Poster #CR-005

A Multi-Center, Randomized Controlled Clinical Trial Evaluating the Effects of ASC in the Treatment of Diabetic Foot Ulcers: Interim Data Analysis of 50 Patients

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Introduction

Diabetic foot ulcers (DFUs) affect 1.5 million Americans with a lifetime risk of a diabetic patient developing an ulcer of 19-34% (1). Nearly 85% of diabetic related amputations are preceded by an ulcer (2). Many therapies exist, which often require repeat applications. An autologous heterogeneous skin construct (ASC) has been developed to treat skin defects with one application. The ability of ASC to close DFUs with a single application was assessed in a multicenter randomized controlled trial, which was IRB approved and pre-registered on Clinicaltrials.gov (NCT03881254).

Methods

All patients received 2 weeks of standard of care (SOC: collagen dressing, clean gauze, and offlloading) following consent. Patients whose index ulcers did not change in area more than 30% were randomized to continued SOC or ASC+SOC. ASC was created from a 1.5cm^2 full-thickness skin harvest from the proximal calf of the affected leg, which was collected in the clinic and sent to an FDA-registered facility (PolarityTE, Salt Lake City, UT) where it was processed into ASC and returned to the provider within 5 days. Harvest sites were closed primarily. ASC was spread evenly across the wound and dressed with non-adherent, non-absorbent dressing. Wounds were documented with digital photography and 3D planimetry (eKare, Baltimore, MD) during weekly dressing changes. Wound closure was verified by 3 plastic surgeons blinded to therapy following determination of closure by the treating investigator. Wounds had to remain closed two weeks after initial closure to be deemed closed. Study was IRB approved (Advarra) and pre-registered with clinicaltrials.gov (NCT03881254).

Results

- 50 patients: 25 ASC+SOC, 25 SOC were enrolled across 13 sites
- 6 SOC patients were withdrawn or lost to follow-up due to: incarceration, osteomyelitis and non-STEMI infarction, tunneling of study wound, secondary blister and infection requiring antibiotics, sepsis with possible pneumonia and cerebrovascular accident, motor vehicle crash with deformity and fracture of both ankles
- Average number of ASC applications: 1.08 (2 patients required an additional application of ASC due to inadvertent ASC removal)
- All harvest sites were closed primarily and remained closed throughout follow-up
- Harvests were taken below the knee of the treated limb for all patients except one taken from the medial thigh
- 1 harvest site developed an infection.
- 94% of ASC applications occurred within 3 days of harvest. 1 ASC application occurred 5 days after harvest

- **Primary Endpoint:** Proportion of wounds closed
  - ASC 72% vs. SOC 32%, p=0.005

- **Secondary Endpoints:**
  - Significantly greater Percent Area Reduction (PAR) at 4, 6, 8, and 12 weeks (88.2% SkinTE vs. 49.6% SOC, p=0.012) – See Table
  - No significant difference in pain scores, wound quality of life, or Semmes-Weinstein Score

- **Adverse Events*:**
  - 77 AEs total allocated to 24 subjects
  - 10 ASC patients had 36 AEs
  - 14 SOC patients had 41 AEs

*Final data source verification pending monitoring delayed by COVID

Patient Demographics

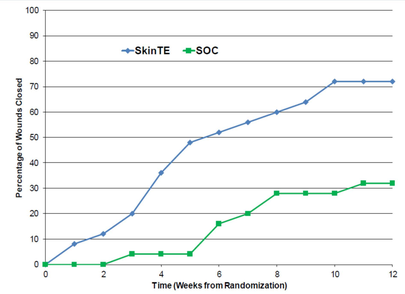
Demographic Variable	SkinTE	SOC	p
Patient age (years)	61.6 (10.25)	59.3 (13.46)	0.51
BMI	32.3 (7.56)	33.4 (7.54)	0.59
Gender			
Male	18 (72)	17 (68)	0.76
Female	7 (28)	8 (32)	
Subject Comorbidities	9.6 (3.29)	10.8 (6.15)	0.40
Creatinine	1.4 (0.61)	1.3 (0.49)	0.37
HbA1c			
Baseline	7.1 (1.37)	7.7 (1.72)	0.16
EOS (interim)	7.1 (1.64)1	8.0 (1.32)2	0.059
Wound area (cm2)	4.3 (4.24) median: 3.6; IQR: 3.2	3.3 (4.31) median: 1.8; IQR: 1.4	0.19
Wound age (weeks)	25.3 (31.41) median: 15.3; IQR: 19	22.1 (22.63) median: 14.0; IQR: 20	0.57
DFU location			
Plantar	21 (84)	21 (84)	1.00
Dorsal	4 (16)	4 (16)	
DFU location			
Toe	4 (16)	5 (20)	
Forefoot	10 (40)	13 (52)	
Midfoot	9 (38)	2 (8)	
Heel	2 (8)	4 (16)	
Ankle	0 (0)	1 (4)	

