# The Efficacy and Safety of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers

## Results of a prospective randomized trial

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**OBJECTIVE** — To determine if a human fibroblast–derived dermal substitute could promote the healing of diabetic foot ulcers.

**RESEARCH DESIGN AND METHODS** — A randomized, controlled, multicenter study was undertaken at 35 centers throughout the U.S. and enrolled 314 patients to evaluate complete wound closure by 12 weeks. Patients were randomized to either the Dermagraft treatment group or control (conventional therapy). Except for the application of Dermagraft, treatment of study ulcers was identical for patients in both groups. All patients received pressure-reducing footwear and were allowed to be ambulatory during the study.

**RESULTS** — The results demonstrated that patients with chronic diabetic foot ulcers of >6 weeks duration experienced a significant clinical benefit when treated with Dermagraft versus patients treated with conventional therapy alone. With regard to complete wound closure by week 12, 30.0% (39 of 130) of Dermagraft patients healed compared with 18.3% (21 of 115) of control patients ($P = 0.023$). The overall incidence of adverse events was similar for both the Dermagraft and control groups, but the Dermagraft group experienced significantly fewer ulcer-related adverse events.

**CONCLUSIONS** — The data from this study show that Dermagraft is a safe and effective treatment for chronic diabetic foot ulcers.

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Patients with diabetes are prone to the development of foot ulcers. Peripheral neuropathy and the resulting loss of sensation render the foot vulnerable to even minor trauma. Fifteen percent of individuals with diabetes will develop a foot ulcer in their lifetime (1). The foot ulcers are the leading cause of hospitalization among people with diabetes and often lead to amputation (2). In 1999, ~92,000 amputations were performed in the United States among people with diabetes (3), and chronic foot ulcers reportedly preceded 70–80% of all diabetes-related amputations (4). Many of these ulcers are slow or fail to heal using conventional treatment. A more effective treatment for foot ulcers would influence a major risk factor for amputation.

Chronic wounds reflect failure of the normal processes of acute wound healing (hemostasis, inflammation, proliferation, epithelialization, and tissue remodeling) that may occur for a number of reasons (5,6). These include low proliferative capacity of the fibroblasts, downregulation of receptors, reduced growth factors, or the absence of a suitable protein matrix in the dermis (7). Keratinocytes are activated and proliferate at the edge of the ulcer but fail to migrate (8), possibly because of the ulcer bed not being a permissive environment.

Consequently, there is a need for more effective therapies that will address the physiological deficiencies that underlie the chronic ulcer. Recently, tissue engineering technologies have produced skin replacement products developed for the specific purpose of treating patients with chronic ulcers.

This article reports on the results from a clinical investigation of the safety and efficacy of Dermagraft, a bioengineered dermal substitute, in the treatment of chronic diabetic foot ulcers.

## RESEARCH DESIGN AND METHODS

### Materials

Dermagraft (Smith and Nephew, Largo, FL) is a cryopreserved human fibroblast–derived dermal substitute. Human neonatal dermal fibroblasts are cultured in vitro onto a bioabsorbable mesh. As they proliferate across the mesh, they secrete human dermal collagen, matrix proteins, growth factors, and cytokines to create a three-dimensional human dermal substitute containing metabolically active, living cells (9). Dermagraft is designed to restore the dermal bed in a diabetic foot ulcer, thereby improving the wound healing process and allowing the patient's

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

**Table 1—*Major inclusion and exclusion criteria***

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Patient is ≥18 years old | • Gangrene is present on any part of the affected foot |
| • Patient has type I or II diabetes | • Patient's ulcer is over a Charcot deformity |
| • Patient's ulcer has been present for a minimum of 2 weeks under the current investigator's care | • Ulcer total surface area is >20 $cm^2$ |
| • Patient's foot ulcer is on the plantar surface of the forefoot or heel and ≥1.0 $cm^2$ in size at day 0 | • Patient's ulcer has decreased or increased in size by 50% or more during the screening period |
| • Patient's ulcer extends through the dermis and into subcutaneous tissue but without exposure of muscle, tendon, bone, or joint capsule | • Severe malnutrition is present as evidenced by albumin <2.0 |
| • Patient's wound is free of necrotic debris and appears to be made up of healthy vascularized tissue | • Patient's random blood sugar reading is >450 mg/dl |
| • Patient has adqequate circulation to the foot as evidenced by a palpable pulse | • Urine ketones are noted to be "small, moderate, or large" |
| | • Patient has a nonstudy ulcer on the study foot that is located within 7.0 cm of the study ulcer at day 0 |
| | • Patient is receiving oral or parenteral corticosteroids, immunosuppressive or cytotoxic agents, coumadin, or heparin |
| | • Patient has a history of bleeding disorder |
| | • Patient has AIDS or is HIV-positive |
| | • Cellulitis, osteomyelitis, or other evidence of infection is present |

own epithelial cells to migrate and close the wound.

