Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of chronic leg ulcers: A randomized clinical trial

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Background: **Venous leg ulcers are a major cause of morbidity, economic loss, and decreased quality of life in affected patients. Recently, biomaterials derived from natural tissue sources have been used to stimulate wound closure. One such biomaterial obtained from porcine small-intestine submucosa (SIS) has shown promise as an effective treatment to manage full-thickness wounds. Our objective was to compare the effectiveness of SIS wound matrix with compression vs compression alone in healing chronic leg ulcers within 12 weeks.**

Methods: **This was a prospective, randomized, controlled multicenter trial. Patients were 120 patients with at least 1 chronic leg ulcer. Patients were randomly assigned to receive either weekly topical treatment of SIS plus compression therapy (n = 62) or compression therapy alone (n = 58). Ulcer size was determined at enrollment and weekly throughout the treatment. Healing was assessed weekly for up to 12 weeks. Recurrence after 6 months was recorded. The primary outcome measure was the proportion of ulcers healed in each group at 12 weeks.**

Results: **After 12 weeks of treatment, 55% of the wounds in the SIS group were healed, as compared with 34% in the standard-care group ($P = .0196$). None of the healed patients treated with SIS wound matrix and seen for the 6-month follow-up experienced ulcer recurrence.**

Conclusions: **The SIS wound matrix, as an adjunct therapy, significantly improves healing of chronic leg ulcers over compression therapy alone. (J Vasc Surg 2005;41:837-43.)**

Venous leg ulcers affect up to 2.5 million patients per year in the United States and are a major cause of morbidity and decreased quality of life.[1,2] Whereas current methods of compressive care have reported ulcer healing rates of 68% to 83% within 24 weeks,[3,4] 12-week healing rates are more commonly only 34% to 42%.[2,5-7] Many ulcers heal but then recur at a 12-month rate of 26% to 28%.[2]

The current standard of care for chronic venous ulcers involves the use of compression bandages as a means to reduce ambulatory venous pressure, control edema, and improve venous return.[8,9] When these conservative methods prove ineffective, surgical intervention is used to either directly address venous reflux or manage the ulcer through skin grafting.[2] Leg ulcers that fail to heal quickly or that recur rapidly are often refractory to conservative compression therapy and may lead to costly hospitalizations or excessive use of home health-care resources, estimated as high as $2200 per ulcer per month.[10]

Recent biotechnologic advances have developed alternative therapies for the treatment of chronic wounds. Rather expensive skin substitutes or more cost-effective biomaterials derived from natural extracellular matrix (ECM) can be used to stimulate wound closure.[11,12] These materials promote granulation and epithelialization of dermal wounds, effectively regulate evaporation and exudation, and help to protect the wound site from bacterial infection. One natural ECM wound-care product, a biomaterial derived from the pig small-intestine submucosa (SIS), has been extensively evaluated in preclinical models and also applied in the clinical setting since its first description in 1989.[13] This thin, translucent layer of the intestine is approximately 0.15 mm thick and consists primarily of a collagen-based ECM. However, unlike purified collagen wound-care products, biologically important components of the ECM, such as glycosaminoglycans (eg, hyaluronic acid),[14] proteoglycans, fibronectin,[15] and growth factors such as basic fibroblast growth factor[16,17] and transforming growth factor β[18] are retained in active forms in the SIS matrix.

This clinical trial was designed to test the hypothesis that chronic full-thickness leg ulcers treated with the SIS wound matrix in addition to standard care would lead to a greater proportion of healed ulcers at 12 weeks when compared with standard care alone. This study is the first complete randomized human clinical trial to assess the

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Table I. Summary of patient inclusion criteria

Characteristic	*Inclusion criteria*
Patient age (y)	≥18 y
Ulcer size (cm^2)	1-64
Ulcer depth	Extends through both the epidermis and dermis, with no exposed tendon or bone
Ulcer duration (mo)	>1 mo
Ulcer location	Between and including the knee and ankle
Wound bed characteristics	Viable wound bed with granulation tissue

