CHAPTER **30**

TREATMENT OF RECALCITRANT FOOT ULCERS WITH DERMAL SKIN ALLOGRAFT IN A CLINICAL OFFICE SETTING

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INTRODUCTION

An extensive bibliography exists that details the efficacy of allograft skin as an adjuvant to jumpstart wound healing in "stalled" wounds (1-4). While the vast body of clinical reports support the use of cryopreserved allograft skin, a proportion of wound treatment has moved into the outpatient clinical setting, where a cohort of clinicians do not have access to a cryo-rated (-80° C) freezer. A room-temperature storage skin allograft is now available that eliminates this necessity of a cryo freezer. Previous studies have looked at the general efficacy of such skin grafts in wound care, but no case study has been published that charts wound healing in recalcitrant lower extremity wounds treated with dermal skin allografts that are stored at room temperature.

Allograft skin is commonly used on a broad spectrum of complex wounds, including lower extremity and foot ulcers caused by diabetes, trauma, and arterial and venous disease (2, 5-9). Once adhered to the wound, allograft skin not only serves as a prophylactic to bacterial invasion (1, 9) but it also recruits immune cells to the wound site to manage bacteria and other contamination (1, 2, 4, 7, 9-12). Biologic closure for the wound is critical to keep bacterial levels sufficiently low to effect healing, and agents that act as biologic dressings are reported to allow inflammatory tissue to function optimally, allowing phagocytosis to occur efficiently (12). Allograft skin acts as a mechanical barrier to help the wound bed preserve electrolytes, proteins, and heat, all critical elements in the healing process and cellular regeneration (1). These factors make AlloSkin RT human skin allograft (AlloSource) an ideal advanced biologic for use in recalcitrant wounds like diabetic foot ulcers that have stalled in the healing process.

AlloSkin RT is a sterile, cellular, dermal skin allograft that is meshed and processed such that it can be stored at room temperature. Because the patient does not need to be taken to the operating room for application of this allograft, it may prove to be an effective and readily accessible treatment modality in the clinical and private office settings for nonhealing diabetic foot ulcers. Furthermore, unlike bioengineered skin substitutes that require cold storage and timely use, once received from the manufacturer, Alloskin RT can be stored at ambient room temperature for a shelf life of 2 years. Regulated by the Food and Drug Administration Center for Biologics Evaluation and Research as a minimally manipulated, transplantable allograft tissue (21 CFR 1270 and 1271) (13), AlloSkin RT is available on the market for homologous use in treating integumental defects.

We will present data regarding the effectiveness of Alloskin RT gathered from 10 clinic patients with refractory lower extremity ulcers who have failed other treatment modalities.

PATIENT AND METHODS

We began a prospective 10-patient case series on recalcitrant (>4 weeks duration) lower limb diabetic ulcers that had not responded to other treatment modalities. The purpose of this study was to define 1) the effectiveness of AlloSkin RT as an adjunct to wound closure in lower extremity diabetic ulcers, 2) the number of AlloSkin RT grafts that are required to achieve wound closure, and 3) expected healing rate associated with use of AlloSkin RT when treating these ulcers with this dermal skin allograft. Our exclusion criterion was the presence of gross infection at the wound site. The study was conducted according to the principles of Good Clinical Practices proposed by the Office for Human Research Protections (OHRP). The Scripps Institutional Review Board (Scripps Office for the Protection of Research Subjects) provided oversight for the conduct of our case study series. Our patient population consisted of 6 men and 4 women with an age range of 42-62 years. All skin ulcers were classified as either Grade 1 or Grade 2 full-thickness ulcers, using the Wagner Classification of Diabetic Foot Ulcers (14):

Grade 0: No ulcer in a high risk foot.
Grade 1: Superficial ulcer involving the full skin thickness but not underlying tissues.
Grade 2: Deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation.
Grade 3: Deep ulcer with cellulitis or abscess formation, often with osteomyelitis.
Grade 4: Localized gangrene.
Grade 5: Extensive gangrene involving the whole foot.

All patients selected for this study were patients of the Scripps Mercy Hospital Clinic. Once the patient was selected, the ulcer description and measurement were recorded. Each ulcer was debrided to healthy granular tissue. During the same visit, the AlloSkin RT skingraft was placed on the wound and secured in place with either 3-0 nylon or steri-strips. The selection was made based on whether or not the patient was neuropathic. The product comes from the processor as a sterile graft, which is applied to the wound in a sterile fashion with the reticular side of the cadaveric dermis down and in contact with the entire wound topography. The wound was dressed with Adaptic and Silvercel (both from Systagenix), 4x4 gauze, Kerlix (Covidien), and wrapped with an Ace Bandage (3M). The patient was instructed to follow-up on a weekly basis. If the wound was on a weightbearing surface, the patient would require non-weightbearing status with crutches or a roll-a-about.

