

Comparative effectiveness of a bilayered living cellular construct and an acellular fetal bovine collagen dressing in the treatment of venous leg ulcers

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Aim: To compare the effectiveness of bilayered living cellular construct (BLCC) and an acellular fetal bovine collagen dressing (FBCD) for the treatment of venous leg ulcers. **Methods:** Data from WoundExpert® (Net Health, PA, USA) was used to analyze 1021 refractory venous leg ulcers treated at 177 facilities. **Results:** Kaplan–Meier analyses showed that BLCC (893 wounds) was superior to FBCD (128 wounds), $p = 0.01$ for: wound closure by weeks 12 (31 vs 25%), 24 (55 vs 43%) and 36 (68 vs 53%); reduction in time to wound closure of 37%, (19 vs 30 weeks); and improvement in the probability of healing by 45%. **Conclusion:** BLCC versus FBCD showed significant differences in both time to and frequency of healing suggesting that BLCC may provide significant cost savings compared with FBCD.

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Keywords: bilayered living cellular construct • comparative effectiveness • fetal bovine collagen dressing • skin substitute • venous leg ulcer • wound closure

Venous leg ulcers (VLUs), also referred to as venous stasis ulcers, are the most common type of chronic leg wound. These often painful wounds represent the majority of leg ulcers [1–3]. VLUs have a prevalence estimated at 1% of adults [4,5], with rates even higher among the elderly (1.7% prevalence, annually) [6]. The annual direct financial cost to US payers for the treatment of chronic VLUs has been estimated to be US\$15 billion [7].

The standard treatment for VLUs is compression therapy. However, with standard care alone, research has shown that up to 75% of patients fail to achieve healing with the use of standard compression therapy [8]. Up to 50% of VLUs remain unhealed at 6 months, 20% at 2 years and approximately 8% at 5 years [9]. Advanced treatment options, such as skin substitutes, have been demonstrated to show safety and effectiveness as adjunctive therapies to accelerate the wound healing process in nonhealing VLUs [10,11]. Treatment algorithms for initiating advanced therapies in VLUs have not been definitively established. Such therapies, however, may be appropriate to use as part of the initial treatment regimen in patients with poor prognostic indicators such as an ulcer size ≥ 10 cm² and an ulcer that has been present ≥ 12 months [12]. Data also suggest that advanced therapies should be considered in VLUs that have not reduced in surface area by at least 40% following 4 weeks of good standard wound care with compression therapy [13].

A bilayered living cellular construct (BLCC; Apligraf, Organogenesis, Inc., MA, USA) is at present the only product that has undergone premarket review and is approved by the US FDA for the treatment of VLUs (premarket approval (PMA)-approved Class III medical device). BLCC is comprised of human neonatal keratinocytes and fibroblasts in an extracellular matrix (bovine collagen and other extracellular matrix proteins) and has been in clinical use for the treatment of VLUs since 1998. In order to gain FDA approval for the treatment of VLUs, BLCC was evaluated in a pivotal randomized controlled trial (RCT) with a sample size of 275 patients that showed, when used in conjunction with compression therapy, BLCC significantly increased the percentage of patients healed

by 6 months and reduced the median time to complete wound closure when compared with an active control (standard compression therapy) [10].

Fetal bovine collagen dressing (FBCD; Primatrix; Integra, NJ, USA) has been cleared by FDA as a 510(k) Class II device for the management of VLU and other skin wounds with the exception of third degree burns. FBCD is an animal-derived acellular collagen dressing that has been processed and treated to remove cellular elements, lipids, carbohydrates and noncollagenous proteins, resulting in a scaffold with physiological amounts of collagen but without viable cells. Retrospective comparison of diabetic foot ulcer and venous stasis ulcer healing outcomes ($n = 40$) between FBCD and BLCC showed that both treatments were highly effective; however, the FBCD-treated wounds healed faster than patients treated with BLCC [14]. FBCD in the published retrospective analysis [14] was demonstrated to be successfully incorporated into standard of care therapy as a primary wound covering for the treatment of VLUs.