Table II. Summary of patient exclusion criteria

- Exposed bone, tendon, or fascia
- Severe rheumatoid arthritis
- History of radiotherapy to the ulcer site
- Uncontrolled congestive heart failure
- Receiving corticosteroids or immune suppressives
- History of collagen vascular disease
- Malnutrition (albumin <2.5 g/dL)
- Known allergy to porcine-derived products
- Received treatment with any other investigational drug or device within the last 30 days
- Ulcer clinically infected
- Uncontrolled diabetes ($HgbA_{1c}$ >12%)
- Previous organ transplantation
- Religious or cultural objection to the use of porcine products
- Undergoing hemodialysis
- Signs of cellulitis, osteomyelitis, or necrotic or avascular ulcer beds
- Ankle-brachial index <0.80
- Active sickle cell disease
- Unable to comply with the procedures described in the protocol
- Enrolled in a clinical evaluation for another investigational wound-care device or drug

$HgbA_{1c}$, Baseline glycosylated hemoglobin.

effectiveness of the SIS wound matrix in the treatment of full-thickness chronic leg ulcers.

METHODS

SIS Wound Matrix. The SIS Wound Matrix (OASIS Wound Matrix, Healthpoint Ltd, Ft Worth, Tex) is a naturally occurring ECM derived from the submucosal layers of the porcine jejunum. Porcine small intestine is subjected to manufacturing processes that render the material free of viral contaminants and minimize the risk of animal-to-human disease transmission (described elsewhere).[19] The SIS is freeze-dried and sterilized with ethylene oxide gas in preparation for clinical use.

Study design. This prospective, randomized, controlled clinical trial, conducted at 12 outpatient sites, was originally designed to enroll 180 patients to detect a 20% difference in 12-week healing of SIS wound matrix–treated patients vs standard of care. Because of delays in patient accrual, the study population was limited to enrollment of 120 patients. Patients older than 18 years who met all entry criteria were randomly assigned to receive either the control treatment (wound cleansing, débridement [as necessary], dressing changes, and compression therapy) or application of the SIS wound matrix in addition to the control treatment. Patients were observed for up to 12 weeks. Patients in the standard-care arm were given the option of crossover treatment with SIS if healing did not occur. A 6-month follow-up visit was also requested.

Study population. This trial was conducted in the United States, United Kingdom, and Canada under the direction of International Conference on Harmonization E6 Good Clinical Practice guidelines. The study protocol and informed consent statements were reviewed and approved by either an independent institutional review board or each location's governing institutional review board or ethics committee. Prospective patients with chronic venous insufficiency (according to clinical presentation and history), positive venous reflux, or both; who met the additional criteria presented in Table I; and who signed informed consent were considered for inclusion. Criteria for exclusion are listed in Table II.

Patients who met the inclusion criteria were required to undergo a 2-week screening period before enrollment. During the screening period, the target ulcer was treated with standard care and compression therapy. Ulcers that exhibited a greater than 50% reduction in surface area during the screening period were excluded from the trial to ensure that the patients enrolled had chronic leg ulcers not adequately responding to conventional therapy. At the completion of the 2-week screening period, eligible patients were randomized to one of the two treatment groups by using a centralized computer system with a block size of four. Investigators were blinded to this randomization scheme to eliminate bias and, upon contacting the computer system, received an automatic faxed confirmation that indicated the patient's assigned group and unique enrollment number.

Protocol and evaluations. The SIS wound matrix group received a piece of the SIS applied directly to the wound bed, followed by the application of a nonadherent dressing (Allevyn; Smith & Nephew, Largo, Fla) and a four-layer compression bandaging system (Profore; Smith & Nephew) to maintain direct contact of the SIS wound matrix with the wound bed and to further protect the healing environment. To apply the SIS wound matrix, the ulcer was routinely cleaned by using gentle irrigation with sterile saline, and the SIS was cut to size slightly larger than the ulcer, placed on the wound bed, and moistened with sterile saline. The standard-care group received an identical nonadherent dressing and four-layer compression bandaging system, but no SIS. During the treatment period, all wounds were evaluated weekly. During these follow-up visits, patients in both treatment groups received wound cleansing, débridement (as clinically necessary at the discretion of the investigator), dressing changes, and compression therapy. Ulcer dimensions were documented by measuring the length and width of the ulcer (length was the longest edge-to-edge measurement of the ulcer, and width was the longest ulcer dimension perpendicular to the

length). In the SIS wound matrix study group, repeat applications of SIS occurred at the weekly evaluation visits, determined as needed by the clinician. SIS was reapplied to the entire nonepithelialized portion of the wound during these visits. The amount of SIS used and the number of dressing changes performed was recorded for each patient on the case report forms.

