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Clinical Efficacy of Ovine Forestomach Matrix and Collagen/Oxidised Regenerated Cellulose for the Treatment of Venous Leg Ulcers: A Retrospective Comparative Real-World Evidence Study

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ABSTRACT

Venous leg ulcers (VLUs) are traditionally managed with standard-of-care dressings, compression and appropriate adjunctive venous interventions for pathologic venous reflux. Due to pathophysiological complexity and underlying patient comorbidities, conducting randomised controlled trials to evaluate the comparative efficacy of advanced treatment modalities is difficult, as many patients would likely be excluded. This retrospective, pragmatic, real-world evidence (RWE) study compared the healing outcomes of VLUs treated with either ovine forestomach matrix (OFM) ($n = 312$) or collagen/oxidised regenerated cellulose (ORC) ($n = 239$) in outpatient wound care centres. Unlike restrictive randomised controlled trials, minimal inclusion and exclusion criteria were applied to create two treatment cohorts that reflected the general VLU population. The incidence (%) of closure was greater in OFM-treated VLUs at 12, 24 and 36 weeks, and this difference was significant at 24 and 36 weeks compared to collagen/ORC. Median time to wound closure was significantly faster ($p = 0.045$) in the OFM cohort (11.1 ± 0.6 weeks) compared to the collagen/ORC group (12.3 ± 1.0 weeks). Cox proportional hazards analysis demonstrated that OFM-treated VLUs had a significantly greater probability of healing (up to ~40%). This RWE comparative efficacy study further substantiates the clinical benefit of OFM in the treatment of chronic wounds, such as VLU, in a real-world patient cohort.

1 | Introduction

Venous leg ulcers (VLUs) present a common challenge, often being resistant to complete and durable closure in response to standard of care (SoC) wound management. This is often a manifestation of underlying systemic and vascular pathology [1]. Also known as venous stasis ulcers, VLUs develop secondary to vascular reflux, occlusion, or a combination of both, and can occur concomitantly with arterial disease, especially given the increased incidence of diabetes and the ageing population. While VLUs have an overall population-based incidence of 0.17%–1.3%, the wound care management of VLUs

Summary

- Venous leg ulcers (VLUs) are challenging to treat and place a significant burden on patients and global healthcare systems.
- Ovine forestomach matrix (OFM) is an extracellular matrix bioscaffold available for the outpatient treatment of VLUs.
- The aim of the study was to use real-world evidence to compare the healing outcomes for VLU treated with OFM to asynthetic reconstituted collagen dressing, collagen/oxidized regenerated cellulose (collagen/ORC).
- The comparative analysis demonstrated that VLU treated with OFM healed significantly faster than when treated with collagen/ORC, and the probability of VLU closure was significantly increased when VLU were treated with OFM.

requires a disproportionate total treatment cost as the defects are chronic and progressive in nature [2]. The cost associated with VLU management is expected to continue to rise in an ageing population combined with an increasing incidence of vascular disease [3]. A recent study estimated the annual global cost of VLU management exceeds $10 billion [4], with other studies reporting figures as high as ~$15 billion in the United States alone [5]. In addition to the financial burden to the healthcare system and individuals, VLUs can have a significant psychosocial toll on patients as the wounds can result in impairment of mobility and decreased quality of life, as well as chronic pain syndromes [6].

Numerous studies have aimed to elucidate the most effective management algorithm to optimise clinical outcomes while controlling costs. Some of these traditional treatment modalities include prescription compression and multilayer compression [7], wound cleansing techniques [8], hydrogels [9], therapeutic ultrasound [10], surgical debridement [11] and venotonics such as micronized purified flavonoid fraction, diosmin hesperidin [12, 13]. It is generally regarded that effective compression, appropriate venous ablation, along with wound bed preparation and debridement, is best practice for the management of these challenging wounds. To facilitate healing of VLUs, dermal substitutes have seen increasingly widespread adoption in outpatient wound care centres (WCCs). Dermal substitutes, referred to as CAMPs (cellular, acellular, and matrix-like products) [14], cellular or tissue-based products (CTP) or 'skin substitutes' are commercially available in many forms, both biologic and synthetic in design. In addition to the variety of technologies that underpin these devices, there is also complexity in payment associated with these products. For example, in the US outpatient WCC setting, CAMPs may be reimbursed as an 'A-code collagen dressing', or as a CTP. Conventionally, dermal substitutes were used as "final step" or "last resort" solution but are increasingly being used as an adjunct to standard of care dressings and are becoming more cost effective. More recently, clinical studies have demonstrated the efficacy of dermal substitutes and wound matrices in addition to SoC compression and wound bed preparation to augment healing of VLUs [15–19]. While these clinical studies are thoughtful, well-designed, and advance the understanding of the role of dermal substitutes in VLU management, the tightly controlled methodology of many studies fail to capture 'real-world evidence' (RWE). Due to rigorous inclusion and exclusion criteria, the most difficult-to-treat patients who are routinely encountered in the outpatient WCC are not represented in these studies [20].

Collagen/oxidised regenerated cellulose (collagen/ORC, Promogran, 3M, USA) has been widely reported in the literature for the treatment of various chronic wounds, including VLUs [21, 22]. When applied to the wound bed, the dressing delivers Type I and Type III collagen as a gelatinous matrix that aids cellular proliferation and wound healing, as well as modulates tissue proteases [23]. More recent technological advances have taken a subtractive approach to the manufacture of dermal substitutes that begin with a source tissue (xenograft or allograft), removing cellular components to leave an intact decellularized extracellular matrix (dECM) bioscaffold. Relative to the synthetic collagen-based dressings, like collagen/ORC, these types of products include numerous biologic proteins that naturally exist in soft tissue and are known to accelerate healing [24]. However, in practice, these non-synthetic, biologic matrices are cost prohibitive for widespread use in outpatient WCCs and are generally reimbursed in US WCCs as CTP products [25]. Only a fraction of wounds that present in US WCCs qualify for reimbursement coverage for a CTP, and as such, this limits their widespread use along with SoC wound management.