BLCC has not been compared with FBCD in comparative effectiveness research (CER) studies in real-world treatment settings. Effective treatment, established in CER studies, is the extent to which an intervention produces its intended effect in routine care conditions (real-world situations). RCTs with positive results, on the other hand, provide evidence of efficacious treatment in controlled, highly constrained conditions that are optimal for obtaining favorable results [15]. Thus, it is important to determine if efficacy reported from the results of RCTs can be translated to everyday, routine practice settings (effectiveness) to support evidence-based practice.

The purpose of this study was to investigate the comparative effectiveness of BLCC to FBCD for the treatment of VLUs in real-world settings using data over a 2-year period from a large wound care-specific electronic medical record (EMR) database (WoundExpert®, Net Health, PA, USA) that is utilized by approximately 20,000 physicians in over 1000 wound care facilities across the USA.

Methods

Study design

This study is a retrospective analysis to compare the effectiveness of BLCC and FBCD for the treatment of VLUs using de-identified EMRs from wound care facilities across the USA in a 2-year period. The primary analyses were median time to and frequency of wound closure evaluated up to 36 months. Wound areas (cm^2) were calculated from wound measurements of length and width. The final visit denoting VLU closure was not always recorded; thus, wound closure was defined as an ulcer achieving an area between 0 and 0.25 cm^2 .

Patients

Patients eligible for inclusion were those documented as receiving at least one treatment of either BLCC or FBCD on a partial or full thickness venous ulcer with the location coded as ankle, lower leg, shin, pretibial or calf. Included baseline wound areas were $1\text{--}40 \text{ cm}^2$ with ulcer duration of longer than 1 month prior to first treatment with BLCC or FBCS. To ensure that analyses were restricted to refractory VLUs, no ulcers were included that achieved $>40\%$ closure within the 4 weeks prior to first treatment with BLCC or FBCD. Wounds without baseline or follow-up area measurements were excluded as well as those where the date of BLCC or FBCD treatment was unknown. Wounds were also excluded if they received skin substitute treatments (Apligraf, Primatrix, Dermagraft, Epifix, Theraskin, Grafix, Graftjacket) on or within 28 days of the first treatment with BLCC or FBCD. Censoring occurred for nonhealed wounds at their last visit with an area measurement. Patients were also censored at the visit where the alternate product was applied (either BLCC or FBCD). Wounds treated with the same product >183 days after the prior application were censored at the visit where the subsequent application occurred. Other concurrent treatments such as hyperbaric oxygen or negative pressure wound therapy were allowed as this was a real-world study of wound care clinical practice not governed by a standardized, single protocol as in RCTs.

Data collection

Data were obtained from the WoundExpert EMR, which was de-identified under the terms and conditions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Net Health provided all treatment records for any patient receiving at least one application of BLCC or FBCD from January 2015 to January 2017 from 177 centers with contracted agreements for the transfer of de-identified data for research purposes. Treatment records included patient baseline demographics including age (years, ≤ 89 per HIPAA), sex, race, wound size and duration, and wound-specific information recorded at each visit including area measurements and treatments.

Table 1. Baseline patient characteristics.

Patient characteristic	BLCC (n = 805)	FBCD (n = 122)	p-value [†]
Age (years), n:	803	122	0.80
– Mean ± SD	69.0 ± 14.2	68.3 ± 14.9	
– Median	70.0	70.0	
Sex, n (%):	798	120	0.17
– Male	378 (47.4)	65 (54.2)	
– Female	420 (52.6)	55 (45.8)	
BMI (kg/m ²), n:	633	95	0.86
– Mean ± SD	33.5 ± 10.7	32.9 ± 9.6	
– Median	31.5	30.6	
Number of wounds per patient, n (%):	805	122	0.22
– Single wound	529 (65.7)	87 (71.3)	
– Multiple wounds	276 (34.3)	35 (28.7)	
Number of wounds per patient:			0.21
– Mean ± SD	1.62 ± 1.13	1.48 ± 0.90	
– Median	1.0	1.0	

[†] For BMI, the p-value is from the Wilcoxon rank-sum test, testing for a difference in distribution between treatments. For other categorical variables, the p-value is from a two-tailed Fisher's exact test, testing for a difference in proportions between treatments. For continuous variables, the p-value is from a two-tailed, two-sample t-test, testing for a difference in means between treatments.

