A Novel Comprehensive Therapeutic Approach to the Challenges of Chronic Wounds: A Brief Review and Clinical Experience Report

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ABSTRACT

Following the clinical perspective and concept that a healthy body will not develop chronic wounds, the central approach for the treatment described here is based on an understanding of how the body transforms the wound microenvironment from a non-healing to a healing state. As part of a comprehensive treatment regimen that includes OCM^{TM} (complete matrix), wound preparation, and skin protectant formulations, the OCM contains components for complete wound healing by attending to the individual needs required to promote the closure of each unique chronic wound. During application of the comprehensive treatment regimen in independent investigator-led trials, the total wound percentage average reduction over the first 4 weeks of treatment was 60% across multiple wound types; median time to total wound closure was 6.9 weeks. Safety testing of the OCM formulation shows no potential allergenicity, no potential sensitization, and no known product-related adverse events. Clinical trials evaluating the OCM formulation as part of the comprehensive treatment regimen of multiple wound types are underway. Results of clinical trials and real-world experiences will expand current knowledge of the wound-healing potential of this novel product.

Keywords: Chronic wound; Complete matrix; OCM; Refractory wound; Wound healing; Comprehensive wound management

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Key Summary Points

The report presents an overview of a combination therapy that includes a complete matrix (OCM™), a novel polyunsaturated fatty acid wound therapy matrix, and summarizes outcomes from real-world experiences in using it to treat various types of chronic or refractory wounds.

OCM is an anhydrous, amorphous solid that contains all natural components, including fish- and plant-derived mono- and polyunsaturated fatty acids (omega 3, 6, and 9), tissue-generating signaling molecules, and nutrients (vitamins A, C, D, and E and minerals).

Treatment with OCM resulted in closure across multiple wound types in 77% of patients with a mean healing time of 6.5 weeks and a 69% area reduction of wounds after 4 weeks of treatment. Safety testing shows no potential allergenicity, no potential sensitization, and no known product-related adverse events.

INTRODUCTION

A chronic wound is one that has failed to proceed through an orderly and timely series of events and does not heal at an expected rate [1]. Wounds that do not respond within 2–4 weeks of standard treatment are considered chronic and are characterized by an abnormal microenvironment (e.g., edema, reduced blood perfusion, inflammation, infection, and tissue degeneration) [2, 3]. Healthy individuals generally do not develop chronic wounds because of the body's natural healing ability; however, the risk of wounds becoming chronic increases with comorbidities, such as diabetes, vasculitis, immune suppression, certain health conditions that cause poor circulation, neuropathy and reduced mobility, or diseases that cause

ischemia [4]. Chronic wounds are generally indicative of a far more serious, underlying condition and should be regarded in a similar manner as, e.g., a lump in breast tissue, with the patient receiving a comprehensive workup including medical history, location, duration, physical assessment, vascular status, skin integrity, and so on. As the general population ages and individuals have an increasing number of comorbid conditions, successfully managing and treating chronic wounds will become increasingly important.

The most common types of chronic wounds are diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), and pressure ulcers (PrUs) [1]. The current annual incidence of DFUs worldwide is between 9.1 and 26.1 million [5]. Approximately 15–25% of patients with diabetes will develop a chronic ulcer at some point during their lifetime, and 1% of those patients will require an amputation [6]. With an aging population, numbers of patients presenting with chronic leg ulcers, including VLUs, have increased [7]. Recurrence rates of VLUs are high, 54–78%, and their chronicity can last for many years, having a devastating impact on an individual's physical and emotional well-being [8–10]. Currently, VLUs lead to an estimated annual direct cost for conservatively managed patients in developed countries as US $5527 per person per year [11]. Finally, PrUs can be a result of reduced mobility, a lack of protective sensation, and less supple skin, i.e., conditions for which risk increases during the aging process [7]. Immune suppression, emotional stress, and advanced age also adversely affect the body's natural healing ability [4].

