An Exploratory Study of Dermal Replacement Therapy in the Treatment of Stage III Pressure Ulcers

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KEY WORDS: pressure ulcer, chronic wound, dermal replacement

ABSTRACT

Objective

To compare the proportion of patients with Stage III pressure ulcers with complete wound closure at Week 24, when treated with conventional therapy or conventional therapy plus a human fibroblast-derived dermal replacement.

Methods

A prospective, multi-center, randomized, single-masked, controlled exploratory study was conducted comparing Dermagraft with conventional therapy alone. The primary measure was wound closure at 24 weeks. Secondary measures were wound closure at Week 12 and the percentage reduction in wound area and volume.

Results

There were no significant differences found between the treatment groups with respect to the proportions of patients healing by Week 24. Two (11%) Dermagraft and 2 control (13%) patients had healed by Week 24. There were no significant differences found between the treatment groups with respect to the percentage reduction in ulcer area or the percentage reduction in ulcer volume by Week 12 (last observa-

tions carried forward). The reduction in wound volume was 41.2% for the Dermagraft arm and 17.4% for the control arm at study end.

Conclusions

The primary study endpoint (proportion of patients with complete wound closure) was observed in a small number of patients. The positive trend in reduction of wound volume achieved in the treatment arm of the study may be significant in facilitating other treatment modalities, such as surgical closure. Further clinical studies are needed to establish the place of dermal replacement therapy in the management of chronic pressure ulcers.

BACKGROUND

The management and treatment of chronic wounds impose a significant burden on health care resources. Treatment of hospital acquired pressure ulcers has been estimated to cost between $2.2 and $3.6 billion per year in the United States[1] depending on the stage of ulcer and patient condition. Only 70 percent of pressure ulcers heal in the first 12 months,[2] and some may fail to heal at all.[3] Patients suffering with pressure ulcers frequently have multiple co-morbidities, such as diabetes, and an overall poor health status, further complicating the management of these wounds.

In spite of recent advances in the understanding of the basic mechanisms of wound healing, the precise mechanisms that prevent chronic wounds from healing are unknown. Published evidence now supports the hypothesis that chronic wounds may be growth factor deficient, or establish a micro-environment that is hostile to the normal repair process.[4,5] A number of growth factors have been identified from acute wound healing studies that are mitogenic and stimulate matrix deposition and angiogenesis.[6,7] Growth factors identified in the process of wound healing include: fibroblast growth factors (FGF), transforming growth factor-beta (TGF-b), vascular endothelial growth factor (VEGF), interleukin-1 (IL-1), and platelet derived growth factor (PDGF).[8-10] Hepatocyte growth factor/scatter factor (HGF/SF) also has a range of effects on wound healing, and influences cell growth and motility.[11-13]

Normally, the acute wound healing process is complete after a few weeks. However, 1 or more interruptions in the orderly sequence of events in wound healing described in Table 1, which include cell migration and proliferation, synthesis of extracellular matrix, angiogenesis, and remodeling, may cause wounds such as pressure ulcers to take months or years to heal. Advanced wound therapies, such as Dermagraft (Smith & Nephew, Inc., Heslington, York, UK) have recently been developed to target the deficiencies of repair associated with non-healing or "compromised"[14] wounds. Dermagraft, a human dermal replacement consists of newborn dermal fibroblasts cultured in vitro onto a bioabsorbable mesh to produce a living, metabolically active human dermal tissue. As the fibroblasts proliferate across the mesh, they secrete human dermal collagen, fibronectin, glycosaminoglycans (GAGs), and other proteins, embedding themselves in a self-produced dermal matrix.[15] No exogenous human or animal collagen, GAGs, or growth factors are added. Through secretion of growth factors found in normal dermis in response to signals from the wound bed, Dermagraft may help to induce angiogenesis, modulate the inflammatory response and enhance the formation of a healthy granulating base capable of supporting the growth and migration of the patients own keratinocytes to facilitate closure.[16-18] The best data for non-operative treat-

Table 2. Bioactivity of Wound Exudates from Healing and Compromised Wounds

HEALING WOUND	COMPROMISED WOUND (eg, Pressure Ulcer)
Stimulates	**Inhibits**
Angiogenesis	Endothelial cell proliferation
Fibroplasia	Fibroblast proliferation
Collagen synthesis	Keratinocyte proliferation
	Collagen synthesis
	Contains elevated protease levels
Contains	**Degrades**
Epidermal growth factor	Growth factors
Fibroblast growth factor	Extracellular matrix components
Platelet derived growth factor	
Transforming growth factor	

