ADVANCES IN WOUND THERAPY

UNDERSTANDING DIFFERENCES BETWEEN CELLULAR AND ACELLULAR THERAPIES IN THE TREATMENT OF CHRONIC WOUNDS

Supported by Osiris Therapeutics, Inc.

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The continued development of advanced wound therapies is quickly changing the field of wound care. With improvements in treatment, clinicians are able to help patients heal quicker and more easily, especially when utilizing cellular and acellular treatment modalities.

We presented Advances in Wound Therapy: Understanding Differences between Cellular and Acellular Therapies in the Treatment of Chronic Wounds in an accredited continuing medical education presentation at the SAWC Spring/WHS 2014 meeting at the Gaylord Palms Hotel and Convention Center in Orlando, Florida. The following non-CME supplement has been adapted from that presentation.

As we continue to emphasize multidisciplinary disease management in the treatment of high-risk patients with chronic wounds, facilitating an optimal wound healing environment and improving the time to healing are critical.

Accordingly, our discussion in this supplement begins with a conceptual framework and the current tools available for treating chronic wounds in our field. We differentiate between cellular and acellular modalities, noting the benefits and risks of each based on current research.

We then launch into a discussion about stem cells and how they are significantly altered in patients with diabetes. Advanced therapies can help address these issues by preserving stem cells and maintaining their functionality.

We reviewed the landscape of various advanced wound care treatments, assessing the clinical and scientific data, and levels of evidence for each. We also explored various case-based scenarios involving some of these advanced modalities in the treatment of chronic wounds.

We would like to thank Osiris Therapeutics for their support of this supplement. We hope that the insights generated through this discussion will help those of us who treat chronic wounds to achieve improved outcomes for our patients.

— Lawrence Lavery, DPM, MPH, and Dot Weir, RN, CWON, CWS

The thoughts and opinions expressed in this supplement are those of the authors and not necessarily those of Osiris Therapeutics.
FACULTY

Lawrence Lavery, DPM, MPH, is a Professor in the Department of Plastic Surgery, as well as Director of Clinical Research in the Department of Plastic Surgery, at the University of Texas Southwestern Medical Center, Dallas, TX. His research group has published 208 peer-reviewed papers and has received extramural funding from the VA, NIH, AHRQ, American Diabetes Association, and two American College of Foot and Ankle Surgeons.

He is the past chair of the American Diabetes Association Foot Care Council and the American Public Health Association Foot Section. He serves on the editorial board for Diabetes Care and has authored more than 100 peer-reviewed papers and several books. His areas of research interest include amputation prevention in high-risk diabetics, epidemiology of diabetic-related amputations, the use of footwear and insoles to prevent re-ulceration in high-risk diabetics, and fracture complications in diabetes.

Dot Weir, CWON, CWS, has been a registered nurse for 38 years, with 34 of those in wound and ostomy care. She has practiced in all areas of healthcare as well as industry. She is board certified by the Wound, Ostomy and Continence Nurses Certification Board (CWON) and the American Board of Wound Management (CWS). She practices part-time at the Wound Healing Center of Osceola Regional Medical Center in Kissimmee, Florida as well as the Wound Care and Hyperbaric Medicine Center at Health Central Hospital in Ocoee, Florida. Ms. Weir is the Co-Chair of the Symposium on Advanced Wound Care (SAWC), was on the founding board of the Association for the Advancement of Wound Care (AAWC), and has held positions as treasurer and president. She has been a member of the WOCN since 1980, the FAET since 1979, and a member of the WHS since 2008. Ms. Weir has authored and co-authored many journal articles and 6 book chapters. She is on the faculty of the Wound Certification Prep Course, Founding Editor of Today’s Wound Clinic, and Co-Chair of Present Wounds for Nurses and Therapists, an e-learning site.

DISCLOSURES

Dr. Lavery is a consultant for Innovative Therapies, Inc. (ITI), KCI Medical, and PamLab. He is on the speaker’s bureau for Innovative Therapies, Inc. (ITI), KCI Medical, PamLab, and Shire Regenerative Medicine. Dr. Lavery has received grant/research support from GlaxoSmithKline, Integra Lifesciences, KCI Medical, MacroCure, Osiris Therapeutics, Smith & Nephew, and ThermoTek. He has received royalties or holds patents with Diabetica Solutions. Dr. Lavery is a stock shareholder with Diabetica Solutions and Prizm Medical Resources.

