A Prospective, Randomized, Controlled, Multi-center, Clinical Trial Examining Healing Rates, Safety, and Cost to Closure of An Acellular Reticular Allogenic Human Dermis* Versus Standard of Care in the Treatment of Chronic Diabetic Foot Ulcers

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ABSTRACT

Acellular dermal matrices have been reported in the literature and have been studied and shown to successfully treat indolent diabetic foot wounds for over 20 years . In this study, we examined a novel, human reticular acellular dermis matrix (HR-ADM) with an open, porous, and uniform framework aseptically processed to retain endogenous matrix proteins.

In a 12-week trial, 40-consecutive patients were enrolled with non-healing diabetic ulcers 1-25cm^2 in size. After a 2-week screening period if the wound failed to reduce in size by 20% using offloading and moist wound care, the patients were randomized to receive either standard of care alginate wound therapy or wound-size-specific acellular-human-reticular dermis applied weekly. Patients were followed for 12 weeks or until one week after healing.

At 6 weeks, 65% of the reticular-acellular-dermis-treated wounds had healed(13/20) compared to 5%(1/20) of the wounds that received Standard of Care dressing (SOC) alone (adjusted p=.00028). At 12 weeks 16/20 patients(80%) healed completely with the human dermis versus only 4/20(20%) with SOC (p=.00036). There was no incidence of increased adverse or serious adverse events between either group. The mean and median cost to closure in the human dermis group was $1475.00 and $963.00 respectively per healed wound.

These finding demonstrate that weekly application of acellular human reticular dermis is an effective treatment for the non-healing diabetic foot wound. Wound size specific pieces may allow for decreased cost to closure and wastage.

BACKGROUND

Nearly 285 million people internationally or close to 6.4% of the world's population is known to have diabetes mellitus[1]. Approximately 25% of diabetics will develop an ulcer in their lower extremity over their lifetime. Studies show that these ulcerations precede nearly 85% of lower extremity amputations[2,3]. The goal of wound healing should be to transform a chronic wound to an acute wound, in order to prevent limb threatening complications[5].

As early as the 1990's, human dermal matrices were illustrated as a viable option to accelerate the wound healing process[4]. HR-ADM is an aseptically processed dermal matrix comprised of reticular dermis. Its unique porous and symmetrical properties have been shown to facilitate dermal fibroblast proliferation and matrix deposition[5]. Limited prospective or retrospective analysis exists regarding the efficacy of skin allografts in chronic wounds. This is the first clinical trial comparing HR-ADM with standard of care in diabetic foot ulcers (DFU).

PURPOSE

The purpose of this prospective, randomized, controlled, parallel, multi-center clinical trial was to compare the proportion of ulcers completely healed by use of HR-ADM versus the standard protocol of wound care (SOC) in diabetic patients with a DFU with adequate arterial perfusion. The study was conducted in five outpatient wound centers and pre-registered in ClinicalTrials.gov (NCT02331147).

References:

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METHODS

Table 1. Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
•Male or female age 18 or older •Type 1 or type 2 diabetes mellitus (ADA diagnostic criteria). •Signed informed consent •Patient's wound diabetic in origin and larger than 1 cm^2. •Wound present for a minimum of 4 weeks duration, with documented failure of prior treatment to heal the wound. •Wound has no signs of infection. •Wound present anatomically on the foot as defined by beginning below the malleoli of the ankle. •Additional wounds may be present but not within 3 cm of the study wound. •Serum creatinine less then 3.0 mg/dL. •HbA1c less than 12% taken prior to randomization •Patient has adequate circulation to the affected extremity, as demonstrated by one of the following within the past 60 days: •Dorsum transcutaneous oxygen test (TCOM) ≥30mmHg •ABI with results of ≥0.7 and ≤1.2 •Doppler arterial waveforms, which are triphasic or biphasic at the ankle of affected leg •Patient is of legal consenting age. •Patient is willing to provide informed consent and is willing to participate in all procedures and follow up evaluations necessary to complete the study.	•Wound probing to bone (UT Grade IIIA-D). •Index wound greater than 25cm^2. •HbA1c greater than 12% within previous 90 days. •Serum creatinine level 3.0mg/dL or greater. •Patients with a known history of poor compliance with medical treatments. •Patients previously randomized into this study, or presently participating in another clinical trial. •Patients currently receiving radiation therapy or chemotherapy. •Patients with known or suspected local skin malignancy to the index wound. •Patients with uncontrolled autoimmune connective tissues diseases. •Nonrevascularizable surgical sites. •Active infection at index wound site •Any pathology that would limit the blood supply and compromise healing. •Patients who have received a biomedical or topical growth factor for their wound within the previous 30 days. •Patients who are pregnant or breast feeding. •Patients who are taking medications that are considered immune system modulators that could affect graft incorporation. •Patients taking a Cox-2 inhibitor. •Patients with wounds healing greater than 20% during the screening period.

