Treatment of diabetic foot ulcers with dehydrated amniotic membrane allograft: a prospective case series

Objective: A diabetic foot ulcer (DFU) is one of the many potential complications associated with diabetes. If not effectively and rapidly treated, DFUs can result in lower extremity amputations. This prospective case series aimed to assess the effectiveness of a dehydrated amniotic-derived tissue allograft (DAMA), with regards to time to wound closure and total number of applications.
Method: Patients were recruited with a neuropathic non-healing DFU(s) despite standard care for at least 4 weeks before the study. The number of DAMA applications and time between applications was based on the physician's judgment. For the majority of patients (n=13/14), offloading, usually total contact casting (TCC), was used in conjunction with DAMA. Wounds were assessed, measured, and photographed every 1–2 weeks.
Results: Cases included 14 patients (11 men, 3 women; mean age 56.7±9.1 years) with 15 non-healing neuropathic DFUs with a mean baseline wound area of 6.5±11.6cm^2 (median: 2.2cm^2; range: 0.1–44.2cm^2) and mean volume of 4.3±10.9cm^3 (median: 0.3cm^3; range: 0–39.8cm^3). All patients in this series achieved complete wound closure within a median time of 5 weeks (range: 1–14 weeks). Wound area was reduced by a median of 58.3% at week 1 and 74.1% at week 3, and volume by a median of 62.8% at week 1, 97.4% at week 3 and by a median of 100% at week 5 and all time points thereafter. Patients received a median of 2 DAMA applications (range: 1–11). In those that required more than 1 application (n=12), DAMA was applied at intervals of 1 week (n=3) or ≥2 weeks (n=9). Smaller wounds (areas <2.2cm^2) closed rapidly (<1 month, 1–2 applications), whereas larger wounds (>2.2cm^2) required >2 weekly/biweekly applications.
Conclusion: The use of DAMA, particularly when coupled with TCC, led to wound closure of DFUs in all patients in this case series, including complex patients with DFUs of ≥1 year in duration, lack of prior response to conservative treatment measures, area >10cm^2 and/or multiple comorbidities. Prospective randomised trials would help to elucidate the precise role of DAMA in these encouraging results.
Declaration of interest: Derma Sciences, Inc. (Princeton, NJ) funded editorial support services.

diabetes ● diabetic foot ulcer ● wound healing ● bioengineered skin substitute

Diabetic foot ulcers (DFUs) are difficult to treat and require extensive wound care interventions, as demonstrated by a study that found that after 20 weeks of standard wound care, nearly 70% still had not healed.[1] There are different approaches to the management of DFUs but ultimately an approach that can help to prevent the 'amputation stairway' of compounding steps from diabetes and neuropathy through to amputation would be of benefit to patients. Standard care options for DFUs include glucose control, treatment of infection, promotion of revascularisation, debridement, offloading, and wound care.[2–5] With regards to offloading, Total Contact Casting (TCC) is considered the cornerstone and gold standard based on its demonstrated efficacy.[6–12]

Advanced adjunctive therapies for non-healing DFUs include hyperbaric oxygen therapy, electric stimulation, negative pressure wound therapy (NPWT), growth factors, and cellular and/or tissue-based products (CTPs).[2,3,13] However, surgery (vascular, nonvascular, and—as a last resort—amputation) may be necessary in some cases.[2] The use of these advanced wound care modalities should be considered if wound area is not reduced by 50% after 4 weeks of standard care management.[14,15]

The CTP reported here is a dehydrated amniotic-derived tissue allograft (DAMA; AMNIOEXCEL; Derma Sciences, Inc., Princeton, NJ), minimally-manipulated sterile amniotic tissue obtained from caesarean section births, with preserved collagen architecture, cytokines, growth factors, matrix markers, and basement membrane.[16,17] Advantages of amniotic membranes include their non-immunogenic and anti-inflammatory properties which help to promote epithelialisation.[17–19]

In this case series, the effectiveness of DAMA is assessed, with regard to time to wound closure and total number of applications, within a protocol of care for DFUs including offloading (majority TCC-EZ Total Contact Casting System, Derma Sciences, Inc., Princeton, NJ).

