiences in more than 2000 patients confirm the results of clinical trials with a 75% probability of a complete granulation response, 61% healing, and a 16% absolute and 71% relative reduction of the risk of amputation. The benefit includes ischemic patients. The safety profile in the current practice was satisfactory. Serious adverse events are not attributable to the treatment; instead, they are attributable to the underlying conditions of the patients.

Prospective, postmarketing active pharmacosurveillance was conducted in 41 hospitals and 19 primary care polyclinics. Patients with DFU received hr-EGF, 25 or 75 μg, intralesionally 3 times per week until complete granulation of the ulcer or a maximum of 8 weeks, adjuvant to standard wound care. The measured outcomes were complete granulation, amputations, and adverse events during treatment, and there was complete lesion re-epithelization and relapse in follow-up (median = 1.2; maximum = 4.2 years). The study included 1788 patients with 1835 DFUs (81% Wagner's grades 3 or 4; 43% ischemic) treated from May 2007 to April 2010. Complete granulation was observed in 76% of the ulcers in 5 weeks (median). Ulcer nonischemic etiology (OR = 3.6; 95% CI, 2.8–4.7) and age (OR = 1.02; 95% CI, 1.01–1.03, for each younger year) were the main variables affecting this outcome. During treatment, 220 (12%) amputations (171 major) were required in 214 patients, mostly in ischemic or Wagner's grade 3 to 5 ulcers. Re-epithelization was documented in 61% of 1659 followed-up cases, and 5% relapsed per year. Adverse events (n = 4171) were reported in 47% of patients. Mild or moderate local pain and burning sensation, shivering, and chills accounted for 87% of the events. Serious events, not related to treatment, occurred in 1.7% of patients. The favorable benefit-to-risk balance confirms the beneficial clinical profile of intralesional hr-EGF in the treatment of DFUs.

Adjuvant therapies and advanced technologies can be used in addition to standard care as a second line of treatment when appropriate. The clinical evolution of patients treated with intralesional hr-EGF together with its drug safety elements corroborate the beneficial clinical profile and therapeutic window for using this product to treat DFU.

Aristides L. Garcia Herrera, MD, PhD*
Vascular Surgery Service of the Clinic Surgical Hospital "José R. López Tabrane", Matanzas University of Medical Sciences, Matanzas City Matanzas, Cuba
E-mail address: aristides.mtz@infomed.sld.cu

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* Address correspondence to A.L. Garcia Herrera.