Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study

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ABSTRACT

This 12-week, prospective, randomised, controlled multi-centre study compared the proportion of healed diabetic foot ulcers and mean healing time between patients receiving acellular matrix (AM) (study group) and standard of care (control group) therapies. Eighty-six patients were randomised into study (47 patients) and control (39 patients) groups. No significant differences in demographics or pre-treatment ulcer data were calculated. Complete healing and mean healing time were 69·6% and 5·7 weeks, respectively, for the study group and 46·2% and 6·8 weeks, respectively, for the control group. The proportion of healed ulcers between the groups was statistically significant ($P = 0.0289$), with odds of healing in the study group 2·7 times higher than in the

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control group. Kaplan–Meier survivorship analysis for time to complete healing at 12 weeks showed a significantly higher non healing rate ($P = 0.015$) for the control group (53·9%) compared with the study group (30·4%). After adjusting for ulcer size at presentation, which was a statistically significant covariate ($P = 0.0194$), a statistically significant difference in non healing rate between groups was calculated ($P = 0.0233$), with odds of healing 2·0 times higher in the study versus control group. This study supports the use of single-application AM therapy as an effective treatment of diabetic, neuropathic ulcers.

Key words: Acellular regenerative tissue matrix ● Bioengineered matrix ● Diabetes mellitus ● Foot ulcer ● Wound

Key Points

- persons with diabetes face a lifetime risk as high as 25% of developing a foot ulcer
- diabetic foot complications are the principal cause of non traumatic lower extremity amputations, accounting for up to 8 of every 10 non traumatic amputations
- previous evidence suggests that up to 85% of diabetic foot and leg amputations may be prevented with the appropriate knowledge of risk factors and application of evidence-based multidisciplinary treatment
- bioengineered skin grafts, including acellular matrix (AM) grafts, are promising alternatives for diabetic lower extremity wounds that often are unresponsive to traditional wound management modalities
- the primary objective of the study was to compare healing rates at 12 weeks between patients receiving AM therapy and standard of care wound management, as measured by wound survivorship
- the secondary objective was to compare mean time to healing between treatment groups
- ninety-three patients were enrolled in a 12-week prospective, randomised, parallel, controlled multicentre clinical trial involving 11 sites

INTRODUCTION

The United States consistently ranks third, behind India and China, on the list of countries with the highest diabetic populations, with an estimated 17·7 million cases in 2000 and a projected 30·3 million cases by 2030 (1). Persons with diabetes face a lifetime risk as high as 25% of developing a foot ulcer (2). Management of diabetic wounds of the lower extremity is critical, as ulcers that are slow to heal have a significant impact on patient quality of life (3–9). Conservative estimates suggest that the cost of treating a diabetic foot ulcer is approximately $28 000 during the 2 years after diagnosis (10). Given the high cost associated with treatment of lower extremity diabetic ulcers, Holzer *et al.* concluded that the development of better treatment strategies is warranted (11). Diabetic foot complications are the principal cause of non traumatic lower extremity amputations, accounting for up to 8 of every 10 non traumatic amputations (12–14). However, previous evidence suggests that up to 85% of diabetic foot and leg amputations may be prevented with the appropriate knowledge of risk factors and application of evidence-based multidisciplinary treatment (12). Bioengineered skin grafts, including acellular matrix (AM) grafts, are promising alternatives for diabetic lower extremity wounds that often are unresponsive to traditional wound management modalities (15).

AM therapy has a long history of use in a wide variety of applications, including head and neck plastic and reconstructive surgery (16–32), abdominal wall reconstruction (33–35) and extremity reconstruction (36–38). AM grafts also have been effective in healing full-thickness burn wounds (39–45). Multiple studies have shown graft integration, host cell infiltration and revascularisation of the AM, with no immune response (18,32,33,44,45). While several studies have reported outcomes in chronic wounds, most are not randomised controlled studies specifically evaluating AM therapy use in diabetic foot ulcers (15,46,47). The primary objective of the study was to compare healing rates at 12 weeks between patients receiving AM therapy and standard of care wound management, as measured by wound survivorship. 'Wound survivorship' refers to the duration of time that the wound persists and is synonymous with the term 'not healed'. The secondary objective was to compare mean time to healing between treatment groups.