Methods

A prospective, case series of patients with DFUs treated with DAMA was conducted at Christian Hospital and Saint Anthony Medical Center in St. Louis, Missouri, from November 2014 to June 2015. Institutional review board approval was received from

R.J. Abdo, DPM, CWS;
E-mail: raymond.abdo@me.com
Christian Northeast Hospital, St. Anthony's Medical Center, St. Louis, MO

Fig 1. Dehydrated amniotic-derived tissue allograft being applied to a wound

each facility. Patients provided written consent to use their cases and photos.

Those included were men or women ≥18 years of age with neuropathic DFU(s) not exhibiting progressive wound closure or healing despite standard care (including any combination of foam, alginates, honey dressings and in some cases advanced modalities) for at least 4 weeks before the study. Wounds had to be <8cm x 4cm, with <20% nonviable tissue and no clinical signs of infection based on clinical assessment. In addition, the patients had to have adequate arterial blood supply to the foot and were receiving medical management for diabetes. If present, osteomyelitis or infection was successfully treated or resolved before DAMA application. Patients were excluded if they were medically unstable, pregnant or had participated in other clinical trials within 30 days before enrolment.

Application of dehydrated amniotic-derived tissue allograft

Following debridement, DAMA was applied by trimming it to fit of the wound (~1mm overlap of wound margins) under sterile conditions. DAMA was allowed to self-adhere (Fig 1) and was then covered with a non-adherent contact layer, secured with retention tape, and then covered with foam dressing. The number of DAMA applications and time between DAMA applications was based on the physician's judgment of need for additional applications.

Adjunctive treatment with an offloading device, most commonly TCC, was provided. Patients were given instructions for wound management in accordance with standard care, including education on the importance of offloading. Follow-up visits were conducted weekly until wound closure. At each visit, the wounds were measured manually by ruler (length x width x depth in cm) and photographed, with exudate type and amount noted, and granulation percentage estimated.

In addition, patient information such as demographics and comorbidities, baseline wound information including onset date, and history including previous treatments, were noted. Vascular flow studies and arterial Doppler ultrasound were conducted and the patients were monitored for signs of adverse events.

The primary study outcome was time to complete wound closure (defined as re-epithelialisation with open area=0 cm^2 and volume=0 cm^3). The secondary outcome was percentage area and volume reduction at week 4 and every 2 weeks after until wound closure. Because the time to complete wound closure ranged from less than 4 weeks to as long as 15 weeks, additional post hoc analyses were performed to determine percentage of wound closure at weekly intervals for weeks 1 through 14.

Statisical analysis

Post hoc analysis included stratifying the cases based on baseline wound area, <2.2 cm^2 or ≥2.2 cm^2, with 2.2 cm^2 being the median area, to identify if baseline wound area impacted the outcomes of time to wound closure and number of DAMA applications.

