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Bridging regenerative biology to wound healing: A prospective, multicenter clinical trial of a dehydrated trilayer amniotic tissue for the treatment of chronic lower extremity diabetic foot ulcers

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Abstract

Aims: Lower extremity chronic diabetic foot ulcers (DFUs) continue to be among the most common cause of long term disability and amputation. Historically, with standard of care (SOC) an average healing rate of only 24.2% is achieved. This prospective, multicenter, single arm trial (NCT07219004) assessed the efficacy of the dehydrated trilayer human amniotic tissue graft, Artacent AC® (Q4190) on nonhealing DFUs.

Methods: A total of 37 participants were recruited in five wound care centers in the United States and from these, 11 patients treated with Artacent AC were analyzed.

Results: Six out of 11 ulcers (55%) completely healed after 12 weeks, with a mean healing duration of 8.8 weeks. The remainder of the wounds experienced sustained improvement with a mean reduction in ulcer area of 68%, 80%, and 84% at weeks 4, 8 and 12, respectively.

Conclusion: These data exceed historic outcomes for patients treated only with SOC and justifies the application of multilayer amniotic tissue grafts, which deliver extracellular matrix architecture, cytokines and growth factor to regulate inflammation, induce angiogenesis, and promote epithelial repair. These findings support the use of Artacent AC as an adjunctive treatment in order to hasten the healing of diabetic foot ulcers. Larger randomized controlled studies are needed to confirm these findings.

Introduction

Diabetic foot ulcers (DFUs) are among the most common and serious complications of poorly controlled diabetes and affect approximately one quarter of patients with this disease.[1] The burden of this disease is significant with more than 500,000 U.S. Medicare beneficiaries experiencing DFUs each year.[2] Therefore, the annual Medicare cost is estimated to range from $6 to $18.7 billion, inclusive of costs related to infection management.[1,3] The presence of a DFU alone increases the risk of serious complications (most notably, lower extremity amputation, and mortality).[2]
Using standard of care (SOC) treatment on chronic DFU wounds, comprising debridement, offloading, infection control, and moist wound bed maintenance, early wound closure is often not achieved, with healing rates of only 24.2% at 12 weeks.[4,5] This failure is in part due to the pathologic microenvironment that is characteristic of chronic wounds: a lack of growth factors and an increase in the activity of destructive proteases.[4]

Timely intervention and expeditious closure of chronic wounds are critical requirements for optimal wound healing.[6,7] Human dried amniotic membrane (HDAM), which is often used in the form of processed dehydrated amnion/chorion allogenic,[3,4] has become a clinically efficacious SOC adjuvant. HDAM provides strong mechanical properties while providing an extracellular matrix (ECM) enriched with cytokines and growth factors such as epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF). The tissue is also fortified with tissue inhibitors of metalloproteinases (TIMPs).[4,8] Importantly, these grafts can be readily manufactured with three layers of the amniotic membrane,[9] allowing for the induction of regenerative processes while inhibiting the negative characteristics of chronic wounds.[4]

Recent preclinical and translational studies have been performed to better describe how trilayer HDAM enhances regenerative potential via structural and biochemical enrichment of the ECM. Histologic and proteomic analyses indicate that the trilayer construct maintains and localizes ECM proteins such as collagen, laminin and fibronectin and contains increased concentrations of cytokines and growth factors responsible for fibroblast, keratinocyte and endothelial cell proliferation. Comprehensive proteomic profiling of more than 200 cytokines and growth factors demonstrated that these biomolecules can be categorized into the wound healing pathways: inflammation modulation and angiogenesis, ECM remodelling, and epithelial regeneration. Quantitative assessment confirmed that the trilayer HDAM exhibits higher concentrations of these bioactive components than do single layer constructs, without increasing manufacturing complexity. Coupled with the histologic data, these findings suggest that the trilayer configured product provides increased mechanical integrity and a more favorable biological environment to support cellular infiltration, tissue granulation, and reepithelialization.[10]

Given these mechanistic insights into HDAM and the successful results reported with single layer amniotic allogenic grafts, the present multicenter, single arm clinical study was designed to assess the efficacy of a trilayer dehydrated amniotic tissue graft (Artacent AC, Q4190, processed by Tides Medical, LLC) as an adjunct to SOC in the management of chronic, non healing DFUs.

Methods

Ethical approval

This study was reviewed and approved by Advarra IRB, under reference number SSU00207781. All participants provided written informed consent prior to enrollment, including consent for publication of anonymized photographs and data.