METHODS

Study design

Ninety-three patients were enrolled in a 12-week prospective, randomised, parallel, controlled multicentre clinical trial involving 11 sites. Institutional review board approval was received for each site and informed consent was obtained from all patients before screening. Patients who were 18 years of age or older, with a diagnosis of type 1 or type 2 diabetes, a University of Texas (UT) grade 1 or 2 diabetic foot ulcer ranging in size from 1 to 25 cm^2, absence of infection based on Infectious Disease Society of America criteria, and adequate circulation to the affected extremity were eligible for inclusion (12,48,49). Adequate circulation was defined as the presence of at least one of three criteria within the previous 60 days: (i) transcutaneous oxygen measurement at the dorsum of the foot greater or equal to 30 mmHg, (ii) ankle brachial index ranging from 0·7 to 1·2, or (iii) at least biphasic Doppler arterial waveforms at the dorsalis pedis and posterior tibial arteries. Patients who were in poor metabolic control (HgA1c greater than 12% within the previous 90 days) were excluded, as were patients with serum creatinine levels of 3·0 mg/dl or greater. Patients with sensitivity to gentamicin, cefoxilin, linocmycin, polymyxin B or

Key Points

- patients in the study group received a single application of a human acellular dermal regenerative tissue matrix graft (4x4 cm GRAFTJACKET Regenerative Tissue Matrix – Ulcer Repair; Wright Medical Technology, Inc., Arlington, TN)
- patients in the control group received standard-of-care wound management consisting of moist-wound therapy with alginates, foams, hydrocolloids or hydrogels at the discretion of the treating physician
- the primary endpoint of the study was the proportion of ulcers that completely healed at 12 weeks
- the secondary endpoint was meantime to healing. Complete healing was defined as 100% re-epithelialisation without drainage

vancomycin also were excluded because of the broth composition in which the AM is processed. Additional exclusion criteria included non revascularable surgical sites, ulcers probing to bone (UT grades 3A to D), and wounds treated with biomedical or topical growth factors within the previous 30 days.

After surgical preparation of the recipient site, patients were randomised into one of two treatment groups. Patients in the study group received a single application of a human acellular dermal regenerative tissue matrix graft (4 × 4 cm GRAFTJACKET® Regenerative Tissue Matrix – Ulcer Repair; Wright Medical Technology, Inc., Arlington, TN). After suturing or stapling the AM graft into place, a silver-based non adherent dressing (Silverlon; Argentum Medical, LLC, Chicago, IL) was applied. Secondary dressings (hydrogel bolsters or moist gauze) were applied routinely at the rate determined by the investigator until complete epithelialisation was achieved or 12 weeks of care had been provided.

Patients in the control group received standard-of-care wound management consisting of moist-wound therapy with alginates, foams, hydrocolloids or hydrogels at the discretion of the treating physician. Alginates used in conjunction with foam typically were used for heavily exudative wounds. For wounds with minimal exudate, hydrocolloids or hydrogels commonly were used. Dressing changes occurred daily, unless recommended otherwise by the treating physician. Standard-of-care management continued until complete epithelialisation occurred or 12 weeks of care had been provided.

Glycosylated haemoglobin measurements were obtained during screening and at study closure. Serum creatinine levels were measured at screening. Patients were evaluated by the investigators at least once every 7 days (±3 days) to obtain ulcer measurements and to perform dressing changes. For both groups, the study ulcer was cleansed with a sterile normal saline solution before wound dressing placement. Rinsing, swabbing or irrigating was acceptable. The surface area and depth of the ulcer were measured and recorded at each visit, in addition to degree of granulation. No granulation was defined as no observed signs of granulation tissue; mild granulation was defined as granulation beginning to fill in, but tissue may not be epithelialised; and marked

granulation was defined as tissue that was filling in and was epithelialised. Acetate tracings of the wound and photographs were obtained after debridement and cleaning of the ulcer at the following intervals: after initial surgical preparation of recipient site, at 4-, 8- and 12-week post-randomisation, and upon study exit or withdrawal. Although debridement is not routine standard of care after AM therapy, it was performed as part of this controlled study in an effort to keep the two treatment populations as homogenous as possible and to minimise possible bias regarding wound size measurements. Wound photographs were taken at a distance of 1 foot (30 cm) with a centimetre label placed so that markings were directly adjacent to the ulcer. If findings were remarkable, wounds were traced and photographed more frequently. Patients received the standard management protocols per group assignment for 12 weeks or until complete healing occurred. Offloading was performed using a removable cast walker (Active Offloading Walker; Royce Medical, Inc., Camarillo, CA). The device was converted to an 'instant total contact cast' to improve adherence to offloading if deemed necessary by the treating physician.

If clinical signs of infection were present, a wound culture was obtained via curettage at the ulcer base after aggressive sharp debridement. Appropriate systemic antibiotic treatment was administered until the infection resolved. Microbiology confirmation and choice of antibiotic therapy were recorded. All other adverse events also were recorded. Other complications possible with AM graft use include maceration, specific or non specific immune response, graft resorption or graft non integration.

