



Real-world data analysis of bilayered living cellular construct and fetal bovine collagen dressing treatment for pressure injuries: a comparative effectiveness study

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Aim: To determine the effectiveness of bilayered living cellular construct (BLCC) versus a fetal bovine collagen dressing (FBCD) in pressure injuries (PRIs). **Methods:** A real-world data study was conducted on 1352 PRIs analyzed digitally. 1046 and 306 PRIs were treated with BLCC and FBCD, respectively. **Results:** Cox healing for BLCC (n = 1046) was significantly greater ($p < 0.0001$) at week 4 (13 vs 7%), 8 (29 vs 17%), 12 (42 vs 27%), 24 (64 vs 45%), and 36 (73 vs 56%). The probability of healing increased by 66%, (hazard ratio = 1.66 [95% CI (1.38, 2.00)]; $p < 0.0001$). Time to healing was 162 days for FBCD and 103 days for BLCC showing a 36% reduction in time to healing with BLCC; ($p < 0.0001$). **Conclusion:** BLCC significantly improved healing of PRIs versus FBCD.

Plain language summary

What is this article about? We compared the effectiveness of a skin substitute, BLCC, to a wound dressing, FBCD, for use in pressure injuries (PRIs). 1352 patient records were evaluated. 1046 and 306 PRIs were treated with BLCC and FBCD, respectively.

What were the results? Results showed that the percentages of patients healed with BLCC were significantly higher than FBCD throughout the study. Patients treated with BLCC had a 66% greater chance of healing, and the time to healing was accelerated by approximately 2 months when compared with FBCD (from 6 months to 4 months).

What do the results mean? We conclude that BLCC significantly improved healing of PRIs compared with FBCD.

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Pressure injuries raise the risk for infection, pain, disability and longer hospital stays associated with increased morbidity and mortality [1,2]. Pressure injuries occur in up to 23% of patients in long-term care and rehabilitation facilities and up to 41% in intensive care units (ICUs) [3,4]. PRIs affect more than 2.5 million individuals annually in the US alone [5,6]. The US national cost of hospital-acquired pressure injuries may exceed \$26.8 billion [6,7]. Availability of safe and effective treatments for PRIs remains a critical, unmet medical need [8,9]. Delivering appropriate PRI therapy remains a daily challenge for patients and wound care providers [8,10]. Pressure injuries (PRIs) are chronic cutaneous wounds localized to the skin or underlying tissues over a bony prominence due to sustained pressure or pressure in combination with shear and tissue deformation. In general, the highest rates for PRIs are reported in critically ill patients in hospital. Populations and treatment settings of highest risk include: ≥ 65 years of age, critical care units, palliative care, spinal cord injuries, obese (by BMI), community care, rehabilitation centers and generally in patients who are sedentary. PRIs have been reported in neonates and children. Adult PRI patients typically demonstrate complicated wounds and multiple comorbidities. Most PRI patients typically present with

partial and full thickness wounds (stages II–IV) [11,12]. The prevalence of PRI varies from approximately 9–32% in long-term care facilities and 3–19% in home-care patients [10,13,14].

A bilayered living cellular construct (BLCC; Apligraf®; Organogenesis Inc., MA, USA), a bioengineered, bilayered, viable skin with living keratinocytes and fibroblasts, is FDA approved for the treatment of venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs) [15–18]. Fetal bovine collagen dress (FBCD; PriMatrix®; Integra Life Sciences, NJ, USA) is an acellular dermal matrix derived from fetal bovine dermis marketed under Section 510(k) of the US Food, Drug, and Cosmetic Act (The Act). Real-world data (RWD) were used to conduct a comparative effectiveness assessment (comparative effectiveness assessment [CEA]) of BLCC versus FBCD for the treatment of PRIs.

The conditions for initiating advanced skin substitute therapies in PRIs have not been established. However, as demonstrated in other chronic wounds studies, advanced therapies may be appropriate to use in patients with poor prognostic indicators such as large size of the wound (e.g., $>10\text{ cm}^2$) and long duration of non-healing (e.g., >6 months) [10,19,20]. Chronic wound data in VLUs and DFUs have shown that treatments other than routine wound care regimens should be considered in ulcers that have not reduced in surface area by $\geq 40\%$ (VLUs) and $\geq 50\%$ (DFU) after 4 weeks of care [21–23].