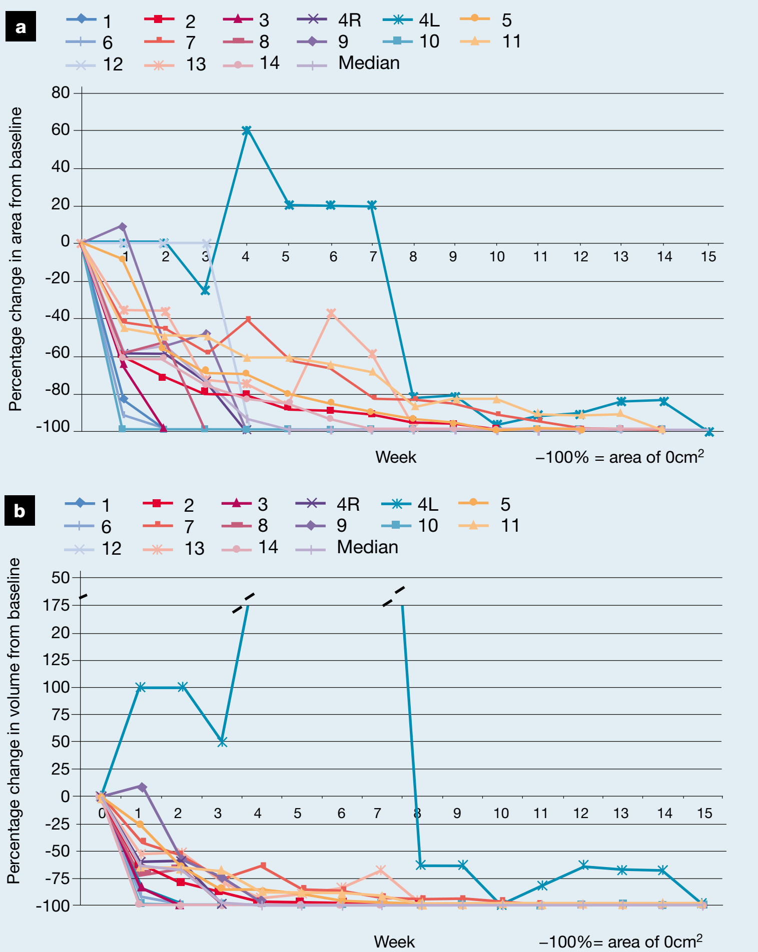
Descriptive statistics were completed by calculating wound area as length x width, wound volume as length x width x depth and percentage of wound closure calculated for area and volume by subtracting wound dimension at various time points from baseline wound dimension, divided by baseline wound dimension multiplied by 100%. The area and volume were recorded until both equaled zero, which was considered the date of complete wound closure. Percentage area and volume reduction calculations per time point were completed using median data given the small sample size and significant variation (i.e. non-normal distribution) of the data. The large variation was primarily due to the decision to include a patient with a large wound that was outside the inclusion criteria range. A last observation carried forward (LOCF) approach was used to compensate for missing data points due to missed appointments.

Results

There were 15 patients with 16 wounds who met the inclusion criteria. A 67-year-old man with Charcot foot with a DFU on the right plantar midfoot was removed from the study after six weekly DAMA applications due to need for surgical repair of the second metatarsal joint. At the time of discontinuation, his wound had decreased from an area of 2.3 cm^2 and volume of 0.7 cm^3 at baseline to 0.4 cm^2 and 0.1 cm^3 (82% and 88% reductions, respectively). Patient 2 had a wound measuring 9.4cm x 4.7cm x 0.9cm but was allowed to enroll, based on the author's judgment and IRB approval, despite the wound exceeding the pre-specified limits for inclusion. In this case, the patient's wound needed all the advanced technology at the author's disposal and therefore the decision was made to try DAMA despite him not meeting the inclusion criteria.

A total of 14 patients with 15 wounds were treated and followed until complete wound closure and were included in the study analysis. The baseline demographics included 11 men and 3 women, mean

Fig 2. Percentage change in wound size per wound over 15 weeks compared with baseline, last-observation-carried-forward analysis. Area (a) and volume (b)



age 56.7±9.1 years (range: 39–68 years). The mean baseline wound area was 6.5±11.6 cm^2 and median area was 2.2 cm^2 (range: 0.1–44.2 cm^2). Mean baseline volume was 4.3±10.9 cm^3 and the median 0.3 cm^2 (range: 0–39.8 cm^3).

For the primary endpoint, mean time to complete wound closure was 7.3±5.3 weeks and median time to closure was 5 weeks (range: 1–15 weeks).

For the secondary endpoint of percentage of wound closure, the median percentage reduction in wound area and volume was 100% at week 5 and all time points thereafter. Fig 2 demonstrates percentage change in area and volume for each of the individual patients as well as the median for the group at weekly intervals for weeks 1–15. Area was reduced by a median of 58.3%, 56% and 74.1% at weeks 1, 2 and 3, respectively, and volume was reduced by a median of 62.8%, 67.3% and 97.4% at weeks 1, 2 and 3, respectively. Patients in this case series were treated with a median of 2 DAMA applications (range: 1–11).

There were three wounds, ranging from 0.1 to 4.5 cm^2 in area and 0.0 to 0.9 cm^3 in volume which closed between weeks 1 and 3 after a single application of DAMA. There were five wounds, with areas of 0.2 to 1.6 cm^2 and volumes of 0 to 0.3 cm^3, which closed between weeks 3 to 5 after two applications. Seven wounds, with areas of 3.0 to 44.2cm^2 and volumes of 0.3 to 39.8cm^3 required more than two applications and took 7 to 15 weeks to achieve complete closure. Patient 2 with a large wound (area 44.2cm^2, volume 39.8cm^3) required 11 DAMA applications. This case is described in more detail in the case vignettes section.