Summary of Treatments up to 1 Year Prior to Study Enrolment

Treatment	SkinTE	SOC	p
Debridement	14 (56)	16 (64)	0.56
Wraps or offloading	12 (48)	10 (40)	0.57
NPWT	0 (0)	2 (8)	0.49
CTP	1 (4)	2 (8)	0.55
Collagen or ORC dressing	8 (32)	6 (24)	0.53
Anti-bacterial dressing	4 (16)	3 (12)	0.68
Non-active dressing	8 (32)	14 (56)	0.087
Antibiotics (any route)	1 (4)	8 (32)	0.023

CTP: cellular and/or tissue-based product; NPWT: negative pressure wound therapy; ORC: oxidized regenerated cellulose

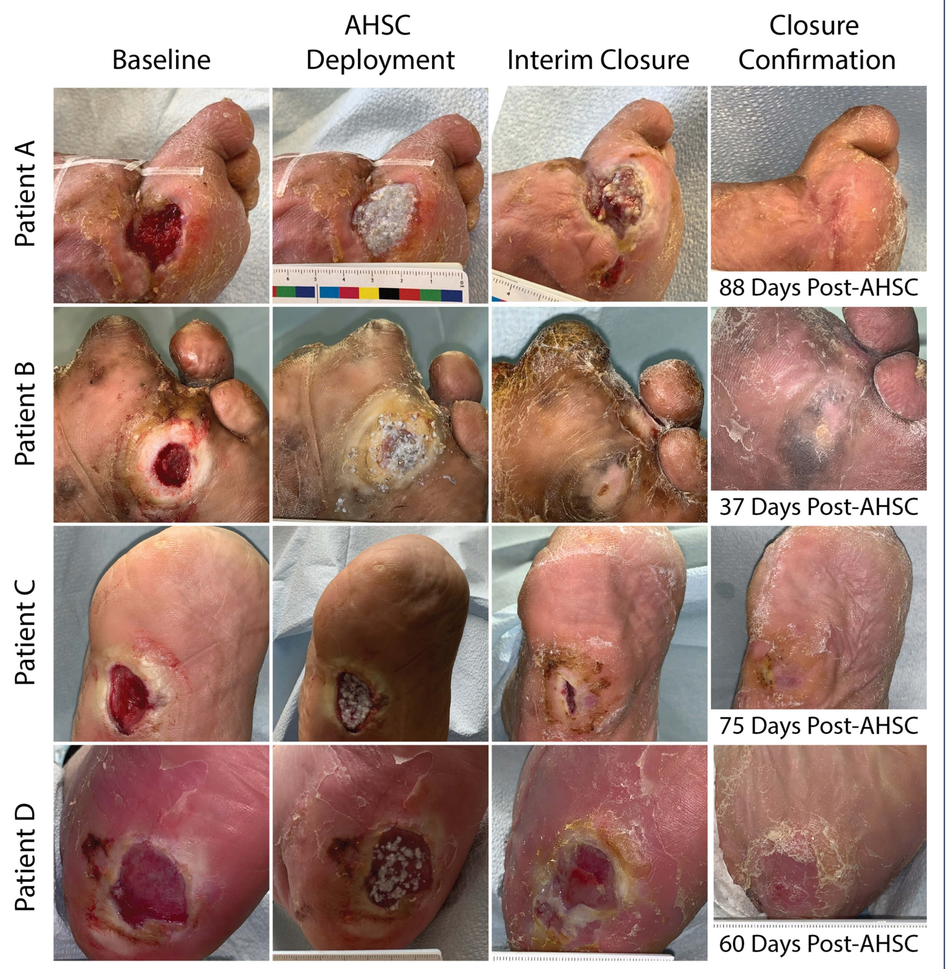
Weekly Closure Rate for Treatment Groups



PAR Rate for Treatment Groups

Week	SkinTE	SOC	p values
4	78.6 (35.6)	24.0 (106.52)	0.00021
6	83.2 (40.89)	43.8 (101.98)	0.004
8	86.6 (39.58)	47.2 (89.85)	0.002
12	88.2 (39.14)	49.6 (101.45)	0.012