The primary endpoint of the study was the proportion of ulcers that completely healed at 12 weeks. The secondary endpoint was mean time to healing. Complete healing was defined as 100% re-epithelialisation without drainage.

AM description

The AM graft is processed from screened donated human skin supplied from United States tissue banks under the guidelines of the American Association of Tissue Banks and in accordance with Food and Drug Administration (FDA) requirements for procurement and processing of banked human tissues (CFR Title 21, Part 1270 and 1271). It is regulated by the

FDA as human tissue for transplantation. The allograft skin is processed minimally to remove epidermal and dermal cells while preserving dermal structure. The resulting allograft serves as a scaffold to support cellular repopulation and revascularisation. Presence of an intact basement membrane complex, retention of collagen and absence of cells are confirmed through histology and immunohistochemistry. Absence of bacterial and fungal pathogens is assured through microbiological cultures. Residual moisture is less than 5%.

Statistical analysis

Statistical analysis was performed using SAS 9.1.3 Service Pack 4 (SAS Institute Inc., Cary, NC). Descriptive statistics, including mean, median, standard deviation, frequency and percentage, were used to describe numerical data. Demographic variables, diabetes type, wound size, time to complete healing for wounds that healed and change in wound size from baseline to most recent follow-up evaluation for wounds that did not heal were compared between the study groups. Pearson's chi-square analysis was used to compare categorical information. For continuous variables that were normally distributed, one-way analysis of variance was used to determine statistical significance. Using time to wound healing as the survival event, Kaplan–Meier survivorship analysis (product limit plot) was used to assess wound healing between treatment groups. Wounds were censored if they failed to heal by the 12-week endpoint or at the latest available clinical assessment or if the patient withdrew from the study. Wound measurements obtained at the latest follow-up evaluation were used for analysis. The log-rank test was used to identify significant differences between survival curves. Cox proportional hazards model analysis was conducted to determine the relationship between wound healing and the following covariates: ulcer size at presentation, index ulcer duration, patient age, body mass index and diabetes type. In addition, hazard ratio estimation was performed to evaluate the association between time to wound healing and the significant covariates. Statistical differences were considered significant when the $P \leq 0.05$ with a power of at least 0·80. Ninety-five percent confidence intervals were used throughout the statistical analysis.

RESULTS

The flow of study enrolment and participation through the clinical trial is diagramed in Figure 1. Of the 93 patients who were enrolled in the study, 7 did not meet the inclusion criteria and were deemed screen failures. The remaining 86 patients were randomised into two treatment groups, with 47 patients (47 ulcers) receiving AM therapy (study group) and 39 patients (39 ulcers) receiving standard of care therapy (control group). Four patients (two in the study group and two in the control group) were enrolled in the study despite having index ulcer sizes less than 1 cm^2 and were considered protocol deviations. Because these patients were randomised and received treatment, they were included in the data analysis. Eight patients, six in the study group and two in the control group, did not complete the clinical trial. In the study group, one patient chose to withdraw from the study at the first week of evaluation and another was withdrawn during the ninth week of participation. Another patient in the study group was removed from study participation and statistical analysis because of patient non compliance that resulted in AM therapy removal. The remaining five patients (three in study group and two in control group) did not continue study participation due to adverse events.

A comparison of demographics between the two treatment groups is presented in Table 1. The majority of patients in both treatment groups had type 2 diabetes and were obese (body mass index of 30·0 or greater). Index ulcer location is compared between treatment groups in Figure 2. For both treatment groups, the most common location was the foot. Pre-treatment ulcer data, including history of index ulcer and ulcer size at presentation, is compared between groups in Table 2. No statistically significant differences in demographic, ulcer location and pre-treatment ulcer variables were observed between treatment groups. Glycosylated haemoglobin levels obtained pre-treatment and at study completion are compared between treatment groups in Table 3 and indicate that metabolic control was maintained throughout the course of study. The differences between treatment groups were not statistically significant at either time interval.

Of the patients completing the clinical trial, complete healing occurred in 32 (69·6%) of the