BLCC treatment of PRIs may prove to be a safe and effective adjunct to standard of care (SOC). BLCC is one of only three skin substitute products approved by the US Food and Drug Administration (US FDA) as a ‘wound treatment’ (FDA approved for VLUs and DFUs). US FDA approval requires a pre-market evaluation establishing safety and effectiveness. Showing ‘compelling’ scientific, medical and clinical data (US Code of Federal Regulations; CFR) in at least one phase III, pivotal, randomized controlled clinical trial [RCT]) is mandated to by the Agency to demonstrate a favorable risk/benefit ratio for a product’s indication for use. In large, randomized clinical trials (RCTs) for the treatment of VLUs and DFUs, BLCC significantly increased the percent of healing and reduced the median time to healing compared with SOC (good wound care recommended by the Wound Healing Society guideline therapies [18,24–29].

A wound covering, FBCD has been cleared by FDA as a 510(k) class II device for the management of chronic and acute 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 non-collagenous 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 [30]. FBCD in the published retrospective analysis was demonstrated to be successfully incorporated into standard of care therapy as a primary wound covering for the treatment of VLUs and DFUs [30].

Based on previous CEA RWD studies of BLCC in VLUs DFU studies, we hypothesized that BLCC use in PRIs would show promising effectiveness results [31–38]. Further, we hypothesized that PRI effectiveness results would be consistent with effectiveness demonstrated in previous RCTs [16,17,39].

Research questions

In this PRI study, RWD were used to conduct a CEA analysis of BLCC versus FBCD for the treatment of PRIs. Research questions included: 1) Would analyses of over one thousand treated patients at over 300 wound care facilities in the US result in robust data to support clinically meaningful conclusions of effectiveness of BLCC versus FBCD? 2) Would RWD CEA show statistically significant differences between BLCC and FBCD treatment groups? Can results of this RWD CEA study help to inform patients, clinicians and policy makers on wound care therapy for PRIs?

General study objective

The general objective of this study was to generate data on large PRI patient populations using real-world data for comparative effectiveness assessments of BLCC and FBCD.

Methods

Study design

This study design is a retrospective analysis of RWD CEA of BLCC and FBCD using a patient de-identified EMRs transferred from Net Health (PA, USA) to Virtu Stat Ltd, (PA, USA). Effectiveness of BLCC was compared

with FBCD for the treatment of PRIs. RWD were used for all computations of clinical outcome results. The data were collected from 315 US wound care facilities collected from 2017 to 2022. The analyses were conducted on 1182 PRI patients. There were 890 BLCC-treated and 292 FBCD-treated patients, respectively. A total of 1352 PRIs were treated with either BLCC or FBCD, and all of these 1352 PRIs were analyzed following intention-to-treat (ITT) principles. There were 1046 BLCC-treated and 306 FBCD-treated PRIs. The primary end points were median time to healing and percentages of patients healed. Primary analyses were time-to-event (TTE, not adjusted for risk factors) and linear regression (adjusted for risk factors). Wound healing outcomes were assessed at the wound care facilities by site personnel. Time and frequency of healing over 36 weeks were compared between treatment groups.

Patients

Patients eligible for inclusion were those documented as receiving at least one treatment of either BLCC or FBCD with at least one documented follow-up visit. Patients were eligible for inclusion in the analysis if they demonstrated stage II–IV PRIs located at anatomical locations including over the sacrum, coccyx, greater trochanter, ischial tuberosity and calcaneus. Patients having wounds with surface areas between 1 and 20 cm² were included. Wounds without baseline or follow-up area measurements were excluded. Censoring occurred for non-healed wounds at their last visit with an area measurement. Patients were also censored at the visit where the alternate product was applied (i.e., BLCC on FBCD-treated PRIs; FBCD on BLCC-treated PRIs).

Data collection

Electronic medical records (EMRs) for wound care management (WoundExpert®; Net Health, PA, USA) were used to evaluate the effectiveness of BLCC versus FBCD for the treatment of pressure injuries (PRIs). Data were obtained from the WoundExpert® electronic medical record (EMR; i.e., electronic case report form, eCRF) which was de-identified under the terms and conditions of the US Health Insurance Portability and Accountability Act of 1996 (HIPAA). Net Health provided all records for all PRI patients receiving at least one application of BLCC or FBCD at the 315 US centers with contracted agreements for the transfer of de-identified data for research purposes. Patient EMRs recorded baseline demographics including patient characteristics (e.g., age in years, ≤89 [per US HIPAA], sex, race and BMI), wound characteristics (e.g., wound size, depth and duration) and treatment characteristics (e.g., number of treatment applications and interval of time between applications). All measurements of wound dimensions were performed at the wound care facility by site personnel using rulers to measure length (i.e., at the longest points) and width (at the widest points) to compute wound areas (cm²) and wound depth (mm) measured using a cotton-tipped applicator gently inserted into the deepest part of the wound].

