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ORIGINAL ARTICLE

Retrospective observational analysis of the use of an architecturally unique dermal regeneration template (Derma Pure®) for the treatment of hard-to-heal wounds

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Abstract

The purpose of this analysis was to evaluate the use of DermaPure, a decellularised human skin allograft, in the treatment of a variety of challenging wounds. This retrospective observational analysis reviewed a total of 37 patients from 29 different wound clinics across the USA. Each patient received one application of DermaPure which was followed until complete closure. A statistical analysis was performed with the end point being complete healing. All wounds on average, had a duration of 56 weeks and healed in an average time of 10·58 weeks. Individual wound categories included diabetic foot ulcers, which healed in 8·21 weeks; venous leg ulcers, which healed in 11·29 weeks; and surgical/traumatic wounds, which healed in 11·8 weeks.

Introduction

It has been estimated that in the USA, there are approximately 2.5–4.5 million people living with chronic wounds (1). Richmond *et al.* stated that these ulcers last approximately for 12 months, have a high reoccurrence rate and can cause significant morbidity (1). Ulcers are classified as vascular (either arterial, venous or mixed), diabetic or pressure ulcers, which in the lower limb are most commonly found on the heel. Other wound types that prove challenging in terms of facilitating closure include those caused by trauma or as a result of dehiscence following surgery. Even with an appropriate standard of care, these wounds do not always heal as expected. They may remain open and in a stalled state for extended time periods, putting additional pressure on clinical and financial resources within health care settings. Chronic wounds can be defined as wounds that fail to proceed through the normal phases of wound healing in an orderly and timely fashion. Factors associated with delayed healing include persistent inflammation, infection or the possible presence of a biofilm that could be resistant to many forms of treatment. The presence of senescent fibroblasts that fail to respond to normal wound-healing stimuli could also contribute to delayed healing. From a physiological standpoint, chronic wounds have an excessive level of proinflammatory cytokines, proteases, reactive oxygen species (ROS), senescent cells, persistent infection and a deficiency of stem cells (2). The increase of ROS production causes damage to the extracellular matrix (ECM) proteins and also causes cell damage. This process unfortunately leads to enhanced stimulation of proteases and proinflammatory cytokines (3). Higher levels of proteases, compared to their inhibitors, lead to the destruction of the ECM, preventing the wound to transition to the proliferative phase and attracting more inflammatory cells (4). High levels of senescent cell populations with impaired proliferative capacities lead

Key Messages

- This was a multicentred retrospective observational analysis of DermaPure, a decellularised allograft. The product was used on different wounds (a total of 37 patients) with only one application. DermaPure was compared to similar products with published studies. It was found that DermaPure had a quicker rate of closure. DermaPure was also used on wounds, such as necrotising fasciitis and traumatic wounds, that had no published similar studies. Complete wound closure was achieved.

Correction added on 29 September 2016, after first online publication: Howard Kimmel and Haley Gittleman's first name and surname have been transposed, and is now corrected.

to unresponsiveness to typical wound-healing signals, directly correlating with failure of the wound to heal (5).

Even with site-specific optimal standards of care, many wounds do not heal and require the use of advanced wound care therapies (6). Currently, there is a large number of such products consisting of wound dressings and a growing segment of biological wound matrices, with the majority of these being acellular in composition (2). Some of these decellularised therapies include dehydrated amniotic/chorionic membrane, porcine intestine, porcine bladder and dermal/epidermal allografts. These decellularised therapies leave in situ many constituents of dermal ECM, which can perform a number of key functions that will direct the healing process. For example, they can function as a substrate into which cells can migrate to promote/initiate angiogenesis and tissue regeneration (7). As an integral component of the residual scaffold, the ECM plays a significant role in regeneration through a dynamic interaction with the body's host cells and growth factors (8). ECM elasticity and porosity play key roles in regulating dynamic interactions between cells and matrix components as well as mediating the binding or release of sequestered growth factors. Consequently, ECM characteristics significantly influence infiltration and cellular positioning within matrices, as well as the proliferation, differentiation and secretion profiles of resident cells (9). The ECM also contains functional components such as glycosaminoglycans, glycoproteins and proteoglycans, which are key to replacing a defective/injured ECM (10).

One type of decellularised therapy is a human dermal allograft, which is harvested from screened donors and prepared using a proprietary process to decellularise the dermis while maintaining the natural structures of the ECM (11). Prospective studies have shown that decelluarised human dermal allografts help heal stalled diabetic foot ulcers and other types of chronic wounds in a timely manner (11–16). Most recently, Walters *et al.* completed a 16-week prospective multicentre assessment of an acellular dermal matrix on diabetic foot ulcers (DFUs), in which they attained 67·9% closure of all wounds treated (17).