Patients in the standard-care group whose wounds did not heal by the 12th week were given the option to receive SIS crossover treatment for 4 weeks and up to an additional 8 weeks if the target ulcer showed responsiveness to the SIS in the first month after crossover (wound size had to decrease by 50% in the first 4 weeks). No standardized regimen was recommended after the study treatment period; however, efforts were made to see all patients at a final 6-month follow-up visit to determine the durability of ulcer closure.

Demographic and baseline data collected included patient sex, race, age, weight, height, baseline glycosylated hemoglobin, baseline albumin, and patient location (outpatient or home-care setting). Baseline ulcer information included ulcer location, duration, status (new or recurrent), and surface area. Baseline medical history information included patient status on each of the following: diabetes, hypertension, endocrine disease, immunosuppression, Alzheimer disease, connective tissue disease, musculoskeletal disease, peripheral vascular disease, and dementia. In addition, baseline levels of granulation tissue and avascular tissue, along with the baseline débridement status and the amount of drainage, were recorded. Baseline characteristics were used as covariates in the final statistical analysis to judge their influence on treatment success.

After treatment initiation, patients were evaluated weekly for up to 12 weeks for healing and complications. The primary outcome measure of the study was prospectively defined as the incidence of complete wound healing by 12 weeks, defined as full epithelialization of the wound with the absence of drainage. The time to healing was computed as the treatment period day during the weekly visit at which the surface area of the wound was noted as zero and completely healed. Adverse events were noted on the case report forms and were recorded at each visit.

Statistical analysis. Study data were collected and entered into a study database by a contract research organization (MED Institute, West Lafayette, Ind) by using quality-control procedures. A quality-assurance check of the database datasets vs the case report forms was performed. The database was transferred to a statistical services company (STATKING Consulting, Inc, Fairfield, Ohio) for independent analysis. All statistical analyses were performed with SAS software (version 8.2 for Windows; SAS Inc, Cary, NC) on the intent-to-treat population.

The frequency of wound healing at 12 weeks in the SIS wound matrix and standard-care treatment groups was analyzed by using the Fisher exact test at the one-sided $\alpha = .05$ level of significance. Healing data were re-examined by using baseline demographics and wound characteristics as covariates. All of these tests were conducted at the two-sided $\alpha = .05$ level of significance.

The difference in healing proportions, adjusting for each of the potential covariates, was tested with the Cochran-Mantel-Haenszel test and the Breslow-Day test of the homogeneity of odds ratios across strata. Time to healing was examined by using a Cox proportional hazards regression model.

Continuous demographic and baseline variables were compared by using analysis of variance. A χ^2 test was used to compare categorical demographic and baseline variable response profiles. The Fisher exact test was used to compare the proportion of patients in each treatment group who experienced adverse events.

Table III. Selected patient and wound baseline demographics

Variable	*SIS Wound Matrix (n = 62)*	*Control (n = 58)*
Age (y)		
Mean ± SEM	63 ± 2	65 ± 2
Range	21-90	36-93
Sex, n (%)		
Male	29 (47%)	21 (36%)
Female	33 (53%)	37 (64%)
BMI (kg/m^2)		
Mean ± SD	32.9 ± 10.6	30.9 ± 10.3
Range	19-80	18-78
Race, n (%)		
White	51 (82%)	46 (79%)
Black	10 (16%)	9 (16%)
Asian	0 (0%)	1 (2%)
Other	1 (2%)	2 (3%)
Ulcer duration, n (%)		
1-3 mo	23 (37%)	18 (31%)
4-6 mo	12 (19%)	7 (12%)
7-12 mo	5 (8%)	7 (12%)
>1 y	21 (34%)	23 (40%)
Not specified	1 (2%)	3 (5%)
Ulcer area (cm^2)		
Mean ± SEM	10.2 ± 1.51	12.1 ± 1.98
Median	6.75	5.12
Range	1.05-58.8	1.15-57.8

SIS, Small-intestine submucosa; *BMI,* body mass index.