In healthy, non-immunocompromised individuals, wound healing progresses through four stages of healing in a process that is complex and exquisitely orchestrated. First, a hemostasis stage forms a clot to seal and protect; then an inflammatory phase occurs during the first few days to further protect against infection, which is followed by a proliferative phase that lasts at least 3 weeks to build new tissue and seal the wound; and finally, a maturation and remodeling phase that can last up to 2 years [4]. Biological processes required for healing—i.e., formation of granulation tissue via cellular

Table 1 Challenges of treating chronic and refractory wounds

Type of wound	Standard treatment approaches [13]	Challenges to treating/healing
Chronic	Debridement	Excessive and painful debridement
	Moisture balance	Excess moisture
	Infection control	Inadequate control of inflammation
	Optimization of comorbidities	Heavy bioburden
		Lack of control of comorbidities
		Adherence to treatment
Refractory	Biologics	Difficult to treat
	Dermal substitutes	

proliferation, angiogenesis, and tissue remodeling—are stalled in chronic nonhealing wounds [12]. The majority of chronic wounds do not move past the inflammatory stage, characterized by bacterial burden, localized edema, poor perfusion, and persistent inflammation (Table 1) [13, 14]. While infection is most common to chronic wounds, the degree of bioburden is a determining factor in the ability of the individual's wound to heal [2].

The presence of bacteria and endotoxins within a wound can cause a prolonged elevation of proinflammatory cytokines (e.g., interleukin-1 and tumor necrosis factor-α) and a prolonged duration of the inflammatory phase, eventually leading to a chronic nonhealing state [15]. An elevation of matrix metalloproteases associated with prolonged inflammation can cause degradation to the extracellular matrix [15]. Infected wounds contain multiple species of bacteria, including *Staphylococcus aureus*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*, and once established, they become persistent and resistant to antimicrobial treatment [16, 17]. Resistance is often conferred by bacteria secreting extracellular polymeric substances, forming a 3-dimensional matrix called a biofilm that supports the adherence of certain microorganisms, including pathogenic bacteria, within the wound [16]. The biofilm increases the resistance of bacteria to antimicrobial and antiseptic treatment, highlighting the need for effective non-antibiotic therapies with antimicrobial properties for chronic nonhealing wounds.

An effective method to remove the biofilm in a chronic wound is by sharp debridement, a procedure recommended by the US Food and Drug Administration (FDA) to not only remove bioburden but also necrotic tissue. Other recommended standard care procedures that are used when needed for nonhealing wounds include off-loading, compression therapy for venous stasis ulcers, establishment of adequate blood circulation, maintenance of a moist wound environment, management of wound infection, wound cleansing, nutritional support (including blood glucose control for individuals with DFUs), and bowel and bladder care for individuals with PrUs at risk of contamination [18].

Every chronic and refractory wound is unique, and the varying pathophysiology of each wound, which affects healing time, depends on its type (e.g., DFU, PrU, VLU), in addition to individual factors such as blood supply, blood pressure, infection, and the patient's preexisting comorbidities [1]. Products designed to manage and regulate chronic or refractory wound healing include, e.g., human- and porcine-tissue-derived skin grafts or collagen matrices (Table 2). However, some of the skin substitutes and cellular tissue products are limited in their use: some are effective when the wound is showing signs of moving out of the inflammatory phase; some can only be used only on certain types of wounds; and some can only be used after treatment with conventional therapy has failed. Products derived from mammalian tissue, primarily those of porcine origin, carry a risk of disease transfer that is addressed through an FDA-required viral inactivation process [1]. If the viral inactivation process is inadequate, then a risk of pathogen transmission and infection remains. The FDA-recommended mitigation measures are aimed at

Table 2 Description and mechanism of action of products, including skin substitutes and cellular tissue products, used for the management of chronic and/or refractory wounds

Product name	Product description	Mechanism of action	Types of wounds	Contraindicated wound types
Apligraf	Bioengineered living cellular skin graft substitute [58] Human source	Activates keratinocytes at the wound edge; corrects and regulates growth factor signaling [59] Restores fibroblast function at the wound base Downregulates fibrosis formation [60]	Chronic wounds with limitations [58]: VLUs after 4 weeks of failed conventional therapy DFUs after 3 weeks of failed conventional therapy	Clinically infected wounds [58]
PuraPly	Combined collagen matrix and PHMB antimicrobial [61] Porcine source [61]	PHMB blocks microbial attachments, helping prevent biofilm reformation [62] The native collagen matrix forms a durable biocompatible scaffold that supports healing [61]	Various wound types [61]: Partial- and full-thickness wounds PrUs Venous ulcers Diabetic ulcers Chronic vascular ulcers Tunneled/undermined wounds Surgical wounds (donor sites/grafts, post Mohs surgery, post laser surgery, podiatric, wound dehiscence) Trauma wounds (abrasions, lacerations, second-degree burns, skin tears) Draining wounds	Third-degree burn wounds [61]