DermaPure, decelluarised human dermal skin allograft

DermaPure (Tissue Regenix, San Antonio, TX) is a unique and architecturally distinct decellularised human skin allograft harvested from screened tissue donors. Once harvested, it is minimally processed according to current FDA guidelines. The end result is a dermal scaffold, the porosity of which is optimised for guided cell infiltration (Figure 1). Using a proprietary dCell® process, the tissue is preserved and found to be 99% free of any donor DNA. This is an important attribute associated with a product of this kind. The minimal DNA content sets DermaPure apart and minimises any possible risk of disease transmission associated with residual DNA that remains in the tissue (18). Much higher levels exist with other technologies that exist in this category of skin substitutes.

The first study of DermaPure in the treatment of chronic wounds was performed by Greaves in 2013 (19). A total of 22 patients were enrolled who had minimal or absent response to standard of care of their chronic wounds after 3 months. Half of these patients had ulcers for longer than 1 year with an average wound age of 4.76 years. The ulcers treated were venous,

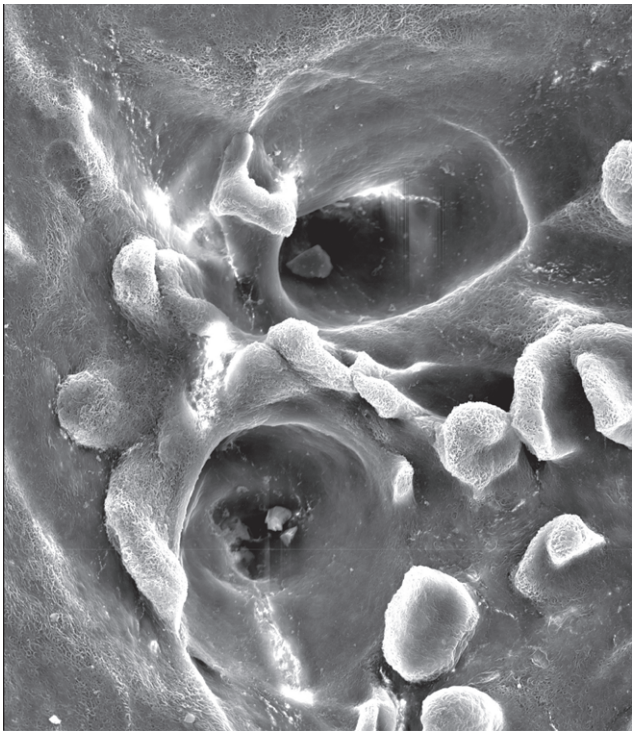

Figure 1 DermaPure imaging on a FEI Quanta 400 (ESEM). Tracts consistent with vascular channels were found, highlighted by organization of collagen around the tract. Vessel sizes reminiscent of capillaries in the papillary dermis and larger venules/arterioles in the reticular dermis.

diabetic or of mixed aetiology and were all on the lower limb. All patients had hydro-surgical debridement of their wound with Versajet◊ followed by a single application of DermaPure. Negative pressure wound therapy was then applied for 1 week. Prior to application, all patients had non-invasive vascular testing and a 1 week course of oral antibiotics. A full-thickness skin biopsy at the wound margin was taken at the time of surgery, and wound biopsies were also obtained at 3 and 6 weeks. Patients were then followed up weekly for 6 weeks, and final observations were made at 4 and 6 months. The primary outcome measure was wound surface area reduction. The authors also evaluated changes in vascularity, collagen levels and fibronectin. Primary outcomes showed wound reduction of 49·51% at 6 weeks, 80% after 4 months and 87% after 6 months. It was also shown that at week 6, there was an increase in haemoglobin flux, which is consistent with an increase in angiogenesis and restoration of vascular channels. Biopsies at week 3 showed that the graft was colonised by host fibroblasts, lymphocytes and neutrophils. These are significant observations because they show how the graft becomes an integral part of the host.

A prospective study on acute wounds using DermaPure was published in 2015 (20). The hypothesis of this study was that there were structural and biochemical variations of biomaterials that may induce differential scar formation after injury. Within this study, 50 healthy subjects had four biopsies of their inner arm, with each site allowed to heal in a different manner: site 1 was allowed to heal by secondary intention; Integra® (Plainsboro, NJ) was applied to site 2; DermaPure was applied to site

3; and site 4 had an autograft which was the biopsy intact tissue which was placed in the defect. Subjects were divided into five groups, with a biopsy performed at day 7, 14, 21 or 28. The histological results showed that the ECM-like DermaPure promotes stable focal adhesions facilitating tissue formation, while softer matrices encouraged transient adhesions and increased cell motility. In turn, cells exert contractile forces on ECM, which modulate matrix components over time. As a result, structural and biomechanical similarities between DermaPure and autografts may contribute to reduced fibrosis noted in the appropriately stained biopsies. The authors also contended that DermaPure resembled the angiogenic properties of an autograft. The authors concluded that DermaPure might stimulate more of a regenerative process than a reparative process.