Of the 12 wounds that required >1 DAMA application, applications were made at approximately weekly intervals for three wounds, and at intervals of ≥2 weeks in the other nine wounds. Results from the post hoc analysis revealed that subjects with baseline wound areas ≥2.2 cm^2 took longer, and required more DAMA applications, to achieve complete closure.

Patient cases

The following two cases provide examples of the types of wounds and patients included in this case series.

Patient 2: large wound

A 58-year-old man presented to the emergency department with a fever and a large, infected abscess (9.4cm x 4.7cm x 0.9cm) on the plantar aspect and wrapping medially of his right foot (Fig 3a and 3b). He had a long history of inconsistent contact with a physician. His comorbidities included diabetes, neuropathy and hypertension. Initial evaluation confirmed uncontrolled hypertension (pulse rate of 99bpm and blood pressure 177/90mmHg) and diabetes (HbA_{1c}=11.2%). Initial culture of the wound revealed it was positive for Gram-positive cocci and Gram-positive bacilli, which was subsequently treated.

In imaging analysis, the patient's X-ray showed a large lateral soft-tissue defect adjacent to the fifth metatarsophalangeal joint, with no osseous erosions. His MRI scan revealed mild acute osteomyelitis of the fifth metatarsal head and fluid collection on the lateral and plantar aspects of the midfoot. Arterial Doppler of the right lower extremity showed triphasic waveforms in the posterior tibial and dorsalis pedis arteries. Pulsatile waveforms were observed in the first digit and his right ankle brachial pressure index (ABPI) was 0.67.

At presentation, the patient underwent surgical debridement, after which he was treated with NPWT with MEDIHONEY gel (MDH, Derma Sciences, Inc., Princeton, NJ) for 4 weeks, followed by offloading with TCC and MDH for 1 week. He then received his first DAMA application (day 0). Wound closure following the first application created two smaller wounds. Data from these two wounds were summed and treated as a single wound for the purposes of the calculations reported in the preceding results. The patient received DAMA applications at approximately weekly intervals and exhibited progressive closure (Fig 3c). The smaller wound closed after 6 DAMA applications (7 weeks from initial DAMA treatment) and the larger wound closed after 11 DAMA applications (14 weeks from initial DAMA treatment) (Fig 3d).

Fig 3. Patient 2. large wound on day of presentation/surgery (a). Post-debridement (b), lateral (top picture) and plantar (bottom picture) views. Intermediate closure after 5 dehydrated amniotic-derived tissue allograft (DAMA) applications (c), lateral (top picture) and plantar (bottom picture) views. Wound closure after 6 DAMA applications (plantar) and 11 DAMA applications (lateral) (d)

Patient 13: refusal of total contact cast

A 64-year-old woman presented with a DFU with dimensions of 2.0cm x 2.0cm x 0.4cm on the plantar surface of the large toe on her right foot (Fig 4a) that had previously been treated with silver alginate. In addition to diabetes, she also had a history of hypertension, neuropathy, degenerative joint disease, renal disease, atrial fibrillation, chronic obstructive pulmonary disease, and coronary artery disease. Her last HbA_{1c} measurement (approximately 2 months prior) was 7.7%.

The wound was surgically debrided and DAMA was applied (day 0). The patient refused TCC, so offloading was provided by a removable postoperative shoe. Secondary dressings included non-adherent dressings, gauze, silicone dressings and mupirocin antibiotic.

At day 21 (3 weeks after initial treatment), the wound measured 1.0cm x 1.1cm x 0.3cm (72.5% area reduction; 79.4% volume reduction) (Fig 4b). A second DAMA was applied, with continued offloading. Over the next 2 weeks (through week 5 of treatment), wound healing was observed without further DAMA applications, such that the wound measured 0.7cm x 0.8cm x 0.3cm at week 5. At the next follow-up visit 1 week later, the wound had increased to 1.8cm x 1.4cm x 0.1cm. Another DAMA was applied, and the patient agreed to switch to TCC for offloading. With continued offloading, the wound continued to progress over the next 3 weeks, such that it was 0.3cm x 0.2cm x 0cm on day 58 (Fig 4c) and closed by day 70 (9 weeks after initial treatment). This case suggests that combination modalities are likely to be more effective than either method alone.