RESULTS

Patients. There were no differences between the standard-care and SIS wound matrix groups with respect to patient demographics and baseline ulcer size and duration (Table III). The mean ulcer size in the SIS wound matrix group was 10.2 cm^2, as compared with 12.1 cm^2 in the standard-care group ($P = .4580$), and the median ulcer size in the SIS wound matrix group was 6.75 cm^2, vs 5.12 cm^2 in the standard-care group. The incidence of patients with an ulcer duration longer than 3 months was 61% in the SIS wound matrix group (34% for >1 year) and 64% in the standard-care group (40% for >1 year). Overall, 10% of patients treated used home care, and 89% were treated on an outpatient basis.

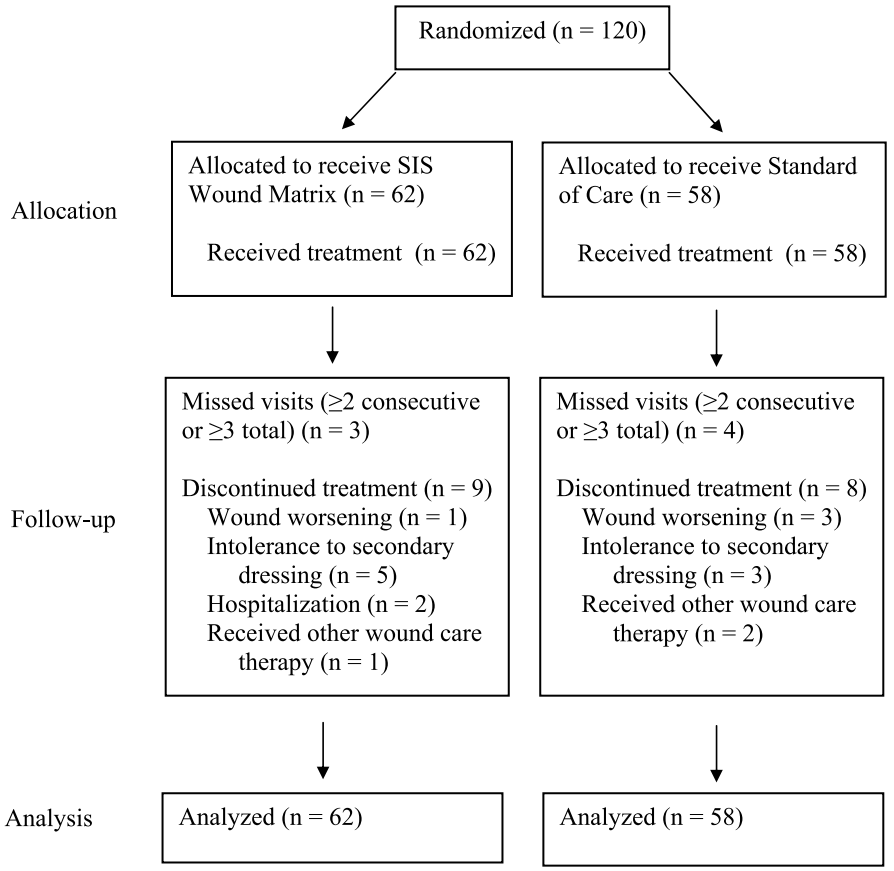

Fig 1. Patient flow through the clinical trial.

Twenty-four patients (20%) of the 120—12 in the SIS wound matrix arm and 12 in the standard-care arm—did not complete the planned 12-week follow-up for reasons other than ulcer healing. These patients were included in the data analysis within their assigned group. Patient flow throughout the study and the reasons for study noncompletion are displayed in Fig 1.

Incidence of healing. Results at the end of the 12-week treatment period showed that healing occurred in 55% (34/62) of patients who received SIS wound matrix plus standard care vs 34% (20/58) of patients who received standard care alone ($P = .0196$), thus indicating statistical superiority. An odds ratio calculation indicated that patients receiving SIS were 2.3 times more likely to have complete wound healing as compared with patients receiving standard care alone (odds ratio, 2.307). In addition to dressing changes during the weekly visits, patients in the SIS wound matrix group had an average of 1.8 dressing changes during the treatment period, compared with 3.4 for the standard-of-care group. On average, eight 3 × 7-cm^2 sheets of SIS were used per patient in the SIS group during the treatment period.