During each visit, the dressings were removed and the wound was re-measured. The investigator would determine if a new graft was necessary depending on percent incorporation of the skingraft during each visit (approximately >90% incorporation required graft change). Regardless of whether or not the wound required a new skin graft, the wound would be redressed in the same manner as described above.

RESULTS

Each patient required at least 7 clinic visits, but the range was 7-20 clinic visits (Table 1). The wound size for our patient population ranged from 5.52 cm^2 to 90.72 cm^2. All patients in this study achieved wound closure. Each patient required at least 2 skingrafts and some patients required up to 5 total skingrafts to achieve full wound closure.

DISCUSSION

Using a paired sample test, the wound closure rate was significant in our patient population between the first and seventh clinic visit versus measured total wound area, with a *P* value of 0.002. The reason we compared the first to the seventh clinic visit was because all of our patients required at least 7 visits (range 7-20) to achieve wound closure.

No complications occurred with the AlloSkin RT graft in our study population. There was hypergranulation reported in Patient 2, which we believe delayed time to wound closure. We did not apply the skingraft on the hypergranulated tissue until it resolved. On that specific case, we applied nitrostick to the hypergranulated tissue, each week, until a healthy smooth wound base was achieved for placement of a new skingraft.

Based on our study, it appears that AlloSkin RT is a satisfactory graft to have available in clinic. The fact that it does not require freezing makes it easily accessible. Office staff could be trained on application so that patient turn-over could increase. All of our patients were enrolled in the study until complete wound closure was achieved. Some patients did require up to 5 grafts and 20 clinic visits. We did not find in our study that our patients healed their wounds quickly, but they were able to progress to wound healing with the graft despite using other treatment modalities and not being able to see wound closure in the past.

Table 1

TOTAL PATIENT CLINIC VISITS, WOUND SIZE (CM^2) AT INITIATION OF STUDY, AND TOTAL NUMBER OF ALLOSKIN RT GRAFTS USED TO ACHIEVE WOUND CLOSURE

PATIENT	1	2	3	4	5	6	7	8	9	10
visit #	10 visits	20 visits	19 visits	7 visits	10 visits	14 visits	9 visits	13 visits	11 visits	7 visits
wound area day#1 (cm2)	24.5	68.88	43.2	44.5	16.5	90.72	26.0	48.98	22.4	5.52
# of total grafts used	3	4	5	3	3	5	3	4	3	2

CASE STUDY

The patient, a 58-year old man with a history of Type II diabetes with lower extremity neuropathy, presented to the Emergency Department with pain in his right foot for 2 weeks. The patient could not recall any trauma to the right foot; however, he is neuropathic. The patient did report pus and drainage from his right second digit nail bed. Upon examination, the patient presented with a black, necrotic, right second digit and dusky-looking first digit. He also had an abscess on the lateral aspect of his right foot. His pulses were good, but the digits were not viable and were very infected, and showed no improvement on intravenous antibiotics.

The patient underwent a second digit amputation as well as an incision and drainage of the right lateral abscess that same night. The patient was taken back to the operating room 3 days later for a delayed primary closure of the second digit amputation site. He was again taken to the operating room 5 days later for resection of the fifth digit, secondary to osteomyelitis (likely from the abscess site on the lateral aspect of the foot that tracked to the fifth digit). At this time, a Wound Vac (KCI) was placed over the lateral aspect of the right foot.

The patient was discharged from the hospital and readmitted through the emergency department 3 weeks later with cellulitis of the right foot with dusky black/gray appearing first, third and fourth digits. The patient was taken to the operating room for a transmetatarsal amputation (TMA). Two weeks following the TMA, the patient presented to the hospital with wound dehiscence at the TMA site. Two separate incision and drainage procedures were performed in the operating room and during the second procedure, a wound vac was placed over the dehisced TMA site. The patient was sent home on a wound VAC and continued the VAC therapy for 12 weeks post-TMA, with thrice-weekly, in-home VAC changes. We saw no decrease in wound size resulting from the VAC therapy. However, the wound was not infected and it had a good healthy granular base (Figure 1).

We began skin graft treatment in the clinic with AlloSkin RT upon cessation of VAC therapy (Visit 1) and monitored the wound progression over a period of 10 office visits (from 3/22/2010 to 5/24/2011). Throughout the course of treatment, we applied AlloSkin RT grafts a total of 3 times (Visits 1, 3, and 7). The product was applied to the wound in a sterile fashion with the reticular side of the cadaveric dermis down and in contact with the entire wound topography. Securing the graft corners with a single stitch,

Figure 1A. Initial debridement, week 0-1.