## Study design

The study was a prospective, single-blind, randomized, controlled investigation at 35 centers across the U.S. that compared a Dermagraft regimen to a control regimen in the treatment of chronic diabetic foot ulcers. Clinical studies evaluating Dermagraft have not been double-blinded because the unique characteristics of this implant preclude the use of a placebo that cannot be distinguished from the true product.

Patients were enrolled in the study between December 1998 and March 2000. At the screening visit, before randomization, study ulcers received sharp debridement and saline-moistened gauze dressings. In addition, patients received off-weight bearing instructions. At the randomization visit (day 0), study ulcers were stratified into one of two groups according to ulcer size: group 1, ≥1 to ≤2 $cm^2$; group 2, >2 to ≤20 $cm^2$. Within these two strata, patients were randomized into either the Dermagraft or the control group. Patients were not informed as to which treatment they received. The group randomized to Dermagraft treatment received their first application at day 0 and received up to seven additional applications at weekly intervals over the course of the study.

Patients in the two study arms received identical treatment with the exception of Dermagraft applications in one treatment arm. Wound dressings consisted of a nonadherent interface, saline-moistened gauze to fill the ulcer, dry gauze, and adhesive fixation sheets (Hypafix). Because it would be important to determine the influence of Dermagraft on heal rates in a "real world" treatment environment, the study allowed patients to be ambulatory, using extra-depth diabetic footwear with custom inserts or healing sandals.

Evaluations for both the Dermagraft and control groups were made weekly until complete wound closure or the patient reached the week 12 visit without healing. At each visit, tracings of the wound margins were made for computer planimetry to document changes in wound size, and photographs were taken for a visual record. Patients received sharp debridement to remove necrotic or hyperkeratinized tissue whenever clinically necessary. Wound closure was defined as "full epithelialization of the wound with the absence of drainage." An ulcer was considered healed only after closure was confirmed at the next weekly visit.

## Patient eligibility

Eligible patients were diabetic adults with a foot ulcer on the plantar surface of the forefoot or heel that was between 1.0 and 20 $cm^2$ at day 0 and that had been present for a minimum of 2 weeks. The ulcer could extend through the dermis and into subcutaneous tissue but without exposure of muscle, tendon, bone, or joint capsule. The patient's ankle-arm index by Doppler was ≥0.7 on the study limb. A list of the major patient eligibility requirements is found in Table 1.

## Investigators

This was a phase III pivotal study conducted at 35 centers throughout the United States.

## Statistical analysis

Data management and analysis of safety and effectiveness data were performed by the Biostatistics and Clinical Data group of Advanced Tissue Sciences.

The original sample size calculation was based on a two-group Fisher's exact test with a 0.0294 one-sided significance level and at least 80% power, resulting in the need for enrolling ~330 patients (165 per group). The original statistical plan called for an interim analysis to be performed after 180 patients completed the study. The 0.0294 level of significance (Pocock method) was not achieved at the interim. At the interim analysis, a relationship between treatment and ulcer duration of >6 weeks was observed and a revised plan was developed using Bayesian statistical methods that took into account findings in the interim analysis.

The Bayesian sequential procedure required a minimum of 60 additional patients (post-interim) to give a reasonable level of assurance that the treatment benefit was being maintained in the subset of interest. Enrollment was to continue until a maximum of 180 additional patients with ulcers of >6 weeks' duration (in addition to the 141 interim patients mentioned above) had accrued or until the

**Table 2—*Summary of patient information***

| | Dermagraft patients | Control patients |
|---|---|---|
| *n* | 130 | 115 |
| Sex | | |
| M | 90 | 91 |
| F | 40 | 24 |
| Age (years) | | |
| Mean | 55.8 | 55.5 |
| Range | 27–83 | 31–79 |
| Race | | |
| Caucasian | 90 | 87 |
| Non-Caucasian | 40 | 28 |
| Diabetes | | |
| Type 1 | 32 | 27 |
| Type 2 | 98 | 88 |
| Ulcer location | | |
| Forefoot/toe | 112 | 102 |
| Heel | 18 | 13 |
| Mean ulcer duration (weeks) | 41 | 67 |
| Ulcer area ($cm^2$) | | |
| Mean | 2.31 | 2.53 |
| Range | 0.75–16.7 | 0.5–18.0 |

posterior probability, $P(p_{DG} > p_{CT} \times$ current data), was at least 99%.

