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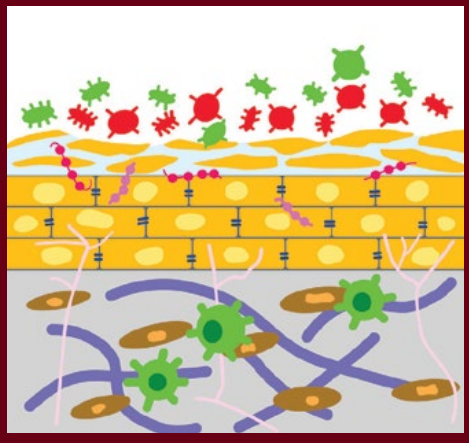
JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS



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SPECIAL FOCUS: ACNE AND ROSACEA

Update on Treatment of Scars

Acne in Patients With Skin of Color

Microfocused Ultrasound for Treating Rosacea

Minimally Invasive Treatment of the Temple

Botanical Treatment for Adults and Children With AD

Oral Antibiotics for Rosacea

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JDD
DRUGS • DEVICES • METHODS

JOURNAL OF DRUGS IN DERMATOLOGY

GUEST EDITORIAL

503 **What Is PFE? It May Just Be Time You Found Out....**
James Q. Del Rosso DO

ORIGINAL ARTICLES

506 **The Use of Oral Antibiotics in the Management of Rosacea**
Arielle R. Nagler MD, James Del Rosso DO

514 **Patient-Reported Outcomes in Acne Patients With Skin of Color Using Adapalene 0.3%–Benzoyl Peroxide 2.5%: A Prospective Real-World Study**
Janet DuBois MD, Gavin Chun Wei Ong MD, Gitanjali Petkar MBBS DDV, Luiz Mauricio Costa Almeida MD, Rajeev Chavda MD, Nabil Kerrouche MSc, Andrew F. Alexis MD MPH

522 **Safety and Effectiveness of Microfocused Ultrasound for Treating Erythematotelangiectatic Rosacea**
Joel Schlessinger MD, Mark Lupin MD FRCPC, David McDaniel MD, Rosalyn George MD

533 **Clinical Validation of the Surface Volume Coefficient for Minimally Invasive Treatment of the Temple**
Sebastian Cotofana MD PhD, Konstantin Koban, Tatjana Pavicic MD, Mariya Yankonva, Konstantin Frank MD, Jeremy B. Green MD, Robert H. Gotkin MD, Lukas Etzel, Riccardo E. Giunta PhD MD, Thilo L. Schenck MD PhD

542 **A Phase 2, Multicenter, Double-Blind, Randomized, Vehicle-Controlled Clinical Study to Compare the Safety and Efficacy of a Novel Tazarotene 0.045% Lotion and Tazarotene 0.1% Cream in the Treatment of Moderate-to-Severe Acne Vulgaris**
Emil A. Tanghetti MD, Leon H. Kircik MD, Lawrence J. Green MD, Eric Guenin PharmD PhD, Susan Harris MS, Gina Martin MOT, Radhakrishnan Pillai PhD

550 **Update on the Treatment of Scars**
Noelani González MD, David J. Goldberg MD JD

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ORIGINAL ARTICLES (CONTD)

557 **Validation of Botanical Treatment Efficiency for Adults and Children Suffering from Mild to Moderate Atopic Dermatitis**
Zoe Diana Draelos MD, Michael Traub ND FABNO, Michael H. Gold MD, Lawrence J. Green MD, Mark Amster MD, Deganit Barak-Shinar PhD, Leon H. Kircik MD

563 **Pharmacokinetic Profile, Safety, and Tolerability of Clascoterone (Cortexolone 17-alpha propionate, CB-03-01) Topical Cream, 1% in Subjects With Facial Acne Vulgaris: An Open-Label Phase 2a Study**
Alessandro Mazzetti MD, Luigi Moro PhD, Mara Gerloni PhD, Martina Cartwright PhD

570 **A Phase 2b, Randomized, Double-Blind Vehicle Controlled, Dose Escalation Study Evaluating Clascoterone 0.1%, 0.5%, and 1% Topical Cream in Subjects With Facial Acne**
Alessandro Mazzetti MD, Luigi Moro PhD, Mara Gerloni PhD, Martina Cartwright PhD

576 **DNA Repair Enzyme Containing Lip Balm for the Treatment of Actinic Cheilitis: A Pilot Study**
Amanda Rosenthal BA, Alexis Lyons MD, Lauren Moy MD, Alexis Wilsons, Kian Mohamadi BS, Jennifer Herrmann MD, Rebecca Tung MD

581 **Connecting the Dots: From Skin Barrier Dysfunction to Allergic Sensitization, and the Role of Moisturizers in Repairing the Skin Barrier**
Tamara Lazic Strugar MD, Alyce Kuo BS, Sophie Seité PhD, Ma Lin MD PhD, Peter Lio MD

587 **Arterial Occlusion and Necrosis Following Hyaluronic Acid Injection and a Review of the Literature**
Laura Doerfler MD, C. William Hanke MD MPH

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EDITORIAL Journal of Drugs in Dermatology

James Q. Del Rosso DO

What Is "PFE"? It May Just Be Time You Found Out....

With all the literature and research we have on acne and rosacea, there are still many unanswered questions. Over time, as we uncover more information on both preexisting and newly recognized pathophysiologic pathways, modes of drug action, alternative therapies, caveats related to basic skin care, and the potential roles for physical modalities, we often find that specific information that we thought was fact, is later altered, expanded, or corrected. What is interesting, and sometimes perplexing to me personally, is how difficult it is for the clinical dermatology community at large to incorporate well-published concepts into everyday clinical practice. In this commentary, I address an example with rosacea that emphasizes the correlation of pathophysiology with clinical manifestations, and the importance of selecting treatment that targets the specific clinical manifestations of rosacea.

If persistent facial erythema (PFE) is the pivotal diagnostic feature of cutaneous rosacea, including in both the presence or absence of papulopustular lesions, why are the vast majority of medical therapy prescriptions within dermatology written for agents that specifically target papulopustular lesions and perilesional erythema?

This statement about topical prescribing data for rosacea is based on information I have had the opportunity to review from a research perspective. Two FDA-approved brand topical alpha-agonists (brimonidine 0.33% gel, oxymetazoline 1% cream) have been available for years, and specifically reduce PFE by constricting the chronically dilated superficial centrofacial vasculature.[1-3] Admittedly, their effects are transient, lasting several hours after application, thus warranting daily use. However, they successfully reduce PFE, which is the diffuse facial redness that intensifies during vasodilatory flares (flushing of rosacea) and persists between flares. In patients with papulopustular rosacea, perilesional erythema resolves as the papules and pustules resolve, leaving behind the diffuse redness of PFE that we so commonly see on the central areas of the cheeks, forehead, and chin. Nevertheless, the majority of prescriptions written for rosacea are for topical metronidazole, topical ivermectin, topical azelaic acid, and oral doxycycline.

If one considers that many cases of rosacea present only with PFE and do not have papulopustular lesions, the question I posed above becomes more perplexing. I think there are many facets to the "composite answer" to this question, which include cost considerations and access to medication, concerns regarding worsening of facial erythema due to the early adverse experiences with topical brimonidine affecting approximately 15% of patients (ie, rebound, paradoxical erythema), uncertainty with how to incorporate alpha-agonist therapy into rosacea management, and inconsistency of educational and promotional activities. However, I believe a major reason is that many clinicians have not fully grasped the concept of PFE of rosacea and the importance of addressing it in rosacea management. Despite spending a lot of time and effort researching, publishing, and discussing rosacea with colleagues, it took me years to grasp the concept of PFE in rosacea. I encourage my colleagues, if they do not yet fully understand or embrace the concept of PFE, to learn more about it, as I believe that will improve their clinical ability to manage rosacea. *Consider the role of PFE in essentially all patients with cutaneous rosacea.*[4-6]

The importance of moving beyond the "subtyping" of rosacea, evaluating the clinical manifestations that are present in a given patient, and addressing which of those manifestations are bothersome to the patient, has been discussed in the literature.[5-8] This allows the clinician to recommend and select therapy that addresses each specific manifestation that is being treated. Ultimately, a combination of medical and physical approaches is warranted, either concomitantly or sequentially, to optimally manage rosacea. I credit my colleague, Dr. Julie Harper, for suggesting to me that the dermatology community at large needs a simple term like "PFE" to relate to. She ignited my desire to write this commentary.

James Q. Del Rosso DO

JDR Dermatology Research/Thomas Dermatology
Las Vegas, NV

References

1. Fowler J Jr, Jackson M, Moore A, Jarratt M, Jones T, Meadows K, Steinhoff M, Rudisill D, Leoni M. Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized, double-blind, and vehicle-controlled pivotal studies. *J Drugs Dermatol.* 2013;12(6):650-656.
2. Stein-Gold L, Kircik L, Draelos ZD, Werschler P, DuBois J, Lain E, Baumann L, Goldberg D, Kaufman J, Tanghetti E, Ahluwalia G, Alvandi N, Weng E, Berk D. Topical oxymetazoline cream 1.0% for persistent facial erythema associated with rosacea: pooled analysis of the two phase 3, 29-day, randomized, controlled REVEAL trials. *J Drugs Dermatol.* 2018;17(11):1201-1208.
3. Del Rosso JQ. Topical a-agonist therapy for persistent facial erythema of rosacea and the addition of oxmetazoline to the treatment armamentarium: where are we now? *J Clin Aesthet Dermatol.* 2017;10(7):28-32.
4. Tanghetti EA, Jackson JM, Belasco KT, Friedrichs A, Hougier F, Johnson SM, Kerdel FA, Palceski D, Hong HC, Hinek A, Cadena MJ. Optimizing the use of topical brimonidine in rosacea management: panel recommendations. *J Drugs Dermatol.* 2015;14(1):33-40.
5. Del Rosso JQ, Thiboutot D, Gallo R, Webster G, Tanghetti E, Eichenfield LF, Stein-Gold L, Berson D, Zaenglein A; American Acne & Rosacea Society. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 5: a guide on the management of rosacea. *Cutis.* 2014;93(3):134-8.
6. Tan J, Berg M, Gallo RL, Del Rosso JQ. Applying the phenotype approach for rosacea to practice and research. *Br J Dermatol.* 2018;179(3):741-746.
7. Gallo RL, Granstein RD, Kang S, Mannis M, Steinhoff M, Tan J, Thiboutot D. Standard classification and pathophysiology of rosacea: The 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol.* 2018;78(1):148-155.
8. Tan J, Almeida LM, Bewley A, Cribier B, Dlova NC, Gallo R, Kautz G, Mannis M, Oon HH, Rajagopalan M, Steinhoff M, Thiboutot D, Troielli P, Webster G, Wu Y, van Zuuren EJ, Schaller M. Updating the diagnosis, classification and assessment of rosacea: recommendations from the global ROSacea COnsensus (ROSCO) panel. *Br J Dermatol.* 2017;176(2):431-438.

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ORIGINAL ARTICLE Journal of Drugs in Dermatology

The Use of Oral Antibiotics in the Management of Rosacea

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ABSTRACT

Rosacea is common inflammatory facial dermatosis. Rosacea has variable manifestations including facial flushing, central facial erythema, telangiectasias, and papulopustular lesions. Treatment of rosacea is challenging given the varied manifestations and incompletely understood etiology, but the treatment of papulopustular presentations often relies on oral antibiotics. Tetracyclines, specifically doxycycline, are the most commonly prescribed antibiotics for rosacea. Other antibiotics that can be used include macrolides, commonly azithromycin, and rarely, metronidazole. This paper will review the evidence for the use of antibiotics in the treatment of rosacea.

J Drugs Dermatol. 2019;18(6):506-513.

INTRODUCTION

Rosacea is a common chronic inflammatory facial dermatosis. The prevalence ranges from 1-20% of the population depending on the demographic of the population being studied and the definition of disease.[1] The presentation can be variable, but it is often associated with recurrent facial flushing, central facial erythema, telangiectasias, and papulopustular lesions. In some patients, rosacea can progress to localized phymatous changes and fibrosis.[2] Classically, rosacea has been classified into four main subtypes: erythematotelangiectatic (ETR), papulopustular (PPR), phymatous, and ocular.[3] More recent publications, however, have recommended more individualized classification of rosacea based on clinical manifestations (phenotypic classification).[4-6]

Rosacea treatment is challenging due to the diversity of clinical manifestations and is often targeted to address the primary manifestations. The flushing (acute vasodilation), persistent background redness, and telangiectasia of rosacea are particularly challenging to treat. Management of these signs relies on topical α1 and α2-adrenergic agonists as well as laser and light-based devices. Selection of treatment for PPR depends on the severity of the lesions. For mild to moderate disease, topical therapies including azelaic acid, metronidazole, and ivermectin are typically utilized. Oral therapies, predominantly antibiotics, have usually been reserved for when topical therapy alone fails or when PPR is more severe.[5] This article will review the usage of oral agents classified as antibiotics for the treatment of rosacea including the proposed mechanism of action, the indications for use, the specific agents used, sub-antibiotic doxycycline therapy, and important considerations when prescribing antibiotics.

Rosacea Pathogenesis

The pathophysiology of rosacea is complex, multifactorial, and incompletely understood. Although dysregulation of both the innate and adaptive immune systems, as well as vascular and neuronal dysfunction likely play a role in this complicated cutaneous condition, innate immune system dysfunction is thought to be a central component of rosacea pathogenesis.[3] The innate immune system plays a key role in the skin's response to insults such as microorganisms, reactive oxygen species (ROS) from ultraviolet radiation, and trauma. Normally, innate immune system activation leads to controlled production of pro-inflammatory cytokines and antimicrobial peptides (AMP) in the skin. In contrast, in patients with rosacea, innate immune system mediators are over expressed leading to increased downstream inflammation.[2,6] Patients with rosacea have elevated baseline expression of cathelcidin, an AMP, and kallkrien 5.[7] Kallikrein 5 is a serine-protease that is the responsible for cleaving cathelicidin into LL-37, its more active form.[8] LL-37 promotes inflammation and angiogenesis. Matrix metalloproteinases (MMPs), in particular MMP2 and MMP9, are also overexpressed in patients with rosacea.[9] MMP9 directly increases activation of kallkrien 5, thereby promoting LL-37 expression. MMPs also contribute to cytokine induced vascular dysfunction.[10]

The initial triggers inciting the innate immune system cascade in rosacea are still not well understood, but microorganisms such as *Demodex folliculorum, Staphylococcus epidermidis, and Heliobacter pylori* are hypothesized to contribute.[11-14] The mechanisms by which these microorganisms promote the development of rosacea is unclear. Several studies have discovered differences in *D. folliculorum, S. epidermidis,* and *H.*

pylori burden in rosacea patients as compared to controls[13-15] although it is unclear whether these changes in microbial burdens are the promoters of rosacea pathophysiology or the result of abnormalities in the innate immune system and the skin microenvironment.

D. folliculorum resides in the sebaceous glands of healthy skin, but a meta-analysis found that rosacea patients have higher prevalence and degree of *D. folliculorum* infestation as compared to controls.[16] *D. folliculorum* is thought to potentially play a role in rosacea pathogenesis by stimulating toll-like receptor 2 (TLR2), which promotes kallkrien 5 production in keratinocytes.[17] However, it is unlikely that *D. folliculorum* colonization is sufficient to stimulate rosacea as studies comparing permethrin 5% cream, metronidazole 0.75% cream, and placebo found that permethrin cream was more effective in decreasing *D. folliculorum* levels, but that was not associated with a change in rosacea.[18]

Bacteria have also been hypothesized to play a role in innate immune system dysregulation in rosacea. *S epidermidis* is the most prevalent commensal bacteria in normal skin. Studies have shown that *S epidermidis* to be singularly abundant in cultured rosacea pustules.[14] Additionally, *S epidermidis* cultured from patients with rosacea secrete virulence factors not seen in control skin.[19] Similarly to *D. folliculorum, S epidermidis* may stimulate innate immune system activation through TLR2 recognition. The role of intestinal bacteria, such as *H. pylori,* in rosacea is also debated. A recent meta-analysis found a weak association between rosacea and *H. pylori* infection, the clinical significance of which is unclear.[20]

Indications for Oral Antibiotics in Rosacea

Antibiotics have been used for the treatment of rosacea for decades.[21] The most common antibiotics used for rosacea are the second generation tetracyclines, doxycycline and minocycline. Other antibiotics, including macrolides and metronidazole, are used less frequently. A retrospective study of commercial claims in the US using the MarketScan and Encounters databases found that between 2005 and 2014, 96% of the 145,100 antibiotic courses for rosacea were tetracyclines and 4% were macrolides.[22]

Published studies evaluating the use of oral antibiotics for rosacea have been limited to those with inflammatory PPR (or ocular rosacea), and have not studied the effects in patients with erythematotelangiectatic or phymatous rosacea.[23,24] There are limited guidelines and consensus recommendations describing the appropriate indications for systemic antibiotic therapy for rosacea. Part of the challenge of creating such guidelines for the treatment of rosacea is the lack of a single updated scale that standardizes severity assessments of rosacea types.[25] Consensus recommendations from the American Acne and Rosacea Society (AARS) on the Management of Rosacea suggest oral therapy, especially sub-antibiotic dose doxycycline, can be used in select patients with moderate to severe disease as well as those with mild inflammatory rosacea who are more likely to adhere to an oral regimen.[24]

Despite the reliance on antibiotics for the treatment of rosacea, there have been calls to limit their prescription. Studies in acne patients have shown systemic antibiotic exposure to be associated with significantly higher rates of pharyngitis, upper respiratory tract infections, and higher oropharyngeal carriage rates of resistant *Streptococcus pyogenes*.[26,27,28] As a result, there are national and international antibiotic stewardship initiatives to curtail the use of antibiotics in chronic conditions like rosacea.[29]

Tetracyclines

Tetracyclines have been used for the treatment of rosacea for approximately five decades.[30] Tetracyclines' widespread use in rosacea is likely the result of their frequent use in acne treatment, beginning in the 1950s.[24] Despite widespread use of tetracyclines, it was not until 2006 that a modified-release doxycycline (doxy-MR) dosed at 40 mg once daily (also referred to as sub-antibiotic dose doxycycline), was specifically approved by the US Food and Drug Administration (FDA) for the treatment of papulopustular rosacea. This agent differed in that it is devoid of antibiotic selection pressure, thereby minimizing the risk of emergence of antibiotic-resistant bacterial strains. [31]

Tetracyclines are thought to be effective in rosacea primarily through anti-inflammatory mechanisms, rather than through their antimicrobial properties. Tetracyclines modulate the immune system by down-regulating the production of pro-inflammatory cytokines and ROS. Specifically, tetracyclines inhibit MMPs thereby decreasing kallkrein 5 and LL-37 activity, modulating pro-inflammatory cytokines, and inhibiting angiogenesis.[32-34]

Today, second generation tetracyclines, including doxycycline and to a lesser extend minocycline, are most frequently used for treatment of rosacea. Compared to their parent drug, tetracycline, second generation tetracyclines have improved bioavailability and side effect profiles.[35,36] Although there are individual differences in capacities for absorption, the bioavailability of second generation tetracyclines is thought to be less influenced by co-ingestion of foods, supplements, or antacids containing metal ions, with the exception of iron.[37]

Doxycycline

Doxycycline is the most common oral therapy utilized in the treatment of rosacea, in part due to its favorable side effect profile. The major side effects associated with doxycycline include photosensitivity, gastrointestinal (GI) upset, and esophagitis.[35]

Antibiotic activity is dependent on a drug concentration threshold that is achieved with higher doses of doxycycline. Doses of doxycycline lower than 50mg/day are below the minimum inhibitory concentration required for antibiotic effects. However, the anti-inflammatory effects of doxycycline do occur at doses that are sub-antibiotic. Studies have shown sub-antibiotic dosing of doxycycline does not exert bacterial selection pressure in the skin, mouth, gastrointestinal tract, and genitourinary tract.[38,39] For rosacea, doxycycline can be dosed at antimicrobial levels (50-200mg daily) and at sub-antibiotic levels (<50mg daily), with both exhibiting anti-inflammatory effects.[30]

Traditionally, doxycycline was dosed at higher, immediate release (IR), antibiotic levels, such as 100mg daily.[40,41] Because IR doxycycline 100mg capsules are available generically, there have been no recent or randomized controlled trials comparing doxycycline to placebo or other oral treatments for rosacea.[32] In study of 67 rosacea patients, mean inflammatory lesions counts decreased significantly after 3 months of doxycycline 100mg daily (P<0.0001) with effects continuing for 2 months after treatment. This study, however, was not blinded or controlled.[42]

With increasing concern about bacterial resistance and the overuse of antibiotics, sub-antibiotic dosing for rosacea has become increasingly common. Several studies have demonstrated the efficacy of sub-antibiotic doses (40mg/day) of doxycycline for the treatment of rosacea.[43-47] Notably, using single-dose pharmacokinetics, 50mg of standard immediate-release (IR) doxycycline given once daily may produce concentrations high enough to promote selection pressure against bacteria.[45] The sub-antibiotic dosing of IR doxycycline is usually 20mg twice daily.[45] A single-center, randomized, double-blind, placebo controlled trial of 40 subjects with papulopustular rosacea (PPR) studied doxycycline hyclate 20mg twice daily plus metronidazole 0.75% lotion versus placebo plus metronidazole 0.75% lotion. The study was 16 weeks in duration, but therapy was discontinued at 12 weeks. In this study, lesion count reduction was significantly greater in the doxycycline group (P<0.01) at week 12 and was maintained at week 16 (P<0.01).[43] Additionally, the global severity score was significantly lower in the doxycycline group as compared to controls at 12 weeks (P=0.04).

The use of sub-antibiotic dose doxycycline for rosacea was further bolstered with the Food and Drug Administration (FDA) approval of a specific doxycycline modified-release 40mg capsule once daily (doxy-MR) in 2006 for PPR. This formulation of doxycycline, the only FDA approved systemic therapy for rosacea, includes 30mg of immediate release and 10mg of delayed release doxycycline, incorporated as beads within the capsule. Doxy-MR has been shown to have pharmacokinetic profiles that do not reach minimum inhibitory concentration of bacteria and thus does not provide microbial selection pressures.[48,49] It also has the advantage of once daily dosing as compared to doxycycline hyclate 20mg twice daily, which has been shown to improve compliance.[50,51] Two phase III, double-blinded randomized placebo- controlled studies evaluated doxy-MR.[45] Combined, there were a total of 537 subjects in these studies, and doxy-MR performed significantly better than placebo beginning at week 3 in terms of lesion counts, patient assessment, and investigator global assessment. Another 12-week multicenter study with 72 patients compared doxy-MR plus metronidazole 1% gel daily to placebo with metronidazole 1% gel daily.[44] The doxycycline group had significantly reduced lesion counts at 4 and 12 weeks compared to controls (P=0.008 and P=0.002, respectively). Global disease severity scores were significantly lower in the doxy-MR group as compared to the placebo group at 12 weeks, and these differences were maintained at 16 weeks. A more recent randomized controlled study correlated improvement in inflammatory markers with treatment success. In this study, comparing doxy-MR to placebo, greater clinical improvement in rosacea as well as decreased cathelicidin expression was seen in the doxycycline group as compared to controls.[52] To date, studies comparing doxycycline hyclate 20mg twice daily to the doxy-MR (which is by definition given once daily) have not been published.

IR doxycycline 100mg daily dosing and sub-antibiotic doxycycline dosing have been compared. A 16 week, randomized, double-blind, controlled, multicenter study compared doxy-MR with metronidazole gel 1% to doxycycline 100mg daily with metronidazole gel 1% in 91 subjects with PPR.[47] The mean change from baseline in inflammatory lesion counts at 16 weeks was not significantly different between the groups. In fact, at 12 weeks, the mean change in erythema scores from baseline was significantly greater in the sub-antibiotic dose as compared to standard dose (P<0.04), but this was not maintained at 16 weeks. Notably, side effects including nausea, diarrhea, vomiting, abdominal pain, and urticaria were greater in patients taking IR doxycycline 100mg daily. A cross-sectional study using a claims database found rosacea patients receiving sub-antibiotic dose doxycycline have fewer gastrointestinal-related disorders (IBD, celiac, GERD, IBS, SIBO, gastritis, *H. pylori* infection) than those taking standard dose doxycycline.[53] Additionally, sub-antibiotic dose doxycycline has a lower risk of photosensitivity, a dose-dependent side effect.[23,54,55] A Cochrane review rated the evidence for MR-doxy to be of high quality.[55]

Given the equivalent efficacy of standard and sub-antibiotic dose doxycycline in PPR, several consensus statements specifically note that sub-antibiotic dosing of doxycycline for rosacea is preferred in most clinical situations. The American Acne and Rosacea Society recommends that in patients with PPR requiring systemic therapy, sub-antibiotic dose doxycycline, whether as 40mg modified-release capsule once daily (doxy-40) or immediate-release doxycycline 20mg twice daily, is the preferred

initial oral treatment.[24] Similarly the Rosacea International Expert Group primarily recommends the use of sub-antibiotic doses in patients requiring oral therapy, limiting the use of higher doses to patients with severe disease to achieve initial therapeutic control in the first 4 weeks.[56]

Minocycline

Minocycline is less commonly used for rosacea than doxycycline. A study querying the National Ambulatory Medical Care Survey data from 1993-2010 found that minocycline was used to treat rosacea in only 8.5% of rosacea visits.[57]This data, however, may not accurately reflect current practices as it included tetracycline which is no longer consistently commercially available. Minocycline has been associated with cutaneous hyperpigmentation (blue/grey discoloration of skin and scars as well as brown pigmentation on anterior legs), vestibular side effects such as vertigo, and, less commonly, drug hypersensitivity syndrome, drug –induced lupus, and autoimmune hepatitis.[58] Additionally, minocycline has not been studied as extensively as doxycycline for rosacea. In fact, there are no placebo-controlled trials studying minocycline in rosacea patients.[59]

Several, non-placebo-controlled studies have demonstrated minocycline's efficacy for the treatment of PPR. A randomized, double-blind study compared minocycline extended release 45mg daily to minocycline extended release 45mg daily in combination with topical azelaic acid.[59] Sixty patients were enrolled and at 12 weeks there were significant changes in total lesion counts (P<0.0001) in both groups, but there was no statistical difference in reductions between the groups (P=0.6). There was no placebo arm in this study, so conclusions could not be drawn on the efficacy of minocycline as compared to placebo. A 2015 Cochrane review rated this study as low quality evidence supporting the use of minocycline in rosacea patients.[55]

Minocycline was compared to doxycycline for rosacea in the DOMINO trial, a randomized, single-blinded, non-inferiority study.[60] In this study, patients with PPR were randomized to doxy-MR or to minocycline 100mg daily. Over a 16-week treatment period, minocycline 100mg was not inferior to doxy-MR in terms of treatment efficacy. However, 12 weeks after treatment had ended, patients in the minocycline group had a lower rate of relapse and reported that rosacea had significantly less impact on their quality of life.[60] In this study, there were no serious adverse events. While minocycline appears to be effective in treating PPR, given its less favorable side effect profile, it is still considered to be a secondary alternative therapy for PPR.[52]

Sarecycline

Sarceycline is a novel tetracycline antibiotic specifically designed for acne. In 2018, Sarecycline was approved by the FDA for use in patients 9 years and older with moderate to severe acne. It is a once daily formulation with both anti-inflammatory effects as well as antibiotic activity against gram-positive bacteria such as *Cutibacterium acnes*.[61,62] Unlike doxycycline and minocycline, however, sarecycline has narrower activity against gram negative bacteria, reducing concerns of microbial resistance.[62,63] The safety profile of sarecycline is generally similar to other tetracyclines including gastrointestinal upset, esophageal erosion, and increased photosensitivity.[61] In two randomized, placebo controlled trials for moderate acne, vestibular side effects and phototoxic reactions occurred in less than 1% of sarecycline patients.[64] Gastrointestinal side effects were also low. In these two placebo-controlled studies, mean inflammatory lesion count decreased by 51.8% and 49.9%. Sarecycline has not yet been studied in rosacea, but in clinical practice, it may eventually be used off-label for rosacea.

Macrolides

Macrolide antibiotics include erythromycin, clarithromycin, and azithromycin (an azalide analog). Macrolides have been shown to exhibit some anti-inflammatory properties, such as modulation of ROS formation and inhibition of neutrophil chemotaxis and activation.[65,54] The use of macrolides in rosacea is limited by the lack of evidence supporting their efficacy as well as concerns about side effect profiles, potential drug-drug interactions, and bacterial resistance.[42,51,66] Most of the studies of macrolides in rosacea have focused on azithromycin and to a lesser extent clarithromycin.[33,67,68] Azithromycin has been used for rosacea at variable and intermittent doses including 500mg three times weekly, 250mg three times weekly, 250mg twice weekly, and 500mg weekly.[33,56,57] Azithromycin can be dosed intermittently because it has a long half-life and attains high tissue levels.[69]

In an open clinical trial, 67 patients with PPR were randomized to receive azithromycin and doxycycline.[42] Patients in the azithromycin group received 500mg three times weekly for the first month, 250mg three times weekly for the second month, and 250mg twice weekly in the third month. Patients in the doxycycline group received 100mg daily for 3 months. This study found statistically significant improvement in lesion counts in both groups, but no statistical difference between the groups.[42] A smaller open label study with 18 patients used the same azithromycin dosing schedule and found inflammatory lesion counts decreased by 89% as compared to baseline at 12 weeks and effects were sustained at 4 weeks after treatment.[67,68] Azithromycin was well tolerated in the study with only minor gastrointestinal discomfort reported in 3 patients. Other studies and case reports have reported improvement in rosacea in patients who had failed or were unable to tolerate other oral rosacea therapies including doxycycline, metronidazole, and isotretinoin.[67,68,70,71] Despite some positive data suggesting azithromycin efficacy for the treatment of rosacea, the Cochrane review for rosacea interventions concluded that published studies investigating azithromycin for rosacea were of low quality, recommending more robust studies.[23,24,72] Neverthe-

less, azithromycin remains an alternative oral therapy option for PPR.[24]

Data are limited on the use of oral clarithromycin for rosacea. One study of 25 patients treated with doxycycline 100mg twice a day for 1 month and then 100mg daily for 1 month or clarithromycin 250mg twice daily for 1 month followed 250mg daily found significant improvement in inflammatory lesion count and subjective measures of rosacea in both groups, but the study was not powered to compare efficacy between groups.[73] Controversially, there has been conflicting data regarding improvement of rosacea after the eradication of *H. pylori* infection with clarithromycin-based regimens.[74,75] Given the lack of data supporting the efficacy of clarithromycin for rosacea and the fact that it is more likely than azithromycin to have GI side effects and drug interactions, it is not commonly recommended for the treatment of rosacea.[24]

Metronizadole

Topical preparations of metronidazole are used commonly for PPR; historically, however, oral metronidazole was also used commonly for rosacea. Evidence for the efficacy of oral metronidazole for rosacea is limited and dated.[24] A double blind study from 1976 of 29 patients with rosacea found that patients treated with metronidazole 200mg twice daily experienced significant improvements in rosacea based on clinician assessments as compared to patients treated with placebo.[76] Another study from 1980 compared metronidazole to standard of care. In this study, patients were treated with metronidazole 200mg twice daily or oxytetracycline, an older tetracycline. Both treatment groups experienced improvement in rosacea using blinded physician severity scales.[77] There have been no recent studies investigating oral metronidazole for rosacea and it is not commonly utilized.[24] An important barrier to its use is the fact that alcohol ingestion must be completely avoided during treatment with oral metronidazole due to a disulfiram-like reaction.

Timing of Onset and Duration of Treatment

Onset of treatment effect and duration of treatment are important therapeutic parameters to patients. Moreover, physician understanding of therapy onset and treatment duration is necessary for providers to appropriately educate patients and manage patients' expectations. In acne, patient understanding of treatment onset and duration is associated with improved adherence to therapy and thus better outcomes.[78]

Timing of onset of oral antibiotics for rosacea is often not a primary endpoint, nevertheless the information is captured in many studies that include serial evaluations of patients with rosacea. For the tetracyclines and the macrolides used in rosacea, most of the improvement occurs within the first 4 weeks of therapy.[42,47,60,67] In a study comparing standard doxycycline 100mg daily to modified release doxycycline 40mg daily, there were similar effect sizes in mean change in inflammatory lesion count at 4, 8, 12, and 16 weeks. Seventy-three percent of the total mean change occurred within the first 4 weeks, but there was continued improvement in lesion count for the entire 16 week study duration.[47] The timing of onset of minocycline in rosacea is less well studied. In the DOMINO trial, comparing minocycline to doxycycline, the only endpoints examined were at 16 and 28 weeks, which does not provide the detail needed to assess timing of onset.[60] A randomized controlled study comparing minocycline 45mg daily with and without azelaic acid evaluated subjects at 4,8,12, and 16 weeks.[59] In the minocycline only group, the mean lesion count decreased by approximately 53% in the first 4 weeks, after which improvement plateaued. Since macrolides have not been studied extensively in rosacea, there is little data on timing of onset. In a randomized, open label study comparing azithromycin to doxycycline, the greatest change in mean lesion count in the azithromycin group occurred in the first 4 weeks during which mean lesion counts decreased by 65%.[42]

Although rosacea is a chronic inflammatory disease, oral antibiotics that engender antibiotic selection pressure and promote bacterial resistance are not a long-term therapeutic solution. Generally, long-term treatment has not been studied in rosacea and most of the trials have been limited to 12-16 weeks in duration.[79] The safety of sub-antibiotic dose doxycycline has been evaluated over longer courses of therapy, ranging from 6 to 9 months.[49,80,81] A recent analysis of MarketScans database suggests that actual clinical use is consistent with the published guidelines. In this study of 72,441 patients with rosacea, the mean duration of 145,100 courses of oral antibiotics was 87.68 days and 79.02% of antibiotic courses were shorter than 3 months.[22]

Importance of Combination Therapy

Topical anti-inflammatory regimens are important as an adjunct to be used in combination with oral therapy, and as maintenance therapy after treatment with an oral agent. Commonly used topicals include metronidazole, azelaic acid, and ivermectin. These typical agents exhibit a variety of potential modes of action including modulation of neutrophil activity and decreased ROS formation (metronidazole, azelaic acid), decreased cathelicidin pathway activity (azelaic acid, ivermectin), and reduction in *Demodex* mites (ivermectin).[69-71]

Combination therapy with oral doxycycline and topical therapy including metronidazole, azelaic acid, and ivermectin has been shown to enhance treatment effects by inducing a faster onset and augmenting the treatment response.[82,83,85] A double-blind, randomized placebo-controlled study found that mean changes in inflammatory lesions were significantly better in patients receiving sub-antibiotic dose doxycycline and metronidazole 1% gel than those receiving sub-antibiotic dose doxycycline alone

at weeks 4,8,12, and 16.[44] One studying comparing a combination of doxycycline plus azelaic acid 15% gel versus doxycycline plus metronidazole gel 1% in 207 patients with rosacea found a trend towards a slightly greater and earlier benefit with the azelaic acid regimen than with metronidazole, but the study was underpowered to find statistical significance.[86]The data on topical ivermectin 1% in combination with doxycycline are more limited. When considering adding topical therapies to rosacea treatment regimens, it is important to ensure that the products do not further disrupt the stratum corneum, which may be already impaired in patients with rosacea.[87] Additional studies are needed to determine the optimal combination of therapies in patients with rosacea on oral antibiotics.

Studies and consensus recommendations have also suggested transitioning to topicals as maintenance therapy for rosacea after oral antibiotic treatment.[56,88,89] A two phase study found that after combination therapy of doxycycline 40mg and azelaic acid, monotherapy maintenance treatment with topical azelaic acid 15% was superior to topical vehicle.[82] In both the vehicle and the azelaic acid maintenance groups, rosacea worsened after cessation of doxycycline, but patients receiving azelaic acid showed significantly less deterioration in inflammatory lesion counts than those receiving vehicle after 8, 16, 20, and 24 weeks of maintenance therapy. Additionally, topical azelaic acid use was associated with a 33% decrease in relative risk of relapse as compared to vehicle. Thus following discontinuation of oral therapy, treatment with topicals should continue as long as the condition is adequately controlled with topical therapy.[56,82,90]

CONCLUSION

Conclusion and Antibiotic Stewardship

Systemic antibiotics have been commonly used for treatment of papulopustular rosacea. Tetracyclines, specifically doxycycline, are the most commonly prescribed antibiotics for rosacea. Other antibiotics that can be used include macrolides, most often azithromycin, and rarely, metronidazole. Despite the widespread use of antibiotics for the treatment of rosacea, only modified release, sub-antibiotic dose doxycycline 40mg once daily has a specific FDA indication for the treatment of papulopustular rosacea.

Of the oral antibiotics used in rosacea, doxycycline has the strongest supporting data. Minocycline may be as effective as doxycycline but has a less favorable side effect profile. Azithromycin is reasonable therapeutic option especially in rosacea patients who cannot tolerate or have failed tetracyclines. Azithromycin has the advantage of intermittent dosing. There is sparse data supporting the use of other macrolides and metronidazole for rosacea.

With the national and international call to use antibiotics responsibly due to concerns for microbial selection pressures, sub-antibiotic dose doxycycline is the favored treatment for rosacea. Sub-antibiotic dose doxycycline provides equivalent therapeutic benefit as standard doxycycline dosing without the bacterial selection pressure. The use of topical agents as combination therapy with oral therapy and as maintenance therapy after oral antibiotic use is discontinued is the recommended approach.

At this time, antibiotics are the most effective oral treatment we have for papulopustular rosacea. Interestingly, dermatologists prescribe more systemic antibiotics per prescriber than members of any other specialty.[91] Given concerns for antibiotic resistance, dermatologists are encouraged to maintain a thorough understanding of the appropriate and responsible use of systemic antibiotics in rosacea.

DISCLOSURE

Arielle Nagler: No conflicts.

James Del Rosso: Consultant for Aclaris, Almirall, BiopharmX, Foamix, Galderma, Leo Pharma, Mayne and Skinfix; Speaker for Aclaris, Almirall, Galderma, and Mayne; Researh Investigator for Aclaris, Almirall, BiopharmX, Foamix, Galderma, Leo Pharma, and Mayne.

REFERENCES

1. Tan J, Berg M. Rosacea: current state of epidemiology. *J Am Acad Dermatol.* 2013;69(6 Suppl 1):S27-35.
2. Steinhoff M, Schauber J, Leyden JJ. New insights into rosacea pathophysiology: a review of recent findings. *J Am Acad Dermatol.* 2013;69(6 Suppl 1):S15-26.
3. Two AM, Wu W, Gallo RL, Hata TR. Rosacea: part I. Introduction, categorization, histology, pathogenesis, and risk factors. *J Am Acad Dermatol.* 2015;72(5):749-758; quiz 759-760.
4. Del Rosso JQ. Update on rosacea pathogenesis and correlation with medical therapeutic agents. *Cutis.* 2006;78(2):97-100.
5. Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol.* 2004;51(3):327-341; quiz 342-324.
6. Del Rosso JQ, Gallo RL, Kircik L, Thiboutot D, Baldwin HE, Cohen D. Why is rosacea considered to be an inflammatory disorder? The primary role, clinical relevance, and therapeutic correlations of abnormal innate immune response in rosacea-prone skin. *J Drugs Dermatol.* 2012;11(6):694-700.
7. Yamasaki K, Di Nardo A, Bardan A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med.* 2007;13(8):975-980.
8. Yamasaki K, Schauber J, Coda A, et al. Kallikrein-mediated proteolysis regulates the antimicrobial effects of cathelicidins in skin. *FASEB J.* 2006;20(12):2068-2080.
9. Jang YH, Sim JH, Kang HY, Kim YC, Lee ES. Immunohistochemical expression of matrix metalloproteinases in the granulomatous rosacea compared with the non-granulomatous rosacea. *Journal of the European Academy of Dermatology and Venereology: JEADV.* 2011;25(5):544-548.
10. Lalu MM, Cena J, Chowdhury R, Lam A, Schulz R. Matrix metalloproteinases contribute to endotoxin and interleukin-1beta induced vascular dysfunction. *Br J Pharmacol.* 2006;149(1):31-42.
11. Lacey N, Delaney S, Kavanagh K, Powell FC. Mite-related bacterial antigens stimulate inflammatory cells in rosacea. *Br J Dermatol.* 2007;157(3):474-481.
12. Rebora A, Drago F, Picciotto A. Helicobacter pylori in patients with rosacea. *Am J Gastroenterol.* 1994;89(9):1603-1604.
13. Zhao YE, Wu LP, Peng Y, Cheng H. Retrospective analysis of the association between Demodex infestation and rosacea. *Arch Dermatol.* 2010;146(8):896-902.
14. Whitfeld M, Gunasingam N, Leow LJ, Shirato K, Preda V. Staphylococcus epidermidis: a possible role in the pustules of rosacea. *J Am Acad Dermatol.*

2011;64(1):49-52.
15. Lazaridou E, Giannopoulou C, Fotiadou C, Vakirlis E, Trigoni A, Ioannides D. The potential role of microorganisms in the development of rosacea. *J Dtsch Dermatol Ges.* 2011;9(1):21-25.
16. Chang YS, Huang YC. Role of Demodex mite infestation in rosacea: A systematic review and meta-analysis. *J Am Acad Dermatol.* 2017;77(3):441-447 e446.
17. Yamasaki K, Kanada K, Macleod DT, et al. TLR2 expression is increased in rosacea and stimulates enhanced serine protease production by keratinocytes. *J Investig Dermatol.* 2011;131(3):688-697.
18. Kocak M, Yagli S, Vahapoglu G, Eksioglu M. Permethrin 5% cream versus metronidazole 0.75% gel for the treatment of papulopustular rosacea. A randomized double-blind placebo-controlled study. *Dermatology.* 2002;205(3):265-270.
19. Dahl MV, Ross AJ, Schlievert PM. Temperature regulates bacterial protein production: possible role in rosacea. *J Am Acad Dermatol.* 2004;50(2):266-272.
20. Jorgensen AHR, Egeberg A, Gideonsson R, Weinstock LB, Thyssen EP, Thyssen JP. Rosacea is associated with Helicobacter pylori: a systematic review and meta-analysis. *J Eur Acad Dermatol.* 2017;31(12):2010-2015.
21. Sneddon IB. A clinical trial of tetracycline in rosacea. *Br J Dermatol.* 1966;78(12):649-652.
22. Rill JS, Lev-Tov H, Liu G, Kirby JS. Dose, duration, and cost: opportunities to improve use of long-term oral antibiotics for people with rosacea. *J Dermatol Treat.* 2018:1-5.
23. van Zuuren EJ, Kramer S, Carter B, Graber MA, Fedorowicz Z. Interventions for rosacea. *The Cochrane Database of Systematic Reviews.* 2011(3):CD003262.
24. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 3: a status report on systemic therapies. *Cutis.* 2014;93(1):18-28.
25. Gallo RL, Granstein RD, Kang S, et al. Standard classification and pathophysiology of rosacea: The 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol.* 2018;78(1):148-155.
26. Margolis DJ, Fanelli M, Kupperman E, et al. Association of pharyngitis with oral antibiotic use for the treatment of acne: a cross-sectional and prospective cohort study. *Arch Dermatol.* 2012;148(3):326-332.
27. Margolis DJ, Bowe WP, Hoffstad O, Berlin JA. Antibiotic treatment of acne may be associated with upper respiratory tract infections. *Arch Dermatol.* 2005;141(9):1132-1136.
28. Levy RM, Huang EY, Roling D, Leyden JJ, Margolis DJ. Effect of antibiotics on the oropharyngeal flora in patients with acne. *Arch Dermatol.* 2003;139(4):467-471.
29. Del Rosso JQ, Webster GF, Rosen T, et al. Status report from the Scientific Panel on Antibiotic Use in Dermatology of the American Acne and Rosacea Society: Part 1: Antibiotic prescribing patterns, sources of antibiotic exposure, antibiotic consumption and emergence of antibiotic resistance, impact of alterations in antibiotic prescribing, and clinical sequelae of antibiotic use. *J Clin Aesthet Dermatol.* 2016;9(4):18-24.
30. Two AM, Wu W, Gallo RL, Hata TR. Rosacea: part II. Topical and systemic therapies in the treatment of rosacea. *J Am Acad Dermatol.* 2015;72(5):761-770; quiz 771-762.
31. Research CfDE. Oracea Clinical Microbiology Review. In: Products DoA-IaO, ed 2006.
32. Alikhan A, Kurek L, Feldman SR. The role of tetracyclines in rosacea. A*m J Clin Dermatol.* 2010;11(2):79-87.
33. Burke B, Eady EA, Cunliffe WJ. Benzoyl peroxide versus topical erythromycin in the treatment of acne vulgaris. *Br J Dermatol.* 1983;108(2):199-204.
34. Lee CZ, Xu B, Hashimoto T, McCulloch CE, Yang GY, Young WL. Doxycycline suppresses cerebral matrix metalloproteinase-9 and angiogenesis induced by focal hyperstimulation of vascular endothelial growth factor in a mouse model. *Stroke.* 2004;35(7):1715-1719.
35. Valentin S, Morales A, Sanchez JL, Rivera A. Safety and efficacy of doxycycline in the treatment of rosacea. *Clin Cosmet Investig Dermatol.* 2009;2:129-140.
36. Perret LJ, Tait CP. Non-antibiotic properties of tetracyclines and their clinical application in dermatology. *Australas J Dermatol.* 2014;55(2):111-118.
37. Leyden JJ, Del Rosso JQ. Oral antibiotic therapy for acne vulgaris: pharmacokinetic and pharmacodynamic perspectives. *J Clin Aesthet Dermatol.* 2011;4(2):40-47.
38. Walker C, Puumala S, Golub LM, et al. Subantimicrobial dose doxycycline effects on osteopenic bone loss: microbiologic results. *J Periodontol.* 2007;78(8):1590-1601.
39. Laboratories G. Oracea (package insert). In:2014.
40. Bikowski JB. Treatment of rosacea with doxycycline monohydrate. *Cutis.* 2000;66(2):149-152.
41. Powell FC. Clinical practice. Rosacea. *NEJM.* 2005;352(8):793-803.
42. Akhyani M, Ehsani AH, Ghiasi M, Jafari AK. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of rosacea: a randomized open clinical trial. *Int J Dermatol.* 2008;47(3):284-288.
43. Sanchez J, Somolinos AL, Almodovar PI, Webster G, Bradshaw M, Powala C. A randomized, double-blind, placebo-controlled trial of the combined effect of doxycycline hyclate 20-mg tablets and metronidazole 0.75% topical lotion in the treatment of rosacea. *J Am Acad Dermatol.* 2005;53(5):791-797.
44. Fowler JF, Jr. Combined effect of anti-inflammatory dose doxycycline (40-mg doxycycline, usp monohydrate controlled-release capsules) and metronidazole topical gel 1% in the treatment of rosacea. *J Drugs Dermatol.* 2007;6(6):641-645.
45. Del Rosso JQ, Webster GF, Jackson M, et al. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. *J Am Acad Dermatol.* 2007;56(5):791-802.
46. Theobald K, Bradshaw M, Leyden J. Anti-inflammatory dose doxycycline (40 mg controlled-release) confers maximum anti-inflammatory efficacy in rosacea. *Skinmed.* 2007;6(5):221-226.
47. Del Rosso JQ, Schlessinger J, Werschler P. Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. *J Drugs Dermatol.* 2008;7(6):573-576.
48. Thomas J, Walker C, Bradshaw M. Long-term use of subantimicrobial dose doxycycline does not lead to changes in antimicrobial susceptibility. *J Periodontol.* 2000;71(9):1472-1483.
49. Skidmore R, Kovach R, Walker C, et al. Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. *Arch Dermatol.* 2003;139(4):459-464.
50. Kardas P. Compliance, clinical outcome, and quality of life of patients with stable angina pectoris receiving once-daily betaxolol versus twice daily metoprolol: a randomized controlled trial. *Vasc Health Risk Manag.* 2007;3(2):235-242.
51. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353(5):487-497.
52. Di Nardo A, Holmes AD, Muto Y, et al. Improved clinical outcome and biomarkers in adults with papulopustular rosacea treated with doxycycline modified-release capsules in a randomized trial. *J Am Acad Dermatol.* 2016;74(6):1086-1092.
53. Lim HG, Fischer A, Rueda MJ, Kendall J, Kang S, Chien AL. Prevalence of gastrointestinal comorbidities in rosacea: Comparison of subantimicrobial, modified release doxycycline versus conventional release doxycycline. *J Am Acad Dermatol.* 2018;78(2):417-419.
54. Layton AM, Cunliffe WJ. Phototoxic eruptions due to doxycycline--a dose-related phenomenon. *Clin Exp Dermatol.* 1993;18(5):425-427.
55. van Zuuren EJ, Fedorowicz Z. Interventions for rosacea: abridged updated Cochrane systematic review including GRADE assessments. *Br J Dermatol.* 2015;173(3):651-662.
56. Elewski BE, Draelos Z, Dreno B, Jansen T, Layton A, Picardo M. Rosacea - global diversity and optimized outcome: proposed international consensus from the Rosacea International Expert Group. *J Eur Acad Dermatol Venereol.* 2011;25(2):188-200.
57. Davis SA, Feldman SR. Patterns of ambulatory care usage and leading treatments for rosacea. *J Dermatolog Treat.* 2014;25(4):275-277.
58. Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. *Clin Ther.* 2005;27(9):1329-1342.
59. Jackson JM, Kircik LH, Lorenz DJ. Efficacy of extended-release 45 mg oral minocycline and extended-release 45 mg oral minocycline plus 15% azelaic acid in the treatment of acne rosacea. *J Drugs Dermatol.* 2013;12(3):292-298.
60. van der Linden MMD, van Ratingen AR, van Rappard DC, Nieuwenburg SA, Spuls PI. DOMINO, doxycycline 40 mg vs. minocycline 100 mg in the treatment of rosacea: a randomized, single-blinded, noninferiority trial, comparing efficacy and safety. *Br J Dermatol.* 2017;176(6):1465-1474.
61. Research CfDEa. Multi-disciplinary review and evaluation of seysara (sarecycline). In:2016.
62. Zhanel G, Critchley I, Lin LY, Alvandi N. Microbiological profile of sarecycline: a novel targeted spectrum tetracycline for the treatment of acne vulgaris. *Antimicrob Agents Chemother.* 2018.
63. Leyden JJ, Sniukiene V, Berk DR, Kaoukhov A. Efficacy and safety of sarecycline, a novel, once-daily, narrow spectrum antibiotic for the treatment of moderate to severe facial acne vulgaris: results of a phase 2, dose-ranging study. *J Drugs Dermatol.* 2018;17(3):333-338.
64. Moore A, Green LJ, Bruce S, et al. Once-daily oral sarecycline 1.5 mg/kg/day is effective for moderate to severe acne vulgaris: results from two identically designed, phase 3, randomized, double-blind clinical trials. *J Drugs Dermatol.* 2018;17(9):987-996.