Study design

This was a prospective, single arm, multicentric, clinical trial (NCT07219004) that was performed across five wound-care clinics in the United States. The aim was to assess the efficacy of HDAM in the treatment of DFUs. Thirty seven adult patients with type 1 or type 2 diabetes and having a qualifying DFU were enrolled. The primary endpoint was the percentage of ulcers that would achieve complete closure within 12 weeks. Time to closure and percentage wound area reduction at week 4, week 8 and week 12 were used as secondary outcomes.

All participants completed a 2-week screening period where they were subjected to SOC treatment to allow time for investigators to verify ulcer stability and determine patient eligibility. Those that satisfied all criteria were then taken through to the 12-week treatment phase where they attended clinic weekly and the wound was assessed and digital imaging performed.

Participants had to be aged ≥18 years, with diabetes, and have a full thickness foot ulcer (0.7-20 cm^2) that had been present between 4 and 52 weeks that was adequately perfused as confirmed by vascular testing. The key exclusion criteria were active infection or cellulitis, osteomyelitis, recent hyperbaric oxygen or advanced tissue product use, immunosuppressive or cytotoxic medications, uncontrolled diabetes (HbA1c ≥12%), or other comorbidities that could

confound study assessments. Patients with bony deformities were excluded from the trial. Pregnant or intending to become pregnant women, subjects with end stage renal disease requiring dialysis, and those participating in another clinical trial within the past 30 days were also excluded.

The 11 patients included in the analysis set received weekly sharp debridement and were treated with Artacent AC and a non-adherent wound veil and covered with a secondary dressing to create a moist wound healing environment. They were then offloaded with the Defender Boot without compression. Patients not compliant with offloading were excluded from the analysis set.

Results

Study population

A total of 37 patients were screened and consented to participate in the study. Of these, four patients were screening failures and did not proceed to treatment. During the treatment phase five patients were lost to follow up, while two withdrew consent prior to completing the study. One patient was withdrawn from the study due to noncompliance with offloading requirements, while one patient was excluded from analysis due to necrotic tissue impinging upon the wound area.

Following data review, 13 patients were identified as having undergone wound bed preparation techniques that, although permitted under the original study protocol, do not align with the current clinical practice guidelines subsequently established by Tides Medical. As the objective of this analysis was to evaluate the efficacy of the trilayer dehydrated amniotic tissue graft (Artacent AC) according to current best practice, these 13 patients were excluded from the efficacy dataset. The remaining 11 patients, whose wound bed preparation was consistent with current best practice, comprised the analysis population.

Wound healing outcomes

Among the 11 patients included in the analysis set, 6 wounds (55%) achieved complete wound closure by week 12 (*Figure 1*). The remaining 5 wounds showed a progressive reduction in wound area over the 12-week period but did not reach complete closure.

Over the 12-week period of the study, all wounds in the analysis set demonstrated progression toward wound healing (*Figure 2*). The mean percent area reduction (PAR) from baseline was 68% at week 4, 80% at week 8, and 84% at week 12.

For the 6 wounds that achieved complete wound healing, the average duration to healing was 8.8 weeks (*Figure 3*). Individual healing times were week 6 (n=1), week 7 (n=1), week 9 (n=1), week 10 (n=2), and week 12 (n=1). These data indicate a steady rate of progressive healing, with most wound healing occurring between weeks 6 and 10.

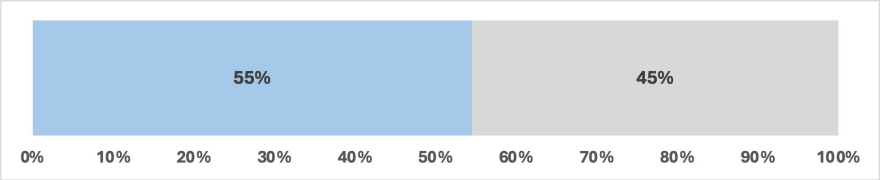

FIGURE 1 | Proportion of wounds achieving complete closure through week 12 following treatment with the trilayer dehydrated amniotic tissue graft.

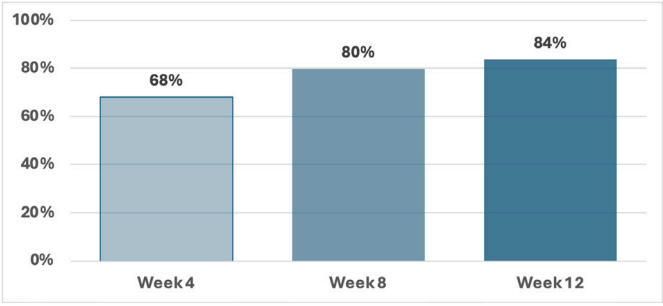

FIGURE 2 | Mean percent area reduction (PAR) over 12 weeks among wounds treated with the tri-layer dehydrated amniotic tissue graft (n=11).