Key Points

- there was a statistically significant difference in proportion of healed ulcers between the treatment groups (P =0.0289, OR =2.7)
- based on the odds ratio, the odds of healing in the study group were 2.7 times higher than in the control group
- no statistically significant difference in mean time to wound healing was observed between treatment groups
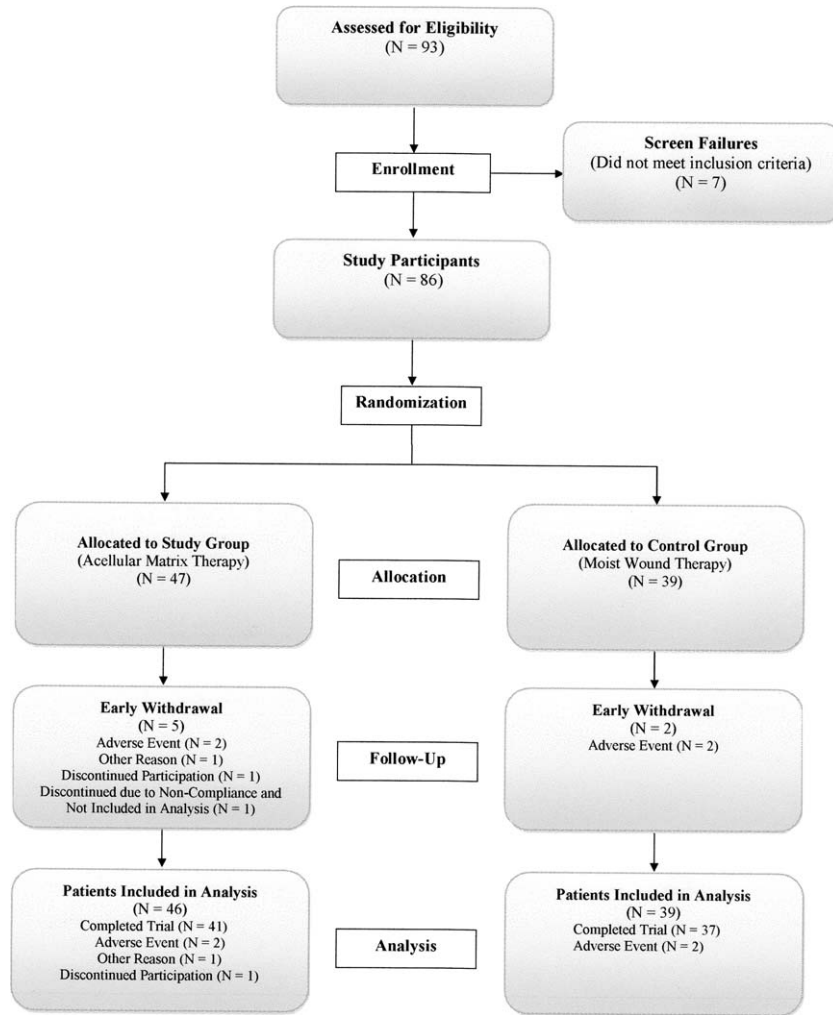

Figure 1. Flow chart of patient accounting for clinical trial.

46 patients in the study group and 18 (46·2%) of the 39 patients in the control group. The time to complete healing is presented in Table 4. There was a statistically significant difference in proportion of healed ulcers between the treatment groups ($P = 0.0289$, OR = 2·7). Based on the odds ratio, the odds of healing in the study group were 2·7 times higher than in the control group. No statistically significant difference in mean time to wound healing was observed between treatment groups.

Complete healing did not occur in 14 (30·4%) of the 46 patients in the study group or in 21 (53·8%) of the 39 patients in the control group. For this non healing subset, no statistically significant differences were calculated between treatment groups in mean final ulcer size, percent of ulcer area completely healed or change from ulcer size at presentation (Table 5).

Despite not healing within the study timeframe of 12 weeks, 12 (85·7%) patients in the study group experienced a decrease in ulcer size and the other 2 (14·3%) patients had ulcers that did not increase or decrease in size. Fifteen (71·4%) patients in the control group experienced a decrease in ulcer size, while five (23·8%) increased in size (mean healing percent = −30·37 ± 19·89, median −25·74, range, −64·11 to −13·71). Three (21·4%) patients in the study group and six (28·6%) patients in the control group had ulcers that were at least 90% healed at the final follow-up evaluation. All but one patient in the control group exhibited mild or marked granulation at the final follow-up evaluation.

Summarising the six adverse events that occurred during the course of the study, one patient in the control group was admitted to the

Table 1 Comparison of demographic variables between treatment groups

Demographic variable	Study group (n = 46)	Control group (n = 39)
Age (years)		
Mean	55·4	58·9
Median	55·0	58·0
Standard deviation	9·6	11·6
Range	32·0–78·0	35·0–93·0
Number of patients	46	39
Body mass index (lbs/in^2)		
Mean	33·1	34·6
Median	32·1	33·5
Standard deviation	6·7	8·5
Range	24·3–52·8	20·9–61·1
Number of patients	45	38
Diabetes mellitus type		
Type 1	5 (10·9%)	2 (5·1%)
Type 2	41 (89·1%)	37 (94·9%)
Number of patients	46	39