Ovine forestomach matrix (OFM) (Endoform Natural, Aroa Biosurgery Limited, New Zealand) was the first biologic dECM product that was made available as an A-code collagen dressing to enable widespread adoption and utilisation in US outpatient WCCs. While the technology contained in OFM is equivalent to many CTP products, the cost of OFM ($USD 8–12/unit) means it can be readily accessed and employed for routine use in WCCs. OFM is a mammalian-derived dECM isolated from ovine forestomach tissue that contains endogenous ECM-derived biomolecules, including structural proteins (e.g., collagens and elastin) and signalling molecules (e.g., PDGF, VEGF, BMPs and KGF) inherent to the tissue regeneration and wound healing cascade [26–28]. In part, the well-documented success of OFM is due to the retained ECM micro-architecture [29, 30], in combination with bioactive proteins and anti-inflammatory properties [31, 32]. In the outpatient WCC setting, OFM has found widespread adoption with over 6 million applications globally, mainly to those patients who may not otherwise have access to dECM-based technologies [33–37]. In a 2022 study, Bosque et al. [38] analysed RWE outcomes in diabetic foot ulcers (DFUs) treated with either OFM or collagen/ORC in the outpatient WCC setting. In this study, the median time to wound closure was significantly faster with OFM treatment (14.6 ± 0.5 weeks) compared to treatment with collagen/ORC (16.4 ± 0.7 weeks) ($p = 0.0015$). A subgroup analysis that was selected for difficult-to-heal wounds demonstrated OFM achieved closure up to ~5.3 weeks faster vs. treatment with collagen/ORC.

This prior comparative RWE study in the treatment of DFUs formed the basis for the current study. In the current study, we sought to compare the relative efficacy of OFM and collagen/ORC in the treatment of VLUs using RWE. The goal of the current study was to determine if OFM, a dECM-based device, demonstrated superior healing outcomes compared to a traditional synthetic reconstituted collagen product (collagen/ORC) in the outpatient WCC management of VLUs.

2 | Materials and Methods

The study protocol was reviewed, and ethical oversight was waived by an independent Institutional Review Board (IRB) (Advarra Institutional Review Board Services, MD, USA). Waiver was granted as the study was retrospective and utilised existing de-identified data. This study was conducted in accordance with the Declaration of Helsinki.

Analysed data were extracted from the Net Health Wound Care (Net Health, Pittsburgh, PA) database and represented records from 1 January 2014 to 30 June 2020 across 449 outpatient WCCs in the United States. A total of 31 883 wounds in 25 762 patients across 223 facilities were pooled for initial analysis (Figure 1). The initial pooled data set was then filtered to identify VLUs that met the inclusion and exclusion criteria (Figure 1). Notably, patients still under active management or palliative care were specifically excluded, as were wounds $\geq 150\,cm^2$, or that lacked baseline wound characteristics or follow-up. VLUs were identified from the diagnosis, and only VLUs with documented compression therapy were included. VLUs treated with either OFM or collagen/ORC were limited to only those wounds that received ≥ 2 applications of either product, but not both products. Patients who had or were receiving angioedema-inducing medications such as calcium channel blockers were identified from the records using the key word searches 'amlodipine', 'nifedipine', 'Norvasc' and 'verapamil'. Patient demographics were retrieved from the records. The payor (i.e., insurance) responsible for the treatment of the VLU was retrieved from the records according to Supporting Information 1.

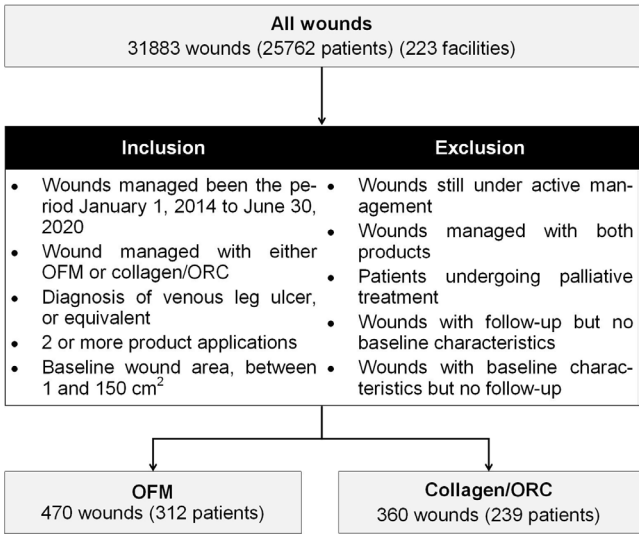

FIGURE 1 | Data filtering of wound records per the inclusion and exclusion criteria to yield two cohorts of VLUs treated with either OFM ($n = 470$) or collagen/ORC ($n = 360$).

From the treatment records, each VLU was additionally assessed for the type of compression used, the type of debridement, and any adjunctive CTP application. Compression types were categorised based on the compression device used, as documented in the record. Key word searches of the records were conducted according to Supporting Information 2, then the compression device categorised as 'Type A', 'Type B' or 'Type A/B', where both categories of device had been used during treatment. In this way, compression therapy employed could be categorised according to how aggressive the documented approach was. Similarly, records were searched to categorise the debridement method used during the treatment of each VLU. Debridement methods were categorised as either 'surgical' or 'other', where 'other' included 'chemical/enzymatic', 'mechanical', 'selective' or 'ultrasonic contact'. Records were interrogated to identify VLUs that had received CTPs during the course of treatment, and the number of CTPs applied to each VLU. All patients were assumed to have appropriate workup and management of their underlying comorbidities. Patients received dressing changes at each weekly WCC visit and secondary dressing changes as needed in between WCC visits.

All statistical analysis was performed using SPSS v28, and a two-tailed p value ≤ 0.05 was taken to indicate statistical significance. Demographic data for the two cohorts were summarised using descriptive statistics (e.g., mean, standard deviation [SD], median frequencies and percentages), and compared using independent t-tests and chi-square tests, as appropriate. Wound age was reported based on the first incidence of the wound, and wound area (cm^2) was calculated from the reported wound length (cm) and wound width (cm) at the first recorded visit. Baseline wound characteristics were summarised using mean (SD) and median (IQR) and compared using independent t-tests or the non-parametric Mann–Whitney U-test, as appropriate.