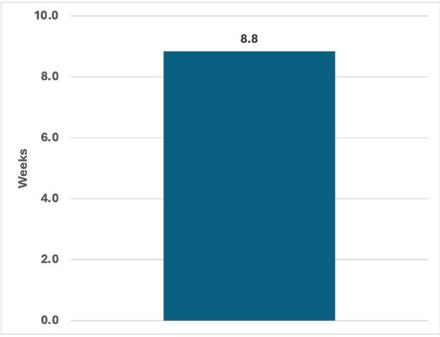

FIGURE 3 | Average duration to complete wound closure for the healed wounds following treatment with the trilayer dehydrated amniotic tissue graft.

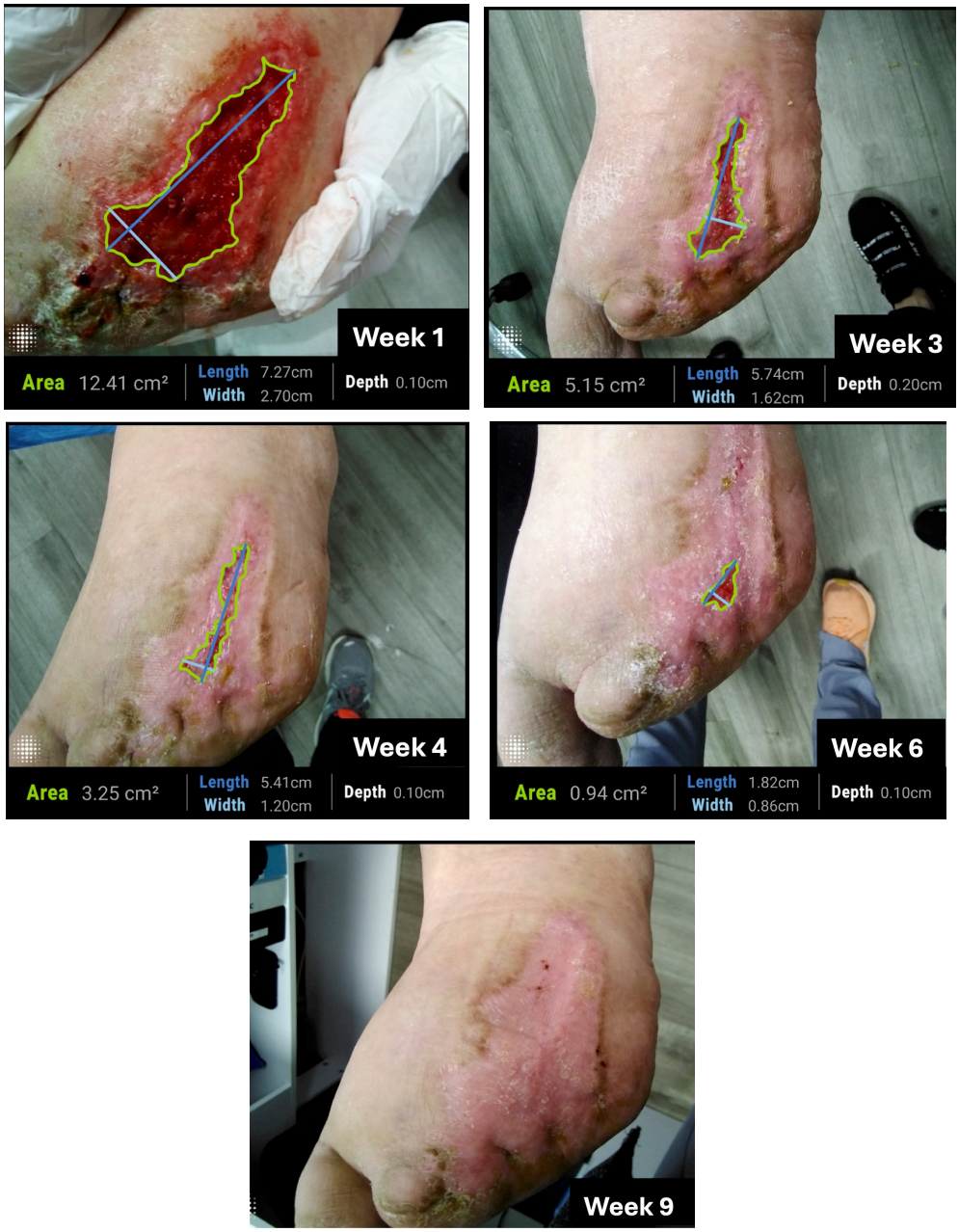

FIGURE 4 | Representative photographic sequence showing progressive wound healing following treatment with the trilayer dehydrated amniotic tissue graft (Artacent AC).