Time to healing. The Cox proportional hazards regression analysis showed an estimated probability of successful healing of 63% at 12 weeks for the SIS wound matrix group and 40% for the standard-care group. A significant difference between the survival curves for the two groups ($P = .0226$) was indicated (Fig 2).

Covariate analysis. The covariate analyses indicated that patients in the SIS wound matrix group maintained a consistent or greater proportion of healing, even when taking into account the presence of comorbidities such as vascular disease ($P = .0253$), type 2 diabetes ($P = .0214$), endocrine disease ($P = .0272$), and hypertension ($P = .0204$). Similarly, this analysis also showed that after adjusting for baseline ulcer size, patients in the SIS group were 3 times more likely to achieve healing than those in the standard-care group ($P = .0067$; odds ratio, 2.996).

Further covariate analysis also indicated that patients in the SIS wound matrix group maintained a consistent or greater proportion of healing whether or not baseline débridement was performed ($P = .0215$). A subgroup analysis on débridement status also indicated that when baseline débridement was performed, patients in the SIS wound matrix group were 4 times more likely to heal than those in the standard-care group. Specifically, 19 (63%) of 30 SIS wound matrix patients who had baseline débridement healed, compared with 8 (30%) of 27 in the standard-care group ($P = .0167$; odds ratio, 4.10).

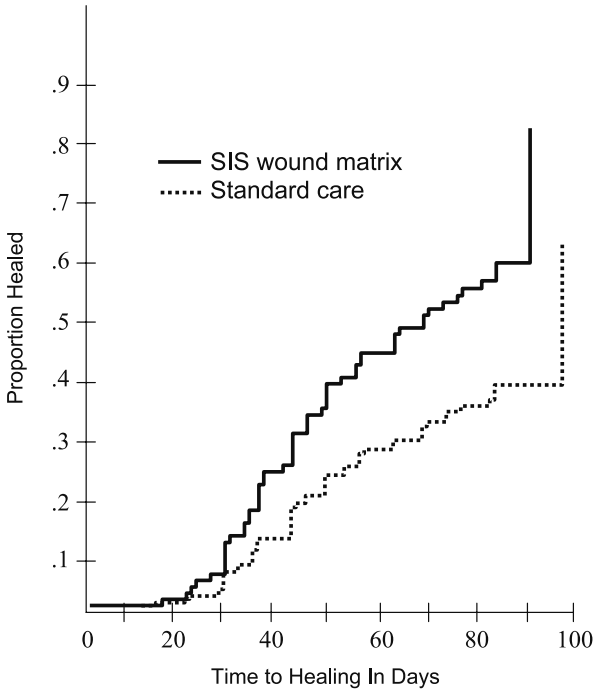

Fig 2. Survival plot analysis for the small-intestine submucosa *(SIS)* wound matrix group and the standard-care group. Success was defined as 100% healing. Patients treated with SIS wound matrix were more likely to heal by 12 weeks than those in the standard-care group ($P = .0226$).

Crossover patients and 6-month follow-up. Nineteen patients randomized to the standard-care arm joined the crossover group treated with the SIS wound matrix. Five (26%) of the 19 crossover patients healed after receiving an average of 4 applications of SIS wound matrix.

A total of 54 patients (45%) were seen at a 6-month or later follow-up visit: 30 in the SIS wound matrix group and 24 in the standard-care group. Of these 54 patients, 29 had healed ulcers within the 12-week study period of treatment, and 26 of the 29 study ulcers remained healed at the 6-month follow-up visit: 19 (100%) of 19 in the SIS wound matrix group and 7 (70%) of 10 in the standard-care group. Of the other 25 patients with ulcers that did not heal within the 12-week study period, 5 patients were healed at the 6-month or later follow-up visit (1 of 11 patients in the SIS wound matrix group and 4 of 14 patients in the standard-care group). Of the 4 standard-care patients whose wounds healed later, 3 were patients treated with SIS wound matrix as part of the crossover group.