Table 2 continued

Product name	Product description	Mechanism of action	Types of wounds	Contraindicated wound types
Kerecis	Intact fish skin graft for tissue regeneration Fish source	Omega-3 anti-inflammatory properties Fish skin has an appropriate surface chemistry and microstructures that facilitate cellular attachment, competent mechanical strength, and biodegradation rate without undesirable by-products [63]	Various wound types [64]: Partial- and full-thickness wounds Trauma wounds Surgical wounds (donor sites, post Mohs surgery, post laser surgery, podiatric, wound dehiscence)	
Epifix	Dehydrated human amniotic membrane allograft [65] Human source	Supports the healing cascade and protects the wound bed to aid in the development of granulation tissue [65] Provides a human-biocompatible extracellular matrix that retains numerous inflammatory and wound-healing regulatory proteins [66, 67]	Various wound types [65]: Dehisced wounds DFUs VLUs PrUs Mohs surgery	Wounds with active or latent infection [65]
Epicord	Dehydrated human umbilical cord allograft (donated from C-sections of live births) [68] Human source	Forms a reinforced matrix to support the wound-healing cascade [69] Protects the wound bed to aid in the development of granulation tissue [69] Provides a biocompatible human extracellular matrix that retains multiple regulatory proteins [69]	Various acute and chronic wounds [68]: Smaller, deeper wounds DFUs VLUs PrUs Post debridement Complex defects	

Table 2 continued

Product name	Product description	Mechanism of action	Types of wounds	Contraindicated wound types
Grafix	Cryopreserved human amniotic membrane [70] Human source	Retains the native components of the human placental membrane: extracellular matrix, growth factors, and endogenous neonatal mesenchymal stem cells, fibroblasts, and epithelial cells [70] The extracellular matrix provides structural support and acts as a growth factor reservoir; growth factors and mediators stimulate growth and repair	Various acute and chronic wounds, including but not limited to the following [70]: DFUs VLUs PrUs Dehisced surgical wounds Burns Acute surgical wounds Pyoderma gangrenosum Epidermolysis bullosa	
Integra BioFix	Tissue allograft derived from allogeneic dehydrated and decellularized amniotic membrane [71] Human source	The extracellular matrix provides a foundation for regeneration, growth factors, fibronectin, integrins, laminins, and hyaluronic acid support cell proliferation, differentiation, and adherence to the scaffold [71]	Intended for use as a wound covering for surgical sites, voids, and tissue defects [71]	
Mirragen Advanced Wound Matrix	Biodegradable, bioactive borate-based glass fiber [72]	Bioactive glass materials have the potential to heal wounds by improving angiogenesis and supporting cell proliferation and differentiation [73]	Acute and chronic soft tissue wounds and injuries [72]	

Table 2 continued

Product name	Product description	Mechanism of action	Types of wounds	Contraindicated wound types
Theraskin	Skin allograft from donated human skin [74]	The allograft contains living cells, endogenous growth factors, and a native extracellular matrix [74]	Including, but not limited to the following [74]: DFUs VLUs PrUs Dehisced surgical wounds Necrotizing fasciitis Traumatic burns Radiation burns	

DFU diabetic foot ulcer, *PHMB* polyhexamethylene biguanide, *PrU* pressure ulcer, *VLU* venous leg ulcer

addressing potential health risks associated with animal-derived materials (e.g., adverse tissue reaction, infection, immunological reaction, pathogen transmission), which may increase the cost of some wound care products [1]. In addition, some wound-healing products are not acceptable to patients who have cultural or religious barriers surrounding the use of mammalian tissue [19]. Potential limitations of some skin substitutes and cellular tissue products highlight the need for a wound-healing therapy suitable for all patients with chronic or refractory wounds of any type or of any duration.

The goals of chronic and refractory wound therapy should be to manage and regulate bioburden, edema, and perfusion [20]. The most effective wound-healing therapy will meet these goals while providing the metabolites, growth factors, and signaling peptides required for the healing of all types of chronic or refractory wounds [13]. An amorphous solid combination drug/device product called OCM™ (Omeza complete Matrix, Omeza, LLC, Sarasota, FL) [21] and supporting therapeutics were developed to follow the clinical perspective and concept that a healthy body will not experience chronic wounds. When wounds are present on a healthy body, they are provided with all components needed for optimal results throughout each stage of healing. Understanding the aspects of an acute wound becoming a chronic wound and how to stimulate the body to transform the wound microenvironment from a non-healing to a healing state was a central concept in the development of this technology.