Figure 4 shows images from a single patient illustrate the wound at weeks 1, 3, 4, 6, and 9 of treatment. Progressive granulation, epithelial advancement, and reduction in wound size are evident, with complete wound healing occurring by week 9. The images demonstrate the characteristic pattern of rapid wound bed improvement and sustained epithelialization observed across the patients in the analysis set.

Discussion

The SOC, which typically encompasses debridement, infection and biofilm management, offloading, and a moist wound environment, is not always effective in supporting the closure of chronic DFUs. Historical data show DFUs treated only with SOC have an average healing rate of only 24.2% at 12 weeks.[4,5] It is in this context that the current multicenter, single arm clinical trial was performed to evaluate the effectiveness of Artacent AC, a dehydrated trilayer amniotic tissue graft, as an adjunct to SOC in the treatment of the chronic, non-healing DFUs.

The study protocol at the time of the study allowed the investigator discretion in relation to the degree of wound bed preparation. Since this study was completed, Tides Medical has developed standardized clinical procedures defining the best wound bed preparation methods prior to using the trilayer dehydrated amniotic tissue graft. In this context, 13

patients who consented and passed into the treatment phase of this trial had wound bed preparation inconsistent with these latest best practice standards, whereas 11 patients experienced wound-bed preparation according to the current day best practice guidelines. The results presented here therefore reflect the best practice wound bed preparation guidelines, ensuring the interpretation of the data is in accordance with contemporary wound management for patients receiving the trilayer dehydrated amniotic tissue graft.

The findings suggest that Artacent AC when administered in combination with SOC is effective in supporting increased rates of wound healing, with 6 of the 11 wounds (54.5%) being completely healed by week 12 compared to the historic healing rate of approximately 24.2% with SOC alone.[4,5] All wounds showed wound healing improvement with a mean PAR of 68% at week 4, 80% at week 8 and 84% at week 12. The average duration to complete healing was 8.8 weeks, with closures occurring at weeks 6, 7, 9, 10, and 12.

The results presented here can be attributed to the known biological characteristics of amniotic tissue. Amniotic membrane is full of cytokines and growth factors - including EGF, bFGF, VEGF, and TIMPs.[3] These factors stimulate cellular proliferation, angiogenesis and extracellular matrix remodeling and inhibit the destructive effects of proteases on the wound. The presence of these factors in the trilayer configuration could explain the increased rates of granulation, reepithelialization, and the overall healing reported in this study.

Conclusion

This prospective, multicenter clinical trial demonstrates that the trilayer dehydrated amniotic tissue graft Artacent AC (Q4190), when used in combination with SOC, induces significant wound healing in previously nonhealing, chronic DFUs. Out of the 11 wounds investigated, 55% of those wounds had undergone complete closure by week 12, and all the wounds showed progression towards healing, with the average reduction of wound area of 84% at week 12 and an average of 8.8 weeks to wound closure. These results are significantly higher than the previously reported healing rates of SOC (24% at 12 weeks[4,5]) alone and are in line with the established benefits of amniotic tissue use when it comes to reestablishing growth factor balance and improving epithelialization of the wound bed.

In summary, these results clearly demonstrate that Artacent AC (Q4190) is a useful adjunct to SOC in the management of chronic, nonhealing DFUs. The closure rate at week 12, being well above the established rate for standard of care alone, supports the therapeutic potential of multilayer amniotic membrane products in the healing of otherwise stalled DFUs.

Study limitations and future work

The key limitations of this study are the small sample size, being single arm, and the retrospective exclusion of patients whose wound bed was not prepared according to the current clinical practice guidelines. Since the original protocol gave the discretion to the physician when it comes to wound bed management, these findings ought to be viewed against the backdrop of changing standards of care. These preliminary findings presented here should be confirmed using larger, prospective randomized controlled trials comparing Artacent AC against SOC.

Acknowledgments

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Conflicts of interest

Mark D Cregan serves as an independent consultant to Tides Medical, LLC, and holds no financial interest in the company. Mohammadali Safavieh, H Frank Burrows, and Mora Melican are employees of Tides Medical, LLC, within the Research & Development and Clinical Affairs divisions and are not involved in the company's commercial operations.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the writing process

AI was used solely to check for grammar and help maintain a consistent voice. No new content was generated, and no sentences were rewritten to change their original meaning. The authors carefully reviewed and approved all text in full.

Author contributions

Mark D Cregan prepared the manuscript for submission. Mohammadali Safavieh, H Frank Burrows, and Mora Melican

are non-commercial representatives of the Tides Medical LLC, who reviewed the data and manuscript prior to submission. The authors carefully reviewed and approved all text in full.

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