Adverse events. A total of 23 complications were observed (Table IV). There was no significant difference between the proportions of patients who experienced at least one adverse event during the study in the two treatment groups ($P = .1920$). There was no significant difference between the proportions of patients who experienced infection-related adverse events in the two treatment groups ($P = .2611$). One (1.6%) of 62 patients had a target ulcer infection-related adverse event in the SIS wound matrix group, whereas 5 (8.6%) of 58 patients had a target ulcer infection-related adverse event in the standard-care group ($P = .1057$).

Table IV. Study complications*

Complication	*SIS Wound Matrix (n = 8)*	*Standard care (n = 15)*
Skin injury	1	1
Allergic reaction or intolerance to secondary dressing	3	3
Seroma	0	1
New ulcer due to compression	0	1
Health deterioration/hospitalization	1	2
Non–target wound infection	1	1
Wound infection	1	6
Death (due to cardiovascular disease)	1	0

SIS, Small-intestine submucosa.
*$P = .1920$ between treatment groups.

DISCUSSION

Patients with long-term venous ulcers represent a subgroup of patients who have failed to respond to standard available therapies and can be considered to have the most difficult-to-treat ulcers. For this patient population, alternatives to standard compression therapy are essential if wound closure is to be achieved, especially given that many patients report difficulty with, noncompliance with, or intolerance to compression therapy.[20] This clinical investigation represents the first multicenter randomized clinical trial designed to assess the effectiveness of a natural ECM biomaterial for the treatment of chronic leg ulcers.

Treatment of chronic leg ulcers with the SIS wound matrix significantly increased the incidence of complete healing at 12 weeks vs standard care; it showed 62% more efficacy than standard compression dressing treatments. A study limitation is potential bias, because blinding of the investigator and patient was not possible. A further limitation of the study is that the establishment of venous disease before enrollment was not always confirmed with duplex imaging, even though all prospective patients had underlying venous disease diagnosed by clinical presentation. The analysis showed that both groups were matched on all demographic data and had ulcers of similar chronicity and size; these variables were therefore eliminated as factors affecting the observed healing rates.

As noted by Phillips et al,[21] baseline ulcer area has been reported as a prognostic indicator for venous ulcer healing outcome. After adjusting for a baseline wound size of 5 cm^2 or more, the covariate analysis in this study indicated that patients were three times more likely to heal in the SIS wound matrix group than were those in the standard-care group. These data suggest that the SIS wound matrix is effective in healing chronic leg ulcers regardless of the baseline ulcer size.

Débridement is also known to be an important consideration in healing venous ulcers,[1] and this was corroborated

by the covariate and subgroup analyses in this study, which showed that when baseline débridement was performed, patients in the SIS wound matrix group were four times more likely to heal than were those in the standard-care group. These data suggest that baseline débridement can positively influence the healing rates observed when SIS is used to treat chronic leg ulcers, and it should therefore be considered as part of a complete treatment program.

The 6-month follow-up analysis revealed that, of the subset of patients studied, 100% of the SIS wound matrix patients whose wounds healed within 12 weeks remained healed 6 months later but that only 70% of the standard-care treatment wounds that had complete healing remained closed. This finding is significant in that recurrence rates after standard compression therapy have been reported to be at least 26% to 28%[3,22] and may be as high as 69%.[2,23] It is important to note that the wounds treated with SIS wound matrix did not recur during the follow-up period, and this suggests that chronic leg wounds treated with SIS in addition to standard care may be less likely to recur than those treated with compression alone. Clearly, the limited number of wounds examined at the 6-month follow-up suggests that additional investigation may be warranted to definitively determine recurrence after treatment with SIS.

Although treatment costs were not rigorously studied in this trial, the number of dressing changes was recorded, as was the average amount of SIS wound matrix applied, to assess the added costs of using SIS wound matrix vs standard care. In addition to dressing changes during the weekly visits, patients in the SIS wound matrix group had an average of 1.8 dressing changes during the treatment period, compared with 3.4 for the standard-of-care group. The average amount of SIS applied per patient was eight 3×7-cm^2 sheets, representing a total cost of approximately $320.00 during the treatment period. Given the high monthly costs of treating chronic venous ulcers, including the relatively expensive multilayer bandage system for compression, the efficacy shown by SIS in leading to a greater incidence of healing and in reducing time to healing vs standard care alone is important in determining the course of treatment and in reducing overall health-care costs.

