Novel Multivalent Wound-Healing Ointment Provides Bioburden Control and Moisture Management: A Retrospective Registry Data Analysis

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ABSTRACT

OBJECTIVE: The purpose of this retrospective registry data analysis was to explore the effectiveness of a novel multivalent topical ointment (Terrasil Infection Control Wound Care Ointment; Aspiera Medical, Woonsocket, Rhode Island), containing a patented mineral complex and 0.2% benzethonium chloride in the treatment of nonhealing acute and chronic wounds.

DESIGN: Aspiera Medical designed a registry to capture physician experiences and treatment results with Terrasil Infection Control Wound Care Ointment. Physicians were asked to enter deidentified patient data into an online registry.

SETTING: Wound clinics in the United States were asked to participate in the registry.

PATIENTS: Physicians at 4 wound clinics treated 30 patients (26 of whom completed the treatment) with various chronic wounds that had persisted for an average of 6 months and entered treatment data into the registry.

INTERVENTIONS: Patients applied the ointment according to physician orders. Concurrent treatments used by patients included offloading, compression wraps, and dressings, such as collagen and calcium alginate. Patients were treated until complete wound closure or lost to follow-up.

MAIN OUTCOME MEASURES: Physicians calculated each patient's percentage wound reduction at each visit.

MAIN RESULTS: Thirty patients were entered into the registry. Pretreatment and posttreatment measurements were available for 26 of them. Patients achieved an average surface area reduction of 84% in a mean of 23 days' treatment.

CONCLUSION: The antimicrobial and moisturizing ointment studied appears to be effective in promoting wound closure in a variety of acute and chronic wounds. Wounds studied included diabetic foot ulcers, venous leg ulcers, venous stasis ulcers, surgical infections, burns, and insect bites. The results of this registry data analysis will be used to inform planned clinical trials.

KEYWORDS: wound closure techniques, wound healing, wound infection, diabetic foot ulcer, pressure ulcer, antimicrobial agents

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INTRODUCTION

Chronic wounds represent a major and likely underappreciated public health challenge. Experts often define a chronic wound as one that does not heal within 1 to 3 months of standard treatment.[1,2] The American Society of Plastic Surgeons defines chronic wounds as those that fail to respond to initial therapy or persist despite appropriate care.[3]

Worldwide, an estimated 1% to 2% of the population in developed countries experience a chronic wound during their lifetime.[4,5] In the United States, chronic wounds afflict an estimated 6.5 million people.[5] This represents more than $20 billion in healthcare costs annually, including the costs of wound care products, healthcare providers, and hospital care.[6] In addition, chronic

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limb ulceration of one form or another afflicts nearly 15% of older American adults.[3] Furthermore, the worldwide prevalence of chronic pressure, venous/arterial, and diabetic wounds is expected to grow 7.6% by 2020.[7,8]

Factors credited for the increasing incidence of chronic wounds in the United States include an aging population and a growing rate of diabetes. The American Diabetes Association reports that in 2012, 29.1 million Americans (9.3% of the population) had diabetes, versus 25.8 million (3%) in 2010.[9] The total global incidence of diabetes is estimated between 350 million,[10] or 2.8% of the world's population,[11] and 382 million.[12] The International Diabetes Foundation predicts that the number of cases worldwide will reach nearly 600 million by 2035.[12]

As many as 25% of persons with diabetes will develop a foot ulcer in their lifetime.[13] Moreover, diabetes is the leading cause of nontraumatic lower-extremity amputation in the United States: on average, 3.9 of every 1000 people with diagnosed diabetes will require a lower-limb amputation.[14] Following amputation, studies show 3- and 5-year mortality for patients with diabetes is 33% and 68%, respectively.[15,16] Along with diabetic foot ulcers (DFUs), common types of chronic wounds include venous leg ulcers (VLUs), pressure ulcers (PrUs), neuropathic ulcers, traumatic ulcers, and arterial ulcers.[17]