BLCC: Bilayered living cellular construct (Apligraf); FBCD: Fetal bovine collagen dressing (Primatrix); SD: Standard deviation.

Statistical analysis

Descriptive data are expressed as mean (standard deviation) and median for continuous variables and n (%) for categorical variables. The level of $p < 0.05$ was established for the purpose of defining statistical significance. Baseline characteristics were reported as observational data for both continuous and categorical variables. Missing covariates were imputed with the mean value of the treatment group. The primary analyses comparing incidence of and median time to wound closure were determined by Kaplan–Meier analysis with a two-tailed log-rank test. The last observation was carried forward for missing data. Cox proportional hazards regression analysis was used to estimate the percentage of VLU with closure at weeks 12, 24 and 36. Median time to wound closure was determined by the Cox proportional hazards regression survivor function. The frequency of wounds closed at week 12, 24 and 36, and median time to wound closure, hazard ratio with 95% CI and p-value were estimated from the Cox model with terms for treatment, baseline wound area, baseline wound duration, baseline wound depth, sex, BMI and patient age at first treatment.

Results

All VLUs that received their first treatment with BLCC or FBCD from January 2015 and January 2017 at all participating Net Health centers were eligible for inclusion. A total of 927 patients with 1021 refractory wounds met the eligibility requirements for inclusion in the analysis. 893 wounds (805 patients) were treated with BLCC, and 128 wounds (122 patients) were treated with FBCD.

Baseline patient characteristics are shown in Table 1, and baseline wound and treatment characteristics are shown in Table 2. Treatment groups were similar with respect to age, sex, BMI and number of wounds per patient. The median age was 70 years old in both groups. Women represented a little more than half of the population in the BLCC group while men represented greater than half of the population in the FBCD group, and the median BMI was comparable between groups (31.5 kg/m² in the BLCC group and 30.6 kg/m² in the FBCD group). Groups were comparable for the percentage of patients presenting with a single wound (65.7 vs 71.3% for BLCC and FBCD, respectively) as well as patients presenting with multiple wounds at baseline (34.3 vs 28.7% for BLCC and FBCD, respectively). Though some nominal differences were observed, the BLCC and FBCD treated wounds were similar for baseline wound area, depth and duration (Table 2). At the first treatment application, the mean wound area was 10.1 cm² in the BLCC group and 10.6 cm² in the FBCD group. The mean wound durations in the BLCC and the FBCD groups were similar, both being >1 year (12.6 and 17.3 months in the BLCC and FBCD treatment groups, respectively).

Treatment characteristics are also shown in Table 2. The median number of treatment applications received was comparable for BLCC and FBCD with a mean of 2.8 ± 1.6 for BLCC and 2.1 ± 1.6 for FBCD. FBCD was used as a single application 46.9% of the time. Multiple applications were used on 53.1% of FBCD-treated ulcers. The percentage of patients treated with a single application with BLCC was 26.3%, and 73.7% had multiple

Table 2. Baseline wound characteristics and treatment characteristics.

Wound and treatment characteristics	BLCC (n = 893)	FBCD (n = 128)	p-value [†]
Wound area (cm ²), n:	893	128	0.22
– Mean ± SD	10.1 ± 9.1	10.6 ± 9.2	
– Median	7.0	7.4	
Wound duration (months) [‡] , n:	740	100	0.03
– Mean ± SD	12.6 ± 32.4	17.3 ± 31.7	
– Median	4.8	5.9	
Wound depth (mm), n:	883	128	0.01
– Mean ± SD	1.8 ± 1.5	2.0 ± 1.1	
– Median	2.0	2.0	
Number of treatment applications:– Mean ± SD	893	128	<0.01
– Median	2.8 ± 1.6 2.0	2.1 ± 1.7 2.0	
Interval between application (days), n:	658	68	<0.01
– Mean ± SD	20.1 ± 22.8	25.2 ± 19.7	
– Median	14.0	21.0	
Single/multiple applications, n (% patients):	893	128	<0.01
– Single	235 (26.3)	60 (46.9)	
– Multiple	658 (73.7)	68 (53.1)	
Number of debridements at or within 28 days prior to day 0 [§] , n (% patients):	893	128	0.65
– 0	192 (21.5)	25 (19.5)	
– 1	141 (15.8)	17 (13.3)	
– 2	137 (15.3)	18 (14.1)	
– 3	132 (14.8)	25 (19.5)	
– 4 or more	291 (32.5)	43 (33.6)	
Other treatments, n (% patients):			
– HBO ₂			
– Day -28 to <day 0	11 (1.4)	2 (1.6)	0.68
– Day 0 to last follow-up visit	17 (2.1)	6 (4.9)	0.11
– NPWT			
– Day -28 to <day 0	25 (3.1)	5 (4.1)	0.58
– Day 0 to last follow-up visit	21 (2.6)	7 (5.7)	0.08