65. Zarogoulidis P, Papanas N, Kioumis I, Chatzaki E, Maltezos E, Zarogoulidis K. Macrolides: from in vitro anti-inflammatory and immunomodulatory properties to clinical practice in respiratory diseases. *Eur J Clin Pharmacol.* 2012;68(5):479-503.
66. Elewski BE. A novel treatment for acne vulgaris and rosacea. *J Eur Acad Dermatol Venereol.* 2000;14(5):423-424.
67. Bakar O, Demircay Z, Gurbuz O. Therapeutic potential of azithromycin in rosacea. *Int J Dermatol.* 2004;43(2):151-154.
68. Fernandez-Obregon A. Oral use of azithromycin for the treatment of acne rosacea. *Arch Dermatol.* 2004;140(4):489-490.
69. Alvarez-Elcoro S, Enzler MJ. The macrolides: erythromycin, clarithromycin, and azithromycin. *Mayo Clin Proc.* 1999;74(6):613-634.
70. Kim JH, Oh YS, Choi EH. Oral azithromycin for treatment of intractable rosacea. J *Korean Med Sci.* 2011;26(5):694-696.
71. Modi S, Harting M, Rosen T. Azithromycin as an alternative rosacea therapy when tetracyclines prove problematic. *J Drugs Dermatol.* 2008;7(9):898-899.
72. van Zuuren EJ, Kramer SF, Carter BR, Graber MA, Fedorowicz Z. Effective and evidence-based management strategies for rosacea: summary of a Cochrane systematic review. *Br J Dermatol.* 2011;165(4):760-781.
73. Torresani C, Pavesi A, Manara GC. Clarithromycin versus doxycycline in the treatment of rosacea. *Int J Dermatol.* 1997;36(12):942-946.
74. Bamford JT, Tilden RL, Blankush JL, Gangeness DE. Effect of treatment of Helicobacter pylori infection on rosacea. *Arch Dermatol.* 1999;135(6):659-663.
75. Mayr-Kanhauser S, Kranke B, Kaddu S, Mullegger RR. Resolution of granulomatous rosacea after eradication of Helicobacter pylori with clarithromycin, metronidazole and pantoprazole. *Eur J Gastroenterol Hepatol.* 2001;13(11):1379-1383.
76. Pye RJ, Burton JL. Treatment of rosacea by metronidazole. *Lancet.* 1976;1(7971):1211-1212.
77. Saihan EM, Burton JL. A double-blind trial of metronidazole versus oxytetracycline therapy for rosacea. *Br J Dermatol.* 1980;102(4):443-445.
78. Huang KE, Carstensen SE, Feldman SR. The duration of acne treatment. *J Drugs Dermatol.* 2014;13(6):655-656.
79. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 5: a guide on the management of rosacea. *Cutis.* 2014;93(3):134-138.
80. Preshaw PM, Novak MJ, Mellonig J, et al. Modified-release subantimicrobial dose doxycycline enhances scaling and root planing in subjects with periodontal disease. *J Periodontol.* 2008;79(3):440-452.
81. Fort Worth TGL, LP. Oracea (doxycycline USP) capsules 40mg (30mg immediately-release and 10mg delayed-release beads) [package insert]. In:2013.
82. Thiboutot DM, Fleischer AB, Del Rosso JQ, Rich P. A multicenter study of topical azelaic acid 15% gel in combination with oral doxycycline as initial therapy and azelaic acid 15% gel as maintenance monotherapy. *J Drugs Dermatol.* 2009;8(7):639-648.
83. Bhatia ND, Del Rosso JQ. Optimal management of papulopustular rosacea: rationale for combination therapy. *J Drugs Dermatol.* 2012;11(7):838-844.
84. Steinhoff M, Vocanson M, Voegel JJ, Hacini-Rachinel F, Schafer G. Topical Ivermectin 10 mg/g and oral doxycycline 40 mg modified-release: current evidence on the complementary use of anti-inflammatory rosacea treatments. *Adv Ther.* 2016;33(9):1481-1501.
85. Del Rosso JQ. Effectiveness and safety of doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads) once daily as add-on therapy to existing topical regimens for the treatment of papulopustular rosacea: results from a community-based trial. *Cutis.* 2010;86(5 Suppl):16-25.
86. Del Rosso JQ, Bruce S, Jarratt M, Menter A, Staedtler G. Efficacy of topical azelaic acid (AzA) gel 15% plus oral doxycycline 40 mg versus metronidazole gel 1% plus oral doxycycline 40 mg in mild-to-moderate papulopustular rosacea. *J Drugs Dermatol.* 2010;9(6):607-613.
87. Dirschka T, Tronnier H, Folster-Holst R. Epithelial barrier function and atopic diathesis in rosacea and perioral dermatitis. *Br J Dermatol.* 2004;150(6):1136-1141.
88. Schaller M, Almeida LM, Bewley A, et al. Rosacea treatment update: recommendations from the global ROSacea COnsensus (ROSCO) panel. *Br J Dermatol.* 2017;176(2):465-471.
89. Schaller M, Gonser L, Belge K, et al. Dual anti-inflammatory and anti-parasitic action of topical ivermectin 1% in papulopustular rosacea. *J Eur Acad Dermatol Venereol.* 2017;31(11):1907-1911.
90. Dahl MV, Katz HI, Krueger GG, et al. Topical metronidazole maintains remissions of rosacea. *Arch Dermatol.* 1998;134(6):679-683.
91. Prevention CfDCa. OUTPATIENT ANTIBIOTIC PRESCRIPTIONS — United States, 2015. 2015; https://www.cdc.gov/antibiotic-use/community/pdfs/Annual-Report-2015.pdf.

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Patient-Reported Outcomes in Acne Patients With Skin of Color Using Adapalene 0.3%-Benzoyl Peroxide 2.5%: A Prospective Real-World Study

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ABSTRACT

Background: Patients with skin of color (SOC) and Fitzpatrick skin types (FST) IV–VI frequently develop acne.
Objective: Evaluate subject-reported outcomes after treatment with adapalene 0.3%/ benzoyl peroxide 2.5% gel (0.3% A/BPO) in subjects with SOC and moderate to severe acne vulgaris.
Methods: This was an open-label interventional study conducted in 3 countries (Mauritius, Singapore, and USA) in subjects of Asian, Latin-American, or black/African-American ethnicity, with an Investigator's Global Assessment (IGA) of moderate or severe facial acne (enrollment 2:1), and FST IV to VI. For 16 weeks, subjects applied 0.3% A/BPO (once daily) and utilized a skin care regimen (oil control foam wash and oil control moisturizer SPF30). Assessments included quality of life (QoL) and subject questionnaires, IGA, Investigator's Global Assessment of Improvement (GAI), postinflammatory hyperpigmentation (PIH; if present at baseline), and safety.
Results: Fifty subjects were enrolled: 20 Asians, 17 black/African-Americans, and 13 Latin-Americans. Most had FST IV (74%) or V (22%), with moderate (70%; IGA 3) or severe (30%; IGA 4) acne. At week 16, 77% of subjects were satisfied or very satisfied with treatment, 56% of subjects had an IGA of 0 or 1 (clear/almost clear), and 87% had a good to excellent improvement in GAI. QoL improved throughout the study for all subjects; subject selection of "no effect at all" of acne on QoL increased from 16% of subjects at baseline to 55% at week 16. Of those with baseline PIH (60%), all were rated very mild to moderate. By week 16, the majority (75%) had no or very mild PIH, and the mean decrease in PIH was 27%. There were no adverse events leading to study discontinuation.
Conclusion: Patients with SOC and moderate or severe facial acne reported high satisfaction with 0.3% A/BPO treatment and experienced good tolerability, improved QoL, treatment efficacy, and improvement in PIH.
Clinicaltrials.gov number: NCT02932267

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INTRODUCTION

Acne vulgaris is a common chronic disorder, constituting the eighth most prevalent disease with an estimated 9% global prevalence.[1] Acne negatively impacts quality of life, whereas effective treatment may improve it.[2] Acne is present among people with all Fitzpatrick skin types (FST) and ethnicities.[3] Patients, including those with darker skin tones typically known as skin of color (SOC) with FST IV–VI, frequently consult dermatologists for acne. For example, in a New York hospital-based dermatology practice, acne was the most common reason for visits in both African-American and Caucasian patients (28% and 21%, respectively).[4] A survey of Brazilian dermatologists revealed that acne was the most frequent cause for consultation (8%), with similar rates between white and non-white patients.[5] Moreover, in Mauritius, a tropical country which is inhabited by a multi-ethnic population of Indian, Asian, Caucasian, and African origin, a hospital-based study among young adults revealed acne to be the most common skin pathology (13%).[6]

In a photograph-based study of 2895 women of 4 ethnicities, acne was more prevalent in African-American and Hispanic women (37% and 32%, respectively) than in Continental In-

dian, Caucasian, and Asian women with lighter phototypes (23%, 24%, and 30%, respectively). There was an even greater difference in hyperpigmentation between groups.[3] Patients with SOC are thought to be more prone to developing acne and postinflammatory hyperpigmentation (PIH).[6] In a survey of 324 patients from 7 Asian countries (52% with FST IV), 58% had PIH (over 1 year for 65% and over 5 years for 22%), and patients reported that PIH was often as, or more bothersome than acne itself.[7] Similarly, a survey of 280 acne patients from 8 Latin-American countries identified a high rate of associated PIH (78%), lasting 1 year or longer in 47%.[8] In the Middle East where FST IV–VI are predominant, dermatologists reported that PIH was present in 87% of their patients with acne, and persisted for at least 1 year in half (53%) of those affected.[9]

Besides photodamage and hyperpigmentation, ethnic differences between SOC and Caucasian individuals in terms of biological characteristics of the skin remains an area of inconsistent results.[10-11] The risks associated with certain sequelae of acne, notably PIH and keloidal or hypertrophic scarring, are quite different in SOC and should guide treatment regimens.[12]

Topical retinoids remain the foundation of acne treatment.[15] A topical retinoid with benzoyl peroxide should be first-line therapy for the majority of patients with inflammatory or comedonal acne, as supported by a current consensus on acne management.[16] This combination affects 3 out of 4 pathophysiological factors in acne: hyperkeratinization, inflammation, and *Cutibacterium acnes* (previously called *Propionibacterium acnes*).[17-18] There may be concern among dermatologists about using topical retinoids in patients with SOC due to a potential increased risk of irritation and PIH.[13-14] This potential risk can be mitigated by incorporating a regimen comprising a gentle cleanser and moisturizer in order to maximize the therapeutic benefits of retinoids.[14]

In a larger Phase 3 trial in subjects with moderate and severe inflammatory acne,[19] Adapalene 0.3%-benzoyl peroxide 2.5% gel (Epiduo® Forte/TactuPump Forte™ gel, hereafter 0.3% A/BPO gel) demonstrated greater success vs. vehicle than did Adapalene 0.1%-benzoyl peroxide 2.5% gel in subjects with severe acne in achieving an Investigator's Global Assessment (IGA) of "clear" or "almost clear" while demonstrating the same tolerability.[20] Moreover, in a post-hoc analysis of FST from the same study, 0.3% A/BPO gel was found to be effective and equally tolerable in both lighter and darker phototypes, however, a low number of participants with FST IV-VI were enrolled in the vehicle group.[21]

Although 0.3% A/BPO gel has been shown to be effective in patients with lighter phototypes, the need remains to further assess the efficacy and tolerability of 0.3% A/BPO gel in patients with SOC. The main objective of the current study was to evaluate SOC subject-reported outcomes after 16 weeks of treatment with 0.3% A/BPO gel in subjects with moderate to severe acne vulgaris of the face.

METHODS

Study Design

This was an open-label, single arm, interventional, 16-week, Phase 4 study conducted at 4 sites in 3 countries (Mauritius, Singapore, and the USA). Study visits occurred as follows: baseline, weeks 2, 8, 12, and 16. Adult subjects had to provide informed consent to confirm their participation. When applicable, an additional assent form was signed by minor subjects before their enrolment in the study. The study protocol was approved by IRBs and independent ethics committees (IECs), and conformed to the Declaration of Helsinki.

Subjects

Male or female subjects of Asian, Latin American, or black/African-American ethnicity with a minimum age of 12 years were included in this study. They had either moderate (IGA 3) or severe (IGA 4) acne and were enrolled in a 2:1 ratio; all had 25-100 inflammatory lesions (papules and pustules), 30-150 non-inflammatory lesions (open and closed comedones) excluding the nose, and no more than two acne nodules (≥1 cm); all were of Fitzpatrick skin phototype IV to VI (ie, burns minimally and always tans well [moderate brown] to never burns, deeply pigmented [black] and tans profusely). Key exclusion criteria included subjects with acne conglobata, acne fulminans, secondary acne, nodulocystic acne, acne requiring systemic treatment, damaged facial skin (eg, sunburned), or severe PIH (score >3 on a PIH scale), a history of active or chronic skin allergies, lupus, atopic dermatitis, perioral dermatitis, dermatomyositis, rosacea, and/or inability to adhere to the wash-out periods for other treatments.

Study Treatment

The investigational product was dispensed to all subjects as were the required skin care products. Subjects were to use Cetaphil® DermaControl™ Oil control Foam Wash twice daily (in the morning and evening), and Cetaphil® DermaControl™ Oil control Moisturizer SPF 30 applied once daily in the morning and re-applied if exposure to the sun occurred during the day.

Subject-Reported Outcomes

Subject-reported outcomes comprised quality of life (QoL) and subject satisfaction questionnaires. The Dermatology Life Quality Index questionnaire (DLQI) or Children's Dermatology Life Quality Index (cDLQI, for children age ≤16 years) questionnaires were completed at baseline (before application of the investigational product), week 12, and week 16/early termination. Subject satisfaction questionnaires were administered at week 12 and week 16/early termination.

Efficacy and Safety Endpoints

To evaluate the efficacy of 0.3% A/BPO gel, IGA of facial acne severity was completed at each visit and was rated on a scale from 0 (clear) to 4 (severe). Additionally, the Investigator's Global Assessment of Improvement (GAI) was performed, noting improvement compared with baseline on a scale from 0 (excellent improvement) to 5 (worse) at week 12 and week 16/ early termination.

Safety endpoints included PIH), tolerability, and adverse events (AEs). The severity of PIH, if present at baseline, was assessed at each visit; any increase in the PIH score was reported as an AE. PIH severity was assessed by the investigator, measured on a scale from 0 (none) to 4 (severe, meaning a large number of areas of PIH, large in size, and markedly darker than the surrounding skin). Local tolerance (erythema, scaling, dryness, stinging/burning) was evaluated using a severity score on a scale from 0 (none) to 3 (severe) at each visit and recorded by the investigator after discussion with the subject. AEs were assessed throughout the study.

Other Endpoints

A questionnaire regarding the cosmetic acceptability of the non-investigational products was completed at week 16/early termination.

Statistical Methods

All endpoints were descriptively summarized for the following populations: Intent-to-treat (ITT; all randomized subjects) and safety (ITT subjects who applied the study drug at least once). The last observation carried forward (LOCF) method was used to impute missing efficacy values.

RESULTS

Subject Disposition and Demographics/Clinical Characteristics

A total of 50 subjects were enrolled and analyzed in both the ITT and safety populations: 20 Asians, 17 black/African-Americans, and 13 Latin-Americans. The majority (84%) completed the study. No subject discontinued the study due to an AE. Of 8 subjects (16%) who discontinued, 3 subjects (6%) asked to withdraw from the study (2 subjects considered the study drug ineffective and 1 subject withdrew for a social reason), 4 subjects (8%) were lost to follow-up, and 1 subject (2%) withdrew due to pregnancy.

Demographic/disease characteristics were overall comparable between groups (Table 1). A similar proportion of females (48%) and males (52%) were enrolled. The average age was 21 years old. At baseline, most had FST IV (74%) or V (22%), with moderate (70%; IGA 3) or severe (30%; IGA 4) acne. Baseline PIH was

TABLE 1.

Baseline Demographics and Disease Characteristics

		Asian (N=20)	Latin American (N=13)	Black/ African-American (N=17)	Total (N=50)
Age (years)	Mean ± SD	22.4 ± 7.0	17.6 ± 4.4	21.6 ± 6.4	20.9 ± 6.4
	Min, Max	15, 49	13, 27	14, 37	13, 49
	< 18 years	5 (25.0%)	8 (61.5%)	8 (47.1%)	21 (42.0%)
	18-65 years	15 (75.0%)	5 (38.5%)	9 (52.9%)	29 (58.0%)
Gender	Female	10 (50.0%)	5 (38.5%)	9 (52.9%)	24 (48.0%)
	Male	10 (50.0%)	8 (61.5%)	8 (47.1%)	26 (52.0%)
Skin Phototype	IV	16 (80.0%)	13 (100.0%)	8 (47.1%)	37 (74.0%)
	V	4 (20.0%)	0 (0.0%)	7 (41.2%)	11 (22.0%)
	VI	0 (0.0%)	0 (0.0%)	2 (11.8%)	2 (4.0%)
Country	Mauritius	4 (20.0%)	0 (0.0%)	12 (70.6%)	16 (32.0%)
	Singapore	16 (80.0%)	0 (0.0%)	0 (0.0%)	16 (32.0%)
	United States	0 (0.0%)	13 (100.0%)	5 (29.4%)	18 (36.0%)
IGA (baseline)	3: Moderate	13 (65.0%)	10 (76.9%)	12 (70.6%)	35 (70.0%)
	4: Severe	7 (35.0%)	3 (23.1%)	5 (29.4%)	15 (30.0%)
PIH (baseline)	0: None	2 (10.0%)	10 (76.9%)	8 (47.1%)	20 (40.0%)
	1: Very mild	6 (30.0%)	2 (15.4%)	5 (29.4%)	13 (26.0%)
	2: Mild	9 (45.0%)	1 (7.7%)	1 (5.9%)	11 (22.0%)
	3: Moderate	3 (15.0%)	0 (0.0%)	3 (17.6%)	6 (12.0%)

IGA: Investigator's Global Assessment; PIH: postinflammatory hyperpigmentation

present in 90% of Asian patients, 53% of black/African-Americans, and 23% of Latin Americans. On average, subjects had a 7-year history of acne, and over half (56%) had a 5-year history.

Subject-Reported Outcomes

Quality of Life

QoL (as measured by DLQI/cDLQI scores) improved throughout the study, regardless of ethnicity. The percentage of subjects reporting "no effect at all" of acne on QoL increased from 16% of subjects at baseline to 55% at week 16 (Figure 1A). The percentage of subjects reporting a "very large" to "extremely large effect" of acne on QoL decreased from 28% at baseline to 4% at week 16.

Satisfaction Questionnaire

High levels of subject satisfaction continued through the end of the study. Overall, most subjects (88%) were satisfied or very satisfied with treatment (from 78% of Asians to 100% of black/African-Americans). At week 12, the majority (81%) were satisfied or very satisfied with treatment effectiveness (from 78% of Asians to 90% of Latin-Americans). Approximately 93% of subjects were not bothered or bothered somewhat by treatment side effects (ranging from 80% of Latin-Americans to 100% of black/African-Americans).

At week 16, over three-fourths (77%) of subjects were overall satisfied or very satisfied with treatment (from 72% of Asians to 82% of black/African-Americans; Figure 1B). Three-fourths (approximately 75%) of all subjects were satisfied or very satisfied with treatment effectiveness (from 67% of Latin-Americans to 82% of black/African-Americans). Approximately 89% of subjects were not bothered or bothered somewhat by treatment side effects (ranging from 67% of Latin-Americans to 100% of black/African-Americans). Half of the entire population (49%) were not bothered at all by side effects.

Efficacy

IGA improved over time in the study population, and the majority were graded as IGA 0-2 at weeks 12 and 16. As shown in Figure 2, 56% of subjects had an IGA score of 0 or 1 (clear/almost clear) at week 16. Improvement is illustrated with photographs of subjects at baseline and week 16 in Figures 4-6.

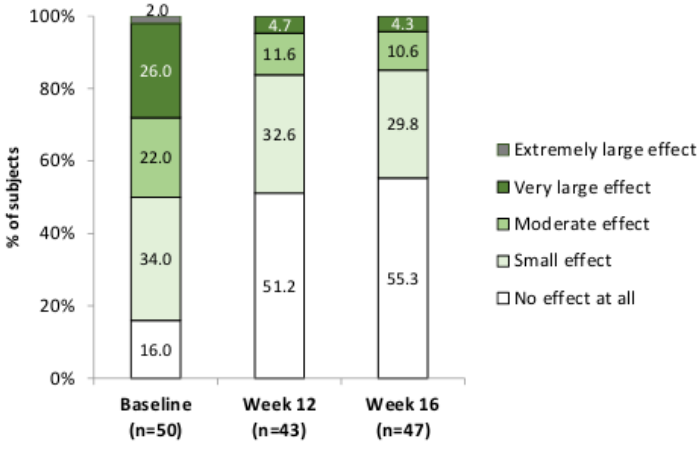
Good to excellent improvement in GAI was observed for the majority across ethnic groups at weeks 12 and 16 (81% and 87%, respectively). At week 16, this ranged from 67% of Latin-Americans to 100% of Asians.

Safety

Of those with PIH at baseline (60%), all were rated very mild to moderate. By week 16, the majority (75%) had no or very mild PIH; the mean percentage decrease in PIH was 27%.

FIGURE 1. Patient-reported outcomes with the 0.3% A/BPO gel treatment. (A) DLQI/cDLQI: effect of disease on Quality of Life from baseline to week 16. (B) Satisfaction at week 16: "Overall, are you satisfied with the treatment?"

(A)



(B)

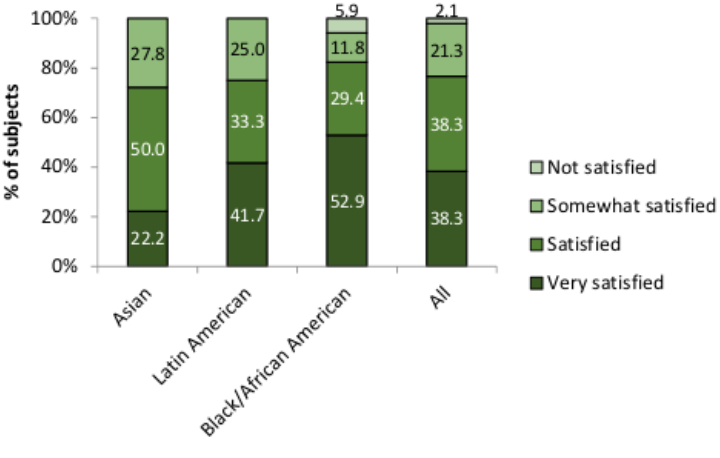


FIGURE 2. IGA: subjects with "clear/almost clear" skin over time.

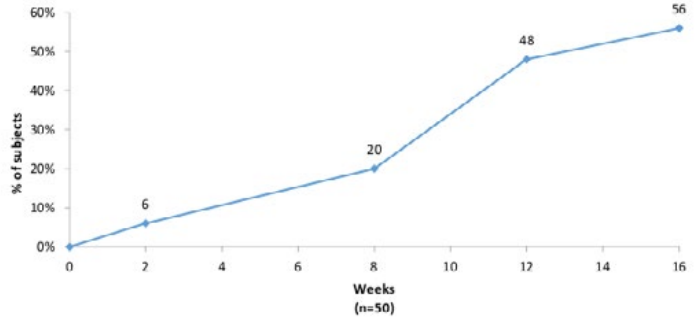
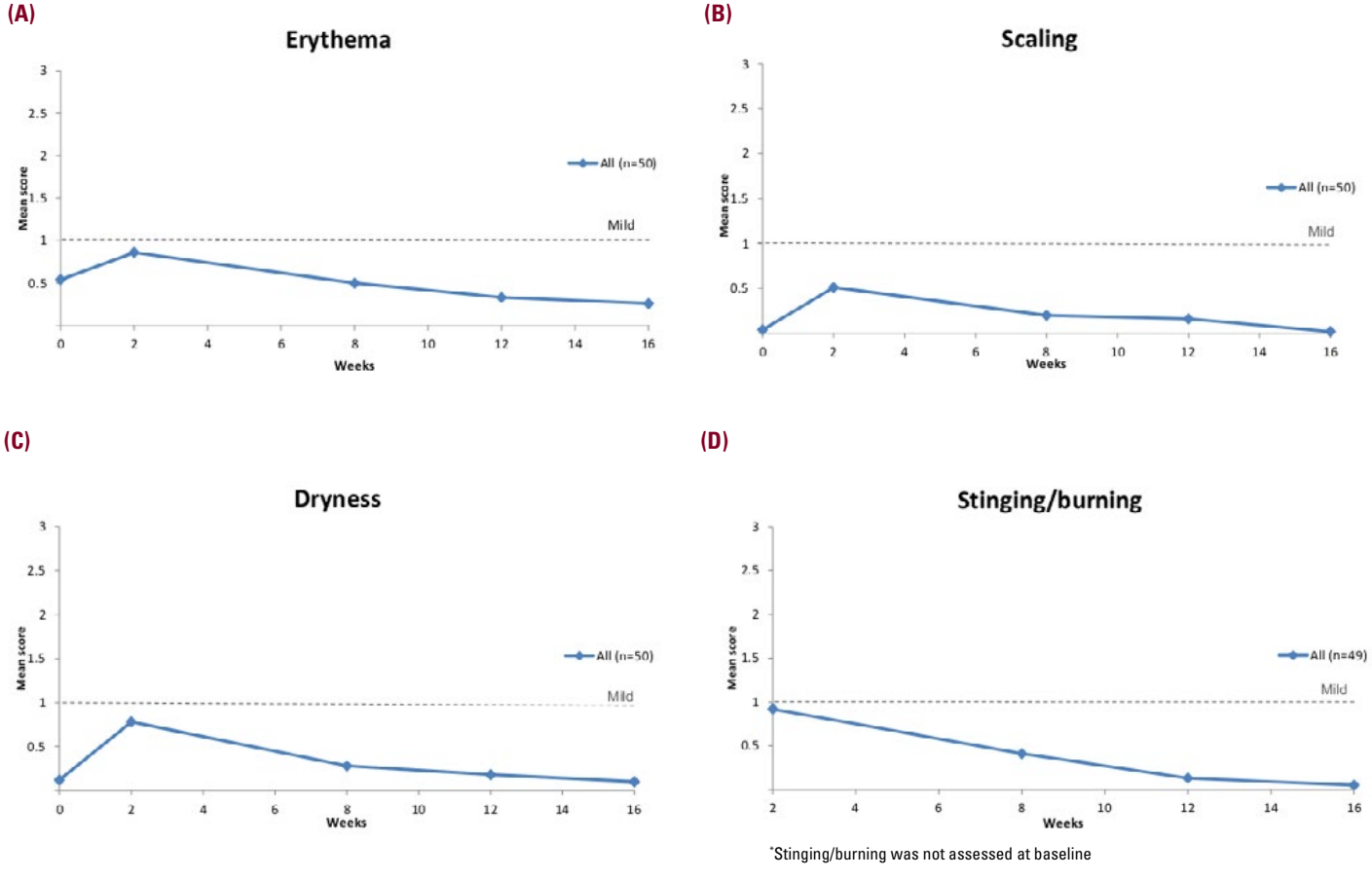


FIGURE 3. Local tolerability (mean scores) (A) Erythema; (B) Scaling; (C) Dryness; (D) Stinging/burning.*



*Stinging/burning was not assessed at baseline

Local tolerance in terms of erythema, scaling, dryness and stinging/burning is illustrated in Figures 3A-D. Treatment with 0.3% A/BPO gel was well-tolerated, with a similar local tolerability profile across the entire population. Not surprisingly, there was a transitory peak of erythema, stinging/burning, and dryness at week 2, which decreased in the following visits. Throughout the study, signs and symptoms generally remained at most, mild.

There were no serious or severe AEs related to 0.3% A/BPO gel treatment, and no AEs leading to study discontinuation. Seven subjects (14%) reported treatment-related AEs but all were mild and dermatological in nature: pruritus (2 subjects, 4%), PIH change (2 subjects, 4%), skin irritation (1 subject, 2%), and cheilitis, eschar, and papular rash (1 subject, 2%).

Other Endpoints: Cosmetic Acceptability Questionnaire

The majority of subjects considered that both the moisturizer and facial cleanser helped them to continue treatment (84% and 96%, respectively), and were a necessary part of their acne treatment (78% and 94%, respectively).

DISCUSSION

Patients with SOC need acne treatment to be adapted to their specific presentation of the disease. One of the recent recommendations from a consensus on acne management is that early and effective treatment should be used to minimize the potential risk for acne scarring.[16] In patients with moderate inflammatory acne, a six-month randomized trial of 0.1% A/BPO gel suggests that treatment reduces the risk of atrophic scar formation compared to vehicle.[22] In an open-label trial of 0.3% adapalene gel in subjects with a history of acne and moderate to severe facial atrophic acne scars, skin texture of the scars improved after 24 weeks of treatment as reported by over 50% of investigators and over 80% of subjects.[23] Additionally, in subjects with moderate or severe facial acne, a six-month, randomized, vehicle-controlled trial demonstrated that 0.3% A/BPO gel prevents and even reduces scar formation.[24] Therefore, 0.3% A/BPO gel may provide greater scarring risk reduction in even more severe acne with comparable tolerability, an area which merits further research. This is consistent with adapalene's dose-dependent effect on inflammatory markers, suggesting that a higher potency of

FIGURE 4. Photographs of subject from the black/African-American ethnic group at (A) baseline (moderate [IGA 3]) and (B) week 16 (almost clear [IGA 1]).

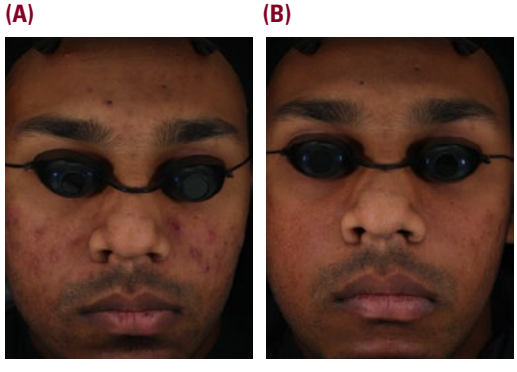


FIGURE 5. Photographs of subject from the Asian ethnic group at (A) baseline (moderate [IGA 3]) and (B) week 16 (almost clear [IGA 1]).

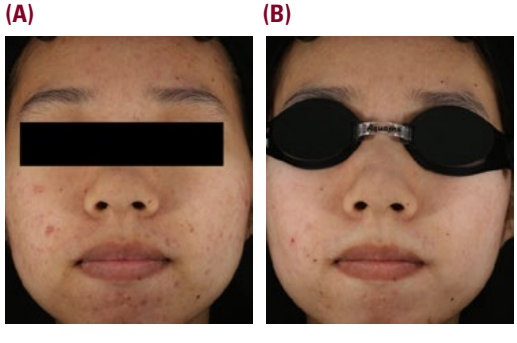
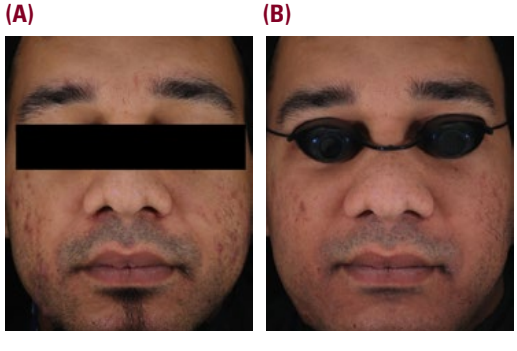


FIGURE 6. Photographs of subject from the black/African-American ethnic group at (A) baseline (moderate [IGA 3]) and (B) week 16 (mild [IGA 2]).



A/BPO can exert a greater anti-inflammatory effect in patients with more severe acne.[25]

In this study, treatment with 0.3% A/BPO gel in subjects with SOC and moderate or severe facial acne was effective with IGA success increasing over time in the entire population. As 0.3% A/BPO gel has previously been found to be effective in achieving acne treatment success regardless of age or gender[26] and in all skin phototypes,[21] our results similarly indicate that treatment can be effectively and safely used, not only in lighter skin phototypes, but also in the population of patients with SOC.

Treatment with 0.3% A/BPO gel was well-tolerated, with no AE leading to study discontinuation. Local tolerability of 0.3% A/BPO gel was consistent with previous results from a Phase 3 trial that found tolerability to be similar to that of the 0.1% A/BPO gel formulation.[27] Importantly, efficacy and safety results were reflected in the high levels of overall subject satisfaction. An encouraging result of the present study was that PIH did not worsen in subjects who were affected at baseline; it even improved in some by the end of the study. Although some dermatologists may be hesitant to prescribe retinoids in patients with SOC,[14] they may be reassured by the results of this study: the use of 0.3% A/BPO gel yielded no observed increased risk of PIH. Nevertheless, although the results of this study are reassuring, this was a single-arm study and its primary objective was to assess subject-reported outcomes, not PIH. Combination of a higher strength retinoid and BPO, as with 0.3% A/BPO gel, provides a powerful treatment option for patients with SOC and moderate to severe acne, without compromising safety.

Limitations to this study included the open-label design. Of note, however, these results are similar to those of randomized controlled trials. The real-life findings of this study provide useful information regarding the safety and tolerability profile of this treatment in patients with SOC. The small number of subjects enrolled makes it difficult to draw conclusions for individual ethnic groups; nevertheless, the study was not designed for this.

Practices that may reduce skin irritation and improve compliance with 0.3% A/BPO gel use are important to address in a clinician-patient discussion. The roles of moisturizers and sunscreens are essential, and, in combination with acne treatment, have been shown to lead to high levels of subject satisfaction, improved adherence, and favorable tolerability.[29-30] In this study, these products were perceived by patients to be a necessary part of their acne treatment and also helpful in ensuring continuation of treatment with 0.3% A/BPO gel. Patient education should, therefore, reinforce the use of skin care products. The observed improvement in quality of life and possibly PIH, which may be of more concern to patients than acne itself, may, in turn, aid the patient in adherence to treatment.

CONCLUSIONS

In this study, subjects with SOC from Asian, black/African-American, and Latin-American ethnicities, and with moderate or severe facial acne, reported high levels of satisfaction with 0.3% A/BPO gel treatment. They also experienced favorable tolerability, improved QoL, treatment efficacy, and no worsening of PIH with improvement observed in some subjects.

DISCLOSURE

Drs. DuBois, Ong, and Petkar are principal investigators for Galderma. Dr. Almeida has served as a researcher for Galderma and Dr. Alexis is a consultant for Galderma. Dr. Chavda is an employee of Galderma, and Mr. Kerrouche is a previous employee of Galderma.

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REFERENCES

1. Tan JK, Bhate K. A global perspective on the epidemiology of acne. *Br J Dermatol.* 2015;172 Suppl 1:3-12.
2. Thomas DR. Psychosocial effects of acne. *J Cutan Med Surg.* 2004;8 Suppl 4:3-5.
3. Perkins AC, Cheng CE, Hillebrand GG, et al. Comparison of the epidemiology of acne vulgaris among Caucasian, Asian, Continental Indian and African American women. *J Eur Acad Dermatol Venereol.* 2011;25(9):1054-60.
4. Alexis A.F., Sergay A.B., Taylor S.C. 2007. Common dermatologic disorders in skin of color: a comparative practice survey. *Cutis.* 2007, Vol. 80.
5. Miot HA, Penna GO, Ramos AMC, et al. Profile of dermatological consultations in Brazil (2018). *An Bras Dermatol.* 2018;93(6):916-928.
6. Kawshar T, Rajesh J. Sociodemographic factors and their association to prevalence of skin diseases among adolescents. *Our Dermatol Online.* 2013;4(3):281-286.
7. Alexis AF, Harper JC, Stein Gold LF, Tan JKL. *Semin Cutan Med Surg.* 2018;37(3S):S71-S73.
8. Abad-Casintahan F, Chow SK, Goh CL, et al. *J Dermatol.* 2016;43(7):826-8.
9. Almeida LM, Maria Isabel Barona MI, Beltran AFM, et al. Prospective online survey confirms high frequency of post-inflammatory hyperpigmentation in Latin America. Data on file.
10. Abanmi A, Al-Enezi M, Al Hammadi A, Galadari I, Kibbi AG, Zimmo S. Survey of acne-related post-inflammatory hyperpigmentation in the Middle East. *J Dermatolog Treat.* 2018:1-4.
11. Kligman AM, Shelley WB. An investigation of the biology of the sebaceous gland. *J Invest Dermatol.* 1958; 30(3):99-125.
12. Grimes P, Edison BL, Green BA, Wildnauer RH. Evaluation of inherent differences between African American and white skin surface properties using subjective and objective measures. *Cutis.* 2004; 73(6):392-6.
13. Davis EC, Callender VD. A review of acne in ethnic skin: pathogenesis, clinical manifestations, and management strategies. *J Clin Aesthet Dermatol.* 2010; 3(4):24-38.
14. See JA, Goh CL, Hayashi N, Suh DH, Casintahan FA. Optimizing the use of topical retinoids in Asian acne patients. J Dermatol. 2018;45(5):522-528.
15. Callender VD. Acne in ethnic skin: special considerations for therapy. *Dermatol Ther.* 2004;17(2):184-95.
16. Leyden J, Stein-Gold L, Weiss J. Why topical retinoids are mainstay of therapy for acne. *Dermatol Ther (Heidelb).* 2017;7(3):293-304.
17. Thiboutot DM, Dréno B, Abanmi A, et al. Practical management of acne for clinicians: an international consensus from the Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2018;78(2 Suppl 1):S1-S23.e1.
18. Leyden JJ, Preston N, Osborn C, Gottschalk RW. In-vivo effectiveness of adapalene 0.1%/benzoyl peroxide 2.5% gel on antibiotic-sensitive and resistant Propionibacterium acnes. *J Clin Aesthet Dermatol.* 2011;4(5):22-6.
19. Dréno B, Pécastaings S, Corvec S, Veraldi S, Khammari A, Roques C. Cutibacterium acnes (Propionibacterium acnes) and acne vulgaris: a brief look at the latest updates. *J Eur Acad Dermatol Venereol.* 2018;32 Suppl 2:5-14.
20. Stein Gold L, Weiss J, Rueda MJ, et al. Moderate and severe inflammatory acne vulgaris effectively treated with single-agent therapy by a new fixed-dose combination adapalene 0.3 %/benzoyl peroxide 2.5 % gel: a randomized, double-blind, parallel-group, controlled study. *Am J Clin Dermatol.* 2016;17(3):293-303.
21. Weiss J, Stein Gold L, Leoni M, et al. Customized single-agent therapy management of severe inflammatory acne: a randomized, double-blind, parallel-group, controlled study of a new treatment—adapalene 0.3%-benzoyl peroxide 2.5% gel. *J Drugs Dermatol.* 2015;14(12):1427-35.
22. Alexis AF, Cook-Bolden FE, York JP. Adapalene/benzoyl peroxide gel 0.3%/2.5%: a safe and effective acne therapy in all skin phototypes. *J Drugs Dermatol.* 2017;16(6):574-581.
23. Dréno B, Tan J, Rivier M, Martel P, Bissonnette R. Adapalene 0.1%/benzoyl peroxide 2.5% gel reduces the risk of atrophic scar formation in moderate inflammatory acne: a split-face randomized controlled trial. *J Eur Acad Dermatol Venereol.* 2017;31:737-742.
24. Loss MJ, Leung S, Chien A, et al. Adapalene 0.3% gel shows efficacy for the treatment of atrophic acne scars. *Dermatol Ther (Heidelb).* 2018; 8(2):245-257.
25. Dréno B, Bissonnette R, Gagné-Henley A, et al. Prevention and reduction of atrophic acne scars with adapalene 0.3%/benzoyl peroxide 2.5% gel in subjects with moderate or severe facial acne: results of a 6-month randomized, vehicle-controlled trial using intra-individual comparison. *Am J Clin Dermatol.* 2018;19(2):275-286.
26. Tenaud I, Khammari A, Dreno B. In vitro modulation of TLR-2, CD1d and IL-10 by adapalene on normal human skin and acne inflammatory lesions. *Exp Dermatol.* 2007;16(6):500-6.
27. Stein Gold L, Werschler WP, Mohawk J. Adapalene/benzoyl peroxide gel 0.3%/2.5%: effective acne therapy regardless of age or gender. *J Drugs Dermatol.* 2017;16(6):582-589.
28. Stein Gold L, Weiss J, Rueda MJ, et al. Moderate and severe inflammatory acne vulgaris effectively treated with single-agent therapy by a new fixed-dose combination adapalene 0.3 %/benzoyl peroxide 2.5 % gel: a randomized, double-blind, parallel-group, controlled study. *Am J Clin Dermatol.* 2016;17(3):293-303.
29. Del Rosso JQ, Brandt S. The role of skin care as an integral component in the management of acne vulgaris: part 2: tolerability and performance of a designated skin care regimen using a foam wash and moisturizer SPF 30 in patients with acne vulgaris undergoing active treatment. *J Clin Aesthet Dermatol.* 2013;6(12):28-36.
30. Kim MR, Kerrouche N. Combination of benzoyl peroxide 5% gel with liquid cleanser and moisturizer SPF 30 in acne treatment results in high levels of subject satisfaction, good adherence and favorable tolerability. *J Dermatolog Treat.* 2018; 29(1):49-54.

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Safety and Effectiveness of Microfocused Ultrasound for Treating Erythematotelangiectatic Rosacea

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ABSTRACT

Background: Anecdotal reports indicate the use of microfocused ultrasound with visualization (MFU-V) improves facial redness.
Objective: The purpose of this pilot study was to assess the safety and effectiveness of MFU-V for improving the signs and symptoms of erythematotelangiectatic rosacea.
Methods & Materials: Healthy adults with a clinical diagnosis of erythematotelangiectatic rosacea were enrolled (N=91). Eligible subjects had baseline Clinician Erythema Assessment (CEA) scores ≥3 and Patient Self-Assessment (PSA) of erythema scores ≥2. Subjects were randomized to receive one or two low-density MFU-V treatments or one or two high-density MFU-V treatments. Subjects were evaluated at 90, 180, and 365 days after treatment. The primary effectiveness endpoint was treatment success, defined as a 1-point change in CEA scores at 90 days post-treatment.
Results: Across groups, 75 to 91.3% of subjects achieved treatment success at 90 days post-treatment. Notable adverse events include bruising (44%), tenderness/soreness (43%), and redness (35%). Treatment results were sustained, lasting up to 1 year. Subject satisfaction was high based on self-assessment questionnaires.
Conclusion: The results of this study demonstrated that a single, high-density MFU-V treatment may be effective for treating erythematotelangiectatic rosacea. Based on these results, a large, randomized controlled study of single, high-density MFU-V treatment for erythematotelangiectatic rosacea is warranted.

J Drugs Dermatol. 2019;18(6):522-531.

INTRODUCTION

Rosacea is a chronic, cutaneous inflammatory syndrome that most commonly affects the convexities of the central face, including the cheeks, chin, nose, eyes, and central forehead. Often characterized by remissions and exacerbations, it manifests as various combinations of cutaneous flushing, erythema, telangiectasia, edema, papules, pustules, ocular lesions and rhinophyma.[1] Individuals are typically affected by some, but not all, of these characteristics, based on the form of rosacea they encounter.