Adapted from Moore K. Compromised wound healing: a scientific approach to treatment. *Br J Community Nurs.* 2003;8:274-278.

ment reports healing rates of 40% for Stage III and 34% for Stage IV pressure ulcers in nursing home patients, and 45% and 30% respectively for hospitalized patients being healed after 1 year.[19-21] Operative therapy of pressure ulcers is unsuccessful long-term, with a 61% ulcer recurrence and a 69% patient recurrence within 9.3 months.[22] This translates to the fact that there is only a 31% successful long-term outcome for surgery. Studies have shown that dermal replacement may facilitate healing in chronic wounds,[23-25] bringing them to a point where surgical intervention is possible to facilitate closure.[26,27] Until recently there has been no long-term outcome data for ulcers treated with exogenous application of growth factors. In a study conducted with a 12 month serial follow up, it was reported that the long-term outcome was better in this growth factor trial than with surgical or standard nonoperative treatment of pressure ulcers.[19] Since only patients receiving exogenously applied cytokines achieved >85% closure during the treatment phase of the trial, the excellent long-term outcome was attributed to the cytokine therapy. A recent Canadian study showed that achieving a positive change in wound environment was associated with significant cost savings.[26] In another study of sequential cytokine therapy in pressure ulcers, the change in difficulty of wound closure (eg, ease of skin graft, ease of flap) was studied in relation to the composite cost.[27] Ease of wound closure steadily improved as wound volume decreased, facilitating wound closure at the bedside with sutures after 35 days of treatment in some patients.

The current exploratory study was conducted to investigate the effects of Dermagraft, a human dermal fibroblast-derived substitute, in conjunction with conventional therapy, in the treatment of Stage III pressure ulcers (pressure ulcers characterized by full-thickness skin loss involving damage or necrosis of subcutaneous tissue that may extend down to, but not through underlying fascia). The justification for the use of Dermagraft in the treatment of pressure ulcers, is its potential to enhance wound healing by providing a bio-engineered human dermis containing normal matrix proteins and growth factors that are secreted by the fibroblasts.[15]

Table 2. Study Criteria

Major inclusion criteria
1. Age > 18 years
2. Stage III sacral pressure ulcer
3. Ulcer (after debridement) is clean and free of both necrotic tissue and infection
4. Ulcer present for at least 2 months, but not more than 24 months, prior to screening
5. Ulcer is > 5 cm^2 and < 50 cm^2
6. If more than 1 ulcer, the distance between ulcers is > 10 cm
7. Ulcer is due solely to pressure damage
Major exclusion criteria
1. Patients with Stage I, II or IV pressure ulcers
2. Patient has more than 3 full thickness (Stage III or IV) pressure ulcers
3. Evidence of undermining, tunneling or sinus tracts > 1 cm after debridement
4. Ulcers previously treated with a surgical flap procedure
5. Bacterial colonization
6. Ulcer decreased or increased in size by 50% during the screening period
7. Underlying non-pressure ulcer etiology

METHODS

The study was a prospective, multi-center, randomized, single-masked, controlled exploratory study conducted in 9 centers in the United States. The primary endpoint of the study was the proportion of patients with complete wound healing at Week 24. A closed wound was defined as a wound with full epithelialization and the absence of drainage. Secondary endpoints were proportion of patients with complete healing at Week 12, time to complete closure, percentage reduction in surface area at Weeks 12 and 24, and the percentage reduction in wound volume by Week 24.

Investigational Review Board (IRB) approval was obtained for the trial protocol, and the clinical evaluation was performed in accordance with the guidelines of the Declaration of Helsinki (1964). Informed consent was obtained from all participants using an IRB approved Patient Informed Consent.

Randomization

After ulcers had been assessed and deemed free of necrotic debris and signs of clinical infection with healthy vascularized tissue, patients were randomized to the Dermagraft or control treatment arm. The time between initial screening and randomization was 2 weeks. Patients were followed for up to 26 weeks after randomization, with a maximum total treatment duration of 24 weeks. In order to avoid investigator bias, patients were allocated to an arm of the study using a computer generated randomization scheme coded and contained in pre-sealed envelopes.

Patients

A total of 34 patients with Stage III pressure ulcers were recruited into the study.