hospital for altered mental status and hypotension during the first week of study participation. A hallux amputation that was deemed not to be related to study treatment was performed 26 days after admission. This patient was censored at week 0. A study group patient was censored at week 1 because of infection that required a hallux amputation. Another study patient was censored at week 2 after the investigator discovered that the AM therapy was no longer on the wound. At the fifth-week evaluation, a patient in the control group presented with an abscess secondary to the study wound and was removed from the study because treatment outside the study protocol was necessary. This patient was censored at week 5. After the eighth week of evaluation, a patient in the study group required vascular surgery to treat a blocked artery, which was unrelated to the AM therapy, and was censored from the analysis at week 8. After repeated incidences of non compliance by
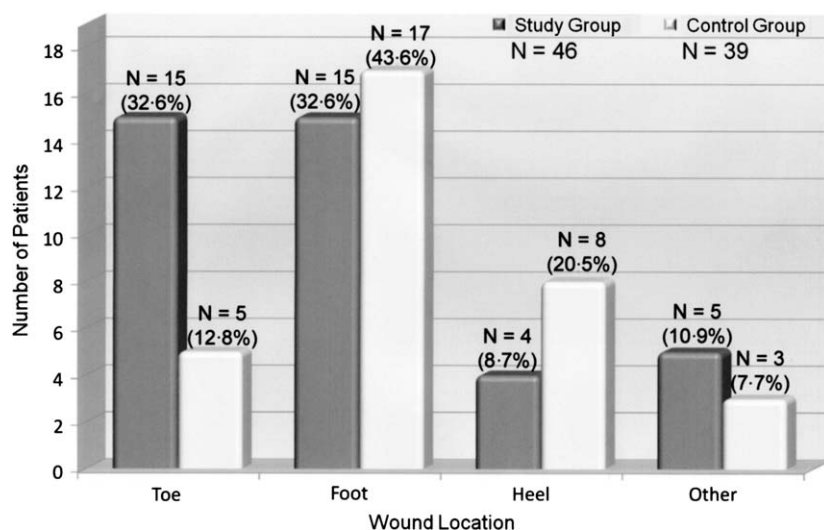
Figure 2. Comparison of index ulcer location between treatment groups.

Table 2 Comparison of pre-treatment ulcer data between treatment groups

	Index ulcer duration (weeks)		Ulcer size at presentation (cm^2)	
	Study group (n = 46)	Control group (n = 39)	Study group (n = 46)	Control group (n = 39)
Mean	23·3	22·9	3·6	5·1
Median	16·0	12·0	2·2	3·2
Standard deviation	22·4	29·8	4·3	4·8
Range	0·00–96·00	3·00–139·00	0·6–23·3	0·4–18·9

Table 3 Comparison of glycosylated hemoglobin levels obtained at pre-treatment and study completion between treatment groups

	Pre-treatment level (%)		Level at study completion (%)	
	Study group ($n = 46$)	Control group ($n = 39$)	Study group ($n = 25$)	Control group ($n = 22$)
Mean	8·2	7·6	8·0	7·1
Median	8·5	7·5	7·8	6·7
Standard deviation	2·0	1·6	1·6	1·5
Range	2·0–11·9	5·6–11·9	5·2–11·0	5·3–11·2

Table 4 Comparison of time to complete healing of ulcers that healed on or before 12 weeks between treatment groups

	Time to complete healing (weeks)	
	Study group ($n = 32$)	Control group ($n = 18$)
Mean	5·7	6·8
Median	4·5	7·0
Standard deviation	3·5	3·3
Range	1·0–12·0	2·0–12·0

a study patient, including use of an offloading device, AM therapy completely dislodged from a plantar wound during the second week of participation. Because of the deviation in management, this patient was not included in the analysis.

The Kaplan–Meier survivorship analysis for time to complete healing is presented in Figure 3. A statistically significant difference in non healing rate was calculated between treatment groups ($P = 0.0075$). At the 12-week endpoint, the non healing rate of 53·8% in the control group was significantly higher than the 30·4% non healing rate observed in the study group. The proportion of healed ulcers at weekly evaluation intervals between treatment groups is presented in Figure 4. Beginning at the 3-week follow-up evaluation, the proportion of healed ulcers in the study group was at least 15% higher than the control group. The Cox proportional hazards model analysis indicated that ulcer size at presentation was statistically significant covariates that should be considered when analysing non healing rate ($P = 0.0194$). Index ulcer duration, age, body mass index and diabetes type were not significant covariates. After adjusting for ulcer size at presentation, there was a statistically significant difference in non healing rate between treatment groups ($P = 0.0233$). The corresponding hazard ratio of 2·0 (95% CI, 1·0–3·5) indicated that the probability of healing is approximately two times greater in the study group than in the control group.