A COMBINATION THERAPY PROTOCOL FOR CHRONIC WOUND CARE

The combination therapy technology described here is composed of three investigative products: OCM [21] and two supporting formulations, a periwound prep with lidocaine (0.8%) and a skin protectant that both follow respective over-the-counter monographs [22, 23]. These products were designed to be applied in sequence (periwound prep, OCM, followed by skin protectant) and to target components of wound healing in chronic or refractory wounds (except third-degree burn wounds), regardless of pathology. All investigative products are anhydrous, with the intention of limiting water availability to provide a hostile environment for microorganism survival [24].

The first step in the treatment protocol is to apply the lidocaine formulation to the peri-wound 5 min prior to debridement, if debridement is required [25, 26]. The OCM product is applied next, directly onto the wound bed. The third step is to apply the skin protectant to the tissue surrounding the wound. The products contained in this combination therapy are noncytotoxic and safe, and OCM has been cleared by the FDA as having no potential allergenicity, no potential sensitization, and no known directly related adverse events (NCT04510376, NCT04510675, and NCT04512274). All three formulations contain no porcine or bovine products, thereby reducing the risk of virus transmission.

OCM Formulation

The OCM formulation contains all natural components, including fish- and plant-derived mono- and polyunsaturated fatty acids (omega 3, 6, and 9), tissue-generating signaling molecules, and nutrients (vitamins A, C, D, and E and minerals). These natural and sustainable components are formulated as an amorphous solid that coats the entire wound and provides a sheet to support the healing process below. The physical properties of OCM provide malleability so that it can easily conform to regular and irregular wound beds and into tunneling wounds.

OCM includes components, such as omega fatty acids, medium-chain triglyceride (MCT) oil (including caprylic acid and monolaurin), and hydrolyzed collagen peptides, that are shown to have anti-inflammatory and antimicrobial properties. Omega fatty acids are known to promote synthesis and activation of immune cells and to reduce inflammation, specifically the omega fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [27, 28]. Found only in oily fish, EPA and DHA have shown positive effects in animal models against rheumatoid arthritis, inflammatory bowel disease, and asthma [27, 29]. Studies with EPA and DHA have also shown disruption of lipid rafts for inhibition of the transcription factor nuclear factor-κB and consequently downregulation of

pro-inflammatory genes [27, 30]. Results of in vitro and in vivo studies have shown that MCT oil regulates the activation of macrophages from an M1-type to M2, and increases the production of anti-inflammatory cytokines while decreasing the production of pro-inflammatory cytokines through upregulation of β-oxidation [31]. Caprylic (octanoic) acid is an eight-carbon, short-chain fatty acid that has shown to be more effective than medium-chain and long-chain fatty acids as an antimicrobial [32, 33]. Caprylic acid is used as an antimicrobial agent in the horticultural industry and in commercial food handling and healthcare facilities [34]. Monolaurin (1-lauroyl-glycerol) is a monoglyceride with antimicrobial and antiviral activity [35]. In humans, lauric acid is converted to monolaurin, which has antimicrobial properties in human breast milk [36]. A recent study incorporated monolaurin into electrospun shellac nanofibers for potential use as a medicated dressing for wound treatment, based on the antimicrobial properties of monolaurin [37]. Importantly, OCM contains hydrolyzed fish collagen peptides that have shown both antimicrobial and antioxidant properties [38]. Results of in vitro studies showed that hydrolyzed collagen peptides induce an anti-inflammatory response that activates both human fibroblast and keratinocyte proliferation [39]. In addition, hydrolyzed collagen peptides promote new collagen formation by signaling to fibroblasts to increase elastin synthesis and the inhibition of metalloproteinase (MMP)-1 and MMP-3 degradation through transforming growth factor beta (TGFβ) signaling [40]. Because of their size, collagen lysates are less susceptible to MMP collagenases, which is an advantage for wound-healing progression from proliferation to remodeling; also, because of other physical properties, they are soluble and can bind calcium ions to improve their bioavailability [38, 41–44]. The hydrolyzed collagen is sourced from North Atlantic white fish skins (Kosher and Halal certified) and contains no additives, preservatives, or sulfites; all ingredients and excipients in the formulation are naturally and sustainably sourced.