The primary outcome was time to closure, and secondary outcomes included the incidence of closure at 12, 24 and 36 weeks. Time to closure included all VLUs that received two or more WCC applications of either product, with a further subgroup analysis for wounds receiving ≥ 4, ≥ 8 and ≥ 12 applications of either product in the WCC. Time to closure was defined as the elapsed time between the first application of either product and subsequent wound closure, where closure was defined as a wound area of $< 0.25\,cm^2$ or where wounds had been recorded in the records as 'closed', 'healed' or 'resolved'. The median time to wound closure and the percentage of wounds closed at 12, 24 and 36 weeks were estimated using the Kaplan–Meier (KM) method. Time to wound closure between the treatment groups was compared using Cox proportional hazard (CPH) regression analysis, with the comparison summarised as the hazard's ratio (HR) with 95% confidence interval (CI). Adjusted analyses of the time to wound closure were undertaken using CPH regression to compare treatment groups, incorporating age, gender, initial wound size, and duration of wound as covariates in the model. Adjusted HRs for the treatment group comparison were estimated from these models for the total sample. The incidence (%) of VLUs closure was statistically compared between treatment groups using Greenwood's standard error estimates.

TABLE 1 | Patient demographics.

Characteristic	OFM	Collagen/ORC	*p*
Patients, *n*	312	239	
Gender, specified, *n* (%)	311 (99.6%)	239 (100%)	
Male, *n* (%)	177 (56.9%)	109 (45.6%)	0.009**
Female, *n* (%)	134 (43.1%)	130 (54.4%)	
Age, specified, *n* (%)	268 (99.6%)	203 (100%)	
Mean ± SD (years) [median]	67.4 ± 13.1 [69.0]	65.8 ± 14.5 [66.0]	0.178
Ethnicity, specified, *n* (%)	261 (83.7%)	189 (79.1%)	
White, *n* (%)	152 (58.2%)	113 (59.8%)	0.015*
Hispanic or Latino, *n* (%)	68 (26.1%)	28 (14.8%)	
Black or African American, *n* (%)	30 (11.5%)	32 (16.9%)	
Other, *n* (%)	9 (3.4%)	15 (7.9%)	
American Indian or Alaskan Native, *n* (%)	1 (0.4%)	0 (0.0%)	
Asian, *n* (%)	1 (0.4%)	0 (0.0%)	
Native Hawaiian or Pacific Islander, *n* (%)	0 (0.0%)	1 (0.5%)	
BMI, mean ± SD	35.7 ± 11.0	35.2 ± 11.0	0.577
Diabetes, *n* (%)	19 (6.2%)	17 (7.8%)	0.478
Lymphedema, *n* (%)	3 (1.0%)	1 (0.4%)	0.637
DVT, *n* (%)	10 (3.2%)	5 (2.1%)	0.426
Calcium channel blockers, *n* (%)	11 (3.5%)	9 (3.8%)	0.881
Smoking status, specified, *n* (%)	262 (83.9%)	165 (69.0%)	
Current	128 (48.9%)	82 (49.7%)	0.840
Never	42 (16.0%)	23 (13.9%)	
Former	92 (35.1%)	60 (36.4%)	

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; n, sample size; SD, standard deviation.
*$p < 0.05$.
**$p < 0.01$.

3 | Results

3.1 | Patient Demographics

Implementation of the study design and adherence to the relatively minimal inclusion and exclusion criteria resulted in a total of 551 patients treated with OFM ($n = 312$) or collagen/ORC ($n = 239$) (Table 1). There was a statistically significant difference in gender between the cohorts, where a higher proportion of males were treated with OFM vs. collagen/ORC. Further, there were statistically significant differences in the ethnicity mix between the two cohorts. This was mainly driven by the higher proportion of patients in the OFM treatment group who identified as Hispanic or Latino (26.1% vs. 14.8%). There was no statistically significant difference in patient age between the cohorts (67.4 ± 13.1 [69.0] years vs. 67.4 ± 13.1 [69.0], in the OFM cohort and collagen/ORC cohort, respectively). There were no significant differences in the BMI, proportion of patients with a diagnosis of diabetes, lymphedema or deep vein thrombosis (DVT). Patients included in the study were smokers (~50%), and there were no significant differences in the smoking status between the two cohorts. An analysis was additionally undertaken to understand the mix of payors between the two cohorts. As expected, in both groups, Medicare coverage represented ~30%–40% of the VLUs (Supporting Information 1).

3.2 | Baseline Wound Characteristics

The 551 patients included in the study represented 830 total VLUs, of which 470 were treated with OFM and 360 were treated with collagen/ORC (Table 2). This represented all patients who had received two or more (≥ 2) product applications in the outpatient WCC and met the CEAP classification C-6, being active VLUs [39]. The median surface area of the VLUs was not statistically different between the two groups, with a median wound surface area of 1.1 (IQR: 0.5, 4.4) cm^2 and 1.1 (IQR: 0.4, 3.1) cm^2 in the OFM and collagen/ORC groups, respectively. Median wound age was also not significantly different between groups, with a median wound age of 3.1 (IQR: 1.0, 9.9) weeks in the OFM

TABLE 2 | Baseline VLU characteristics.

Characteristic	OFM	Collagen/ORC	*p*
All VLU ≥ 2 WCC product applications			
Number of VLU, *n*	470	360	
VLU area, median [IQR] (cm^2)	1.1 [0.5, 4.4]	1.1 [0.4, 3.1]	0.564
VLU age, median [IQR] (weeks)	3.1 [1.0, 9.9]	3.8 [0.6, 11.4]	0.952
VLU per patient, median [IQR]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	0.504
Number of VLU by WCC product applications			
All VLU (≥ 2 WCC product applications)	470	360	
VLU with ≥ 4 WCC product applications	287	191	
VLU with ≥ 8 WCC product applications	153	93	
VLU with ≥ 12 WCC product applications	95	53	

Abbreviations: IQR, interquartile range; n, sample size; WCC, out-patient wound care centre.