[†] For categorical variables, the p-value is from a two-tailed Fisher's exact test testing for a difference in proportions between treatments. For continuous variables, the p-value is from a two-tailed, two sample t-test, testing for a difference in means between treatments.

[‡] Wound duration was reported in days and converted to months (30 days = 1 month).

[§] Day 0 defined as first application visit.

BLCC: Bilayered living cellular construct (Apligraf); FBCD: Fetal bovine collagen dressing (Primatrix); HBO₂: Hyperbaric oxygen; NPWT: Negative pressure wound therapy; SD: Standard deviation.

applications. For patients receiving multiple applications, the median interval between applications was longer with FBCD compared with BLCC (21.0 vs 14 days). Groups were similar with regard to the number of debridements at or within 28 days prior to or post the initial treatment application. Treatment with hyperbaric oxygen or negative pressure wound therapy prior to or concurrent with BLCC or FBCD treatment rarely occurred (<6% of wounds treated) and comparable between groups (Table 2).

After adjusting for treatment, treatment characteristics, baseline wound area, baseline wound duration, baseline wound depth, sex, BMI and patient age at first treatment application, Cox proportional hazards analysis showed that BLCC treatment significantly improved the median time to VLU wound closure by 37%, achieving the end point 11 weeks sooner than FBCD-treated patients (19 weeks for BLCC vs 30 weeks for FBCD; $p = 0.01$) (Figure 1). The estimated incidence of wound closure for BLCC compared with FBCD was significantly improved by week 12 (31.0 vs 25.0%), week 24 (55.0 vs 43%) and week 36 (68 vs 53%); $p = 0.01$ (Figure 2). BLCC treatment increased the probability of wound closure compared with FBCD by 45% showing a hazard ratio (HR) of 1.45 (95% CI: 1.08, 1.94), $p = 0.01$.

Discussion

This is the first comparative effectiveness study to evaluate BLCC and FDCD for the treatment of VLUs. The ulcers in the patient population evaluated were refractory or nonhealing with routine care. Ulcers in both study groups showed a duration of >1 year, failed to achieve $\geq 40\%$ wound closure in 4 weeks prior to the first treatment application, and had a mean size of >10 cm² at baseline, all negative risk factors for healing [11,13,16,17]. That the wounds in this analysis were required to have closed by <40% prior to treatment with either BLCC or FBCD is