Unlike acute wounds, chronic wounds essentially stall in 1 or more stages of the normal healing process because of excessive bacterial burden, inappropriate moisture balance, and/or inadequate circulation.[18] To address such factors in a comprehensive, orderly fashion, the key principles of wound bed preparation and management have evolved to include tissue management, inflammation and infection control, moisture balance, and edge advancement, known collectively as the TIME algorithm.[18,19]

In brief, tissue management includes any of several methods for removing necrotic tissue overlying the wound base, partly because this tissue promotes bacterial growth and may obscure signs of local wound infection.[1] Such bacteria can produce harmful metalloproteinases that adversely affect extracellular matrix components during healing, as well as compete for scarce local resources such as oxygen.[20] Controlling infections and inflammation requires reducing the bacterial burden—specifically, its density and pathogenicity.[21] Physicians commonly prescribe systemic antibiotics, after cultures confirm the responsible microorganisms and their sensitivities, for wound infection and associated inflammation.[22,23]

Numerous topical antimicrobials are available to the wound care practitioner. These include silver gels, foams, creams, and alginates, as well as agents with antimicrobial properties that do not contain silver, such as polyhexamethylene biguanide (also known as polihexanide/PHMB), honey dressings, and cadexomer iodine. Not only do optimal topical wound treatments ensure a moist wound bed, but increasingly, they also contain ingredients such as antiseptics that might help optimize the healing process.[24] In keeping with this approach, the study ointment is designed to address bacterial burden and wound bed moisture.

Many antimicrobial agents, such as topical antibiotics, antiseptics, and silver preparations, have been investigated for possible toxicity toward skin and other human cells. Studies show that triple antibiotic ointments can significantly inhibit keratinocyte growth rate,[25] as well as having deleterious effects on fibroblast viability.[26] Triple antibiotic ointment use has shown an increase in inflammation through the promotion of cytokine interleukin 6.[26]

Regarding silver-releasing dressings, a meta-analysis of 1399 patients found that silver dressings significantly improved wound healing, reduced odor and pain-related symptoms, and decreased wound exudates versus other approaches.[27] When cytotoxicity was measured in an assay that involved 24-hour in vitro incubation, however, silver products were among the 3 most cytotoxic antimicrobials in a study done by Kempf et al.[28] Another study noted a significant delay of reepithelialization when using silver dressings.[29] Lastly, PHMB has displayed amoebicidal properties, but it exhibited more cytotoxicity toward keratocytes than its equally efficient counterpart, chlorhexidine.[30]

Preclinical studies using an investigational product, Terrasil Infection Control Wound Care Ointment (Aspiera Medical, Woonsocket, Rhode Island), have shown it to be relatively noncytotoxic.[31] In addition, there have been no reports of adverse reactions to the ointment in clinical use since its introduction in 2012.[32]

Optimal wound healing also requires maintaining a wound bed moist enough to avoid eschar formation and promote reepithelialization and formation of granulation tissue, while avoiding excessive moisture, which could result in maceration at the wound edges.[33] To achieve these goals, physicians can choose from a variety of dressings depending on the wound bed's moisture level. Highly exudative wounds, for example, might require absorptive alginate dressings or negative-pressure wound therapy, which helps drain excess fluid. Conversely, a dry wound eschar might benefit from an occlusive or semiocclusive dressing, such as a hydrocolloid.[1]

MATERIALS AND METHODS

Physicians used a 0.2% benzethonium chloride antiseptic ointment formulated with a multivalent complex that includes positively charged ions with multiple electromotive valences. Positively charged ions are strongly attracted to the negatively charged ions commonly found on the outer membrane of bacterial cells, whether gram positive or gram negative.[34–36]

In addition, clinical observations suggest that the inactive vehicle ingredients jojoba seed oil (*Simmondsia chinensis*) and natural

beeswax (*Cera alba*) in the test formulation are capable of managing moisture without causing maceration in the wound or periwound area. Studies also have shown that jojoba oil facilitates cutaneous penetration of active ingredients.[37,38]

In vitro data were obtained from Aidance Scientific, and these studies suggest that the ointment is effective in reducing bacterial burden as demonstrated in Figures 1 and 2.