A similar study was performed evaluating angiogenesis and the acute wound (21). This study mirrored the previous study, with the only minor difference being one less biopsy at day 42. Skin microcirculation was evaluated by analyzing the levels of haemoglobin flux and oxyhaemoglobin concentrations through non-invasive measures. Biopsy samples were evaluated for endothelial marker CD31, and these samples were also evaluated for gene expressions of PROK2, HIF2A, HIF3A and MT6-MMP. The former markers are genes associated with angiogenesis. The results demonstrated that both DermaPure and the autograft had organised vascular channels at the graft/host interface at Day 21, while the test comparator with the softer matrix did not. An increased expression of the pro-angiogenic PROK2 and MT6-MMP and CD31 was also seen in the DermaPure group, with maximum expression of CD31 at week 3. Both haemoglobin flux and oxyhaemoglobin concentrations were also elevated at week 3 in the DermaPure group compared to all the other groups, coinciding with the re-establishment of the vascular channels at week 3.

The hierarchy of laboratory, clinical and histological evidence leads to the conclusion that DermaPure may offer a very promising addition to the armamentarium of products designed to promote wound healing. The uniqueness of structure, biomechanical properties and biologically derived human components has been shown to address deficiencies of repair in both acute and chronic wounds. To further add to the consistency of this growing evidence base, an opportunity arose to conduct a retrospective, observational analysis of the clinical use of this dermal regeneration template in a large number of wound clinics across the USA.

Materials and methods

Design

The current study reports a retrospective observational analysis of 37 patients who received a single application of DermaPure for treatment of their wounds that had resisted attempts to achieve closure. The wound types reviewed included DFUs ($n = 14$), venous leg ulcers (VLU, $n = 7$), surgical/traumatic wounds ($N = 12$) and other ($n = 4$). The primary endpoint was the complete closure of the wound. Secondary outcome measures evaluated wound healing by level of chronicity and wound size. All patients reviewed had wounds $> 1\ cm^2$ in size and a wound duration of >30 days. Wound size was measured on a weekly basis for 20 weeks or until closure. The graft was applied and secured with a non-adherent dressing over it. Common components of standardised care across all sites included debridement, infection control, off-loading if a plantar DFU was present and compression if the wound was a VLU. Complete healing/closure was defined as 100% epithelisation.

Statistical analyses

Descriptive statistics were prepared using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R Version 3.12 (R Core Team (2014) R: a language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria). Average time to heal in weeks was determined for each wound type along with wound age, duration at application (<1 year old versus ≥ 1 year old) and wound size at application (<5 sq. cm versus ≥ 5 sq. cm). Further stratification was performed for wound age and size at application for each wound type. The proportion of wounds completely healed at week 12 was also examined by wound size quartile. Multivariate logistic regression was used to evaluate the association between the proportion of healed wounds after 12 weeks with wound size and age duration at the time of initial application. Overall healing rates with 95% confidence intervals were examined using the Kaplan–Meier method. Patients who did not heal by 24 weeks were considered unhealed. The time to heal by each different wound type was also analysed.

Results

There were a total of 29 centres that treated a total of 37 patients. Patient characteristics are presented in Table 1. A high proportion of patients (51·4%, $n = 19$) had wounds located on their foot, with wounds on the leg being the second most common location (27·0% $n = 10$). The most common wound type was DFUs (37·8%, $n = 14$), followed by VLUs (18·9%, $n = 7$), with the remaining wounds being either traumatic or surgical. The average wound size at application for all wounds was $12.88\ cm^2$ (SD = 18·68 cm), and the average wound age at application was 55·8 weeks (SD = 27·89 weeks). The average time to heal for all wounds was 10·58 weeks (SD = 6·76 weeks). Complete healing for DFUs was 52% at 4 weeks, 73% at 8 weeks and 85% at 12 weeks. Complete healing for VLUs was 49% at 4 weeks, 70% at 8 weeks and 81% at 12 weeks.