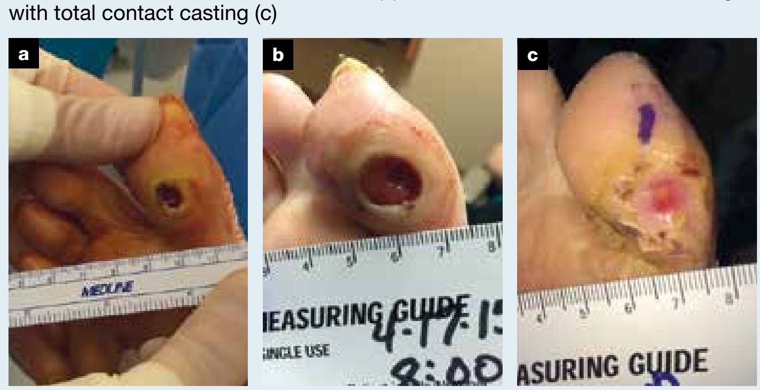
Discussion

This case series demonstrates that the use of DAMA, particularly in combination with TCC, can contribute to the closure of DFUs. Smaller wounds (i.e., areas <2.2 cm^2) generally closed rapidly (usually within 1 month) following 1 or 2 DAMA applications and adequate offloading, whereas larger wounds generally required weekly or biweekly applications over a longer treatment duration (7–15 weeks), combined with effective offloading (TCC), before closure was achieved.

Given adherence to treatment is so vital, it is important for physicians to set realistic expectations for patients, explaining that offloading and ongoing wound treatment applications over time are essential to achieve complete healing of their DFU and that larger wounds often require longer treatment. A positive outcome remains likely with good adherence to treatment.

In the current series, wound closure was achieved in all patients, even those with DFUs of greater than 1 year in duration before DAMA treatment with a lack of response to conservative treatment measures. Furthermore, wound closure was observed with wounds with areas >10 cm^2 (and one wound >40 cm^2), in a patient that needed bilateral wound care and casting, and in patients with multiple comorbidities.

Fig 4. Patient 13 refusal of total contact cast. Baseline wound (a). Three weeks after first dehydrated amniotic-derived tissue allograft (DAMA) application and offloading with post-operative shoe (b). Near complete closure at week 8 of treatment, after 3 DAMA applications and 2 weeks of offloading with total contact casting (c)



As large wounds (such as patient 2 with area >40 cm^2) often necessitate amputation, this case illustrates the potential for DAMA when coupled with TCC to assist in the closure of large wounds, which may help to prevent amputation.

Furthermore, in a prospective, randomised, non-blinded, single-center study of 25 patients with DFUs >1 cm^2 to <2 cm^2 and at least 4 weeks' duration treated with standard wound care (SOC) and a dehydrated amniotic membrane (1 to 6 applications) or SOC alone found the wound area reduced by 97.1% with the dehydrated amniotic membrane versus 32.0% with SOC (p<0.001) at 4 weeks and by 98.4% versus –1.8%, respectively, at 6 weeks (p<0.001).[25] Complete closure occurred at 6 weeks (92% versus 8%, respectively; p<0.001),[25] which was similar to the median time to closure of 5 weeks observed in the current case series.

A retrospective analysis of a different dehydrated amniotic membrane in the treatment of various chronic wounds found after 12 weeks of care, 76.1% of wounds were closed (67.6% of venous leg ulcers and 85.2% of DFUs).[13] With respect to DAMA, a recent case series with nine wounds in patients with diabetes and/or vascular disease found a mean time to closure of 5.7 weeks after a mean of 2.7 applications,[22] similar to the results here. Moreover, a recent multi-centre RCT found that 33% of subjects in the DAMA plus SOC cohort (n=15) achieved complete wound closure at or before week 6, compared with 0% of the SOC alone cohort (n=14), (intent-to-treat population, p=0.017). There was a more robust response noted in the per protocol population, with 45.5% of subjects in the DAMA and SOC cohort achieving complete wound closure, while 0% of SOC-alone subjects achieved complete closure (p=0.0083), which further align with the mean and median times to closure observed in the current case series.[26]

In this case series, in the majority of cases DAMA was combined with offloading with TCC. According to a recent consensus guideline, TCC is the preferred method for offloading DFUs.[12] Indeed, TCC is more effective than other offloading methods, particularly removable methods, which may, in part, be attributable to enforced adherence.[10,12,27] Yet, TCC is greatly underused in practice.[28–30] As such, advanced therapies such as CTPs are unlikely to be successful without offloading.[12] The benefits of TCC versus other methods of offloading are illustrated by the case of patient 13 presented here.