Patients meeting the study criteria at Day 0 (Table 2) were included in the study. In patients presenting with multiple ulcers, the largest ulcer meeting the inclusion and exclusion criteria was selected.

Assessments

Patients were recruited from the Stage III ulcer population. Patient characteristics (including age, height, weight, gender, race, tobacco, and alcohol use) were recorded at the screening visit. Three photographs of the ulcer site immediately before and after debridement were taken as a pictorial record of the study

Table 3. Number of Patients Attending Each Visit (ITT)

	Control	Dermagraft	Total
Screening	16 (100%)	18 (100%)	34 (100%)
Week 0	16 (100%)	18 (100%)	34 (100%)
Week 1	16 (100%)	18 (100%)	34 (100%)
Week 2	15 (94%)	16 (89%)	31 (91%)
Week 3	16 (100%)	15 (83%)	31 (91%)
Week 4	14 (88%)	14 (78%)	28 (82%)
Week 5	14 (88%)	13 (72%)	27 (79%)
Week 6	10 (63%)	11 (61%)	21 (62%)
Week 7	9 (56%)	10(56%)	19 (56%)
Week 8	6 (38%)	9 (50%)	15 (44%)
Week 9	6 (38%)	9 (50%)	15 (44%)
Week 10	7 (44%)	10 (56%)	17 (50%)
Week 11	7 (44%)	9 (50%)	16 (47%)
Week 12	6 (38%)	10 (56%)	16 (47%)
Week 13	5 (31%)	9 (50%)	14 (41%)
Week 14	5 (31%)	9 (50%)	14 (41%)
Week 15	5 (31%)	9 (50%)	14 (41%)
Week 16	5 (31%)	8 (44%)	13 (38%)
Week 17	5 (31%)	7 (39%)	12 (35%)
Week 18	5 (31%)	5 (28%)	10 (29%)
Week 19	5 (31%)	7 (39%)	12 (35%)
Week 20	5 (31%)	6 (33%)	11 (32%)
Week 21	4 (25%)	7 (39%)	11 (32%)
Week 22	5 (31%)	6 (33%)	11 (32%)
Week 23	4 (25%)	7 (39%)	11 (32%)
Week 24	5 (31%)	5 (28%)	10 (29%)

* Patient Population = ITT population

ulcer. Ulcer tracings were performed at the initial and subsequent weekly follow-up visits on a Zip-Loc plastic bag and transferred on to an ulcer area grid for planimetry. The following data was recorded: location, stage, size, appearance, condition of the surrounding skin, undermining, pressure relief methods used, fecal, and urinary incontinence. Pressure ulcer area was determined by direct measurement (length in cm x width in cm). Pressure ulcer volume was determined by alginate mold method.[27] Laboratory evaluations including hematology, serum chemistry and quantitative and qualitative bacteriology were recorded at the initial and final study visit.

Assessments were performed weekly until either, the patient had a second confirmation of wound closure, or Week 24 (through to Week 26 if the wound closure was first observed at Week 24).

Treatment

Patients were randomized to the Dermagraft or control arm of the study. *Dermagraft Arm:* Up to two pieces of Dermagraft were applied side by side to the ulcer weekly for the first 3 applications (Day 0, Week 1, and Week 2) plus a combination of a non-adherent dressing, saline-moistened gauze and Allevyn (Smith & Nephew, Inc., Heslington, York, UK) foam dressing. If the ulcer, as measured by the ulcer grid, had not closed by at least 25% since the previous week, an additional weekly implan-

Table 4. Demographics of Patients

Parameter	Dermagraft (n=18)	Control (n=16)	Total (n=34)
Age			
Mean ± SD	69.4 ± 16.5	69.1 ± 18.5	69.3 ± 17.2
Sex			
Male	12 (67%)	11 (69%)	23 (68%)
Female	6 (33%)	5 (31%)	11 (32%)
Race			
White	15 (83%)	13 (81%)	28 (82%)
Black	2 (11%)	3 (19%)	5 (15%)
Other	1 (6%)		1 (3%)
Smokers			
Yes	5 (28%)	3 (19%)	8 (24%)
No	13 (72%)	13 (81%)	26 (76%)
Alcohol			
Yes	3 (17%)	3 (19%)	6 (18%)
No	15 (83%)	13 (81%)	28 (82%)

tation of Dermagraft (up to a total of 16 applications) was performed. No additional pieces of Dermagraft were implanted in ulcers ≤ 0.5 cm^2.
Control Arm: A combination of a non-adherent dressing, saline-moistened gauze and Allevyn were applied to the ulcer. Patients were assessed weekly for a maximum of 26 weeks post-randomization.