TABLE 3 | Wound management.

	OFM	Collagen/ORC	*p*
Compression type, specified, *n* (%)[a]	469 (99.8%)	360 (100%)	
Type A, *n* (%)	0 (0.0%)	4 (1.1%)	0.032*
Type B, *n* (%)	377 (80.4%)	273 (75.8%)	
Type A/B, *n* (%)	92 (19.6%)	83 (23.1%)	
Debridement type, specified, *n* (%)	384 (81.7%)	244 (67.8%)	
Surgical, *n* (%)	229 (48.7%)	158 (43.9%)	0.199
Other,[b] *n* (%)	155 (33.0%)	86 (23.9%)	
CTP applications			
VLU with CTP application	72 (15.3%)	31 (8.6%)	0.004**
CTP applications, median [IQR]	3.0 [2.0, 6.0]	3.0 [2.0, 4.0]	0.248

Abbreviations: IQR, interquartile range; n, sample size.
[a]One VLU in the OFM cohort was recorded only as 'compression'.
[b]Where 'other' included; 'chemical/enzymatic', 'mechanical', 'selective', or 'ultrasonic contact'.
*$p < 0.05$.
**$p < 0.01$.

group and 3.8 (IQR: 0.6, 11.4) weeks in the collagen/ORC group. Similarly, there was no difference in the number of VLUs per patient between the two groups, with medians of 1.0 (IQR: 1.0, 2.0) for both cohorts. While all VLUs included in the study represented those that had received 2 or more product applications, additional subgroup analysis was conducted on VLUs that had received 4 or more (≥ 4), 8 or more (≥ 8) and 12 or more (≥ 12) product applications in the WCC. As expected, the more challenging VLUs that required more visits to the WCC for product applications represented a smaller proportion of the overall VLUs included in the study. For example, the total number of VLUs that required 12 or more product applications was 148 across the two cohorts (Table 5).

3.3 | Additional Wound Management

Compression type, debridement type and the application of any CTPs during the course of treatment were retrieved from the records. Compression type, categorised as either 'Type A' or 'Type B', based on the compression method, was compared between the two cohorts (Table 3). There were significant differences in the compression type between the two cohorts, with the OFM treated cohort having a higher proportion of 'Type B' compression, which represented more aggressive compression devices (Supporting Information 2). VLUs in the collagen/ORC cohort had a smaller proportion of 'Type B' compression and a higher proportion of mixed compression methods (Type A/B) relative to the OFM cohort. There were no differences in the debridement methods used between the two cohorts, with ~40%–50% of VLUs in both groups receiving more aggressive surgical debridement. There was a significant number of OFM-treated VLUs that additionally received a CTP product as part of treatment (Table 3); however, for those VLUs that did receive a CTP, the number of CTP applications was equivalent between the two cohorts, with a median of 3.0 product applications.

3.4 | Median Time to Close

Using KM survival analysis (Figure 2A), the median time to wound closure (weeks) was estimated for all wounds (Table 4, Figure 2B). For all wounds, the mean time to closure was significantly shorter in patients who received OFM (11.1 ± 0.6 weeks) compared to collagen/ORC (12.3 ± 1.0 weeks) ($p = 0.045$) (Table 4, Figure 2B). Time to closure was also analysed for VLUs that received ≥ 4, ≥ 8 and ≥ 12 product applications; VLUs that received ≥ 4 or ≥ 8 OFM applications closed significantly faster than collagen/ORC treated VLUs (14.3 ± 1.0 vs. 18.1 ± 1.9 weeks, and 15.6 ± 1.8 vs. 24.0 ± 3.2 weeks) (Table 4, Figure 2B). For VLUs that received ≥ 12 product applications, the time to closure was reduced for the OFM treated cohort

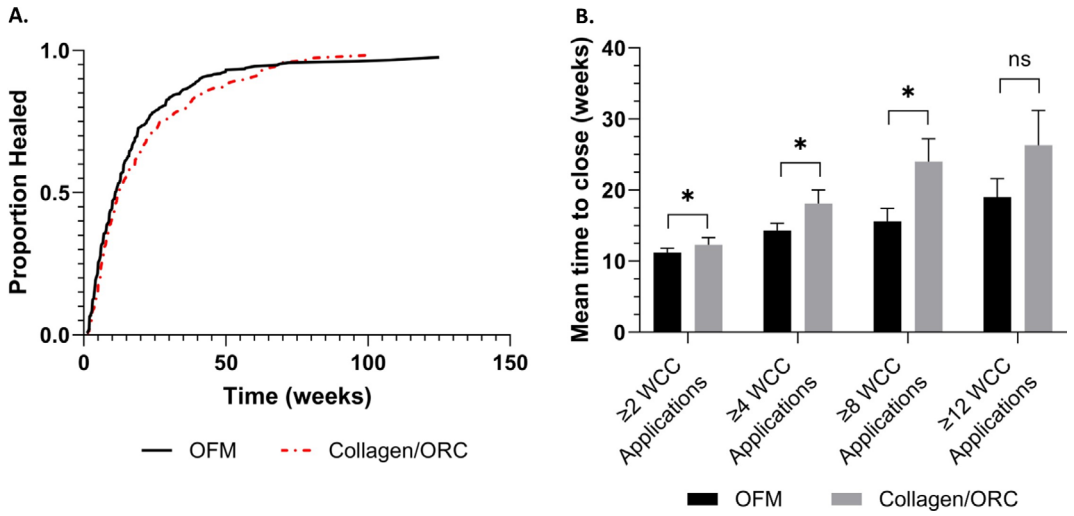

FIGURE 2 | (A) Cumulative proportion healed of OFM and collagen/ORC treated wounds. (B) Median time to wound closure. Error bars represent standard errors. ns, not significant; *$p < 0.05$.

TABLE 4 | Median time to close.