Average time healed

DFUs had the lowest average time to heal (8·21 weeks), while traumatic wounds had the highest (20 weeks). VLUs had an average time to heal of 11·29 weeks, whilst surgical wounds healed within 15·67 weeks (Table 2). The majority of wounds were less than 1 year old, with an average age of approximately 32 weeks. Wounds that were less than 1 year old at application had a lower average time to heal compared to wounds that were 1 year old or older at application (10·08 weeks versus 13·30 weeks, respectively). Wounds that were less than 5 sq. cm at application had a lower average time to heal compared to wounds that were greater or equal to 5 sq. cm at application (8·14 weeks versus 12·77 weeks, respectively). Regardless of

Table 1 Patient characteristics ($n = 37$).

Wound location (%)	
Foot	19 (51·4%)
Leg	10 (27·0%)
Arm	1 (2·7%)
Breast	1 (2·7%)
Chest	1 (2·7%)
Elbow	1 (2·7%)
Lip	1 (2·7%)
Sacral	1 (2·7%)
Shoulder	1 (2·7%)
Toe	1 (2.7%)
Wound type (%)	
DFU	14 (37·8%)
VLU	7 (18·9%)
Surgical	6 (16·2%)
Trauma	6 (16·2%)
Other	4 (10·8%)
Wound size at application (cm^2) [mean (sd)]	12·88 (18·68)/DFU 13.23/VLU 14/Surg. and Traumatic 12·25
Wound age at application (weeks) [mean (sd)]	55·88 (27·89)/DFU 36·6 /VLU 40·23/Surg. and Traumatic 11
Weeks to heel [mean (sd)]	10·58 (6·76)

wound duration, DFUs healed in the shortest period of time. Of the wounds that were less than five sq. cm at application, VLUs had the lowest average time to heal (6·00 weeks), while surgical wounds had the highest average time to heal (12·00 weeks). In contrast, of the wounds that were at least 5 sq. cm at application, DFUs had the lowest average time to heal (10·00 weeks), while surgical wounds had the highest average time to heal (16·40 weeks).

Proportion healed

The average proportion of wounds healed by 4 weeks was 49·58% (SD = 31·79%). The proportion of wounds healed by 12 weeks was examined by size quartile: 93·67% of the first size quartile (0·02–2·4 cm), 100% for the second size quartile (2·55–6·33 cm), 82·33% for the third size quartile (7.36–10 cm) and 82·38% for the fourth size quartile (12·88–72 cm).

Logistic regression

The binary response of being healed by week 12 was modelled by wound size and wound age at application (Table 3). Only wound size at application was found to be statistically significant ($P = 0·0490$). For every centimetre increase in wound size, the odds of being healed by 12 weeks significantly reduced by 5·1% (OR = 0·949). For every month's increase in wound duration at application, the odds of being healed by 12 weeks reduced by 2·4% (OR = 0·976). This finding was not statistically significant at the $\alpha = 0·05$ level ($P = 0·1459$).

Kaplan–Meier

The proportion of patients who remained unhealed was plotted over time in weeks (Figure 1). Patients who did not heal by 24 weeks were considered unhealed. Of the 37 patients, 36 were healed by 24 weeks. The median healing time was 10·5 weeks [95% CI: (6 weeks, 13 weeks)]. This proportion was also plotted over time in weeks by wound type (Figure 2). All patients with DFUs and VLUs healed by 24 weeks, whereas one patient with surgical/trauma wounds did not heal by 24 weeks. Patients with necrotising fasciitis had the lowest median heal time (4·5 weeks), followed by DFUs (7·5 weeks), VLUs (11 weeks), surgical wounds (15 weeks) and trauma wounds (17·5 weeks) (Figure 3).

Table 2 Average time to heal in weeks

Group	Average time healed	Standard deviation
All	10·58 weeks	6·76 weeks
DFUs	8·21 weeks	3·89 weeks
VLUs	11·29 weeks	4·15 weeks
Surgical wounds	15·67 weeks	8·55 weeks
Wounds < 1 year old	10·08 weeks	6·07 weeks
Wounds ≥ 1 year old	13·30 weeks	8·08 weeks
Wound size < 5 cm	8·14 weeks	5·93 weeks
Wound size ≥ 5 cm	12·77 weeks	6·70 weeks

Group	Subgroup	Average time healed	Standard deviation
Stratified by wound age at application			
Wounds < 1 year old	DFUs	8·00 weeks	4·24 weeks
	VLUs	10·25 weeks	2·99 weeks
	Surgical wounds	9·33 weeks	3·79 weeks
Wounds ≥ 1 year old	DFUs	9·00 weeks	2·65 weeks
	VLUs	12·67 weeks	5·77 weeks
	Surgical wounds	22·00 weeks	6·93 weeks
Stratified by wound size at application			
Wound size < 5 sq. cm	DFUs	6·88 weeks	3·44 weeks
	VLUs	6·00 weeks	Only one patient
	Surgical wounds	12·00 weeks	Only one patient
Wound size ≥ 5 sq. cm	DFUs	10·00 weeks	4·00 weeks
	VLUs	12·17 weeks	3·76 weeks
	Surgical wounds	16·40 weeks	9·34 weeks

DFU, diabetic foot ulcers; VLU, venous leg ulcers.