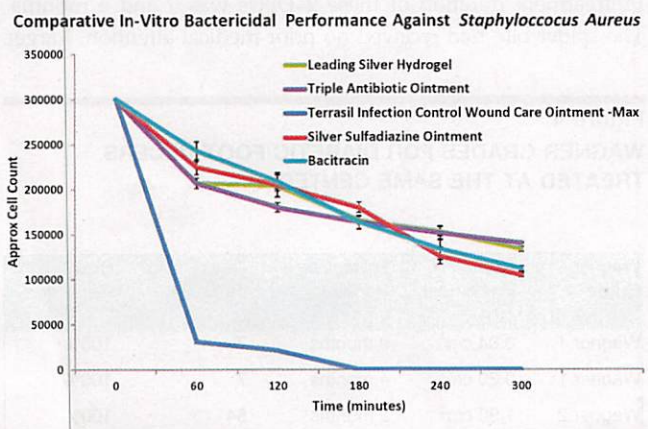
To assess the effectiveness of the ointment in promoting wound healing, physicians at 4 geographically separate wound care centers in the United States treated 30 adult patients with nonhealing wounds that had persisted for more than 30 days. These wounds included diabetic, venous, and arterial ulcers, as well as traumatic wounds, including full-thickness burns, and postsurgical wounds. The physicians then entered deidentified treatment data, including wound measurements and characteristics into the registry. Schulman Associates Institutional Review Board (IRB) determined that because the patient registry took the form of a series of deidentified case studies the study activities did not involve human subjects as defined by federal regulations [45 CFR 46.102(f)] and therefore were not subject to IRB review requirements and did not require IRB approval.[39]

Ultimately, 26 patients completed the treatment, and 4 patients failed to complete the treatment. Some failed to return for follow-up, and in other cases, the necessary data and photographs were unavailable.

Although patients underwent treatment at 4 separate wound care centers, these centers used a standardized wound care treatment plan. Patients generally applied the study ointment once daily, except in cases involving compression therapy, in which it was applied 1 to 3 times weekly, at the time of rewrapping the extremity. Physicians measured wound length, width, and depth during each patient's initial visit and at weekly follow-up visits. Physicians treated patients for 4 weeks, although some patients' treatment continued for up to 9 weeks. Entering wound measurements into the registry allowed physicians to correlate the size of each wound at baseline with the end of treatment for all patients who completed their treatment.

Along with the ointment, patients used various concurrent treatments prescribed by their treating physicians. These ranged from offloading to assorted pressure wraps and dressings, as well as topical agents such as collagen and calcium alginate.

Figure 1.
COMPARISON OF BACTERICIDAL PERFORMANCE AGAINST *STAPHYLOCCOCUS AUREUS*



The line graph shows the results of an in vitro study to determine the comparative bactericidal performance of 5 topical agents against *Staphylococcus aureus*.

RESULTS

Diabetic foot ulcers represented more than one-third of the treated wounds (n = 10) (Figure 3). Other wounds treated included 6 VLUs, 3 PrUs, 3 postsurgical wounds, 2 venous stasis ulcers, 1 full-thickness burn, and 1 spider bite. The age of the treated wounds averaged approximately 6 months, and the vast majority of patients were of Medicare age.

Analysis by Wound Type

The largest size reductions, 100% and 98%, occurred with the spider bite and the burn wound, respectively (at 7 and 21 days' treatment, respectively). Clearly, these high closure rates are skewed by the fact that each category includes only a single representative wound.