Limitations

Limitations of this case series include the small sample size and non-randomised, non-blinded study design with no active comparison group. In addition, the potential contribution to healing from TCC and other adjunctive therapies cannot be differentiated from effects of DAMA alone. These observations suggest the need for a prospective, randomised, controlled clinical study to compare the use of DAMA combined with TCC versus TCC alone, which is currently underway.[31] The cases included both acute and chronic wounds; therefore, for future studies it would be of interest to assess the impact of DAMA on acute versus chronic wounds with respect to time to healing and percentage of closure. Lastly, longer-term follow-up studies are needed to ascertain whether these patients will experience re-ulceration or will be able to avoid further excision and amputation.

Conclusion

In this case series, DAMA, particularly when coupled with TCC, contributed to the successful closure of DFUs that had not responded to SOC or, in some cases, advanced wound care modalities. The rapid closure noted is despite the inclusion of some complex patients with DFUs of greater than 1 year in duration, area greater than 10 cm^2 and/or multiple comorbidities. These results from this feasibility study suggest that the potential for the use of DAMA to facilitate repair of skin and combined with TCC to protect the wound from sheering and pressure, warrants further investigation. JWC

Acknowledments

The author thanks the staff at the Wound Care & Hyperbaric Center at Christian Hospital (St. Louis, MO) and St. Anthony Wound Care Center (St. Louis, MO).

References

1 Margolis, D.J., Kantor, J., Berlin, J.A. Healing of diabetic neuropathic foot ulcers receiving standard treatment. A meta-analysis. Diabetes Care 1999; 22: 5, 692–695.
2 Yazdanpanah, L., Nasiri, M., Adarvishi, S. Literature review on the management of diabetic foot ulcer. World J Diabetes 2015; 6: 1, 37–53.
3 Braun, L., Kim, P. J., Margolis, D.et al. What's new in the literature: an update of new research since the original WHS diabetic foot ulcer guidelines in 2006. Wound Repair Regen 2014; 22: 5, 594–604.
4 Alexiadou, K., Doupis, J. Management of diabetic foot ulcers. Diabetes Ther 2012; 3: 1, 4.
5 Wounds International. Best practice guidelines: Wound management in diabetes foot ulcers. 2014. Available at: http://bit.ly/1TXiWOO (accessed 4 June 2016).
6 Armstrong, D.G., Nguyen, H.C., Lavery, L.A. et al. Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care 2001; 24: 6, 1019–1022.
7 Armstrong, D.G., Lavery, L.A., Wu, S., Boulton, A.J. Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. Diabetes Care 2005; 28: 3, 551–554.
8 Katz, I.A., Harlan, A., Miranda-Palma, B.et al. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care 2005; 28: 3, 555–559.
9 Piaggesi, A., Macchiarini, S., Rizzo, L.et al. An off-the-shelf instant contact casting device for the management of diabetic foot ulcers: a randomized prospective trial versus traditional fiberglass cast. Diabetes Care 2007; 30: 3, 586–590.
10 Lavery, L. A., Higgins, K. R., La Fontaine, J.et al. Randomised clinical trial to compare total contact casts, healing sandals and a shear-reducing removable boot to heal diabetic foot ulcers. Int Wound J 2015; 12: 6, 710–715.
11 Mueller, M.J., Diamond, J.E., Sinacore, D.R.et al. Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. Diabetes Care. 1989; 12: 6, 384–388.
12 Snyder, R.J., Frykberg, R.G., Rogers, L.C.et al. The management of diabetic foot ulcers through optimal off-loading