DISCUSSION

The results of this study support previous literature documenting successful use of AM therapy (16-50). In addition, this study provides further evidence that bioengineered skin grafts such as AM grafts are effective treatment options for diabetic lower extremity wounds. The use of AM therapy offers several advantages compared with other bioengineered skin grafts. First, the graft is an immunologically inert, acellular, replacement scaffold derived from human cadaver tissue and comprised of collagen and extracellular protein matrices. It provides a favorable microenvironment for bioingrowth by promoting nutritional diffusion and cellular proliferation at the graft site

Table 5 Comparison of ulcers that did not completely heal at or on 12 weeks between treatment groups

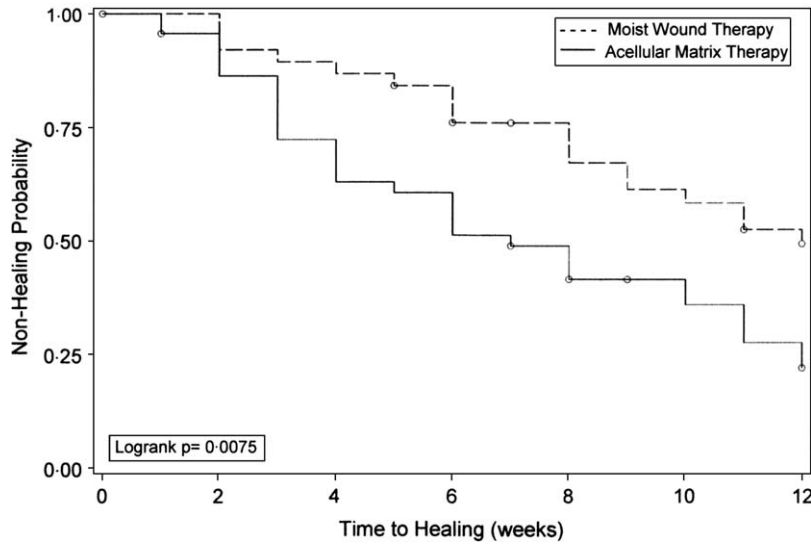|	Final wound size (cm²)		Percent healed (presentation versus final wound size) (%)	
	Study group ($n = 14$)	Control group ($n = 20$)	Study group ($n = 14$)	Control group ($n = 20$)
Mean	1·9	3·5	49·1	47·2
Median	1·1	1·1	46·3	65·2
Standard deviation	2·3	5·2	35·9	52·0
Range	0·01–9·0	0·02–19·5	0·00–99·9	−64·1 to 99·4

Figure 3. Kaplan–Meier survivorship analysis for time to complete healing by treatment.

(51–54). These properties result in the rapid revascularisation and cellular repopulation of the matrix scaffold (55–58). The cells then respond to local growth factor and biomechanical stimuli, transitioning the scaffold into nascent, vital dermal tissue. Because AM therapy provides a scaffold onto which the body may build dermal tissue, a single application often is sufficient for complete healing. In the current study, the ulcers that healed in the study group received only one application of the AM therapy. Although many other bioengineered grafts contain growth factors,

they do not offer the scaffold onto which dermal tissue may be built. Multiple applications of these grafts, therefore, may be required for the body to build a sufficient base to achieve complete healing.

Because the graft is derived from human tissue and its structural and biochemical integrity are retained during processing, it is easily recognised by the body's immune system and, therefore, does no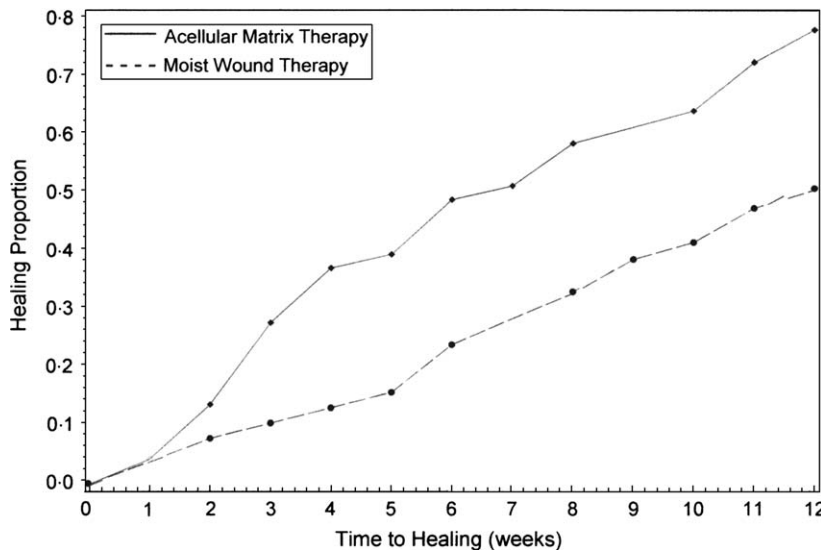t provoke a foreign body or inflammatory tissue response (44,55,59). In addition, as all cellular components are extracted during manufacturing, the scaffold does

Figure 4. Healing proportion curve by treatment.

