A Randomized Controlled Trial Comparing a Human Acellular Dermal Matrix Versus Conventional Care for the Treatment of Venous Leg Ulcers

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ABSTRACT

Introduction. Venous leg ulcers (VLUs) are often chronic and difficult to treat, which makes alternative options to conventional care necessary to improve ulcer healing rates. While human acellular dermal matrices (ADMs) have shown promise in treating diabetic foot ulcers, no comparative studies have been published regarding VLU treatment. Decellularized ADMs (D-ADMs) have been used successfully in the treatment of a wide variety of wound repairs and may be effective in treating VLUs. **Objective.** This study is a multicenter, randomized, controlled, open-label trial designed to evaluate the safety and efficacy of D-ADM compared with conventional wound care management in patients with chronic ulcers of the lower extremity. **Materials and Methods.** Patients were randomly assigned to receive either D-ADM or standard of care (control) in a 2:1 ratio. Treatment began at week 0 and wounds were evaluated on a weekly basis until wound closure was observed or the patient completed 24 weekly follow-up visits. **Results.** Eighteen patients were included in the D-ADM arm and 10 patients in the control arm. There was a strong trend of reduction in percent wound area for D-ADM patients with an average reduction of 59.6% at 24 weeks versus 8.1% at 24 weeks for control patients. In addition, healed ulcers in the D-ADM arm remained closed at a substantially higher rate after termination than healed ulcers in the control. **Conclusions.** In this report, the authors note the successful increase in healing rates and rate of percent wound closure as compared with conventional care options.

KEY WORDS

venous stasis ulcer, venous leg ulcer, matrix, acellular dermal matrix, DermACELL

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Venous leg ulcerations (VLUs) are present in more than 1 million patients in the United States alone.[1] They are often chronic and represent a treatment challenge for clinicians. Leading factors contributing to VLUs are venous insufficiency due to dysfunction of the calf muscle pump, venous valve dysfunction, and poor mobility.[1,2] Patients with VLUs often suffer from immobility, insomnia, social isolation, restrictions on activities of daily living, and severe pain.[2,3] Reports of pain intensity vary among studies, ranging from 29% of patients with moderate to severe pain[4] to about 65% of patients experiencing severe pain.[5,6] In addition to the numerous quality of life issues, VLUs place an enormous financial burden on both the health care system and patients themselves. One study reports 76% of patients felt financially impacted by the ulcer.[6] In 2011, the cost of managing a single VLU averaged $16 524 and escalated to $30 765 for ulcers that did not heal by 12 weeks.[7]

Conservative treatments such as compression therapy (including both bandaging and intermittent pneumatic compression), limb elevation, and several different types of dressings are often initially attempted.[1,2] Advanced treatment modalities include debridement, application of various dressings designed to balance moisture, and application of advanced biological dressings. Living skin equivalents, such as Dermagraft (Organogenesis, Canton, MA) and Apligraf (Organogenesis),[8-12] have been the most studied biological dressings, though their success has been limited. Human acellular dermal matrices (ADMs) have been successful in treating diabetic foot ulcers (DFUs)[13-21]; however, reports of their use for treatment of VLUs remain limited.

One human ADM, a decellularized ADM (D-ADM; DermACELL AWM; LifeNet Health, Virginia Beach, VA), is prepared using a patented decellularization process involving an anionic nondenaturing detergent and recombinant endonuclease, resulting in removal of at least 97% of DNA and DNA content.[13] This is followed by