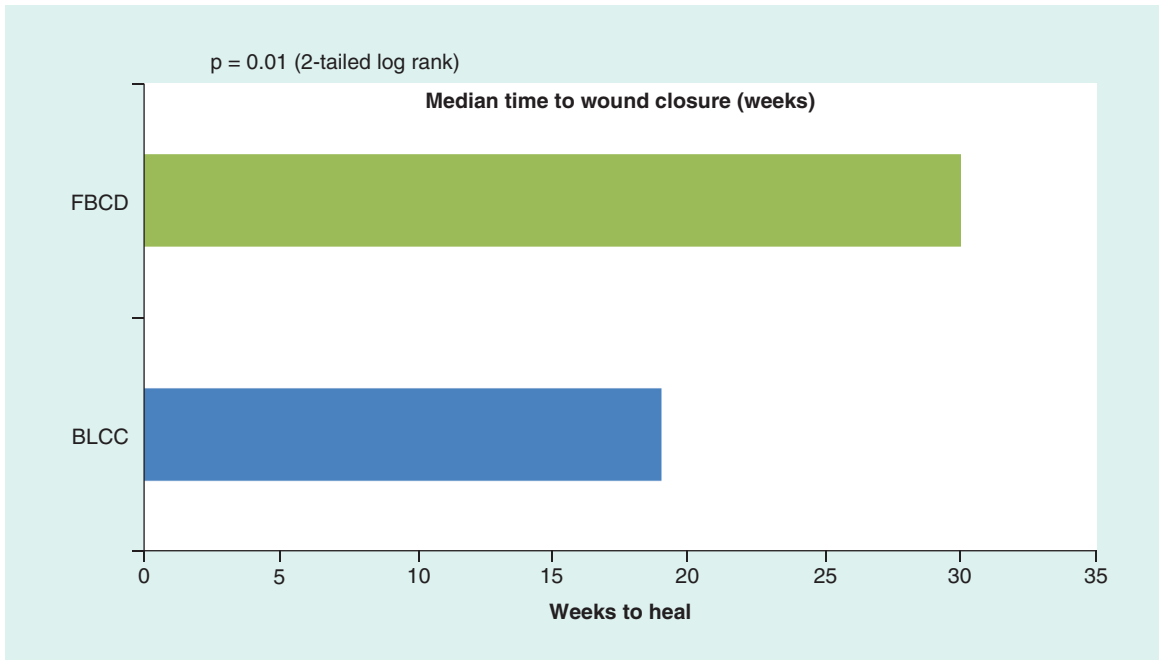


Figure 1. Median time to wound closure.
BLCC: Bilayered living cellular construct (Apligraf); FBCD: Fetal bovine collagen dressing (Primatrix).

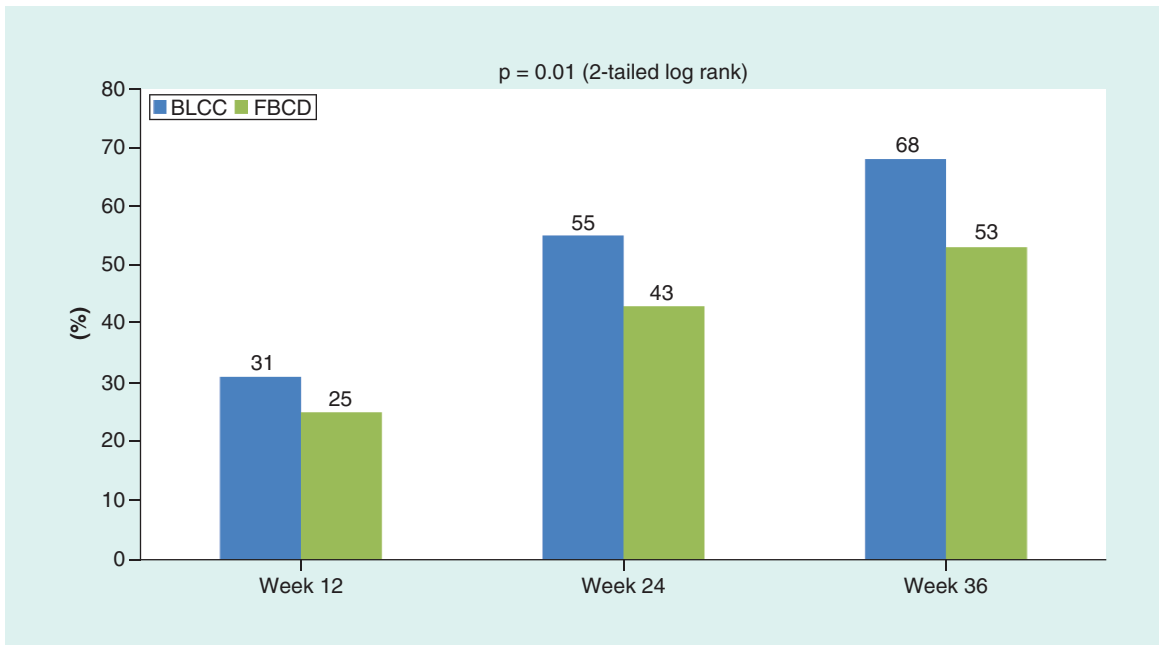


Figure 2. Percent wounds achieving wound closure.
BLCC: Bilayered living cellular construct (Apligraf); FBCD: Fetal bovine collagen dressing (Primatrix).

consistent with common, current clinical practice where the use of this prognostic indicator has become widely adopted to identify patients who may benefit from advanced wound care therapy, including skin substitutes. In this retrospective CER study analysis, BLCC demonstrated wound closure at significantly higher frequencies and in significantly less time compared with FBCD. BLCC increased the probability of wound closure by 45% over the 36 weeks of observation.