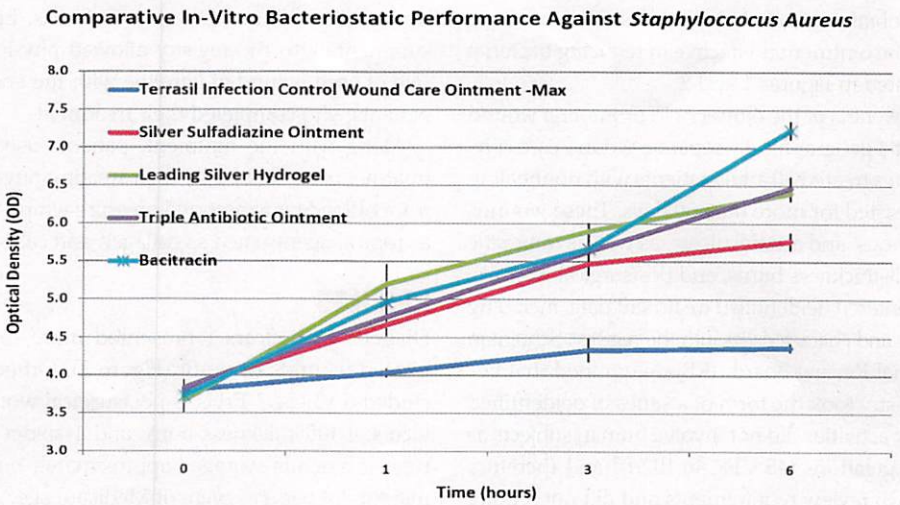
In contrast, the largest wound categories represented, DFUs and VLUs (including stasis ulcers), achieved average reductions of 83.2% and 49.9% (at an average of 22 and 31 days, respectively). In aggregate, VLUs achieved the lowest closure rate among wound types studied with at least 3 wounds in the sample (the 2 stasis ulcers achieved an average 11% reduction, which might be explained by their large average starting size of 13.9 cm^2 and their short average treatment time of 21 days).

Diabetic Foot Ulcers

On average, the 10 DFUs measured 4.4 cm at the start of the data collection. Wagner grades were available for 4 of the DFUs treated at the same center. The widely used Wagner classification system assesses the depth of ulceration and presence of osteomyelitis or gangrene,[40] as follows[41]:

- grade 0: high-risk foot without ulceration
- grade 1: superficial ulcer with exposed subcutaneous tissue
- grade 2: deep ulcer with exposed tendon and deep structures
- grade 3: ulcers extend to the deep tissue, with associated soft tissue abscess or osteomyelitis
- grade 4: ulcers include feet with localized gangrene
- grade 5: foot ulcers with extensive gangrene

Figure 2.
COMPARISON OF BACTERIOSTATIC PERFORMANCE AGAINST *STAPHYLOCCOCUS AUREUS*



The line graph shows the results of an in vitro study to determine the comparative bacteriostatic performance of 5 topical agents against *Staphylococcus aureus*.

The 4 DFUs for which Wagner grades were available included 2 Wagner grade 1, 1 Wagner grade 2, and 1 Wagner grade 3. Results for these wounds are shown in Figure 4.

Venous Leg and Other Ulcers

The 6 VLUs were among the larger wounds in the registry. Pretreatment VLU sizes ranged from 3.4 to 17.7 cm^2, with an average of 7.7 cm^2. In addition, the 3 postsurgical wounds achieved a mean size reduction of 94.2% at 25 days' treatment, versus a mean size reduction of 79% at 29 days for the 3 PrUs.

Aggregate Analysis

After treatment with the ointment, all patients achieved a reduction in wound size; specifically, an average surface area reduction of 84.1% at a mean of 23 days' treatment (Figure 5). Viewed in aggregate, at 7 to 14 days' treatment, the 26 patients on average experienced approximately 65% closure, versus approximately 93% closure at treatment days 15 through 45.

In addition, 10 patients experienced 100% wound closure at a mean of 27 days. Among these patients, the number of treatment days required to achieve 100% closure ranged from 7 (3 patients) to 63 (1 patient). Wounds that achieved full closure included 4 DFUs and 1 each of the following: VLU, foot ulcer related to peripheral vascular disease, PrU, postsurgical crush injury, surgical infection, and brown recluse spider bite.