Statistical analysis

Descriptive data are expressed as mean (standard deviation) and median for continuous variables and n (%) for categorical variables. An alpha level of $p < 0.05$ was used for statistical significance. Continuous and categorical baseline characteristics were reported as observational data. Missing data were imputed using a mixed-effects model of repeated measures (MMRM) with the mean value of the BLCC group. The primary analyses comparing incidence and median time to wound closure were computed by Kaplan–Meier (K-M) analysis with a two-tailed log-rank test. Cox proportional hazards regression analysis was used to estimate the percentage of PRIs healed at week 4, 8, 12, 24 and 36. Median time to wound closure was determined by the method of K-M. The frequency of healed wounds closed at week 4, 8, 12, 24 and 36, and median time to wound closure, hazard ratio (HR) with 95% CI and p-value (Wald test) were estimated from the Cox model with terms that included: treatment, baseline wound area, baseline wound duration, baseline wound depth, sex, BMI and patient age at first treatment.

Results

All PRIs that received their first treatment with BLCC or FBCD between 2017 and 2022 at all participating Net Health centers were eligible for analysis. A total of 1182 patients with PRIs met the eligibility requirements for inclusion in the analysis. 1046 wounds (890 patients) were treated with BLCC and 306 wounds (292 patients) were treated with FBCD. Patient, wound and treatment characteristics are shown in Table 1. Treatment groups were similar with respect to age, sex, baseline wound area, interval of time (days) between treatment applications. The median age was 70 and 69 years old in the BLCC and FBCD groups, respectively. Women represented a 58.1% of the population in the BLCC group and 54.9% in the FBCD group. Men represented slightly less than

Table 1. Patient, wound and treatment characteristics.

Patient and wound characteristic	BLCC (n = 1046)	FBCD (n = 306)	p-value
Age (years), n	872	291	0.133
Mean $\pm$ SD	68.2 $\pm$ 15.3	66.0 $\pm$ 17.4	
Median	70.0	69.0	
Sex, n (%)	878	288	0.337
Female	510 (58.1)	158 (54.9)	
Male	368 (41.9)	130 (45.1)	
Wounds treated/patient, n	890	292	<0.0001
Mean $\pm$ SD	1.97 $\pm$ 1.73	1.19 $\pm$ 0.69	
Median	1.00	1.00	
Wounds treated/patient (categorical), n	890	292	<0.0001
Single wound, n (%)	490 (55.1)	260 (89.0)	
Multiple wounds, n (%)	400 (44.9)	32 (11.0)	
Baseline wound area (cm ²), n	1046	306	0.063
Mean $\pm$ SD	6.90 $\pm$ 11.03	6.33 $\pm$ 14.83	
Median	2.90	2.40	
Baseline wound depth (mm), n	1019	303	<0.0001
Mean $\pm$ SD	3.1 $\pm$ 4.8	7.5 $\pm$ 8.99	
Median	2.0	4.0	
Baseline wound duration (months), n	798	235	<0.0001
Mean $\pm$ SD	6.54 $\pm$ 10.52	9.34 $\pm$ 15.70	
Median	3.88	5.68	
Applications per wound, n	1046	306	0.023
Mean $\pm$ SD	2.15 $\pm$ 1.59	2.43 $\pm$ 1.93	
Median	2.00	2.00	
Interval (days) between applications, n	538	174	0.421
Mean $\pm$ SD	25.8 $\pm$ 26.7	27.5 $\pm$ 37.2	
Median	19.3	17.4	

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

half of the population in both the BLCC and FBCD groups (41.9 vs 45.1%, respectively). The two groups were comparable for mean wound area at baseline, $p = 0.063$ (BLCC, 6.90 ± 11.03 cm² vs FBCD, 6.33 ± 14.83 cm²). Notably, the percentages of patients presenting with a single wound were 55.1 versus 89.0% for BLCC and FBCD; $p < 0.0001$, and the percentages of patients presenting with multiple wounds at baseline were 44.9 versus 11.0% for BLCC and FBCD; $p < 0.0001$. Baseline wound depths (mm) for BLCC versus FBCD were 3.1 ± 4.8 versus 7.5 ± 8.99 ; ($p < 0.0001$). Baseline wound durations (months) were 6.54 ± 10.52 for BLCC and 9.34 ± 15.70 for FBCD; ($p < 0.0001$).

