

TheraSkin[®]

Real Skin Wound Therapy

*Retrospective
Cohort Study of 188
Patients treated
with a Biologically
Active Human Skin
Allograft (TheraSkin[®])
for Diabetic Foot &
Venous Leg Ulcers*

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PRESENTED AT THE OCTOBER 2010
DLS CONFERENCE

Abstract

We conducted a retrospective study of 188 consecutive patients treated at the Inova Mt. Vernon Hospital Wound Care Center (Alexandria, VA), with either a diabetic foot ulcer (DFU) (n=54) or venous leg ulcer (VLU) (n=134). Multivariate logistic regression was utilized to evaluate the relationship between baseline wound size and the percentage of wounds closed after 12 and 20 weeks from initial allograft (TheraSkin) application.

Inclusion/exclusion criteria required the wound to have been present for at least 30 days (4.2 weeks) — actual average duration of the wounds was 20.6 weeks (+24.6 SD) in the DFU subset and 17.9 weeks (+30.3 SD) in the VLU subset. Additionally, the inclusion/exclusion criteria required the wound size to be $\geq 1 \text{ cm}^2$ — actual average mean wound size being 6.2 cm^2 (+11.8 SD) in the DFU subset and 11.8 cm^2 (+22.5 SD) in the VLU subset.

Percent of DFUs closed at 12 and 20 weeks were 60.38% and 74.10%, respectively. Percent of VLUs closed at 12 and 20 weeks were 60.77% and 74.60%, respectively. The average number of TheraSkin grafts required to achieve the closure rates were 2.03 (+1.47 SD) at 12 weeks and 3.23 (+2.77 SD) at 20 weeks.

Introduction

Biologically active adjunctive therapies have become a new standard of care to treat wounds that have failed to sufficiently progress after 4 weeks of traditional wound care. We examined the use of TheraSkin (provided by LifeNet Health, Virginia Beach, VA and marketed by Soluble Systems, Newport News, VA), a biologically active cryopreserved human skin allograft, for the treatment of DFUs and VLUs.

TheraSkin is a human skin allograft procured from consented donors within 24 hours of death. Donors are extensively screened and the allograft is processed pursuant to rigorous regulations promulgated by the FDA and the American Association of Tissue Banks. TheraSkin is cryopreserved (-70°C) while the tissue cells are still alive. The process preserves the naturally existing human growth factors, cytokines and collagen.

TheraSkin differs significantly from the decellularized products (Alloderm, GraftJacket, etc.), which contain only collagen, with naturally existing growth factors removed.¹

TheraSkin and the bio-engineered skin substitutes, Apligraf and DermaGraft, are all biologically active and provide growth factors from cellular and/or extracellular reservoirs which stimulate mitogenesis, chemotaxis, and angiogenesis, and trigger the wound

Growth Factors	Cytokines	Collagen
PDGFA	TNF	Type I
PDGFD	IL1a	Type III
VEGFD (FiGF)	IL1b	Type IV
VEGFA	IL2	Type V
EGF	IL3	Type VI
IGF	IL4	Type IX
TGFA	IL5	Type X
FGF2	IL6	Type XI
TGFB1	IL12	Type XII
TGFB3	IL13	Type XIV
HGF	IL16	Type XV
BMP7	IL17A	Type XVII
	IL18	Type XVIII
	IL25, 27, 32	Type XX

Table 1: Growth Factors, Cytokines and Types of Collagen found in TheraSkin as determined by independent laboratory testing, Univ. of Albany, Protein Analysis Study, Albany, NY, Oct 2009 and Univ. of Maryland, Instit. of Human Virology, Baltimore, MD, Feb 2010.

to heal. Each of these products have living cells, but TheraSkin also has a fully developed extracellular matrix that provides an “at ready” supply of growth factors and cytokines to the wound. A comprehensive list of the growth factors, cytokines and collagen types found in TheraSkin are listed in Table 1.

Dermagraft contains human fibroblasts. Apligraf and TheraSkin contain both human fibroblasts and keratinocytes. TheraSkin has substantially more Collagen Types I, III and IV than Dermagraft and Apligraf (Bovine) (see Figure 1).

Our objective was to determine if TheraSkin, a biologically active human skin allograft containing growth factors, cytokines and collagen, would heal chronic wounds that have failed to close with traditional wound care.

Hypothesis

We hypothesized that a biologically active human skin allograft (TheraSkin) would be a safe and effective treatment for both DFUs and VLUs. We will examine this by retrospectively evaluating a statistically significant number of consecutive patients treated with TheraSkin.