Some small wounds achieved 100% healing in only 7 days. These wounds included 2 DFUs measuring 0.04 and 0.2 cm^2, respectively, and a spider bite that originally measured 0.78 cm^2. Pretreatment duration of these 2 DFUs was 9 and 4 months. The spider bite had received no prior medical attention. Larger

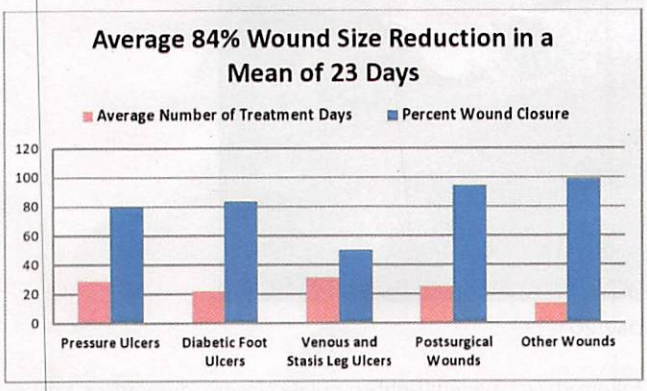
Figure 3.
ANALYSIS BY WOUND TYPE

		At Intake			At Conclusion				
Wound Type	Completed Case Quantity	Smallest Wound cm^2	Largest Wound cm^2	Average Size cm^2	Smallest Wound cm^2	Largest Wound cm^2	Average Size cm^2	Average Percent Reduction	Average No. of Days
Diabetic Foot Ulcer	10	0.04	11.40	4.40	0.00	5.70	1.14	83.2%	22
Leg Ulcer (Venous and Stasis)	8	3.40	17.70	9.28	0.00	16.00	5.21	49.9%	31
Pressure Ulcer	3	4.64	14.40	7.99	0.00	2.60	1.20	79.0%	29
Spider Bite (Brown Recluse)	1	0.78	0.78	0.78	0.00	0.00	0.00	100%	7
Postsurgical Wound	3	0.40	39.00	13.34	0.00	6.75	2.25	94.2%	25
Burn	1	448.00	448.00	448.00	9.00	9.00	9.00	98.0%	21
	26							84.1%	23

Figure 4.
WAGNER GRADES FOR DIABETIC FOOT ULCERS TREATED AT THE SAME CENTER

Wagner Grade	Size at Enrollment	Preregistry Period	Days Using Terrasil	Size Reduction
Wagner 1	0.04 cm^2	9 months	7	100%
Wagner 1	0.20 cm^2	4 months	7	100%
Wagner 2	1.90 cm^2	2 months	54	100%
Wagner 3	3 .00 cm^2	9 months	27	73%

Figure 5.
AGGREGATE ANALYSIS OF WOUND SIZE FOLLOWING TREATMENT



DFUs, however, also healed fairly quickly. The largest of these DFUs were 10.35 and 11.4 cm^2, which in 7 days achieved healing rates of 80% and 78%, respectively. Their pretreatment duration was 2 months and 1 month, respectively.

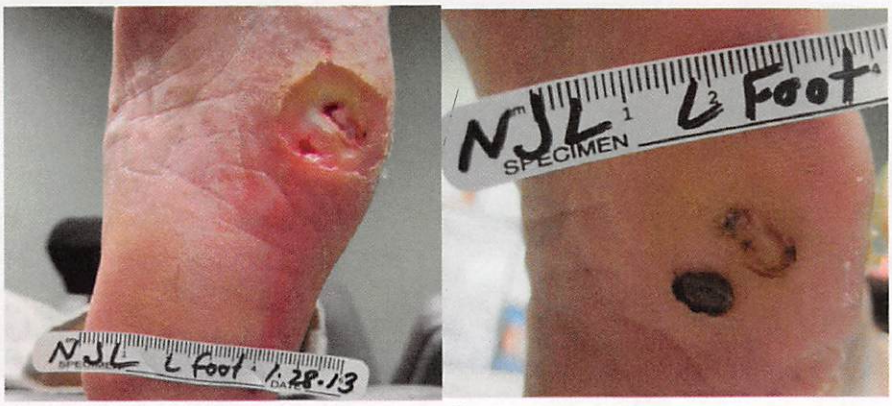
In Case 1, daily application of the ointment, with dry dressing and offloading (with a Charcot restraint orthotic walker boot), enabled a Wagner grade 1 DFU of 9 months' duration to achieve 100% closure in 1 week (Figure 6). The wound, located on the left plantar foot, initially measured 0.2 × 0.2 × 0.1 cm. Previous treatments this patient had tried included silver alginate dressing and offloading. Offloading is widely considered to be part of the criterion standard for care of DFUs, and a robust body of literature supports the efficacy of total contact casting in particular as the criterion standard among offloading methods.[42] Additional offloading devices include removable casts, half shoes, healing sandals, and custom-built braces.[42] Offloading can significantly improve clinical outcomes for DFUs. However, it should also be noted that before using the ointment this patient had used the Charcot restraint orthotic walker boot, as well as silver alginate dressing, with little effect.