In order to address the potential impact of sex, age and BMI as individual patient characteristics on comparative clinical outcomes of BLCC and FBCD, three additional Cox analyses were performed. When treatment was adjusted for: sex as a categorical variable, HR = 1.42 (95% CI: 1.06, 1.91); $p = 0.02$; age as a continuous variable, HR = 1.44 (95% CI: 1.07, 1.93); $p = 0.02$; and BMI as a continuous variable, HR = 1.42 (95% CI: 1.06, 1.91); $p = 0.02$. These data are consistent with the outcomes reported in our primary Cox analysis when terms for treatment, treatment characteristics, baseline wound area, baseline wound duration, baseline wound depth, sex, BMI and patient age at first treatment are all included (HR = 1.45 [95% CI: 1.08, 1.94]; $p = 0.01$). These data would appear to indicate that the comparative effectiveness outcomes of BLCC and FBCD are minimally affected by sex, age and BMI when these patient characteristics are considered in isolation from multivariate wound and treatment characteristics.

Efficacy reflects the degree to which an intervention produces the expected result under the carefully controlled conditions of a clinical research protocol. RCTs provide the best method for establishing efficacy and are considered to have high 'internal validity' because of randomization, careful selection of participants and standardized treatment practices proscribed by the clinical protocol [18,19]. The conditions of an RCT are intended to maximize the probability of showing differences between treatment groups if they exist. RCTs act as the basis of FDA premarket review (New Drug Applications [NDAs], Biologics License Applications [BLAs], and PMAs) of clinical evidence for the approval of drugs, biologics and Class III devices. For guideline therapy, RCTs are generally considered level 1 evidence and the 'gold standard' in determining if a product can actually work. However, RCTs have limitations. The generalizability or 'external validity' of data generated may be problematic if RCT data alone are interpreted in the absence of real-world data [20]. The strict criteria for patient inclusion (which may exclude 'higher risk' patients), rigorous monitoring and adherence to treatment protocols may create an environment not reflective of clinical practice conditions in the community at large, and patients treated in RCTs may not truly represent typical patient populations treated where these products are utilized [21]. CER studies do not narrowly select patient populations but rather reflect interventions as typically used in practice without forced standardization. CER analyses may therefore be interpreted as more widely applicable and complementary to RCTs since CERs evaluate treatments in ordinary settings and in broader populations [22].

In effectiveness studies, performance is often reduced in less homogeneous populations treated outside of expert clinical research centers and in a less rigorous fashion. Thus, it is important to determine if efficacy can be translated to routine practice settings. Although strict comparisons between RCTs and the results presented here cannot be made because of differences in study design and patient populations, we found the incidence of complete wound closure for the 146 BLCC-treated patients in the pivotal RCT was 63% at week 24. These data correlated well with the wound closure rates of 55 and 68% at weeks 24 and 36, respectively in this CER analysis [10]. To date, there has not been a prospective RCT reporting the results of FBCD versus standard of care compression therapy in VLUs to allow for a comparison with the outcomes demonstrated in this CER study.

VLUs have been estimated to affect approximately 2.5 million patients in the USA [23,24]. The economic burden of VLUs on the US healthcare system in an analysis of 81,000 chronic VLU patients [7,25] was determined to be approximately US\$18 billion annually in direct costs. Medicare VLU patients receiving skin substitutes analyzed over the same time period showed total healthcare costs were US\$537 per week higher for patients who were still incurring VLU-related costs ('nonhealed' ulcers) compared with those no longer incurring VLU-related costs ('healed' ulcers). Of this amount, US\$377 per week were for selected services considered directly related to VLU treatment [7]. Therefore the 11-week difference in median time to wound closure (19 weeks for BLCC vs 30 weeks for FBCD) in the current analysis could result in estimated cost savings of between US\$4100 and US\$5900 per patient based on the differences in median time of having an open ulcer. This estimate likely understates the overall economic burden of nonhealing VLUs as it does not include 20% of the total costs of care not covered by Medicare. Analyses of two deidentified insurance claims databases showed that VLU treatment costs were directly proportional to the frequency of and time to healing. Medicare patients with nonhealed VLUs had 78% more hospitalization days, 50% more emergency department visits, 27% more outpatient office visits and 60% more days of home healthcare [7]. Important indirect costs not factored in must also be taken into consideration. These indirect costs include those associated with quality of life and lost productivity because of patient and caregiver missed days of work. Further specifics on relative costs would require a database with more detailed information than was available for this analysis.