The different forms of rosacea include erythematotelangiectatic (ETT), papulopustular (PP), phymatous, and ocular.[2] The causes of rosacea are poorly understood, but appear to involve chronic inflammation, environmental triggers, ingested foods, and microorganisms, either alone or in combination.[2] Although it occurs primarily among elderly, fair-skinned individuals, the prevalence of rosacea is poorly characterized. Estimates range from 5% in the US and Russia[3,4] to 10-13% in Sweden and Germany.[1,4] The primary clinical feature of ETT rosacea is transient or persistent facial erythema which, if left untreated, may progress to disfiguring papules or pustules.[5,6] Consequently, patients with rosacea have a higher incidence of social embarrassment, social anxiety, depression, stigmatization and decreased self-esteem[5,7-9] leading to diminished quality of life.[5,10-12]

The only FDA-approved systemic agent for treating rosacea is a modified-release doxycycline product.[13] This agent is only indicated for the treatment of inflammatory papules and pustules associated with rosacea in adult patients. It is not effective for treating generalized erythema.[13] Carvedilol, a nonselective β-blocker with α-1 blocking activity, has been used off-label to treat erythema and flushing.[14] Other systemic agents, which are used off-label, for treating rosacea-related papules and pustules include tetracyclines, macrolides, metronidazole, and isotretinoin.[14]

Azelaic acid gel is FDA-approved for the topical treatment of inflammatory papules and pustules of mild-to-moderate rosacea; however, the efficacy of this product for treating erythema in the absence of papules and pustules has not been evaluated.[15] The only FDA-approved topical product for persistent facial flushing is brimonidine tartrate gel, an α-2 agonist,[16] while topi-

cal oxymetazoline hydrochloride, an α-1A agonist, is approved for persistent facial erythema. Topical ivermectin and metronidazole are approved for treating papulopustular rosacea.[17,18] Approved energy-based treatments for rosacea include radiofrequency,[19] lasers[20] and intense-pulsed-light devices.[21] Some, but not all, patients with rosacea achieve beneficial results with currently available systemic, topical, and energy-based therapies.

In contrast to systemic and topical treatments for rosacea, the current study evaluated a noninvasive aesthetic device that uses microfocused ultrasound (MFU) to produce small (<1 mm^3) thermal lesions or coagulation zones within the dermal and subdermal layers of the skin (Ultherapy® System; Merz North America, Raleigh, NC).[22] Following treatment with MFU, heated collagen in the skin immediately contracts, followed by neocollagenesis and collagen remodeling.[23] The result is tightening and lifting of lax skin. The device can also perform ultrasound imaging, which ensures the device is properly coupled to the dermis for safe energy delivery and to visualize non-target tissues, such as bone (MFU-V; DeepSEE®; Merz North America, Raleigh, NC). In the US, the MFU-V device is FDA cleared for lifting the brow,[24,25] submental, and neck tissue,[26] and improving lines and wrinkles of the décolleté.[9,27]

When used for other indications, anecdotal reports indicate the use of MFU-V improves facial redness. We hypothesized that using MFU-V to create focal lesions in the dermis and subdermis and coagulate blood vessels in the superficial plexus would reduce the increased blood flow in the skin of individuals with rosacea. The objective of this pilot study was to assess the safety and effectiveness of MFU-V for improving the signs and symptoms of erythematotelangiectatic rosacea.

MATERIALS AND METHODS

Study Subjects

Healthy male and female subjects 18 to 65 years old with a clinical diagnosis of erythematotelangiectatic rosacea were enrolled. Eligible subjects had a Clinician Erythema Assessment (CEA) score ≥3 and a Patient Self-Assessment (PSA) of erythema score ≥2 at Screening and at Baseline (day 0). Subjects agreed not to undergo any other treatment for rosacea during the study and follow-up period, to refrain from the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) prior to each study treatment, and from chronic use of NSAIDs during the entire post-treatment study period. Prior, chronic NSAID users agreed to undergo a 4-week washout period before the first treatment. Subjects also expressed their willingness to continue their current skin-care regimen and to comply with protocol requirements, including follow-up visits and abstaining from exclusionary procedures for the duration of the study. Subjects of childbearing potential provided a negative urine pregnancy test result and were not lactating at Visit 1 and agreed to use an acceptable method of birth control during the study.

Exclusion Criteria

Subjects with the following conditions or disorders were excluded from study participation: >5 prominent (>0.2 mm wide) telangiectasias in the areas to be treated with the exception of the lateral sides of the nose; other forms of rosacea (papulopustular, phymatous, ocular rosacea, rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) or concomitant facial dermatoses similar to rosacea (peri-oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, or acute lupus erythematosus); ≥3 facial inflammatory rosacea lesions (papules or pustules); intense flushing due to a single trigger, such as post-menopausal hot flashes or particular food vs. both intense and less intense flushing due to many common triggers; current treatment with monoamine oxidase inhibitors, barbiturates, opiates, sedatives, systemic anesthetics, α-agonists, or anticoagulants; chronic non-steroidal anti-inflammatory drugs within the past 4 weeks; topical brimonidine tartrate within the previous 2 weeks; systemic corticosteroid or immunosuppressive drugs or antipruritic drugs including antihistamines within 24 hours of study visits; <3 months of stable dose therapy with tricyclic antidepressants, cardiac glycosides, β-blockers or other vasodilating antihypertensives; current diagnosis of Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome, or clinically diagnosed depression (unless on a stable treatment regimen); history of post-inflammatory hyperpigmentation; presence of an active systemic disease that may affect wound healing; severe solar elastosis; significant scarring that would interfere with assessing treatment results; open wounds or lesions in the intended treatment area; acne vulgaris; active or metallic implants in the treatment area; marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin in the areas to be treated; chronic drug or alcohol abuse or smoking (timeframe, past 5 years); history of autoimmune disease, Bell's palsy, epilepsy or diabetes; microdermabrasion or glycolic acid peels in the treatment areas (4 weeks) prior to study participation; treatment with injectable dermal fillers including hyaluronic acid (12 months), calcium hydroxyapatite (12 months), long-lasting hyaluronic or poly-L-lactic acid (24 months) or permanent fillers (ever); neurotoxins (3 months); ablative resurfacing laser treatment; nonablative, rejuvenative laser or light treatment (6 months); surgical dermabrasion or deep-facial peels; use of systemic retinoids (6 months) or topical retinoids (2 weeks); concurrent enrollment or participation in any study involving the use of investigational devices or drugs (30 days).

Study Procedures

The Screening Visit occurred within 14 days of the Baseline Visit and included a review of subject medical history, current medications, inclusion and exclusion criteria, a physical ex-

amination, a urine pregnancy test, if applicable, and informed consent. In addition, five, standardized, digital 2-D images were obtained using fixed camera and lighting conditions as follows: front, right 45°, left 45°, right 90°, and left 90° (Visia®, Canfield Scientific, Inc., Parsippany, NJ). Baseline evaluations included the Rosacea Classification Assessment (rosacea scorecard), Dermatology Life Quality Index (DLQI) Assessment, colorimeter assessment, vertical (mid-pupil line) and horizontal (lateral to the nasal crease) measurements, and a urine pregnancy test (as needed).

Prior to the initial treatment, areas of skin to be treated were identified. The first MFU-V treatment was performed within 14 days of the baseline visit and the second treatment was performed 14 days after the first treatment. Ultrasound gel was applied to the transducer, which was placed on the targeted skin surface, and an ultrasound image was obtained. An image was obtained for each area of the proposed treatment area with the MFU-V device to ensure coupling between the transducer and skin and to avoid non-target tissue, such as bone. One hour prior to each treatment, subjects were administered ibuprofen 800 mg. Five different MFU transducers were available for use, with up to three different, dual-depth transducers used on each subject:

1. 4 MHz with a 4.5 mm focal depth
2. 7 MHz with a 3.0 mm focal depth
3. 7 MHz with a 3.0N mm focal depth (narrow version of transducer 2)
4. 10 MHz with a 1.5 mm focal depth
5. 10 MHz with a 1.5N mm focal depth (narrow version of transducer 4)

The first transducer used was the 4-4.5mm, then the 7-3.0mm or 7-3.0N mm, followed by the 10-1.5N mm. During the procedure, multiple treatment MFU-V lines 2 to 3 mm apart and 25 mm long were placed within the target area. The planned energy delivery was 0.90 joules for the 4-4.5 mm transducer, 0.30 joules for the 7-3.0 mm and 7-3.0N mm transducers, and 0.18 joules for the 10-1.5N mm transducer.

The initial protocol specified that enrolled subjects would be randomized to one of four dual-depth MFU-V treatment groups (Figures 1 and 2):

- Group A received two low-density treatments;
- Group B received three low-density treatments;
- Group C received two high-density treatments; and
- Group D received three high-density treatments.

Low density treatment consisted of a minimum of 15 treatment lines per treatment square while high-density treatment consisted of a minimum of 30 treatment lines per square. Each treatment line required approximately 3 seconds to perform.

TABLE 1.

Effectiveness Measures		
Scale Scores	**Clinician Erythema Assessment**	**Patient Self-Assessment**
0, Clear	Clear skin with no signs of erythema	Clear of unwanted redness
1, Almost Clear	Almost clear; slight redness	Nearly clear of unwanted redness
2, Mild	Mild erythema; definite redness	Somewhat more redness than I prefer
3, Moderate	Moderate erythema; marked redness	More redness than I prefer
4, Severe	Severe erythema; fiery redness	Completely unacceptable redness

It is important to note that after three subjects were treated in each group, the protocol was amended to exclude the third treatment session due to excessive patient discomfort. Regarding the reasoning for the worsening pain, it can be reasonably expected that the cumulative effect of treating the same areas of the midface in intervals of 2 weeks between each treatment session may lead to increased pain and discomfort. The amended protocol specified that enrolled subjects would be randomized to receive either one or two low-density (Group A or B) or one or two high-density (Group C or D) MFU treatments administered 14±4 days apart (with the exception of the nose area, which received a single-depth treatment). Remaining subjects were randomized to one of four dual-depth MFU-V treatment groups:

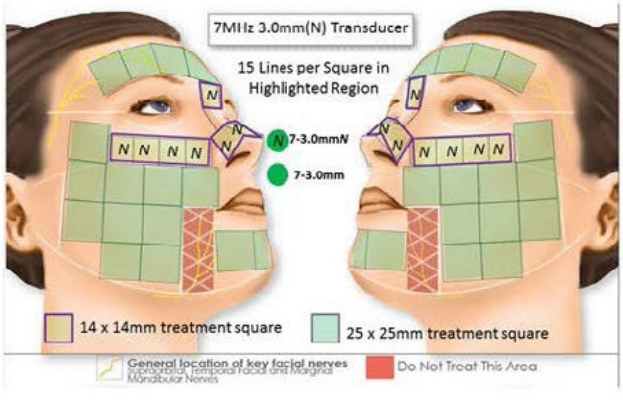
- Group A received one low-density treatment;
- Group B received two low-density treatments;
- Group C received one high-density treatment; and
- Group D received two high-density treatments.

Effectiveness Measures

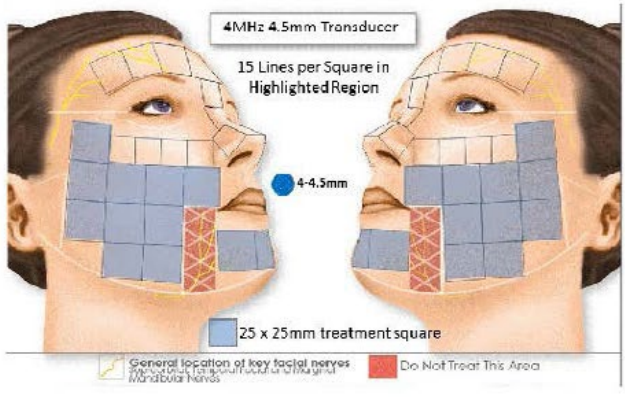
Subjects were evaluated at 90±14 days, 180±21 days and 365±30 days after treatment. During each evaluation, the same five 2-D digital images were obtained and the Clinician Erythema Assessment (CEA), Patient Self-Assessment (PSA) (Table 1) and the Dermatology Life Quality Index (DLQI) were completed. DLQI scores ranged from 0-1 (No effect), 2-5 (Small effect), 6-10 (Moderate effect), 11-20 (Very large effect), and 21-30 (Extremely large effect). The CEA and PSA scales were specifically developed and statistically validated for evaluating erythema.[28,29] At baseline and each follow-up visit, a colorimeter (Konica Minolta CR-10; Konic Minolta Sensing Americas, Inc., Ramsey, NJ) was used to measure the level of redness, yielding an objective assessment of erythema intensity. Colorimetric measurements, evaluating only the red-green spectrum, were obtained on the left and right cheeks, at the intersection of the mid-pupil line, and lateral to the nasal crease; for each subject, the mean of these three measurements was used in the study analyses. The

FIGURE 1. Treatment maps for Groups A and B. Initially, Group A received two low-density treatments and Group B received three low-density treatments; however, after three subjects were treated in each group, the protocol was amended to one low-density treatment in Group A and two low-density treatments in Group B. Low density treatment consisted of a minimum of 15 treatment lines per treatment square while high-density treatment consisted of a minimum of 30 treatment lines per square.

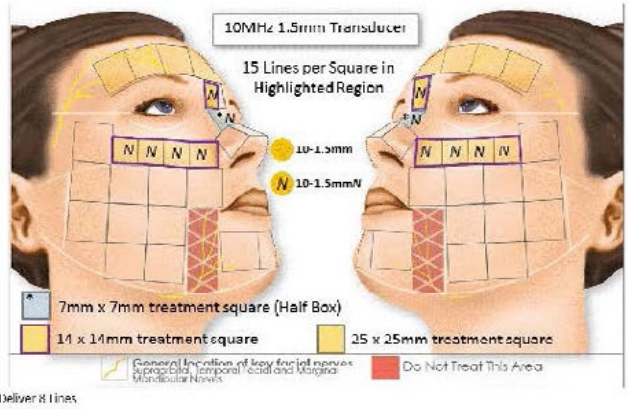
Group A/ B



Group A/ B



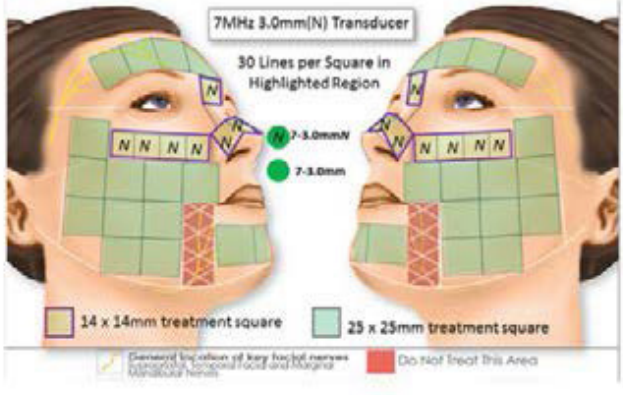
Group A/ B



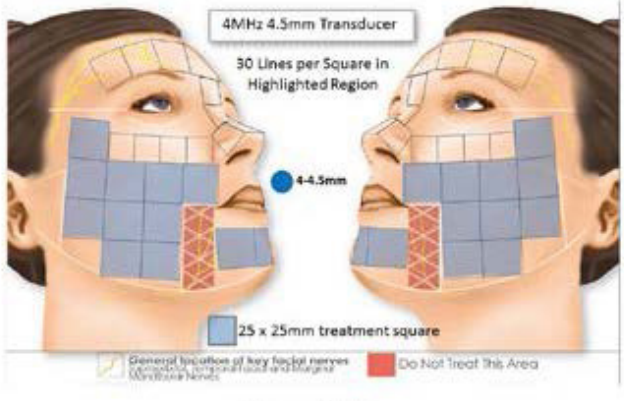
* Deliver 8 Lines

FIGURE 2. Treatment maps for Groups C and D. Initially, Group C received two high-density treatments and Group D received three high-density treatments; however, after three subjects were treated in each group, the protocol was amended to one high-density treatment in Group C and two high-density treatments in Group D. Low density treatment consisted of a minimum of 15 treatment lines per treatment square while high-density treatment consisted of a minimum of 30 treatment lines per square.

Group C/ D



Group C/ D



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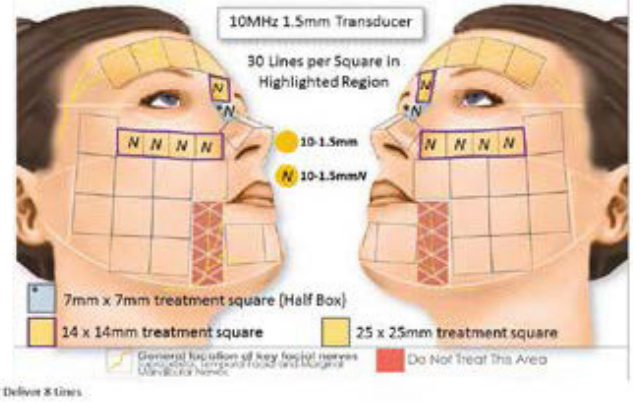


* Deliver 8 Lines

Rosacea Classification Assessment (rosacea scorecard) was completed during the 180-day assessment.

The primary endpoint was the change in baseline erythema assessed on the 5-point CEA scale at 90 days post-treatment. A 1-grade improvement for CEA and PSA Scales represents an effect that is noticeable by both investigators and patients and is considered clinically relevant. Therefore, similar to other studies,[30] treatment success was defined as 1-grade improvement on the CEA Scale. Secondary endpoints included the CEA Scale scores at all other post-treatment time points and the PSA, DLQI, and colorimetry at all post-treatment time points.

Safety Measures

Facial sensory and motor assessments were performed before and after each MFU-V treatment. If a subject experienced a nerve-related adverse event such as numbness, paresthesia, and/or muscle weakness from the first treatment, the second treatment was not to be performed. Treatment discomfort was assessed using a validated 11-point (0-10) Numeric Rating Scale.[31] Pain scores were obtained following each treated area and for each treatment depth and a mean pain score was determined for area and treatment depth. Adverse events were elicited from each subject at each visit and by phone approximately 3 days after each treatment. During each follow-up visit, subjects were queried about changes in concomitant medications and the treatment area was visually examined. Additional pregnancy testing was performed at the 180- and 365-day time points.

The Rosacea Classification Assessment was completed at the 180-day visit to determine if other aspects of rosacea had remained the same, improved or worsened. This evaluation included an assessment of Post-Erythema Revealed Telangiectasia (PERT) in which initially indistinguishable telangiectasias in the intensely red skin are observed after the erythema fades.

Data Analysis

Categorical variables were summarized as frequencies and percentages in each category. Continuous and ordinal variables were summarized as number of subjects (n), means, standard deviations, medians, and ranges (min, max). The primary effectiveness analysis was performed using subjects who completed the 90-day assessment. This was a pilot study intended to gather data for generating sample size estimates for a future pivotal trial. It was estimated that a sample size of 80 subjects (20 subjects per group) with 90-day data would achieve a two-sided 95% confidence interval of 20%, assuming a population success rate of 75%. All statistical programs were written in SAS® version 9.2 (SAS Institute, Inc., Cary, NC).

Ethics

Each subject provided informed consent prior to participating in any study-related activities. Subjects also provided consent for study-required photography and agreed to adhere to photography procedures, such as removing jewelry and avoiding makeup. This study protocol and related documents were approved by the Institutional Review Board at the University of Texas Southwestern Medical Center, Dallas, TX.

TABLE 2.

Demographics and Baseline Characteristics	
Characteristic, *N=88*	Mean (SD) min, max, or n (%)
Overall Mean Age (SD), min, max	49.8 (9.6), 21, 65
Mean Age (SD); Median (min, max)	
Group A, n=20	49.2 (9.4); 49.5 (21, 60)
Group B, n=22	51.5 (9.0); 49.5 (31, 64)
Group C, n=24	48.9 (11.4); 53.0 (24, 65)
Group D, n=22	49.6 (8.4); 51.5 (32, 61)
Overall Mean BMI (SD), min, max	28.7 (5.1), 19.9, 49.6
Mean BMI (SD); Median (min, max)	
Group A, n=20	27.5 (6.6); 25.3 (19.9, 49.6)
Group B, n=22	30.3 (5.3); 29.9 (20.7, 42.0)
Group C, n=24	27.8 (4.2); 27 (20.2, 37.8)
Group D, n=22	29 (4.0); 28.9 (21.2, 37.3)
Gender, n (%)	
Female	79 (89.8)
Male	9 (10.2)
Ethnicity, n (%)	
Non-Hispanic/Non-Latino	88 (100.0)
Race, n (%)	
White	88 (100.0)
Fitzpatrick Skin Type, n (%)	
I	5 (5.7)
II	36 (40.9)
III	47 (53.4)
Clinician Erythema Assessment (scale of 0-4)	
3 – Moderate	77 (87.5)
4 – Severe	11 (12.5)
Patient Self-Assessment of Erythema (scale of 0-4)	
2 – Mild	4 (4.5)
3 – Moderate	72 (81.8)
4 – Severe	12 (13.6)
Treatment Groups, n	
Group A - Low Density, 1 Tx + 2 Tx[a]	17 + 3
Group B - Low Density, 2 Tx + 3 Tx[a]	19 + 3
Group C - High Density, 1 Tx + 2 Tx[a]	21 + 3
Group D - High Density, 2 Tx + 3 Tx[a]	19 + 3
TOTAL	88

[a]12 subjects received two or three treatments prior to the protocol amendment which reduced the number of treatments to one or two.

TABLE 3.

Primary Endpoint: 90-Day Clinician Erythema Assessment (CEA) (n=84)[a]								
Baseline CEA Assessment	Clear	Almost Clear	Mild	Moderate	Severe	Total	Success (n)	Percent (95% CI)
Overall								
3, Moderate	1	16	43	14	0	74	Yes (69)	82.1% (72.3%, 89.7%)
4, Severe	0	0	0	9	1	10	No (15)	17.9%
Group A								
3, Moderate	1	3	9	4	0	17	Yes (15)	75.0% (50.9%, 91.3%)
4, Severe	0	0	0	2	1	3	No (5)	25.0%
Group B								
3, Moderate	--	7	10	5	--	22	Yes (17)	77.3% (54.6%, 92.2%)
4, Severe	--	--		--	--		No (5)	22.7%
Group C								
3, Moderate	--	5	13	2	--	20	Yes (21)	91.3% (72.0%, 98.9%)
4, Severe	--	0	0	3	--	3	No (2)	8.7%
Group D								
3, Moderate	--	1	11	3	--	15	Yes (16)	84.2% (60.4%, 96.6%)
4, Severe	--	0	0	4	--	4	No (3)	15.8%

[a]The 90-day visit was completed by 84 of the 88 enrolled patients.

TABLE 4.

Secondary Endpoint: 180- and 365-Day Clinician Erythema Assessment[a]				
Treatment Groups	180-Day Visit (n=84)	≥1-Grade Improvement, n (%)	365-Day Visit (n=81)	≥1-Grade Improvement, n (%)
Group A	19	18 (94.7)	18	17 (94.4)
Group B	22	20 (90.9)	21	18 (85.7)
Group C	23	19 (82.6)	22	21 (95.4)
Group D	20	16 (80.0)	20	17 (85.0)

[a]The 180- and 360-day visits were completed by 84 and 81 of the 88 enrolled patients, respectively.

RESULTS

Among the 91 enrolled subjects, three were screen failures; 88 subjects were randomized and treated and most completed the 90-day (n=84), 180-day (n=84), and 365-day (n=81) follow-up evaluations. The enrolled subjects were predominately female (89.8%) and white (100%); however, there were no significant differences across groups with respect to age or body mass index (BMI). Demographics and baseline characteristics are summarized in Table 2.

Effectiveness Endpoints

The primary endpoint assessing change in baseline CEA scale scores at 90 days post-treatment and subjects achieving treatment success are summarized in Table 3. Across groups, 75 to 91.3% of subjects achieved treatment success. The secondary endpoints of CEA Scale scores at days 180 and 365 are summarized in Table 4, PSA Scale scores are summarized in Table 5, mean DQLI scores are summarized in Table 6, and changes in mean colorimeter values are summarized in Table 7. The results of a cross-analysis of top-performing treatments groups, based on CEA, PSA, and colorimeter measures of effectiveness, are shown in Table 8. It should be noted that this study was not powered for effectiveness.

Safety Outcomes

The use of pretreatment analgesics is summarized in Table 9. Mean pain scores for each treatment group are summarized in Table 10. Some pain scores were not recorded correctly for the nose

TABLE 5.

Changes in Baseline Patient Self-Assessment Scores						
Treatment Groups	Day 90 (n=84)	Treatment Success[a] n (%)	Day 180 (n=84)	Treatment Success[a] n (%)	Day 365 (n=81)	Treatment Success[a] n (%)
Group A	20	12 (60.0)	19	14 (73.7)	18	12 (66.7)
Group B	22	16 (72.7)	22	16 (72.7)	21	16 (76.2)
Group C	23	16 (69.6)	23	15 (65.2)	22	16 (72.7)
Group D	19	14 (73.7)	20	15 (75.0)	20	12 (60.0)

[a]Defined as a 1-grade improvement.

TABLE 6.

Dermatology Life Quality Index Scores							
Treatment Group, n (%)	Baseline, n=88 (Group A, n=20; B, n=22; C, n=24; D, n=22)				Day 90, n=84 (Group A, n=20; B, n=22; C, n=23, D, n=19)		
	No Effect	Small Effect	Moderate Effect	Very Large Effect	No Effect	Small Effect	Moderate Effect
Group A	3 (15.0)	12 (60.0)	3 (15.0)	2 (10.0)	10 (50.0)	6 (30.0)	4 (20.0)
Group B	7 (31.8)	7 (31.8)	7 (31.8)	1 (2.2)	17 (77.2)	4 (18.1)	1 (4.5)
Group C	5 (20.8)	12 (50.0)	7 (29.2)	--	13 (56.5)	8 (34.8)	2 (10.5)
Group D	3 (13.6)	13 (59.0)	4 (18.1)	2 (9.0)	9 (47.4)	9 (47.4)	1 (5.2)
Treatment Group, n (%)	Day 180, n=84 (Group A, n=19; B, n=22, C, n=23, D, n=20)				Day 365, n=81 (Group A, n=18; B, n=21; C, n=22; D, n=20)		
	No Effect	Small Effect	Moderate Effect	Very Large Effect	No Effect	Small Effect	Moderate Effect
Group A	11 (57.9)	7 (36.8)	1 (5.2)	9 (50.0)	9 (50.0)	--	--
Group B	11 (50.0)	10 (45.4)	1 (4.5)	11 (52.3)	9 (42.9)	1 (4.8)	--
Group C	12 (52.2)	9 (39.1)	2 (8.7)	14 (63.6)	6 (27.2)	1 (4.5)	1 (4.5)
Group D	11 (55.0)	8 (40.0)	1 (5.0)	8 (40.0)	10 (50.0)	2 (10.0)	--

TABLE 7.

Mean Colorimetry Values[a]							
Treatment Groups	Baseline (n=88)	Day 90 (n=84)	Responders, n (%)[a]	Day 180 (n=84)	Responders, n (%)[a]	Day 365 (n=81)	Responders, n (%)[a]
Group A	20	20	15 (75.0)	19	14 (73.7)	18	13 (72.2)
Group B	22	22	14 (63.6)	22	15 (68.1)	21	15 (71.4)
Group C	24	23	13 (56.5)	23	16 (69.6)	22	19 (86.4)
Group D	22	18	13 (72.2)	20	14 (70.0)	20	16 (80.0)

[a]Proportion of responders with a decrease in red-green colorimetry spectrum.

TABLE 8.

Cross-Analysis of Top-Performing Treatment Groups			
Effectiveness Measure	Day 90	Day 180	Day 365
CEA	Group C	Group A	Group C
PSA	Group D	Group D	Group B
Colorimeter	Group A	Group A	Group C

CEA, Clinician Erythema Assessment; PSA, Patient Self-Assessment.

TABLE 9.

Pain Medications			
Pain Medication	Treatment 1	Treatment 2	Treatment 3
Ibuprofen 800mg	87	36	1[a]
Lorazepam[b]	0	1	1
Hydrocodone/ Acetaminophen[b]	1	1	0
Oxycodone/ Acetaminophen[b]	0	1	1
Dimenhydrinate[b]	0	1	1

[a]Received two doses. [b]Protocol violation.

(protocol deviation); however, all pain scores were considered regardless of a protocol deviation for that subject or treatment.

A summary of treatment-related adverse events (AEs) is provided in Table 11. Notable AEs include bruising (44%), tenderness/soreness (43%), and redness (35%). Reported AEs (N=172) were definitely related (n=145), probably related (n=17), possibly related (n=8), and unrelated (n=2). AE severity was rated as mild (n=167), moderate (n=4), and missing (n=1). An analysis of AEs by treatment group revealed a higher proportion of subjects with paresthesia in Group D (31.8%; *P*=0.0028), a higher proportion of tenderness and soreness in Groups B and D (54.5% and 54.5% for each Group; *P*=0.0537). Subjects with two treatments experienced more tenderness and soreness than subjects with one treatment (*P*=0.0005). The mean number of treatment-related AEs per subject was higher in Groups B and D (2.4 and 2.9) than Groups A and C (1 and 1.5). Subjects that received two treatments reported more AEs than those with one treatment.

TABLE 10.

Mean Pain Scores[a]					
Low-Density Groups Mean (SD), min, max	Group A		Group B		
	Treatment 1 (n=20)	Treatment 2 (n=3)	Treatment 1 (n=22)	Treatment 2 (n=21)	Treatment 3 (n=2)
4-4.5mm Transducer	6.5 (2.2) 2, 10	5.3 (1.9) 2, 7	5.9 (2.4) 2, 10	5.7 (2.5) 0, 10	7.0 (0.8) 6, 8
7-3.0mm Transducer	3.9 (2.5) 0, 10	3.7 (2.9) 0, 10	3.9 (2.1) 0, 10	3.9 (2.3) 0, 10	5.0 (2.2) 3, 8
10-1.5mm Transducer	4.9 (2.8) 0, 10	5.4 (2.3) 2, 9	4.6 (2.4) 0, 10	4.9 (2.9) 0, 10	7.7 (2.0) 4, 9
High-Density Groups, Mean (SD) min, max	Group C		Group D[b]		
	Treatment 1 (n=24)	Treatment 2 (n=2)	Treatment 1 (n=22)	Treatment 2 (n=15)	
4-4.5mm Transducer	6.7 (2.3) 1, 10	5.0 (2.4) 3, 8	6.4 (3.0) 0, 10	6.6 (3.2) 1, 10	
7-3.0mm Transducer	4.4 (2.2) 0, 10	4.2 (3.5) 1, 10	4.4 (2.7) 0, 10	4.6 (2.7) 0, 9	
10-1.5mm Transducer	5.6 (2.7) 0, 10	5.6 (3.5) 1, 10	5.5 (3.1) 0, 10	5.9 (2.8) 0, 10	

[a]Pain severity assessed using a validated 11-point (0-10) Numeric Rating Scale. Some pain scores were not recorded because an incorrect area of the nose was treated and pain was assessed in the incorrect area.
[b]After three subjects were treated in each group, the protocol was amended to exclude the third treatment session. The amended protocol specified that enrolled subjects would be randomized to receive either one or two low-density (Group A or B) or one or two high-density (Group C or D) MFU treatments.

TABLE 11.

Treatment-Related Adverse Events			
Adverse Event	Events, n (%)	Subjects, n (%)	Mean Event Duration (Days)
Aphthous Ulcer	1 (0.6)	1 (1.1)	10.0
Bruising	50 (29.1)	39 (44.3)	10.2
Oily Skin	1 (0.6)	1 (1.1)	2.0
Paresthesia/Numbness	9 (5.2)	9 (10.2)	12.5
Edema/Welts/Swelling	16 (9.3)	15 (17.0)	9.0
Erythema/Redness	46 (26.7)	33 (35.2)	4.7
Tenderness/Soreness	47 (27.3)	38 (43.2)	12.9
Worsening of Rosacea	2 (1.2)	2 (2.3)	31.0

DISCUSSION

The objective of this pilot study was to assess the safety and effectiveness of MFU-V for improving the signs and symptoms of erythematotelangiectatic rosacea. Treatment groups were well-balanced with respect to age and BMI; however, most subjects were female (89.8%), and white and non-Hispanic (100%). Based on CEA and PSA scores, most enrolled subjects had moderately severe rosacea (87.5% and 81.8%, respectively) at the baseline assessment.

The primary endpoint was the change in baseline erythema on the 5-point CEA scale at post-treatment day 90. Treatment success, defined as a 1-grade improvement on the CEA Scale, was achieved by subjects with moderately severe rosacea in each treatment group, with the greatest improvement for subjects in Groups C (91.3%) and D (84.2%) who were treated with high density MFU-V. Subjects in Groups A and B had success rates of 75.0% and 77.3%, respectively, with an overall success rate of 82.1% for all four treatment groups. Subjects with severe rosa-

FIGURE 3. Mean change in Clinician Erythema Assessment Scale scores. The best performing groups were Group C at day 90 (91%), Group A at day 180 (95%), and Group C at day 365 (96%).

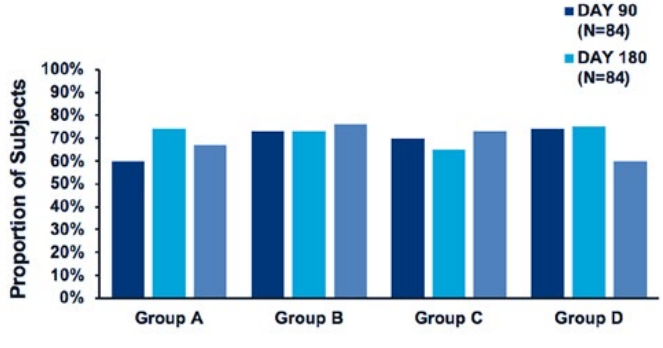
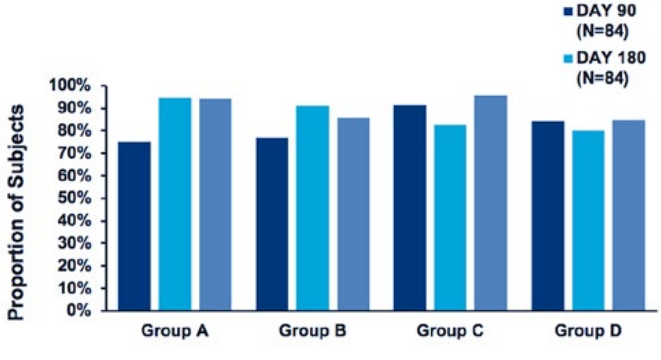


FIGURE 4. Mean change in Patient Self-Assessment Scale scores. The best performing groups were Group D at day 90 (74%), Group D at day 180 (75%), and Group B at day 365 (76%).



cea at baseline assessment did not achieve treatment success (≥1-point improvement in 90-day CEA Scales scores); however, a ≥1-grade improvement in CEA Scale scores was achieved by 80.0% to 94.7% of subjects at day 180 and 85.0% to 95.4% at day 365 as one of the secondary endpoints. Based on changes in baseline PSA scores, most subjects achieved treatment success, which increased slightly over time at day 90 (60.0 to 73.7%), day 180 (65.2 to 75.0%), and day 365 (60.0 to 76.2%).

DLQI scores measured the impact of rosacea on overall quality of life and ranged from No Effect to Extremely Large Effect. Improvements in DLQI scores were noted across all treatment groups. At baseline, subjects reporting No Effect ranged from 13.6 to 31.8%, increasing to 40.0 to 63.6% at day 365. There was a corresponding decrease in subjects reporting a Moderate Effect from 15.0 to 31.8% at baseline to 4.5 to 10% at day 365. Although five subjects reported Very Large Effect at baseline, this score was only reported one other time by a Group C subject at day 365. No subjects reported a Very Large effect at the baseline or any follow-up visits.

Based on mean colorimetry values, treatment success ranged from 56.5 to 75% at day 90, 68.1 to 73.7% at day 180, and 71.4 to 86.4% at day 365, indicating modest improvement in erythema intensity.

The results of a cross-analysis of top-performing treatment groups for each measure of effectiveness showed Group A and Group C were each top performer three times across different outcome measures (Table 8). Additional improvement comparisons for CEA, PSA, and colorimetry by treatment group and number of treatments revealed no differences in baseline characteristics or endpoints. As CEA was the primary endpoint, Group C (91.3%), treated with high density MFU-V, was the top performing group.

Although pretreated with analgesics, subjects experienced excessive discomfort during a third MFU-V treatment in the original protocol. Among the subjects treated with two MFU-V sessions, pain scores were generally the same for both treatments (Table 10). Pain scores were generally higher with the 4-4.5mm transducer, which was used on all subjects. The most common treatment-related adverse events were bruising (29.1%), tenderness or soreness (27.3%), and erythema or redness (26.7%). All adverse events resolved in less than 14 days except for worsening of rosacea (n=2), which persisted for 31 days. This pilot study is the first demonstration of the effectiveness of MFU-V for treating erythematotelangiectatic rosacea. These results support the hypothesis that using MFU-V to create focal lesions in the dermis and sub-dermis and coagulate blood vessels in the superficial plexus reduces the increased blood flow in the skin of individuals with rosacea. In addition, MFU-V may improve overall skin health by repairing the damaged skin barrier and changing the demodex environment resulting in fewer demodex.

Overall, the effect of treatment was sustained, lasting for at least 1 year, and subject satisfaction was high based on patient self-assessment questionnaires. Other energy-based devices have been reported to be effective for treating erythematotelangiectatic rosacea; however, some of these studies were not controlled or had small sample sizes. For example, lasers were shown to be effective in a small (N=8) open-label study[32] as well as a small (N=14) randomized, double-blind trial.[33]The results of a larger, laser study (N=50) were subjective and based on survey results.[34] One small study (N=16)[35] and two larger studies (N=50-122)[21,36] have demonstrated the effectiveness of intense pulsed light (IPL); however, none of these were randomized, controlled studies. One study (N=21) demonstrated the effectiveness of a device that combines IPL with radiofrequency.[37] Of note, two published comparative studies report radiofrequency is more effective than IPL[20] and IPL and lasers are equally effective.[38] Based on the available data from this and similar studies, we believe a large, randomized, controlled study demonstrating the effectiveness of single, high-density MFU-V treatment for erythematotelangiectatic rosacea is warranted.

CONCLUSION

While all treatment groups performed relatively well in this study, the results demonstrated that a single, high-density MFU-V treatment may be the most efficacious for treating erythematotelangiectatic rosacea. The results were sustained, persisting for at least 1 year following treatment, and subject satisfaction was high. Similar to previous MFU-V studies, most reported adverse events were mild and transient in nature. There were no serious adverse events reported for the study. Based on the results of this study, a large, randomized controlled study of single, high-density MFU-V treatment for erythematotelangiectatic rosacea is warranted.

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REFERENCES

1. Wilkin J DM, Detmar M, Drake L, Feinstein A, Odom R, et al. Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol.* 2002;46.
2. Vemuri RC, Gundamaraju R, Sekaran SD, et al. Major pathophysiological correlations of rosacea: a complete clinical appraisal. *Int J Med Sci* 2015;12:387-96.
3. Wehausen B, Hill DE, Feldman SR. Most people with psoriasis or rosacea

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are not being treated: a large population study. *Dermatol Online J* 2016;22.
4. Tan J, Schöfer H, Araviiskaia E, et al. Prevalence of rosacea in the general population of Germany and Russia - the RISE study. *J Eur Acad Dermatol Venereol* 2016;30:428-34.
5. Moustafa F, Lewallen RS, Feldman SR. The psychological impact of rosacea and the influence of current management options. *J Am Acad Dermatol* 2014;71:973-80.
6. Steinhoff M, Schmelz M, Schauber J. Facial erythema of rosacea - aetiology, different pathophysiologies and treatment options. *Acta Derm Venereol* 2016;96:579-86.
7. Egeberg A, Hansen PR, Gislason GH, et al. Patients with rosacea have increased risk of depression and anxiety disorders: a Danish nationwide cohort study. *Dermatology* 2016;232:208-13.
8. Bonsall A, Rajpara S. A review of the quality of life following pulsed dye laser treatment for erythemotelangiectatic rosacea. *J Cosmet Laser Ther* 2016;18:86-90.
9. Halioua B, Cribier B, Frey M, et al. Feelings of stigmatization in patients with rosacea. *J Eur Acad Dermatol Venereol* 2017;31:163-68.
10. Cresce ND, Davis SA, Huang WW, et al. The quality of life impact of acne and rosacea compared to other major medical conditions. *J Drugs Dermatol* 2014;13:692-7.
11. Böhm D, Schwanitz P, Stock Gissendanner S, et al. Symptom severity and psychological sequelae in rosacea: results of a survey. *Psychol Health Med* 2014;19:586-91.
12. van der Linden MM, van Rappard DC, Daams JG, et al. Health-related quality of life in patients with cutaneous rosacea: a systematic review. *Acta Derm Venereol* 2015;95:395-400.
13. Oracea® (doxycycline) capsules for oral use [Prescribing Information. Galderma Laboratories LP, Fort Worth, TX.
14. Schaller M, Schöfer H, Homey B, et al. State of the art: systemic rosacea management. *J Dtsch Dermatol Ges.* 2016;14:29-37.
15. Finacea® (azelaic acid) Gel 15%. [Prescribing Information 2002]. Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ.
16. Mirvasco® (brimonidine) topical gel [Prescribing Information 2015]. Galderma Laboratories, LP, Fort Worth, TX.
17. Soolantra® (ivermectin) Cream [Prescribing Information 2014]. Galderma Laboratories LP, Fort Worth, TX.
18. Metrogel® (metronidazole) Gel [Prescribing Information 2011]. Galderma Laboratories, LP, Fort Worth, TX.
19. Say EM, Okan G, Gökdemir G. Treatment outcomes of long-pulsed Nd: YAG laser for two different subtypes of rosacea. *J Clin Aesthet Dermatol* 2015;8:16-20.
20. Kim SJ, Lee Y, Seo YJ, et al. Comparative efficacy of radiofrequency and pulsed dye laser in the treatment of rosacea. *Dermatol Surg* 2017;43:204-09.
21. Lim HS, Lee SC, Won YH, et al. The efficacy of intense pulsed light for treating erythematotelangiectatic rosacea is related to severity and age. *Ann Dermatol* 2014;26:491-5.
22. ULTHERA® Operation & Maintenance Manual. Ulthera, Inc., Mesa, AZ.
23. White WM, Makin IR, Barthe PG, et al. Selective creation of thermal injury zones in the superficial musculoaponeurotic system using intense ultrasound therapy: a new target for noninvasive facial rejuvenation. *Arch Facial Plast Surg* 2007;9:22-29.
24. Brobst RW, Ferguson M, Perkins SW. Ulthera: initial and six month results. *Facial Plast Surg Clin North Am.* 2012;20:163-76.
25. Alam M, White LE, Martin N, et al. Ultrasound tightening of facial and neck skin: a rater-blinded prospective cohort study. *J Am Acad Dermatol* 2010;62:262-9.
26. Baumann L, Zelickson B. Evaluation of micro-focused ultrasound for lifting and tightening neck laxity. *J Drugs Dermatol* 2016;15:607-14.
27. Fabi SG, Goldman MP, Dayan SH, et al. A prospective multicenter pilot study of the safety and efficacy of microfocused ultrasound with visualization for improving lines and wrinkles of the décolleté. *Dermatol Surg* 2015;41:327-35.
28. Tan J, Liu H, Leyden JJ, et al. Reliability of clinician erythema assessment grading scale. *J Am Acad Dermatol* 2014;71:760-3.
29. Tan J, Almeida LM, Bewley A, et al. Updating the diagnosis, classification and assessment of rosacea: recommendations from the global ROSacea COnsensus (ROSCO) panel. *Br J Dermatol* 2017;176:431-38.
30. Fowler J, Tan J, Jackson JM, et al. Treatment of facial erythema in patients with rosacea with topical brimonidine tartrate: correlation of patient satisfaction with standard clinical endpoints of improvement of facial erythema. *J Eur Acad Dermatol Venereol* 2015;29:474-81.
31. Hawker GA, Mian S, Kendzerska T, et al. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res* (Hoboken) 2011;63:S240-52.
32. Baek JO, Hur H, Ryu HR, et al. Treatment of erythematotelangiectatic rosacea with the fractionation of high-fluence, long-pulsed 595-nm pulsed dye laser. *J Cosmet Dermatol* 2017;16:12-14.
33. Alam M, Voravutinon N, Warycha M, et al. Comparative effectiveness of nonpurpuragenic 595-nm pulsed dye laser and microsecond 1064-nm neodymium:yttrium-aluminum-garnet laser for treatment of diffuse facial erythema: A double-blind randomized controlled trial. *J Am Acad Dermatol* 2013;69:438-43.
34. Strand M, Bergqvist G, Griffith S, et al. The effect of recurrent pulsed dye laser treatments in rosacea patients. *J Cosmet Laser Ther* 2017;19:160-64.
35. Liu J, Liu J, Ren Y, et al. Comparative efficacy of intense pulsed light for different erythema associated with rosacea. *J Cosmet Laser Ther* 2014;16:324-7.
36. Kassir R, Kolluru A, Kassir M. Intense pulsed light for the treatment of rosacea and telangiectasias. *J Cosmet Laser Ther* 2011;13:216-22.
37. Taub AF, Devita EC. Successful treatment of erythematotelangiectatic rosacea with pulsed light and radiofrequency. *J Clin Aesthet Dermatol* 2008;1:37-40.
38. Neuhaus IM, Zane LT, Tope WD. Comparative efficacy of nonpurpuragenic pulsed dye laser and intense pulsed light for erythematotelangiectatic rosacea. *Dermatol Surg* 2009;35:920-8.

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Clinical Validation of the Surface Volume Coefficient for Minimally Invasive Treatment of the Temple

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ABSTRACT

Objective: The aim of the present study is to compare the temporal surface volume coefficient obtained in the cadaveric model from subdermal and supraperiosteal injections to the clinical setting when treating temporal hollowing.

Material and Methods: A total of 36 subjects were included in this investigation, 17 patients (16 females, 1 male; 46.3 ± 8.9 years; 25.5 ± 2.8 kg/m^2) and 19 cadaveric specimens (11 females, 8 males; 76.4 ± 11.5 years; 24.0 ± 5.1 kg/m2). Subdermal and supraperiosteal injections were performed and live subjects were evaluated and followed for 12 months. The surface volume coefficients were calculated using 3D surface volume scanning and compared for validity.

Results: No statistically significant difference was detected between the clinical outcome scores of the subdermal vs supraperiosteal injection technique. The supraperiosteal injection technique utilized significantly more product 1.20 ± 0.5 cc [range: 0.50 – 2.6 cc] compared to the subdermal 0.71 ± 0.2 cc [range: 0.30 – 1.20 cc] vs with $P< 0.001$. This difference was consistent with the different values of the cadaveric surface volume coefficient (subdermal vs supraperiosteal): 1.00 ± 0.2 vs 0.70 ± 0.2. At 12-month follow-up, the product loss was 19% for the subdermal injection and 21% for patients treated with supraperiosteal injections.

Conclusion: The results of the study support the clinical validity of the surface volume coefficient. They demonstrate that the different injection volumes necessary to deliver aesthetically appealing results when utilizing the subdermal vs the supraperiosteal technique can be explained by the region-specific surface volume coefficient.