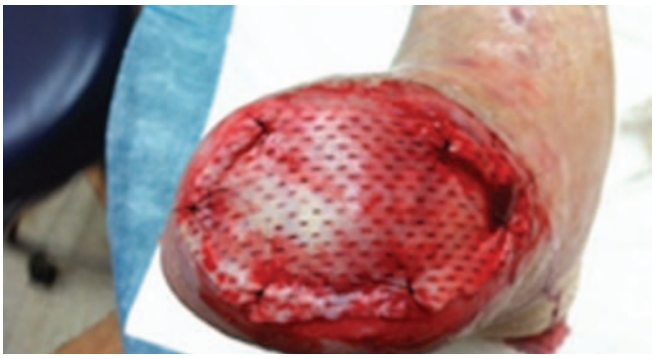

Figure 1B. Graft placement, week 0-1.

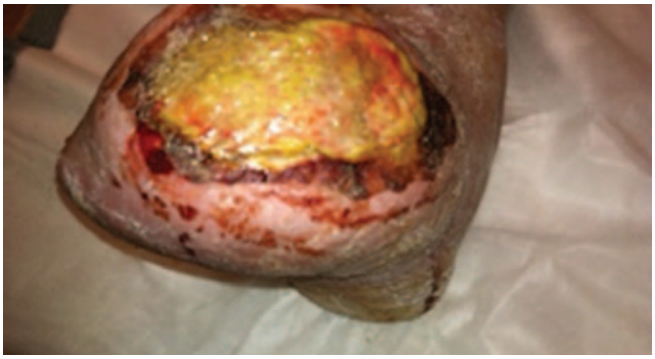

Figure 1C. Week 1 follow up.

we dressed the wound with Adaptic and Silvercel, 4x4 gauze, Kling, Kerlix, and wrapped with an Ace bandage.

Weekly, we removed the dressings, inspected and measured the wound, and debrided the peri-wound area. The graft "took" to the wound and we only reapplied the graft when needed (at about 80-90% incorporation of graft tissue) so as to not disturb the ingrowth of new tissue. We off-loaded the appropriate lower extremity with a postoperative shoe and crutches, and we did not allow the patient to get the foot wet during the entirety of the treatment period (Figures 2-4).

The wound area decreased consistently and was closed ("healed") at the tenth clinic visit, with an average healing rate of 2.45 cm^2 per week (Figure 5). The patient was neuropathic and had no pain before or during treatment, although he does now complain of pain at the TMA site over which the wound has healed. We have seen the patient in the clinic three times since the wound closed. The wound is still closed and the patient is doing very well (Figure 6).

CONCLUSION

AlloSkin RT appears to be an efficacious alternative to cryopreserved skin allografts, and appropriate for use in the out-patient wound clinic when treating diabetic foot ulcers. This diabetic foot ulcer required three 80 cm^2 AlloSkin RT grafts over the 10-week course of treatment. The total cost for these 3 grafts would have been approximately $3,000.

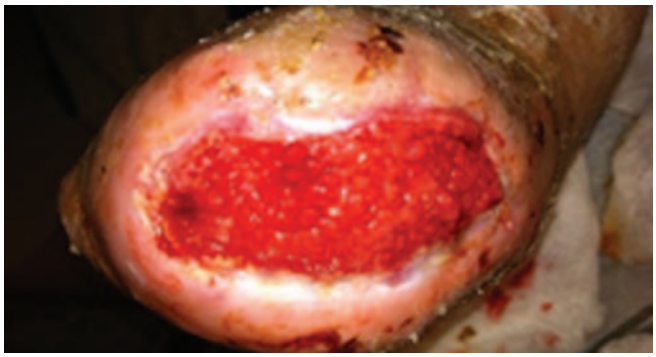

Figure 2A. Progress after 2 weeks of treatment.

Figure 2B. Application of a new graft, and week 3 follow up.

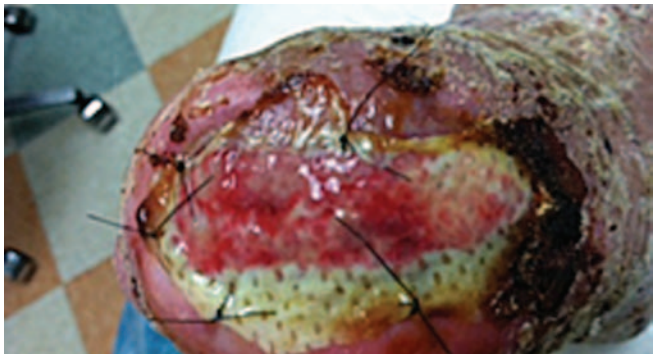

Figure 3A. Appearance, weeks 4-6.