	OFM (weeks ± SE)	Collagen/ORC (weeks ± SE)	Difference (weeks)	*p*
All VLU (≥ 2 WCC product applications)	11.1 ± 0.6	12.3 ± 1.0	1.1 (9.3%)	0.045*
VLU with ≥ 4 WCC product applications	14.3 ± 1.0	18.1 ± 1.9	3.9 (21.3%)	0.029*
VLU with ≥ 8 WCC product applications	15.6 ± 1.8	24.0 ± 3.2	8.4 (35.1%)	0.041*
VLU with ≥ 12 WCC product applications	19.0 ± 2.6	26.3 ± 4.9	7.3 (27.7%)	0.090
VLU receiving a CTP				
Median time to closure	30.7 ± 1.8	38.1 ± 8.6	7.4 (19.5%)	0.403

Note: *$p < 0.05$.
Abbreviations: SE, standard error; WCC, out-patient wound care centre.

(19.0 ± 2.6 vs. 26.3 ± 4.9 weeks), but that difference was not significant ($p = 0.090$).

More VLUs in the OFM cohort had received a CTP as part of their wound management (Table 3). A KM analysis was additionally undertaken to assess any difference in the time to closure for those VLUs that did receive a CTP. Of those VLUs in the OFM and collagen/ORC cohorts that did receive a CTP, the median time to closure was 30.7 ± 1.8 and 38.1 ± 8.6 weeks, respectively, but this difference was not significant ($p = 0.403$) (Table 4).

3.5 | Incidence of Closure

The incidence of healing (%) was increased for OFM-treated VLUs at all time points assessed (12, 24 and 36 weeks), and across all groups analysed (≥ 2, ≥ 4, ≥ 8 and ≥ 12 applications), relative to collagen/ORC treated VLU (Table 5, Figure 3). While the difference was not significant at 12 weeks (52.3% [95% CI: 47.6%, 57.0%] vs. 48.6% [95% CI: 43.3%, 54.0%]), the increase in the incidence of closure of all VLUs (≥ 2 product applications) was significant at 24 and 36 weeks (Table 5, Figure 3A). This trend was also seen in the subgroup analysis (≥ 4, ≥ 8 and ≥ 12 applications), where OFM treatment increased the incidence of closure at 12, 24 and 36 weeks (Table 5).

3.6 | CPH Analysis

To further compare wound closure across the two treatment groups, a CPH regression model was applied as an unadjusted model and adjusted for age, gender, wound size, and wound duration (Table 6, Figure 4A). Without adjustment, OFM demonstrated a ~17% ($p = 0.061$), 26% ($p = 0.031$) and 36% ($p = 0.042$) greater probability of achieving wound closure across the ≥ 2, ≥ 4 and ≥ 8 application groups when compared to collagen/ORC. When adjusted for patient age and gender, and wound size and age, OFM demonstrated a significantly greater probability of achieving wound closure of up to ~40% (Table 6, Figure 4A).

TABLE 5 | Incidence of closure.

	OFM	Collagen/ORC	
	% [95% CI]	% [95% CI]	*p*
All VLU (≥2 WCC product applications)			
Incidence of closure—12 weeks	52.3% [47.6%, 57.0%]	48.6% [43.3%, 54.0%]	0.313
Incidence of closure—24 weeks	77.6% [73.6%, 81.6%]	69.2% [64.0%, 74.4%]	0.012*
Incidence of closure—36 weeks	86.3% [82.9%, 89.7%]	79.7% [75.0%, 84.4%]	0.027*
VLU with ≥4 WCC product applications			
Incidence of closure—12 weeks	41.2% [35.3%, 47.0%]	36.6% [29.6%, 43.7%]	0.331
Incidence of closure—24 weeks	70.1% [64.5%, 75.7%]	57.1% [49.7%, 64.6%]	0.007**
Incidence of closure—36 weeks	82.2% [77.4%, 87.0%]	70.9% [63.7%, 78.1%]	0.011*
VLU with ≥8 WCC product applications			
Incidence of closure—12 weeks	37.2% [29.5%, 45.0%]	31.3% [21.6%, 41.0%]	0.346
Incidence of closure—24 weeks	65.5% [57.7%, 73.3%]	49.6% [39.0%, 60.3%]	0.018*
Incidence of closure—36 weeks	79.8% [73.1%, 86.5%]	66.1% [55.6%, 76.6%]	0.031*
VLU with ≥12 WCC product applications			
Incidence of closure—12 weeks	32.4% [22.9%, 42.0%]	27.3% [15.1%, 39.6%]	0.518
Incidence of closure—24 weeks	60.4% [50.3%, 70.5%]	44.0% [30.1%, 57.9%]	0.061
Incidence of closure—36 weeks	79.0% [70.5%, 87.6%]	60.8% [46.5%, 75.0%]	0.031*

Abbreviations: CI, confidence interval; WCC, out-patient wound care centre.
*$p < 0.05$.
**$p < 0.01$.

The analysis identified significant differences between the cohorts with respect to compression type and CTP applications (Table 3). A further CPH multivariate analysis was undertaken incorporating compression type and skin substitute applications as further covariates. This analysis demonstrated that the treatment effect (OFM vs. collagen/ORC) persisted and was independent of these covariates ($p = 0.002$).

3.7 | Product Applications

When considering all VLU cohorts, the mean number of product applications for the OFM and collagen/ORC cohorts was 8.7 ± 14.5 (median, 5.0) and 7.9 ± 12.5 (median, 4.0), respectively (Table 7, Figure 4B). While this difference was significant for all VLUs in the study population, there was no difference in the number of product applications for the subgroups representing more challenging VLUs, that is, VLUs that received ≥4, ≥8 and ≥12 product applications.