The surgical infection case (Case 2), located on the patient's left nipple (Figure 7), had persisted for more than 6 weeks before initiating treatment with the ointment. On presentation, it measured 0.8 × 0.8 × 0.1 cm, with 10% granulation and some drainage. After 20 days of once-daily ointment application (and concurrent use of dry dressing), the wound was 100% smaller, with 100% granulation. Previous therapies this patient had tried included negative-pressure therapy and Dakin's (sodium hypochlorite solution) packing.

Regarding partial wound closures, 8 patients experienced 50% to 99% wound closure, at a mean of 30 days. Case 3 (Figure 8) involved a PrU of the left great toe with underlying chronic venous disease and bilateral lower-extremity lymphedema. This wound of 9 months' duration measured 2.6 × 1.9 cm at the beginning of treatment and had resisted treatments that included debridement and 4-layer compression wraps. After 2 weeks' application of Terrasil ointment (3–5 times weekly, with continued use of 4-layer compression wraps), the wound achieved 80% closure.

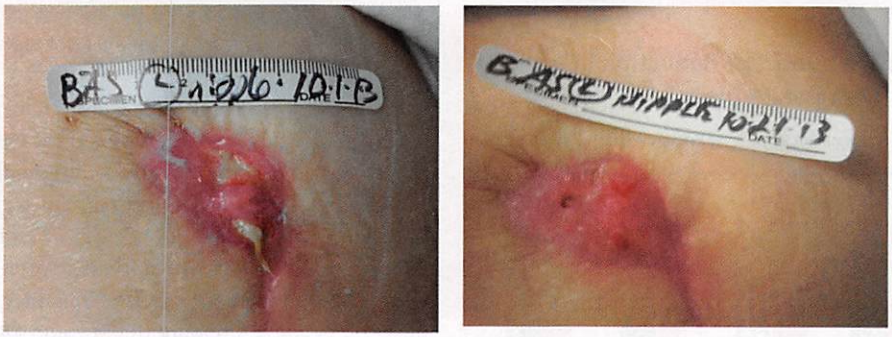
Case 4 (Figure 9) involved a VLU of 1 month's duration that presented with edema related to venous stasis. Initially, this wound measured 1.1 × 3.5 cm, with 100% granulation tissue and an intact periwound area. After 6 weeks of once-weekly ointment use under compression, the wound's size decreased by 85% (to 0.7 × 0.8 cm), with 100% granulation tissue. In outpatient

Figure 6.
CASE 1



Day 1 Day 7

Figure 7.
CASE EXAMPLE



Surgical infection, Day1 | Day 20

wound care settings, such as the ones involved in this registry, standard procedures include placing compression on the compression and having the patient return 1 week later for a recheck and dressing change.

The total number of treatment days required among patients who achieved partial wound closure ranged from 7 to 56 (2 patients each). Among this group, 3 wounds—1 DFU, 1 PrU, and 1 full-thickness burn—achieved 90% to 99% closure at a mean of 44.3 days. The remaining patients experienced between 11% and 47% closure at a mean of approximately 17 days.