OCM also includes the vitamins A, C, and D, all of which have been seen in wound studies to support new tissue synthesis [45–49]. Ascorbyl palmitate is the fat soluble form of vitamin C and is frequently used in topical formulations because it is more stable that some aqueous forms [50]. As an amphipathic molecule, the structure not only allows incorporation into the formulation but also across cell membranes. In an in vitro study in keratinocytes, ascorbyl palmitate was shown to reduce intracellular levels reactive oxygen species at low doses [51]. In other studies, it was seen as an essential cofactor for collagen transcription and for post-translational modification of type I and type III collagen. Vitamins A and D are known to have a positive effect on the inflammatory response in chronic wounds, and vitamin D, as a pleiotropic steroid hormone, also plays a role as an antibacterial by upregulating cathelicidin, an immune cell signaling peptide [52, 53]. Vitamin A also modulates epithelial cells and fibroblasts and is known to stimulate epithelialization [54].

Depending on the individual needs of the patient and their wound(s), OCM can be used in conjunction with other wound-healing therapies, including standard care, hyperbaric oxygen therapy, and negative pressure therapy, or in sequence with skin substitutes or cellular tissue products.

Clinical Experience

Allergenicity of OCM was assessed in 25 healthy adult participants based on skin prick reactions compared with positive and negative controls (NCT04510376). Results showed no potential allergenicity of OCM (no positive response) among 23 evaluable participants. The sensitization potential of OCM was evaluated in 58 healthy participants (aged 18–65 years) in a randomized study (NCT04510675). Participants were randomly assigned to receive repetitive and continuous patch applications of OCM or 0.9% aqueous sodium chloride (negative control) to the same site over 3 weeks for a total of nine induction applications. Application sites were evaluated after each patch removal,

followed by a 10- to 17-day rest period. A challenge application was applied to untreated sites for approximately 48 h. Evaluation of challenge sites were from 30 min to 72 h after patch removal. There were three cases of slight erythema during induction and one case of grade 0 irritation on day 17. During the challenge phase, one participant had slight patchy or confluent erythema 48 h after application assessment (not indicative of sensitization). No other participants experienced irritation, and OCM was determined to be safe for use. Skin protectant and anti-inflammatory properties of OCM on damaged skin were assessed in a single-blind study with 22 healthy participants (NCT04512274). Occlusive patches with 0.75% sodium lauryl sulfate (SLS) solution were applied to the forearm for approximately 24 h to induce an inflammatory response. Clinical grading of the test sites was performed before SLS application, after removal of the SLS patches on day 1, and then 10 min after the first OCM application. Clinical grading was subsequently performed before OCM application on days 2 to 4. The induction of inflammation elicited significant erythema during the study, which, on a scale of 1 to 4, was reduced to a greater extent by OCM versus untreated control: post SLS, 3.05 vs 3.09; day 1, 2.86 vs 3.20; day 2, 2.23 vs 3.34; day 3, 1.34 vs 3.09; and day 4, 0.14 vs 2.16. Data from the transepidermal water loss (TWEL) measurements showed no statistically significant differences between test sites before OCM application and after SLS application, confirming study validity. Application of OCM led to statistically significant improvements in skin barrier versus untreated sites ($P < 0.05$). No adverse events were reported during the study.