Methods

This was a retrospective observational study in which data was collected by medical chart review beginning September, 2009 in reverse chronological order on all

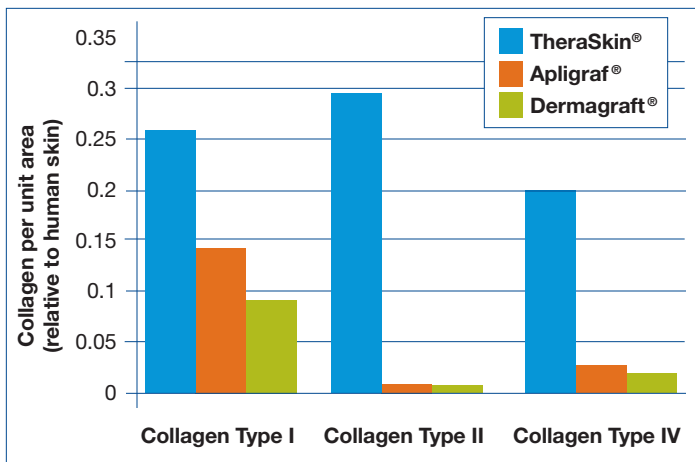


Figure 1: Quantitative and Comparative Analysis of Collagen Types I, III and IV found in TheraSkin®, Apligraf®, and Dermagraft® by Univ. of Maryland, Institute of Human Virology, Baltimore, MD, Feb 2010.

patients treated at the Inova Mt. Vernon Hospital Wound Care Center (Alexandria, VA) with either a DFU or a VLU that met study inclusion and exclusion criteria. The final eligible cohort consisted of 188 subjects, with 134 VLUs and 54 DFUs.

Patients were treated on a schedule determined by the treating physician. Necessary debridement and application of new allografts were determined by the treating physician. The study ended when any of the following occurred: wound closure or 20 weeks after initial allograft application; infection requiring surgical incision and drainage; patient or physician decision; or loss to follow-up or death.

The primary outcome measure was the percentage of wounds healed (defined as 100% epithelialization) at 12 and 20 weeks. Patients were considered treatment failures if any of the above endpoints other than documented wound healing occurred.

The sample size was determined assuming that 24.2% (95% CI 19.5 – 28.8) of the historical control group will have total wound closure after 12 weeks. This was based on a meta-analysis of standard of care wound closure rates.² Therefore, with 185 patients; there is 80% power to reject the null hypothesis that there will be no difference in proportion of wounds healed between groups, based on a maximal difference to detect of .204, assuming a type 1 error of 5%.

The proportion of wounds healed at 12 and 20 weeks was evaluated. Influence of other covariates was evaluated through multivariate logistic regression. Serious and non-serious adverse events (related and not related to target ulcer) were also recorded.

When TheraSkin was applied, the graft site was prepared with thorough debridement. TheraSkin was thawed using three 30 second rinses with normal sterile saline at room temperature and placed over the wound with dermal surface facing the wound bed. The allograft

was secured in place using either Steri-strips or sutures (see Figure 2). Venous leg ulcers also were treated with compression therapy. Diabetic foot ulcer patients wore fixed ankle boots or similar off-loading devices to relieve pressure around the ulcer site.

Results

Percent of DFUs closed at 12 and 20 weeks were 60.38% and 74.10%, respectively. Percent of VLUs closed at 12 and 20 weeks were 60.77% and 74.60%, respectively. Of the patients with wounds that did not close, five were lost to follow-up and although unknown, classified as non-healed wounds. The average number of TheraSkin grafts required to achieve the closure rates were 2.03 (+1.47 SD) at 12 weeks and 3.23 (+2.77 SD) at 20 weeks, with a range of one to eight allografts applied.

Statistical significance was maintained for the venous and diabetic categorical wound area variables both in univariate and multivariate evaluations.

Adverse events, both related and not related to the study treatment were recorded (Table 2). All related non-serious adverse events were identified as soft tissue infection requiring oral antibiotics (up to 20 weeks). There were three related serious adverse events with a total of three patients requiring hospitalization for intravenous antibiotics (n=2) or incision and drainage (n=1) due to the development of infection. Records indicated that 13% of patients with diabetic foot ulcers had prior osseous debridement for osteomyelitis. 3% and 1.5% of venous ulcers had prior incision and drainage and debridement for osteomyelitis, respectively.

Representative examples of a typical DFU and VLU treated with TheraSkin are shown in Figure 2 and Figure 3, respectively.