Table 1. Screening criteria for inclusion and exclusion

INCLUSION CRITERIA	EXCLUSION CRITERIA
Age ≥21 and ≤80 years, presence of a single target VLU with a CEAP Grade 6	HbA_{1c} <12% within 90 days of screening visit, serum creatinine concentrations ≥3.0mg/dL within 30 days prior to screening
Duration of the target VLU ≥ 60 days, absence of infection, wound area ≥1cm² and <25cm², wound depth ≤9 mm	Application of biomedical or topical growth factors or living skin equivalents to the target wound within 30 days prior to screening
Ability to comply with offloading and dressing change requirements	Recent revascularization procedure to increase blood flow in the target limb
Determination of adequate circulation defined as having at least 1 of the following criteria within the past 60 days: $TcPO_2$ at the dorsum of the foot ≥30mmHg, ABI ranging from 0.8–1.2, or at least biphasic Doppler arterial waveforms at the dorsalis pedis and posterior tibial arteries	Sensitivity to potential D-ADM processing reagents gentamicin, polymyxin B, vancomycin, N-lauroyl sarcosinate, Benzonase[a], or glycerol
	Presence of severe peripheral vascular disease, active infection, untreated malignancy, active Charcot's disease, necrosis, purulence, or sinus tracts in the ulcer that could not be removed by debridement

VLU: venous leg ulcer; CEAP: Clinical severity, Etiology, and Anatomy and Pathophysiology ulcer classification; HbA_{1c}: hemoglobin; $TcPO_2$: transcutaneous oxygen measurement; ABI: ankle-brachial index; D-ADM: decellularized acellular dermal matrix

[a] Merck KGaA, Darmstadt, Germany

storage in a glycerol solution and low-dose, low-temperature gamma radiation that results in a terminally sterilized graft with a sterility assurance level (SAL) of 10^{-6}, consistent with a typical medical device. It is shipped and stored at an ambient temperature and requires no rehydration prior to application.[14,15] The D-ADM has been shown to support recellularization and revascularization in a rodent model[16] and has been implemented in a wide variety of clinical applications including severe burn scar resurfacing,[17] breast reconstruction,[18,19] the treatment of DFUs,[20-24] and chronic wounds of other etiologies.[25,26] The successful use of D-ADM in the treatment of these wound reepithilializations suggests it may be effective in treating VLUs, which can be chronic and difficult to treat. Here, the authors describe the results of a randomized controlled trial that compared the use of D-ADM with conventional care for the treatment of chronic VLUs.

MATERIALS AND METHODS

Design and objectives

This study on VLUs is a component of the largest multicenter, randomized, controlled, open-label trial of human ADM designed to evaluate the safety and efficacy of D-ADM compared with conventional wound care management in patients with chronic ulcers of the lower extremity (ClinicalTrials.gov, NCT01970163). All patients from the VLU component are included here, and these results have not been previously published. The other trial component, a study focusing on treatment for chronic DFUs, has been published separately.[23] The study design, methods, and informed consent were reviewed and approved by a central institutional review board (IRB), Western International Review Board, as well as site-specific IRBs. There were 8 implanting surgeons from 7 medical centers in 5 states enrolling patients with VLUs. These patients were randomly assigned to the D-ADM or conventional care treatment arms in a 2:1 ratio. Numbered envelopes containing the treatment designation were prepared by an outside contract research organization. Investigators were blinded to the randomization codes that matched each envelope. The envelopes were only opened after a patient successfully passed screening, thus providing the investigator with the randomized arm. Because it was not possible to continue blinding the investigator once treatment was applied due to the nature of treatment (ie, the ADM is visible upon application), a blinded, independent adjudicator also evaluated healing status of all wounds as a secondary check to prevent bias.

The purpose of this study was to explore the treatment response of D-ADM through comparison with a control group. The primary endpoint compared the full wound closure rates between the 2 groups. The secondary endpoints included comparing the reduction in wound size over time, time to wound closure, and treatment-related adverse events.

Patient population

To be included in the study, patients provided voluntary consent and written authorization for use and disclosure of protected health information as well as needed to meet all inclusion criteria while avoiding all exclusion criteria (**Table 1**).

Assessment methods

Treatment began at week 0, and wounds were evaluated on a weekly basis until wound closure was observed or the patient completed 24 weekly follow-up visits. Baseline measurements were taken immediately preceding treatment. The duration of VLUs prior to treatment was determined using the length of time from the date of onset of the ulcer to the patient's baseline visit.