## RESULTS

### Demographics

The relevant patient information at baseline in the two treatment groups is shown in Table 2. The randomization schedule used for the study resulted in the Dermagraft and control groups being comparable. There were no statistically significant differences (Fisher's exact test and two-sided *t* test or Kruskall-Wallis test) with respect to any demographic characteristics between the two groups.

Of the 245 patients with chronic ulcers, 19% (46 of 245) discontinued before the end of the 12-week study. The reasons for discontinuation were comparable between the two treatment groups. The majority of the patients who discontinued had an adverse event requiring treatment that warranted withdrawal from the study.

### Efficacy

At the interim analysis, a significant difference in wound closure rate at week 12 was observed between the Dermagraft and control groups for patients with chronic ulcers (ulcers of >6 weeks' duration). Additional patients were enrolled until the required Bayesian sequential procedure stopping end point was achieved (98.4% probability of benefit).

When all patients had completed the study, there were 245 patients who had ulcers of >6 weeks' duration. The results showed that treatment with Dermagraft produced a significantly greater proportion (30%) of healed ulcers compared with the control group (18%) (Table 3).

For patients with forefoot/toe ulcers, 29.5% (33 of 112) of Dermagraft-treated wounds achieved closure compared with 19.6% (20 of 102) of control wounds ($P = 0.065$); for heel ulcers, 33% (6 of 18) of Dermagraft-treated wounds achieved closure compared with 8% (1 of 13) of control wounds ($P = 0.10$).

The secondary effectiveness end points were time to reach complete wound closure and percentage of wound closure by week 12. The Dermagraft-treated group had a significantly faster time to complete wound closure than the control group ($P = 0.04$). After controlling for ulcer area and sex, Dermagraft-treated patients were still 1.7 and/or 1.6 times more likely to have complete wound closure at any given time than were the control patients, respectively. By week 12, the median percent wound closure for the Dermagraft group was 91% compared with 78% for the control group ($P = 0.044$).

From daily patient diaries, information gathered revealed that both the Dermagraft and control groups were on their feet an average of 8 h a day during the study.

### Safety

Data from all randomized patients were included in the safety analyses. The overall incidence of adverse events was comparable between the Dermagraft group (67%) and the control group (73%; NS). The number of patients who developed study ulcer–related adverse events (i.e., local wound infection, osteomyelitis, and cellulitis) was significantly lower in the Dermagraft-treated patients (19%) than in the control patients (32%; $P = 0.007$) (Table 4).

The percent of patients who underwent a surgical procedure involving the study ulcer was 8% (13 of 163) in the Dermagraft group and 15% (22 of 151) in the control group ($P = 0.07$). Osteomyelitis was the predominant reason for surgery in both groups. There were no adverse device effects or unanticipated adverse device effects reported. No adverse laboratory findings were associated with the use of Dermagraft.

## CONCLUSIONS

— The patient with a diabetic foot ulcer remains a challenging medical, economic, and social problem. Despite dedicated care, many patients will suffer from ulcers that do not heal and become chronic. The longer the ulcer persists, the greater the possibility that the patient will develop a serious infection that can lead to hospitalization and possible amputation (10).

The conventional treatment chosen for this study comprised debridement, saline-moistened gauze, and pressure-relieving orthotics. The use of custom-fitted special shoes and custom-molded

**Table 3—*Number of patients with complete wound healing by week 12***

| | Treatment | | | |
|---|---|---|---|---|
| | Dermagraft patients | Control patients | Bayesian probability | *P* |
| Interim analysis: patients with ulcers of >6 weeks' duration at screening: $n = 141$ | 19/71 (27%) | 9/70 (13%) | NA | 0.031 |
| Final analysis (trial complete): all patients with ulcers of >6 weeks' duration at screening: $n = 245$ | 39/130 (30%) | 21/115 (18%) | 98.4% | 0.023 |