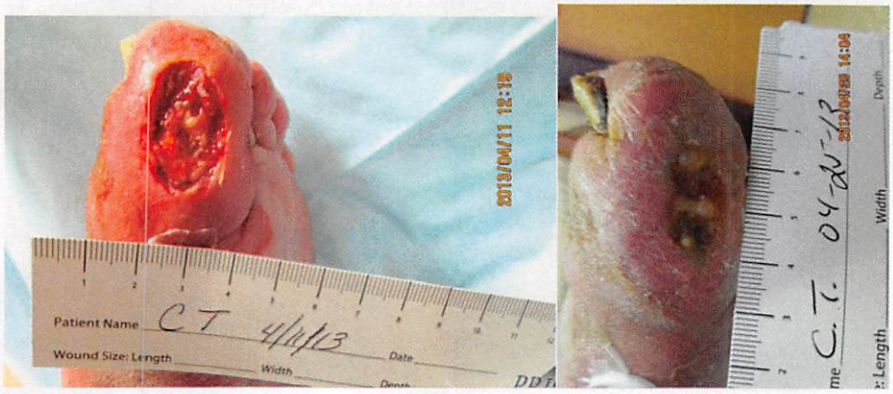
Overall, the number of days that patients used the study ointment varied from 7 to 63. Wounds treated for 7 days included 4 DFUs (with preregistry durations ranging from 1 to 9 months), 1 spider bite, and 1 VLU. The wound treated for 63 days was a VLU of 8 months' preregistry duration. Investigators followed each patient until complete closure, dropout, or a maximum of 2 months from the patient's study start date.

The frequency of ointment application also varied, from twice daily to once weekly, at the time of a dressing change. The variation in frequency of ointment application was based on the discretion of the principal investigator at each wound center, as well as the requirements for changing of secondary dressings.

DISCUSSION

The ointment simultaneously appears to maintain a moist wound healing environment and may reduce bacterial bioburden. This may provide both clinical and economic advantages in preparation of the chronic wound bed, whether through direct healing as a result of the ointment or in preparation for use of more advanced wound healing techniques.

Figure 8.
CASE 3



Pressure ulcer, Day 1 | Day 14

Figure 9.
CASE 4

Venous leg ulcer, Day 1 Day 42

Physicians observed that the ointment proved particularly effective in wounds with low levels of exudate, where adding moisture without causing maceration at wound edges often proves difficult. Although the ointment appears to control bioburden and manage moisture effectively, physicians who prescribed the product reported that because of the ointment's viscosity and potential to occlude it may not be indicated for heavily draining wounds.

The registry's strengths included its prospective nature, along with its inclusion of a relatively diverse range of wounds. This registry was intended to inform a future clinical trial in which investigators will evaluate additional factors, such as dosing variations and reduction in bacterial burden associated with the ointment.

Limitations of the registry included its small sample size and lack of a control or blinded comparison group. In addition, there was no tracking of adverse events. Furthermore, the wide variety of wounds treated and the variety in product usage regimens make drawing general conclusions difficult. Also, the fact that many patients applied their own medications and self-reported their application frequency made it difficult to assess patient adherence with complete accuracy.

The fact that patients continued with concurrent treatments, such as pressure wraps, dressings, and offloading, makes it difficult to differentiate if the ointment alone explains the rate at which wounds healed or if it was a result of combination treatments. Similarly, data regarding patients' pretreatment medical histories were limited, and data regarding how patients with underlying conditions were treated, including how many patients received systemic antibiotics, were not recorded. Also, physicians did not indicate whether wounds were infected upon entry into the study. The choice to use a topical antimicrobial was made by the physicians in the wound clinics when they suspected the presence of bioburden. Physicians also did not measure antimicrobial activity of the ointment.

Because this was a registry, physicians included patients prospectively, at the time patients presented, focusing mainly on the wounds' duration. The authors intend to use the results shown in this data analysis as a springboard for larger, more comprehensive clinical research that addresses the discussed limitations.

CONCLUSIONS

This retrospective registry data analysis suggests that the ointment may be effective in controlling bacterial bioburden and maintaining a moist wound healing environment. The registry permitted the physicians to evaluate the ointment on a variety of wound types. These data will be used to inform more comprehensive clinical research. ●

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