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INTRODUCTION

Facial aging is a multi-factorial process resulting in a range of physiologic and morphologic changes in both the hard and soft tissues of the face – the bones, ligaments, muscles, fasciae, subcutaneous fat, and skin.[1–6] The use of soft-tissue filler injections to address the signs of facial aging has increased according to a statistical survey by the American Society of Plastic Surgeons. Between the years 2000 and 2017, the number of soft tissue filler procedures increased by 312%.[7]

Soft tissue fillers are frequently utilized to restore the age-related loss of soft tissue volume of the face.[8–10] Recent studies have indicated that depending on the targeted layer, various aesthetic outcomes can be expected.[11] Injections into the subdermal plane ie, into the superficial facial fat compartments, can result in better surface projection when compared to placing the product in the supraperiosteal plane ie, into the deep facial fat compartments and vice versa, depending on the targeted facial region. A measure for estimating this region-specific effect was recently introduced and termed the surface volume coefficient (SVC).[11] The SVC is calculated by dividing the absolute change in scanned 3D surface projection (cc) by the amount of injected volume (cc) and provides information on the surface effect of a certain amount of injected volume, which could thus be considered the clinical effectiveness of an injected material.

Temporal volume loss can be treated via the injection of soft tissue filler into the subdermal or supraperiosteal plane while respecting regional danger zones. These danger zones are located in Layer 3 (location of the anterior branch of the superficial temporal artery), Layer 4 (intra-fascial plane; location of the motor branches of the facial nerve), Layer 6 (location of the medial zygomatico-temporal (sentinel) vein), and Layer 10 (location of the anterior and posterior deep temporal arteries). Positioning of the product thus needs to be carefully evaluated and balanced weighing safety primarily while considering aesthetic outcome. Injecting the material into the subdermal

planes (Layer 2) carries the risk of product visibility and surface irregularities, whereas the supraperiosteal injection (Layer 9) carries the risk of intracranial penetration,[12] intraarterial product placement,[13] and product migration. To account for potential product loss and thus clinical ineffectiveness, an increased volume is required for this technique.

To date, the SVC has been calculated in the cadaveric model only and was not validated in live subjects, thus the clinical applicability of this novel measure is unclear. The aim of the present study is to compare the temporal SVC obtained in the cadaveric model from subdermal and supraperiosteal injections to the clinical setting to determine whether the SVC will help to guide injection procedures of the temple in terms of volume injected and longevity of aesthetic outcome.

MATERIALS AND METHODS

Clinical Study Sample

The investigated clinical study sample consisted of 16 females and 1 male with a mean age of 46.3 ± 8.9 years and mean body mass index (BMI) of 25.5 ± 2.8 kg/m^2. Individuals were included in this study if temporal hollowing was present and if they had no previous minimally invasive or surgical treatment of the temple. Patients were not included in the study if they had any contraindication for treatment with soft tissue fillers or if they had any active infection at or near the temple or a known allergy/hypersensitivity to hyaluronic acid-based filler material.

Written information and verbal explanations about the aims and the scopes of the study as well as the risks of the procedure were provided to the participants prior to initiation. Following the Declaration of Helsinki protocols (1996),[14] written informed consent to participate in this study was obtained from all participants. This study was conducted in accordance with regional laws and good clinical practice and was approved by the Ethics Committee of the Ludwig-Maximilian University Munich, Germany (Reference Number: 266-13).

Cadaveric Study Sample

The cadaveric study sample consisted of 19 fresh frozen (non-embalmed) cephalic specimen obtained from human donors (11 females, 8 males) with a mean age of 76.4 ± 11.5 years and a mean BMI of 24.0 ± 5.1 kg/m^2. Body donors were screened and not included in this analysis if they had previous facial surgeries, trauma, or diseases that disrupted the integrity of the facial anatomy. Each body donor provided informed consent while alive for the use of their body for medical, scientific, and educational purposes.

Clinical Injection Procedure

Individuals were randomly assigned to either the subdermal injection group or to the supraperiosteal injection group. Subdermal injections were performed in nine individuals (temporal volume scale 2.56 ± 0.5) whereas supraperiosteal injections were performed in eight individuals (temporal volume scale 2.63 ± 0.5). No statistically significant difference between the two groups was noted before the treatment with P=0.692.

Subdermal injection technique: After topical disinfection with alcohol of the temporal skin anterior to the hairline, a stiff 22G 2" blunt tip cannula was inserted from the midportion of the zygomatic arch and advanced into the temple in an anterior, superior and posterior (up to the hairline) direction. The cannula was advanced in the subdermal plane guided by visual control, superficial to the superficial temporal fascia and thus superficial to the superficial temporal artery. The product (Belotero Volume®, Merz Pharma GmbH, Frankfurt, Germany) was injected in a retrograde and fanning fashion with continuous movement. To achieve an aesthetically appealing outcome as judged by the treating investigator, a mean volume of 0.71 ± 0.25 cc [range: 0.4 – 1.2 cc] was injected per side (Figure 1).

Supraperiosteal injection technique: After topical disinfection with alcohol of the temporal skin anterior to the hairline, a 30 G 1/2" sharp tip needle was inserted perpendicular to the skin

FIGURE 1. Before and after image of a treated female with the subdermal injection technique being applied to the right temple. The after image was taken immediately after treatment (= baseline). Red arrows indicate the direction and extent of product placement.

FIGURE 2. Before and after image of a treated male with the supraperiosteal injection technique being applied to the left temple. The after image was taken immediately after the treatment (= baseline). Red dot indicates skin penetration and bone contact location.

FIGURE 3. 3D surface scanning heat map of the subdermal technique being applied to the left temple of a body donor. Blue color indicates volume increase whereas red color indicates volume decrease. 3D reconstruction of a multiplanar CT scan shows the positioning of the contrast agent in the left temple (red circle).

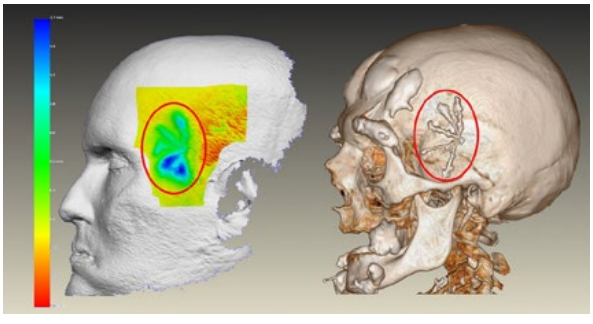
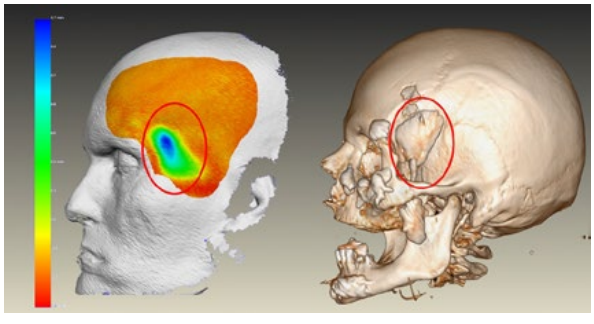


FIGURE 4. 3D surface scanning heat map of the supraperiosteal technique being applied to the left temple of a body donor. Blue color indicates volume increase whereas red color indicates volume decrease. 3D reconstruction of a multiplanar CT scan shows the positioning of the contrast agent in the left temple (red circle).



surface. The single skin insertion point was 1cm cranial and 1cm lateral to the intersection of the temporal crest and the superior orbital rim. The needle was advanced until contact with the bone was established. After negative aspiration (at least 4 seconds), the product (Belotero Volume®, Merz Pharma GmbH, Frankfurt, Germany) was slowly applied. To achieve an aesthetically appealing outcome as judged by the treating investigator, a mean volume of 1.20 ± 0.54 cc [range: 0.5 – 2.6 cc] was injected per side (Figure 2).

Cadaveric Injection Procedure

The subdermal plane of the temple (located in Layer 2) and the supraperiosteal plane (located in Layer 9) were identified and injected using either a 22G 2" blunt tip cannula or a 30G 1/2" sharp tip needle, respectively. The subdermal plane was visually confirmed by the superficial movement of the cannula (Figure 3), whereas the supraperiosteal plane was confirmed as the needle was in contact with bone throughout the duration of the injection (Figure 4). Each plane was injected using contrast enhanced material consisting of Visipaque™ 320 mg/ml (Iodixanol, GE Healthcare, Little Chalfont, United Kingdom) and Resource®ThickenUp™ Clear (Nestlé HealthCare Nutrition GmbH, Vienna, Austria). The injectate was highly viscoelastic – comparable to hyaluronic acid based soft-tissue filler – to avoid diffusion outside the intended plane. A mean of 0.66 ± 0.13 cc [range: 0.5 – 0.8 cc] of radiopaque product was injected into the subdermal plane, and a mean of 2.70 ± 0.62 cc [range: 1.0 – 3.0 cc] was injected into the supraperiosteal plane.

Clinical Outcome Measures

Patients were bilaterally assessed before treatment, immediately after, at 1 month, 6 months, and 12 months following treatment. At each visit, the global aesthetic improvement scale (GAIS)[15] and the temporal volume scale[16] were evaluated by an independent clinically trained observer (Figures 5 and 6).

The temporal volume scale[16] assessed the volume of the temple according to the following classification: 0 = No volume loss; 1 = Mild volume loss; 2 = Moderate volume loss; 3 = Severe volume loss; 4 = Very severe volume loss (Figure 5).

The GAIS semi-quantitatively scored the changes observed after an intervention according to the following classification: 1 = Little or no improvement (0-10% change when compared to the pre-treatment picture); 2 = Minute improvement (11-25% change); 3 = Fair improvement (26-50% change); 4 = Good improvement (51-75% change); 5 = Excellent improvement (>75% change; Figure 6).

3D Surface Volume Scanning

In the clinical setting, a 3D surface volume scan was performed for each temple prior to and immediately following the injection procedure the injection procedure and at all follow-up visits. In the cadaveric setting, the 3D surface volume scan was performed before and after the injection procedure only (Figures 3 and 4).

3D surface volume scanning was performed using an Eva® 3-dimensional surface imaging device (Artec 3D Inc., Luxembourg). All scanning procedures were performed and analysed by the same investigators.

Statistical Analyses

The temporal SVC for each injection technique (subdermal vs supraperiosteal) and for each follow-up visit was calculated by dividing the absolute change in scanned surface projection (cc) by the amount of injected volume (cc). This coefficient provides information on the surface effect of a defined amount of injected volume, which could represent the clinical effectiveness of the injected material. A coefficient of 1.0 could be interpreted as very efficient whereas a coefficient of 0 could be regarded as non-efficient ie, none of the injected material had an effect on the surface. Surface volume coefficients were compared between different injection techniques using an unpaired t-test,

FIGURE 5. Bar graph of the temporal volume scale (mean with +/-1 standard deviation indicated by the whiskers) comparing the subdermal (orange) and the supraperiosteal (blue) injection technique. Non-significant comparisons are termed n.s..

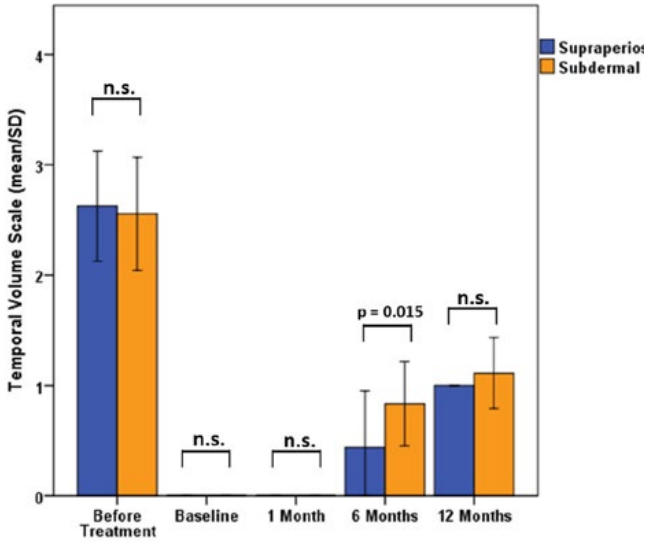


FIGURE 6. Bar graph of the global aesthetic improvement scale (mean with +/-1 standard deviation indicated by the whiskers) comparing the subdermal (orange) and the supraperiosteal (blue) injection technique. Non-significant comparisons are termed n.s..

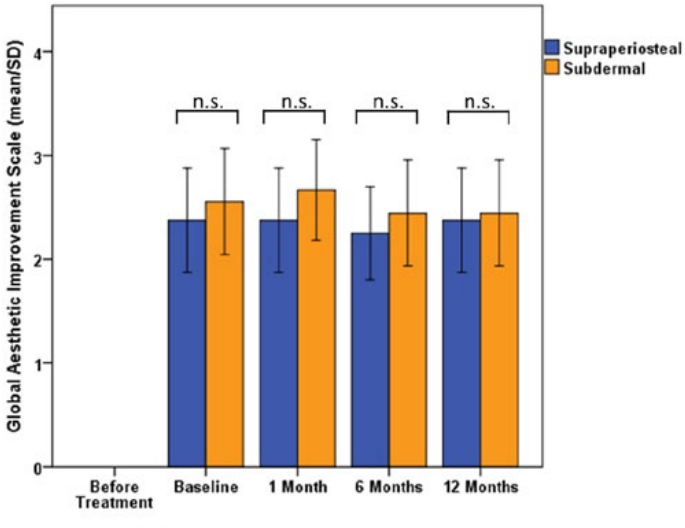


FIGURE 7. Box plot of the surface volume coefficient (mean with +/-1 standard deviation indicated by the horizontal black line inside the bars and the whiskers) for the subdermal injection technique immediately after the treatment (= baseline), at 1 month, at 6 months, and at 12 months follow up. Comparisons between time points and to the cadaveric surface volume coefficient are shown. Non-significant comparisons are termed n.s..

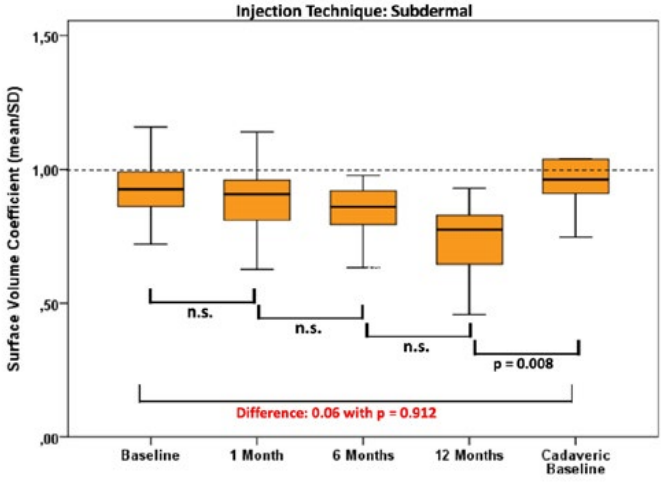


FIGURE 8. Box plot of the surface volume coefficient (mean with +/-1 standard deviation indicated by the horizontal black line inside the bars and the whiskers) for the supraperiosteal injection technique immediately after the treatment (= baseline), at 1 month, at 6 months, and at 12 months follow up. Comparisons between time points and to the cadaveric surface volume coefficient are shown. Non-significant comparisons are termed n.s..

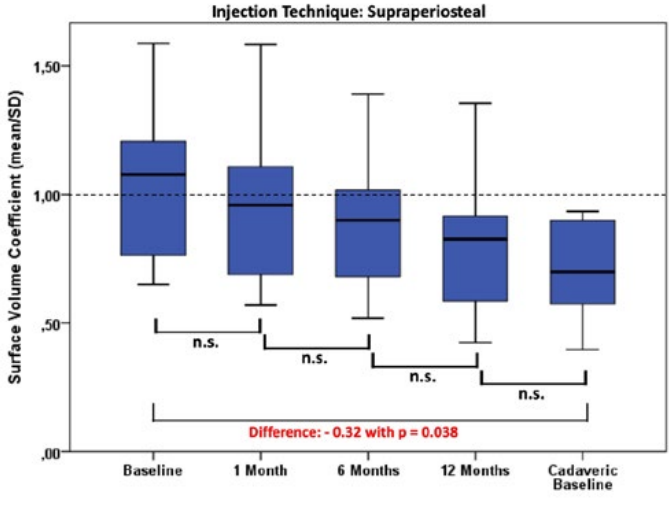
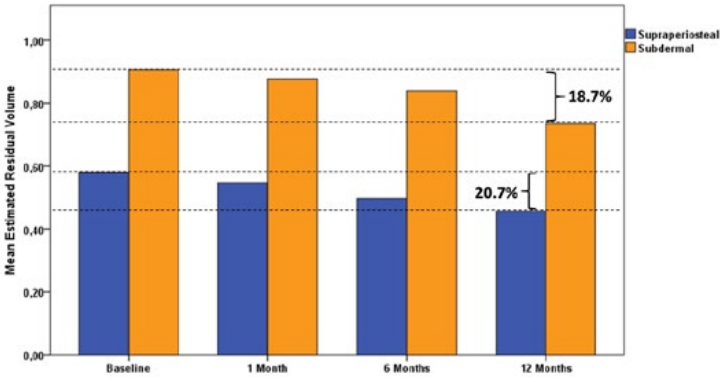


FIGURE 9. Bar graph showing the mean residual volume after the injection of soft tissue filler (subdermal vs supraperiosteal): 0.71 ± 0.2 cc vs. 1.20 ± 0.5 cc. The residual volume is calculated by using the ration between 3D surface scanning and surface volume coefficient.



RESULTS

Clinical Outcome

Before the treatment, the mean temporal volume scale was 2.56 ± 0.5 (best to worst, ie, 0 to 4) for those going to be treated with the subdermal technique and 2.63 ± 0.5 for those going to be treated with the supraperiosteal technique with P=0.692 (Table 1, Figure 5). After the application of 0.71 ± 0.2 cc [range: 0.30 – 1.20 cc] using the subdermal technique and 1.20 ± 0.5 cc [range: 0.50 – 2.6 cc] using the supraperiosteal technique (difference of injected volume P<0.001), a significant improvement was noted. For both injection techniques, the improvement was sustained at every subsequent follow-up visit (1 month, 6 months and 12 months) and represented a statistically significant from baseline P< 0.001 (Figure 5).

After the treatment, the GAIS was 2.65 ± 0.5 for the subdermal technique and 2.38 ± 0.5 for the supraperiosteal technique (Table 1, Figure 6). This improvement was sustained until the final follow-up visit at 12 months. No statistically significant difference was observed between techniques at any follow-up visits.

Surface Volume Coefficient (clinical setting)

The SVC was calculated by dividing the absolute change in scanned 3D surface projection (cc) by the amount of injected volume (cc). Immediately post injection, the SVC was 0.94 ± 0.2 for the subdermal technique and 1.02 ± 0.3 for the supraperiosteal technique. No statistically significant difference was noted between the two techniques (P>0.05) for all assessment time points (Table 1, Figures 7 and 8).

A steady decrease in the surface projection using 3D surface scanning was noted over the period of 12 months with a loss of 18.8% in surface projection for the subdermal and 21.1% for the supraperiosteal product groups (Table 1).

Assuming constant SVCs (values used from baseline measurements), the loss of product during a 12-month period was 18.7% from the initially injected volume into the subdermal plane and 20.7% from the supraperiosteal plane injections (Figure 9).

Comparison Clinical vs Cadaveric Surface Volume Coefficient

In the cadaveric setting, a mean of 0.66 ± 0.1 cc [range: 0.50 – 0.80 cc] of product was injected subdermally whereas a mean of 2.70 ± 0.6 cc [range: 1.00 – 3.00 cc] was injected supraperiosteally (difference of injected volume between techniques was P<0.001). The resulting SVC was for the subdermal technique 1.00 ± 0.2 vs 0.70 ± 0.2 for the supraperiosteal injection technique with P=0.09. The difference between these 2 values ie, 0.30, can be interpreted as a region-specific parameter.

TABLE 1.

Values (presented in mean with +/-1 SD) for the Global Aesthetic Improvement Scale (GAIS), Temporal Volume Scale (TVS), the 3D Surface Scanning and the Calculated Surface Volume Coefficient (SVC) for the Different Follow-up Time Points

	Before Treatment	Immediately After Treatment	1 Month Follow-up	6 Months Follow-up	12 Months Follow-up
GAIS (mean (SD); subdermal vs. supraperiosteal)	n/a	2.65 (0.5) vs. 2.38 (0.5)	2.67 (0.5) vs. 2.38 (0.5)	2.44 (0.5) vs. 2.25 (0.4)	2.44 (0.5) vs. 2.38 (0.5)
TVS (mean (SD); subdermal vs. supraperiosteal)	2.56 (0.5) vs. 2.63 (0.5)	0.00 (0.0) vs. 0.00 (0.0)	0.00 (0.0) vs. 0.00 (0.0)	0.83 (0.4) vs. 0.44 (0.5)	1.11 (0.3) vs. 1.00 (0.0)
3D surface scanning in cc (mean (SD); subdermal vs. supraperiosteal)	n/a	0.64 (0.2) vs. 1.14 (0.37) ***	0.62 (0.2) vs. 1.08 (0.3) ***	0.60 (0.2) vs. 0.98 (0.3) ***	0.52 (0.2) vs. 0.90 (0.4) ***
SVC (mean (SD); subdermal vs. supraperiosteal)	n/a	0.94 (0.2) vs 1.02 (0.3)	0.90 (0.2) vs. 0.97 (0.3)	0.86 (0.1) vs. 0.88 (0.3)	0.75 (0.1) vs. 0.80 (0.3)

Comparing the SVC from the cadaveric model to the clinical setting, no significant difference was noted between the values at baseline, 1 month, and at 6 months using the subdermal injection technique. At 12 months however, a statistically significant difference was noted (clinical vs cadaveric): 0.75 ± 0.2 vs 1.00 ± 0.2 with *P*=0.008 (Figure 7). For the supraperiosteal injection technique, the baseline values obtained from the clinical setting differed significantly from the surface volume coefficient in the cadaveric model (clinical vs cadaveric): 1.02 ± 0.3 vs 0.70 ± 0.2 with *P*=0.038. No other statistically significant differences were noted (Figure 8).

DISCUSSION

The results of this clinical (n = 17) and cadaveric (n = 19) study provides evidence for the validity of the SVC. In the clinical model, we were able to show that aesthetically appealing results could be obtained by either the subdermal or by the supraperiosteal filler injection technique; irrespective of randomly assigned treatment group. However, to achieve statistically non-different results (when evaluated via the temporal volume scale and the GAIS assessed by an independent observer; Figures 5 and 6), the supraperiosteal injection technique utilized significantly more product 1.20 ± 0.5 cc [range: 0.50 – 2.6 cc] than the subdermal 0.71 ± 0.2 cc [range: 0.30 – 1.20 cc] *P*< 0.001. During the 12-month follow-up, subdermally injected temples lost 19% in surface projection whereas supraperiosteally injected lost 21%. Accounting for the different volumes injected, the product loss was 0.135 cc per year for the subdermal technique and 0.252 cc for the supraperiosteal technique. This different behaviour of the two layers of the temple (Layer 2 vs Layer 9) is reflected by the different values of the cadaveric SVC, subdermal vs 1.00 ± 0.2 vs supraperiosteal 0.70 ± 0.2. This difference in SVCs reflects the requirement for 69% more injected product into the supraperiosteal plane to achieve a non-statistically significantly different clinical result compared to individuals treated with the subdermal technique. The cadaveric SVC was similar up to 6 months follow-up (not 12 months) for the subdermal injection technique performed and similar to the 12 months follow-up (not baseline, 1 month, 6 months) measurement applying the supraperiosteal injection technique obtained in the clinical setting.

One strength of this investigation is that patients were randomly assigned into the two treatment groups (subdermal vs supraperiosteal) with no statistically significant difference in the baseline temporal volume scale. Another strength is that the identical product with the same viscoelastic properties was utilized for both injection techniques. This increases the comparability between the two injection techniques, eliminates the product influence on the clinical outcome, and enables the analysis of the tissue effect exclusively. Moreover, the clinical results were verified in the cadaveric model, which validates the cadaveric model and thus facilitates its use in future clinical studies.

Limitations of the present investigation were that a small clinical sample was investigated with (subdermal vs supraperiosteal) 9 vs 8 individuals per group and that only one product was used. Using a larger sample can provide a more robust fundament for any results obtained and might allow the inclusion of a different product to be tested with different viscoelastic properties. Another limitation is that the exact same product was not injected into the live patients as the cadavers, though the viscoelastic properties were similar.

The SVC is calculated by dividing the absolute change in scanned 3D surface projection (cc) by the amount of injected volume (cc) and provides information on the surface effect of a certain amount of injected volume, which could thus be considered the clinical effectiveness of an injected material. Previous studies have reported on regional differences of the SVC and have characterized it as a region-specific parameter.[11] Different facial regions (ie, upper vs middle vs lower face) have been shown to have different SVC values. It has also been shown that within the same facial region the coefficients vary depending on the layer injected, superficial vs deep fat compartments.[3,6] Additionally, the coefficient depends on the volumization capacity of the used product. A softer product with a better tissue integration and a lesser volumizing capacity might result in a smaller coefficient whereas a higher viscosity product with a reduced tissue integration and a higher water-binding capacity might result in a higher value of the SVC.

In the present study, the same product was injected into the subdermal and the supraperiosteal plane. To obtain the same aesthetically appealing outcome to volumize the temple, 69% more product had to be injected into the supraperiosteal plane (as compared to the subdermal plane). This difference was reflected by the different values of the cadaveric SVC (subdermal vs. supraperiosteal): 1.00 ± 0.2 vs 0.70 ± 0.2. These values indicate that 100% of the injected product into the subdermal plane results in surface projection and only 70% of the injected product does when injected into the supraperiosteal plane. This difference in SVC potentially explains why the loss rate for the supraperiosteal injected material is increased by 86.7% (0.135cc vs 0.252 annual loss rate of subdermal vs supraperiosteal) when compared to the subdermal injection. Interestingly, when comparing the SVCs obtained from the clinical setting (subdermal vs supraperiosteal): 0.94 ± 0.2 vs 1.02 ± 0.3 no statistically significant difference was noted.

As the coefficient is a region-specific parameter, it is plausible that the clinical outcome of the temple is different when 2 distinct layers are injected. This region-specificity, however, must be considered in the context of specific product characteristics. Injectables might interact differently with the targeted regional tissue depending on its material (ie, hyaluronic acid vs calci-

um hydroxyapatite vs. poly-L-lactic acid). Thus, the SVC in the non-cadaveric model should be understood as a product- AND region-specific measure as compared to the cadaveric model where it is a region-specific measure only. The difference between cadaveric (subdermal vs. supraperiosteal; 1.00 ± 0.2 vs 0.70 ± 0.2) and clinical (subdermal vs supraperiosteal; 0.94 ± 0.2 vs 1.02 ± 0.3) coefficients could be due to the altered blood pressure, muscular contraction, altered temperature, and tissue turgor pressure, which altogether are absent in the cadaveric model. However, the cadaveric model was able to reveal a difference in the coefficients, which was clinically observed in the amount of injected product.

The present study provides loss rates of an injected product and estimates the residual product (Figure 9) depending on its injected layer of the temple. The remainder of product in the tissue can be regarded as residual volume and is responsible for the longevity of a treatment. The loss rate of a product can be influenced by the product material, its tissue integration capacity, and the location where the product was injected; facial region and fascial layer. The latter is region-specific and is best reflected by the SVC, which has been shown in the current study to provide a valid explanatory model for the measured loss rates during a follow-up period of 12 months.

The cadaveric model is to date the closest model to reality and the most reliable experimental model available; a plethora of previous studies have used this model to provide valid results to the scientific community.[17–23] However, the general limitation of this model is whether one is able to generalize the results to clinical practice. The present study provides evidence for the validity of the SVC, a novel region and product-specific parameter. Comparing the temporal coefficients obtained from the cadaveric model to a future clinical scenario, it can be stated that the SVC is capable to predict clinical outcome up to 6 months if the subdermal plane is the focus and an outcome at 12 months (and potentially longer) when the supraperiosteal plane is investigated.

CONCLUSION

The results of this investigation provide evidence for the validity of the SVC obtained from a cadaveric model. They show that differences in applied volume to obtain aesthetically appealing results when utilizing the subdermal vs the supraperiosteal technique can be explained by the region-specific SVC. Knowing the SVC, percentage loss rates and the residual volume can be calculated. Therefore, understanding both region-specific and depth-specific SVCs may potentially guide aesthetic practitioners towards more targeted and cost-effective treatments. From a practitioner's perspective, the subdermal technique seems to be more cost-effective as it provides efficient and long-lasting results like the supraperiosteal technique, with lesser amounts of injected product.

DISCLOSURES

None of the other authors listed have any commercial associations or financial disclosures that might pose or create a conflict of interest with the methods applied or the results presented in this article.

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REFERENCES

1. Gierloff M, Stöhring C, Buder T, Gassling V, Açil Y, Wiltfang J. Aging changes of the midfacial fat compartments. *Plast Reconstr Surg.* 2012;129(1):263-273.
2. Cotofana S, Fratila A, Schenck T, Redka-Swoboda W, Zilinsky I, Pavicic T. The anatomy of the aging face: a review. *Facial Plast Surg.* 2016;32(03):253-260.
3. Schenck TL, Koban KC, Schlattau A, et al. The functional anatomy of the superficial fat compartments of the face. *Plast Reconstr Surg.* 2018;141(6):1351-1359.
4. Schenck TL, Koban KC, Schlattau A, et al. Updated anatomy of the buccal space and its implications for plastic, reconstructive and aesthetic procedures. *J Plast Reconstr Aesthetic Surg.* 2018;71(2).
5. Cotofana S, Mian A, Sykes JM, et al. An update on the anatomy of the forehead compartments. *Plast Reconstr Surg.* 2017;139(4):864e-872e.
6. Cotofana S, Gotkin RH, Frank K, et al. The functional anatomy of the deep facial fat compartments–A detailed imaging based investigation. *Plast Reconstr Surg.* 2019;143(1):53-56.
7. American Society of Plastic Surgeons. Cosmetic Plastic Surgery Statistics. https://www.plasticsurgery.org/documents/News/Statistics/2017/plastic-surgery-statistics-full-report-2017.pdf. Web. Accessed February 28th, 2019.
8. Suwanchinda A, Rudolph C, Hladik C, et al. The layered anatomy of the jawline. *J Cosmet Dermatol.* 2018;17(4):625-631.
9. Suwanchinda A, Webb KL, Rudolph C, et al. The posterior temporal supraSMAS minimally invasive lifting technique using soft-tissue fillers. *J Cosmet Dermatol.* 2018;17(4):617-624.
10. Pilsl U, Rosmarin W, Anderhuber F. The premaxillary space: A location for filler injection? *Dermatologic Surg.* 2014;40(3):301-304.
11. Cotofana S, Koban K, Frank K, et al. The surface-volume-coefficient of the superficial and deep facial fat compartments–A cadaveric 3D volumetric analysis. *Plast Reconstr Surg.* 2019;In Print.
12. Philipp-Dormston WG, Bieler L, Hessenberger M, et al. Intracranial penetration during temporal soft tissue filler injection–Is it possible? *Dermatologic Surg.* 2017;44(1):84-91.
13. Beleznay K, Carruthers JDA, Humphrey S, Jones D. Avoiding and treating blindness from fillers. *Dermatologic Surg.* 2015;41(10):1097-1117.
14. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects–WMA–The World Medical Association. Web. Accessed https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed February 28th, 2019.
15. Carruthers A, Carruthers J. A validated facial grading scale: The future of facial ageing measurement tools? *J Cosmet Laser Ther.* 2010;12(5):235-241.
16. Carruthers J, Jones D, Hardas B, et al. Development and validation of a photonumeric scale for evaluation of volume deficit of the temple. *Dermatol Surg.* 2016;42(Suppl 1):S203-S210.
17. Frank K, Koban K, Targosinski S, et al. The anatomy behind adverse events in hand volumizing procedures. Plast Reconstr Surg. 2018;141(5):650e-662e.
18. Furnas DW. The retaining ligaments of the cheek. *Plast Reconstr Surg.* 1989;83(1):11-16.
19. Wong C-H, Hsieh MKH, Mendelson B. The tear trough ligament. *Plast Reconstr Surg.* 2012;129(6):1392-1402.
20. Mendelson BC, Muzaffar AR, Adams WP. Surgical anatomy of the midcheek and malar mounds. *Plast Reconstr Surg.* 2002;110(3):885-96; discussion 897-911.
21. Rohrich RJ, Arbique GM, Wong C, Brown S, Pessa JE. The anatomy of suborbicularis fat: implications for periorbital rejuvenation. *Plast Reconstr Surg.* 2009;124.

22. Wan D, Amirlak B, Rohrich R, Davis K. The clinical importance of the fat compartments in midfacial aging. *Plast Reconstr Surg Glob Open*. 2013;1(9):e92.
23. Rohrich RJ, Pessa JE, Ristow B. The youthful cheek and the deep medial fat compartment. *Plast Reconstr Surg*. 2008;121(6):2107-2112.

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STILL AVAILABLE

Atopic Dermatitis: A Review of Topical Treatment

An overview of recent advances in AD, specifically topical corticosteroids, which remain a fundamental component of treatment algorithms

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ORIGINAL ARTICLE Journal of Drugs in Dermatology

A Phase 2, Multicenter, Double-Blind, Randomized, Vehicle-Controlled Clinical Study to Compare the Safety and Efficacy of a Novel Tazarotene 0.045% Lotion and Tazarotene 0.1% Cream in the Treatment of Moderate-to-Severe Acne Vulgaris

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ABSTRACT

Background: Tazarotene has been extensively studied in clinical trials and is widely used to treat acne vulgaris (acne). Irritation potential has limited its use.

Objective: To compare efficacy, safety, and tolerability of a novel formulation tazarotene 0.045% lotion based on polymeric emulsion technology, and tazarotene 0.1% cream in patients with moderate-to-severe acne.

Methods: A total of 210 patients, 12 years and older were randomized to receive tazarotene 0.045% lotion, tazarotene 0.1% cream, or respective vehicle in double-blind, randomized, vehicle-controlled, 12-week study evaluating safety and efficacy (inflammatory and noninflammatory lesion counts and using Evaluator Global Severity Scores [EGSS]). In addition, patients completed a patient satisfaction survey (PSS), and acne-specific quality of life (QoL) questionnaire. Safety and cutaneous tolerability were assessed throughout.

Results: A novel tazarotene 0.045% lotion demonstrated statistically significant superiority to vehicle in reducing inflammatory and noninflammatory lesion counts (P=.006 and P<.001) and clearly more effective in treatment success at week 12. In addition, at less than half the concentration, tazarotene 0.045% lotion was numerically more effective than tazarotene 0.1% cream. Mean percent reductions in inflammatory and noninflammatory lesions were 63.8% and 56.9%, compared with 60.0% and 54.1% with tazarotene 0.1% cream at week 12. Treatment success assessed by the investigator or patients' self-assessment was also numerically greater with tazarotene 0.045% lotion. There were no significant differences in patient satisfaction or QoL between the two active treatments. Both were well-tolerated, however, there were more treatment-related adverse events with tazarotene 0.1% cream (5.6% versus 2.9%); most common being application site pain.

Limitations: This study was primarily designed to direct the phase 3 program and some of the results are post hoc analyses.

Conclusions: A novel tazarotene 0.045% lotion provides statistically significant greater efficacy than vehicle in terms of lesion reduction, and numerically better treatment success than tazarotene 0.1% cream; with a highly favorable safety and tolerability profile in moderate-to-severe acne patients.

J Drugs Dermatol. 2019;18(6):542-548.

INTRODUCTION

Topical retinoids (eg, tazarotene, tretinoin, adapalene) have played an important role in the management of acne vulgaris (acne). They reduce visible lesions and inhibit the development of microcomedones and new lesions.[1-3] Retinoids normalize the abnormal desquamation process by reducing keratinocyte proliferation and promoting differentiation,[4] as well as modulating several important inflammatory pathways.[4-10] Extensive clinical data have shown retinoids to be highly effective in acne, and they are recommended as the cornerstone of topical therapy.[11] Comparative studies between tazarotene, tretinoin and adapalene have generally reported greater efficacy with tazarotene, but more irritation.[12-20]

A key aspect of acne management has been the ongoing evolution of topical treatments that use innovative delivery solutions and optimal formulations to help minimize irritation, without

compromising efficacy. A novel lotion formulation was developed using a polymeric emulsion, with the aim of improving both efficacy and tolerability. This polymeric emulsion technology provides a more uniform distribution of active and moisturizing excipients at the surface of the skin, which should enhance efficacy and minimize irritation.

In this report data from a comparative phase 2 clinical study where patients with moderate-to-severe acne were treated with tazarotene 0.045% lotion, tazarotene 0.1% cream, or vehicle are presented.

METHODS

Study Design

This was a multicenter, randomized, double-blind, vehicle-controlled, clinical study in patients with moderate-to-severe acne who met specific inclusion/exclusion criteria as described below. Protocol received approval from the appropriate institutional review board (IRB) for each center before patient enrollment and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practices (GCP) and in compliance with local regulatory requirements. All patients were informed of the study details and provided written consent.

Patients were enrolled with an Evaluator Global Severity Score [EGSS] score of 3 (moderate) or 4 (severe). Treatments were randomized (2:2:1:1) to tazarotene 0.045% lotion, tazarotene 0.1% cream, and vehicle lotion or cream (to ensure blinding). Data on vehicle are combined in the result presented here. All patients applied study medication to the face once-daily in the evening for 12 weeks; after being instructed to gently washing their face with a non-medicated cleanser.

Study Population

Approximately 210 patients were planned for enrollment. Eligible patients were of any gender, race and ethnicity aged 12 years and older who presented with 20 to 40 inflammatory lesions (papules, pustules, and nodules), 20 to 100 noninflammatory lesions (open and closed comedones), and two nodules or less. Women of childbearing potential were required to have a negative urine pregnancy test result and to agree to use an effective form of contraception for the duration of the study. A washout period of up to 1 month was required for patients who used previous prescription and over-the-counter acne treatments (and six months for systemic retinoids). Investigator approved non-mediated facial cleanser, moisturizer, and sunscreen was allowed.

Efficacy Evaluation

Efficacy evaluations comprised inflammatory, and noninflammatory lesion counts and an EGSS at screening, baseline, and during treatment (at weeks 2,4, 8, and 12) performed by the investigator. Primary efficacy endpoints included mean absolute change from baseline to week 12 in inflammatory and noninflammatory lesion counts, and the proportion of patients who achieved at least a 2-grade reduction from baseline to week 12 in EGSS and were 'clear' or 'almost clear'. Other efficacy endpoints included mean percent change from baseline to week 12 in inflammatory and noninflammatory lesion counts. Data for vehicle lotion and cream were pooled for the efficacy analysis.

Additional analyses were performed to evaluate the impact of treatment on other patient outcomes. These included a Patient Satisfaction Survey (PSS) with scores ranging from 1-10 (where 10 was the most satisfied); a validated Acne-Specific Quality of Life (Acne-QoL) questionnaire (Merck & Co, Inc. Whitehouse, NJ); and a Subject Self-Assessment (SSA) scale (using a 7-point scale, where 0=worse and 6=clear). The SSA was assessed at baseline and weeks 2, 4, 8, and 12; PSS and Acne-QoL were completed at baseline and week 12.

Safety Evaluation

Cutaneous safety (erythema, scaling, hypopigmentation, and hyperpigmentation) and tolerability (itching, burning, and stinging) were assessed using a 4-point scale where 0=none, 1=mild, 2=moderate and 3=severe. The investigator assessed erythema, scaling, and hyper-/hypopigmentation at the time of the study visit. Itching, burning, and stinging were solicited from the patient and recorded as an average of the patient's symptoms during the period since the previous visit.

Safety was also evaluated through reported adverse events (AEs), which were summarized by treatment group, severity, and relationship to study medication.

Statistical Analysis

The intent-to-treat (ITT) population comprised all patients randomized and provided with study drug and vehicle. The safety population comprised all randomized patients who were presumed to have used the study medication or vehicle at least once and who provided at least one post baseline evaluation. The primary method of handling missing efficacy data in the ITT analysis set was last observation carried forward (LOCF). No imputations were made for missing safety data.

Reductions in lesion counts are presented as means and contrast p-values are from a ranked analysis of covariance with factor of treatment and the respective baseline lesion count as covariate. Significance of EGSS reductions were obtained from a Cochran-Mantel-Haenszel (CMH) test.

All statistical analyses were conducted using SAS® version 9.3 or later. Statistical significance was based on 2-tailed tests of the null hypothesis resulting in *P* values of 0.05 or less.

All AEs occurring during the studies were recorded and classified on the basis of medical dictionary for drug regulatory activities terminology (MedDRA) for the safety population. The frequency of patients with one or more AEs during the study was tabulated by treatment group.

RESULTS

Baseline Characteristics

Total of 210 patients were enrolled across 16 investigative sites in the United States, randomly assigned to tazarotene 0.045% lotion (N=69), tazarotene 0.1% cream (N=72), or vehicle (N=69) and included in the ITT analysis, see Figure 1. Patients were treated with vehicle lotion (N=34) or vehicle cream (N=35) to ensure blinding, however vehicle results are combined in these analyses. Overall, 189 patients (90%) completed the study, including 65 patients (94.2%) on tazarotene 0.045% lotion, 63 patients (87.5%) on tazarotene 0.1% cream, 61 patients (88.4%) on combined vehicle. The most common reasons for study discontinuation were 'lost to follow-up (N=12)' or 'subject request (N=5)'. One patient treated with tazarotene 0.1% cream discontinued due to adverse event. Four patients were excluded from the safety population due to no post-baseline safety assessment.

Demographic data (Table 1) was similar across the treatment groups. The mean age was 21.2 to 23.3 years. There was a slightly higher proportion of female patients overall (55.2%); 61.4% were Caucasian, with 28.6% Black or African American. There were no noticeable differences between treatment groups in regard to baseline lesion counts, or EGSS. At baseline, the mean number of inflammatory and noninflammatory lesions ranged from 27.2 to 28.3 and 36.6 to 37.6, respectively. At baseline, 92.4% of patients had moderate acne (EGSS=3).

Efficacy

Lesion Counts

Tazarotene 0.045% lotion resulted in statistically significant reductions in both inflammatory and noninflammatory lesion reductions compared to combined vehicle at week 12. Mean percentage change from baseline to week 12 in inflammatory lesion counts was 63.8% versus 51.4% with the combined vehicle (P=.006), and in noninflammatory lesion counts 56.9% versus 35.2% with vehicle (P<.001), see Figures 2 and 3. Tazarotene 0.045% lotion showed a greater reduction from baseline to week 12 in inflammatory and noninflammatory lesions when compared with tazarotene 0.1% cream, but differences were not significant (P=.680 and .612).

Median percent change from baseline to week 12 in inflammatory and noninflammatory lesion counts with tazarotene 0.045% lotion was 72.4% and 62.5% versus 66.7% and 56.4% with tazarotene 0.1% cream and 60.0% and 42.3% with vehicle, respectively.

FIGURE 1. Patient disposition ITT population (all randomized subjects, N=210).

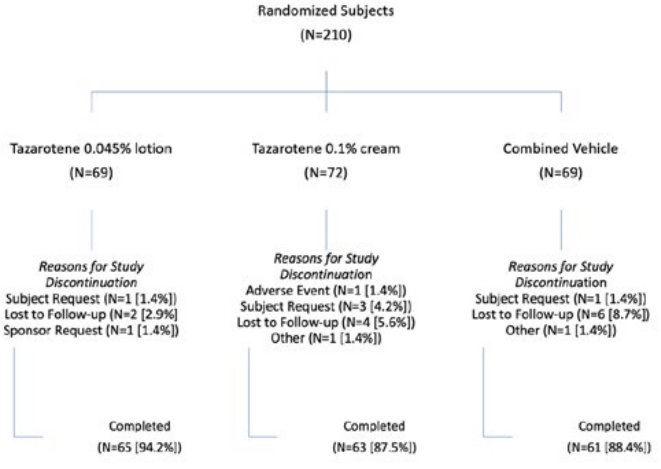


TABLE 1.

Demographics and Baseline Characteristics (ITT population)	Tazarotene 0.045% Lotion (N=69)	Tazarotene 0.1% Cream (N=72)	Combined Vehicle (N=69)
Age			
Mean years (SD)	23.3 (10.20)	22.0 (8.96)	21.2 (8.44)
Sex N (%)			
Male	32 (46.4%)	31 (43.1%)	31 (44.9%)
Female	37 (53.6%)	41 (56.9%)	38 (55.1%)
Ethnicity N (%)			
Hispanic or Latino	27 (39.1%)	29 (40.8%)	25 (36.2%)
Not Hispanic or Latino	42 (60.9%)	42 (59.2%)	44 (63.8%)
Race N (%)			
American Indian or Alaska Native	1 (1.4%)	0 (0.0%)	2 (2.9%)
Asian	4 (5.8%)	4 (5.6%)	2 (2.9%)
Black or African American	21 (30.4%)	16 (22.2%)	23 (33.3%)
Native Hawaiian or Other Pacific Islander	1 (1.4%)	0 (0.0%)	1 (1.4%)
White	41 (59.4%)	50 (69.4%)	38 (55.1%)
Other	1 (1.4%)	2 (2.8%)	3 (4.3%)
Evaluator's Global Severity Score N (%)			
3 – Moderate	64 (92.8%)	66 (91.7%)	64 (92.8%)
4 – Severe	5 (7.2%)	6 (8.3%)	5 (7.2%)
Inflammatory Lesion Count			
Mean (SD)	28.3 (6.00)	27.3 (5.95)	27.2 (5.49)
Noninflammatory Lesion Count			
Mean (SD)	37.6 (14.70)	36.6 (13.31)	36.6 (13.17)

FIGURE 2. Percent change in mean inflammatory lesions from baseline to week 12. (ITT population): Comparison of Tazarotene 0.045% lotion, Tazarotene 0.1% cream, and vehicle.