DFUs Treated with ASC



Inclusion/Exclusion Criteria

Inclusion Criteria:

- At least 18 years old.
- Presence of a DFU Wagner 1 grade that does not extend through the dermis or subcutaneous tissue that does not involve the tendon, muscle, or bone, on any aspect of the foot, provided it is at or below the aspect of the medial malleolus.
- The index ulcer will be the largest ulcer if two or more DFUs are present with the same Wagner grade and will be the only one evaluated in the study. If other ulcerations are present on the same foot, they must be more than 2 cm distant from the index ulcer.
- Index ulcer (i.e. current episode of ulceration) has been present for greater than four weeks prior to the initial screening visit, as of the date subject consents for study.
- Index ulcer is a minimum of 1.0 cm^2 and a maximum of 25 cm^2 at first screening visit (SV1) and first treatment visit (TV1).
- Adequate circulation to the affected foot as documented by a dorsal transcutaneous oxygen measurement (TCOM) or a skin perfusion pressure (SPP) measurement of ≥ 30 mmHg, or an Ankle Branchial Index (ABI) of ≥ 0.7 and ≤ 1.2 or Arterial Doppler with a minimum of biphasic flow within 3 months of SV1, using the affected study extremity.
- The index ulcer has been offloaded for at least 14 days prior to randomization.
- Females of childbearing potential must be willing to use acceptable methods of contraception (birth control pills, barriers or abstinence) during the course of the study and undergo pregnancy tests.
- Subject understands and is willing to participate in the clinical study and can comply with weekly visits and the follow-up regimen.
- Subject has read and signed the IRB/IEC approved Informed Consent Form before screening procedures have been completed.
- The index ulcer has a clean granular base, is free of necrotic debris, and appears to be healthy vascularized tissue at time of placement of treatment product.

Exclusion Criteria:

- Index ulcer(s) deemed by the investigator to be caused by a medical condition other than diabetes.
- Index ulcer, in the opinion of the investigator, is suspicious for cancer and should undergo an ulcer biopsy to rule out a carcinoma of the ulcer.
- Subjects on any investigational drug(s) or therapeutic device(s) within 30 days preceding the first Screening Visit (SV1).
- History of radiation at the ulcer site (regardless of time since last radiation treatment).
- Index ulcer has been previously treated or will need to be treated with any prohibited therapies, such as chlorhexidine or collagenase. Subjects with a history of more than two weeks treatment with immunosuppressants (including systemic corticosteroids > 10mg daily dose), cytotoxic chemotherapy, or application of topical steroids to the ulcer surface within one month prior to first Screening visit, or who receive such medications during the screening period, or who are anticipated to require such medications during the study.
- Presence of any condition(s) which seriously compromises the subject's ability to complete this study or has a known history of poor adherence with medical treatment.
- In the opinion of the Investigator, the subject is non-compliant with offloading or index ulcer dressing prior to randomization.
- Osteomyelitis or bone infection, cellulitis, or "active" Charcot's arthropathy of the affected foot near the site of the wound or on the same limb as the index ulcer as verified by X-ray, MRI, or bone biopsy within 30 days prior to randomization if any of the aforementioned conditions are expected. (In the event of an ambiguous diagnosis, the Principal Investigator will make the final decision.)
- Subject is pregnant or breast-feeding.
- Presence of diabetes with poor metabolic control as documented with an HbA1c ≥12.0 within 30 days of randomization.
- Subjects with end stage renal disease as evidenced by a serum creatinine of greater than 3.0 mg/dl within 120 days of randomization.
- Target wound has presence of local active soft tissue infection or Gangrene involving the treatment site.
- Index ulcer has reduced or increased in area by 30% or more after 14 days of SOC from SV1 to the TV1/randomization visit.
- In the opinion of the Investigator, evidence of unstable human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening.

Conclusions

ASC treatment resulted in a 2.25x significantly greater proportion of DFUs closed within 12 weeks of treatment with a single application (and re-application in two ASC patients due to inadvertent removal of original ASC) and a significantly greater PAR at 4, 6, 8, and 12 weeks. ASC treatment was amenable to high volume outpatient wound care clinics and patients with wound size and disease severity commonly encountered in outpatient practice. There were no significant differences between treatment groups in pain, wound quality of life, and Semmes-Weinstein Score. ASC treatment did not result in more AEs than SOC. However, one ASC harvest site developed a superficial infection.

Disclosures

The Professional Education and Research Institute, whose Medical Director is Charles Zelen, DPM, received research support from PolarityTE to administer this clinical trials. Authors have received funding to assist in conducting the study.

References

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