Wound closure was defined as 100% reepithelialization of the wound without drainage. A second visit took place 2 weeks after initial wound closure observation to confirm complete wound closure. All healed ulcers were followed for an additional 12 weeks after the confirmation of wound closure to monitor whether the

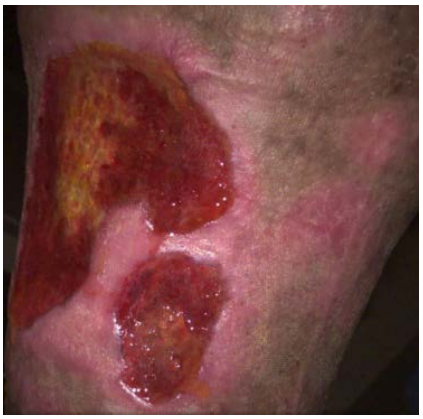

Figure 1. Preoperative venous leg ulcer at baseline with an area of 6.6cm² after debridement.

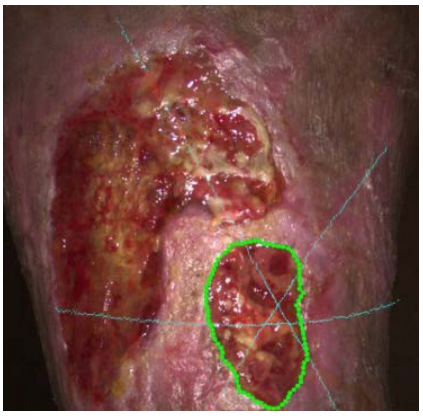

Figure 2. The same venous leg ulcer was still visible and demonstrated early incorporation at 1 week following treatment.

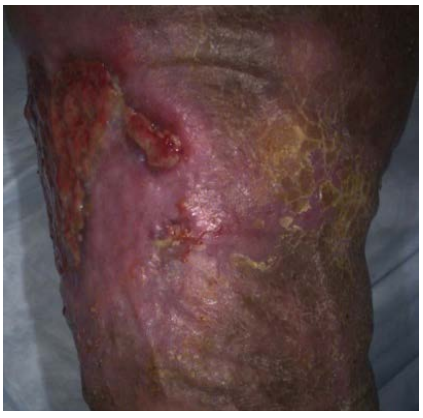

Figure 3. Wound was completely closed at 11 weeks following treatment with a single application of decellularized acellular dermal matrix.

wound remained healed. Measurements of wound area were taken and recorded using Silhouette Advanced Wound Assessment and Management System (Aranz Medical, Merivale, Christchurch, New Zealand). Percent wound area reduction (PWAR) was calculated using the equation [PWAR= ((WMTI-BM)/BM)*-100], where WMTI is wound measurement at treatment interval and BM is baseline measurement taken after debridement.

Application procedure

At baseline, all wounds were debrided to remove necrotic tissue. Wound size was recorded using the imaging system pre- and post-debridement as well as prior to dressing application (**Figure 1**).

For patients in the treatment arm, D-ADM was applied and covered with an appropriate nonadherent dressing (**Figure 2**). A second application of D-ADM was allowed no fewer than 2 weeks and no later than 12 weeks after the first application of D-ADM if the treating physician deemed wound healing had arrested. No additional criteria were provided to the investigators to determine if a wound should receive a second application of D-ADM. Patients could receive a maximum of 2 applications, including the first application applied at baseline.

Wounds in the conventional care arm underwent wound therapy consisting of alginates, foams, or hydrogels. At the baseline visit, necrotic tissue was removed through debridement using a sharp blade, scissors, or Versajet system (Smith & Nephew, London, UK). The wound then was covered with a moist or dry gauze at the treating physician's discretion. The dressing was left in place for 7 ± 2 days; the dressing was only to be removed at weekly visits. If deemed necessary by the treating physician, additional debridement was performed at subsequent clinic visits to remove any necrotic tissue.