Treatment characteristics are also shown in Table 1. The mean number of treatment applications between groups showed significant differences: BLCC-treated PRIs had fewer treated applications than FBCD-treated PRIs (2.15 ± 1.59 vs 2.43 ± 1.93 , respectively; $p = 0.023$).

After adjusting for treatment, treatment characteristics, baseline wound area, baseline wound duration, baseline wound depth, sex, BMI and patient age at first treatment application, K-M and Cox analysis demonstrated that BLCC treatment significantly improved the median time to PRI wound closure by 36%, achieving the healing end point 59 days sooner than FBCD-treated patients (103 days for BLCC vs 162 days for FBCD; $p < 0.0001$), (Figure 1). The percent healing for BLCC compared with FBCD was significantly improved by week 4 (13 vs 7%), 8 (29 vs 17%), 12 (42 vs 27%), 24 (64 vs 45%), and 36 (73 vs 56%); $p < 0.0001$ (Figure 2). BLCC treatment increased the probability of wound closure compared with FBCD by 66% showing a Hazard Ratio (HR) = 1.66 (95% CI [1.38, 2.00]).

Discussion

Results of RWD CEA studies have become increasingly important to clinicians, patients, Boards of Health (BOH; regulatory bodies) and third party payers [40,41]. We report the first RWD CEA study examining outcomes of BLCC and FBCD for the treatment of PRIs. We found PRIs treated with BLCC had higher rates of healing in less time compared with those treated with FBCD increasing the probability of healing by 66%.

Studies using RWD can be used to show comparative effectiveness of treatment options on patient clinical outcomes. Data from RWD CEAs can guide clinicians to limit overuse of ineffective therapies and underuse of effective therapies [42,43]. Real-world comparative effectiveness assessments can aid in answering key questions

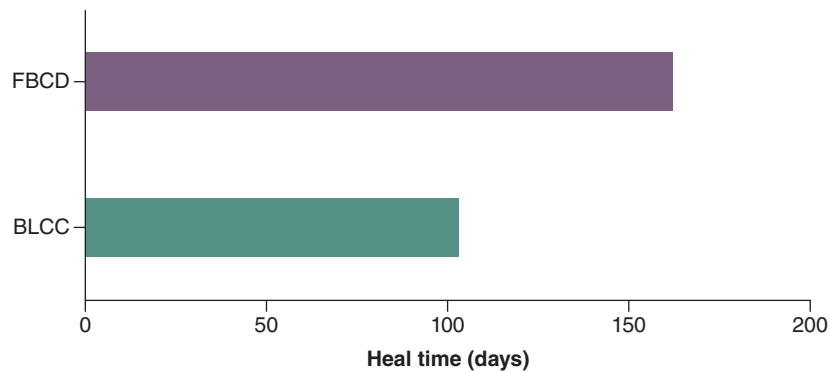


Figure 1. Median time to healing.

BLCC: Bilayered living cellular construct; FBCD: Fetal bovine collagen dressing.

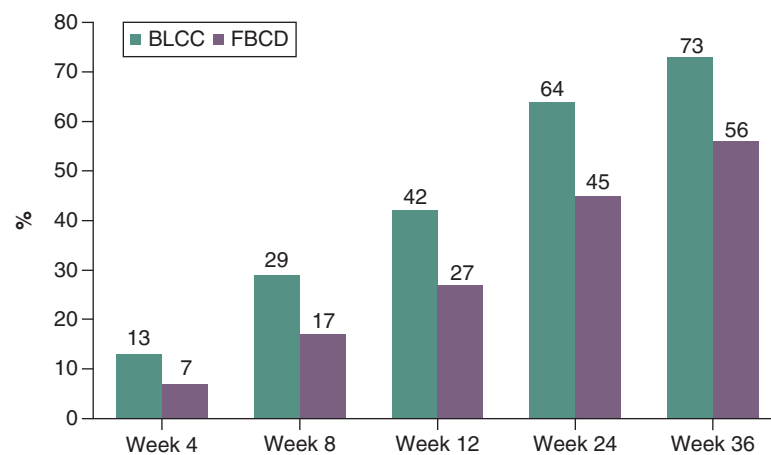


Figure 2. Percentage of healed wounds.