Table 3 Logistic regression results

Outcome: healed by 12 weeks Effect	Odds ratio	95% CI	*P*-value
Wound size at application	0·949	(0·902, 1·000)	0·0490
Wound age at application	0·976	(0·944, 1·009)	0·1459

Discussion

This retrospective review of the efficacy associated with the use of a human-derived novel dermal regeneration template targeted the most common yet challenging wound types (Figure 4). The majority of patients had long standing DFUs >24 weeks, which met the universally accepted definition of hard-to-heal wounds. According to Sheehan, DFUs with >50% healing within 4 weeks have a greater chance to heal (22). Our data showed that 52% of patients achieved 100% healing at 4

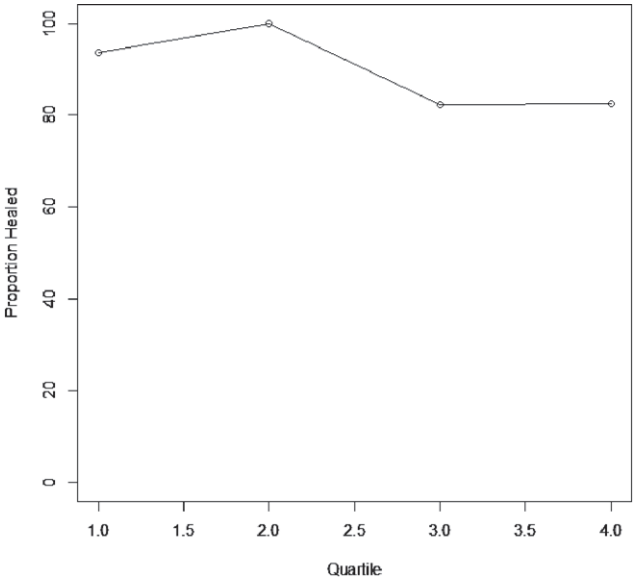

Figure 2 Proportion of wounds completely healed at week 12 by size quartile.

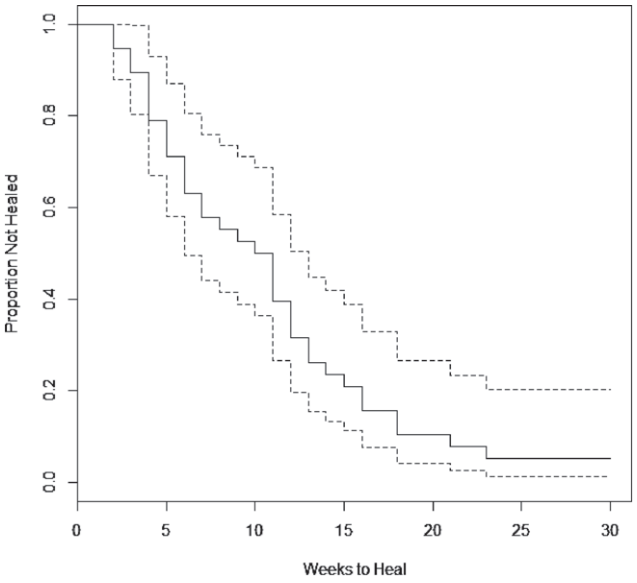

Figure 3 Overall healing rate.

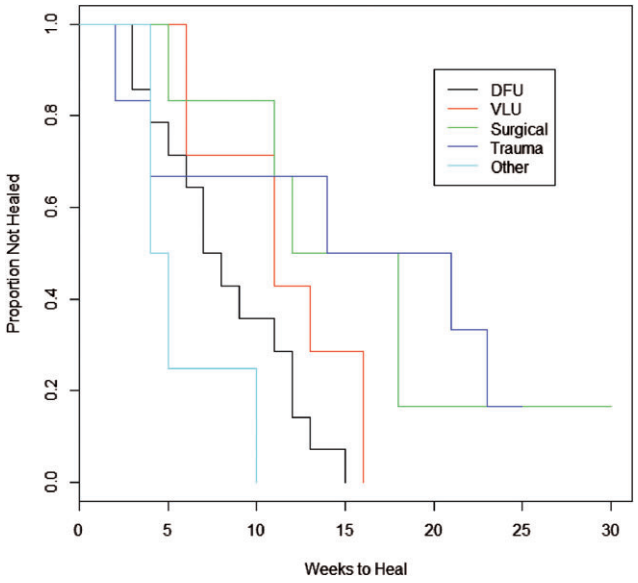

Figure 4 Healing rate by wound type.