Safety Evaluations
All patients were followed for safety until either the patient had a second confirmation of complete wound closure or reached the Week 24 visit (through to Week 25 if the first observation of complete wound closure was Week 24).

A physical examination was performed and recorded at the screening and final study visit. Measurements included: physical, nutritional, skin, neurological and cardio-respiratory status. Evidence of rejection, infection and bleeding was recorded according to current standards of care, and any symptoms or other discomfort related to the application of Dermagraft noted.

Adverse events (AEs), including any adverse change in the patient's condition, or any deterioration or exacerbation of a pre-existing medical condition, as observed by the investigator, or reported by the patient, were recorded.

Statistical Methods
Statistical analysis was conducted using SAS (SAS/STAT Guide for Personal Computers, Version 8.2, Cary, North Carolina) package for personal computers. All significance tests were two-sided. The sample size was based on feasibility considerations, however as an exploratory study, it was not powered to detect differences between the 2 treatment groups.

Values for ulcer area and volume (as measured by the weight of alginate mould) were calculated at Week 12, and compared using the Mann-Whitney U

Table 5. Reduction in Ulcer Volume (grams) to Study Discontinuation

Parameter		Dermagraft (n=18)	Control (n=16)	Total (n=34)
Week 0	Mean	13.5	12.2	12.9
	Median ± SD	10.4 ± 11.4	8.8 ± 10.4	9.2 ± 10.8
Final volume	Mean	9.1	11.1	10.0
	Median ± SD	5.2 ± 10.3	8.3 ± 10.9	5.9 ± 10.5
Reduction*	Mean	4.5	1.1	2.9
	Median ± SD	2.2 ± 11.8	2.0 ± 4.8	2.1 ± 9.2
% reduction†	Mean	18.7	4.1	11.8
	Median ± SD	41.2 ± 84.3	17.4 ± 95.8	26.1 ± 88.8

Patient population = ITT population
* Week 0 - Final
† Percentage reduction = ((Week 0 volume - final volume) / Week 0) x 100

test. Hodges-Lehmann estimates of the difference in the medians of area and volume were calculated using a 95% confidence interval. The primary variable of complete healing by Week 24, and secondary variable of closure by Week 12 were compared between patients using Fischer's exact test. All patients with a Day 0 visit were included in the Intention to Treat (ITT) population. Patients who attended at least 75% of scheduled study visits were included in the evaluated population.

The following variables were derived for each patient:
Total number of pieces of Dermagraft applied and total number of study visits
Absolute reduction in ulcer area, calculated as: Initial area (Day 0) - area at Week X
Percentage reduction in ulcer area, calculated as: ((Initial area - area at Week X) / initial area) x 100.
Reduction in ulcer volume was calculated from the recorded weight of the alginate moulds.
Linear advance was calculated using Gilman's formula[28] as

$$\frac{\text{(area at week i - area at week i-1)}}{\text{(perimeter at week i + perimeter week i-1)/2}}$$

The mean weekly Gilman's d over the first four weeks of the trial derived as:

$$\frac{\text{(Gilman's d at Week 4) x 7}}{\text{Number of days from Day 0 to the Week 4 ulcer tracing}}$$

and repeated to obtain the mean weekly Gilman's d for each patient during the trial.

RESULTS

Number of Patients and Baseline Characteristics

Nine participating sites enrolled 34 patients. Table 3 provides details of the number of patients attending each visit. By Week 12, 16 patients remained in the study (10 in the Dermagraft arm and six in the control arm) and by Week 24, 10 patients remained in the trial (five patients in each arm).