Both the treatment and control arms were placed in compression therapy and followed weekly by the site investigator or wound care research staff. Weekly follow-up visits occurred until full wound closure was observed (100% reepithelialization) or the 24-week follow-up visit was reached (**Figure 3**). If wound closure was observed, a second visit occurred 2 weeks later and was considered the termination visit if the wound was still closed. Otherwise, the patient continued weekly follow-up visits until wound closure was observed or the 24-week follow-up visit was reached. Follow-up visits occurred at 4, 8, and 12 weeks following final confirmation of complete wound closure in order to ascertain

Table 2. Comparison of demographic variables between treatment groups

		D-ADM (n=18)	CONTROL (n=10)
Age (y)	Mean	64.6	61.8
	Median	64.5	58.5
	SD	12.9	16.9
	Range	43–87	43–83
BMI	Mean	33.5	32.9
	Median	28.9	29.6
	SD	10.9	9.1
	Range	20.1–64.4	24.0–49.6
Diabetes	Type 1	0 (0%)	0 (0%)
	Type 2	8 (44.4%)	3 (30%)

D-ADM: decellularized acellular dermal matrix; SD: standard deviation; BMI: body mass index

whether the wound remained healed. Assessments were completed on wound area and epithelialization.

Statistical methods

Hypothesis testing and continuous data analyses were performed using *t* tests at a 2-sided $\alpha = 0.05$. As an exploratory pilot study, there was no expectation of statistical significance.

RESULTS

Twenty-eight patients completed at least 12 weeks of follow-up, with 18 patients in the D-ADM arm and 10 in the conventional care arm. While the D-ADM arm contained a greater number of patients compared with the conventional care arm, all other demographic data were similar between groups (**Table 2**). The average pretreatment ulcer duration at baseline was 661 days and 466 days for D-ADM and conventional care, respectively. The average postdebridement ulcer size at baseline was 7.3 cm^2 for the D-ADM arm and 10.1 cm^2 for conventional care. Neither the average ulcer duration ($P = .3803$) nor the average baseline ulcer area ($P = .2731$) were significantly different between the 2 groups. Of the 18 patients receiving D-ADM, 9 (50%) received a second application during the course of the study.

At 24 weeks, 1 application of D-ADM demonstrated a substantial increase in the healing rate over conventional care (44.4% vs. 33.3%, respectively), though this difference was not significant (**Table 3**). The healing rates at 24 weeks for all applications D-ADM and conventional were comparable (29.4% vs. 33.3%, respectively) (**Table 3**). Healed ulcers in the D-ADM arm remained healed at a substantially higher rate after termination than healed ulcers in the conventional care arm (**Table 4**). Reduction in wound area was similar for both the D-ADM and conventional care arms up until week 9, when several wounds in the conventional care arm began to revert back to their baseline wound size (**Figure 4**). A strong trend of reduction in wound area was seen for patients in the D-ADM arm at 24 weeks, with an average reduction of 59.6%, in contrast to the conventional care arm with an average reduction of 8.1% at 24 weeks (**Table 3**). In addition, the wound area increased by more than 100% in size for one-third (3/9) of patients in the conventional care arm. Patients that received a single application of D-ADM began closing more quickly, thereby achieving statistically significant reduction of percent wound area over conventional care by 10 weeks.

In order to gather additional information on factors that may affect the healing of VLUs, wounds also were stratified according to ulcer size (≤ or > 10 cm^2) and duration (< or > 1 year prior to treatment). While significant trends of improvement were seen in all these stratified groups treated with D-ADM, sample numbers were too low to determine statistical significance as expected. Substantial wound area reduction was seen in wounds present for < 1 year in the D-ADM arm compared with conventional care at 74.1% versus 2.0%, respectively (**Figure 5**).