**Table 4—*Patients experiencing an infection, cellulitis, and osteomyelitis involving the study ulcer***

| | Dermagraft | Control | Total | *P** |
|---|---|---|---|---|
| *n* | 163 | 151 | 314 | |
| Infection | 17 (10.4%) | 27 (17.9%) | 44 (14.0%) | 0.073 |
| Osteomyelitis | 14 (8.6%) | 13 (8.6%) | 27 (8.6%) | 1.000 |
| Cellulitis | 12 (7.4%) | 14 (9.3%) | 26 (8.3%) | 0.547 |
| Overall | 31 (19.0%) | 49 (32.5%) | 80 (25.5%) | 0.007 |

*Based on a two-sided Fisher's exact test. Data are *n* (%). Infections include all local wound infections, not including osteomyelitis and cellulitis.

inserts for all study patients helped to ensure that off-weighting methods were standardized among all study patients. Based on discussions with investigators, it was decided not to require a period of total off-loading as part of the treatment regimen. Such a protocol requirement would not be reflective of what most patients are able to commit to in their daily activities.

The randomization schedule used for the study resulted in the Dermagraft and control groups being comparable, with no statistically significant differences in characteristics between the treatment groups. Approximately 80% of the patients completed the study, and the majority of patient discontinuations were related to the occurrence of an adverse event requiring treatment that warranted study termination. Overall, <3% of patients were lost to follow-up.

This study demonstrated that the addition of Dermagraft to a regimen of diabetic foot ulcer treatment, including debridement, infection control, and pressure offloading, resulted in a significant benefit compared with the regimen without Dermagraft. It was significantly effective when used for the treatment of chronic diabetic foot ulcers of >6 weeks' duration (Table 3). Statistical analysis of the data indicated that the probability that Dermagraft provides a treatment benefit was 98.4%. These findings are consistent with other studies showing that patients with diabetic foot ulcers had better healing following Dermagraft treatment compared with control treatment even over a 6-month follow-up (11,12).

Also, Dermagraft was not associated with the development of any specific adverse event. The incidence of ulcer infection, cellulitis, or osteomyelitis was similar in this study to that reported for other prospective randomized trials treating diabetic foot ulcers with bio-active products (13,14). There were significantly fewer ulcer related adverse events in the Dermagraft group, which may be related to more rapid wound coverage, reducing the chance of ulcer infection or cellulitis.

The pathophysiology of the diabetic foot ulcer is complicated. Those ulcers that have adequate blood supply and that have sufficient viable cells capable of providing the appropriate protein matrix and necessary growth factors should heal. Ulcers that do not heal acutely and become chronic are presumed to have critical deficiencies in these or other parameters (e.g., patient compliance with off-loading regimens). Dermagraft is a bioengineered dermal substitute that laboratory data suggest has two principal modes of action. It provides living, human dermal fibroblasts that deposit matrix proteins and facilitate angiogenesis (15,16). It also provides a preformed collagen matrix, receptors, and bound growth factors that facilitate the migration of the patients' epithelial cells that close the wound (17). With these properties, it is reasonable to presume that Dermagraft would promote the healing of chronic ulcers. At the interim analysis, it was evident that the Dermagraft treatment was most effective in treating ulcers of >6 weeks' duration. This finding probably reflects the fact that the longer duration ulcers (i.e., >6 weeks) are deficient in many of the factors necessary for healing and are most likely to benefit from Dermagraft treatment.

One potential problem that could arise from the application of a human dermal substitute onto an allogeneic host is that it may initiate an immune response leading to its rejection. However, there was no evidence of rejection of Dermagraft in the study. This is believed to be due to inherent properties of Dermagraft. It is derived from neonatal human tissue that has undeveloped HLA tissue markers. Furthermore, fibroblasts from dermis are relatively nonantigenic and do not express HLA-DR markers (18). Therefore, Dermagraft is not expected to cause an immune reaction.

It is important to emphasize that Dermagraft must be used along with other standard principles of diabetic foot ulcer care including routine debridement, pressure offloading, infection control, and moist wound healing. Without adhering to these important principles, the addition of an active adjunctive modality is unlikely to result in improved healing rates (19,20).

In conclusion, Dermagraft has been shown in this multicenter, prospective randomized study to be safe and effective for the treatment of chronic diabetic foot ulcers.

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## APPENDIX

### The Dermagraft Diabetic Foot Ulcer Study Group

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