Ms. Weir is on the advisory board or is a consultant for Mölnlycke Health Care, Spiracur, Smith & Nephew, Hollister, Organogenesis, and Central Medical Systems. She is on the speaker’s bureau for Osiris Therapeutics, Spiracur, Smith & Nephew, Hollister, Organogenesis, Mölnlycke Health Care, and BSN Medical.
In the diverse field of wound care, clinicians must be prepared with the necessary education and tools to heal patients. Even then, new challenges will be presented and innovative solutions found. Over the last few decades, wound care has become more advanced. With continually developing technology, the success rate of healing the most difficult wounds will greatly improve. In order to be successful in this role, clinicians must begin with the knowledge of how far wound care has come and how to create a conceptual framework.

CREATING A CONCEPTUAL FRAMEWORK

We have gone from simple disease awareness to a true focus on disease management as it relates to helping patients heal. We focus more on the wound environment and wound healing. Now we are really thinking about how we can prepare the wound and how it can actually impact cellular activity and wound healing. We are also focusing on time to healing, which is not only important from a morbidity and mortality standpoint, but also from a cost perspective. Wound healing is ultimately a multidisciplinary effort involving physicians, podiatrists, nurses, physical therapists, PAs, and other vital staff members.

TOOLS FOR TREATMENT

When we look at some of the products that we have to advance wound healing, they can be classified as either being cellular (containing living cells) or acellular (cells have been devitalized with or without removal from matrices). The sources of those can be biologic, coming from animals (equine, bovine, porcine, ovine, sharks, etc.), from human sources (cadaveric skin, placental tissues, neonatal fore skins), or from plants. Cellular products may also be made by combining cells with synthetic scaffolds, things that are not naturally present in our tissues but are able to coexist with our tissues, or they may be a composite of cells with both biologic and synthetic materials.

The goal of most cellular skin substitutes is to restore some sort of skin barrier and to promote wound closure. We want the cells to be able to secrete things like collagen and other extracellular matrix proteins. Cellular skin substitutes have the ability to interact and respond with their environment, and then synthesize the growth factors and extracellular matrix proteins that are needed based on the needs of that wound.

The cellular modalities are able to provide temporary wound coverage. They also help protect against losing moisture and provide some bacterial protection at least early on after application. These cellular products are not skin grafts. There is no vascularization and no ingrowth of vessels into the grafts. They do not integrate into the tissues and there is not necessarily any permanent persistence.

Interestingly, a recent study by Hu et al looked at bilayer cell therapies that were placed on partial-thickness skin graft
understanding differences between cellular and acellular therapies in the treatment of chronic wounds

... donor sites. At the end of 10 weeks, they did biopsies to look for the DNA persistence of the cellular product that had been placed on the donor sites and only 2 out of the 10 did have some residual persistence.

Another recent case by Serena et al was serendipitous. He put a bilayered skin substitute on a large wound. Ten months later, the patient returned with a wound in the previously treated area. A biopsy of the wound for human leukocyte antigen revealed the presence of donor DNA from the bilayered living cell therapy, suggesting that some cases may persist for longer periods in patients without underlying skin disease or immunosuppression.

One of the advantages of cellular therapies is that they do have active living cells in the construct. These cells, such as keratinocytes and fibroblasts, do have the ability to produce and synthesize various types of mediators such as cytokines and growth factors. In a product with a combination of two different cell types, a certain set of growth factors may come from the keratinocytes, which would then stimulate the fibroblast and synthesize other kinds of growth factors or cytokines in that particular wound.

Acellular matrices are usually human- and animal-derived products. They have been processed to devitalize cells, which can then be removed from matrices or left in them, leaving behind the collagen matrix and destroying any kind of pathogens by sterilization of the product as well as taking out anything that might cause some kind of an immune response. These are primarily collagen products that can be cross-linked. Cross-linking will stabilize them, make them more durable, inhibit or reduce the speed at which they biodegrade, and help prolong the presence in the wound. Many of these matrices can act as a biological modulator that helps to influence biological processes such as healing.

Acellular matrices interact with the wound bed. They provide scaffolding and can act as a sacrificial substrate to bind matrix metalloproteinases. The metalloproteinases then break down the matrix rather than the naturally occurring collagen in the wound. They provide support, a temporary scaffold for cellular migration and attachment, and can promote granulation tissue formation. At some point, they may contain certain growth factors that may or may not be present when the product is put on the wound. The optimal response is going to be achieved using a matrix...
that is as close as possible to the tissue that it is replacing. However, most collagen products are biologically recognized, which means that the source is not typically a problem.