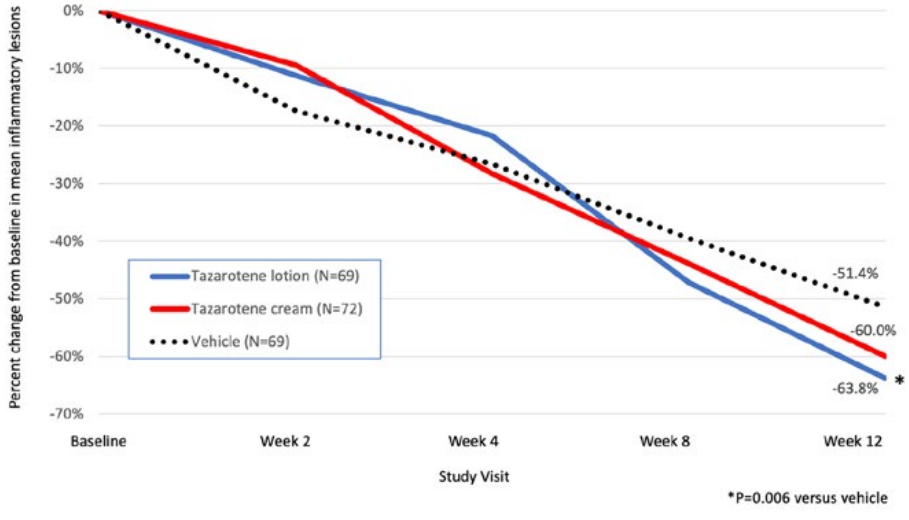
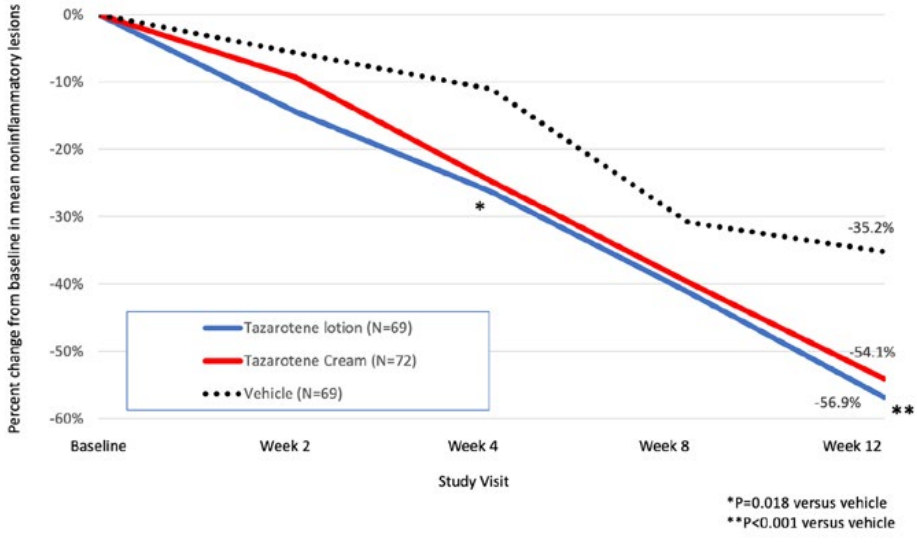


FIGURE 3. Percent change in mean noninflammatory lesions from baseline to week 12 (ITT population): Comparison of Tazarotene 0.045% lotion, Tazarotene 0.1% cream, and vehicle.



Treatment Success

Treatment success was defined as at least a 2-grade improvement in global severity by EGSS and 'clear' or 'almost clear'. At week 12, 18.8% of patients achieved treatment success with tazarotene 0.045% lotion compared to 10.1% with combined vehicle (*P*=.148; Figure 4). Tazarotene 0.045% lotion showed a greater treatment success at week 12 when compared with tazarotene 0.1% cream (16.7%), but differences were not significant.

Subject Self-Assessment (SSA)

Tazarotene 0.045% lotion showed a greater numerical treatment success ('clear' or 'almost clear') at week 12 in terms of SSA when compared with tazarotene 0.1% cream (*P*=.768). Treatment success was achieved in 38.5% of patients, compared with 35.9% and 24.6% (tazarotene 0.01% cream and combined vehicle [*P*=.096], respectively).

FIGURE 4. Treatment success based on Evaluator's Global Severity Scores (ITT population): Comparison of Tazarotene 0.045% lotion, Tazarotene 0.1% cream, and vehicle.

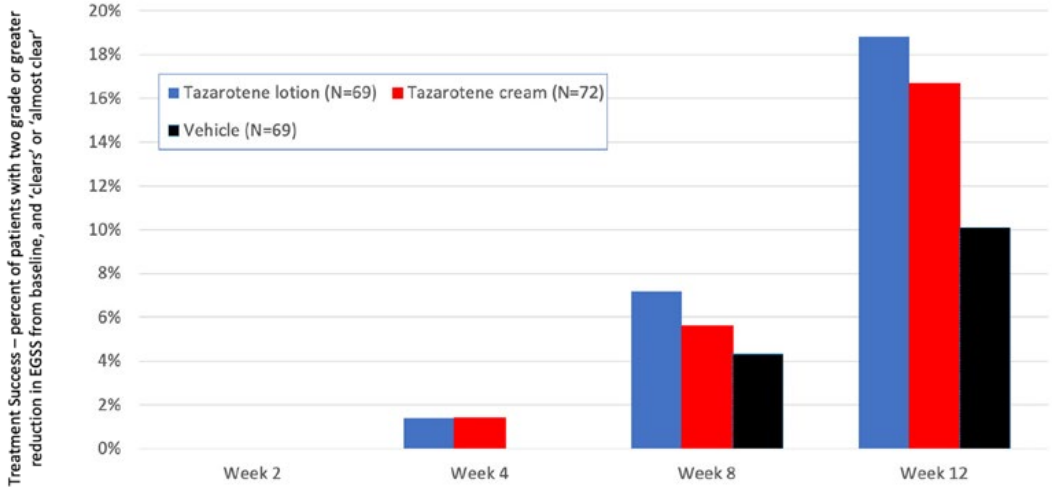
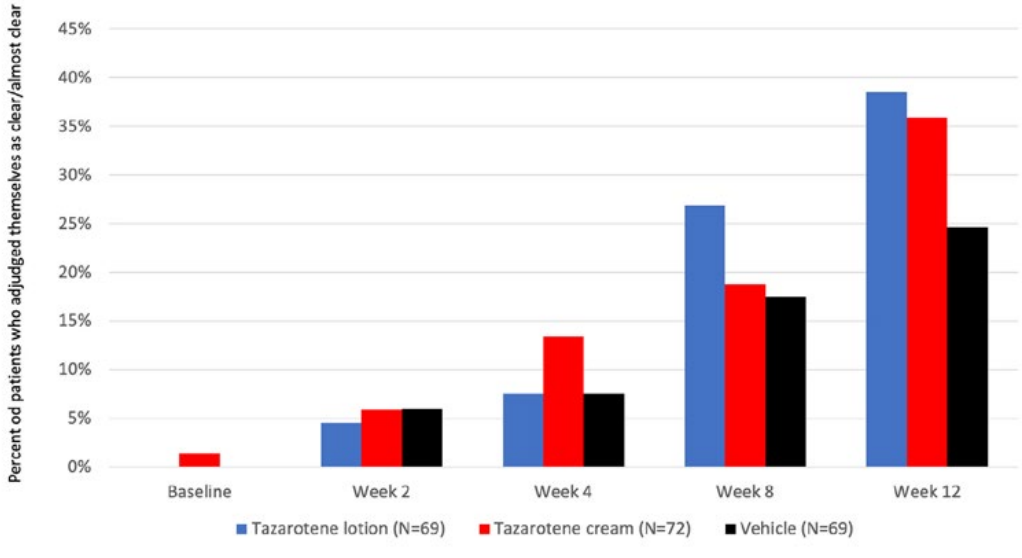


FIGURE 5. Subject Self-Assessment (SSA) at each evaluation (ITT Population 'Clear' or 'Almost Clear' [>=90%]): Comparison of Tazarotene 0.045% lotion, Tazarotene 0.1% cream, and vehicle.



Patient Satisfaction (PSS) and Quality of Life

There were no significant differences in PSS mean scores at week 12 between tazarotene 0.045% lotion and tazarotene 0.1% cream (P=.372) or combined vehicle (P=.242). Overall, patients treated with tazarotene 0.045% lotion assessed their treatment satisfaction higher than tazarotene 0.1% cream (mean score of 7.7 versus 7.4).

There were also no statistically significant differences in the improvement between treatment groups based on the mean Acne-QoL assessments in each of the 4 evaluated domains. Improvements in self-perception, role-emotional, and role-social were similar with tazarotene 0.045% lotion and tazarotene 0.1% cream, and markedly greater than those achieved in the combined vehicle groups. In terms of acne symptoms improvement, the absolute change from baseline with tazarotene 0.045% lotion was again greater than that achieved with the combined vehicle, however tazarotene 0.1% cream only demonstrated an improvement similar to that achieved with vehicle.

Safety

A higher proportion of patients treated with tazarotene 0.1% cream (26.8%) reported treatment-emergent AEs compared with tazarotene 0.045% lotion (14.7%) or combined vehicle (13.4%). TEAEs were mostly mild or moderate and unrelated to study drug (Table 2). Treatment-related AEs were more common with tazarotene 0.1% cream. There were two reports of application site pain (2.9%) with tazarotene 0.045% lotion; compared with three reports with tazarotene 0.1% cream (4.2%).

Cutaneous Safety and Tolerability

Each of the signs and symptoms of cutaneous safety and tolerability (scaling, erythema, hypopigmentation, hyperpigmentation, itching, burning, and stinging) showed improvements from baseline to week 12. There were slight increases in mean scores for scaling, burning and stinging at week 4, consistent with tazarotene's safety profile, but these reduced at subsequent study visits. All mean scores were ≤0.6 (where a score of 1=mild); scores being similar or slightly lower at interim study visits with tazarotene 0.045% lotion compared with tazarotene 0.1% cream, especially in terms of scaling, itching, burning, and stinging at weeks 2 and 4.

TABLE 2.

Treatment-Emergent and Related Adverse Event (AE) Characteristics through Week 12 (Safety population, N=206)

	Tazarotene Lotion (N=68)	Tazarotene Cream (N=71)	Combined Vehicle (N=67)
Patients reporting any TEAE	10 (14.7%)	19 (26.8%)	9 (13.4%)
Patients reporting any SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients who died	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients who discontinued due to TEAE	0 (0.0%)	1 (1.4%)	0 (0.0%)
Severity of AEs reported			
Mild	6 (8.8%)	12 (16.9%)	9 (13.4%)
Moderate	2 (2.9%)	7 (9.9%)	0 (0.0%)
Severe	2 (2.9%)	0 (0.0%)	0 (0.0%)
Relationship to study drug			
Related	2 (2.9%)	4 (5.6%)	0 (0.0%)
Unrelated	8 (11.8%)	15 (21.1%)	9 (13.4%)
Treatment Related AEs reported by ≥1% patients			
Application site pain	2 (2.9%)	3 (4.2%)	0.(0.0%)
Application site erythema	0 (0.0%)	1 (1.4%)	0 (0.0%)
Application site exfoliation	0 (0.0%)	1 (1.4%)	0 (0.0%)
Application site dryness	0 (0.0%)	1 (1.4%)	0 (0.0%)
Erythema	0 (0.0%)	1 (1.4%)	0 (0.0%)

DISCUSSION

Despite recommendations to use retinoids as first-line acne treatment,[11,21] they remain underutilized.[22-24]The slow onset of action in the treatment of inflammatory lesions,[25] and the widely recognized irritation potential of these agents have somewhat limited their use. Consequently, several attempts have been made to alleviate these efficacy and tolerability issue using new delivery technology. The clinical benefits observed with tazarotene 0.1% foam,[26,27] 0.1% cream,[28] and 0.1% gel[29] appear similar, although no direct comparisons exist in the literature.

The rationale behind the development of a novel lotion formulation of tazarotene stemmed from its proven efficacy in acne and the fact that a lotion formulation is the easiest and most acceptable formulation for application to the face; but also the potential for tazarotene cream (and to a lesser extent foam[26]) to cause concentration dependent skin irritation and dryness, which had been shown to be both bothersome in many patients and may impact adherence and successful acne treatment. For example, pooled results from several clinical studies showed that 14% of patients treated with tazarotene 0.1% foam reported irritation and 7% dryness, compared with only 1% using vehicle.[30]

Tazarotene 0.045% lotion is a novel topical treatment for moderate-to-severe acne leveraging polymeric emulsion technology with the aim to improve both efficacy and tolerability. The polymeric emulsion technology affords more uniform deposition of active, excipients and moisturizers onto the skin surface. This phase 2 study is the first to compare a novel formulation of tazarotene 0.045% lotion with commercially available tazarotene 0.1% cream in patients with moderate-to-severe acne. Tazarotene 0.045% lotion was significantly superior to vehicle in reducing both inflammatory and noninflammatory lesions; and numerically more effective than tazarotene 0.1% cream despite the two-fold difference in tazarotene concentration. Median reductions in inflammatory and noninflammatory lesions with tazarotene 0.045% lotion were 72% and 63%, respectively, at 12 weeks.

The only treatment-related AE with tazarotene 0.045% lotion observed was application site pain (2.9%). Skin reactions (such as scaling, burning, and stinging) were infrequent, had onsets early in the treatment period, were mostly mild and appeared transient. Erythema and itching noted at baseline improved progressively with daily tazarotene 0.045% lotion treatment. Again, these data concur with those in other clinical trials of retinoids where the peak of cutaneous irritation typically occurs within the first 1-2 weeks and subsides.[31]

CONCLUSIONS

Tazarotene 0.045% lotion was developed using a polymeric emulsion technology. In this phase 2 study of patients with moderate-to-severe acne, tazarotene 0.045% lotion was as effective as the higher concentration tazarotene 0.1% cream, with fewer treatment-emergent adverse events.

DISCLOSURES

Drs Tanghetti, Kircik and Green were study investigators. Dr Kircik and Green are advisors to Ortho Dermatologics. Dr Guenin, Pillai, and Ms Harris and Martin are employees of Bausch Health Americas, Inc.

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REFERENCES

1. Thielitz A, Abdel-Naser MB, Fluhr JW, et al. Topical retinoids in acne–an evidence-based overview. *J Dtsch Dermatol Ges* 2008;6:1023–1031.
2. Thielitz A, Helmdach M, Ropke EM, et al. Lipid analysis of follicular casts from cyanoacrylate strips as a new method for studying therapeutic effects of antiacne agents. *Br J Dermatol* 2001;145:19–27.
3. Del Rosso JQ. Pharmacotherapy review: topical tazarotene, a composite review of clinical and research experience with focus on optimal use and safety. *J Am Osteopath Coll Dermatol* 2004;1(2):55–59.
4. Czernielewski J, Michel S, Bouclier M, et al. Adapalene biochemistry and the evolution of a new topical retinoid for treatment of acne. *J Eur Acad Dermatol Venereol* 2001;15(Suppl 3):5–12.
5. Michel S, Jomard A, Demarchez M. Pharmacology of adapalene. *Br J Dermatol* 1998;139(Suppl 52):3–7.
6. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol* 2003;49:S1–37.
7. Thielitz A, Gollnick H. Topical retinoids in acne vulgaris: update on efficacy and safety. *Am J Clin Dermatol* 2008;9:369–81.
8. Yeh L, Bonati LM, Silverberg NB. Topical retinoids for acne. *Semin Cutan Med Surg* 2016;35:50–56.
9. Millikan LE. The rationale for using a topical retinoid for inflammatory acne. *Am J Clin Dermatol* 2003;4(2):75–80.
10. Thiboutot DM, Gollnick HP. Treatment considerations for inflammatory acne: clinical evidence for adapalene 0.1% in combination therapies. *J Drugs Dermatol* 2006;5(8):785–794.
11. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74(945–73):e33.
12. Pariser D, Colón LE, Johnson LA, Gottschalk RW. Adapalene 0.1% gel compared to tazarotene 0.1% cream in the treatment of acne vulgaris. *J Drugs Dermatol.* 2008;7(6 Suppl):s18-23.
13. Thiboutot D, Arsonnaud S, Soto P. Efficacy and tolerability of adapalene 0.3% gel compared to tazarotene 0.1% gel in the treatment of acne vulgaris. *J Drugs Dermatol* 2008;7(6 Suppl):s3–s10.
14. Webster GF, Berson D, Stein LF, et al. Efficacy and tolerability of once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.025% gel in the treatment of facial acne vulgaris: a randomized trial. *Cutis* 2001;67:4–9.
15. Leyden JJ, Tanghetti EA, Miller B, et al. Once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.1% microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. *Cutis* 2002;69:12–19.
16. Dosik JS, Arsonnaud S. Tolerability comparison of adapalene gel, 0.3% versus tazarotene cream 0.05% in subjects with healthy skin. *J Drugs Dermatol* 2007;6(6):632-638.
17. Kircik LH. Tretinoin microsphere gel pump 0.04% versus tazarotene cream 0.05% in the treatment of mild-to-moderate facial acne vulgaris. *J Drugs Dermatol* 2009;8(7):650-654.
18. Webster GF, Guenther L, Poulin YP, et al. A multi-center, double-blind, randomized comparison study of the efficacy and tolerability of once-daily tazarotene 0.1 % gel and adapalene 0.1 % gel for the treatment of facial acne vulgaris. *Cutis* 2002; 69: 4–11.
19. Shalita A, Miller B, Menter A, et al. Tazarotene cream versus adapalene cream in the treatment of facial acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. *J Drugs Dermatol* 2005;4:153-158.
20. Tanghetti EA, Dhawan S, Green L, et al. Randomized comparison of the safety and efficacy of tazarotene 0.1% cream and adapalene 0.3% gel in the treatment of patients with at least moderate facial acne vulgaris. *J Drugs Dermatol* 2010;9(5):549-558.
21. Nast A, Dreno B, Bettoli V, et al. European evidence-based (S3) guidelines for the treatment of acne. *J Eur Acad Dermatol Venereol* 2012;26(Suppl 1):1–29.
22. Pena S, Hill D, Feldman SR. Use of topical retinoids by dermatologists and non-dermatologists in the management of acne vulgaris. *J Am Acad Dermatol* 2016;74:1252–1254.
23. Balkrishnan R, Fleischer AB Jr, Paruthi S, Feldman SR. Physicians underutilize topical retinoids in the management of acne vulgaris: analysis of US National Practice Data. *J Dermatolog Treat* 2003;14:172–176.
24. Balkrishnan R, Bhosle MJ, Camacho F, at al. Prescribing patterns for topical retinoids: analyses of 15 years of data from the national ambulatory medical care survey. *J Dermatolog Treat* 2010;21:193–200.
25. Leyden J, Stein Gold L, Weiss J. Why topical retinoids are the mainstay of therapy for acne. *Dermatol Ther* 2017;7:293-304.
26. Jarratt M, Werner CP, Alió Saenz AB. Tazarotene foam versus tazarotene gel: a randomized relative bioavailability study in acne vulgaris. *Clin Drug Investig* 2013;33:283–289.
27. Feldman SR, Werner CP, Alió AS. The efficacy and tolerability of tazarotene foam, 0.1%, in the treatment of acne vulgaris in 2 multicenter, randomized, vehicle-controlled, double-blind studies. *J Drugs Dermatol* 2013;12(4):438-446.
28. Shalita AR, Berson DS, Thiboutot DM, et al. Effects of tazarotene 0.1 % cream in the treatment of facial acne vulgaris: pooled results from two multicenter, double-blind, randomized, vehicle-controlled, parallel-group trials. *Clin Ther* 2004;26:1865-1873.
29. Shalita AR, Chalker DK, Griffith RF, et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. *Cutis* 1999;63:349-354.
30. Epstein EL, Stein Gold L. Safety and efficacy of tazarotene foam for the treatment of acne vulgaris. *Clin Cosmet Investig Dermatol* 2013;6:123-125.
31. Leyden J, Grove G, Zerweck C. Facial tolerability of topical retinoid therapy. *J Drugs Dermatol* 2004;3:641–651.

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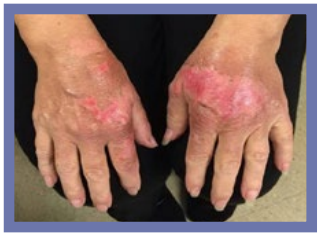

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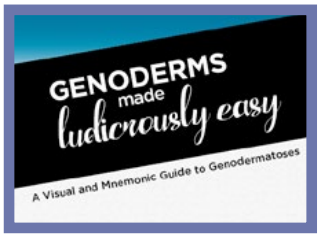

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Update on the Treatment of Scars

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ABSTRACT

Background: Treatment of scars continues to be a persisting challenge. Scar classification is paramount in determining an appropriate treatment strategy. They can be classified into hypertrophic, keloid, or atrophic scars. With the increasing demand for less invasive procedures that result in equal or greater outcomes, there has been an increase in the variety of procedures for the management of scarring.
Methods: A Pubmed search was performed for the most recent papers on scar treatments. Findings and applications are discussed in this review.
Results: Studies evaluating the efficacy and safety of microneedling, filler agents, toxins, silicone gels, and laser devices such as ablative, non-ablative, fractional, SRT, and radiofrequency are discussed.
Conclusion: Review of the literature revealed a myriad of options for the treatment of different scar types. Although there is not vast evidence in the literature in regard to combination treatments, these are becoming more popular, and it is the author's opinion that combination treatments yield better overall results.

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INTRODUCTION

Treatment of scars remains a persisting challenge. Scarring can be classified as a fibrous tissue disorder, which can occur as a consequence of inflammatory or non-inflammatory processes.[1] Abnormal scarring is a well-known complication of wound healing; moreover scars can cause cosmetic, functional, and even psychological impact. Scar classification is paramount in determining an appropriate treatment strategy. They can be classified into hypertrophic, keloid, or atrophic scars.[2]

Hypertrophic scars are characterized by their indurated and at times erythematous appearance, which is caused by the overgrowth of capillary vessels secondary to chronic inflammation.[3] They typically develop secondary to trauma; burn injury, or insect bites. Traditionally, depending on the type and severity of the hypertrophic scar at hand, intralesional corticosteroids, silicone gel sheeting, or intralesional fluorouracil (5-FU) were being used. However, in the past decades, lasers have taken a front seat in the treatment of these types of scars and have aided in the delivery of the aforementioned medications.

Atrophic scars usually develop after an inflammatory process and can be the result of collagen loss and dermal atrophy. These tend to develop after insults to the skin such as acne, varicella, or trauma.[4] These can cause an indentation or depression in the skin. Given that acne is such a common pre-existant concurrent disorder, it constitutes the vast majority of atrophic scars. In the case of atrophic scars, ablative lasers, chemical peels, and subcision were paramount in the past in treating these troublesome scars. Procedures such as ablative resurfacing have posed a challenge as such an approach might not be used in all skin types, and potentially could have a trying side effect profile. Less invasive treatments used posed difficulty in achieving the type of results sought after by the provider and/or patient.

With the increasing demands of patients to have less invasive procedures that result in equal or greater outcomes, there has been an increase in the variety of procedures for the management of scarring. Multiple studies have led to multiple treatment strategies for the improvement of the different types of scars. Patient evaluation and expectations should be done and discussed prior to the initiation of any treatment. Treatment combinations are typically the best option for patients. The recent development of non-ablative lasers, radiofrequency devices, and different uses of fillers and toxins amongst others have broadened the scope with which we can treat scars. This article will review the most current treatment strategies used to treat hypertrophic, keloidal, and atrophic scarring.

Microneedling

Microneedling (MN) is a relatively new treatment option. As the demand for less invasive but efficacious procedures is growing, MN fits in this category. This modality has been studied extensively recently, and more studies have been performed on

acne scarring, than in any other form of scarring, demonstrating statistically significant efficacy, used as MN monotherapy or combined with other modalities such as platelet rich plasma, or chemical peels.[2,5–10] A series of 3 to 5 treatments spaced 2-4 weeks apart has been shown to result in a 50-70% improvement of scarring.[5,10] When compared to non-ablative fractional Erbium 1,340-nm laser with treatments every 3 months, there was no statistical difference between groups on the Quantitative Global Grading System for Post-Acne Scarring scale at 2 and 6 months post-treatment.[11] A randomized, blinded study of 30 subjects comparing MN to trichloroacetic acid (TCA) showed clinical improvement in acne scarring of both groups, with no statistically significant difference in percentage improvement.[12]

A few studies on combination therapy of MN with PRP have shown mostly positive results.[13–17] Other combination therapies with chemical peels (such as 35% or 70% glycolic acid peels),[18,19] and other studies incorporating subcision and TCA along with MN have also shown success in treating these types of scars.[20] Other studies have shown efficacy in treating burn injury and split-thickness grafts post thermal injury. In addition, a group treated with vitamin C and A prior to MN showed 80% improvement overall.[16,21,22] Lastly, MN has also been used to treat varicella induced atrophic scars with evident improvement.[10,23,24]

Fillers

Most, if not all, fillers are currently being used to treat scarring. The literature is ample with examples of filler improved acne scarring. The various options include hyaluronic acid fillers, autologous fat, and biosynthetic polymers such as poly-l-lactic acid, poly methylmethacrylate, and calcium hydroxylapatite, the last three lasting longer than the others. Most of these approaches will require repeat treatments to maintain results.

A phase 3 double blind, double randomized, multi-center-controlled trial was done to demonstrate the safety and effectiveness of PMMA-collagen for acne scarring where 147 subjects underwent PMMA collagen vs. saline injections and were followed up for 6 months. Success was achieved by 64% of those treated with PMMA-collagen in comparison to 33% in control subjects.[25] In another study, twelve subjects with moderate to severe acne scarring received microdroplet injections of hyaluronic acid after fractional laser resurfacing, and immediate visual improvement was noted.[26] In a study by Goldberg et al, ten subjects with a variety of scars were treated with calcium hydroxylappatite. Saucerized scars demonstrated improvement in this study, while ice-pick scars did not respond. Results were shown to last for up to a year.[27] Although silicone injection treatments of acne scars are not approved by the FDA as fillers,[28] microdroplet injections of silicone either alone or in combination with cross-linked hyaluronic acid in expert hands have been shown to also be a treatment option.[29,30]

A few case studies have demonstrated the success of hyaluronic acid fillers in treating chronic atrophic or depressed scars, due to trauma,[31] steroid atrophy,[32,33] morphea,[34] and even post-Mohs surgery.[35] Subjects post Mohs surgery were treated with either hyaluronic acid or calcium hydroxylappatite. Both were effective with durations lasting 8 and 9 months respectively.[35]

Toxin

Treatment with botulinum toxin is undertaken mainly to avoid and treat hypertrophic scars. In 2000, a randomized controlled trial was done to evaluate the cosmetic outcome of primates with facial wounds. Standard excisions were made, and subject were treated either with botulinum toxin A or normal saline. The botulinum toxin-treated group showed significantly better scar outcomes than did the control group at 3-month follow-up.[36] This was again reproduced in human subjects in 2006, when subjects were treated with botulinum toxin or placebo after cutaneous surgery on the forehead. The toxin treated group demonstrated significant greater scar outcomes.[37] A separate study of 40 subjects examining scar outcomes on cheeks and forehead after scar revision treated with injection of botulinum toxin also achieved significant improvement based on objective and subjective scales.[38] Moreover in a study by Ziade et al 30 subjects were randomized to receive botulinum toxin or placebo following facial wounds. Subjects were followed up at 1 year, and results were mixed, statistically significant improvement was shown by the visual analog scale, but was not shown in the other study evaluations.[39] Intralesional injection of botulinum toxin has also been used to treat keloids and has demonstrated improvement in the treated scar at a one-year follow up.[23]

Silicone Gels

The mechanism by which silicone products may help to prevent excessive scar formation is by restoring the water barrier through its provided semi-occlusion and hydration of the stratum corneum.[40] Topical silicone gels have been used for years to treat hypertrophic scars.[41] However, literature as to the effectiveness of silicone gels in preventing hypertrophic scars appears to be mixed. In a study by Gold et al subjects undergoing skin surgery were divided into low risk and high-risk groups, in terms of abnormal scarring, and randomized to receive silicone gel sheets 48 hours after surgery. Silicone gel sheets were effective in preventing abnormal scars in 39% of the high-risk group who used the sheets vs 71% of those in the high-risk group who did not apply them.[42] In another randomized control trial, silicone gel was applied to median sternotomy wounds. Although the majority of subjects developed hypertrophic scars, scar scores were significantly better on the silicone gel treated group.[43] Conversely, a study by Sakuraba et al demonstrated that by applying a silicone gel sheet to median sternotomy wounds 2 weeks after surgery, and replacing it every 4 weeks for 24 weeks prevented the formation of a keloid scar at 24 weeks post-op.[44] A study in Korean subjects studied the effect

of silicone gel sheeting on normal surgical scars and showed improvement in pigmentation, vascularity, and height of scar in the silicone gel group at the 3-month follow up.[45]

A newly developed silicone gel has proven to be a highly effective treatment for a series of cases including post-procedure healing after fractional CO2 laser treatment where skin debris was exfoliated after only 3-5 days. An observational study done on 105 subjects showed re-epithelialization as early as 7 days post procedure in comparison to healing times of standard post treatment care. The silicone gel decreased post procedure burning sensation, erythema, and superficial skin temperature.[46] In addition to post-laser treatment, the SG has been used on non-healing scalp wounds, and on a case of a 6 month old with a scar caused by third degree burns.[47,48] All cases resulted in beneficial outcomes, with shorter recovery times, and soothing effects. Applying the silicone gel on chronic non-healing wounds resulted in induced re-epithelialization after 2 weeks.[47]

Treatment With Lasers and Light Energy Devices

Hypertrophic and Keloid Scars

Various lasers have been used to treat hypertrophic scars and keloids. The majority of studies have been done using the 595-pulsed dye laser (PDL).[49] This device is typically known for its capability to reduce erythema; however it has also been shown to reduce scar volume and to improve scar texture. Early scar intervention with the PDL can control angiogenesis and minimize the extent of scarring.[50] It has been shown to decrease TGF-B expression, fibroblast proliferation, induce matrix metalloproteinases (MMP), and collagen type III deposition.[1,3,51,52] A case series confirming the efficacy of PDL in combination with intralesional corticosteroids proved the efficacy of this laser in treating breast reduction surgery scars.[53] PDL can be considered as first- or second-line light therapy for erythematous immature hypertrophic scars and linear hypertrophic scars. It can also be used as second-line therapy for severely pruritic and erythematous keloids. Side effects include predominantly transient purpura, blistering, and crusting. Recently the 1064 Nd:YAG laser has been evaluated in the treatment of hypertrophic scars. Most studies reveal high recurrence rates, especially with respect to keloids. However, one study of 22 Japanese subjects with keloids or hypertrophic scars, demonstrated efficacy of this laser. Nonetheless, the efficacy decreased with thickness of the scar. The authors indicated it would be best for recent scars or thinner hypertrophic scars.[3] Additionally, a randomized split-scar study was done on twenty subjects with hypertrophic scars, half of the scar was treated with the 595 nm PDL, while the other half was treated with the 1064nm Nd:YAG laser. There was no statistical difference between the two modalities at one month follow up.[54]

Burn scars and wounds have mostly shown to respond to both PDL and ablative fractional devices and have shown the greatest benefit for these subjects. Ablative fractional devices can help release skin contractures in burn wounds and allow for improved range of motion for these subjects. Fractional ablative lasers have also been shown to provide a better outcome in comparison to non-ablative fractional resurfacing lasers, and a better safety profile when compared to their traditional ablative counterparts.[55–60] Ten subjects with hypertrophic burn scars were treated with a single treatment of fractional CO2 ablative laser. Quality of life, scar firmness, and texture all improved over the course of 6 months.[60]

Atrophic Scars

Although full field ablative high energy CO2 lasers were historically the mainstay treatment for atrophic scars, fractional devices, such as fractional CO2, Er:YAG lasers, and even the PDL, have largely replaced this modality.[61,62] Fractional Er:YAG lasers have been shown to improve color, texture, thickness, irregularity, and overall subject satisfaction when compared to fully ablative Er:YAG treatment.[63,64] Fractionated lasers are safer to use in a wide range of skin types. They have been shown to be more useful for boxcar or rolling scars, and not as efficacious with ice-pick scars. A retrospective, single-center study was performed on atrophic acne scars, burn scars, or traumatic scars with a non-ablative, fractional (NAFL) 1550-nm Erbium glass laser, with high-energy parameters, at 4-week interval for 4-8 sessions. Atrophic acne scars had the best outcomes; other types of scars didn't respond as well.[4]

Recently, other devices have been evaluated for the treatment of atrophic scars, mainly acne scars. These can be classified as non-ablative, non-fractional devices. Among these newest modalities are the 1319-nm pulsed, the 1320-nm Nd:YAG, and the 1450-nm diode lasers, which have all been used to treat posttraumatic facial scars.[54,65–68] In addition a picosecond laser using a photomechanical approach has been studied in the treatment of facial acne scars. In this study, Brauer et al treated 20 subjects with acne scars, using a 755-nm picosecond laser. Subjects ranged from being satisfied to extremely satisfied with regards to improvement in appearance and texture of their scars. Three-dimensional analysis demonstrated a 24.3% improvement in scar volume. Furthermore, histologic analysis revealed increased density of elastic fibers, and an increase in dermal collagen and mucin. Results were noted to be comparable to that of fractional ablative laser treatments.[69]

SRT

Superficial radiation therapy is most commonly used on keloids, and usually as an adjunct to post keloid resection.[70] Radiation inhibits new vessel formation and the proliferation of fibroblasts, which results in decreased collagen production.[71]

This mechanism of action was also confirmed by a study from Ji et al. Their data suggested that radiation can prevent the recurrence of keloids by controlling their fibroblast proliferation, and inducing premature cellular senescence by cell toxicity and arresting the cell cycle.[72] Most studies are retrospective and include a combination of keloid excision and post-radiation therapy. A study done with 5 year follow up showed keloids treated with radiation therapy post excision, the probability of relapse at 1 year was 9% and at 5 years was 16%, without any difference in location of the scar.[73] Radiation therapy has also been combined with PRP, and shown success with 95.5% non-recurrence rate at 3 months,[74] and 94% non-recurrence rate at 3 year follow up[72] in two separate studies treating keloids post-excision. Overall, radiation therapy has been used for over 20 years in the treatment of keloids. Today's highly controlled superficial radiation therapy (SRT) devices may lead to even better outcomes.

Radiofrequency (RF)

(RF) is a new technology, which uses electric current instead of light to exert its effects on the skin by producing focal thermal damage to the dermis. Because of its mechanism of action RF may be associated with fewer side effects in comparison to other lasers.[75] RF can be further categorized as monopolar, unipolar, and bipolar RF. Most studies have been undertaken for the treatment of atrophic scars. Monopolar RF has been used to treat active cystic acne scarring. In another study of a bipolar RF device, a 50% improvement was noted in one subject; and a 25-50% improvement was noted in two other subjects.[76] A prospective, open-label clinical trial was undertaken of 12 Caucasian subjects with moderate to severe acne scars. All received 3–5 treatments with bipolar fractionated RF (FRF). 50% of subjects were satisfied and 50% reported to be very satisfied with the treatment.[77] There have been various studies done on Asian skin (Japanese and Korean), showing moderate to significant improvement, with both subjective and objective assessment percentage increases in appearance at 3-month follow up. However severe acne scars did not improve in one of the studies; authors hypothesized this could be secondary to inadequate treatment intervals.[78,79] A multicenter clinical trial involving Asian and Caucasian subjects using bipolar RF treatment reported similar improvements in both ethnicities, with 40% in acne scar improvement, as well as improvements in pore and skin texture, with no adverse effects.[80] Rongsaard and Rummaneethorn compared fractional bipolar RF device to an erbium-doped non-ablative 1550nm laser treating atrophic acne scars in skin types II-IV in a split face study. Each subject received three treatments at 4-week intervals; results comparing both cheeks were not statistically different.[81,82] A composite study reviewing 15 articles found that there are many small studies showing promising results for the use of FRF on acne scars, however the author concluded there is a need for larger studies comparing RF to established procedures such as ablative and non-ablative lasers.[80] Microneedle RF and bipolar RF seem to offer the best treatment outcomes for atrophic acne scarring.[83]

SUMMARY AND CONCLUSIONS

Treatment for scarring be it hypertrophic or atrophic scars remains a challenge. Every scar should be considered unique, and each scar may require a customized approach, where various modalities might need to be employed to reach the best outcome. To date there are various therapeutic options for scar management. This paper describes the myriad of options available to patients and physicians, ranging from non-invasive to more invasive light-based energy sources. Many treatment options may lead to improvement with minimal risk of complications.

Based on papers reviewed and recent scar guidelines, treatment should be attempted with silicone gel, PDL, 1064 Nd:YAG, and CO2 or Erbium: YAG lasers for more hypertrophic and chronic burn scars, mostly concentrating on the use of fractional lasers which carry a lesser side effect profile. Atrophic scars on the other hand, seem to respond best to numerous modalities, of which fractional ablative and non-ablative lasers as well as radiofrequency seem to be the most effective. The newest additions to the armamentarium are PMMA collagen fillers, among other available filler agents. All the above treatments can be coupled with other treatments such as PRP, Vitamin C, intralesional corticosteroids, or chemical peels to potentially increase their effectiveness. For those patients looking for less invasive options, and whose skin types prevent them from being treated with some of the aforementioned modalities, microneedling and or radiofrequency should be considered. It is the author's opinion that combination treatments yield better overall results.

DISCLOSURES

The authors have no conflicts.

REFERENCES

1. Alster T. Laser scar revision: comparison study of 585-nm pulsed dye laser with and without intralesional corticosteroids. *Dermatol Surg.* 2003;29(1):25-29. http://www.ncbi.nlm.nih.gov/pubmed/12534508. Accessed December 16, 2017.
2. Werschler WP, Few JW, Jacob CI et al. Advancing the Care of Post-Acne Scarring: Expert Insights Into New Treatment Options. *J Drugs Dermatol.* 1461;15(5):518-525. http://jddonline.com/articles/dermatology/S1545961616P0518X/2. Accessed December 16, 2017.
3. Akaishi S, Koike S, Dohi T, Kobe K, Hyakusoku H, Ogawa R. Nd:YAG Laser Treatment of Keloids and Hypertrophic Scars. *Eplasty.* 2012;12:e1. http://www.ncbi.nlm.nih.gov/pubmed/22259645. Accessed December 16, 2017.
4. Gokalp H. Evaluation of nonablative fractional laser treatment in scar reduction. *Lasers Med Sci.* 2017;32(7):1629-1635. doi:10.1007/s10103-017-2303-x.
5. Alam M, Han S, Pongprutthipan M, et al. Efficacy of a needling device for the treatment of acne scars. *JAMA Dermatology.* 2014;150(8):844. doi:10.1001/jamadermatol.2013.8687.
6. Camirand A, Doucet J. Needle dermabrasion. *Aesthetic Plast Surg.* 21(1):48-51. http://www.ncbi.nlm.nih.gov/pubmed/9204168. Accessed December 16, 2017.
7. Fabbrocini G, Fardella N, Monfrecola A, Proietti I, Innocenzi D. Acne scarring

treatment using skin needling. *Clin Exp Dermatol.* 2009;34(8):874-879. doi:10.1111/j.1365-2230.2009.03291.x.
8. Fabbrocini G, De Vita V, Monfrecola A, et al. Percutaneous collagen induction: an effective and safe treatment for post-acne scarring in different skin phototypes. *J Dermatolog Treat.* 2014;25(2):147-152. doi:10.3109/09546634.2012.742949.
9. Majid I. Microneedling therapy in atrophic facial scars: an objective assessment. *J Cutan Aesthet Surg.* 2009;2(1):26-30. doi:10.4103/0974-2077.53096.
10. Dogra S, Yadav S, Sarangal R. Microneedling for acne scars in Asian skin type: an effective low cost treatment modality. *J Cosmet Dermatol.* 2014;13(3):180-187. doi:10.1111/jocd.12095.
11. Cachafeiro T, Escobar G, Maldonado G, Cestari T, Corleta O. Comparison of nonablative fractional erbium laser 1,340 nm and microneedling for the treatment of atrophic acne scars: a randomized clinical trial. *Dermatol Surg.* 2016;42(2):232-241. doi:10.1097/DSS.0000000000000597.
12. Leheta T, El Tawdy A, Abdel Hay R, Farid S. Percutaneous collagen induction versus full-concentration trichloroacetic acid in the treatment of atrophic acne scars. *Dermatol Surg.* 2011;37(2):207-216. doi:10.1111/j.1524-4725.2010.01854.x.
13. Ibrahim MK, Ibrahim SM, Salem AM. Skin microneedling plus platelet-rich plasma versus skin microneedling alone in the treatment of atrophic post acne scars: a split face comparative study. *J Dermatolog Treat.* September 2017:1-6. doi:10.1080/09546634.2017.1365111.
14. Fabbrocini G, De Vita V, Pastore F, et al. Combined use of skin needling and platelet-rich plasma in acne scarring treatment. *Cosmet Dermatology.* 2011.
15. Asif M, Kanodia S, Singh K. Combined autologous platelet-rich plasma with microneedling verses microneedling with distilled water in the treatment of atrophic acne scars: a concurrent split-face study. *J Cosmet Dermatol.* 2016. doi:10.1111/jocd.12207.
16. Chawla S. Split face comparative study of microneedling with prp versus microneedling with vitamin c in treating atrophic post acne scars. *J Cutan Aesthet Surg.* 2014;7(4):209-212. doi:10.4103/0974-2077.150742.
17. Nofal E, Helmy A, Nofal A, Alakad R, Nasr M. Platelet-rich plasma versus CROSS technique with 100% trichloroacetic acid versus combined skin needling and platelet rich plasma in the treatment of atrophic acne scars: a comparative study. *Dermatol Surg.* 2014;40(8):864-873. doi:10.1111/dsu.0000000000000091.
18. Sharad J. Combination of microneedling and glycolic acid peels for the treatment of acne scars in dark skin. *J Cosmet Dermatol.* 2011;10(4):317-323. doi:10.1111/j.1473-2165.2011.00583.x.
19. Rana S, Mendiratta V, Chander R. Efficacy of microneedling with 70% glycolic acid peel vs microneedling alone in treatment of atrophic acne scars-A randomized controlled trial. *J Cosmet Dermatol.* 2017;16(4):454-459. doi:10.1111/jocd.12377.
20. Garg S, Baveja S. Combination therapy in the management of atrophic acne scars. *J Cutan Aesthet Surg.* 2014;7(1):18. doi:10.4103/0974-2077.129964.
21. Šuca H, Zajíček R, Vodsloň Z. Microneedling - a form of collagen induction therapy - our first experiences. *Acta Chir Plast.* 2017;59(1):33-36. http://www.ncbi.nlm.nih.gov/pubmed/28869385. Accessed December 16, 2017.
22. Aust MC, Fernandes D, Kolokythas P, Kaplan HM, Vogt PM. Percutaneous Collagen induction therapy: an alternative treatment for scars, wrinkles, and skin laxity. *Plast Reconstr Surg.* 2008;121(4):1421-1429. doi:10.1097/01.prs.0000304612.72899.02.
23. Zhibo X, Miaobo Z. Intralesional botulinum toxin type a injection as a new treatment measure for keloids. *Plast Reconstr Surg.* 2009;124(5):275e-277e. doi:10.1097/PRS.0b013e3181b98ee7.
24. Costa IMC, Costa MC. Microneedling for varicella scars in a dark-skinned teenager. *Dermatol Surg.* 2014;40(3):333-334. doi:10.1111/dsu.12396.
25. Karnik J, Baumann L, Bruce S, et al. A double-blind, randomized, multicenter, controlled trial of suspended polymethylmethacrylate microspheres for the correction of atrophic facial acne scars. *J Am Acad Dermatol.* 2014;71(1):77-83. doi:10.1016/j.jaad.2014.02.034.
26. Halachmi S, Ben Amitai D, Lapidoth M. Treatment of acne scars with hyaluronic acid: an improved approach. *J Drugs Dermatol.* 2013;12(7):e121-3. http://www.ncbi.nlm.nih.gov/pubmed/23884503. Accessed December 16, 2017.
27. Goldberg DJ, Amin S, Hussain M. Acne scar correction using calcium hydroxylapatite in a carrier-based gel. *J Cosmet Laser Ther.* 2006;8(3):134-136. doi:10.1080/14764170600891632.
28. Wollina U, Goldman A. Fillers for the improvement in acne scars. *Clin Cosmet Investig Dermatol.* 2015;8:493. doi:10.2147/CCID.S86478.
29. Barnett JG, Barnett CR. Treatment of acne scars with liquid silicone injections: 30-year perspective. *Dermatol Surg.* 2005;31(11 Pt 2):1542-1549. http://www.ncbi.nlm.nih.gov/pubmed/16416636. Accessed December 16, 2017.
30. Fulton J, Caperton C. The optimal filler: immediate and long-term results with emulsified silicone (1,000 centistokes) with cross-linked hyaluronic acid. *J Drugs Dermatol.* 2012;11(11):1336-1341. http://www.ncbi.nlm.nih.gov/pubmed/23135085. Accessed December 16, 2017.
31. Khan F, Richards K, Rashid RM. Hyaluronic acid filler for a depressed scar. *Dermatol Online J.* 2012;18(5):15. http://www.ncbi.nlm.nih.gov/pubmed/22630585. Accessed December 16, 2017.
32. Richards KN, Rashid RM. Twenty-four-month persistence of hyaluronic acid filler for an atrophic scar. *J Cosmet Dermatol.* 2011;10(4):311-312. doi:10.1111/j.1473-2165.2011.00589.x.
33. Hasson A, Romero WA. Treatment of facial atrophic scars with Esthélis, a hyaluronic acid filler with polydense cohesive matrix (CPM). *J Drugs Dermatol.* 2010;9(12):1507-1509. http://www.ncbi.nlm.nih.gov/pubmed/21120258. Accessed December 16, 2017.
34. Choksi AN, Orringer JS. Linear morphea-induced atrophy treated with hyaluronic acid filler injections. *Dermatol Surg.* 2011;37(6):880-883. doi:10.1111/j.1524-4725.2011.02030..x.
35. Kasper DA, Cohen JL, Saxena A, Morganroth GS. Fillers for postsurgical depressed scars after skin cancer reconstruction. *J Drugs Dermatol.* 2008;7(5):486-487.http://www.ncbi.nlm.nih.gov/pubmed/18505145. Accessed December 16, 2017.
36. Gassner HG, Sherris DA, Otley CC. Treatment of facial wounds with botulinum toxin A improves cosmetic outcome in primates. *Plast Reconstr Surg.* 2000;105(6):1948-53-5.http://www.ncbi.nlm.nih.gov/pubmed/10839391. Accessed December 16, 2017.
37. Gassner HG, Brissett AE, Otley CC, et al. Botulinum toxin to improve facial wound healing: A prospective, blinded, placebo-controlled study. *Mayo Clin Proc.* 2006;81(8):1023-1028. doi:10.4065/81.8.1023.
38. Wilson AM. Use of botulinum toxin type a to prevent widening of facial scars. *Plast Reconstr Surg.* 2006;117(6):1758-1766. doi:10.1097/01.prs.0000209944.45949.d1.
39. Ziade M, Domergue S, Batifol D, et al. Use of botulinum toxin type A to improve treatment of facial wounds: a prospective randomised study. *J Plast Reconstr Aesthet Surg.* 2013;66(2):209-214. doi:10.1016/j.bjps.2012.09.012.
40. Mustoe TA. Evolution of silicone therapy and mechanism of action in scar management. *Aesthetic Plast Surg.* 2008;32(1):82-92. doi:10.1007/s00266-007-9030-9.
41. Meaume S, Le Pillouer-Prost A, Richert B, Roseeuw D, Vadoud J. Management of scars: updated practical guidelines and use of silicones. *Eur J Dermatol.* 24(4):435-443. doi:10.1684/ejd.2014.2356.
42. Gold MH, Foster TD, Adair MA, Burlison K, Lewis T. Prevention of hypertrophic scars and keloids by the prophylactic use of topical silicone gel sheets following a surgical procedure in an office setting. *Dermatol Surg.* 2001;27(7):641-644. http://www.ncbi.nlm.nih.gov/pubmed/11442615. Accessed December 16, 2017.
43. Chan KY, Lau CL, Adeeb SM, Somasundaram S, Nasir-Zahari M. A randomized, placebo-controlled, double-blind, prospective clinical trial of silicone gel in prevention of hypertrophic scar development in median sternotomy wound. *Plast Reconstr Surg.* 2005;116(4):1013-20-2. http://www.ncbi.nlm.nih.gov/pubmed/16163087. Accessed December 16, 2017.
44. Sakuraba M, Takahashi N, Akahoshi T, Miyasaka Y, Suzuki K. Use of silicone gel sheets for prevention of keloid scars after median sternotomy. *Surg Today.* 2011;41(4):496-499. doi:10.1007/s00595-010-4265-5.
45. Rhee S-H, Koh S-H, Lee D-W, Park B-Y, Kim Y-O. Aesthetic Effect of Silicone Gel on Surgical Scars in Asians. *J Craniofac Surg.* 2010;21(3):706-710. doi:10.1097/SCS.0b013e3181d83fec.
46. Sandhofer M, Schauer P. The safety, efficacy, and tolerability of a novel silicone gel dressing following dermatological surgery. *Skinmed.* 10(6):S1-7. http://www.ncbi.nlm.nih.gov/pubmed/23346665. Accessed January 30, 2018.
47. Marini L, Odendaal D, Smirnyi S. Importance of scar prevention and treatment-an approach from wound care principles. *Dermatol Surg.* 2017;43 Suppl 1:S85-S90. doi:10.1097/DSS.0000000000001001.
48. Monk EC, Benedetto EA, Benedetto A V. Successful treatment of nonhealing scalp wounds using a silicone gel. *Dermatol Surg.* 2014;40(1):76-79. doi:10.1111/dsu.12366.
49. Alster TS, Handrick C. Laser treatment of hypertrophic scars, keloids, and striae. *Semin Cutan Med Surg.* 2000;19(4):287-292. doi:10.1053/sder.2000.18369.
50. Vrijman C, van Drooge AM, Limpens J, et al. Laser and intense pulsed light therapy for the treatment of hypertrophic scars: a systematic review. *Br J Dermatol.* 2011;165(5):934-942. doi:10.1111/j.1365-2133.2011.10492.x.
51. Alster TS, Williams CM. Treatment of keloid sternotomy scars with 585 nm flashlamp-pumped pulsed-dye laser. *Lancet (London, England).* 1995;345(8959):1198-1200. http://www.ncbi.nlm.nih.gov/pubmed/7739306. Accessed December 16, 2017.