4 | Discussion

Previously, we used an RWE approach to demonstrate significantly improved healing outcomes for DFUs treated with OFM compared to collagen/ORC [38]. The current study is a follow-up analysis using the same wound database to assess the RWE outcomes of the two products when treating VLUs. OFM-treated VLUs healed significantly faster with a mean time to closure of up to ~8.5 weeks, which represents a ~35% reduction in the time to wound closure vs. VLUs treated with collagen/ORC (Table 4). CPH analysis demonstrated that VLUs treated with OFM had a ~40% increase in the probability of healing (Table 6), relative to collagen/ORC treatment. Published reports describing the use of OFM in the treatment of VLU have to date been limited to case series. Bohn and Gass [35] reported a 12-week incidence of closure of 95.7% from a retrospective series of 23 VLUs and estimated from descriptive survival analysis that 50% of wounds closed by 7–8 weeks of treatment. Lullove [40] provided a subgroup analysis from a retrospective analysis of various chronic wounds treated with OFM. The author reported an average time to closure of 10.4 weeks and a 12-week incidence of closure of 60.7% from a series of 28 VLUs. Treatment of VLUs with OFM has also been described in retrospective case reports from other authors [41–43]. The current study represents the largest analysis to date of healing outcomes following the treatment of VLUs with OFM. Data regarding reconstituted collagen/ORC have been widely published for the outpatient management of chronic wounds, including VLUs [21, 44]. Schmutz et al. [45] compared healing outcomes between VLUs treated with either collagen/ORC or an investigational dressing. In the collagen/ORC-treated cohort, only ~13% of VLUs were judged closed at 12 weeks. Vin et al. [46] reported a 49% ($n = 18/37$) incidence of healing at 12 weeks with twice-weekly applications of collagen/ORC.

The two patient cohorts derived in the current study were essentially equivalent with respect to patient demographics and reported comorbidities (e.g., BMI and diabetes) (Table 1). The

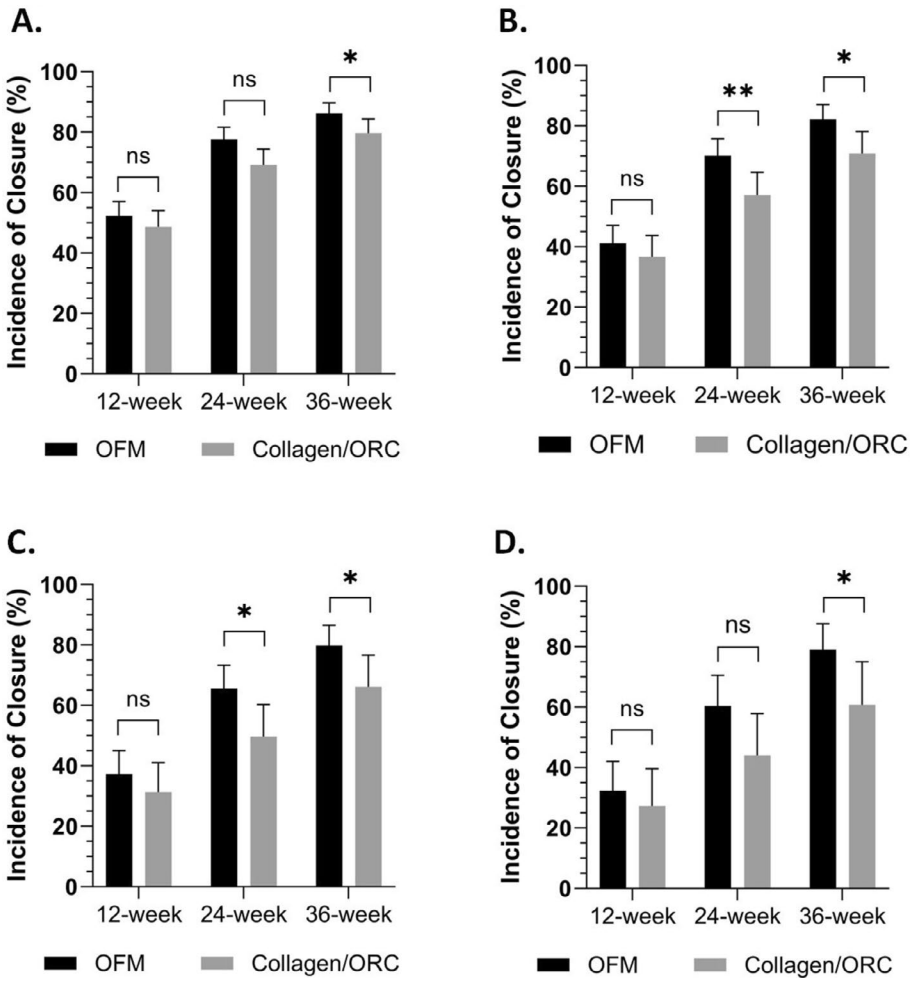

FIGURE 3 | Incidence of closure at 12, 24 and 36 weeks for (A) All VLU (≥2 WCC product applications); (B) VLU with ≥4 WCC product applications; (C) VLU with ≥8 WCC product applications; and (D) VLU with ≥12 WCC product applications. Error bars represent upper and lower 95% confidence intervals. ns, not significant; *$p < 0.05$; **$p < 0.01$.

TABLE 6 | CPH regression analysis.

	Un-adjusted		Adjusted[a]	
	Hazard ratio (95% CI)	***p***	**Hazard ratio (95% CI)**	***p***
All VLU (≥2 WCC product applications)	1.168 (1.004, 1.360)	0.045*	1.160 (0.993, 1.355)	0.061
VLU with ≥4 WCC product applications	1.260 (1.024, 1.550)	0.029*	1.268 (1.022, 1.573)	0.031*
VLU with ≥8 WCC product applications	1.357 (1.013, 1.819)	0.041*	1.375 (1.011, 1.869)	0.042*
VLU with ≥12 WCC product applications	1.402 (0.949, 2.072)	0.090	1.408 (0.918, 2.162)	0.117

Abbreviations: CI, confidence interval; WCC, out-patient wound care centre.
[a]Where regression analysis was adjusted for age, gender, wound size and wound age.
*$p < 0.05$.

ethnicity mix was significantly different, primarily driven by the higher proportion of Latino or Hispanic patients in the OFM cohort. Concomitant lymphatic dysfunction, specifically phlebolymphedema, is commonly associated with VLUs, though incidence rates are not widely reported in the literature and remain largely underdiagnosed [47], in part due to lack of adequate educational efforts [48]. In the current study, when records were interrogated to identify patients diagnosed with lymphedema, only ~1% of patients had a diagnosis of lymphedema recorded (Table 1). This finding may reflect the misdiagnosis or underdiagnosis of lymphatic disease in these patients or incomplete patient records. Diagnosis of lymphatic disease, such as phlebolymphedema, is challenging due to the lack of formal training, non-specific diagnostic testing, and overlapping with other chronic venous diseases that manifest as peripheral oedema [3].