Demographic characteristics of randomized patients were comparable across the 2 treatment groups (Table 4). The majority of patients were male

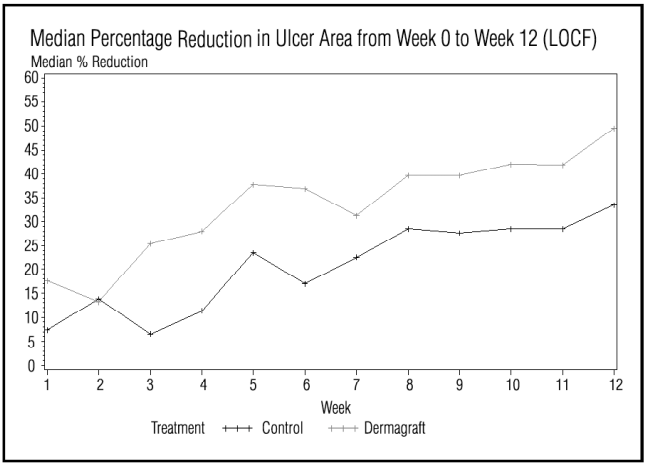

Figure. Percentage reduction in ulcer area

Caucasians, with an overall mean age of 69.3 years. A higher percentage of patients enrolled in the Dermagraft arm of the study were smokers (5/18; 28% vs. 3/16, 19%). The overall percentage of alcohol use was 6/34 (18%) and was not significantly different between the 2 treatment groups.

Ulcer Characteristics

The treatment groups were well matched in terms of ulcer characteristics. The majority, 22/33 (67%), of ulcers were located in the sacral area, 8/33 (24%) on the trochanter and 3/33 (9%) on the ischium. All ulcers were classified as Stage III pressure ulcers. The mean initial ulcer area was 19.8 cm^2 (range 5.2 cm^2 to 60.7 cm^2) for the Dermagraft arm and 21.1 cm^2 (range 3.5 cm^2 to 51.2 cm^2) for the control arm. The median duration of the study ulcer was comparable between the 2 arms, with Dermagraft treated ulcers being present for 30.2 weeks (range 6 to 95.3 weeks) and Controls having a median duration of 29.2 weeks (range 4.0 to 104.0 weeks). Four (12%) of the ulcers had healed previously and recurred.

Twenty-seven (79%) ulcers had healthy surrounding skin, 3 (9%) had inflamed surrounding skin, 3 (9%) had macerated surrounding skin, and 1 ulcer was categorized as "other". Thirty-one (91%) patients were incontinent with 1 (3%) having urinary incontinence only, 4 (13%) having fecal incontinence only, and 26 (84%) having both urinary and fecal incontinence.

Ulcer Closure

Two (11%) of the Dermagraft and 2 of the Control ulcers had healed by Week 24. There was no difference between the treatment groups with respect to the proportions of patients healed by Week 24. At Week 12, one (6%) Dermagraft and 2 (13%) Control ulcers had healed.

The median percentage reduction in ulcer area at Week 12, last observations carried forward (LOCF), was 49.5% (range –81.7% to 100%) for the Dermagraft patients and 33.5% (range –77.5% to 100%) for the controls. There was no evidence of a difference between the 2 groups with respect to the percentage reduction in ulcer area by Week 12.

Ulcers with Incomplete Closure

The median percentage reduction in ulcer area at Week 12 (LOCF) was 38.8% (range –201.7% to 100%) for Dermagraft and 17.4% (range –434.5% to 100%) for the controls (Figure). The median percentage reduction in ulcer volume to study discontinuation was 41.2% for the Dermagraft arm and 17.4% for the Control arm (Table 5).

Wound Infections

A total of 6 infections (18%) were reported during the study (3 patients in the Dermagraft treatment group and 3 patients in the Control group), with each of the 6 patients experiencing 1 wound infection during the trial.

Safety Evaluations

Both treatment groups demonstrated similar patient withdrawal rates prior to Week 24 (72% Dermagraft, 69% Control). This level of withdrawal was attributed to the high level of morbidity associated with this patient population.

There were no adverse device effects (ADE's) or unanticipated adverse device effects (UADE's) reported in this study. Sixty-seven adverse events were reported during the course of this trial. With respect to these adverse events, 28 (41.8% of all events reported) of these events were in the control group and 39 (58.2% of all events reported) adverse events were in the Dermagraft group. Seven of these events (10%) were related to the study ulcer. Nine of these events were rated as severe (13%). Six deaths occurred in the study (17.6% percent of the total study population), and were attributed to the high level of morbidity in this patient population. Five patients were in the Dermagraft group and 1 patient in the control. No deaths were attributed to the study device.