We also have the human placenta, the use of which was first described in a large series of wounds as far back as 1910 (Figure 1). Fresh placenta is a combination of growth factors, collagen rich extracellular matrix, and viable cells such as neonatal fibroblasts, epithelial cells, and mesenchymal stem cells (Figure 2).

When we look at the tissue composition, we look at the actual structure of the placenta (Figure 2). There is the amnio-
on with active cells in the epithelial layer, the active basement membrane, the compact layer, and other cells, including stromal type cells.

In amniotic products alone, there are a variety of native extracellular matrix proteins, structural ones that help to provide tissue integrity such as the various collagens as well as elastin. In human tissue, we know this allows for elasticity, provides an organization to the matrix, a reservoir for growth factors, and other types of molecules. Proteoglycans help to retain moisture, and glycoproteins promote cell migration, adhesion, and mediate the interactions between the cells and extracellular matrix.

STEM CELLS

Stem cells provide matrix proteins, cytokines, and growth factors. The promise of stem cells is that they will be able to regulate things that we don’t even know need to be regulated. Stem cells should identify areas where there is high inflammation and down-regulate that; stimulate blood vessel formation; and recruit and support fibroblast and epithelial cell functions.

In patients with diabetes, there are a reduced number of stem cells and they are less effective (Figure 3). These patients have lower levels of growth factors and decreased numbers of functional stem cells. Their morphology is altered, growth is decreased, differentiation is decreased, and there are more dysfunctional cells that are senescent with increased apoptosis (Table 1). As the population ages and obesity increases, we are going to have older people with less functional stem cells in their native state. Applying a product that will provide stem cells could be an advantage for these patients.

The plethora of new products and some of the new changes in reimbursement have made us look to and learn more about the pathways for regulatory approval for some of these products. A lot of these products, collectively called human cellular- and tissue-based products or HCT/Ps, can be obtained from human tissue donors, processed and used in the exact same role in the recipient. It is tissue for tissue, skin for skin, tendon for tendon, bone for bone. The uses are regulated so they are intended for homologous use. They are expected to undergo minimal manipulation but they are strictly registered. Registration establishes proven good tissue practices and other procedures to prevent introduction, transmission, and spread of any kind of communicable disease by the modality.

When we look at the placental-derived acellular products, they are conceptually similar to the other acellular products. Most of them are comprised of dehydrated amnion and/or chorion membrane, and they reportedly retain the biologically active growth factors, cytokines, and tissue inhibitors of metalloproteinases 1, 2, and 4. They also contain other soluble mediators, but not the mesenchymal stem cells (MSCs) themselves. The soluble mediators may be able to recruit host MSCs and
provide biological extracellular matrix for cell ingrowth.

When we look at the cellular placental products, they are manufactured so they do retain the cells. They retain the extracellular matrix and the growth factors that are naturally found. They also contain those younger healthier neonatal MSCs. They contain epithelial cells, fibroblasts, and extracellular matrices that provide the three-dimensional support that allows for and promotes cellular adhesion and migration.7

One method of preserving these and having them available for our use is through cryopreservation. The majority of the studies on cryopreserv-
tation pertain to ocular science but there is significant impact on the structure and function of placental tissues. Comparing fresh tissue vs. dried vs. cryopreserved, there are differences when looking at the architecture (Table 2 and Figure 4).\textsuperscript{8-11}

**CELLULAR THERAPIES VS ACELLULAR THERAPIES**

There has been an explosion of products in this market, including bioengineered tissue, skin substitutes, and acellular dermal matrix products. However, one question remains: are cellular therapies better than acellular therapies?

Cellular therapies probably require slightly more work because they have to be stored in a freezer or delivered in a specific time period rather than being stored on a shelf for a longer period of time. Right now, there is no direct comparison as it is cost-prohibitive. Medicare is dividing these products into three categories for hospital-based clinics: high cost, low cost, and pass-throughs. Depending on your CMS carrier, some of the products from each category will be approved for reimbursement (Table 3). When deciding which products to use, the evidence pyramid, ranging from double-blind randomized controlled trials to \textit{in vitro} research, should be part of the decision.