We recognize that this study design analyzing real-world data, like all retrospective analyses, introduces 'noise' into the study environment that typical prospective RCTs minimize. A limitation of this study is that EMR databases

often are not developed for research purposes, and variability in recording practices of individual clinics exists. Even with the WoundExpert EMR data collection system, uniform data reporting is not monitored. Although certain fields within the WoundExpert EMR were reliably and consistently completed (such as wound measurements), information regarding the type of secondary dressings was found to be less consistently reported and often entered as 'free text' making reliable analyses problematic. Completion of some baseline patient information fields such as medical history, prior surgical interventions or concomitant medications, varied across centers. Additionally, the reporting of all safety-related outcomes, adverse events or ulcer recurrences were not possible as this information was not uniformly captured. Finally, given the lack of randomization, there is a possibility of bias in selection of patients for BLCC or FBCD at the centers involved in patient care. However, given the large number of wounds and centers providing information for the analysis, it is less likely that a uniform bias was present that affected the study results. Additionally, Cox analyses used to determine wound closure outcomes adjusted for multiple covariates and corrected for any imbalances between groups that might have arisen based on entry criteria.

There were also many advantages that the WoundExpert afforded. Because of the large sample sizes of the two treatment groups in the Net Health database, we were able to investigate outcomes in refractory, 'hard-to-heal' VLU and excluded wounds that had reduced in size >40% in the 4 weeks prior to the first application of investigational treatment. It is notable that percent reduction in wound size of <40% at 4 weeks from baseline has been reported as the strongest negative predictor of nonhealing in VLUs (i.e., identifies VLUs that will not achieve wound closure in a timely fashion) [13]. This 4-week prognostic milestone has been selectively adopted across the field of wound care to identify patients who may benefit most from intervention with advanced therapies; however, few previous studies have employed criteria that apply this measurement for inclusion. These results may provide important data to help guide treatment decisions for patients with recalcitrant wounds.

Conclusion

These real-world data showed that BLCC, compared with FBCD, significantly improved the probability, speed, and the incidence of wound closure in VLUs.

Summary points

- This is the first comparative effectiveness research study that compares the clinical outcomes of a bilayer living cellular construct (BLCC) and an acellular fetal bovine collagen dressing (FBCD) for the treatment of venous leg ulcers (VLUs) in a real-world setting.
- Treatment with BLCC significantly improves the incidence and speed of VLU wound closure compared with FBCD.
- The effectiveness of BLCC in these analyses was supportive of the efficacy results from the pivotal BLCC trial in VLUs.
- BLCC showed a 45% greater probability of wound closure when compared with FBCD.
- BLCC demonstrated accelerated time to wound closure of 37%, an 11-week improvement compared with FBCD.
- The incidence of wound closure was superior with BLCC versus FBCD at all time points in the study.
- Improvements in the probability, speed and the incidence of wound closure in VLUs treated with BLCC suggest a greater clinical benefit as well as a potential cost savings benefit.
- Electronic healthcare databases when used in Comparative Effectiveness Research studies offer the benefit of providing robust sources of data in large study populations over long observation periods.

Financial & competing interests disclosure

This study was funded by Organogenesis, Inc. ML Sabolinski, serves as managing member of Sabolinski LLC., Franklin, MA, USA. ML Sabolinski serves as a consultant for Organogenesis Inc., AOBiome, Neumedicines and Allergan. G Gibbons, serves as a consultant and speaker for Organogenesis, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

De-identified patient data released to Organogenesis, Inc. were consistent with the terms and conditions of Net Health's client contracts and the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Net Health was not involved in the analysis, interpretation or reporting of the data.

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