Key Points

- the purpose of this study was to compare the proportion of healed ulcers and the mean time to healing between patients receiving AM therapy and standard of care management
- at the end of the study, complete healing and mean time to healing were 69.6% and 5.7 weeks, respectively, for the study group and 46.2% and 6.8 weeks, respectively, for the control group

not contain immune response targets. No specific or non specific immune responses were observed in the current study. Conversely, many of the other commercially available bioengineered grafts are xenografts, produced from either bovine or porcine sources, and have been shown to induce an inflammatory reaction in both animal models and in humans (60,61).

The purpose of this study was to compare the proportion of healed ulcers and the mean time to healing between patients receiving AM therapy and standard of care management. The study population was comprised of patients with UT grade 1 or 2 diabetic foot ulcers ranging in size from 0·4 to 25 cm^2 and most commonly located on the foot. There was not a significant difference in demographics, ulcer location and pre-treatment ulcer data between treatment groups, reinforcing the randomisation process and also suggesting that any differences in outcomes are more likely the result of differences in treatment. Complete healing was determined by the proportion of wounds that healed at or within the 12-week study duration. At the end of the study, complete healing and mean time to healing were 69·6% and 5·7 weeks, respectively, for the study group and 46·2% and 6·8 weeks, respectively, for the control group. The odds of healing in the study group were 2·7 times higher than in the control group. Ulcers in the study group also healed on average 1 week sooner than those receiving moist therapy, although this trend did not reach significance.

Factoring in time, the rate of wound healing was assessed by performing a Kaplan–Meier survivorship. At the 12-week endpoint, the non healing rate of 53·8% in the control group was significantly higher than the 30·4% non healing rate observed in the study group. This finding is of clinical significance because of the importance of healing a wound as quickly as possible. Because wound healing is influenced by multiple factors, including ulcer size, a Cox proportional hazards model analysis was performed. After adjusting for ulcer size at presentation, which was determined to be a clinically and statistically significant covariate, the probability of healing was approximately two times greater in the study group than in the control group.

Two patients in the control group experienced adverse events during the course of study. One was hospitalised during the first week of study participation and subsequently required a hallux amputation. The other was removed from the study after 5 weeks to administer treatment for an abscess that developed secondary to the study wound. Of the study group patients completing the clinical trial, no complications possible with AM therapy, such as maceration, immune response, graft resorption or graft non integration were reported. However, one study patient required a hallux amputation because of an infection that may or may not have been related to AM therapy use. Two AM therapy failures were noted in the study group. In the first case, the investigator discovered that the AM therapy no longer was on the wound when the patient returned for the second-week evaluation, with no explanation provided by the patient. After repeated incidences of patient non compliance, including weight-bearing ambulation, AM therapy completely dislodged from a plantar wound in another patient during the second week of participation. Despite the investigator's attempt to gain patient compliance by prescribing a wheelchair, the adverse event occurred because the patient used the index foot to manoeuvre in the wheelchair.

Three other published studies report the results of AM therapy for diabetic lower extremity ulcers at specific endpoints (46,47,50). Although direct comparison between these studies and the current one is difficult because of differences in demographics, co-morbidities, wound complexities and study endpoints, the proportions of ulcers healed and corresponding mean times to healing are summarised in Table 6. The other prospective study involved full-thickness Wagner grade 2 ulcers (50). The other two were 20-week studies comprised of more complex wounds, with the Winters *et al.* study involving all UT grades, including infected and/or ischemic wounds (46,47). The proportion of wounds healed at 12 weeks and an analysis of UT grade 2A wounds at 20 weeks were provided in the discussion portion of the Winters *et al.* study (47). Given the difference in wound complexity, the current study had an approximately three times higher proportion of healed wounds with a two times shorter mean time to healing compared with the 12-week data reported by Winters *et al.* (47). Graft failure rates were similar between studies, with lack of patient adherence to care being a factor potentially influencing these rates. The proportion of UT grade 2A ulcers healed at 20 weeks ranged from 50·0% to

82·4% in the Winters et al. (47) and Martin et al. studies (46).