The improved healing outcomes seen in VLUs treated with OFM mirror those reported in the prior RWE analysis focused

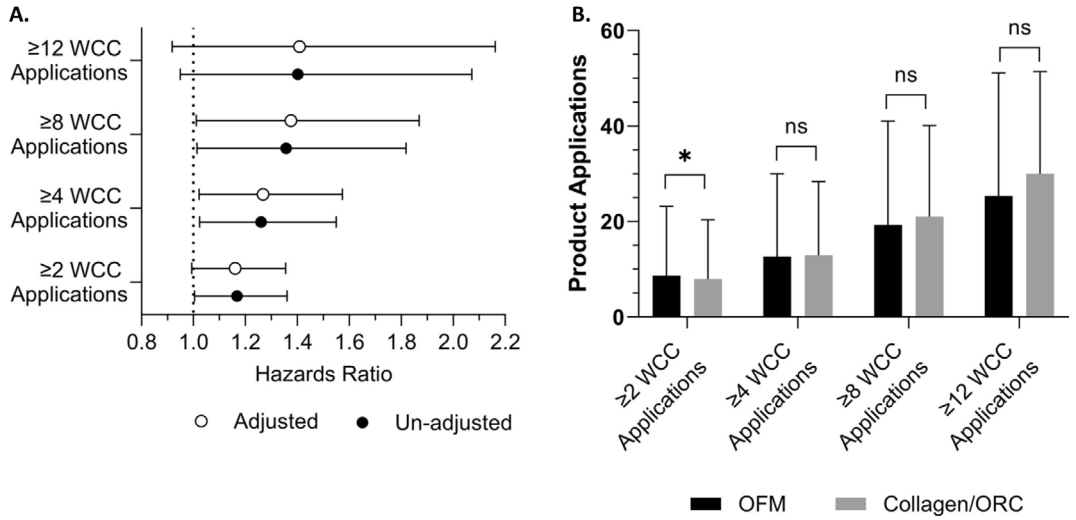

FIGURE 4 | (A) Forest plot of hazards ratios (HRs) from unadjusted and adjusted CPH analysis. Error bars represent the upper and lower 95% CI. Dotted line represents HR = 1.0. (B) Product applications. Error bars represent the standard deviation of the mean; ns, not significant; *$p < 0.05$.

TABLE 7 | Product applications.

	OFM	Collagen/ORC	
	Mean ± SD [median]	**Mean ± SD [median]**	***p***
All VLU (≥2 WCC product applications)	8.7 ± 14.5 [5.0]	7.9 ± 12.5 [4.0]	0.010*
VLU with ≥4 WCC product applications	12.7 ± 17.3 [8.0]	12.9 ± 15.5 [7.0]	0.294
VLU with ≥8 WCC product applications	19.3 ± 21.7 [14.0]	21.0 ± 19.1 [13.0]	0.936
VLU with ≥12 WCC product applications	25.3 ± 25.8 [19.0]	30.0 ± 21.4 [22.0]	0.121

Abbreviations: SD, standard deviation; WCC, out-patient wound care centre.
*$p < 0.05$.

on the treatment of DFUs, where OFM treatment reduced the time to closure by up to ~5.3 weeks [38]. In the current study, we were careful to control for, and assess, ancillary wound management, including compression, debridement, and the use of CTPs that may have an effect on the healing outcomes observed. Effective compression remains the gold standard for the management of VLUs [13]. Given the importance of compression on the fate of VLU healing, only VLUs with documented evidence of compression were included in the current RWE analysis. Further, we interrogated the patient records to understand the type of compression utilised during treatment. The majority of VLUs (~75%–80%) (Table 3) included in the study used compression devices that would be considered to be more aggressive ('Type B', Supporting Information 2) (e.g., multi-layer compression and oedema wear). Differences were significant between the two cohorts, where the OFM treated cohort had a higher proportion of 'Type B' compression, and the collagen/ORC cohort had a higher proportion of mixed compression devices (Type A/B) (Table 3). However, the differences in healing outcomes between the two groups were shown to be driven by the treatment (i.e., OFM vs. collagen/ORC), not the difference in the relative proportions of the compression type. One limitation of real-world data is the reliance on patient records to adequately capture wound interventions. For example, in the current data set, there was a reasonable proportion of VLUs across both cohorts (~20%–30%) where the method of debridement could not be established (Table 3). However, the majority of VLUs received surgical sharp debridement (~40%–50%), and any differences between the cohorts were not significant.

CTPs are commonly used for the treatment of VLUs and have been shown to be clinically effective [49]. While certain CTP products, like OFM comprise dECM, a key difference is that OFM is billed as a surgical A-code 'dressing' and can therefore be prescribed on an outpatient basis in conjunction with SoC wound therapy via Durable Medical Equipment in the United States. Therefore, in clinical practice, this means OFM is accessible as an immediate treatment of VLUs that can be applied by the patient or any provider between WCC visits, regardless of the site of care. This feature has led some authors to propose that OFM should be used as part of wound bed preparation prior to CTP application in order to address tissue chronicity [50]. Applying this to practice, Ferreras et al. [37] demonstrated in a comparative retrospective study that treatment of chronic wounds with OFM prior to CTP application increased the incidence of wound closure by 95.5%, reduced the time to close wounds by 22.6%, and decreased CTP utilisation by 59.7%. In the conduct of the current study, and consistent with RWE, we did not exclude VLUs that additionally received CTP products as part of their treatment. A small subset (~10%–15%) of VLUs in both cohorts received CTP products, with a median of 3.0 applications, in addition to treatment with OFM or collagen/ORC. The OFM cohort had a significantly greater proportion of VLUs that received a CTP vs. the collagen/ORC group (15.3% vs. 8.6%, $p = 0.004$), however, like compression, this difference did

not account for the significantly improved healing in the OFM cohort, as determined through multivariate analysis.