Study groups:

N=20 each for HR-ADM+SOC and SOC only

Endpoints:

Primary: Proportion of patients healed at 6 weeks
Secondary: Proportion of patients healed at 12 weeks

Study design:

1. Patients demonstrating < 20% wound area healing within 2 week of initial screening were randomized into either of the two treatment arms.
2. Weekly patient visits included sharp debridement, cleaning, graft application, dressing change, photography, and wound measurement via acetate tracing and length,width,depth ruler measurement. Offloading was also employed.
3. Validation visit one week after 100% epithelialization of wound was required to confirm closure.

Data analysis:

1. Parametric or non-parametric tests used as appropriate
2. Adjusted two-sided p values < 0.05 were considered significant
3. PASW 19 (IBM, Chicago, IL) was used to perform the statistical testing

RESULTS

1. At 6 weeks, 65% of the HR-ADM–treated wounds had healed (13/20) compared to 5% (1/20) for SOC only (adjusted p=0.00028). See Figure 2a.
2. At 12 weeks, 80% of the HR-ADM–treated wounds (16/20) had healed compared to 20% (4/20) of the DFUs in the SOC group (adjusted p=0.00036). See Figure 1 and Figure 2a.
3. Mean initial wound area for HR-ADM group was larger than SOC group (4.7cm^2 vs. 2.7cm^2), however demonstrated a greater percent wound area reduction over time. See Figure 2b.
4. Mean applications to closure for HR-ADM was 4.7.
5. Mean cost to closure for HR-ADM was $1475.

RESULTS (cont.)

Figure 1. Representative case example of patient healed with HR-ADM

Patient history:

- 41 y/o Type II diabetes with peripheral neuropathy presenting with chronic, non- healing right plantar forefoot ulceration
- 4 week ulcer history, with history of recurrent forefoot ulcers
- HbA1C 9.3%, Serum creatinine 0.9 mg/dL

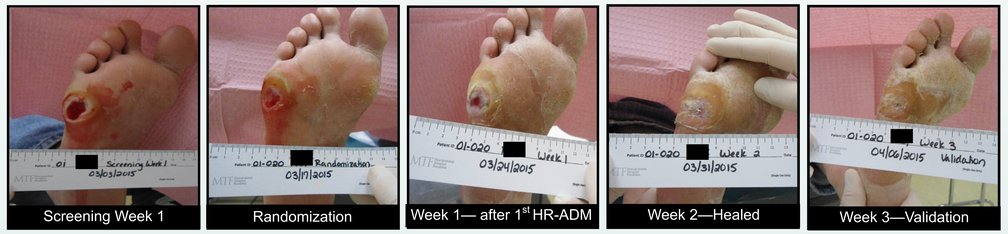
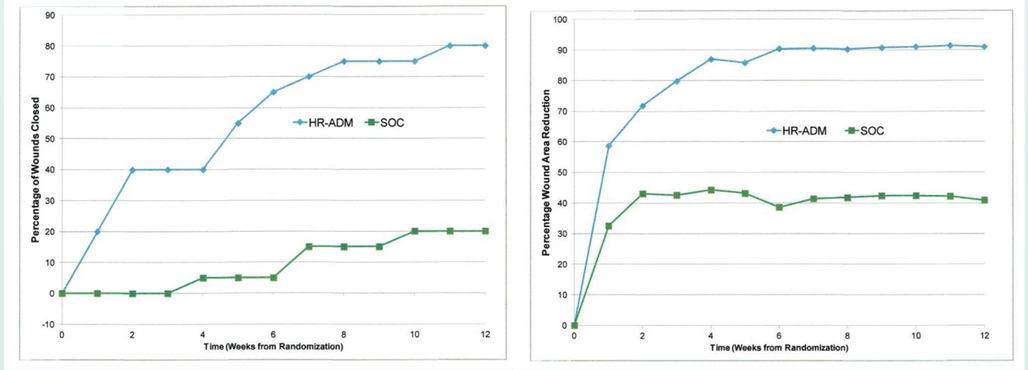


Figure 2a. Percentage of wounds closed by week by treatment group.
Figure 2b. Percentage of wound area reduction by week by treatment group.



CONCLUSIONS

This study demonstrated that DFUs treated weekly with HR-ADM healed more rapidly compared to DFUs treated with SOC at 6 and 12 weeks. Level 1 evidence supports the use of HR-ADM for treatment of chronic DFUs. Wound size specific pieces may allow for decreased cost to closure and wastage.

***HR-ADM = AlloPatch® Pliable is a registered trademark of Musculoskeletal Transplant Foundation, Edison, NJ**
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