Table 3. Summary of results for VLU per protocol patients

	D-ADM (1 app)	D-ADM (all apps) [a]	CONTROL
No. of patients at 24 wks	9	17	9 [a]
% of wounds completely closed by 24 wk (n)	44.4% (4)	29.4% (5)	33.3% (3)
Mean % reduction in wound area from baseline at 12 wk (n)	76.3% [b] (9) *P*=.0447	49.7% (18)	28.5% (10)
Mean % reduction in wound area from baseline at 24 wk (n)	84.3% (9)	59.6% (17)	8.1% (9)

[a] One patient in the D-ADM all applications group was lost to follow-up after the Week 19 visit. One patient in the control group withdrew consent after the Week 13 visit due to an inability to comply with the weekly follow-up visit schedule.
[b] Denotes statistical significance between D-ADM and control ($P \leq .05$).
VLU: venous leg ulcer; D-ADM: decellularized acellular dermal matrix; app: application

Table 4. Percentage of healed wounds that remained closed at post termination visits [a]

	D-ADM	CONTROL	*P* VALUE
4 wk	100% (4/4)	66.7% (2/3)	.2482
8 wk	75.0% (3/4)	33.3% (1/3)	.3074
12 wk	75.0% (3/4)	33.3% (1/3)	.3074

[a] Post termination data not available for all healed patients at each follow-up time point.
D-ADM: decellularized acellular dermal matrix

DISCUSSION

Venous leg ulcerations are a serious medical condition. Advanced biologic dressings have shown promise in their treatment, with one type being biologically active human skin equivalents (HSE). These bilayer skin products are composed of living human dermal fibroblasts derived from neonatal foreskin.[8] One allogeneic HSE mixes living fibroblasts from neonatal skin with bovine collagen, while others incorporate a polyglactin mesh.

In a randomized, multicenter trial, Falanga et al[8] compared an allogeneic HSE to compression therapy alone among 293 patients. At the 6-month follow-up, a significantly higher percentage of patients receiving the HSE treatment had healed (63% vs. 49%; *P* = .02) and experienced faster time to complete wound closure (61 vs. 181 days; *P* = .003) than the conventional treatment group. Though nonsignificant, improvements were seen in the time needed for complete closure in HSE-treated ulcers < 6 months' duration. Both HSE-treated chronic ulcers (defined as ulcer duration > 6 months) and HSE-treated stage III ulcers (defined as visible muscle) experienced significantly shorter time periods needed for complete closure compared with conventional treatment (92 vs. 190 days, *P* = .001, and 83 vs. 183 days, *P* = .003, respectively).

In a published subanalysis of patients in the above study who had ulcers of > 1 year duration,[9] similar improvements were seen in both the healing rate and time to complete closure of ulcers in the HSE treatment group versus the compression therapy only group. By the 6-month follow-up, 47% of ulcers treated with HSE had healed completely versus 19% of ulcers treated with compression therapy alone (*P* < .005). Also, the median time to complete wound closure was significantly shorter for the HSE group (*P* < .005). The significant difference in healing rates began at 6-week follow-up and continued through 6 months. The HSE was 60% more effective over conventional treatment in wound closure (*P* < .01) at all time points.

A retrospective chart review[10] identified 13 patients with 21 chronic VLUs who were treated with allogenic HSE after at least 1 conventional treatment failed. The authors[10] found that when only conventional treatment was used, ulcers increased in size by an average 0.72 cm^3 per week for the 6 months preceding the initiation of treatment with HSE. After an average of 1.5 treatments with HSE, ulcer size reduced an average of 60.5% from baseline measurements.