Discussion

Our study demonstrated a 60.38% and 74.10%, closure rate among DFU patients treated with TheraSkin after 12 and 20 weeks, respectively, with the average mean wound size being 6.2 cm² (+11.8 SD). The study further demonstrated a 60.77% and 74.60%, closure rate among

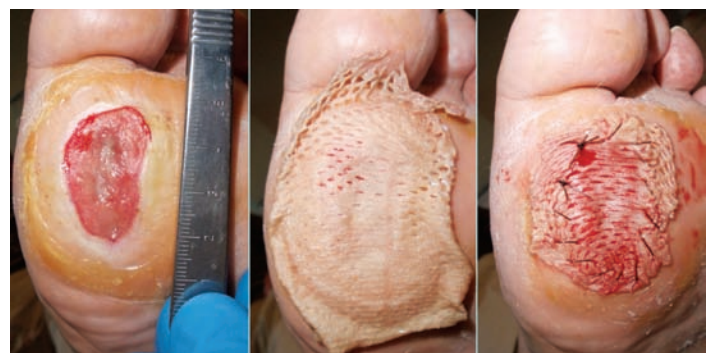


Figure 2: Diabetic foot ulcer treated with TheraSkin.

	DFU	VLU
None	81.48% (44)	87.31% (117)
Related, Nonserious	16.67% (9)	8.21% (11)
Related, Serious	0% (0)	0.75% (1)
Not Related, Nonserious	0% (0)	2.24% (3)
Not Related, Serious	1.85% (1)	1.49% (2)

Table 2: Analysis of adverse events in study population.

VLU patients treated with TheraSkin after 12 and 20 weeks, respectively, with the average mean wound size being 11.8 cm² (+22.5 SD). The average number of grafts required was 2.03 (±1.47) at 12 weeks and 3.23 (+2.77 SD) at 20 weeks, with a range of 1-8 grafts.

Although our study is not a head-to-head study and we acknowledge that the ability to generalize across studies is limited by the differences in study design, we provide the following data from various studies on Apligraf and Dermagraft for comparison.

There are 2 large RCTs using Apligraf for DFUs.^{3,4} Veves, et al, involved 112 patients, and achieved a 56% closure rate at week 12, with the average mean wound size being 2.97 cm² (+3.1 SD). A study by Steinberg, et al, examined 72 subjects and they achieved a 55.2% closure rate after 12 weeks. In each of these studies, an average of 4 grafts was required to achieve closure.

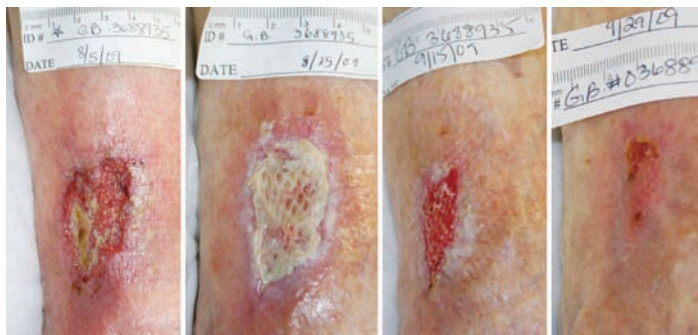


Figure 3: Venous leg ulcer healing after a single application of TheraSkin.

We also considered the study by Marston, et al, which used Dermagraft on 130 patients treated for DFUs.⁵ In this study, they observed a 30.0% closure rate after 12 weeks, with the average mean wound size being 2.31 cm² (range 0.75-16.7 cm²). They did not disclose the actual number of grafts used in order to achieve closure, but a separate study by Zelan, et al,⁶ indicated that an average of approximately 5.8 grafts were used to achieve closure by week 12 in their study.

Although there are no large studies describing the use of Dermagraft for VLUs, there have been several studies

which demonstrate the efficacy of Apligraf for the treatment of VLUs. Falanga and Sabolinski⁷ reported a closure rate of 47% after 6 months of treatment with Apligraf and compression therapy on 120 patients, with the average mean wound size being 1.82 cm² (+3.39 SD). Falanga, et al,⁸ also conducted a study with VLUs having an average mean size of 1.33cm² (+2.69 SD), and demonstrated an average closure time of 11.9 weeks in this patient population.

Conclusion

We found TheraSkin to be noncontributory to any adverse events, showing the safety of TheraSkin in this study population. The study also appears to show that only a few applications of TheraSkin grafts are required to achieve closure. Finally, this study shows TheraSkin to be a highly effective biologically active therapy to treat DFUs and VLUs which have failed to show progression of healing after 4 weeks of traditional wound care.

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Disclosures

Adam Landsman, DPM, PhD, receives compensation as a clinical advisor to Soluble Systems and LifeNet Health and is a member of the Clinical Advisory Board of Soluble Systems.

Acknowledgements

The authors would like to thank Inova Mt. Vernon Hospital, and Bill Bartow, PA, for their cooperation in making this study possible, and also LifeNet Health (Virginia Beach, VA) and Soluble Systems (Newport News, VA) for funding this study.