BLCC: Bilayered living cellular construct; FBCD: Fetal bovine collagen dressing.

about particular patient populations and conditions by using active comparators and employing broad inclusion criteria to evaluate large, diverse populations that are representative of patients treated in routine practice [44]. RCTs determine efficacy (i.e., whether a product can work in a controlled setting). RCTs show safety and efficacy data and serve as the cornerstone for agency pre-market review and pre-market authorizations to commercialize drugs, biologics and class III devices (US FDA device classification). RWD CEA studies, on the other hand, show whether a post-approved product does work in widespread use [45]. Products that demonstrate efficacy in RCTs may perform differently in general clinical practice where variability in treatment applications, patient compliance and other clinically meaningful factors tend to impact the net benefits of a chosen treatment modality [46,47]. RWD CEA research allows for valid determinations of the applicability of efficacy results to diverse patient populations treated in multiple settings. Concordant efficacy and effectiveness clinical outcomes data across RCT and RWD studies, respectively are indicative of robust, strong data [43,48,49].

The RWD CEA study we report for BLCC-treated PRI wounds shows consistent results with the RCT results demonstrated in the VLU and DFU phase III trials for US FDA BLCC approvals. It has previously been demonstrated that the two pivotal phase III RCT results, one for VLUs and one for DFUs, were comparable to each other [16,17,50]. The BLCC DFU RCT showed a median time and frequency to healing observed of 65 days and 56% (week 12) [17,18]. The BLCC VLU RCT showed a median time and frequency of healing of 61 days and 57% (week 24) [18,51]. These BLCC efficacy data for VLU and DFU are reasonably consistent with the results observed in the RWD CEA study of BLCC versus FBCD in PRIs, (Figures 1 & 2). In the RWC CEA study, median time to healing was 103 days for BLCC and percentages of healing were 64% (week 24) and 73% (week 36; Figures 1 & 2). Notably, time to healing was accelerated in the two RCTs and the RWD CEA studies when compared with control-treated wounds. The percent improvement in time to healing was 66% (VLUs), 28% (DFUs) and 36% (PRIs), respectively. The finding that healing of PRIs treated with BLCC was accelerated by 36% when compared with FBCD (i.e., for BLCC, 103 days to heal; for FBCD, 162 days: 36% decreased time to healing in

favor of BLCC; $p < 0.05$) was particularly noteworthy given that the BLCC-treated group in the PRI study was compared with an active control. For the VLU and DFU trials, per US FDA guidance, BLCC was compared with standard of care (SOC; e.g., water balance dressings, compression for VLU; water balance dressings, off-loading and debridement for DFU).

A significant advantage of using RWD for analysis is that clinical effectiveness results are more likely to be generalizable to broad, diverse patient populations reflective of clinicians' practices when compared with RCT efficacy results. Issues of data variability that may arise in observational, cohort wound studies or even in many RCTs, may be significantly reduced by employing RWD CEA study designs where large numbers of patients and wounds are analyzed. High variability in healing values have been reported in the literature for partial area reductions of PRIs, times to healing and percentages of healed PRIs. Both times to healing and percentages of healing have demonstrated broad ranges, between approximately 100–180 days and 20–40% for times and percentages, respectively [9,52,53]. The most important consequence of studies with disparate results is that clinicians and policy makers have had difficulties generalizing study results to everyday, clinical practice. Compared with RCTs for wound products, in the current RWD CEA PRI study we included a large number of wound care centers ($n = 315$), patients ($n = 1,182$), PRIs ($n = 1,352$) and longer durations of patient follow-ups (36 weeks). Only one standardized eCRF (WoundExpert) was used across all wound care facilities and uniform coding/programming was applied to all raw patient data. Statistical analyses were performed by one principal statistician (Virtu Stat Ltd; PA, USA) on the intention-to-treat (ITT) study population. Principled statistics were employed for all analyses, Kaplan-Meier (K-M) survival, life tables methods were used to show unadjusted (e.g., no statistical adjustments for patient, wound and treatment characteristics) results and Cox proportional hazards regression (Cox) analyses demonstrated adjusted results that acted as sensitivity analyses. Primary, secondary and exploratory analyses were done using all patient data. In consideration of real-world study design, adherence to our study plan and results that summarized patient demographics, wound characteristics and treatment characteristics, we take the position that our sample of PRI patients treated with BLCC or FBCD is reasonably representative of the general PRI patient population treated with other wound care products in a variety of practice settings (i.e., outpatient and in-patient wound care environments). The external validity of our RWD CEA study results compares favorably to small, under-powered RCT results and certainly observational case series. Under the conditions of study, we regard the current RWD PRI findings as uniquely generalizable. Interpretation of the results may be applied more broadly and to larger PRI populations beyond the study population. Given the context that PRIs pose significant management challenges where few effective therapies exist, alternative treatments to routine dressings and off-loading are needed.