While polyglactin mesh-based HSE is not indicated for use in the treatment of VLUs,[27] literature comparisons may still be informative. In a multicenter, randomized controlled trial of 366 patients, Harding et al[11] compared treatment using polyglactin mesh-based HSE versus standard therapy alone to treat chronic VLUs that did not have visible muscle, tendon, or bone exposure. The HSE treatment healed 34% of patients by 12 weeks compared with 31% for the control group, which was not statistically significant (*P* = .235). A similar trend of nonsignificant improvement was seen for HSE in the percentage of ulcers healed by 24 weeks (52% vs. 49%), time to healing, and median percentage reduction in ulcer area. Krishnamoorthy et al[12] also compared treatment with polyglactin mesh-based HSE versus conventional treatment in 53 patients with VLUs. At 12 weeks, 38% of patients in the treatment group that received either 4 or 12 pieces of HSE, 15% of patients that received compression therapy alone, and 7% of

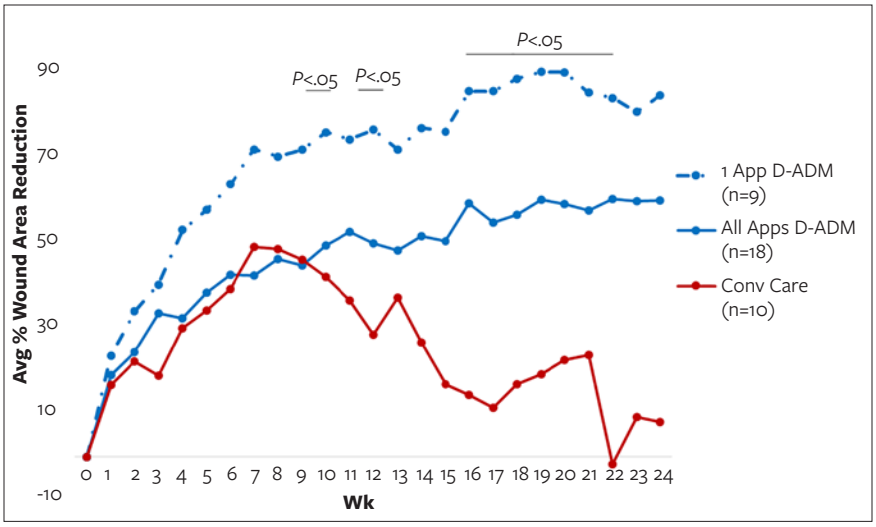

Figure 4. Average percent wound area reduction over 24 weeks for D-ADM and conventional care. Statistical significance between 1 application of D-ADM and conventional care was present at weeks 10, 12, and 16–22.
Avg: average; App: application; D-ADM: decellularized acellular dermal matrix; Conv Care: conventional care

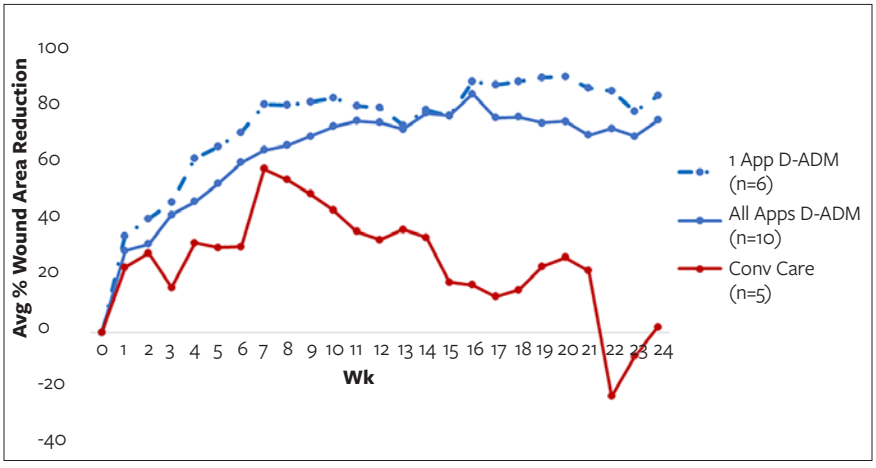

Figure 5. Effect of D-ADM and conventional care on the treatment of ulcers with an ulcer duration ≤ 1 year prior to treatment through 24 weeks of follow-up.
Avg: average; App: application; D-ADM: decellularized acellular dermal matrix; Conv Care: conventional care

patients that received 1 piece of HSE had healed. While none of the differences were statistically significant, it is of interest to note the effect that different quantities of HSE had on healing compared with conventional treatment.