**CURRENTLY AVAILABLE PRODUCTS**

There are currently a large number of products available. Dermagraft (Organogenesis, Inc.) is a cryopreserved human fibroblast derived from neonatal foreskin. It has three randomized clinical studies with two of the studies demonstrating effectiveness for diabetic foot ulcers (DFUs) and one study not demonstrating effectiveness for venous leg ulcers (VLUs).\textsuperscript{12-14} The pivotal trial on the platelet derived growth factor data for diabetic foot ulcers took place nearly 20 years ago.\textsuperscript{15} Our standard of care and what we expect from clinical

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\caption{Diabetes alters the regenerative potential of MSCs}
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Characteristics of Diabetic MSCs & \\
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Morphology & Altered \\
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Growth & Decreased \\
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Differentiation & Decreased \\
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Senescence and Apoptosis & Increased \\
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trials has changed. Regarding the clinical results from the study by Marston et al, only 30% of people healed in the 12-week study with Dermagraft and 18% healed in the control group. These are not impressive results. The time to healing was not reported, but there was significant reduction in infection in the people who got Dermagraft and they healed faster.

Apligraf (Organogenesis, Inc.) is a bilayered, epidermal and dermal layer product derived from neonatal foreskin. It is not cryopreserved. There are several high-level randomized clinical studies, including DFU studies and VLU studies, for this product. In a randomized DFU study involving 208 patients, 56% of people healed in the treatment group and 38% healed in the control group. There was faster healing time, but not a significant difference in infections. Only in the subgroup with osteomyelitis was there a difference in adverse events. The VLU data was also significant.

EpiFix (MiMedx Group, Inc.) is an acellular product made from placental tissue. It has collagen types IV, V, and VII. It is a product you can put on the shelf and it is not cryopreserved. There is a small, single-center, randomized clinical study on this product with 25 people in the treatment groups (13 EpiFix, 12 control). It has the best results that have ever been reported in any DFU study.

| TABLE 2. Cryopreservation Maintains Structure and Functionality of Placental Tissues |
|---------------------------------|-----------------|-----------------|-----------------|
| Structural and Functional Characteristics | Fresh | Dried | Cryopreserved |
| Tissue thickness | 85-90 mM | 45 mM | 90mM |
| Tissue degeneration | Not observed | Vacuolar degeneration | Not observed |
| Basement membrane ECMs | Intact | Degraded | Intact |
| TIMPs, TGFs, CTGF, IL-1ra, etc | Not reported | Not detectable | Sustain |
| Number of supported cultures | Not reported | 30% | 100% |
| Outgrowth area after day 18 | Not reported | 10-20 mm² | >100 mm² |

for the treatment group and probably the worst for the control group but the study is underpowered. There was a significant reduction in the time to healing. No infections were reported in the treatment group whereas 17% of the control group had infections.

Grafix (Osiris Therapeutics, Inc.) is a cryopreserved product derived from placental tissues in planned C-sections. This product has a single-blind clinical study that is currently still in review and a case series that was published last December. In the phase 4 clinical study, 62% of people healed in the treatment group, 21% in the control group, with significantly faster healing and fewer adverse events in the treatment group.

Graftjacket (KCI Medical) is an acellular regenerative tissue matrix. Reyzelman et al did a randomized, multicenter study comparing Graftjacket to moist wound healing for diabetic foot ulcers. It is a little bit unusual because there is a big difference in randomization in the two treatment arms. A noncompliant patient was removed from the study. According to the results, 70% healed, but if you put the noncompliant patient back in the study, 68% healed in the treatment group. In the control arm, 46% healed, which is still significant. The P value is .048. There was a significant difference in the time to healing if you take out the noncompliant patients.

Oasis (Smith & Nephew, Inc.) is an acellular product and there are several small, randomized clinical studies. One of the most vital studies is a VLU study that shows a significant increase in healing with people who are treated with the Oasis product. The

Figure 4. When comparing cryopreserved tissue to dried tissue, there are definite differences in the architecture of the tissues.
time to healing is not reported. There is not a significant reduction in infections in this group. The DFU studies that involved separate comparisons of Oasis to Regranex (Smith & Nephew, Inc.) and Dermagraft found no significant differences in the proportion of people who healed.23,25

There are a lot of randomized clinical studies for using Integra (Integra LifeSciences) for burns, but not so much in the diabetic foot. There is one small descriptive clinical study with 11 patients that suggests 64% wound healing.26 No infections were reported but this is a very small retrospective clinical experience.