52. Dierickx C, Goldman MP, Fitzpatrick RE. Laser treatment of erythematous/hypertrophic and pigmented scars in 26 patients. *Plast Reconstr Surg.* 1995;95(1):84-90-2.http://www.ncbi.nlm.nih.gov/pubmed/7809272. Accessed December 16, 2017.
53. Goppold A, Kaune KM, Buhl T, Schön MP, Zutt M. 595nm pulsed dye laser combined with intralesional corticosteroids in hypertrophic symptomatic scars following breast reduction surgery. *Eur J Dermatol.* 21(2):262-263. doi:10.1684/ejd.2010.1230.
54. Al-Mohamady AE-SAE-H, Ibrahim SMA, Muhammad MM. Pulsed dye laser versus long-pulsed Nd:YAG laser in the treatment of hypertrophic scars and keloid: A comparative randomized split-scar trial. *J Cosmet Laser Ther.* 2016;18(4):208-212. doi:10.3109/14764172.2015.1114648.
55. Willows BM, Ilyas M, Sharma A. Laser in the management of burn scars. *Burns.* 2017;43(7):1379-1389. doi:10.1016/j.burns.2017.07.001.
56. Anderson RR, Donelan MB, Hivnor C, et al. Laser treatment of traumatic scars with an emphasis on ablative fractional laser resurfacing: consensus report. *JAMA dermatology.* 2014;150(2):187-193. doi:10.1001/jamadermatol.2013.7761.
57. Oh BH, Hwang YJ, Lee YW, Choe YB, Ahn KJ. Skin characteristics after fractional photothermolysis. *Ann Dermatol.* 2011;23(4):448. doi:10.5021/ad.2011.23.4.448.
58. Kim HS, Lee JH, Park YM, Lee JY. Comparison of the effectiveness of nonablative fractional laser versus ablative fractional laser in thyroidectomy scar prevention: A pilot study. *J Cosmet Laser Ther.* 2012;14(2):89-93. doi:10.3109/14764172.2012.672746.
59. Hultman CS, Friedstat JS, Edkins RE, Cairns BA, Meyer AA. Laser resurfacing and remodeling of hypertrophic burn scars: the results of a large, prospective, before-after cohort study, with long-term follow-up. *Ann Surg.* 2014;260(3):519-29-32. doi:10.1097/SLA.0000000000000893.
60. Poetschke J, Dornseifer U, Clementoni MT, et al. Ultrapulsed fractional ablative carbon dioxide laser treatment of hypertrophic burn scars: evaluation of an in-patient controlled, standardized treatment approach. *Lasers Med Sci.* 2017;32(5):1031-1040. doi:10.1007/s10103-017-2204-z.
61. Alster TS, West TB. Resurfacing of atrophic facial acne scars with a high-energy, pulsed carbon dioxide laser. *Dermatol Surg.* 1996;22(2):151-4-5. http://www.ncbi.nlm.nih.gov/pubmed/8608377. Accessed December 16, 2017.
62. You H-J, Kim D-W, Yoon E-S, Park S-H. Comparison of four different lasers for acne scars: resurfacing and fractional lasers. *J Plast Reconstr Aesthet Surg.* 2016;69(4):e87-95. doi:10.1016/j.bjps.2015.12.012.
63. Kwon SD, Kye YC. Treatment of scars with a pulsed Er:YAG laser. *J Cutan Laser Ther.* 2000;2(1):27-31. http://www.ncbi.nlm.nih.gov/pubmed/11446088. Accessed December 16, 2017.
64. Tidwell WJ, Owen CE, Kulp-Shorten C, Maity A, McCall M, Brown TS. Fractionated Er:YAG laser versus fully ablative Er:YAG laser for scar revision: Results of a split scar, double blinded, prospective trial. *Lasers Surg Med.* 2016;48(9):837-843. doi:10.1002/lsm.22562.
65. Rogachefsky AS, Hussain M, Goldberg DJ. Atrophic and a mixed pattern of acne scars improved with a 1320-nm Nd:YAG laser. *Dermatol Surg.* 2003;29(9):904-908. http://www.ncbi.nlm.nih.gov/pubmed/12930330. Accessed December 16, 2017.
66. Tanzi EL, Alster TS. Comparison of a 1450-nm diode laser and a 1320-nm Nd:YAG laser in the treatment of atrophic facial scars: a prospective clinical and histologic study. *Dermatol Surg.* 2004;30(2 Pt 1):152-157. http://www.ncbi.nlm.nih.gov/pubmed/14756642. Accessed December 16, 2017.
67. Jih MH, Friedman PM, Kimyai-Asadi A, Goldberg LH. Successful treatment of a chronic atrophic dog-bite scar with the 1450-nm diode laser. *Dermatol Surg.* 2004;30(8):1161-1163. doi:10.1111/j.1524-4725.2004.30347.x.
68. Wada T, Kawada A, Hirao A, Sasaya H, Oiso N. Efficacy and safety of a low-energy double-pass 1450-nm diode laser for the treatment of acne scars. *Photomed Laser Surg.* 2012;30(2):107-111. doi:10.1089/pho.2011.3063.
69. Brauer JA, Kazlouskaya V, Alabdulrazzaq H, et al. Use of a picosecond pulse duration laser with specialized optic for treatment of facial acne scarring. *JAMA Derm.* 2015;151(3):278-284. doi:10.1001/jamadermatol.2014.3045.
70. Norris JE. Superficial x-ray therapy in keloid management: a retrospective study of 24 cases and literature review. *Plast Reconstr Surg.* 1995;95(6):1051-1055. http://www.ncbi.nlm.nih.gov/pubmed/7732115. Accessed December 16, 2017.
71. Reish RG, Eriksson E. Scar Treatments: Preclinical and Clinical Studies. *J Am Coll Surg.* 2008;206(4):719-730. doi:10.1016/j.jamcollsurg.2007.11.022.
72. Ji J, Tian Y, Zhu Y, et al. Ionizing irradiation inhibits keloid fibroblast cell proliferation and induces premature cellular senescence. *J Dermatol.* 2015;42(1):56-63. doi:10.1111/1346-8138.12702.
73. Ragoowansi R, Cornes PGS, Moss AL, Glees JP. Treatment of keloids by surgical excision and immediate postoperative single-fraction radiotherapy. *Plast Reconstr Surg.* 2003;111(6):1853-1859. doi:10.1097/01.PRS.0000056869.31142.DE.
74. Jones ME, Hardy C, Ridgway J. Keloid management: A retrospective case review on a new approach using surgical excision, platelet-rich plasma, and in-office superficial photon x-ray radiation therapy. *Adv Skin Wound Care.* 2016;29(7):303-307. doi:10.1097/01.ASW.0000482993.64811.74.
75. Lolis MS, Goldberg DJ. Radiofrequency in cosmetic dermatology: a review. *Dermatologic Surg.* 2012;38(11):1765-1776. doi:10.1111/j.1524-4725.2012.02547.x.
76. Montesi G, Calvieri S, Balzani A, Gold MH. Bipolar radiofrequency in the treatment of dermatologic imperfections: clinicopathological and immunohistochemical aspects. *J Drugs Dermatol.* 2007;6(9):890-896. http://www.ncbi.nlm.nih.gov/pubmed/17941360. Accessed December 16, 2017.
77. Verner I. Clinical evaluation of the efficacy and safety of fractional bipolar radiofrequency for the treatment of moderate to severe acne scars. *Dermatol Ther.* 2016;29(1):24-27. doi:10.1111/dth.12275.
78. Kaminaka C, Uede M, Matsunaka H, Furukawa F, Yamamoto Y. Clinical studies of the treatment of facial atrophic acne scars and acne with a bipolar fractional radiofrequency system. *J Dermatol.* 2015;42(6):580-587. doi:10.1111/1346-8138.12864.
79. Kim JE, Lee HW, Kim JK, et al. Objective evaluation of the clinical efficacy of fractional radiofrequency treatment for acne scars and enlarged pores in asian skin. *Dermatologic Surg.* 2014;40(9):988-995. doi:10.1097/01.DSS.0000452625.01889.c3.
80. Forbat E, Al-Niaimi F. Fractional radiofrequency treatment in acne scars: Systematic review of current evidence. *J Cosmet Laser Ther.* 2016;18(8):442-447. doi:10.1080/14764172.2016.1225964.
81. Rongsaard N, Rummaneethorn P. Comparison of a fractional bipolar radiofrequency device and a fractional erbium-doped glass 1,550-nm device for the treatment of atrophic acne scars: a randomized split-face clinical study. *Dermatol Surg.* 2014;40(1):14-21. doi:10.1111/dsu.12372.
82. Dunbar SW, Goldberg DJ. Radiofrequency in cosmetic dermatology: an update. *J Drugs Dermatol.* 2015;14(11):1229-1238. http://www.ncbi.nlm.nih.gov/pubmed/26580871. Accessed December 16, 2017.
83. Simmons BJ, Griffith RD, Falto-Aizpurua LA, Nouri K. Use of radiofrequency in cosmetic dermatology: focus on nonablative treatment of acne scars. *Clin Cosmet Investig Dermatol.* 2014;7:335-339. doi:10.2147/CCID.S74411.

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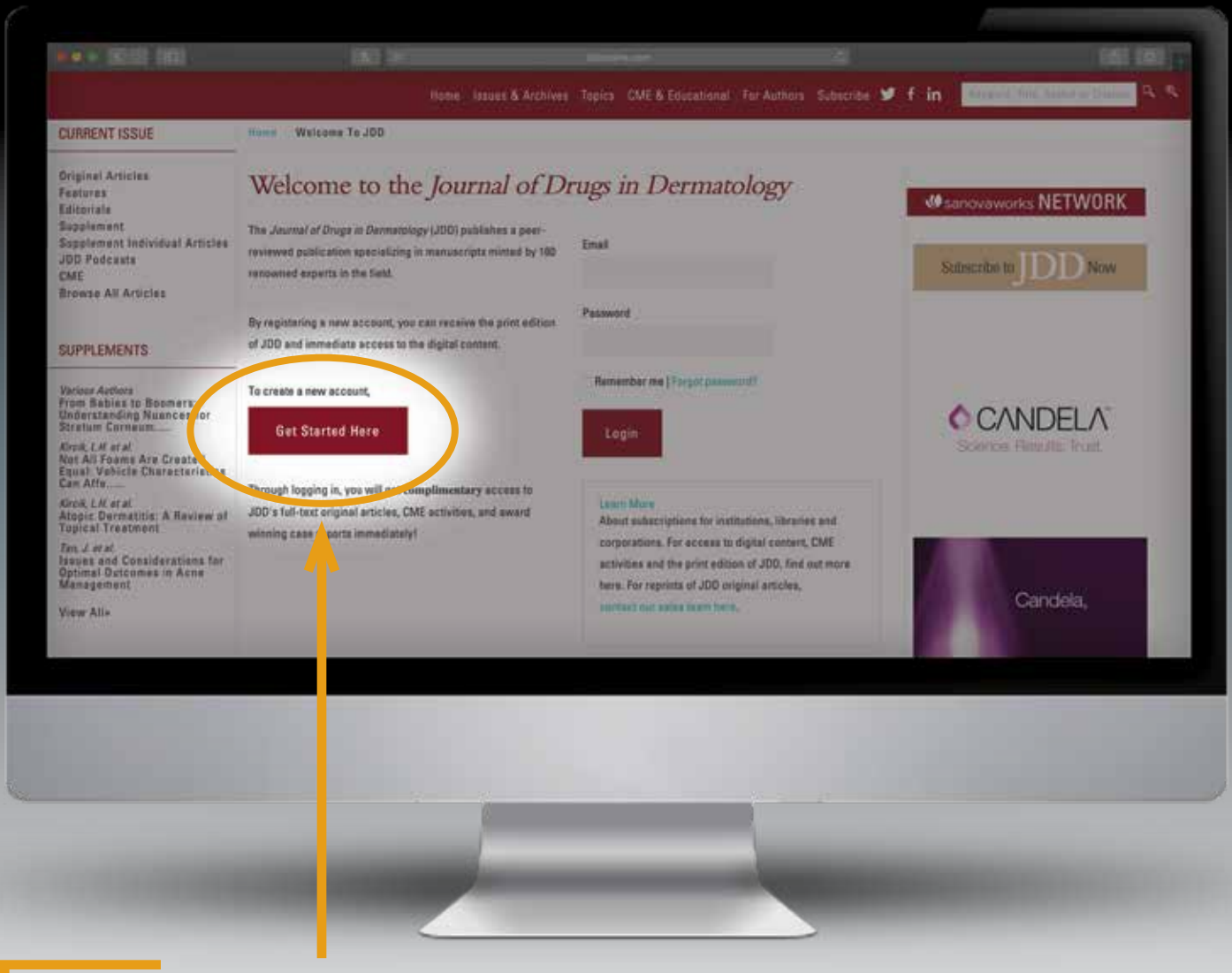

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Validation of Botanical Treatment Efficiency for Adults and Children Suffering from Mild to Moderate Atopic Dermatitis

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ABSTRACT

Objective: The study was conducted to determine the efficiency of the botanicals combination incorporated in the Kamedis Eczema Therapy Cream (the tested product) for adults and children suffering from mild to moderate Atopic Dermatitis.
Design: The study designed as an interventional, multi-center, double-blind, randomized, controlled study.
Setting: Subjects were evenly randomly divided into three treatment groups: tested product, vehicle, and comparator. The vehicle used was the identical tested product without the botanical combination while the comparator was a leading OTC brand in the US market. All three above groups used a similar Kamedis wash for the body and face following by one of the three randomized treatment creams for the affected areas on the face and body.
Participants: One hundred and eight (108) subjects with uncomplicated, stable, mild to moderate atopic dermatitis recruited and qualified for the study; 71 females and 37 males, age 3 to 73.
Measurements: The investigator assessed the severity of each subject using the Investigator Global Assessment (IGA) and affected body surface area (BSA) at each of the visit days 0, 7, 14, and 28.
Results: The tested product demonstrated an improvement in IGA and BSA over the vehicle at every visit across treatment time, proving the validation that the botanical product is much more effective and beneficial than the same product without the botanicals. The tested product as well as the comparator reached exactly the same percentage, 34%, of 'clear' IGA subjects of the enrolled subjects, presenting advantage over the vehicle. The BSA improvement comparison analysis of the tested product over the vehicle yielded statistically significant *P* value of 0.0369.
Conclusion: The study results approve and validate that the botanical combination is the key factor for the efficacy and improvement of the AD symptoms within this study population.

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INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease with a lifetime prevalence of 10-20% in children and 1-3% in adults.[1] AD usually starts in early infancy and is typified by pruritus, erythematous papulovesicular lesions, xerosis (dry skin), and lichenification of the skin.[2] In severe cases, intense pruritus (itching) and scratching may lead to secondary infection.[1] AD is usually associated with other atopic diseases as asthma and other allergic reactions.

Without an understanding of the complex and multifactorial pathogenesis of AD, treatment can be difficult and often unsatisfactory. When the structural integrity of the outer skin layer is compromised by injuring the aggregation of keratin filaments supporting the skin barrier, as in a mutation, pathogens, or allergens, toxins are able to pass through the hyperpermeable barrier, and create chronic inflammation.[3-5]

Currently, there is no cure for the disease. Management of AD focuses on controlling the severity and duration of AD symptoms. In mild to moderate cases, treatment includes reduction of exposure to triggering factors and topical application of emollients and steroid-free barrier creams as well as topical corticosteroids. In more severe cases, the condition is often treated with systemic corticosteroids and immunosupressive

agents such as methotrexate, cyclosporin, and azathioprine. Due to their potential side effects, the last-mentioned treatments are not recommended for long-term use, especially in young children.[6-11]

Kamedis Eczema Therapy Cream (the tested product) is a barrier-based non-steroidal homeopathic formula emulsion based on botanicals, which is especially formulated to manage the symptoms of various dermatoses such as atopic dermatitis, contact dermatitis, nummular dermatitis, hand dermatitis, radiation dermatitis, and burns. This emulsion acts by adhering to the injured tissue, eliminating exogenous and contaminated factors related to dermatitis, protecting the skin from further irritation, and maintaining a moist skin environment.

Kamedis Eczema Therapy Cream developed to include a combination of six botanicals: Rheum Palmatum, Sanguisorba Officinalis, Ailanthus Altissima, Scutellaria Baicalensis, Cnidium Monnieri, and Glycyrrhiza Glabra with diluted sulphur. The botanicals are known from the literature to have significant anti-inflammatory and anti-allergic activities that assist in the relief of AD symptoms.[12-13] The purpose of this research was to validate the effectiveness of the botanicals for the treatment of AD. In order to meet this goal, a vehicle product formula was developed to be verified in comparison with the tested product. The vehicle product was designed to include all ingredients in the same relevant percentages as in the tested product without the combination of the six mentioned botanicals.

The analytical evaluation in this research was performed by using both Investigator Global Assessment (IGA) scale and the body surface area (BSA) for AD. The IGA score is based on the severity of erythema, infiltration, population, and oozing, and is selected by an overall appearance of the lesions at a given time point. The involved surface area that composed the total BSA in AD is a crucial factor in grading the degree of severity. The BSA is presented as a percentage index for the involved lesional features and locations.[14]

METHODS

One hundred and eight (108) subjects with uncomplicated, stable, mild to moderate atopic dermatitis were recruited and qualified for the study, 71 female and 37 male, ages 3 to 73.

The study was designed as an interventional, multi-center, double-blind, randomized, controlled study. The study was conducted under Institutional Review Board (Integreview IRB, Austin, TX), a signed informed consent form and a photographic release form were obtained from each subject prior to performing any study procedure.

Subjects enrolled according to the inclusion criteria with 2 years of age and older, mild to moderate atopic dermatitis that meet the Hanifin and Rajka criteria and was stable for 7 days. Pregnant women were not included in the study and a negative urine pregnancy test result was required for each of the visits of every female subject with childbearing potential. The exclusion criteria list included another dermatological disease that could interfere with clinical evaluation, previous subject history of allergy to cosmetic products or specific relevant ingredients, treatment by topical or systemic immunomodulators for atopic dermatitis or steroids 14 days prior to the beginning of the study, treatment by phototherapy 28 days prior to the beginning of the study, any experimental treatment within 14 days prior to the beginning of the study, and expected extensively sun exposure during the study period.

In the study, subjects were evenly randomly divided into three treatment groups, 36 subjects in total were enrolled for each of the following treatment groups: tested product, vehicle, and comparator. The vehicle used was the tested product without the botanical combination and the comparator was a leading OTC brand in the US market. All three above groups used a similar Kamedis wash for the body and face and one of the three randomized treatment creams for the affected areas on the face and body.

Subjects were requested to apply the treatment product twice daily following Kamedis wash, as per instructions, morning and evening.

The study duration was 28 days (4 weeks), with study visits occurring at baseline (day 0), day7, day 14 and day 28. Subjects underwent facial and body investigator evaluation and AD lesion assessment by dermatologist at each of the visit days. Digital photos were taken of the affected lesions at each visit in one of the study's sites (33 subjects) by a Nikon D-90 camera in a Canfield 3-point head mount with an IntelliFlash system and a consistent f-stop for reproducibility at all time points.

The investigator assessed the severity of each subject using Investigator Global Assessment (IGA) and affected Body Surface Area (BSA) at each of the visit days 0, 7, 14 and 28. The BSA was estimated by assessing the affected percentage of the following body areas: head, trunk, upper limbs and lower limbs for children and adults. For mild to moderate AD, the diagnosed BSA is typically lower than 10%.

For the IGA parameter, the following grading scale was used: 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe, and 5=very severe. During and following the treatment, on days 0, 7, 14, and 28, the subjects completed Dermatology Life Quality Index (DLQI) and by the end of the treatment, on day 28, a sponsor supplied marketing questionnaire, which also provided their comments for the entire experience.

The statistical analysis used a two-way analysis of variance (ANOVA) with visit and treatment/control as main factors and the interaction between them. A significant interaction would mean that the difference between the treatment and the control is not similar across visits. Factors with *P* values smaller than 0.05 are considered as statistically significant. For each parameter, the original scores have been transformed to percentage of improvement by calculating the percentage of increased score comparing to the score measurement of each patient at baseline (day 0).

RESULTS

Of 108 subjects enrolled, 99 subjects completed the study. Nine subjects did not complete the study following the base line (BL) visit due to personal reasons that are not connected to the study. No adverse experiences or events occurred during the course of the trial.

Demographic characteristics of the subjects are presented (Table 1). No significant statistical difference was observed in IGA and BSA characteristics between each of the randomly selected treatments groups in the BL visit (day 0), however, a slight trend of more severe subjects was included in the tested product group comparing to the other two groups (Figure 1).

At each visit, the investigator assessed the subject IGA and BSA. The IGA is presented in severity index score evaluation. The number of subjects reached the 'clear' or '0' score evaluation was counted per each treatment and the clear percentage was calculated out of the total subjects successfully enrolled from for each treatment group (Table 2). The BSA is calculated by the relatively summation of all specific body areas affected percentages from the total body surface affected percentage (Figure 1).

The IGA severity scale parameter was examined by counting all subjects that reached the 'clear' or '0' evaluation index with the relatively percentage among the total number of the examined treatment product enrolled subjects. The tested product as well as the comparator reached exactly the same percentage, 34%, of 'clear' subjects out of the enrolled subjects (Table 2). Both the tested product and the comparator showed a higher percentage of 'clear' subject over the vehicle during the course of the study. The vehicle showed 19% only of 'clear' subjects from the total enrolled with this treatment. Again, showing the effectiveness or the benefit of the botanicals in the treatment of AD. Analysis of the accumulated number of 'clear' and 'almost clear' ('0' and '1' IGA evaluation scores) did not show any significant different between the three treatment products.

The BSA raw data is a decreasing total percentage over time per each of the treatments (Figure 1). The improvement analysis of the BSA total percentage is presented (Figure 2). The

TABLE 1.

Subject Demographic Characteristics	
Characteristic	**Value**
Age Range (years)	3-73 years old
Sex	Women - 71 (66%)
	Men - 37 (34%)
Race	African American - 58 (54%)
	Caucasian - 50 (46%)

FIGURE 1. BSA raw data collected per each visit in weeks duration.

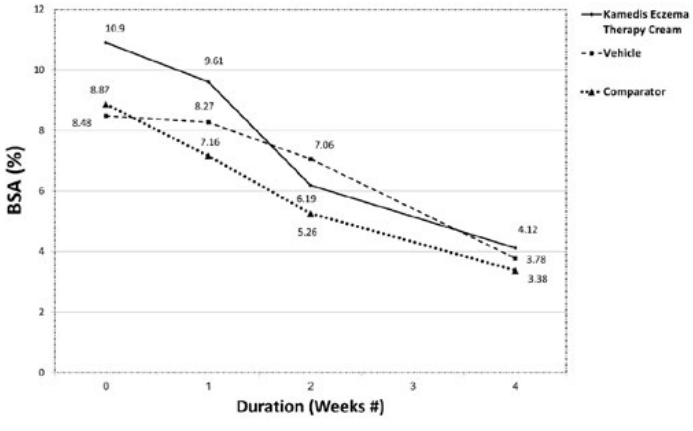
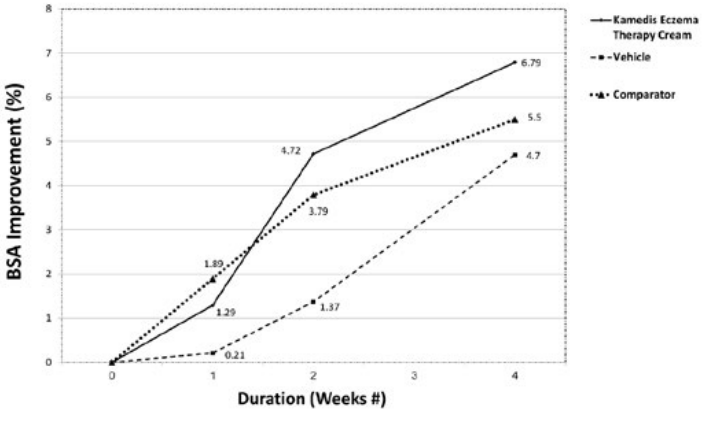


TABLE 2.

Clear Score IGA Percentage of Enrolled Subjects			
Product	**# of 'Clear' Subjects (IGA=0) following 4 weeks of treatment**	**Total # of Subjects who concluded the study**	**Percentage of 'Clear' out of 'Total' (%)**
Kamedis Eczema Therapy Cream	11	32	34
Vehicle	6	32	19
Comparator	12	35	34
Total	**29**	**99**	**29**

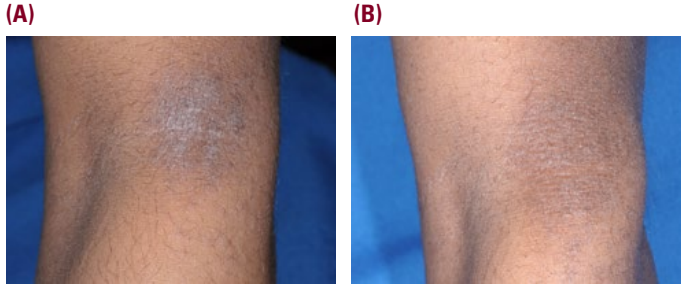
FIGURE 2. BSA improvement per each visit in weeks duration.



total BSA improvement percentage of the enrolled subjects per each treatment was standardized to the BL in order to enable a comparison between the alternative treatments. It should be mentioned that the severity of the enrolled subjects for the tested product was higher in BL comparing to the other two treatments, 10.9% of severity versus 8.48% and 8.87% for the vehicle and the comparator, respectively (see Figure 1). In general, it can be seen that the tested product demonstrated an improvement over the vehicle at every visit across treatment time, proving that the botanical product is much more effective and beneficial than the same product without the botanicals. On day 28 by the end of the treatment duration, the improved BSA with the tested product reached 6.79% versus 4.7% with the vehicle treatment. The tested product maintained its advantage over the vehicle during the course of all visits up to the final visit on day 28. An observed difference in the BSA improvement over the vehicle was achieved after one week (day 7) of treatment (1.29% vs 0.21%) and continued to expand over the vehicle after the following week (day 14) with 4.72% versus 1.37% until reached the final improvement detected after a month of treatment (day 28). The tested product showed an advantage over the comparator on week 2 (day 14) and the end of the treatment on week 4 (day 28). The tested product achieved 4.72% improvement on week 2 and 6.79% on week 4 versus 3.79% on week 2 and 5.5% on week 4 for the comparator. On week 1 (day 7), the comparator showed an advantage over the tested product, 1.89% of improvement versus 1.29% of the tested product. This preliminary trend changed over time keeping the tested product advantage until the end of the treatment. A comparison between the tested product and the vehicle BSA improvement yielded *P* value of 0.0369, which is statistically significant, therefore validates the botanical combination is a factor in efficacy and improvement of AD symptoms within this study population. *P* value of 0.0655 was achieved on week 4 for the tested product compared to both the vehicle and comparator alternative treatments.

In addition to the measured and calculated parameters, clear improvement was visually evident following 4 treatment weeks of the tested product (Figure 3a and 3b).

FIGURE 3. Visual improvement after 28 days (A) before treatment on day 0 (B) following treatment on day 28.



DISCUSSION

The main purpose of the presented study was to evaluate the efficacy of the botanicals that are the major novelty of the tested product for the treatment of AD. The tested product is based on 6% herbal botanical ingredients with anti-inflammatory and anti-bacterial activity such as the Rheum Palmatum, Sanguisorba Officinalis, Ailanthus Altissima, Scutellaria Baicalensis, Cnidium Monnieri, and Glycyrrhiza Glabra. The Rheum Palmatum and Scutellaria baicalensis also show anti-oxidative activity, which may assist in improving and relieving the severity of eczema lesions. The botanicals were selected due to their characteristics and were chosen out of hundreds of botanicals due to thorough literature review that was followed by in vitro studies on artificial skin model.

In order to examine the option of leveraging the treatment by the usage of the botanicals, a vehicle product was developed. The vehicle product was designed to include all ingredients in the same ratio as in the tested product excluding the botanicals. The tested product was found to be much more effective and very valuable in improving the AD severity and evaluated symptoms compared to the vehicle at every evaluated visit until the end of the treatment. The result was validated by both IGA index and BSA improvement calculation for the entire population that was tested in this multi-center study. This means that the botanicals demonstrated better results over time, especially between 2 to 4 weeks, in which the results become more visible and can be easily evaluated. The BSA improvement following the 4 weeks of treatment was increased by more than 40% from 4.7% to 6.79% and the IGA by more than 80% from 19% of clear subjects with the vehicle to 34% with the tested product.

The comparator was added to the study in order to examine the comparative effect of an OTC leading product in the US using colloidal oatmeal for the treatment of AD. It could be easily seen that the comparator was found to be much better than the vehicle, however less effective than the tested product. The IGA analysis of the comparator showed similar results to the tested product with an advantage comparing to the vehicle results. The BSA improvement analysis of the comparator changed its trend after the first week of treatment. Once the first week of treatment showed an early improvement with the comparator with regards to the tested product, the following visits at 2 weeks and 4 weeks showed a different trend. While the comparator kept increasing its improvement, the tested product improved more and showed better effectivity in terms of BSA improvement percentages.

Over the years, numerous randomized double-blinded studies[15-17] were presented and published. In some of them, a vehicle was used for comparison purposes, while in others a comparator product was used. None of these studies used the

vehicle tested formula in order to validate the efficacy of the exclusively botanicals combination that is the major and most important component of the final formula. This is the innovatively approach and the advantage of this study. While the vehicle emollient yielded good results in terms of skin barrier, the tested product usage managed to present statistically significant validation effect of the botanical complex incorporation.

DISCLOSURES

Z.D. Draelos received a research grant from Kamedis to conduct the research presented. M. Traub serves on the Medical Advisory Board for Kamedis and performed clinical research for this project. M.H. Gold performed clinical research for this project. L.J. Green is on the medical advisory board for Kamedis and was a principal investigator in this study. M. Amster has done clinical research functioning as the PI and been compensated by Kamedis, Novartis, Leo, Valeant, UCB, Allergan, Botanix, Biopharmx, Foamix Menlo, and Nielsen Biosciences. D. Barak-Shinar is an employee of Kamedis Ltd, the manufacturer of the Kamedis Eczema Therapy Cream as well as the sponsor of this study. L.H. Kircik has served as an investigator, advisory board member, and consultant for Kamedis. *Financial Support:* This study was wholly funded by Kamedis Ltd.

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REFERENCES

1. Leung DYM, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest.* 2004;113(5): 651-657.
2. Yao TC, Ou LS, Yeh KW, et al. Associations of age, gender, and BMI with prevalence of allergic diseases in children: PATCH study. *J Asthma.* 2011;48(5):503-510.
3. Brook I, Frazier EH, Yeager JK. Microbiology of infected atopic dermatitis. *Int J Dermatol.* 1996;35(11):791-793.
4. Elias PM, Schmuth M. Abnormal skin barrier in the etiopathogenesis of atopic dermatitis. *Curr Opin Allergy Clin Immunol.* 2009;9(5):437-446.
5. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet.* 2006;38(4):441-446.
6. Bjorksten B, Sepp E, Julge K, et al. Allergy development and the intestinal microflora during the first year of life. *J Allergy Clin Immunol.* 2001;108(4):516-520.
7. Faergemann J. Atopic dermatitis and fungi. *Clin Micro Rev.* 2002;15(4):545-563.
8. Saurat JH and Hanifin JM. Understanding atopic dermatitis: pathophysiology and etiology. *J Am Acad Dermatol.* 2001;45 (Suppl. 1):s67-s68.
9. Nomura I, Goleva E, Howell MD, Hamid QA, Ong PY, Hall CF, Darst MA, Gao B, Boguniewicz M, Travers JB, Leung DY. Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. *J Immunol.* 2003;171:3262-3269.
10. Ong PY, Ohtake T, Brandt C, Strickland I, Boguniewicz M, Ganz T, Gallo RL, Leung DY. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med.* 2003;347:1151-1160.
11. Sawamura D, Goto M, Shibaki A, Akiyama M, McMillan JR, Abiko Y, Shimizu H. Beta defensin-3 engineered epidermis shows highly protective effect for bacterial infection. *Gene Ther.* 2005;12:857-861.
12. Nebus J, Nystrand G, Fowler J, Wallo W.A daily oat based skin care regimen for atopic skin (n=25) *J Am Acad Dermatol.* 2009;60:AB67.
13. Saeedi M, Morteza-Semmani K, Ghoreishi M-R, The treatment of atopic dermatitis with licorine gel. *J Dermatolog Treat.* 2003;(14):1-3.
14. Reuter J, Wolfle U, Weckesser S, Schempp C. Which plant for which skin disease? Part 1: atopic dermatitis, psoriasis, acne, condylome and herpes simplex. *Journal of the German Society of Dermatology.* 2010;(8):788-796.
15. Klovekorn W, Tepe A, Danesch U. A randomized, double blind vehicle controlled, half side comparison with herbal ointment containing Mahonia aquifolium, Viola tricolor and Centella asiatica for the treatment of mild-to-moderate atopic dermatitis. *Int J Clin Pharamacol Ther.* 2007;45(11):583-591.
16. Boguniewicz M, Alexis AF, Beck LA, Block J, Eichenfield LF, Fonacier L, Guttman-Yassky E, Peller AS, Pariser D, Silverberg JI, Lebwohl M. Expert perspectives on management of moderate-to-severe atopic dermatitis: a multidisciplinary consensus addressing current and emerging therapies. *J Allergy Clin Immunol Pract.* 2017;5(6):1519-1531.
17. Boguniewicz M, Zeichner JA, Eichenfield LF, Hebert AA, Jarratt M, Lucky AW, Paller AS. MAS063DP is effective monotherapy for mild to moderate atopic dermatitis in infants and children: a multicenter, randomized, vehicle-controlled study. *J Pediatr.* 2008;152(6):854-859.

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ORIGINAL ARTICLE Journal of Drugs in Dermatology

Pharmacokinetic Profile, Safety, and Tolerability of Clascoterone (Cortexolone 17-alpha propionate, CB-03-01) Topical Cream, 1% in Subjects With Acne Vulgaris: An Open-Label Phase 2a Study

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ABSTRACT

Clascoterone (cortexolone 17α-propionate, CB-03-01) 1% cream, a topical, androgen receptor (AR) inhibitor under investigation for the treatment of acne vulgaris, is rapidly metabolized to cortexolone in human plasma. The primary objectives of this study were to determine the pharmacokinetic (PK) properties and adrenal suppression potential of clascoterone topical cream, 1% in subjects with acne vulgaris.

Study Design: This study was an open-label, multicenter study in 42 subjects ≥12 years of age with moderate-to-severe acne (Grade 3-4 on the Investigator's Global Assessment [IGA]), on the face, chest and/or back. Cohort 1(>18 years of age) and Cohort 2 (12-18 years of age) applied clascoterone topical cream, 1% twice daily (BID) for 14 days. Primary safety endpoints included hypothalamic-pituitary-adrenal (HPA) axis response to cosyntropin via a Cosyntropin Stimulation Test (CST) upon screening (day 1) and at day 14 (HPA axis suppression was defined as a post-stimulation serum cortisol level <18 µg/dL at day 14); and PK evaluation including concentration-time profiles of clascoterone and cortexolone in plasma—PK parameters were determined using "non-compartmental" analysis. Secondary safety endpoints included clinical laboratory testing, local and systemic adverse events (AEs), physical examination/vital signs, and electrocardiogram (ECG).

Results: 42 subjects (Cohort 1=20, Cohort 2= 22) enrolled. Cohort 1 was comprised of 15 females (15/20, 75%) and 5 males (5/20, 25%), non-Hispanic/Latino (20/20, 100%), mean age is 24.4 years. Cohort 2 was comprised of 12 females (12/22, 54.5%) and 10 males (10/22, 45.5%), non-Hispanic/Latino (21/22, 95.5%), and mean age is 15.6 years. Three subjects (3/42,7%), 1 adult and 2 adolescents, demonstrated an abnormal HPA axis response with post-stimulation serum cortisol levels ranging from 14.9 to 17.7 µg/dL at day 14. All returned to normal HPA axis function, four weeks after day 14. None showed clinical evidence of adrenal suppression. Clascoterone plasma concentrations achieved PK steady-state by day 5. Clascoterone systemic exposure was similar between both cohorts. At steady-state, plasma concentrations increased ~1.8 to 2.1 fold versus first dose with mean (coefficient of variation [CV] %) maximum plasma concentrations of 4.4 ng/mL (67%) and 4.6 ng/mL (103%) in Cohort 1 and Cohort 2, respectively. Cortexolone plasma concentrations trended below the lower limit of quantitation (0.5 ng/mL) in both cohorts. Local skin reactions (LSRs) were mostly mild, with only one moderate case of pruritus. There were nine AEs categorized as follows: definitely related (N=2), probably related (N=4), unlikely/not related (N=3), to clascoterone.

Conclusion: This study demonstrates the safety and tolerability of clascoterone topical cream, 1% in adolescents and adults with acne vulgaris treated BID for 14 consecutive days.

J Drugs Dermatol. 2019;18(6):563-568.

INTRODUCTION

Acne is a chronic inflammatory skin condition of the pilosebaceous glands that typically begins at puberty and may continue through adulthood, with flares often coinciding with increases of serum androgens.[1,2] Over 85% of adolescents[3] and 40% of adults develop late onset acne.[4] It is one of the most common dermatological disorders in the world[5] with its incidence and severity influenced by genetics and environment.[1,6]

Endogenous androgens, particularly testosterone and dihydrotestosterone (DHT), mediate excess sebum production in the skin, driving abnormal keratinization and desquamation leading to obstruction of the pilosebaceous duct which allows *Cutibacterium acnes* (formerly *Propionibacterium acnes*) to proliferate.[7,8] Proinflammatory mediators are released in response, triggering localized inflammation and exacerbation of acne lesion eruption.[7]

Clascoterone is a novel AR inhibitor with a chemical structure characterized by a fused 4-ring backbone identical to that of DHT.[9-11] It competes with DHT for binding to androgen receptors in the skin and appears to be mechanistically similarly to oral antiandrogens[9-11]; in cultured human seboctyes, clascoterone reduced sebum production and inflammatory cytokines.[9] Unlike oral anti-androgens with known systemic side effects, clascoterone acts at the site of application influencing multiple cellular and molecular acnegenic pathways with minimal systemic exposure.[9-11] Clascoterone is rapidly hydrolyzed by the skin and plasma esterases to cortexolone,[10-12] an inactive metabolite found in all human cells and tissues.[13]

The objective of this Phase 2a study was to determine the PK and adrenal suppression potential properties of clascoterone topical cream, 1% in subjects with acne vulgaris.

METHODS

Study Design and Objectives

This open-label, multicenter study was designed to evaluate PK and systemic exposure, safety, and tolerability of clascoterone topical cream, 1% in subjects with acne. The study protocol, consent form, participant recruitment materials, and other relevant documents were submitted to an Institutional Review Board for review and were approved prior to study initiation. The study was conducted in accordance with Title v21 of the U.S. Code of Federal Regulations, the International Conference on Harmonization guidelines, current Good Clinical Practice principles, the Declaration of Helsinki, and local regulatory requirements. All patients and their parents or guardians provided written informed consent before enrollment.

Study Population

The study involved two cohorts Cohort 1 (>18 years of age) and Cohort 2 (12-18 years of age). Enrollment in Cohort 2 began after Cohort 1 completed the study. Subjects with moderate-to-severe acne (Grade 3-4 on the IGA), on the face, chest and/or back were enrolled. The study included a screening visit, a baseline visit and three scheduled follow-up visits. Cohort 1 completed the study and then Cohort 2 was enrolled after an interim safety review was performed by the medical monitor to confirm there were no material safety issues in Cohort 1. Following the completion of consent and screening procedures, including a washout of excluded concomitant medications, additional tests, such as a physical examination, a dermatologic exam, ECG, routine laboratory tests, drug and viral screens, a urinary pregnancy test (UPT) for all females who were not post-menopausal or surgically sterile, and a Cosyntropin Stimulation Test (CST), were performed.

Eligible subjects returned for the baseline visit. On day 1, blood was collected immediately before the application of the clascoterone (cortexolone 17α-propionate, CB-03-01) topical cream, 1% for baseline plasma concentrations of clascoterone and cortexolone.

Study Treatment

Subjects applied 6 grams of clascoterone topical cream, 1% to their entire face, shoulders, upper chest and upper back (treatment area) on day 1. The exception were subjects <18 years of age with a body surface area <1.6 m^2 and they applied 4 grams. Subjects had blood sampled at 1, 2, 4, 6, 8, 10, and 12 hours after the first application to measure plasma clascoterone and cortexolone concentrations. After the last blood draw, subjects applied the second dose in the clinic (under supervision), and were instructed to apply the cream to the treatment area every 12 hours at the same time daily.

Study Assessments

At baseline, day 5, and day 10 visits, subjects returned to clinic for evaluation. Prior to each visit, subjects were to 1) apply the cream to the treatment area 12 hours prior to appointment and record the appliction time; 2) if possible, shower approximately two hours prior to arriving at the clinic; 3) withhold application of the cream on the morning of the visit; and 4) bring all tubes of cream to the clinic for weighing. At each visit, subjects had blood taken prior to the morning application for determination of plasma clascoterone and cortexolone concentrations. After the blood draw, subjects applied the cream to the treatment area under staff supervision.

During the final visit, (day 14), prior to application of the cream in the clinic, subjects had blood and urine collected for routine laboratory tests (hematology, clinical chemistry, and urinalysis), ECG, UPT (if applicable), and determination of trough plasma clascoterone and cortexolone concentrations. CSTs were performed within an hour of the screening CST to determine changes in the adrenal system. Additional PK blood samples were taken at 1, 2, 4, 6, 8, 10, and 12 hours post-application. All tubes of returned cream were weighed. All subjects were discharged from the study at this visit unless there was evidence of adrenal suppression.

The investigator assessed safety by evaluating local and systemic AEs during each visit; local skin reaction assessments at baseline and days 5, 10, and 14; physical examination/vital signs and routine laboratory tests on days 1 and 14; and UPT on days 1, 2, and 14. ECGs were performed on days 1 and 14. Efficacy was not assessed.

Compliance

A subject was considered compliant with the dosing regimen if the cream was applied ≥80% of the expected applications prior to the day 14 HPA assessment. Subjects included in the PK analysis must have applied ≥80% of expected applications and the final three doses as prescribed prior to the day 14 PK assessment.

Cosyntropin Stimulation Testing

During day 1 and 14 visits, a CST was performed on each subject. If a subject's day 14 CST showed an abnormal HPA axis response, the cream was considered to have caused the abnormal CST result. The serum cortisol assays were analyzed at ACM Global Central Laboratory (Rochester, NY).

PK Assessment

A total of 16 blood samples were collected per subject for analysis of clascoterone and cortexolone concentrations in plasma. Blood samples were collected at 1, 2, 4, 6, 8, 10, and 12 hours after the first and last topical application of clascoterone. In addition, blood samples were obtained prior to the morning dose on days 5 and 10. All plasma samples were frozen after collection and sent to MicroConstants Inc. (San Diego, CA) for analysis using a HPLC.

Routine Laboratory Testing

During day 1 and 14 visits, urine and blood samples for chemistry, hematology, and urinalysis were collected from each subject and sent to ACM Global Central Laboratory (Rochester, NY) analysis.

LSRs

Before and after first application on days 1, 5, 10, and 14, the investigator documented the presence of telangiectasia, skin atrophy, and striae rubrae and evaluated the severity of erythema, edema, and scaling/dryness. A five-point ordinal scale (0 = none, 1= trace/minimal, 2 = mild, 3 = moderate, and 4 = severe) was used to assess the severity of these reactions.

During the screening process, stinging/burning and pruritus were assessed before and after the first application. At days 5, 10, and 14, subjects were asked to rate the severity of any stinging/burning and pruritus (0 = none, 1= mild, 2 = moderate, and 3 = severe) that occurred in the treatment area since the last visit.

Adverse Events

After the baseline visit, subjects were questioned specifically about the status of any ongoing AEs during each subsequent visit. AEs were coded using the MedDRA coding dictionary version 16.0.

Statistical and Analytical Plans

The SAS® 9.3 statistical software package and ClinPlus® Report v4 were used to provide table data. Analyses of PK data, however, were performed using WinNonlin Phoenix version 6.3, Excel 2013, and the SAS® 9.3 statistical software package.

For continuous variables, descriptive statistics included the number of subjects with nonmissing data, mean, median, standard deviation (SD), minimum and maximum values. Frequency counts and percentages were reported for categorical data. For PK parameters, data were summarized using geometric mean and CV% of the geometric mean.

Data Analysis

PK parameters were determined using non-compartmental analysis. Trough plasma concentrations were used to assess achievement of steady-state via a one-way repeated-measure (Helmert contrasts) analysis of variance (ANOVA) using observed and rank/log transformed data. The time at which there was no statistically significant difference between day X and the mean of all subsequent days was the time by which steady-state was achieved.

RESULTS

Study Population

Fifty-seven subjects were screened for this study. Forty-two subjects (20 adults and 22 adolescents) were enrolled and included in the analysis of HPA axis response, pharmacokinetics, and safety (Table 1).