Pilot studies to assess OCM response in the clinic were conducted by 16 investigators, including wound care-certified podiatrists, surgeons, nurse practitioners, and dermatologists, in clinical settings such as physicians' offices, wound care centers, outpatient clinics, and skilled nursing facilities. This real-world assessment of OCM as part of a combination therapy protocol included patients with various types and ages of chronic and refractory wounds. Data from these independent investigator-led trialing of the products showed that of 60
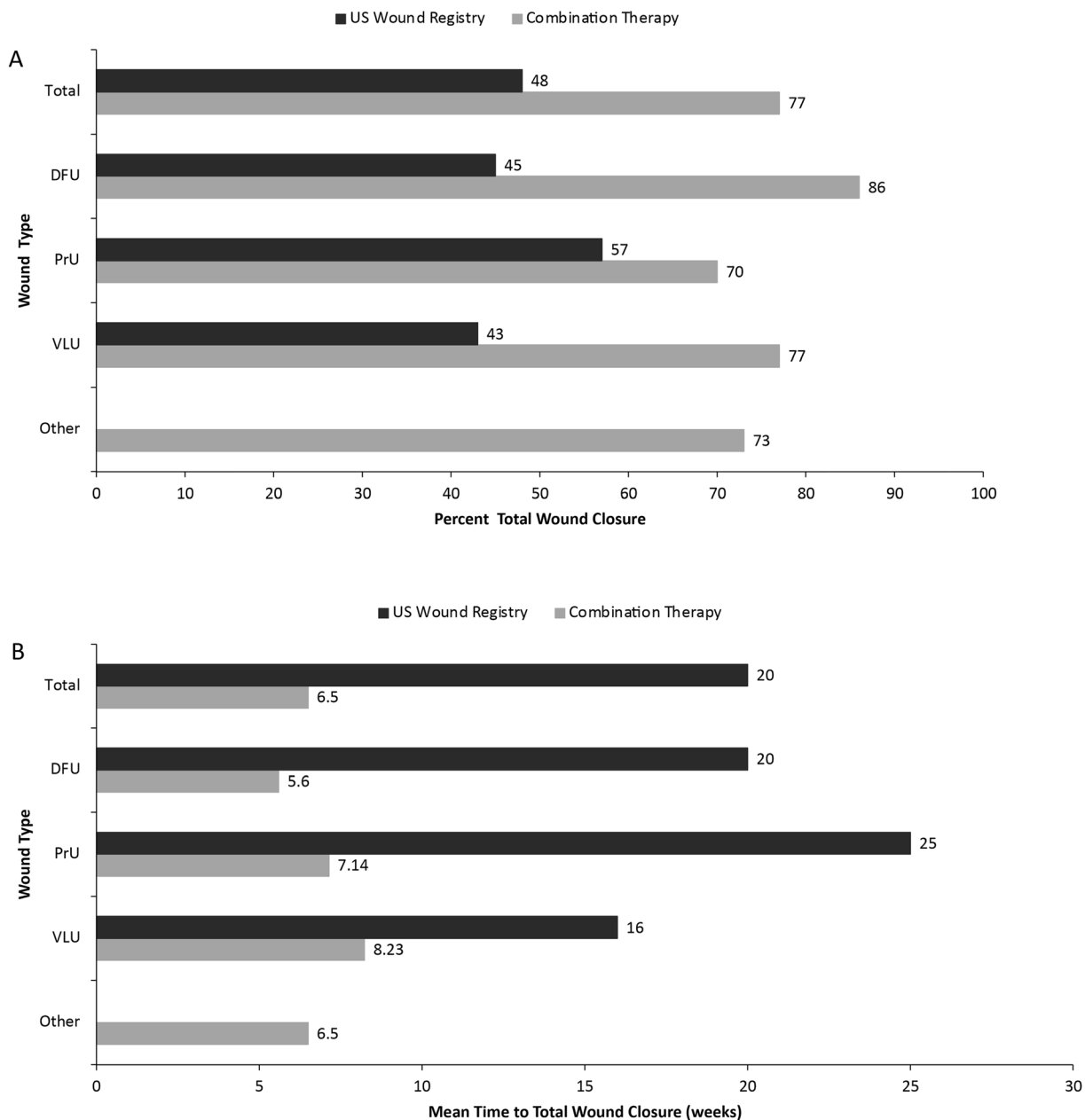
Fig. 1 A Total wound closure and **B** mean time to total wound closure with combination therapy and from the US Wound Registry [55]. *DFU* diabetic foot ulcer, *PrU* pressure ulcer, *VLU* venous leg ulcer

evaluable chronic wound cases, 86%, 77%, 70%, and 73% of patients with DFUs, VLUs, PrUs, and other wound types, respectively, experienced wound closure after receiving combination therapy (Fig. 1A). For the DFU wounds, the mean wound size was 3.18 cm^2 (range $0.16–15.4 \text{ cm}^2$), for VLUs 8.80 cm^2 (range $1.62–37.39 \text{ cm}^2$), 1.77 cm^2 (range $0.5–5.81 \text{ cm}^2$)