Theraskin (Soluble Systems, LLC) is a human skin allograft with dermis and epidermis. It has some retrospective case series data in a large number of VLUs and DFUs with a high proportion of wounds that healed. They don’t report healing time or adverse events.27

Looking at the products that have randomized clinical studies and those that have high quality DFU studies that are powered in a reasonable way and report the evidence, there are just a few of products that are commercially available. In the DFU space, Dermagraft, Apligraf, Grafix and Graftjacket have higher-level, randomized clinical studies. In the VLU space, Apligraf and Oasis have supportive randomized controlled trials.

We have now changed the way we do clinical studies after looking at these cellular products in this space and their healing. Offloading is much better and more studies are requiring debridement on a regular basis as opposed to improvised debridement by the clinician. Perhaps the quality of what we do in the control arm is better but if you look at the data, these studies report 21% healing, 18%, 38%, and 46% in the control arms of these studies (Table 4).12,16,20,21 The time to closure is faster in the three studies that report it (Grafix, Apligraf and Graftjacket) and there are fewer

<table>
<thead>
<tr>
<th>TABLE 3. Medicare Payment Changes: CTPs*</th>
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<tbody>
<tr>
<td><strong>“High Cost CTPs”</strong></td>
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<td>Apligraf</td>
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<td><strong>“Low Cost CTPs”</strong></td>
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<td>Oasis</td>
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<td><strong>CTPs with Pass-Through Status in 2014</strong></td>
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<td>Grafix</td>
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*As of April 2014
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adverse events but not in the Graftjacket group. The odds ratio in the likelihood that the wounds would heal is the highest in the Grafix group. There is about a sixfold increased likelihood that people would heal in the Grafix study and the other studies range from a 2 to 2.4 odds ratio (Table 4).12,16,20,21

CHRONIC WOUNDS: TIME DRIVEN OR PATIENT DRIVEN?

What makes a wound really chronic? The literature states that 90 days is supposedly what defines a wound as chronic. It is unlikely that clinicians will wait 90 days to determine that a wound is chronic after debridement, wound preparation, compression, and offloading. When we look at what makes a wound chronic, is it time driven? Has the wound been there because it has been open for a long time? There are a lot of bacteria and proteases because of an extremely hostile environment. Due to the proteases and the hostility of the environment, we have growth factors and matrix proteins that are breaking down. We know that the cell surface receptors are going to be altered in one such wound environment. These types of wounds also get stuck in a chronically inflamed state. There is cellular senescence and there are those wounds that simply have not had adequate treatment. In this case, could the chronicity also be patient driven?

There are studies that have suggested prognostic indicators for time to healing. In regard to VLUs, Gelfand et al and Phillips et al found that if there is not a 40% reduction in the venous leg group by week 4, it is unlikely that the wound is going to achieve complete closure.
by 24 weeks.\textsuperscript{28,29} For diabetic foot ulcers, Sheehan et al found that if there is not a 50\% reduction in the wound size by 4 weeks, then it is unlikely to achieve complete healing by 12 weeks (\textbf{Figure 5}).\textsuperscript{30} Keeping that in mind, it should give us the impetus to consider advanced wound care modalities as early as possible.

The other things to consider about patient selection with more advanced wounds are the type, history, and duration of the wounds. We cannot forget about atypical wounds or traumatic wounds. For example, if a patient has a large avulsive injury on the leg and he or she comes in with hemosiderin staining, there is a bigger picture that we need to address before expecting the wound to heal.

\textbf{CASE REPORTS}

\textbf{Case Report 1}

A 34-year-old male patient with a past medical history of diabetes, ischemic cardiomyopathy, and ventricular tachycardia presented with an infected AICD device. His ventricular or cardiac device became infected and required removal. He was on several different medications for these ailments. The patient was required to wear a life vest to monitor his heart and react in the event that something went wrong until the wound healed. At his initial visit, we applied a cellular amnion product pre-debridement. The wound closed at day 21 so the patient could have another surgery and have a new device implanted (\textbf{Figure 6}).

\textbf{Case Report 2}

In this case, a 42-year-old male patient with a history of recurrent diabetic foot ulcers, right great toe amputation, hypertension, hyperlipidemia, type
2 diabetes mellitus for 15 years, and a hemoglobin A1c of 8 presented with a diabetic foot ulcer that had been present for 6 months. Initially, he was debrided and put into a contact cast. We also used a cellular amnion product on the wound. By day 30, his wound was epithelialized (Figure 7).