Controlling for the number of product applications can be challenging when aggregating data collected solely from WCCs. In this study, when all wounds were analysed, the mean number of product applications was 8.7 (median, 5) for OFM and 7.9 (median, 4) for collagen/ORC (Table 7). However, this only captures product applications that occurred at the outpatient WCC, and therefore most likely underestimates the true product application rates for collagen/ORC. For example, studies report that collagen/ORC is typically applied every 48–72 h and can be applied more frequently with highly exudative wounds [51, 52]. Conversely, OFM examined in this study (Endoform Natural) is typically applied on a weekly basis [42]. As such, the product applications for collagen/ORC reported herein likely underestimate the actual product applications by up to two to seven times due to product applications occurring every 24–72 h outside of WCC visits.

The pathogenesis of VLUs is multifactorial, involving genetic, environmental, lifestyle and systemic factors. Ultimately, this leads to soft tissue breakdown due to impaired vascular supply [53]. VLUs are known for having a highly pro-inflammatory microenvironment and a dysregulated cytokine profile, and new vessel formation requires the regulation of this inflammatory environment [54]. There are stark compositional differences between OFM and collagen/ORC, and a possible reason for the comparative performance of OFM in the treatment of VLUs is the naturally occurring biomolecules present in OFM that are known to reduce inflammation and promote angiogenesis. For example, OFM contains several modulators of tissue protease (e.g., matrix metalloproteinases and neutrophil elastase) activity, such as TIMP4, serpins and alpha-2-macroglobulin [27], and in vitro testing has demonstrated that OFM is a broad-spectrum inhibitor of proteases associated with wound chronicity [32]. The in vivo models OFM have been shown to be anti-inflammatory and demonstrate constructive remodelling [31, 55, 56]. OFM contains native ECM proteins that are essential for new blood vessel formation, including structural proteins like collagen, basement membrane proteins such as laminin, collagen IV and perlecan, as well as cell regulators like fibroblast growth factor (FGF2), bone morphogenic proteins (BMP), platelet-derived growth factor (PDGF) and connective tissue growth factor (CTGF) [26, 27]. These proteins serve as both foundational building blocks and stimulators for cells involved in the remodelling process, particularly perlecan, a growth factor-binding proteoglycan that plays a critical role in tissue repair and angiogenesis [57] and endothelial glycocalyx, a layer of glycoproteins and proteoglycans lining blood vessels that regulate vascular permeability and signalling pathways [58]. Likely due to these components, OFM exhibits angiogenic bioactivity, with preclinical data showing OFM induced significantly increased vascular cell migration and vascular branching in chick chorioallantoic membrane assays compared to collagen/ORC [59]. Importantly, new vessel formation has been observed in animal models of soft tissue healing [55, 56, 59]. Finally, it has been demonstrated that OFM recruits progenitor (localised mesenchymal stem cells) in vitro [28]. The recruitment of these multipotent cells to the site of damaged tissue is a crucial step for rebuilding new blood vessels, as these pluripotent cells are essential for angiogenesis. This process likely contributes significantly to the angioconductive properties of the material, resulting in enhanced soft tissue repair and regeneration.

5 | Limitations

The current study had all the limitations inherent in RWE analysis. Retrospective analysis of wound records assumes that requisite data is recorded accurately and is complete, and as we have seen previously [38], and in the current study, data are often incomplete or missing in the records and are referred to as 'Missing Completely at Random' (MCAR) data. For example, in the current study, we found a reasonable number of VLUs with no reported information on the method of debridement and could only assume that debridement was used as part of best practice wound care. Similarly, the patient comorbidities (e.g., diabetes, lymphedema and DVT) and medications (calcium channel blockers) may be underestimated due to the reliance on real-world patient records. Endovenous ablation, including radiofrequency ablation, laser ablation and ultrasound guided foam sclerotherapy, among other procedures are commonly used, in conjunction with compression therapy to treat the underlying pathophysiology of VLU [60]. When interrogating the current wound database, information relating to ablation was absent, and as such we have assumed that ablation and branch varicosity management, where required, had been undertaken appropriately as part of best practice VLU management. However, these limitations are offset by the large sample sizes that can be obtained with RWE. In the current study we did not elect to match cohorts, but instead undertook a pragmatic approach to deriving the two equivalent cohorts. This approach was justified as the absence of matched cohorts was addressed by adjusting data as part of the CPH analysis.

6 | Concluding Remarks

OFM and collagen/ORC represent two different technologies for the treatment of chronic wounds. While collagen/ORC comprises reconstituted collagen and chemically modified cellulose, OFM represents a newer class of dECM technology, where the key differentiator is the biological components present in the product. Previous RWE demonstrated significantly improved healing outcomes when DFUs were treated with OFM. In this follow-up study, we have taken a similar RWE approach and shown that OFM treatment significantly reduced the median time to closure, the incidence of closure, and the probability of closure compared to collagen/ORC when used to treat VLUs.

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Ethics Statement

The study protocol was reviewed, and ethical oversight was waived by an independent Institutional Review Board (IRB) (Advarra Institutional Review Board Services, MD, USA). Waiver was granted

as the study was retrospective and utilised existing deidentified data. This study was conducted in accordance with the Declaration of Helsinki.

Conflicts of Interest

Rebecca Aburn, MN, NP is a clinical consultant for Aroa Biosurgery Limited. Abigail E. Chaffin, MD is a clinical consultant for Aroa Biosurgery Limited. Gregory A. Bohn, MD is a clinical consultant for Aroa Biosurgery Limited. Christopher Frampton, PhD received research funding to provide the statistical analysis for this study. Brandon A. Bosque, DPM is an employee of Aroa Biosurgery Limited. Sandi G. Dempsey, PhD is an employee of Aroa Biosurgery Limited. D. Adam Young, PhD is an employee of Aroa Biosurgery Limited. Barnaby C.H. May, PhD is an employee of Aroa Biosurgery Limited.

Data Availability Statement

Data are subject to third-party restrictions. The data that supports the findings of this study are available from Net Health. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available Net Health with the permission of Net Health.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.