DISCUSSION

The primary study endpoint (proportion of patients with complete wound closure by Week 24) was observed in a small percentage of patients. A high number of early withdrawals were observed during the course of the study. By Week 12, there were 16 patients (6 Control and 10 Dermagraft) evaluated for the 12-week analysis. By Week 24, there were 10 patients remaining in the study (5 patients in each treatment group). The high withdrawal rate was attributed to the high level of morbidity associated in this patient population, as is in common with other pressure ulcers studies, reflecting the difficulty of conducting any investigation into the effects of different therapeutic regimens in the management these wounds.[29]

Two patients in each treatment arm healed by Week 24 (11% for Dermagraft and 13% for Control). Percent change in ulcer area by Week 12 and Week 24 were secondary endpoints for the study. There was no evidence of a difference in treatment groups in the Week 12 analyses. The median percent area reduction by Week 12 for Dermagraft was 49.5%. Control patients demonstrated a median value of 33.5% area reduction by Week 12.

With respect to volume reduction (as determined by alginate mould technique), Dermagraft patients showed 41.2% median wound volume reduction versus 17.4% volume reduction in the control group by Week 12.

Over the last 15 years, a number of studies have considered the ability of initial wound healing rates to predict complete healing. The parameters for measuring healing that have shown promise in assessing initial healing rate for reliable prediction of future healing are: linear inward progression of the wound edge, change in wound area, and percent change in wound area, and more recently, percentage change in wound volume. A correlation between a reduction in wound area and healing has been shown in studies investigating diabetic[30,31] and venous ulcers,[32-34] but this has not been shown in the treatment of pressure ulcers. In 1988, Resch et al[35] postulated that pressure ulcer volume might be a more accurate technique to document and record wound healing. Recent studies in pressure ulcers have shown that reduction in wound volume may be a more accurate predictor of healing than either linear progression or area.[27,36]

Prior to 2000, a number of studies had reported that change in area and percent change in area were not reliable parameters for predicting healing.[28,37,38] These studies demonstrated how a reduction in area tends to exaggerate

the progress of larger wounds and percent area reduction exaggerates the progress of smaller wounds.[28,39] It has been argued that the association between wound geometry and these parameters prevented healing rates of one size and shape from being reliably extrapolated to all others, and that this would compromise their comparison in clinical trials.[28,37,38] However, some studies have demonstrated that initial rates of percent change in wound area predict complete healing, but these studies have been small or not statistically well supported.[40-42]

Pressure ulcers are often extremely difficult to manage and refractory to conservative therapy. The aim of management may be to stabilize the wound so that surgical closure can take place. One study has shown that as wound volume decreases the ease of wound closure steadily improves,[27] and that ease of closure can be correlated with significant cost savings. Reducing wound volume in Stage III and IV pressure ulcers could mean that these wounds can be taken to a point where a small operation such as a skin graft or wound edge approximation is a viable option to achieve closure.[43] The reduction in wound volume of 41.2% achieved in patients treated with Dermagraft in the current study is important in that improved wound status may help facilitate simpler surgical management.

In assessing any intervention in the management of refractory wounds, such as pressure ulcers, complete closure may not be a realistic endpoint for any study. Clinically it may be more important to bring the wound to a point where other treatment modalities, such as grafting or flap, are a viable option. Angiogenesis is an important component of the healing process in pressure ulcers, and requires a sustained concentration gradient of chemotactic, angiogenic factor that can induce the directional migration of capillary endothelial cells into the wound site.[44] Dermagraft may help to induce angiogenesis, modulate the inflammatory response, and enhance the formation of healthy granulating base capable of supporting the growth and migration of the patient's own keratinocytes. The need for new therapies can be justified when the frequency of non-healing in pressure ulcers is 30% to 40%. The results of this exploratory study support the use of Dermagraft in Stage III pressure ulcers.

The current exploratory study was not powered to detect differences between the 2 arms of the study, and so caution should be taken in interpreting the results. A large number of patients had withdrawn by Week 24, 13 (72%) Dermagraft and 11 (69%) control patients, and reflects the difficulty of conducting studies in this area. This high drop-out rate has been reported in a number of other studies, and compounds the difficulty of producing evidence based guidelines for this wound type; as Stage III and IV pressure ulcers rarely heal within the time-frame of most protocols. The reduction in wound volume in the Dermagraft arm may support the hypothesis that wound volume is an important prognostic indicator in the management of chronic ulcers, and that the implantation of Dermagraft into these wounds may help to overcome deficiencies in the repair mechanisms associated with them. Further clinical studies are needed to confirm these observations.

FINANCIAL DISCLOSURE

This clinical study was sponsored by Smith and Nephew, Inc, makers of Dermagraft.

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