It is our opinion that the SIS wound matrix was easy to apply, was well tolerated by the patients, and did not induce any clinically observable adverse immunologic reactions with repeated application. These observational findings are consistent with other reports that have shown that the SIS wound matrix does not cause antibody formation in leg ulcer patients, even after repeated application.[24] These observations and clinical findings are consistent with the known properties of the SIS biomaterial, support preclinical findings,[25-27] and support the initial observations of effectiveness in humans.[11,12]

The pathogenesis of venous ulceration remains debated, but regardless of the exact mechanism of venous ulcer development, it is well established that these ulcers contain high levels of matrix-degrading enzymes[28] and also fail to contract and epithelialize at the rate of an acute wound in a patient who does not have venous reflux. It has been suggested, therefore, that active treatment to stimulate closure and modulate the wound environment is necessary to stimulate the healing process.[1] Standard-care treatments for venous leg ulcers include weekly wound cleansing, débridement, dressing changes, and compression therapy. This standard care has been reported to lead to healing after 12 weeks in approximately 34% to 40% of patients.[5,6] The standard-care multilayer bandage compression system used in this study led to healing in 34% of treated wounds, but the addition of SIS wound matrix as an adjunct to the standard-care treatment improved the healing rate to 55%. Unlike purified collagen dressings or palliative standard-care treatments, the SIS wound matrix is an active treatment that stimulates wound closure. SIS contains a complex composition of active factors known to stimulate the proliferation and differentiation of various cell types.[14-18] It also stimulates neovascularization in surgical cases[29] and enhances wound contraction and closure in animal models.[25] SIS also contains collagen and heparan sulfate proteoglycans,[30] which sequester matrix metalloproteases and other matrix-degrading enzymes[31] and prevent them from catabolizing the immature matrix as the wound heals. Although a definitive link between the composition of the SIS wound matrix and its positive effects on chronic wounds has not been established, the presence of cell growth and differentiation factors within the matrix and the matrix's ability to bind proteases suggest that these matrix components may be essential to the positive healing capabilities of this material.

In conclusion, these results demonstrate that within the setting of a comprehensive wound-management program, application of the SIS wound matrix increases the incidence of complete closure of chronic leg ulcers, speeds the rate at which healing occurs, and may reduce the incidence of ulcer recurrence. This suggests that substantial patient benefit can be achieved with the use of SIS wound matrix as an adjunct to the current standard-of-care treatment.

REFERENCES

1. Brem H, Kirsner RS, Falanga V. Protocol for the successful treatment of venous ulcers. Am J Surg 2004;188(1A Suppl):1-8.
2. Barwell JR, Davies CE, Deacon J, Harvey K, Minor J, Sassano A, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet 2004;363:1854-9.
3. Barwell JR, Taylor M, Deacon J, Ghauri AS, Wakely C, Phillips LK, et al. Surgical correction of isolated superficial venous reflux reduces long-term recurrence rate in chronic venous ulcers. Eur J Vasc Endovasc Surg 2000;20:363-8.
4. Bello M, Scriven M, Hartshorne T, Bell PR, Naylor AR, London NJ. Role of superficial venous surgery in the treatment of venous ulceration. Br J Surg 1999;86:755-9.
5. Falanga V, Sabolinski M. A bilayered living skin construct (APLIGRAF) accelerates complete closure of hard-to-heal venous ulcers. Wound Repair Regen 1999;7:201-7.
6. O'Brien JF, Grace PA, Perry IJ, Hannigan A, Clarke Moloney M, Burke PE. Randomized clinical trial and economic analysis of four-layer compression bandaging for venous ulcers. Br J Surg 2003;90:794-8.
7. Robson MC, Phillips TJ, Falanga V. Randomized trial of topically applied repifermin (recombinant human keratinocyte growth factor-2)