PRIs are characterized by unique sequelae and PRI patients demonstrate high rates of co-morbidities and high rates of mortality that point to questions that may be addressed by RWD studies. Patients with PRIs generally heal poorly and are at risk for infection, cellulitis, osteomyelitis, sepsis and death. Development of PRIs are associated with poor overall prognosis for patients [12]. An increased risk of death has been associated with the presence of PRIs, however, the PRI may be a sign of the severity of underlying comorbidities instead of an independent predictor of mortality [53]. With real-world datasets of hundreds of wound care facilities, and thousands of patients, Cox modeling methods requiring extremely large databases of patient and wound covariates could be applied to identify statistically significant risk factors (positive or negative) for clinical outcomes. RWD CEAs are well suited to identify the complex relationships between comorbidities, disease sequelae, PRI pathophysiology, wound healing outcomes and patient reported/patient centric outcomes (PROs/PCOs) [29].

Of note, like all retrospective analyses, we recognize that this RWD study introduces 'noise' into the clinical study environment that is diminished in prospective RCTs. A limitation of this study is that electronic medical record databases often are not developed for effectiveness research purposes [54]. Differences between individual treatment centers exist. Even with the WoundExpert EMR data collection system, uniform data reporting is not actively monitored (e.g., RCT) [35]. The possibility of patient selection bias did exist. That randomization was not done in this RWD CEA study, selection of patients for BLCC or FBCD was made on site by the treating clinician at the wound care facility. However, using ITT principles lead to the largest number of centers ($m = 315$), patients ($n = 1182$) and wounds ($n = 1352$) available in our database to contribute to the results. Given that 1352 PRIs were assessed over 36 weeks, it was unlikely that clinician bias or any imbalance between groups in potential risk factors for healing 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 [55].

However, reliance on eCRFs to capture RWD does offer advantages in collecting patient data such as enabling longitudinal analyses of log-fold greater numbers of patients over significantly longer periods of time than in RCTs.

Conclusion

RWD CEA analyses as secondary databases are expected to become increasingly important as tools to inform clinicians, regulatory bodies, third party payers and other policy makers on the comparative benefits of wound treatments [46,47,56].

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

Summary points

- This is the first comparative effectiveness assessment (CEA) 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 pressure injuries (PRIs) in a real-world setting.
- Treatment with BLCC significantly improves the incidence and speed of PRI wound closure compared with FBCD.
- The effectiveness of BLCC in these analyses was supportive of the efficacy results from the pivotal BLCC trials in venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs).
- BLCC showed a 66% greater probability of wound closure when compared with FBCD.
- BLCC demonstrated accelerated time to wound closure of 36%, an 59-day 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 PRIs treated with BLCC compared with FBCD showed clinical effectiveness benefits.
- Limitations include: real-world data studies introduce 'noise' into the clinical study environment that is diminished in prospective RCTs, EMRs often are not developed for effectiveness research, and differences between individual treatment centers exist.
- Electronic healthcare databases when used in real-world data, comparative effectiveness research studies offer significant advantages of robust sources of data, large study populations, and extended observation periods.

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Competing interests disclosure

ML Sabolinski serves as Chief Medical Officer and Managing Member of Sabolinski LLC, Franklin, MA, USA. ML Sabolinski serves as a paid consultant for Organogenesis. T Archambault (Virtu Stat Ltd, PA, USA) served as principal statistician for this study. The authors have no other competing interests or relevant affiliations with any organization/entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

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

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