weeks. Previous retrospective studies with a similar graft type, for example, Williams and Holewinski, reported their results for 16 patients with DFUs and achieved an average healing time of 10·96 weeks; unfortunately, there was no average ulcer duration listed (18), which makes a direct comparison difficult. Martin *et al.* reviewed 17 consecutive patients with DFUs of a mean wound size of 4·5 cm^2 who received a single application of an acellular human dermis. The average wound duration was 29·8 weeks. The average time to healing was 8·9 weeks (23). In a larger retrospective study, Winters *et al.* reviewed the outcomes of 100 DFUs (13). The average wound age was 20·4 weeks, and the average time to complete healing was 13·8 weeks. There have been two randomised controlled trials (RCTs) and two pilot studies of acellular human dermis for DFUs (12,17,24,25).

There have been only two multicentre RCTs evaluating technologies similar to the one described in this article. In 2009, Reyelman and coworkers published results from a 12 week prospective multicentred study where 47 patients received a single application of an acellular human dermis (12). The average ulcer duration was 23·3 weeks, with an average ulcer size of 3·6cm^2, and 70% of the ulcers were healed at 12 weeks. Winters *et al.* conducted a similar study examining two different products comprised of acellular human dermis compared to conventional standard of care (17). The 12-week endpoints of healing for both acellular human dermis products were 65% and 56·3%, respectively. When comparing all retrospective trials conducted using an acellular dermis, DermaPure healed similar challenging ulcers statistically faster. Reviewing all the data, both retrospective and prospective, ulcers treated with DermaPure were present for a longer duration (33·7 weeks) and were larger in size (13·24cm^2), yet healed 8·21 weeks faster.

In a retrospective study of DFUs and VLUs using a cryopreserved human dermis, a healing rate of 67% was reported with an average of 3·23 applications (26). In this study, the average baseline wound size was 6·2 cm^2 in the DFU group and 11·8 cm^2 in the VLU group, with an average wound duration of 18·7 weeks. Desman published a study looking at DFUs, VLUs and surgical/traumatic wounds treated with a similar acellular human allograft (27). The study had a total of 36 patients with 7 DFUs, 18 VLUs and 11 surgical/traumatic wounds. There were, on average, 3·3 applications of the matrix, with an average time to closure of 11·2 weeks for DFUs, 8·2 weeks for VLUs and 9·6 weeks for traumatic wounds, with an overall closure rate of 9·2 weeks for all wounds. The endpoints are nearly identical to the current analysis with some exceptions. At 20 weeks, the total wounds healed in the Desman study were 58%, while the current analysis had 100% healing. The Desman study also used, on average, more than one application. When compared

to all the previously described studies, DermaPure healed all wounds with one application and had nearly 100% healing by 20 weeks for wounds that were larger and were of a longer duration. When comparing DermaPure to the two other studies that included VLUs, the healing rate at 20 weeks was better, and while time to heal was similar, the other studies required more than one application to heal.

The replacement of areas of skin destruction represents a formidable challenge to the attending health care professional. Solutions were developed in the form of Dermal Regeneration Templates (DRTs), with the clinical goal of providing early wound coverage and neodermis formation, minimising the need for autograft dermis. Other advantages of such an approach include simplicity and reliability of technique and pliability and expected superiority of the cosmetic appearance of the resulting scars. Skin substitutes comprise of a range of heterogeneous biomaterials designed to accelerate wound healing through the process of guided cell attraction to the scaffold element of the template, which culminates in the provision of ECM, which facilitates the process of wound closure. Skin substitute characteristics include biocompatibility, porosity and elasticity that strongly influence cellular behaviour during the healing process and may induce differential scar formation after cutaneous injury (20).