CONCLUSION
In conclusion, our role and how we interact in these patients’ lives is helping them heal. If we stay patient focused and practice diligence on the patients’ side, but also stay wound focused and use that wound assessment to drive the treatment decisions we make, we will ultimately make good decisions that lead to proper, efficient wound healing.

Q&A WITH THE PRESENTERS
Q: How do you choose cellular vs. acellular products to treat your patients?
Dr. Lavery: I don’t use a lot of products in this space that don’t have evidence when there are products that do. They are all going to cost a similar amount and you are going to get reimburshed a similar amount. It depends on the severity of the wound and resources that are available. I tend to use cellular products when possible. I live in a bizarre world where there is a tissue bank that regulates everything that may have ever come in contact with tissue so it is a lot harder for me to get new products into my facility. In regard to acellular products, Oasis has been on our formulary and that is the only one we have been able to get into our facility. My experience has been with Oasis in clinic. In the operating room, I have access because of burns and plastic surgery to Integra, AlloDerm and Graftjacket. It is not just a clinical decision anymore. There are people filtering my choices.
Ms. Weir: I think it is important whenever we can to just get experience and see how things work in our hands. We must learn what is available, where storage is possible, what services or representatives from the company are available.
available, and if there are patient assistance programs. There are a lot of things that can go on, but it still boils down to contracts and other factors within each hospital or hospital system.

Q: Can you comment on how easy it is to use a cryopreserved product? How is it stored? Do you have to have it delivered on the same day or can you store it in the hospital freezer? How does it work in practice?

Dr. Lavery: Cryopreserved products are kept in -80° freezers. In the practice environment I was in before I came to Dallas, we had a freezer in clinic so we would keep about 20 pieces in our clinic at a time. Our staff was well versed in our wound clinic. They under-

Figure 7. In case report 2, the patient presented with a diabetic foot ulcer that had been present for 6 months (A). After the wound was debrided (B), the patient was placed into a contact cast. The patient subsequently received application of an amnion product on the wound (C). By day 30, the wound was epithelialized (D).
stood the preparation process and they would prep the foot and prep the product. It is not a difficult process and it is easy once your team understands how to use it.

Ms. Weir: As the influencer or the support person in a clinic, once you learn how to thaw whatever you are using, the products are not particularly difficult to use. It is about how you fit this into your schedule and the tasks that you do in time to get the product ready before the procedure is performed. Any of the cryopreserved products for our facility are shipped on dry ice and the individual companies would be able to tell us how long the product can stay in the clinic.

Q: If you were an insurance company, why would you approve anything?

Dr. Lavery: I think that is an interesting question. With clinical outcomes and treatment, what is likely the biggest cost as an insurance provider? It is hospitalization so faster healing and fewer complications mean fewer hospitalizations and fewer amputations. You can probably treat a lot more people less expensively as an outpatient than you can going over your diagnosis-related group (DRG) with repeat trips to the operating room and imaging and labs for someone who gets admitted to the hospital. As an insurer, you want to keep these people out of the hospital because once they have a wound, about 60% of people are going to get infected and about a third of those people are going to end up in the hospital. Once that happens, they are coming back. I think it is a lot less expensive to do things in clinic even with expensive products that work. You shouldn’t pay for expensive products that don’t work. The most expensive product is one that doesn’t work.

Ms. Weir: We need to know how these things work in our hands. There is going to come a point in time with outpatient care in which we are going to be given a bundled amount of money and that is all we are given to heal the patient. Spending more money up front or incuring more cost up front and healing them in a shorter period of time will probably tip the scales for the better.

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A Natural Approach to Wound Treatment

- Designed for application directly to acute and chronic wounds, including but not limited to, diabetic foot ulcers and venous leg ulcers
- Flexible, conforming and adheres to complex anatomies
- Available in multiple sizes

Randomized Multi-Center Trial Comparing Grafix vs. Conventional Care in 97 Patients With Diabetic Foot Ulcers

- Median time to closure was 42 days compared to 70 days for the control group (n=97, p=0.019)
- 50% fewer infections occurred in the Grafix group than control (18% vs. 36%, p=0.044)

1a. Rate of improvement between healing rates over control.