building consensus guidelines and practical recommendations to improve outcomes. J Am Podiatr Med Assoc 2014; 104: 6, 555–567.
13 Regulski, M., Jacobstein, D.A., Petranto, R.D.et al. A retrospective analysis of a human cellular repair matrix for the treatment of chronic wounds. Ostomy Wound Manage. 2013; 59: 12, 38–43.
14 Warriner, R.A., 3rd, Cardinal, M. TIDE Investigators. Human fibroblast-derived dermal substitute: results from a treatment investigational device exemption (TIDE) study in diabetic foot ulcers. Adv Skin Wound Care 2011; 24: 7, 306–311.
15 Sheehan, P., Jones, P., Caselli, A.et al. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care 2003; 26: 6, 1879–1882.
16 AMNIOEXCEL Product Information Sheet. 2015. Derma Sciences Inc. Available at: http://bit.ly/1Y5LrJw (accessed 5 June 2016).
17 Werber, B. Martin, E. A prospective study of 20 foot and ankle wounds treated with cryopreserved amniotic membrane and fluid allograft. J Foot Ankle Surg 2013; 52: 5, 615–621.
18 Parolini, O., Solomon, A., Evangelista, M., Soncini, M. Wound Practice and Research In Berven, E. (ed). Human Plancenta; Structure and development. Nova Science Publishers, Inc, 2010.
19 Ueta, M., Kweon, M.N., Sano, Y.et al. Immunosuppressive properties of human amniotic membrane for mixed lymphocyte reaction. Clin Exp Immunol 2002; 129: 3, 464–470.
20 Shah, A.P. Using amniotic membrane allografts in the treatment of neuropathic foot ulcers. J Am Podiatr Med Assoc 2014; 104: 2, 198–202.
21 Penny, H., Rifkah, M., Weaver, A. et al. Dehydrated human amnion/chorion tissue in difficult-to-heal DFUs: a case series. J Wound Care 2015; 24: 3, 104–111.
22 Lintzeris, D., Yarrow, K., Johnson, L. et al. Use of a Dehydrated Amniotic Membrane Allograft on Lower Extremity Ulcers in Patients with Challenging Wounds: A Retrospective Case Series. Ostomy Wound Manage 2015; 61: 10, 30–36.
23 Sheikh, E.S., Sheikh, E.S., Fetterolf, D.E. Use of dehydrated human amniotic membrane allografts to promote healing in patients with refractory non healing wounds. Int Wound J 2014; 11: 6, 711–717.
24 Forbes, J. Fetterolf, D.E. Dehydrated amniotic membrane allografts for the treatment of chronic wounds: a case series. J Wound Care 2012; 21: 6, 290–296.
25 Zelen, C.M., Serena, T.E., Denoziere, G. Fetterolf, D.E. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. Int Wound 2013; 10: 5, 502–507.
26 Morona, J.K., Buckley, E.S., Jones, S. et al. Comparison of the clinical effectiveness of different off-loading devices for the treatment of neuropathic foot ulcers in patients with diabetes: a systematic review and meta-analysis. Diabetes Metab Res Rev 2013; 29: 3, 183–193.
27 Snyder, R. J., Shimozaki, K., Tallis, A. et al. A Prospective, Randomized, Multicenter, Controlled Evaluation of the Use of Dehydrated Amniotic Membrane Allograft Compared to Standard of Care for the Closure of Chronic Diabetic Foot Ulcer. Wounds 2016; 28: 3, 70–77.
28 Snyder, R.J., Frykberg, R.G., Rogers, L.C. et al. The management of diabetic foot ulcers through optimal off-loading: building consensus guidelines and practical recommendations to improve outcomes. J Am Podiatr Med Assoc 2014; 104: 6, 555–567.
29 Fife, C.E., Carter, M.J., Walker, D. et al. Diabetic foot ulcer off-loading: The gap between evidence and practice. Data from the US Wound Registry. Adv Skin Wound Care 2014; 27: 7, 310–316.
30 Wu, S.C., Jensen, J.L., Weber, A.K. et al. Use of pressure offloading devices in diabetic foot ulcers: do we practice what we preach? Diabetes Care 2008; 31: 11, 2118–2119.
31 ClinicalTrials.gov. A comparison of TCC-EZ using human amnion allograft vs. TCC-EZ and standard wound care in treating diabetec foot ulcers. Available at: http://1.usa.gov/1PDsBYS (accessed 4 June 2016).