for PrUs, and 16.86 cm^2 (range $1.1–74.42 \text{ cm}^2$) for other wound types. Mean time to total wound closure for the 60 cases was 5.6 weeks for DFUs, 8.2 weeks for VLUs, 7.1 weeks for PrUs, and 6.5 weeks for other wound types (Fig. 1B). Although not a direct comparison to the combination therapy outcomes, data from the US Wound Registry reported a 48% total wound
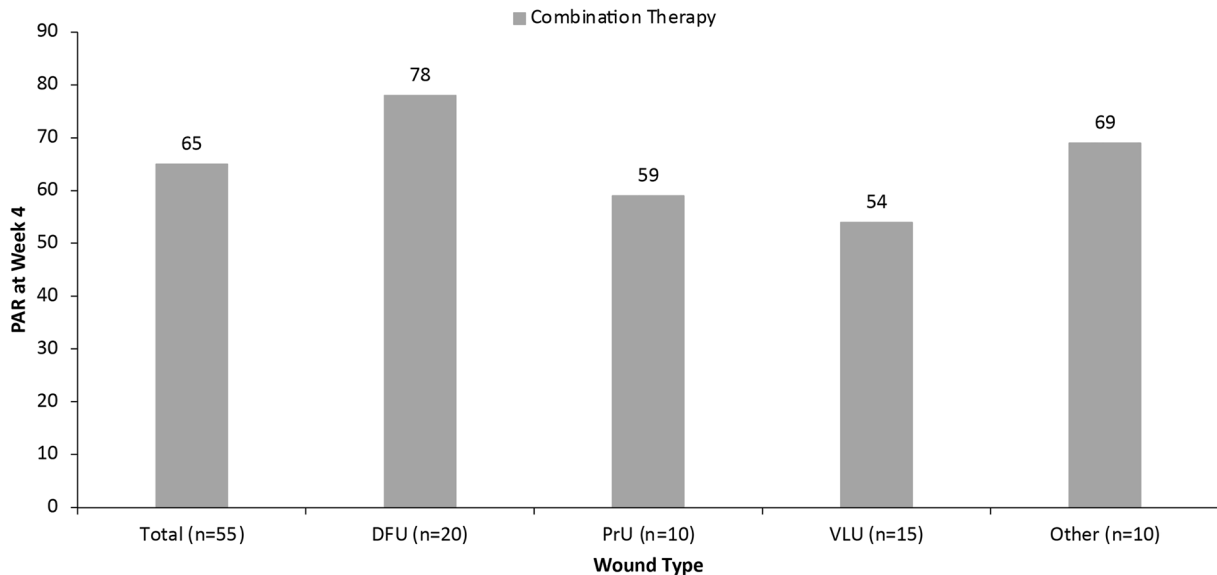
Fig. 2 PAR of the wound at week 4 of combination therapy. *DFU* diabetic foot ulcer, *PAR* percent area reduction, *PrU* pressure ulcer, *VLU* venous leg ulcer

closure rate with a mean time of 20 weeks to complete healing across patients with DFUs, VLUs, and PrUs (Fig. 1A, B) [55].

It is reported that if the area of a wound has not reduced more than 50% after 4 weeks of treatment, then the chances of the wound closing are less than 9% [56]. On the basis of this report, we evaluated the total wound percent average reduction (PAR) after the first 4 weeks of treatment with the combination therapy. In 55 evaluable cases that included DFUs ($n = 20$), VLUs ($n = 15$), PrUs ($n = 10$), and other wound types ($n = 10$), the total PAR was 69% (Fig. 2). In addition, the total average time to wound closure was 6.5 weeks (Fig. 1B). Patients in this dataset had comorbid conditions and/or lifestyle challenges that were not beneficial for their innate healing ability, but complete closure of their chronic or refractory wounds was observed. As an example, a 56-year-old male patient presented to a wound care clinic with a lower extremity venous stasis ulcer (24 mm × 22 mm) of 7-month duration. The patient had a history of hypertension, hypercholesterolemia, and venous stasis disease. His wound had not responded to previous treatment with silver alginate and amnion products. After five weekly applications of the

combination therapy and a compression wrap, the patient experienced complete closure of his wound (Fig. 3).

Data collected here was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Patients, who were not involved in the research other than receiving treatment for their condition, signed informed consent regarding use of their data.