to accelerate wound healing in venous ulcers. Wound Repair Regen 2001;9:347-52.
8. Angle N, Bergan JJ. Chronic venous ulcer. Br Med J 1997;314:1019-23.
9. Falanga V. Venous ulceration. J Dermatol Surg Oncol 1993;19:764-71.
10. Olin JW, Beusterien KM, Childs MB, Seavey C, McHugh L, Griffiths RI. Medical costs of treating venous stasis ulcers: evidence from a retrospective cohort study. Vasc Med 1999;4:1-7.
11. Brown-Etris M, Cutshall WD, Hiles MC. A new biomaterial derived from small intestine submucosa and developed into a wound matrix device. Wounds 2002;14:150-66.
12. Demling RH, Niezgoda JA, Haraway GD, Mostow EN. Small intestinal submucosa wound matrix and full-thickness venous ulcers: preliminary results. Wounds 2004;16:18-22.
13. Badylak SF, Lantz GC, Coffey A, Geddes LA. Small intestinal submucosa as a large diameter vascular graft in the dog. J Surg Res 1989;47: 74-80.
14. Hodde JP, Badylak SF, Brightman AO, Voytik-Harbin SL. Glycosaminoglycan content of small intestinal submucosa: a bioscaffold for tissue replacement. Tissue Eng 1996;2:209-17.
15. McPherson TB, Badylak SF. Characterization of fibronectin derived from porcine small intestinal submucosa. Tissue Eng 1998;4:75-83.
16. Hodde JP, Hiles MC. Bioactive FGF-2 in sterilized extracellular matrix. Wounds 2001;13:195-201.
17. Hodde JP, Ernst DMJ, Hiles MC. Bioactivity of FGF-2 in Oasis wound matrix after prolonged storage. J Wound Care 2005;14:23-5.
18. McDevitt CA, Wildey GM, Cutrone RM. Transforming growth factor-β1 in a sterilized tissue derived from the pig small intestine submucosa. J Biomed Mater Res 2003;67A:637-40.
19. Hodde JP, Hiles MC. Virus safety of a porcine-derived medical device: evaluation of a viral inactivation method. Biotechnol Bioeng 2002;79: 211-6.
20. Berliner E, Ozbilgin B, Zarin DA. A systematic review of pneumatic compression for treatment of chronic venous insufficiency and venous ulcers. J Vasc Surg 2003;37:539-44.
21. Phillips TJ, Machado F, Trout R, Porter J, Olin J, Falanga V. Prognostic indicators in venous ulcers. J Am Acad Dermatol 2000;43:627-30.
22. Ghauri ASK, Taylor MC, Deacon JE, Whyman MR, Earnshaw JJ, Heather BP, et al. Influence of a specialized leg ulcer service on management and outcome. Br J Surg 2000;87:1048-56.
23. Monk BE, Sarkany I. Outcome of treatment of venous stasis ulcers. Clin Exp Dermatol 1982;7:397-400.
24. Hodde J, Hiles M, Sillings N, Metzger D. Host accommodation of acellular xenogeneic matrix. Proceedings of the 12th International Congress of Immunology and 4th Annual Conference of FOCIS; July 2004; Medimond Srl, Bologna, Italy. p. 429-32.
25. Prevel CD, Eppley BL, Summerlin DJ, Sidner R, Jackson JR, McCarty M, et al. Small intestinal submucosa: utilization as a wound dressing in full-thickness rodent wounds. Ann Plast Surg 1995;35:381-8.
26. Allman AJ, McPherson TB, Badylak SF, Merrill LC, Kallakury B, Sheehan C, et al. Xenogeneic extracellular matrix grafts elicit a Th2-restricted immune response. Transplantation 2001;71:1631-40.
27. Badylak S. The extracellular matrix as a scaffold for tissue reconstruction. Semin Cell Dev Biol 2002;13:377-83.
28. Nwomeh BC, Liang HX, Cohen IK, Yager DR. MMP-8 is the predominant collagenase in healing wounds and nonhealing ulcers. J Surg Res 1999;81:189-95.
29. Badylak S, Kokini K, Tullius B, Simmons-Byrd A, Morff R. Morphologic study of small intestinal submucosa as a body wall repair device. J Surg Res 2002;103:190-202.
30. Hurst RE, Bonner RB. Mapping of the distribution of significant proteins and proteoglycans in small intestinal submucosa by fluorescence microscopy. J Biomater Sci Polym Ed 2001;12:1267-79.
31. Yu WH, Woessner JF. Heparan sulfate proteoglycans as extracellular docking molecules for matrilysin (matrix metalloproteinase 7). J Biol Chem 2000;275:4183-91.

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