The average number of inflammatory and non-inflammatory lesions was similar for both cohorts at baseline (Table 2). The majority of subjects in Cohort 1 (14/20, 70%) and Cohort 2 (18/22, 81.8%) had moderate facial acne vulgaris based on the IGA scores. The proportion of subjects with acne on the shoulders, upper chest, and upper back was similar across both cohorts.

TABLE 1.

Demographics and Baseline Characteristics		
Characteristic	Cohort 1 N (%) N = 20	Cohort 2 N (%) N = 22
Sex		
Female	15 (75.0%)	12 (54.5%)
Male	5 (25.0%)	10 (45.5%)
Ethnicity		
Non-Hispanic or Latino	20 (100.0%)	21 (95.5%)
Hispanic or Latino	0 (0.0%)	1 (4.5%)
Race		
White	17 (85.0%)	21 (95.5%)
Asian	1 (5.0%)	0 (0.0%)
Black or African American	1 (5.0%)	0 (0.0%)
Multiple	1 (5.0%)	1 (4.5%)
Age (years)		
Mean	24.4	15.6
Median	23	16
SD	5.84	1.33
Minimum to Maximum	18.0 to 40.7	12.8 to 17.6

TABLE 2.

Baseline Clinical Evaluations of Each Cohort		
Parameter	**Cohort 1**	**Cohort 2**
Inflammatory Lesions†		
N	20	22
Mean	32.8	32.6
Median	30	29
SD	11.27	11.38
(Minimum, Maximum)	(20, 61)	(20, 62)
Non-Inflammatory Lesions†		
N	20	22
Mean	40.8	43.7
Median	29	35
SD	22.32	30.04
(Minimum, Maximum)	(22, 106)	(20, 155)
IGA†		
Moderate	14 (70.0%)	18 (81.8%)
Severe	6 (30.0%)	4 (18.2%)
Total	20 (100.0%)	22 (100.0%)
Shoulder Acne		
No	7 (35.0%)	8 (36.4%)
Yes	13 (65.0%)	14 (63.6%)
Total	20 (100.0%)	22 (100.0%)
Upper Chest Acne		
No	1 (5.0%)	9 (40.9%)
Yes	19 (95.0%)	13 (59.1%)
Total	20 (100.0%)	22 (100.0%)
Upper Back Acne		
No	2 (10.0%)	0 (0.0%)
Yes	18 (90.0%)	22 (100.0%)
Total	20 (100.0%)	22 (100.0%)

†Facial acne vulgaris assessments.

Measurement of Treatment Compliance

All enrolled subjects were compliant and applied at least 80% of the expected number of applications. The minimum percent of expected doses applied was 92.6% for Cohort 1 and 96.3% for Cohort 2.

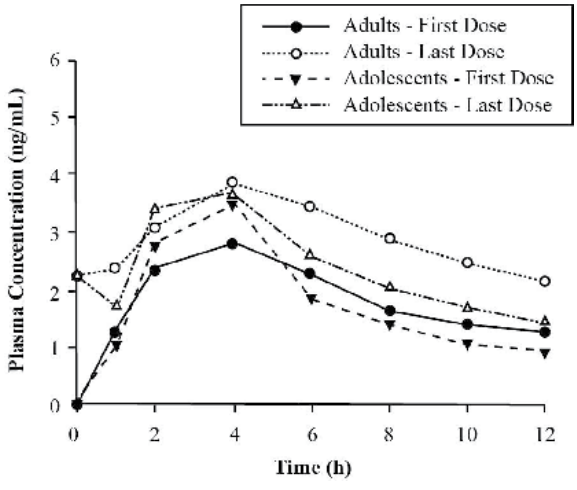
Extent of Exposure

All subjects in Cohort 1 applied 6 grams of cream per application along with 14 subjects in Cohort 2. Eight subjects in Cohort 2 applied 4 grams of cream per application.

HPA Axis Response and Serum Cortisol Levels

HPA axis responses to CSTs were dichotomized to normal and abnormal. Three (3/42, 7%) subjects (1/20, 5.0% in Cohort 1; 2/22; 9.1% in Cohort 2) demonstrated laboratory evidence of abnormal HPA axis response at day 14 documented by a 30-minute post-stimulation serum cortisol level of <18 µg/dL with modest post-stimulation serum cortisol levels between 14.9 µg/dL to 17.7 µg/dL under maximal use conditions. All three of these abnormal CST results were documented as AEs. Follow-up post-CST cortisol levels returned to normal for all three subjects approximately four weeks after day 14. The average post-CST cortisol level at day 14 was 26.7 and 22.8 mcg/dL Cohort 1 and 2, respectively, with a range of 17.7-42.6 mcg/dL (Cohort 1) and 14.9-28.0 mcg/dL (Cohort 2).

FIGURE 1. Mean clascoterone plasma concentration-time profiles following first and last topical application of 4 or 6 g clascoterone topical cream, 1% every 12 hours to adult and adolescents subjects, respectively.



The three subjects whose cortisol was suppressed applied a mean total amount of 144.1 grams (median 158.6 grams) versus 153.48 grams (median 163.7 grams) for subjects who did not exhibit cortisol suppression over the 14-day treatment period. Subjects who showed HPA axis suppression applied less cream than subjects who did not have suppression; thus, HPA axis suppression does not appear to be correlated to the total amount of cream applied.

Pharmacokinetics of Clascoterone Topical Cream, 1%

The PK of clascoterone topical cream, 1% was assessed after a single topical application and again at steady state (after topical application every 12 hours for 14 days) in all subjects.

Based on clascoterone trough plasma concentrations (Figure 1), steady-state was achieved by 96 hours (day 5; first sample obtained after the 12-hour sample on day 1). Clascoterone systemic exposure associated with topical application was similar between Cohort 1 and Cohort 2. At steady-state, plasma concentrations increased ~ 1.8 to 2.1 fold as compared to the first dose with mean (CV%) maximum plasma concentrations of 4.4 ng/mL (67%) and 4.6 ng/mL (103%) in Cohort 1 and Cohort 2 subjects, respectively.

Cortexolone plasma concentrations trended below the lower limit of quantitation (0.5 ng/mL) in both cohorts which precluded an assessment of cortexolone pharmacokinetics. (Figure 1).

The results indicate that clascoterone plasma concentrations were at steady-state during the day 14 assessment of clascoterone affect on adrenal suppression.

Although the mean clascoterone maximum (C_{max}), average (C_{avg}), and minimum (C_{min}) steady-state plasma concentrations in subjects with adrenal suppression tended to be higher than in those subjects with no adrenal suppression, there was overlap in the mean ± SD and in the observations range. No clear relationship between adrenal suppression and clascoterone exposure could be established.

Local Skin Reactions

With the exception of one moderate case of pruritus and one report of telangiectasia, all other LSRs were mild or minimal on day 14. Skin atrophy, striae rubrae, and edema were absent for all subjects at each visit. Mild or minimal pruritus was reported in seven subjects, erythema and stinging/burning were each reported in four subjects, and scaling/dryness was reported in three subjects. The subject with telangiectasia only had trace lesions on the face pre- and post-application at day 1 and at all follow-up study visits.

Adverse Events

A total of eight subjects (8/42, 19%; Cohort 1=5 and Cohort 2=3) reported at least one AE with the overall total number of nine AEs—four (three abnormal CST results, 1 application site folliculitis) were deemed related to the cream. All other AEs were unlikely or not related to the cream and included upper respiratory infection (2), diarrhea (1), ecchymosis on the right arm (1), and right ear infection (1). With the exception of one AE (diarrhea) that was moderate in severity, all other AEs were mild. None of the AEs required a change in dosing and only one was not resolved at the completion of the study. There were no discontinuations of the study cream due to AEs.

Changes observed in vital signs at day 14 from day 1 were unremarkable. ECG results were normal at both day1 and 14 for the majority of subjects. Most subjects with an abnormal or borderline ECG result at day 1 had a normal ECG result at day 14. There were two subjects (1 from each cohort) who had normal ECG results on day 1 and then borderline/abnormal ECG results at day 14.

DISCUSSION AND CONCLUSIONS

In this phase 2a, open-label study, twice daily treatment with clascoterone topical cream, 1% for 14 days demonstrated limited systemic exposure to clascoterone and favorable safety and tolerability in subjects with acne vulgaris. Clascoterone is quickly hydrolyzed by the skin and plasma esterases into the inactive parent cortexolone, the primary metabolite.[11,12]

The study results support the safety of clascoterone topical cream, 1% with respect to adrenal suppression and systemic exposure in adolescents and adults with acne vulgaris treated twice daily for two weeks. Three subjects (7%) demonstrated an abnormal HPA axis response with modest post-stimulation serum cortisol levels between 14.9 µg/dL to 17.7 µg/dL upon study completion. All subjects returned to normal HPA axis function at their initial follow-up visit approximately four weeks after day 14.

The mean clascoterone maximum (C_{max}), average (C_{avg}), and minimum (C_{min}) steady-state plasma concentrations in subjects with adrenal suppression tended to be higher than in those subjects with no adrenal suppression, yet there was no clear relationship between adrenal suppression and clascoterone exposure.

PK steady-state was achieved by day 5; systemic exposure was similar between cohorts. Cortexolone plasma concentrations trended below the lower limit of quantitation (0.5 ng/mL) in both adult and adolescent subjects indicating that clascoterone plasma concentrations were at PK steady state during the assessment of adrenal suppression potential at day 14.

Most LSRs were mild or minimal with pruritus the most frequent LSR. AEs were mostly mild or moderate with four of nine deemed probably or definitely related to the cream. All other AEs were unlikely related or not related to the cream. None of the AEs were serious; none required a change in dosing, and only one was not resolved upon study completion. Changes observed in vital signs at day 14 from day 1 were unremarkable. These findings (AEs, laboratory results, LSRs) were consistent with expectations for this trial and no material safety issues or trends were identified. Efficacy was not evaluated in this study. Clascoterone topical cream, 1% is being developed for use as the first topical androgen inhibitor for the treatment of acne in males and females. The PK data demonstrate the rapid and substantial conversion of the parent molecule to a known inactive metabolite.[11-13] Oral anti-androgens are associated with significant side effects[7,14] demonstrating the clear benefits of topical clascoterone; it acts at the site of application only, reaching androgen receptors in the pilosebaceous units to limit androgen-mediated sebum production and inflammation,[9] with minimal systemic exposure and a favorable safety profile. Phase 3 clinical investigations of clascoterone topical cream, 1%, recently concluded and Phase 2 studies are underway investigating clascoterone solution for the treatment of androgenetic alopecia.

DISCLOSURES

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Italy. Drs. Mazzetti and Moro are employees of Cassiopea SpA; Dr. Gerloni is a consultant to Cassiopea SpA and Dr. Cartwright is an employee of Cassiopea Inc.

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The authors are fully responsible for the content of this manuscript.

REFERENCES

1. Taylor M, Gonzalez M, Porter R. Pathways to inflammation: acne pathophysiology. *Eur J Dermatol.* 2011;21(3):323-333.
2. Arora MK, Yadav A, Saini V. Role of hormones in acne vulgaris. *Clin Biochem.* 2011;44(13):1035-1040.
3. Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol.* 2013;168(3):474-485.
4. Rocha MA, Bagatin E. Adult-onset acne: prevalence, impact, and management challenges. *Clin Cosmet Investig Dermatol.* 2018;1:11:59-69.
5. American Academy of Dermatology. Skin Conditions by the Numbers. Available at: https://www.aad.org/media/stats/conditions/skin-conditions-by-the-numbers. Accessed December 20, 2018.
6. Bataille V, Snieder H, MacGregor AJ, et al. The influence of genetics and environmental factors in the pathogenesis of acne: a twin study of acne in women. *J Invest Dermatol.* 2002;119(6):1317-1322.
7. Lai JJ, Chang P, Lai KP, et al. The role of androgen and androgen receptor in skin-related disorders. *Arch Dermatol Res.* 2012;304(7):499-510.
8. Dréno B, Pécastaings S, Corvec S, et al. Cutibacterium acnes (Propionibacterium acnes) and acne vulgaris: a brief look at the latest updates. *J Eur Acad Dermatol Venereol.* 2018;32(Suppl 2):5-14.
9. Cortexolone 17α-propionate (clascoterone) is a novel androgen receptor antagonist that inhibits production of lipids and inflammatory cytokines from sebocytes in vitro. Rosette C, Agan FJ, Mazzetti A, Moro L, Gerloni M. *J Drugs Dermatol.* 2019 May 1; 18 (5): 217:223
10. Ferraboschi P, Legnani L, Celasco G. et al. A full conformational characterization of antiandrogen cortexolone-17α-propionate and related compounds through theoretical calculations and nuclear magnetic resonance spectroscopy. *Med Chem Commun.* 2014;5: 904-914.
11. Celasco G, Moro L, Bozzella R, et al. Biological profile of cortexolone 17alpha-propionate (CB-03-01), a new topical and peripherally selective androgen antagonist. *Arzneimittelforschung.* 2004;54(12):881-886.
12. Barth JH. Alopecia and hirsuties. Current concepts in pathogenesis and management. *Drugs.* 1988;35(1):83-91.
13. Dehertogh R, Hoet JJ, Materazzi F, Ekka E. The fate of 1,2-3H Cortexolone in Man. *Acta Endocrinol* (Copenh). 1964;47:165-176.
14. Elsaie ML. Hormonal treatment of acne vulgaris: an update. *Clin Cosmet Investig Dermatol.* 2016;9:241-248.

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A Phase 2b, Randomized, Double-Blind Vehicle Controlled, Dose Escalation Study Evaluating Clascoterone 0.1%, 0.5%, and 1% Topical Cream in Subjects With Facial Acne

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ABSTRACT

Androgens play a key role in acne pathogenesis in both males and females. Clascoterone (CB-03-01, Cortexolone 17α propionate) cream is a topical anti-androgen under investigation for the treatment of acne. The results from a phase 2b dose escalating study are discussed.

Methods: Primary objective: to compare the safety and efficacy of topical creams containing clascoterone 0.1% (twice daily [BID]), 0.5% (BID), or 1% (daily [QD] or BID) versus vehicle (QD or BID) in male and female subjects ≥12 years with facial acne vulgaris. Efficacy was assessed by: Investigator's Global Assessment (IGA)–the overall severity of acne using a five-point scale (from 0=clear to 4=severe); inflammatory and non-inflammatory acne lesion counts (ALC); and subject satisfaction with treatment–subjects assessed overall treatment satisfaction using a 4-point scale. Safety assessments: local and systemic adverse events (AEs), physical examination/vital signs, laboratory tests, local skin reactions (LSRs), and electrocardiograms (ECGs). Treatment success required a score of "clear" or "almost clear" (IGA score of 0 or 1) and a two or more-grade improvement from baseline.

Results: 363 subjects (N=72, 0.1% BID; N=76, 0.5% BID; N=70, 1% QD; N=70, 1% BID; and N=75, vehicle QD or BID) enrolled. 304 subjects (83.7%) completed the study. Intention to Treat (ITT) population: 196/363 (54.0%) females; 167/363 46.0%) males; (257/363 (70.2%) were white; average age=19.7 years. Demographic and baseline characteristics were similar across all groups. Treatment success at week 12 were highest for the 1% BID (6/70, 8.6%) and 0.1% BID (6/72, 8.3%) groups versus vehicle (2/75, 2.7%). Absolute change in inflammatory (P=0.0431) and non-inflammatory (P=0.0303) lesions was statistically significant among the treatment groups. The median change from baseline at week 12 in inflammatory and non-inflammatory lesions was greatest in the 1% BID group -13.5 and -17.5, respectively. Similar results were observed for the secondary efficacy endpoints whereby the highest success rate and greatest reduction in lesion counts from baseline to week 12 occurred with 1% BID.

93/363 subjects (25.6%) reported ≥1 AEs; total number of AEs=123 with 2 probably/possibly related to treatment (N=1, 1% QD group). Subjects with ≥1AEs: 0.1% BID=25.0%, 0.5% BID=38.2%, 1% QD=22.9%, 1% BID=18.6%, and vehicle=22.7%. AEs were mostly mild in severity and similar across all groups. Most AEs (93/121 76.8%) resolved by the end of the study. Erythema was the most prevalent LSR; 36.8% had at least minimal erythema at some point during the study.

Conclusions: All clascoterone cream concentrations were well tolerated with no clinically relevant safety issues noted. Clascoterone 1% BID treatment had the most favorable results and was selected as the best candidate for further clinical study and development. Two Phase 3 investigations of clascoterone topical cream, 1% for the treatment of moderate-to-severe acne vulgaris in individuals ≥9 years recently concluded.

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INTRODUCTION

Acne vulgaris is a chronic inflammatory skin condition characterized by obstruction and inflammation of the pilosebaceous units within the skin. It is the most common skin disorder in the world affecting 85% of the population.[1] In the United States, approximately 50 million cases of acne occur annually.[2]

Endogenous androgens play a key role in acne pathogenesis in males and females.[3] Androgen-induced excess sebum production, inflammation, and hyperkeratinization clog hair follicles and produces a local environment that encourages *Cutibacterium acnes* (formerly *Propionibacterium acnes*) colonization and infection.[4] These acnegenic events contribute to the formation of acne comedones, pustules, papules, nodules, and/or cysts.

Clascoterone is a new entity whose chemical structure is

characterized by a fused 4-ring backbone identical to that of dihydrotestosterone (DHT).[5,6] Thus, it acts as an androgen receptor inhibitor, competing with DHT for binding to the androgen receptors in the skin and reducing DHT's proinflammatory and sebum inducing effects within the pilosebaceous unit.[6-9] Clascoterone is rapidly hydrolyzed by the skin and plasma esterases to cortexolone, an inactive metabolite found in all human cells and tissues.[5,10]

For this reason, unlike oral anti-androgens that are associated with numerous systemic side effects,[4] clascoterone acts at the site of application with minimal systemic exposure; no notable clinical systemic side effects,[6] such as prolonged hypothalamic-pituitary-adrenal axis activation or testosterone fluctuations, have been reported in clinical trials to date.[6-9]

Topical application of clascoterone cream may reduce acne lesions at the site of application through multiple cellular and molecular mechanisms. For example, in cultured primary human seboctyes, clascoterone reduced sebum production and inflammatory cytokines.[7]

The purpose of this Phase 2b study was to evaluate the efficacy and safety of various concentrations of clascoterone cream. In this vehicle-controlled study, male and female patients ≥12 years with acne applied clascoterone cream or vehicle topically once or twice daily for 12 weeks. Treatment with clascoterone topical cream, 1% resulted in reductions in acne lesions and greater treatment success versus vehicle.

METHODS

This was a multicenter (N=13), randomized double-blind, vehicle controlled, consecutive groups dose escalation study. The study protocol, consent/assent form, participant recruitment materials/process, and other relevant documents were submitted to an institutional review board for review and approval prior to study initiation. The study was conducted in accordance with Title v21 of the U.S. Code of Federal Regulations, the International Conference on Harmonization guidelines, current Good Clinical Practice principles, the Declaration of Helsinki, and local regulatory requirements. All patients and their parents or guardians provided written informed consent before enrollment. Male and female subjects ≥12 years with moderate to severe facial acne vulgaris defined as an IGA of 2 (mild), 3 (moderate), or 4 (severe) and at least 20 (up to 75) inflammatory lesions (papules, pustules, and nodules/cysts) and 20 (up to 100) non-inflammatory lesions (open and closed) were eligible to enroll and assigned to a sequential treatment cohort, receiving either one of the clascoterone creams or vehicle cream to apply once or twice daily for 12 weeks.

Subjects in the first cohort (Cohort 1) were randomized (4:1) to twice daily treatments with clascoterone 0.1% cream vs vehicle cream. After all subjects in Cohort 1 completed at least four weeks of treatment, an interim safety review was completed by the medical monitor. Dose escalation occurred only after the medical monitor recommendation and sponsor approval to proceed to the next cohort.

Clinical efficacy evaluations included a) IGA describing the overall severity of acne using a five-point scale from 0=clear to 4=severe, and b) ALC — inflammatory lesions (papules, pustules and nodules/cysts) and non-inflammatory lesions (open and closed comedones), including those on the nose. All acne lesions on the nose were counted separately.

Treatment groups are defined as 1) 0.1% clascoterone cream (BID); 2) 0.5% clascoterone cream (BID); 3) 1% clascoterone cream (QD); 4) 1% clascoterone cream (BID); and 5) vehicle cream (QD or BID). The clascoterone and vehicle study creams were indistinguishable. At least eight hours was required between applications for BID dosing.

Efficacy

Primary endpoints were 1) the proportion of subjects achieving success in each treatment group at week 12/end of study (EOS) using the dichotomized IGA with success defined as a score of 0 (clear) or 1 (almost clear) and a two or more-grade improvement from baseline; and 2) change from baseline inflammatory and non-inflammatory ALC in each treatment group at week 12/EOS.

The investigator assessed efficacy as follows: 1) IGA (5-point scale) was used to calculate the overall severity of acne score of 0=clear to 4=severe–this is a static morphological scale that refers to a point in time and not a comparison to baseline — and a two or more grade improvement from baseline was assessed at each visit; 2) ALC — inflammatory lesions (papules, pustules and nodules/cysts) and non-inflammatory lesions (open and closed comedones) on the face were counted and recorded separately at each visit; and 3) overall study subject satisfaction with the treatment was evaluated during the week 12/EOS visit using the following scale: 1=excellent (very satisfied), 2=good (moderately satisfied), 3=fair (slightly satisfied), and 4=poor (not satisfied at all).

Safety

The investigator assessed safety by utilizing the following endpoints: 1) local and systemic AEs — every visit (baseline, weeks 2, 4, 8, and 12/EOS); 2) the absence or presence (and severity) of the following local skin reactions: telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus at every visit; 3) physical examination/vital signs at baseline, weeks 4 and 12/EOS; 4) clinical laboratory testing (hematology, clinical chemistry, and urinalysis) at baseline, weeks 4, 8, and 12/EOS; 5) ECG at baseline, weeks 4 and

12/EOS; and 6) urine pregnancy testing in all women who were not postmenopausal or surgically sterile at baseline, weeks 4, 8, and 12/EOS.

Statistical Analysis
The SAS® 9.4 statistical software package and ClinPlus® Report v4 were used to provide all tables and data listings.

For continuous variables, descriptive statistics included the number of subjects with non-missing data (n), mean, median, standard deviation, minimum, and maximum. For categorical variables, the number and percentage of subjects within each category were presented. Subject data listings sorted by treatment group, study site, and subject number were provided for all data.

Summaries were provided for each treatment group. The vehicle group incorporated the data from vehicle-treated subjects in the four dose cohorts. The statistical analyses evaluated the five treatment groups without consideration of cohort.

Efficacy Analyses
The efficacy analyses were conducted on the ITT and Per Protocol populations with the ITT population considered the primary population for statistical analysis.

Treatment Success Based on IGA at Week 12
The treatment groups were compared with respect to the proportions of subjects with treatment success at week 12/EOS using Fisher's exact test. Treatment success was defined as a score of "clear" or "almost clear" (IGA score of 0 or 1) and a two or more-grade improvement from baseline.

Absolute Change in Inflammatory and Non-Inflammatory Lesion Counts at Week 12
The absolute change from baseline to week 12/EOS in total inflammatory and non-inflammatory lesion counts (including the lesions on the nose) was analyzed by rank analysis of covariance (ANCOVA). The model included terms for treatment and study site with the baseline total inflammatory and non-inflammatory lesion count serving as the covariate. Pairwise comparisons of the treatments were performed by rank ANCOVA.

Safety Analyses
All subjects in the study population were included in the summaries of safety data.

Dosing Compliance
Subjects were considered compliant with the dosing regimen if they applied at least 80% of the expected number of applications and were without significant protocol dosing deviations.

Adverse Events
AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15. Verbatim terms were mapped into a MedDRA system organ class and preferred term.

Electrocardiogram
ECGs were evaluated by the San Diego Cardiac Center (San Diego, CA) for any clinically significant changes during the study period. Results and descriptive statistics were provided by treatment group at each visit. Changes in the overall interpretation (normal/borderline/abnormal) of the ECG from baseline to week 12/EOS were examined using shift tables.

Local Skin Reactions
The frequency distribution of the severity scores of LSRs were summarized by treatment group with frequency counts and percentages at baseline and all follow-up visits.

Vital Signs and Weight
Descriptive statistics were provided for the observed and change from baseline in vital signs and weight at weeks 4 and 12 by treatment group.

Safety Laboratory Tests
Change from baseline in the hematology, clinical chemistry, and urinalysis analytes were assessed at each follow-up visit using shift tables by analyte and by conventional reference range flags (low/normal/high).

Concomitant Medications and Concurrent Therapies/Procedures
Concomitant medications and concurrent therapies/procedures were provided in a subject listing and coded using the WHO drug dictionary (format C version March 2012).

Subject Satisfaction with Treatment
The frequency distributions of the subject satisfaction with treatment scores at week 12/EOS were provided by treatment group in the ITT population.

Determination of Sample Size
The sample size of 90 randomized subjects per cohort (72 on active treatment and 18 on vehicle) was selected empirically.

RESULTS

A total of 505 subjects were screened and 363 subjects enrolled in the ITT population (N=72, 0.1% BID; N=76, 0.5% BID; N=70, 1% QD; N=70, 1% BID; and N=75, vehicle (QD or BID).

Of the 363 enrolled subjects, 304 (83.7%) completed the study and 59 (16.3%) terminated early.

TABLE 1.

Demographics for the ITT Population						
	Clascoterone 0.1% BID (N = 72)	Clascoterone 0.5% BID (N = 76)	Clascoterone 1.0% QD (N = 70)	Clascoterone 1.0% BID (N = 70)	Vehicle QD or BID (N = 75)	All (N = 363)
Sex at Birth	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Female	36 (50.0%)	42 (55.3%)	38 (54.3%)	37 (52.9%)	43 (57.3%)	196 (54.0%)
Male	36 (50.0%)	34 (44.7%)	32 (45.7%)	33 (47.1%)	32 (42.7%)	167 (46.0%)
Ethnicity	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Hispanic or Latino	22 (30.6%)	20 (26.3%)	6 (8.6%)	15 (21.4%)	13 (17.3%)	76 (20.9%)
Non-Hispanic or Latino	50 (69.4%)	56 (73.7%)	64 (91.4%)	55 (78.6%)	62 (82.7%)	287 (79.1%)
Race	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
American Indian or Alaskan	0 (0.0%)	1 (1.3%)	0 (0.0%)	2 (2.9%)	0 (0.0%)	3 (0.8%)
Asian	1 (1.3%)	3 (4.0%)	4 (5.7%)	4 (5.7%)	4 (5.3%)	16 (4.4%)
Black or African American	12 (16.7%)	14 (18.4%)	16 (22.9%)	20 (28.6%)	12 (16.0%)	74 (20.4%)
Native Hawaiian or Other	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	2 (0.6%)
Other	1 (1.3%)	2 (2.6%)	0 (0.0%)	2 (2.9%)	4 (5.3%)	9 (2.5%)
White	58 (80.6%)	54 (71.0%)	50 (71.4%)	42 (60.0%)	53 (70.7%)	257 (70.8%)
Age (years)						
N	72	76	70	70	75	363
Mean	19.8	20.4	18.3	21.0	19.2	19.7
Median	19.0	19.0	16.0	20.0	18.0	18.0
Standard Deviation	5.77	6.31	6.14	6.22	5.25	5.99
Minimum, Maximum	12.0, 43.0	12.0, 42.0	12.0, 35.0	12.0, 38.0	12.0, 35.0	12.0, 43.0

TABLE 2.

Primary Efficacy Endpoint Results					
	Clascoterone 0.1% BID (N = 72) N (%)	Clascoterone 0.5% BID (N = 76) N (%)	Clascoterone 1.0% QD (N = 70) N (%)	Clascoterone 1.0% BID (N = 70) N (%)	Vehicle QD or BID (N = 75) N (%)
Primary Efficacy Endpoint #1					
IGA Treatment Failure at Week 12	66 (91.7%)	73 (96.1%)	68 (97.1%)	64 (91.4%)	73 (97.3%)
IGA Treatment Success at Week 12	6 (8.3%)	3 (3.9%)	2 (2.9%)	6 (8.6%)	2 (2.7%)
					P-value= 0.3065
Primary Efficacy Endpoint #2 Absolute Change, Inflammatory Lesions at Week 12 vs. Baseline					
Mean	-7.3	-5.6	-7.9	-11.1	-8.3
Median	-11.0	-7.5	-8.5	-13.5	-8.0
Standard Deviation	14.20	11.26	12.31	14.07	12.86
Range	-31 to +43	-23 to +32	-45 to +25	-39 to +38	-50 to +34
Absolute Change, Non-Inflammatory Lesions at Week 12 vs. Baseline					
Mean	-8.8	-6.3	-8.1	-15.8	-5.9
Median	-10.0	-10.0	-6.0	-17.5	-9.0
Standard Deviation	17.38	26.68	20.47	20.11	18.47
Range	-50 to +69	-56 to +171	-48 to +85	-63 to +34	-45 to +64

Subjects were included in the treatment group to which they were randomized. All subjects received the treatment to which they were randomized. The ITT population considered as the primary population for statistical analysis.

The Safety population included all subjects enrolled in the study who were randomized and applied a test article at least once (N=363). Subjects were included in the treatment group based on the treatment that they received.

Demographics

Demographics were generally comparable across all five treatment groups (Table 1).

At baseline, the majority of study subjects had moderate (Grade 3) acne (247/363, 68.0%) with the remainder of subjects evenly divided with mild (Grade 2; 60/363, 16.5%) or severe (Grade 4; 56/363, 15.4%) acne. The clascoterone 1% cream BID group had the most subjects with severe acne at baseline (20/70, 28.6%) and with mild acne (18/70, 25.7%), yet less than half of the subjects with moderate acne (32/70, 45.7%). Baseline acne severity by IGA was similar across all groups, with the exception of the clascoterone 1% BID group noted above.

Treatment Success

For the primary efficacy endpoints, treatment success parameters, previously defined at week 12/EOS, were highest for the clascoterone 1% cream BID (6/70, 8.6%) and clascoterone 0.1% BID (6/72, 8.3%) groups followed by clascoterone 0.5% BID (3/76, 3.9%), clascoterone 1% QD (2/70, 2.9%), and vehicle (2/75, 2.7%; Table 2). Although there was a higher proportion of treatment success in the clascoterone 1% BID group, there were no statistically significant differences among treatments with clascoterone cream at various concentrations with regard to IGA success at week 12/EOS.

The greatest median change from baseline at week 12/EOS in inflammatory and non-inflammatory lesions was detected in subjects treated with clascoterone cream 1% BID (-13.5 and -17.5, respectively). Regarding inflammatory lesions change at week 12/EOS from baseline, the clascoterone 1% BID group had significantly greater decrease ($P<0.05$) than the clascoterone 0.5% BID, clascoterone 1% QD, and vehicle groups. With respect to non-inflammatory lesions, the clascoterone 1% BID group had significantly greater decrease ($P<0.05$) than the clascoterone 0.5% BID, clascoterone 1% QD, and vehicle groups at week 12/EOS from baseline.

Subject Satisfaction with Treatment

Subject satisfaction at week 12/EOS was similar across all five treatment groups. The highest satisfaction score (ie, excellent and good) was reported by subjects treated with clascoterone cream 1% BID (72.6%), followed by clascoterone 0.1% BID (68.3%), clascoterone 1% QD (66.7%), vehicle (64.2%), and clascoterone 0.5% BID (61.4%).

Safety

Of the 123 total AEs, only two (burning at application site) occurred in the same subject, were mild in severity and were deemed possibly related to clascoterone 1% cream QD,. AEs, related and unrelated to test article application, by treatment group are shown in Table 3.

With the exception of three AEs that were severe (miscarriage, right ankle fracture, right arm fracture), all other AEs were mild (88/121, 72.7%) or moderate (30/121, 24.8%). Only one AE (urinary tract infection; deemed unrelated to test article) led to the subject's discontinuation from the study. The majority of AEs (93/121; 76.9%) were resolved without sequelae at the conclusion of the study. Of the remaining AEs, 9 were in the process of resolving, 4 were not resolved, 3 were resolved with sequelae, and 12 had no known outcome at the conclusion of the study.

Local Skin Reactions

The results of this study demonstrated that application of clascoterone cream once or twice daily at a variety of concentrations (0.1%, 0.5%, and 1%) was well-tolerated upon application. The incidence of all LSRs (telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus) was similar across treatment groups and minimal throughout the study. The majority of subjects (>98%) across all five treatment groups had an absence of telangiec-

TABLE 3.

Adverse Events Observed in Treatment Groups						
	Clascoterone 0.1% BID (N = 72) N (%)	Clascoterone 0.5% BID (N = 76) N (%)	Clascoterone 1.0% QD (N = 70) N (%)	Clascoterone 1.0% BID (N = 70) N (%)	Vehicle QD or BID (N = 75) N (%)	All (N = 363) N (%)
Number of Events†	19 (15.4%)	43 (35.0%)	23 (18.7%)	19 (15.4%)	19 (15.4%)	123 (100.0%)
Number of Subjects‡	18 (25.0%)	29 (38.2%)	16 (22.9%)	13 (18.6%)	17 (22.7%)	93 (25.6%)

†Percentages are based on the total number of events
‡Each subject counted once. Percentages are based on the number of subjects in the treatment group.

tasia. Three subjects had severe skin atrophy at baseline that persisted throughout the study; no new cases of atrophy were observed. Most subjects did not have skin atrophy (>84%), striae rubrae (>92%), edema (>95%), stinging/burning (>93%) or scaling/dryness (>84%) during any assessment. Most cases of scaling/dryness were mild and only a few cases of moderate scaling/dryness (maximum number in any group throughout the study was N=1). More than >63% did not experience erythema. Pruritus was absent in >82% of subjects during the study, yet a few mild and moderate cases occurred at baseline pre-application. During the follow-up visits (maximum number in any group throughout the study was N=2), most LSRs were mild in severity and no new cases occurred. Erythema was the most frequently observed LSR.

Safety Laboratory Tests

No notable laboratory tests' trends were noted in any of the treatment groups, similarly laboratory changes from baseline during the study period were generally unremarkable from baseline to week 12/EOS.

DISCUSSION

Clascoterone cream represents the first potential topical androgen receptor inhibitor for the treatment of acne vulgaris. This study provides preliminary evidence of the efficacy and safety of clascoterone topical cream, 1% in persons with facial acne and the foundation for determining the concentration of clascoterone cream for advancement to Phase 3.

Two pivotal Phase 3 trials were initiated to assess the efficacy and safety of clascoterone topical cream, 1% compared with vehicle in >1400 subjects, ≥9 years of age, with moderate to severe acne (NCT 02608476) and recently concluded with final results forthcoming. An open label extension study is underway (NCT: 02682264).

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The authors are fully responsible for the content of this manuscript.

DISCLOSURE

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REFERENCES

1. Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol.* 2013; 168(3):474-485.
2. American Academy of Dermatology. Skin Conditions by the Numbers. Available at: https://www.aad.org/media/stats/conditions/skin-conditions-by-the-numbers. Accessed December 20, 2018.
3. Harper JC. Evaluating hyperandrogenism: a challenge in acne management. *J Drugs Dermatol.* 2008; 7(6):527-30.
4. Lai JJ, Chang P, Lai KP, et al. The role of androgen and androgen receptor in skin-related disorders. *Arch Dermatol Res.* 2012; 304(7):499-510.
5. Celasco G, Moro L, Bozzella R, et al. Biological profile of cortexolone 17alpha-propionate (CB-03-01), a new topical and peripherally selective androgen antagonist. *Arzneimittelforschung.* 2004; 54(12):881-886.
6. Ferraboschi P, Legnani L, Celasco G, et al. A full conformational characterization of antiandrogen cortexolone-17α-propionate and related compounds through theoretical calculations and nuclear magnetic resonance spectroscopy. *Med Chem Commun.* 2014; 5:904-14.
7. Cortexolone 17α-propionate (clascoterone) is a novel androgen receptor antagonist that inhibits production of lipids and inflammatory cytokines from sebocytes in vitro. Rosette C, Agan FJ, Mazzetti A, Moro L, Gerloni M. *J Drugs Dermatol.* 2019 May 1; 18 (5): 217:223
8. Mazzetti A, Moro L, Gerloni M, Cartwright M. Pharmacokinetic profile, safety, and tolerability of clascoterone (Cortexolone 17-alpha propionate, CB-03-01) topical cream 1% in subjects with mild to moderate acne vulgaris: an open-label phase 2a study. *J Drugs Dermatol.* Submitted and in review.
9. Data on File. Cassiopea SpA. 2019.
10. Dehertogh R, Hoet JJ, Materazzi F, Ekka E. The fate of 1,2-3H Cortexolone in Man. *Acta Endocrinol* (Copenh). 196447:165-76.

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ORIGINAL ARTICLE Journal of Drugs in Dermatology

DNA Repair Enzyme Containing Lip Balm for the Treatment of Actinic Cheilitis: A Pilot Study

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ABSTRACT

Background: DNA repair enzymes have been shown to reduce actinic keratoses and non-melanoma skin cancers, but their use for the treatment of actinic cheilitis has not been studied.

Objective: The purpose of this pilot study was to examine the efficacy of a DNA repair enzyme lip balm containing T4 endonuclease in reducing the severity of actinic cheilitis in patients who applied the lip balm twice daily for 3 months.

Methods: We performed a prospective study in which 29 patients with a diagnosis of actinic cheilitis underwent a 3-month trial using a topical DNA repair enzyme lip balm containing T4 endonuclease applied to the lips twice daily. The primary, objective outcome was percent of actinic lip involvement, measured using computer software by dividing the calculated affected surface area by the calculated total surface area. Additional outcomes included pre- and post-intervention determination of an actinic cheilitis score on the Actinic Cheilitis Scale, which visually and tactilely quantifies the percentage of lip involvement, amount of roughness, erythema, and tenderness as well as a physician assessment using the Global Aesthetic Improvement Scale.

Results: Twenty-five of the 29 enrolled patients completed the trial. The lip balm significantly decreased the percentage of affected lip surface area ($P<0.0001$). According to the Actinic Cheilitis Scale, data demonstrate that the lip balm significantly decreased the percentage of lip involvement ($P=0.002$), amount of roughness ($P=0.0012$)), erythema ($P=0.0020$), and tenderness ($P=0.0175$). The total Actinic Cheilitis Scale score also significantly improved after the 3-month treatment period ($P<0.0001$). According to the Global Aesthetic Improvement Scale, the average score for all 26 patients was 1.04.

Conclusion: This study suggests that topical DNA repair enzyme lip balm containing T4 Endonuclease could potentially be a safe and efficacious way to improve and treat actinic cheilitis.

J Drugs Dermatol. 2019;18(6):576-579.

INTRODUCTION

Actinic cheilitis (AC), also known as actinic keratosis (AK) of the lips, is a common lesion of the lower lip caused by chronic exposure to ultraviolet light.[1] Among sun-exposed populations, the prevalence of AC is nearly 10%, and most commonly affects white, older males.[2] AC is characterized by scaling, dryness, edema, erythema, tenderness, fissuring, crusting, and discoloration of the affected lip.[3] As a precancerous condition, anywhere from 10 to 30% of cases can potentially undergo malignant transformation into squamous cell carcinoma (SCC).[4] Further, almost all SCCs located on the lower lip originate from AC.[1]

The current standard of care for actinic cheilitis includes cryotherapy, electrocautery, vermilionectomy, or laser ablation.[5] While there are no FDA-approved topical therapies, retinoids, 5-fluorouracil, imiquimod, and photodynamic therapy are often used by practicing clinicians.[6] While these procedures and topical methods confer acceptable clinical improvement, many are associated with significant side effects including pain, irritation, redness, edema, and significant downtime. The discomfort caused by these therapies often leads to patient-initiated discontinuation and, subsequent, reduced clinical efficacy. From the patient perspective, there is a need for less inflammatory, more comfortable treatment approaches for AC.

Topical DNA repair enzymes may serve as a promising option for the management of actinic cheilitis and the prevention of skin cancer development. Studies have demonstrated the efficacy of topical DNA repair enzymes, specifically, T4 endonuclease V (T4N5), in decreasing basal cell carcinomas, squamous cell carcinomas and actinic keratoses,[7-9] however, these enzymes have yet to be studied in the management of AC. The

objective of the present study is to assess the efficacy of a DNA repair enzyme lip balm containing T4N5 in reducing the severity of actinic cheilitis in patients applied twice daily for a period of 3 months.

MATERIALS AND METHODS

Twenty-nine patients with a diagnosis of actinic cheilitis were recruited from a private dermatology office in Southern California. Inclusion criteria included patients with a diagnosis of actinic cheilitis who were in good health and able to provide informed consent. Exclusion criteria included patients under the age of 18, pregnant or breastfeeding women, prior treatment of actinic cheilitis within the past 3 months, prior ablative laser therapy to the lips, including fractional erbium and CO_2 lasers, presence of any skin disease that might interfere with the study treatments, presence of hypertrophic and hyperkeratotic lesions or cutaneous horns within the treatment area, and any diagnosis of untreated skin cancer of the lip.

Patients were instructed to apply the DNA repair enzyme lip balm twice a day, refrain from eating or drinking for 10 minutes after application, and refrain from using other lip products for the duration of the study. Subjects were given a bland lip balm with a sun protective factor of 30 to be used prior to when outdoors during the day. Patients followed-up at 1-month intervals for the duration of the treatment. Photos were taken at each visit. Images taken at baseline and at the final visit at 3-month visit were assessed. The primary, objective outcome measure was percentage of AC lip involvement, which was calculated using computer software, Adobe Photoshop Creative Suite Standard Design 6 (manufactured by Adobe Inc. in San Jose, CA). The entire lower lip was traced from a two-dimensional photograph to calculate a total surface area. Then, AC lesions on the lower lip were outlined to generate individual affected surface areas. These were summed, and then divided by the total surface area of the lower lip. A percentage of involvement was then calculated for all lip photos at baseline and at 3-months. A secondary outcome measure was clinical efficacy defined as a reduced actinic cheilitis score on the Actinic Cheilitis Scale (Figure 1). A tertiary outcome measure included physician scoring using the Global Aesthetic Improvement Scale by a board-certified Dermatologist (Figure 2).

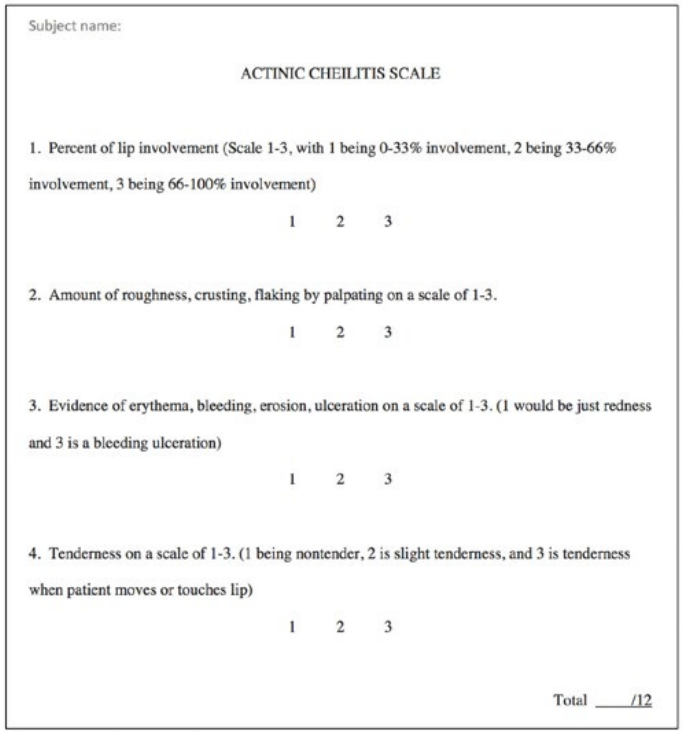
Statistical analyses of the primary and secondary objectives were performed by paired (dependent) t-tests, setting statistical significance to $P<0.05$.

RESULTS

Twenty-five out of 29 patients completed the study. Nineteen were female and 10 were male. Patients ranged in age from 22-89 years (mean age was 59.7 years). Table 1 details the percentage of affected surface area of the lower lip at baseline and after 3-months. There was an an average reduction of affected lip surface area of 13.8%, which proved to be statistically significant when baseline and 3-month percentages were compared ($P<0.0001$).

Actinic Cheilitis Scale (ACS) scores at baseline and after three months of treatment are reported in Table 1. The average ACS score at baseline was 7.7 and at the end of the study period was 5.9 ($P<0.0001$). There was also significant decrease in all four components included in the ACS score: percentage of lip involvement, amount of roughness, erythema, and patient-reported tenderness ($P=0.002$; 0.0012; 0.002; 0.0175, respectively). Eighty percent of patients had an improvement in their overall ACS score, 20% had no change in their score, and none had

FIGURE 1. Actinic Cheilitis Scale.



Subject name:

ACTINIC CHEILITIS SCALE

1. Percent of lip involvement (Scale 1-3, with 1 being 0-33% involvement, 2 being 33-66% involvement, 3 being 66-100% involvement)

1 2 3

2. Amount of roughness, crusting, flaking by palpating on a scale of 1-3.

1 2 3

3. Evidence of erythema, bleeding, erosion, ulceration on a scale of 1-3. (1 would be just redness and 3 is a bleeding ulceration)

1 2 3

4. Tenderness on a scale of 1-3. (1 being nontender, 2 is slight tenderness, and 3 is tenderness when patient moves or touches lip)

1 2 3

Total ____/12

FIGURE 2. Global Aesthetic Improvement Scale (GAIS).

(3) Very Much Improved	Optimal cosmetic result; complete disappearance of lentigines
(2) Much Improved	Marked improvement in appearance from the initial condition, but not completely optimal
(1) Improved	Obvious improvement in appearance from the initial condition, but a touch-up is indicated
(0) No Change	The appearance is essentially the same as the original condition
(-1) Worse	The appearance is worse than the original condition

TABLE 1.

Percentage of Lower Lip Involvement, as Calculated by Affected Surface Area Divided by Total Surface Area of the Lower Lip, at Baseline and 3-Months, and Percent Improvement		
Percentage of Affected Total Lower Lip Surface Area at Baseline (%)	Percentage of Affected Total Lower Lip Surface Area at 3-Months (%)	Percent Improvement (%)
17	11.3	5.7
43	20.1	22.9
19.2	19.8	-0.6
27.3	13.5	13.8
32	16.3	15.7
22.9	21.5	1.4
17.6	11.9	5.7
23.3	8.3	15
29	12.7	16.3
35	16.9	18.1
55.9	27.3	28.6
33.3	25.7	7.6
31.9	26.3	5.6
48.8	27.1	21.7
54	42.5	11.5
28.8	20.4	8.4
48.5	17.3	31.2
38	29.2	8.8
42.5	28.9	13.6
35.1	30.2	4.9
28.1	10.9	17.2
38.3	15.9	22.4
31.8	20.1	11.7
46.7	11	35.7
1.5	0	1.5

TABLE 2.

Average Actinic Cheilitis Scale Scores					
	Pre	STD Deviation	Post	STD Deviation	*P*-value by Paired T-Test
% Involvement	2.4	0.7	2.0	0.8	0.0020
Flaking	2.1	0.5	1.6	0.6	0.0012
Erythema	1.7	0.6	1.3	0.6	0.0020
Tenderness	1.4	0.5	1.1	0.4	0.0175
Total Score	7.7	2.0	5.9	1.9	<0.0001

TABLE 3.