A more practical and physiological approach would be to develop scaffold-based solutions from decellularised human cadaveric skin that has comparable biomechanical properties to the injured tissue. Cells would intuitively be primed to do what they do in situ, hence restoring normality to an abnormal situation. This would result in the restoration of skin architecture with successful scar outcomes. DermaPure is a bioengineered skin substitute that mimics native skin in terms of structure and rapidly integrates with surrounding tissue to actively stimulate cell migration, angiogenesis and epithelialisation (28). Through a patented, gentle decellularisation process, a graft is produced that consists of much less immunogenic ECM, which allows it to serve as an initial permanent implant that can be repopulated with the recipient's cells. During the healing process, fibrosis is an ill-defined term to describe ECM deposition from normal wound healing to pathological scarring (20). The whole wound healing process results in a differential development of fibrotic tissue, which will have a major impact on aesthetic outcomes. Recent findings have shown that the use of DermaPure in human wounds resulted in reduced dermal fibrosis compared to equivalent injuries treated with a bovine-derived matrix and those healed by secondary intention (20). Differences in matrix composition, architecture and cellular content between biomaterials may account for this variability. Therapies to ameliorate the fibrotic response to injury remain elusive. An exciting property associated with the use of DermaPure is that it could be used to create a shift in the processes associated with scarring to a more regenerative form of healing. This raises the exciting thought that the future direction of tissue-based products will not just be focused on dermal regeneration but also on the concept of dermal refinement, in which restoration of normal skin architecture with minimal scarring is the primary goal.

Living cell-based skin substitutes have been studied in RCTs for the treatment of DFUs and VLUs (29–32). The healing rates, wound age, wound size and number of applications in all of the living cell-based trials were significantly different than the current retrospective analysis. Clinicians have to determine the most efficacious way of healing an ulcer while being fiscally conscious. Redekop performed a cost-effectiveness study in 2003 (33). Within this study, he compared the 12-month cost of an advanced wound care skin products to the standard of care for DFUs. The conclusion was that the higher cost of the advanced wound care product was offset by the decrease in amputations and serious infections. Although the cost of DermaPure might be higher than the traditional standard of care, DermaPure was the most cost effective of all the advanced wound care products because it usually only requires a single application to heal.

Limitations

There are some limitations within the paper. Although statistical analysis was performed, being a retrospective cohort study, it is still considered level 2 evidence. There were numerous trial sites, but each site allowed the clinician to perform what they considered to be standard of care. There were no inclusion or exclusion criteria in this analysis. Patient's comorbidities along with critical lab values were not included in this analysis.

Conclusion

A single application of DermaPure results in the complete healing of stalled DFUs in approximately 2 months, VLUs in < 3 months, surgical wounds < 4 months and traumatic wounds < 5 months. A comparison of DermaPure to other prospective trials of acellular human dermis used to treat DFUs showed that DermaPure healed more effectively with fewer applications. No prospective trials on the treatment of VLUs with acellular human dermis exist. Comparisons to two retrospective trials reveal that DermaPure is more effective at healing with fewer applications. DermaPure heals chronic wounds in both an efficient and timely manner and also has the added economic benefit of being cost effective.

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References

1. Richmond NA, Maderal AD, Vivas AC. Evidence-based management of common chronic lower extremity ulcers. *Dermatol Ther* 2013;**26**:187–96.
2. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. *Adv Wound Care* 2015;**4**:560–82.
3. Schreml S, Szeimies RM, Prantl L, Karrer S, Landthaler M, Babilas P. Oxygen in acute and chronic wound healing. *Br J Dermatol* 2010;**163**:257–68.
4. McCarty SM, Percival SL. Proteases and delayed wound healing. *Adv Wound Care (New Rochelle)* 2013;**2**:438–47.
5. Stanley A, Osler T. Senescence and the healing rates of venous ulcers. *J Vasc Surg* 2001;**33**:1206–11.
6. Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment. A meta-analysis. *Diabetes Care* 1999;**22**:692–5.