DISCUSSION

When assessing wound-healing rates from clinical trials, it is important to consider enrollment criteria and the potential exclusion of patients with significant comorbidities and more severe refractory wounds [55]. In randomized trials specifically, it is necessary to minimize the variables between the cohorts so that equivalent comparisons can be made. Also, as time to closure in chronic wounds can be lengthy, patients are required to commit to regular weekly treatment visits for longer than 3 months. As a result of the comorbidities that most patients with chronic wounds endure daily, consenting trials can select for healthier, more compliant patients. In consideration of

Fig. 3 Case study of total closure of a chronic venous stasis ulcer after 5 weeks of combination therapy

the cost and resources needed for potential lengthy healing rates, protocols may also limit enrollment to smaller-sized wounds so that endpoints can be met sooner. These factors can lead to trial results that translate poorly to the general population of patients with chronic wounds that wound care providers treat in the clinics.

The time range of wound-healing duration reported from the control cohorts from 48 randomized clinical trials of patients with chronic wounds treated with various products varies from a mean of 5.1 weeks in patients with DFUs to a median of 36 weeks in patients with VLUs [55]. The 12-week mean healing rates reported were 42.7% (range 12.5–88.3%) in patients with VLUs, 37.9% (range 4.0–90.6%) in patients with DFUs, and 40.0% (range 36.0–44.0%) in

patients with PrUs [55]. In comparison, an analysis of real-world data gathered by the US Wound Registry show 12-week healing rates of 44.1% for VLUs, 30.5% for DFUs, and 29.6% for PrUs [55].

Acknowledging the size of the dataset presented for the combination therapy and understanding the necessity to evaluate the efficacy of OCM in a controlled setting, clinical trials are currently underway for its further evaluation. Study NCT05291169 is a randomized trial that includes patients with VLUs and compares treatment with OCM combined with standard of care to standard of care alone. This trial includes fluorescent imaging of the wounds to compare the bioburden over time between the treatment and control groups. Study NCT05921292 is a multisite trial

evaluating chronic wounds of multiple etiologies and includes patients who are usually excluded from clinical trials (e.g., current smoking status, higher body mass index, and comorbidities). Study NCT05417425 is a single-site trial of patients with DFUs to evaluate PAR at 4 weeks and then after 12 weeks of combination therapy compared to standard of care. In addition to the clinical trials, animal and preclinical studies are underway to further elucidate OCM's mechanism of action. In vitro and porcine in vivo studies are currently being conducted to assess antimicrobial properties of all components of the combination therapy; near-infrared perfusion pilot studies are scheduled to evaluate OCM's effect on perfusion and lymphedema studies are planned to identify mechanisms for reducing edema in chronic wounds.

One of the challenges for wound care professionals is that there is little evidence for the selection of an appropriate therapy [57]. To address this and other challenges inherent to managing chronic wounds, it is necessary that wound care products are evaluated for efficacy and safety in both randomized trials and in trials with broader inclusion criteria and narrower exclusion criteria. Results compiled from these various types of studies will hopefully lead to a better understanding of a product's value in closing a chronic wound, especially in the therapeutic area of wound management where patient compliance is possibly the greatest challenge for the clinicians. In addition to wound-closure rate, clinically relevant and patient-centered outcomes of wound healing should focus on reduced amputation, reduced economic burden, improved function/ambulation, and improved quality of life [55].

CONCLUSION

The novel combination wound-healing therapy provides unique formulations with the intention of meeting individual healing needs, allowing each patient's body to utilize the specific components to address the deficient aspects of their specific wound. Patients in the dataset described here presented with comorbid conditions and/or lifestyle challenges that were not beneficial for their innate healing ability; however, 77% of patients experienced complete closure of their chronic or refractory wounds after being treated with the combination therapy.

Clinical trials evaluating the combination therapy for the treatment of DFUs (NCT05417425), VLUs (NCT05291169), and wounds/ulcers of multiple etiologies (NCT05921292) are underway. Results of studies assessing mechanism of action and results of these clinical trials will expand and enhance current evidence supporting use of the combination therapy in chronic or refractory wounds in the real world.

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Declarations

Conflict of Interest. Griscom Bettle is a former employee of Omeza, LLC; Desmond Bell and Suzanne Bakewell are employees of Omeza, LLC.

Ethical Approval. Data collected here was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Patients, who had no involvement in the research other than being treated for their condition, signed informed consent regarding use of their data.

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