In addition to comparing the current study results with previous AM therapy studies, a historical control group also is available for comparison. Margolis et al. performed a meta-analysis that assessed the percentage of neuropathic diabetic foot ulcers that healed after receiving good standard of care (62). The meta-analysis was limited to control arms from randomised controlled trials of non infected wounds that reported the percentage of healed wounds after a set treatment duration (62). Margolis et al. defined good care as a standard care regimen consisting of debridement, wound care with either saline-moistened gauze or placebo gel and gauze, and instructions to patients regarding the importance of avoiding weight-bearing ambulation, which were components of the wound management protocol in the current study (62). Based on group-level or study-level data, 24·2% of diabetic neuropathic ulcers healed after 12 weeks of good treatment, with 30·9% of ulcers healing after 20 weeks of good wound care (62). Despite the lack of heterogeneity between the studies included in the meta-analysis, the percentage of wounds healed at 12 and 20 weeks remained relatively constant among the studies (62). Margolis et al. concluded by recommending that their data be used as a benchmark by physicians to shape patient expectations regarding chances of healing and by regulatory agencies and managed care corporations to determine what percentage of wounds should be healed within a set time period (62). The 12-week healing rates of 69·6% and 46·2% for the study and control groups, respectively, in the current study are two to three times above this recommended benchmark. These successful results support the treatment of diabetic, neuropathic ulcers using the wound management protocols employed in this study.

Strengths of this study include the prospective, randomised, controlled design and the multicentre involvement. Although 12 weeks is a common assessment endpoint in wound studies, continued follow-up would be beneficial. Among the ulcers that did not heal, 21·4% and 28·6% in the study and control groups, respectively, were at least 90% healed compared with their measurements at presentation. In addition, 85·7% patients in the study group experienced a decrease in ulcer size, whereas the

Key Points

- strengths of this study include the prospective, randomised, controlled design and the multi-centre involvement
- although 12 weeks is a common assessment endpoint in wound-studies, continued follow-up would be beneficial

Table 6 Summary of ulcer healing proportion and mean time to healing for published AM therapy diabetic ulcer studies

Study	Study design	Study endpoint (weeks)	Ulcer type	Ulcer location	Number of cases	Proportion of healed ulcers, n (%)	Mean time to healing (weeks)	AM therapy failures
Current study	Prospective	12	UT grades 1A and 2A	Foot	46	32 (69·6%)	5·7	2 (4·3%) (1 non compliance, 1 unknown)
Brigido (50)	Prospective	16	Full-thickness, Wagner grade 2	Lower extremity (85·7% foot)	14	12 (85·7%)	11·9	0 (0/0%)
Martin et al. (46)	Retrospective	20	UT grade 2A	Foot	17	14 (82·4%)	8·9	0 (0/0%)
Winters et al. (47)	Retrospective	12	UT grades 1–3	Lower extremity (86·0% foot)	100	22 (22·0%)	9·6	
		20	UT grade 2A		18	9 (50·0%)	9·8	
		20	UT grades 1–3		100	91 (91·0%)	13·8	1 (1%) (non compliance)

Key Points

- the results of this prospective, randomised, multicentre study indicate that diabetic foot ulcers treated with AM therapy have a two to three times higher probability of healing compared with those with standard of care management
- the study also suggests that the probability of healing in 12 weeks may be affected by initial wound size
- this study lends further support to the safety of AM therapy, as infection and possible graft-related complications did not occur
- the proportion of wounds healed also exceeds a recommended benchmark for assessing wound treatment methods
- based on the successful results obtained with AM therapy and the clinical importance of prompt wound healing in overall outcome, the use of AM therapy for the treatment of diabetic, neuropathic ulcers is supported

remaining 14·3% had ulcers that did not increase or decrease in size. Although 71·4% patients in the control group experienced a decrease in ulcer size, the remaining 23·8% had ulcers that increased in size. Therefore, because a large percentage of ulcers were improving in size at the conclusion of the study, observing the ulcers for another 4–12 weeks would be beneficial in determining how many more ulcers would heal and in identifying any further differences in healing proportion or mean complete healing time between treatment groups. The additional data also would allow more comparisons to other studies in the literature.

The results of this prospective, randomised, multicentre study indicate that diabetic foot ulcers treated with AM therapy have a two to three times higher probability of healing compared with those with standard of care management. The 69·6% proportion of healed ulcers in the study group was significantly higher than the 46·2% proportion of healed ulcers in the study group. In addition, at the 12-week endpoint, the non healing rate of 53·8% in the control group was significantly higher than the 30·4% non healing rate observed in the study group. The study also suggests that the probability of healing in 12 weeks may be affected by initial wound size. This study lends further support to the safety of AM therapy, as infection and possible graft-related complications did not occur. The proportion of wounds healed also exceeds a recommended benchmark for assessing wound treatment methods. Based on the successful results obtained with AM therapy and the clinical importance of prompt wound healing in overall outcome, the use of AM therapy for the treatment of diabetic, neuropathic ulcers is supported.

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