7. Mulder GHK, Kirsner R, Lee D, Serena T. International Consensus. Acellular matrices for the treatment of wounds. An expert working review. *Wounds Int* 2010.
8. Schultz GS, Davidson JM, Kirsner RS, Bornstein P, Herman IM. Dynamic reciprocity in the wound microenvironment. *Wound Repair Regen* 2011;**19**:134–48.
9. Greaves NS, Ashcroft KJ, Baguneid M, Bayat A. Current understanding of molecular and cellular mechanisms in fibroplasia and angiogenesis during acute wound healing. *J Dermatol Sci* 2013;**72**:206–17.
10. Badylak SF, Freytes DO, Gilbert TW. Extracellular matrix as a biological scaffold material: Structure and function. *Acta Biomater* 2009;**5**:1–13.
11. Greaves NS, Iqbal SA, Baguneid M, Bayat A. The role of skin substitutes in the management of chronic cutaneous wounds. *Wound Repair Regen* 2013;**21**:194–210.
12. Reyzelman A, Crews RT, Moore JC, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. *Int Wound J* 2009;**6**:196–208.
13. Winters CL, Brigido SA, Liden BA, Simmons M, Hartman JF, Wright ML. A multicenter study involving the use of a human acellular dermal regenerative tissue matrix for the treatment of diabetic lower extremity wounds. *Adv Skin Wound Care* 2008;**21**:375–81.
14. Yonehiro L, Burleson G, Sauer V. Use of a new acellular dermal matrix for treatment of nonhealing wounds in the lower extremities of patients with diabetes. *Wounds* 2013;**25**:340–4.
15. Iorio ML, Shuck J, Attinger CE. Wound healing in the upper and lower extremities: a systematic review on the use of acellular dermal matrices. *Plast Reconstr Surg* 2012;**130**:232S–41.
16. Capito AE, Tholpady SS, Agrawal H, Drake DB, Katz AJ. Evaluation of host tissue integration, revascularization, and cellular infiltration within various dermal substrates. *Ann Plast Surg* 2012;**68**:495–500.
17. Walters J, Cazzell S, Pham H, Vayser D, Reyzelman A. Healing rates in a multicenter assessment of a sterile, room temperature, acellular dermal matrix versus conventional care wound management and an active comparator in the treatment of full-thickness diabetic foot ulcers. *Eplasty* 2016;**16**.
18. Williams ML, Holewinski JE. Use of a human acellular dermal wound matrix in patients with complex wounds and comorbidities. *J Wound Care* 2015;**24**:261–2, 4–7.
19. Greaves NS, Benatar B, Baguneid M, Bayat A. Single-stage application of a novel decellularized dermis for treatment-resistant lower limb ulcers: positive outcomes assessed by SIAscopy, laser perfusion, and 3D imaging, with sequential timed histological analysis. *Wound Repair Regen* 2013;**21**:813–22.
20. Greaves NS, Iqbal SA, Hodgkinson T, et al. Skin substitute-assisted repair shows reduced dermal fibrosis in acute human wounds validated simultaneously by histology and optical coherence tomography. *Wound Repair Regen* 2015;**23**:483–94.
21. Greaves NS, Lqbal SA, Morris J, et al. Acute cutaneous wounds treated with human decellularised dermis show enhanced angiogenesis during healing. *PLoS One* 2015;**10**:e0113209.
22. Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care* 2003;**26**:1879–82.
23. Martin BR, Sangalang M, Wu S, Armstrong DG. Outcomes of allogenic acellular matrix therapy in treatment of diabetic foot wounds: an initial experience. *Int Wound J* 2005;**2**:161–5.
24. Brigido SA, Boc SF, Lopez RC. Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. *Orthopedics* 2004;**27**:s145–9.
25. Brigido SA. The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. *Int Wound J* 2006;**3**:181–7.
26. Landsman AS, Cook J, Cook E, et al. A retrospective clinical study of 188 consecutive patients to examine the effectiveness of a biologically active cryopreserved human skin allograft (TheraSkin(R)) on the treatment of diabetic foot ulcers and venous leg ulcers. *Foot Ankle Spec* 2011;**4**:29–41.
27. Desman E, Bartow W, Anderson LH. Human skin allograft for patients with diabetic foot ulcers, venous leg ulcers, or surgical/traumatic wounds retrospective, descriptive study. *Ostomy Wound Manage* 2015;**61**:16–22.
28. Greaves NS, Morris J, Benatar B, Alonso-Rasgado T, Baguneid M, Bayat A. Acute cutaneous wounds treated with human decellularised dermis show enhanced angiogenesis during healing. *PLoS One* 2015;**10**:e0113209.
29. Edmonds M, European, Australian Apligraf Diabetic Foot Ulcer Study G. Apligraf in the treatment of neuropathic diabetic foot ulcers. *Int J Low Extrem Wounds* 2009;**8**:11–8.
30. Veves A, Falanga V, Armstrong DG, Sabolinski ML, Apligraf Diabetic Foot Ulcer S. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care* 2001;**24**:290–5.
31. Marston WA, Hanft J, Norwood P, Pollak R, Dermagraft Diabetic Foot Ulcer Study G. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care* 2003;**26**:1701–5.
32. Harding K, Sumner M, Cardinal M. A prospective, multicentre, randomised controlled study of human fibroblast-derived dermal substitute (Dermagraft) in patients with venous leg ulcers. *Int Wound J* 2013;**10**:132–7.
33. Redekop WK, McDonnell J, Verboom P, Lovas K, Kalo Z. The cost effectiveness of Apligraf treatment of diabetic foot ulcers. *Pharmacoeconomics* 2003;**21**:1171–83.