Figure 3B. A new graft was applied at week 6.

Figure 4A. Appearance at weeks 7-8.

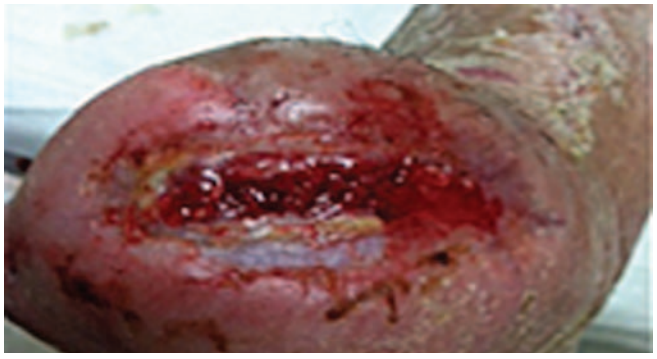

Figure 4B. Appearance at weeks 7-8.

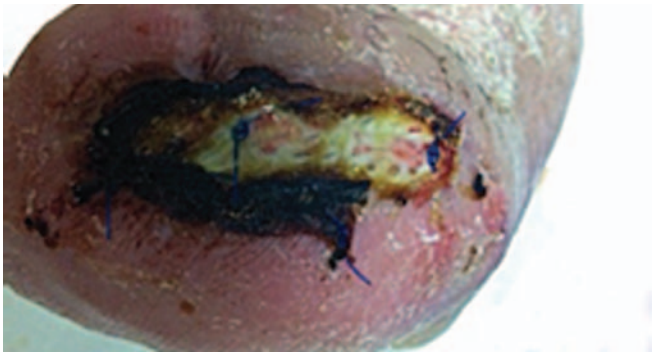

Figure 4C. Appearance at weeks 7-8.

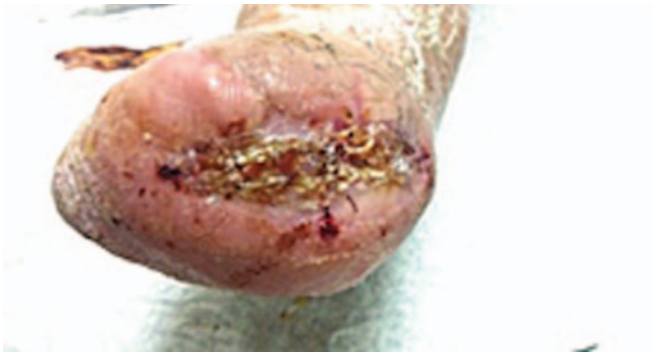

Figure 4D. Appearance at week 8.

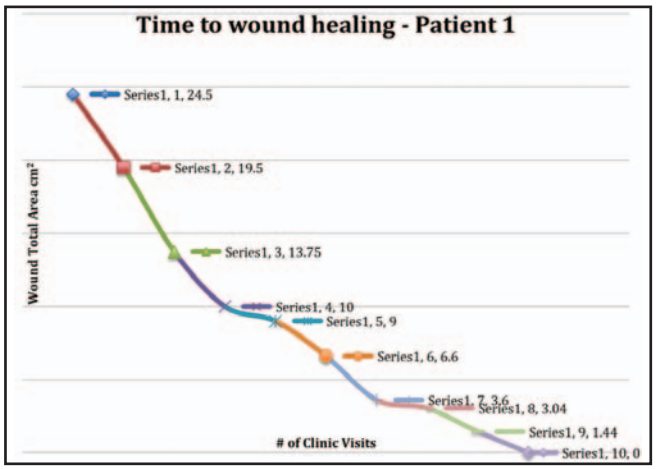

Figure 5. Time to wound healing with skin allograft.

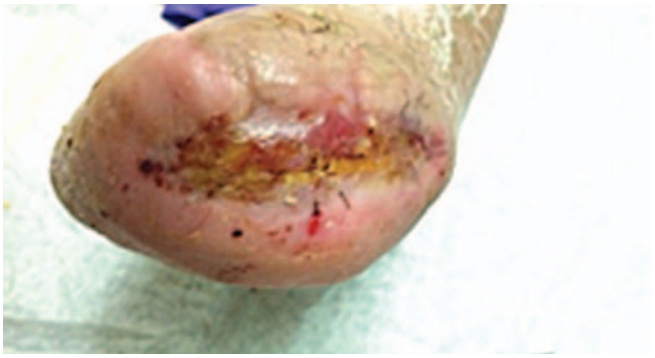

Figure 6A. Appearance at week 9.

Figure 6B. Wound closure is achieved, week 9.

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