The results presented here for D-ADM compare favorably with those reported for allogeneic HSE and exceed those reported for polyglactin mesh-based HSE. Ulcers treated with a single application of D-ADM also displayed a much higher healing rate than ulcers treated with conventional care. Although total applications D-ADM ulcers had a similar healing rate to conventional care, a considerably higher percentage of these healed wounds remained closed through 12 weeks following termination. The D-ADM-treated ulcers demonstrated a greater reduction in wound size over the conventional care for both healed and nonhealed ulcerations and among nonhealed ulcerations alone. Substantial wound area reduction also was observed in D-ADM-treated ulcers of chronic nature,[28] having a nearly 2-year average duration at baseline, which is substantially longer than those presented in other studies (**Table 5**[10-12]). Venous leg ulcers with a duration > 12 months are reported to be significantly slower to heal.[28] One study[1] predicted a healing potential for chronic VLUs of 22%, which is a considerable drop from the 80% healing potential predicted for ulcers < 3 months duration. The difficulty in healing ulcers of longer duration may be related to cellular changes, including altered cellular phenotypes, changes in integrins, and an early breakdown of collagen and growth factors.[28-31] Wounds that were < 1 year in duration or < 10 cm^2 exhibited a greater reduction in wound size at 24 weeks than those wounds that were treated with conventional care. The low reported healing rates and biochemical changes in chronic VLUs and subanalysis of wounds < 1 year duration argue that VLUs should be aggressively treated before the wound reaches 1 year duration. Rapid wound resolution of VLUs have the potential to increase patient quality of life and decrease indirect and direct health care costs.[32-35]

LIMITATIONS

There were several limitations to this pilot study. The small patient population and unbalanced proportion between the 2 groups (2:1) ensured a low probability of achieving statistical significance. However, as a pilot study, the purpose was to explore the potential for therapeutic benefits from using D-ADM in patients with VLUs, an area with scarce information, and achieving statistical significance was not expected. Accordingly, the larger proportion of D-ADM patients provided a better understanding of its therapeutic effects and safety profile, both of which are critical information for use in designing future trials. Another limitation of this study was the lack of criteria for investigators to follow as to when a second application would be appropriate. Such formal guidelines do not exist with this new material and was left to individual clinician discretion.

Finally, although the lack of blinding for study investigators would be considered a limitation, an independent adjudicator blinded to treatment type evaluated the healing status of all wounds as a secondary check to prevent bias. The kappa score of 0.923 indicated *very good* interrater reliability between the study investigators and the blinded, independent adjudicator. Furthermore, the adjudicator scored 1 additional wound treated with D-ADM as healed that the study investigators scored as unhealed, suggesting investigator bias was not an issue despite the lack of blinding.

CONCLUSIONS

While ADMs have shown promise in treating DFUs, no comparative studies have been published regarding their use to treat VLUs. This exploratory study demonstrated D-ADM increased healing rates and reduction in wound size compared to conventional care. The D-ADM also presented a favorable profile compared to the published literature on HSEs, which can require several applications. These early results support the use of D-ADM for treating chronic VLUs. Further larger prospective, randomized controlled studies are warranted to better assess its place in clinical practice.

Table 5. Literature comparisons of venous leg ulcer duration at baseline (range)

STUDY	MEASUREMENT METRIC	TREATMENT GROUP	CONTROL GROUP
Cazzell et al (present study)	Mean, wk	94.4 (12.4–414.7)	66.6 (15.6–123.3)
Harding et al[11]	Mean, wk	49.7 (8.9–262.1)	45.3 (9.9–470.4)
Krishnamoorthy et al[12]	Median, wk	6.8 (1.2–37.1) [a]	
Fivenson and Scherschun[10]	Median, wk [b]	0 (0–336) [a]	

[a] Study only contained a single group
[b] Metric was presented in months and converted here into weeks (1 mos = 4 wk)

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