Changes in Actinic Cheilitis Scale	
	% Patients (N)
Improvement in Actinic Cheilitis Scale Score	80 (20)
No Improvement in Actinic Cheilitis Scale Score	20 (5)
Worsening of Actinic Cheilitis Scale Score	0 (0)

FIGURE 3A AND 3B. 73-year-old female at baseline (3A) and after 3 months of treatment (3B).

(3A) (3B)

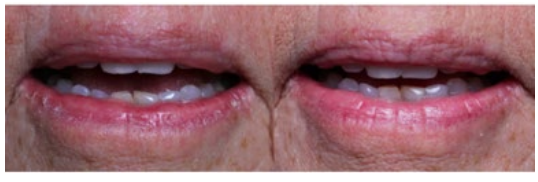


FIGURE 4A AND 4B. 73-year-old female at baseline (4A) and after 3 months of treatment (4B).

(4A) (4B)

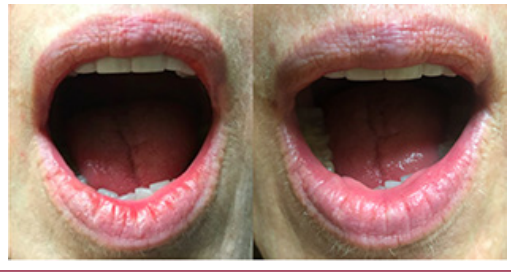


FIGURE 5A AND 5B. 55-year-old female at baseline (5A) and after 3 months of treatment (5B).

(5A) (5B)

FIGURE 6A AND 6B. 79-year-old male at baseline (6A) and after 3 months of treatment (6B).

(6A) (6B)

worsening of their score (Table 2). According to GAIS, the average improvement was 1.04, indicating obvious improvement on visual assessment. Before and after photographs of four patients are shown in Figures 3 through 6. No adverse events were reported with use of the topical lip balm.

DISCUSSION

A variety of treatments are available for actinic cheilitis, many of which are either invasive or associated with undesirable side effects, such as pain, irritation, erythema, edema and significant downtime. These adverse effects often limit patient compliance and, therefore, their efficacy. Topical DNA repair enzymes, on the other hand, have no side effects and can be used indefinitely in a safe and effective manner, as demonstrated by this pilot study and previous studies.

Topical T4 Endonuclease V (T4N5), a DNA repair enzyme derived from the UV-resistant microbe *Micrococcus luteus*, has shown promise in skin cancer prevention. T4N5 enhances DNA repair by removing cyclobutane pyrimidine dimers (CPDs) induced by UVR. To efficiently penetrate the stratum cornum, this enzyme is encapsulated within liposomes, which facilitate entry into keratinocyte nuclei.[10-12] Once exposed to CPDs, T4N5 repairs damaged DNA by catalyzing two reactions: the first uses glycosylase, which releases thymine and causes an apurinic site; the second involves lyase, which incises the phosphodiester backbone, causing a single stranded break. An exonuclease then removes bases around this site, and a polymerase fills the gap, thereby repairing the photodamaged DNA.[14]

Both in vitro and in vivo studies have demonstrated the protective benefits of topical DNA repair enzymes. T4N5 has been shown to reduce the number of CPDs in both mice and human skin organ cultures.[15] Further, a prospective, multicenter, double-blinded study (n=30) demonstrated a 68% reduction in new AKs (P=0.004) and a 30% reduction in new BCCs (p=0.006) in patients with Xeroderma Pigmentosum after use of topical T4N5 for one year.[7] DeBoyes et al[9] and Stoddard et al.[8] confirmed the ability of T4N5 to reduce AKs in their respective clinical trials. These findings suggest that topical application of T4E may be helpful in reduction of pre-malignant lesions and, in turn, skin cancer prevention.

Our present study provides further supportive data that topical DNA repair enzymes can help to repair photodamaged skin. The results demonstrate that twice daily application of topical DNA repair enzyme lip balm for 12 weeks decreased actinic cheilitis in the majority patients, as defined by the percentage of involved lip surface area, the ACS score, and physician GAIS. Our study also demonstrates that the lip balm may improve symptoms of AC, such as tenderness, flakiness, dryness, and ulceration. Such results suggest that DNA repair enzyme topical vehicles can contribute as another modality in skin cancer chemoprevention. They provide clinically beneficial results with minimal to no adverse effects, when compared to other topical options, such as retinoids, 5-Fluorouracil, and Imiquimod.

Limitations of this pilot study include a relatively short follow-up time of three months and small sample size. Further randomized controlled studies employing larger patient population with a longer follow-up period, and varying frequencies of daily lip balm application, are needed to confirm our data and assess the long-term effects of topical DNA repair enzyme lip balm. It will be important to demonstrate that topical DNA repair enzyme products can not only improve AC, but can also decrease the incidence of SCC on the lip. Additionally, selection bias may exist within our study population, as the four patients who failed to complete the study may have been unhappy with the product or failed to see any significant improvement quickly enough to meet their expectations. Adherence to study protocol may have also affected our results, as it is difficult to control for strict patient compliance in trials of this nature. Additionally, 2 of our patients moved out of state during the study period and sent self-taken photos for final assessment, making it more difficult to accurately quantify AC lesions and qualify overall improvement. Finally, our study protocol included twice daily application of lip balm; future studies may want to examine the effects of more or less frequent application.

In conclusion, this study suggests that topical DNA repair enzyme lip balm can be used twice daily without inflammatory adverse effects and may potentially be an efficacious means to manage actinic cheilitis.

DISCLOSURES

The authors have no conflicts of interest to declare.

REFERENCES

1. Gomes JO, de Vasconcelos Carvalho M, Fonseca FP, et al. CD 1a+ and CD 83+ Langerhans cells are reduced in lower lip squamous cell carcinoma. *J Oral Pathol Med.* 2016;45(6):433-9.
2. Miranda AM, Soares LG, Ferrari TM, et al. Prevalence of actinic cheilitis in a population of agricultural sugarcane workers. *Acta Odontol Latinoam.* 2012;25(2):201-7.
3. Cohen JL. Erbium laser resurfacing for actinic cheilitis. *J Drugs Dermatol.* 2013;12(11):1290-2.
4. Lopes ML, Silva Júnior FL, Lima KC, et al. Clinicopathological profile and management of 161 cases of actinic cheilitis. *An Bras Dermatol.* 2015;90(4):505-12.
5. Shah AY, Doherty SD, Rosen T. Actinic cheilitis: a treatment review. *Int J Dermatol.* 2010;49:1225-1234.
6. Dufresne RG, Curlin MU. Actinic Cheilitis. *Dermatol Surg.* 1997; 23(1):15-21.
7. Yarosh D, Klein J, O'Connor A, et al. Effect of topically applied T4 endonuclease V in liposomes on skin cancer in xeroderma pigmentosum: a randomised study. *Lancet.* 2001;357(9260):926-9.
8. Stoddard M, Herrmann J, Moy L, Moy R. Improvement of actinic keratoses using topical DNA repair enzymes: A randomized placebo-controlled trial. *J Drugs Dermatol.* 2017;16(10):1030-1034.
9. DeBoyes T, Kouba D, Ozog D, et al. Reduced number of actinic keratoses with topical application of DNA repair enzyme creams. *J Drugs Dermatol.* 2010;9(12):1519-21.
10. Kabir Y, Seidel R, Mcknight B, Moy R. DNA repair enzymes: an important role in skin cancer prevention and reversal of photodamage--a review of the literature. *J Drugs Dermatol.* 2015;14(3):297-303.
11. Yarosh D, Bucana C, Cox P, et al. Localization of liposomes containing a DNA repair enzyme in murine skin. *J Inves Dermatol.* 1994;103(4):461-8.
12. Yarosh D, Klein J. The role of liposomal delivery in cutaneous DNA repair. *Adv Drug Deliv Rev.* 1996;18(3):325-33.
13. Kuraoka I. Diversity of endonuclease V: From DNA repair to RNA editing. *Biomolecules.* 2015;5(4):2194-206.
14. Yarosh D, Alas LG, Yee V, et al. Pyrimidine dimer removal enhanced by DNA repair liposomes reduces the incidence of UV skin cancer in mice. *Cancer Res.* 1992;52(15):4227-31.

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Connecting the Dots: From Skin Barrier Dysfunction to Allergic Sensitization, and the Role of Moisturizers in Repairing the Skin Barrier

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ABSTRACT

The skin is one of the largest immunologic organs in the body and a continuous target for allergic and immunologic responses. Impairment of the skin barrier increases the likelihood of external antigens and pathogens entering and creating inflammation, which can potentially lead to skin infections, allergies, and chronic inflammatory diseases such as atopic and contact dermatitis. Functionally, the skin barrier can be divided into four different levels. From outermost to innermost, these highly interdependent levels are the microbiome, chemical, physical, and immune levels. The objective of this review is to provide an update on current knowledge about the relationship between skin barrier function and how dysfunction at each level of the skin barrier can lead to allergic sensitization, contact dermatitis, and the atopic march, and examine how to best repair and maintain this barrier through the use of moisturizers.

J Drugs Dermatol. 2019;18(6):581-586.

INTRODUCTION

The skin is one of the largest immunologic organs in the body and a continuous target for allergic and immunologic responses. Rising incidences of allergies have been reported worldwide. While the cause of this rise is not totally clear, it has been attributed to factors such as poor nutrition, stress, use of antibiotics, and growing up in clean urban homes while exposed externally to high air pollution.[1-5] The skin barrier is the first interface between the environment and our immune system. This interface is constantly exposed to endogenous and exogenous factors including ultraviolet radiation, pollution, and damaging skincare products. Impairment of the skin barrier increases the likelihood of external antigens, irritants, and pathogens passing into the skin and driving inflammation, potentially leading to skin infections, allergies, and chronic inflammatory skin diseases such as atopic dermatitis (AD) and contact dermatitis (CD).[6] This phenomenon has been referred to as "transcutaneous sensitization", and is highly dependent on skin barrier dysfunction.[7]

Skin Barrier Anatomy

Anatomically, the skin barrier can be divided into the epidermis and the dermis. The epidermis primarily consists of keratinocytes arranged in several layers, with the stratum corneum (SC) at the top, a layer of cornified keratinocytes that physically prevents invaders from entering. The dermis contains collagen and elastin fibers, fibroblasts, proteoglycans, and nerve endings.

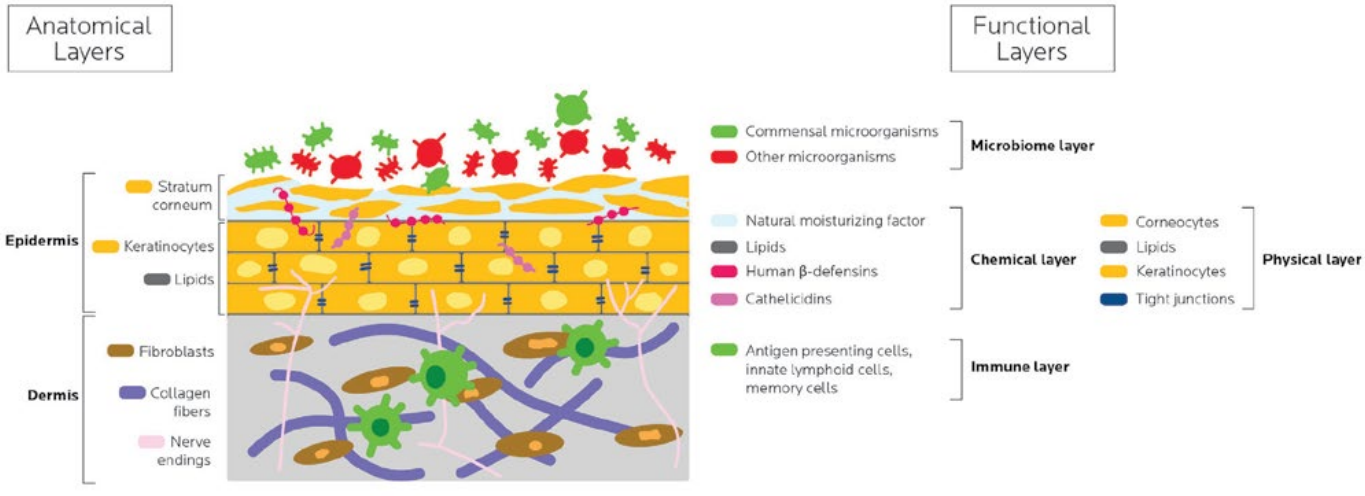
Functionally, the skin barrier can be divided into four strata: the microbiome, chemical, physical, and immune layers (Figure 1). The microbiome layer consists of living microbial communities. The chemical layer includes natural moisturizing factors (NMF), human β-defensins, and the acid mantle, which maintains an acidic surface pH.[8] Tight junctions and the SC constitute important parts of the physical layer, which also produces some of the compounds of the chemical layer. Sensing danger signals through pathogen- and damage-associated molecular patterns, resident immune cells of the immune layer work to clear invasions, repair the barrier, and maintain homeostasis. While each layer has unique functions, it also works interdependently in upholding overall integrity of the skin barrier.[9]

The Skin Microbiota and Dysbiosis

Like the gut microbiota, the healthy skin microbiota is fairly stable.[10,11] It is populated by commensal organisms including bacteria, viruses, fungi, and mites, with the *Staphylococcus*, *Cutibacterium*, and *Corynebacterium* genus dominating. It is thought that commensal bacteria regulate potentially pathogenic species. As the outermost layer, microbial communities are first responders to changes in the environment and transmit signals to the immune system.[9,12]

Dysbiosis, or disruption of balance in the microbiome layer, has been extensively studied in the context of AD, the first

FIGURE 1. Anatomical and functional layers of the skin barrier.



step of the atopic march.[13] In AD skin, *Staphylococcus aureus* is more abundant than normal, with reduced populations of other species. While exact mechanisms of dysbiosis contributing to barrier disruption have not been fully elucidated, several factors likely contribute, including the production of exotoxins by *Staphylococcus aureus*.[14] The distribution of bacterial communities on the cutaneous surface depends on factors such as moisture content, temperature, environment, and sebaceous gland abundance.[15] Regulating skin microbiota could be one way to control AD, restore the skin barrier, and potentially prevent subsequent development of IgE sensitization and atopic march.[16-18]

The Chemical Skin Barrier

The chemical layer includes antimicrobial compounds such as human β-defensins, NMF, and lipids. NMF includes hygroscopic compounds, amino acids, and their derivatives. Many of these are products of filaggrin breakdown, some of which may have antimicrobial properties.[9] Human β-defensins, or host peptides in the skin known for their direct antimicrobial activity, have been shown to attract immune effector cells and induce cytokine and chemokine production in keratinocytes. They also regulate tight junction and epidermal barrier function.[19,20] Cathelicidins are another group of antimicrobial peptides that play a similar role.[21] Commensal skin bacteria also produce antimicrobial peptides that can protect against *Staphylococcus aureus*.[18]

In healthy individuals, the skin pH is generally maintained between 4-6, and deviation can result in abnormal permeability.[9] Removal of natural antimicrobial peptides and elevation of skin pH from the use of alkaline products create an unfavorable environment for the healthy skin microbiota, further demonstrating the interdependence of the levels.[22] Additionally, following experimental skin barrier disruption and provocation of irritant contact dermatitis (ICD), changes in skin lipid composition were reported.[23] The sulfur-rich part of the SC may act as a redox barrier, buffering chemicals coming into contact with the skin.[24]

The Physical Skin Barrier

Disruption of the physical layer of the skin barrier enhances entry of foreign substances. Corneocytes, which are flattened and denucleated mature keratinocytes, constitute the "bricks" of the SC, while lipid-rich "mortar" fills the gaps between.[25] Below the SC is the stratum granulosum, made of keratinocytes that have granules containing proteins such as filaggrin. Keratinocytes also produce lipids such as triglycerides and cholesterols functioning as part of the chemical level. Tight junction proteins connect adjacent keratinocytes within the stratum granulosum to form a barrier against water and solutes.[9]

Filaggrin, an important protein of the epithelial barrier, aggregates and organizes keratin filaments.[26] Mutations in the gene for filaggrin are a major risk factor for developing AD.[27] Defects in skin barrier result from a combination of factors including filaggrin defects and deficiency of other skin barrier proteins, enhancing allergen sensitization via the skin.[28] Importantly, even for individuals with normal filaggrin genes, in the presence of inflammatory mediators, Th2 signaling increases susceptibility to AD.[29] Specifically, keratinocytes differentiated in the presence of Th2 cytokines IL-4 and IL-13 demonstrate decreased filaggrin expression.[30] This may be why individuals with AD are more likely to acquire CD.[23,31] Mutations in the same gene have been linked to increased risk of developing food allergies.[32]

Chronic skin diseases including AD, ichthyosis, and psoriasis often present with a disturbed SC. Patients with these diseases are advised to avoid contact with irritants or allergens that can lead to CD.[23]

The Immune Skin Barrier

The immune layer includes resident antigen presenting cells, innate lymphoid cells, adaptive memory cells, and others, all working together. Because cells of the immune level are distributed throughout the skin, this level is highly intertwined with the others. It responds to various signals and directs subsequent behavior of the epithelium.[9] For example, cells in the skin express toll-like receptors, a type of pattern recognition receptor that responds to pathogen-associated molecular patterns.[33,34] When these receptors are engaged, cells secrete substances such as cytokines and human β-defensins.[15] Following impairment of physical barrier, allergens and irritants can come into contact with cells of the immune barrier, particularly Langerhans cells, which process these exogenous haptens and initiate T-cell responses.[23] Previous research has shown that disruption of the physical barrier subsequently leads to an increase in Langerhans cells even in the basal layers and upper epidermis where these cells are not usually found. Increased numbers of epidermal Langerhans cells have also been found in allergic contact dermatitis (ACD) and ICD.[35]

Skin Barrier Dysfunction Can Lead to Allergic Sensitization and Atopic March

Disruptions to the skin barrier increase the likelihood of irritants, pathogens, and allergens provoking inflammatory responses. Because skin barrier compromise can consequentially lead to other allergic reactions such as to food and potentially progress to diseases such as CD, it seems especially important to address disruptions early. Skin barrier disruption has been shown to cause AD early in life, which can subsequently lead to allergic rhinitis and asthma, a phenomenon known as the atopic march.[36] AD is a skin disease that causes chronic pruritus often beginning in the first years of life and resolving by adulthood in only about 60% of the population. Numerous studies have pointed to AD as the first step in the progression of the atopic march.[37]

Furthermore, allergies can develop by sensitization through skin.[26] Food sensitization is six times more likely to develop in children with AD than in those without.[38] A study of adult workers at a mouse research facility found that physician-diagnosed eczema was a risk factor for mouse sensitization as determined through skin-prick testing and suggests that skin barrier dysfunction may increase risks of aeroallergen sensitization not only in childhood but throughout life.[39]

However, allergies can develop as a consequence of skin barrier defects even in the absence of the development of AD and the atopic march. In fact, neonatal skin barrier dysfunction at birth predicts food allergies at 2 years of age, even without AD.[40] Similarly, even in the absence of AD, children with skin barrier defects are more likely to develop asthma.[26]

Skin Barrier Dysfunction Can Lead to Contact Dermatitis

CD can be irritant (80%) or allergic (20%) and, unlike AD, can develop later in life. ICD is a non-immunologic, inflammatory reaction to irritating agents including solvents, detergents, alcohol, and other chemicals which result in dose-dependent direct tissue damage. Excessive wetness, due to prolonged contact with water, perspiration, or bodily fluids can also lead to ICD. ICD lesions are typically erythematous, dry, possibly edematous and fissuring, with symptoms of burning, tingling or soreness within minutes to hours of contact with the irritant. ACD is an immunologic, delayed-type hypersensitivity reaction to an allergen, which is usually a small molecular weight molecule or hapten that conjugates with skin proteins and induces activated epidermal keratinocytes to release inflammatory cytokines. This immunologic response eventually leads to sensitization to an allergen upon initial contact, and upon subsequent exposure, an elicitation phase occurs. The main symptoms of ACD are pruritus and the appearance of an erythematous eruption, typically scaly, edematous, or vesicular in the acute stage and lichenified in the chronic stage. The cutaneous eruption due to ACD is usually delayed by a few days.[31]

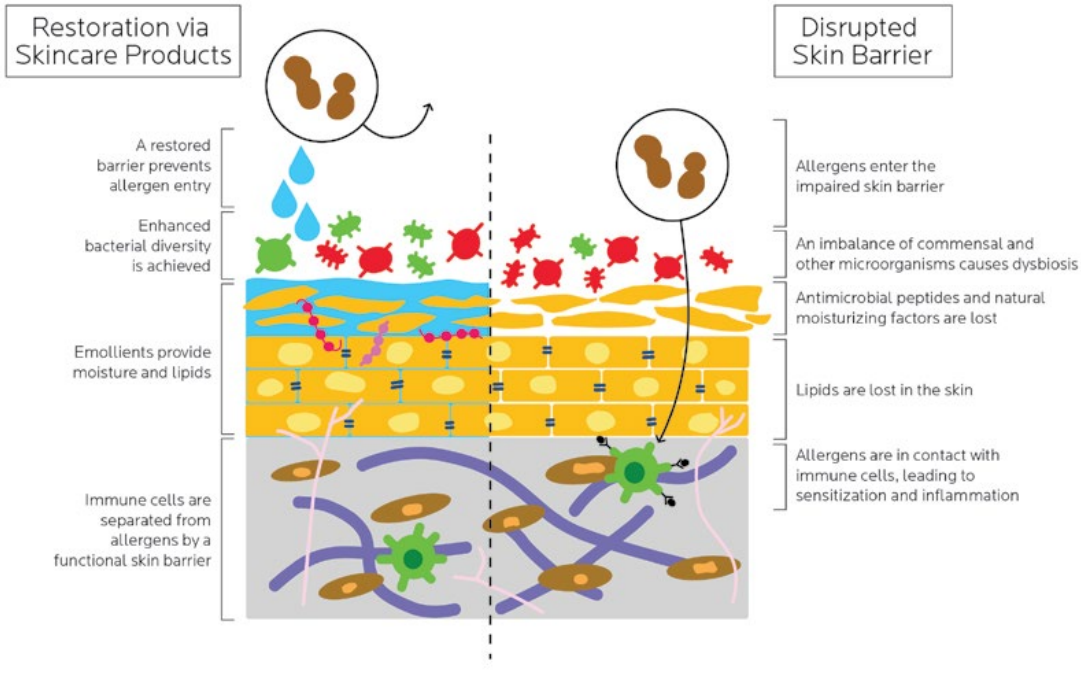
Irritants and allergens were once strictly distinguished. However, the distinction is now blurring, as in many cases, CD cannot be definitively attributed to irritant or allergic mechanisms by clinical observation. ICD and ACD commonly overlap as many allergens at high enough concentrations can also act as irritants. For example, strong allergens such as poison ivy are also irritants.[23] Dysfunctional skin barriers increase the chance of allergen entry into the epidermis and understanding how to minimize penetration of chemicals is important in preventing CD.

Repair of the Skin Barrier May Be a Therapeutic Strategy in the Prevention of Allergic Sensitization, Atopic March, and Contact Dermatitis

Dysfunction at any functional level of the skin barrier can lead to atopic march, allergies, and CD; therefore, repair of the barrier before these conditions progress is essential. Most research on early intervention in skin barrier repair pertains to AD, however, similar logic can be presumed for prevention of ACD, as ACD shares molecular mechanisms with AD, including increased cellular infiltrates and cytokine activation.[41] Additionally, patients with AD are more likely to develop CD.

As dysfunction can occur in various levels of the cutaneous barrier, repair should, therefore, target multiple levels. Recently, a study on infants evaluating the colonization of pathogens on skin demonstrated that increased commensal staphylococci early in life lowered the risk of developing AD by 12 months. The most prevalent species associated with protection from AD development were *Staphylococcus epidermidis* and *Staphylococcus cohnii*.[42] Furthermore, exposure to antibiotics in the first

FIGURE 2. Restoration of the disrupted skin barrier via skincare products.



year of life increases the risk of childhood AD.[43] Collectively, these findings confirm an important role of skin microbiota in the development of cutaneous tolerance and maintaining the skin barrier against allergens.

AD has also been linked to sensitization to food allergens, leading to food allergies. Randomized trials have been conducted to determine the efficacy of applying emollients to newborn babies to prevent AD development in infancy and in childhood.[44-47] Daily use of one emollient reduced cumulative incidence of AD at six months.[44] Fewer newborns given moisturizers developed AD and those with AD had significantly higher sensitization rates against egg whites.[45] Use of a slightly acidic ceramide-rich emollient on newborns showed a trend toward reduced risk of both AD and food sensitization.[46] Thus, in the context of preventing allergic sensitization, and atopic march, targeting AD through skin barrier repair via emollient usage in infancy is especially important and research indicates there may be an optimal window of time for doing so.[37,48] However, in other skin diseases such as CD that can develop at any age, targeting skin barrier repair via emollient usage later in life may be justified for similar reasons.

The Role of Moisturizers in Skin Barrier Repair

Epicutaneous antigens are sensitizers that lead to allergy development, especially in the setting of a dysfunctional skin barrier. It is important to counsel patients that skincare is as much about what is excluded as it is about what is included in a product. Avoidance of common allergens such as fragrance, unnecessary botanicals, or certain preservatives should be advised, especially for atopic patients.

Emollients can help repair the skin barrier (Figure 2).[44-46] Emollients improve the barrier function of the SC by providing water and lipids, and slightly acidic emollients can potentially enhance ceramide synthesis.[49] Sufficient lipid replacement therapy reduces inflammation and restores epidermal function. Conventional barrier ointments form protective films over the skin barrier which are impermeable to environmental allergens and irritants but can also trap heat in the area, prevent perspiration, and cause discomfort. They may also be perceived as cosmetically unacceptable, which can directly affect adherence.[50] Newer products focus on cosmetically elegant formulations with minimalist ingredient lists, that also seek to promote the delivery of pharmacological substances through the SC.[51]

Recently, the focus of skincare products that enhance the cutaneous barrier has been on targeting the restoration of the microbiome layer.[13,52,53] These newer formulas not only protect the skin but also help manage inflammation and neuromediator activation to preserve both the skin barrier and diversity in microbiota. Incorporation of prebiotics, or components that selectively modulate desired bacterial growth, may be helpful.[15] Prebiotics include ingredients like thermal spring waters, such as from La Roche-Posay, France, which have unique mineral components and trace elements.[54] Additionally, usage of an emollient containing thermal spring waters, shea butter, and

niacinamide has not only been shown to increase bacterial diversity but also to improve AD symptoms.[55]

CONCLUSION

The various functional levels (microbiome, chemical, physical, immune) of the skin barrier are all necessary to maintain skin integrity and are highly interdependent. Dysfunction can occur at solitary or multiple points and may have a domino effect on other levels. It is increasingly clear that barrier dysfunction leads to allergic sensitization, the atopic march, and CD. Thus, maintenance and restoration of the skin barrier are paramount to preventing these conditions. This may be achieved to greater and lesser degrees through the use of various moisturizers.

In an ideal product, each aspect of the skin barrier would be considered. Attributes such as avoiding preservatives that can damage the microbiota while perhaps even having pre- or probiotics to support the microbiota, using pH-neutral and gentle ingredients to support the chemical layer, combining occlusives, humectants, and emollients for the physical barrier, and avoiding fragrance and common allergens and irritants to minimize the chance for immune activation are all desirable and should be considered when evaluating a potential moisturizer.

DISCLOSURES

S. Seité is employee of La Roche-Posay, France. M. Lin has served as a consultant for L'Oreal/La Roche-Posay. P. Lio has served as a consultant and speaker for L'Oreal/La Roche-Posay. He has also been a consultant/advisor for Micreos, Pierre-Fabre, Johnson & Johnson, Syncere Skin Systems, Altus Labs, AOBiome, Galderma, IntraDerm, Unilever, and is a board member of the National Eczema Association. T. Lazic Strugar has served as a consultant for L'Oreal/La Roche-Posay. P. Lio and T. Lazic Strugar received a writing grant from L'Oreal for this manuscript. A. Kuo has no conflicts.

REFERENCES

1. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Body mass index and physical activity in relation to asthma and atopic diseases in young adults. *Respir Med.* 2006;100(9):1518-1525.
2. Bloomfield SF, Rook GAW, Scott EA, Shanahan F, Stanwell-Smith R, Turner P. Time to abandon the hygiene hypothesis: new perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene. *Perspect Public Heal.* 2016;136(4):213-224.
3. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. *Nature.* 2016;529(7585):212-U208.
4. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clin Exp Immunol.* 2010;160(1):1-9.
5. Kuo CH, Kuo HF, Huang CH, Yang SN, Lee MS, Hung CH. Early life exposure to antibiotics and the risk of childhood allergic diseases: an update from the perspective of the hygiene hypothesis. *J Microbiol Immunol Infect.* 2013;46(5):320-329.
6. Gilles S, Akdis C, Lauener R, et al. The role of environmental factors in allergy: A critical reappraisal. *Exp Dermatol.* 2018;27(11):1193-1200.
7. Jin H, He R, Oyoshi M, Geha RS. Animal models of atopic dermatitis. *J Invest Dermatol.* 2009;129(1):31-40.
8. Surber C, Humbert P, Abels C, Maibach H. The acid mantle: a myth or an essential part of skin health? *Curr Probl Dermatol.* 2018;54:1-10.
9. Eyerich S, Eyerich K, Traidl-Hoffmann C, Biedermann T. Cutaneous barriers and skin immunity: differentiating a connected network. *Trends Immunol.* 2018;39(4):315-327.
10. Faith JJ, Guruge JL, Charbonneau M, et al. The long-term stability of the human gut microbiota. *Science.* 2013;341(6141):1237439.
11. Oh J, Byrd AL, Park M, Program NCS, Kong HH, Segre JA. Temporal stability of the human skin microbiome. *Cell.* 2016;165(4):854-866.
12. Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol.* 2011;9(4):244-253.
13. Seite S, Bieber T. Barrier function and microbiotic dysbiosis in atopic dermatitis. *Clin Cosmet Investig Dermatol.* 2015;8:479-483.
14. Nakamura Y, Oscherwitz J, Cease KB, et al. Staphylococcus delta-toxin induces allergic skin disease by activating mast cells. *Nature.* 2013;503(7476):397-401.
15. Baldwin HE, Bhatia ND, Friedman A, Eng RM, Seite S. The role of cutaneous microbiota harmony in maintaining a functional skin barrier. *J Drugs Dermatol.* 2017;16(1):12-18.
16. Bjerre RD, Bandier J, Skov L, Engstrand L, Johansen JD. The role of the skin microbiome in atopic dermatitis: a systematic review. *Br J Dermatol.* 2017;177(5):1272-1278.
17. Kobayashi T, Glatz M, Horiuchi K, et al. Dysbiosis and staphylococcus aureus colonization drives inflammation in atopic dermatitis. *Immunity.* 2015;42(4):756-766.
18. Brunner PM, Leung DYM, Guttman-Yassky E. Immunologic, microbial, and epithelial interactions in atopic dermatitis. *Ann Allergy Asthma Immunol.* 2018;120(1):34-41.
19. Kiatsurayanon C, Niyonsaba F, Smithrithee R, et al. Host defense (Antimicrobial) peptide, human beta-defensin-3, improves the function of the epithelial tight-junction barrier in human keratinocytes. *J Invest Dermatol.* 2014;134(8):2163-2173.
20. Kiatsurayanon C, Ogawa H, Niyonsaba F. The role of host defense peptide human beta-defensins in the maintenance of skin barriers. *Curr Pharm Des.* 2018;24(10):1092-1099.
21. Niyonsaba F, Kiatsurayanon C, Ogawa H. The role of human beta-defensins in allergic diseases. *Clin Exp Allergy.* 2016;46(12):1522-1530.
22. Schmid-Wendtner MH, Korting HC. The pH of the skin surface and its impact on the barrier function. *Skin Pharmacol Phys.* 2006;19(6):296-302.
23. Proksch E, Brasch J. Abnormal epidermal barrier in the pathogenesis of contact dermatitis. *Clin Dermatol.* 2012;30(3):335-344.
24. Pickard C, Louafi F, McGuire C, et al. The cutaneous biochemical redox barrier: a component of the innate immune defenses against sensitization by highly reactive environmental xenobiotics. *J Immunol.* 2009;183(11):7576-7584.
25. Nishifuji K, Yoon JS. The stratum corneum: the rampart of the mammalian body. *Vet Dermatol.* 2013;24(1):60-72 e15-66.
26. Han H, Roan F, Ziegler SF. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. *Immunol Rev.* 2017;278(1):116-130.
27. Howell MD, Kim BE, Gao P, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol.* 2007;120(1):150-155.
28. van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ.* 2009;339:b2433.
29. Liang Y, Chang C, Lu Q. The genetics and epigenetics of atopic dermatitis-filaggrin and other polymorphisms. *Clin Rev Allergy Immunol.* 2016;51(3):315-328.
30. Pellerin L, Henry J, Hsu CY, et al. Defects of filaggrin-like proteins in both lesional and nonlesional atopic skin. *J Allergy Clin Immunol.* 2013;131(4):1094-1102.
31. Fonacier LS, Dreskin SC, Leung DY. Allergic skin diseases. *J Allergy Clin Immunol.* 2010;125(2 Suppl 2):S138-149.
32. Venkataraman D, Soto-Ramirez N, Kurukulaaratchy RJ, et al. Filaggrin loss-of-function mutations are associated with food allergy in childhood and adolescence. *J Allergy Clin Immunol.* 2014;134(4):876-882 e874.
33. Miller LS, Modlin RL. Toll-like receptors in the skin. *Semin Immunopathol.* 2007;29(1):15-26.
34. Volz T, Kaesler S, Biedermann T. Innate immune sensing 2.0 - from linear activation pathways to fine tuned and regulated innate immune networks. *Exp Dermatol.* 2012;21(1):61-69.
35. Proksch E, Brasch J, Sterry W. Integrity of the permeability barrier regulates epidermal Langerhans cell density. *Br J Dermatol.* 1996;134(4):630-638.
36. Weidinger S, Novak N. Atopic dermatitis. *Lancet.* 2016;387(10023):1109-1122.
37. Bantz SK, Zhu Z, Zheng T. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *J Clin Cell Immunol.* 2014;5(2).
38. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immun.* 2016;137(4):1071-1078.
39. Grant T, Dantzer J, Keet C, et al. Physician-diagnosed eczema is an independent risk factor for incident mouse skin test sensitization in adults. *Allergy Asthma Proc.* 2018;39(4):311-315.
40. Kelleher MM, Dunn-Galvin A, Gray C, et al. Skin barrier impairment at birth predicts food allergy at 2 years of age. *J Allergy Clin Immunol.* 2016;137(4):1111-1116 e1118.

41. Gittler JK, Krueger JG, Guttman-Yassky E. Atopic dermatitis results in intrinsic barrier and immune abnormalities: implications for contact dermatitis. *J Allergy Clin Immunol.* 2013;131(2):300-313.
42. Kennedy EA, Connolly J, Hourihane JO, et al. Skin microbiome before development of atopic dermatitis: Early colonization with commensal staphylococci at 2 months is associated with a lower risk of atopic dermatitis at 1 year. *J Allergy Clin Immun.* 2017;139(1):166-172.
43. Tsakok T, McKeever TM, Yeo L, Flohr C. Does early life exposure to antibiotics increase the risk of eczema? A systematic review. *Brit J Dermatol.* 2013;169(5):983-991.
44. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol.* 2014;134(4):818-823.
45. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol.* 2014;134(4):824-830 e826.
46. Lowe AJ, Su JC, Allen KJ, et al. A randomized trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitization: the PEBBLES pilot study. *Br J Dermatol.* 2018;178(1):e19-e21.
47. Chalmers JR, Haines RH, Mitchell EJ, et al. Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomised controlled trial. *Trials.* 2017;18(1):343.
48. Natsume O, Ohya Y. Recent advancement to prevent the development of allergy and allergic diseases and therapeutic strategy in the perspective of barrier dysfunction. *Allergol Int.* 2018;67(1):24-31.
49. Hachem JP, Crumrine D, Fluhr J, Brown BE, Feingold KR, Elias PM. pH directly regulates epidermal permeability barrier homeostasis, and stratum corneum integrity/cohesion. *J Invest Dermatol.* 2003;121(2):345-353.
50. Del Rosso JQ. Factors influencing optimal skin care and product selection In: Draelos ZD, Thaman LA, eds. *Cosmetic Formulation of Skin Care Products* New York, NY: Taylor & Francis; 2006:115-121.
51. Hon KL, Leung AK, Barankin B. Barrier repair therapy in atopic dermatitis: an overview. *Am J Clin Dermatol.* 2013;14(5):389-399.
52. Lane ME, Hadgraft J, Oliveira G, Vieira R, Mohammed D, Hirata K. Rational formulation design. *Int J Cosmetic Sci.* 2012;34(6):496-501.
53. Al-Ghazzewi FH, Tester RF. Impact of prebiotics and probiotics on skin health. *Benef Microbes.* 2014;5(2):99-107.
54. Seite S. Thermal waters as cosmeceuticals: La Roche-Posay thermal spring water example. *Clin Cosmet Investig Dermatol.* 2013;6:23-28.
55. Seite S, Flores GE, Henley JB, et al. Microbiome of affected and unaffected skin of patients with atopic dermatitis before and after emollient treatment. *J Drugs Dermatol.* 2014;13(11):1365-1372.

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Arterial Occlusion and Necrosis Following Hyaluronic Acid Injection and a Review of the Literature

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ABSTRACT

With the rising popularity of fillers for facial rejuvenation coupled with the paucity of regulations on credentialing of qualified injectors, the number of filler related complications is increasing. Although the majority of complications are mild, vascular occlusion is the most feared and dangerous. Minimizing risk of vascular complications through a comprehensive understanding of vascular anatomy and careful technique is important. Physicians who perform filler injections should also be able to promptly recognize complications and manage them. We report a case of vascular occlusion successfully managed using high dose hyaluronidase and provide a review of the literature including incidence, management, and techniques to prevent vascular complications.

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INTRODUCTION

With the rising popularity of fillers for facial rejuvenation coupled with the paucity of regulations on credentialing of qualified injectors, the number of filler related complications is increasing. Although the majority of complications are mild, vascular occlusion is the most feared and dangerous. Minimizing risk of vascular complications through a comprehensive understanding of vascular anatomy and careful technique is important. Physicians who perform filler injections should also be able to promptly recognize complications and manage them. We report a case of vascular occlusion successfully managed using high dose hyaluronidase and provide a review of the literature including incidence, management, and techniques to prevent vascular complications.

REPORT OF A CASE

A 36-year old woman presented to clinic with necrosis of the left nasolabial fold area and ala following hyaluronic acid injection. The injection was performed by a mobile nurse practitioner two days prior to presentation. 1cc of Juvederm Ultra (hylaluronic acid gel, Allergan, Irvine CA) was reportedly injected using needle technique into bilateral nasolabial folds via 3 injection points per side. She did not recall excessive pain or discomfort during the injection. However, that evening she noted blotchy discoloration and tenderness of the left nasolabial fold. With unremitting symptoms, the patient contacted the nurse practitioner who performed the injection and was advised to continue icing the area. On the second day following the injection, pustules appeared on the left nasolabial fold prompting the patient to seek further evaluation at our clinic.

On examination, a 3 x 2 cm mottled, erythematous plaque with overlying pustules extended from the left upper cutaneous lip to the left nasal tip (Figure 1). Prompt treatment for vascular occlusion was initiated. 2cc (300 U) of hyaluronidase (Hylenex) was injected using a needle into the subcutaneous tissue over the entire left nasolabial fold area and left ala. Other measures were recommended including warm compress, aspirin 80mg BID, and nitroglycerin ointment BID. The patient was started on prophylactic Cephalexin 500mg TID and Valcyclovir 1g BID, as well as a Methylprednisolone taper. Wound care included mupirocin ointment BID as well as petrolatum.

FIGURE 1. Crusting and pustules are present in the nasolabial fold area and lateral nose two days following hyaluronic acid injection.

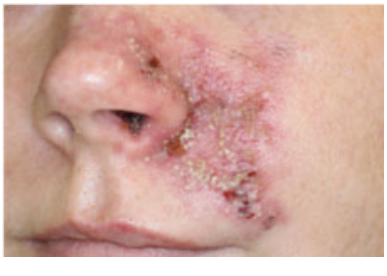


FIGURE 2. Crusting and pustules are resolving two days following hyaluronidase injection.

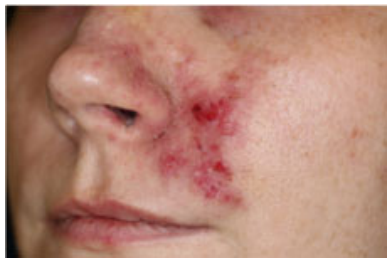


FIGURE 3. Mild erythema is present four weeks following treatment.

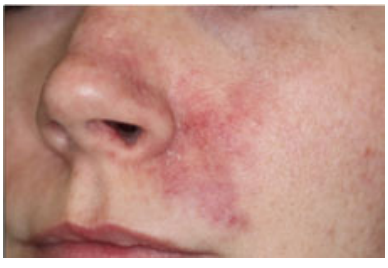
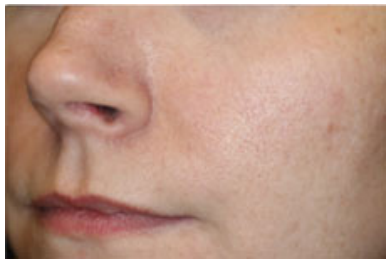


FIGURE 4. The skin has a normal appearance seven months following treatment.



Follow-up the following day revealed less tenderness and erythema but an increased number of pustules. 1cc (150 U) of Hylenex was injected diluted with 1cc of 2% lidocaine using a 27-gauge cannula. Over the next several days, the tenderness and erythema improved significantly (Figure 2). Four days post hyelenx injections the overlying crust was gently debrided and the nitroglycerin ointment was discontinued. Examination one month later revealed only mild erythema and edema (Figure 3). Seven-month follow-up showed an excellent outcome with no noticeable scarring (Figure 4).

DISCUSSION

Incidence of Filler Complications

Fillers are a popular, non-invasive modality for patients to enhance their appearance as they counteract age-related volume loss. The total number of soft-tissue filler treatments for facial rejuvenation has increased dramatically from 652,885 in 2000 to 2,691,265 in 2017.[1] The number and diversity of injectors has also increased. In addition to board certified dermatologists, plastic surgeons, and otolaryngologists. Other physicians not highly trained in facial anatomy perform injections as well as many non-physicians. Depending on each state's regulations, injectors can include nurse practitioners, physician assistants, dentists, registered nurses, and estheticians. Currently, 24 states allow nurse practitioners to order Allergan product without collaboration with a physician. There are many unregulated sources for fillers online and internationally giving rise to an alarming trend.

In most cases, fillers are used without clinically significant complications. The true incidence of complications is difficult to measure. Rayees et al examined reportable adverse events listed in the US Food and Drug Administration's (FDA) and Manufacturer and User Device Experience (MAUDE) databases.[2] The most common complications secondary to hyaluronic acid injections included: swelling (43%), infection (41.5%), and pain (24.0%).[2] While less common, tissue necrosis secondary to vascular occlusion or compression (8.5%), and blindness from embolized filler (0.4%) are the most dreaded.[2]

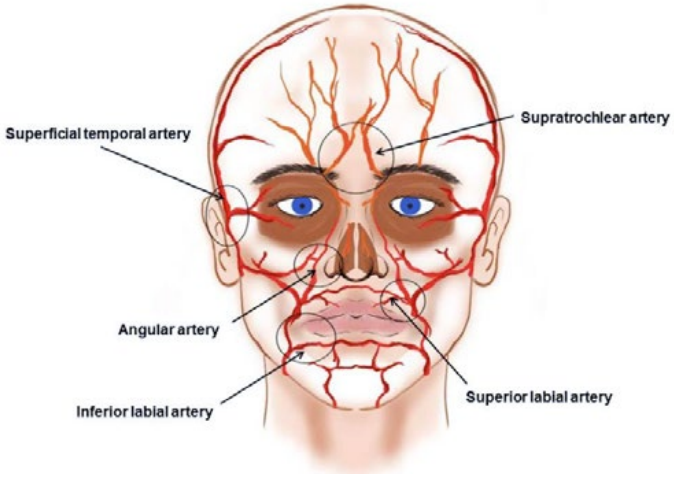
Vascular Occlusion Complications by Location

Vascular occlusion occurs as a result of injection of filler directly into an artery and less commonly by compression of vasculature by extra-vascular filler material. Occlusion can lead to localized tissue ischemia in the distribution of the artery injected. The abundant vascular anastomoses of the face also mean that sites distant to the injection site can also be damaged via embolization.

Intra-arterial injection is more likely to occur in certain areas that are in the vicinity of a named vessel. These "high-risk" areas include the glabella (supratrochlear and supraorbital arteries), nose (lateral and dorsal nasal arteries), alar groove (angular artery), and lip (superior and inferior labial arteries) (Figure 5).[2-7,13] While caution is needed when injecting in these high-risk areas, there are no safe areas. There are reports of vascular occlusion in the cheek, marionette area, and periorbital region.[2-7,13]

Tissue damage can also occur distant to the site of injection via embolization. Nasal injections may lead to inadvertent injection into the dorsal nasal artery. The dorsal nasal artery is a terminal branch of the ophthalmic artery. If the dorsal nasal artery is injected, the filler may travel in a retrograde manner and can reach the ophthalmic arteries. Occlusion of the ophthalmic artery is a devastating consequence often resulting in irrevers-

FIGURE 5. Arterial supply of the face and high-risk areas for necrosis secondary to vascular occlusion following injection.



ible blindness.[8-11] Complications from arterial embolization have been reported in other locations as well. Sudden unilateral hearing loss has been reported following intra-arterial injection of the superficial temporal artery.[12] This is postulated to have occurred due to compromise of the blood supply to the middle ear and tympanic membrane.[12]

Signs and Symptoms of Vascular Occlusion

Signs of vascular occlusion at the time of treatment are often overlooked.[13] The most commonly reported sign is an immediate blanching of the skin that that evolves into a reticulated, violaceous dusky pattern within a few hours of injection or by the next day.[13-14] Immediate pain is an important identifying feature of intra-arterial filler injection though frequently not present. One survey found immediate pain was only reported in 40% of cases, with 28% reporting it later that day and 20% the following day.14 Immediate pain is often not appreciated by the patient due to local anesthetic mixed in most fillers, pretreatment with local anesthesia, or nerve block. Pain is often noted later that day as the lidocaine effect dissipates. Sterile blisters and pustules are frequently reported on day 3 followed by crusting and necrosis after day 6.[14] If there is immediate concern for vascular occlusion, comparing the capillary refill time of the zone in question to the normal skin either adjacent or on the contralateral side is recommended.[14]

Management of Vascular Occlusion

All injectors should have an established treatment protocol for vascular occlusion and supplies in place. Treatment algorithms for the management of vascular occlusion are numerous and evolving. More recent guidelines outline the prompt injection of high dose hyaluronidase and vigorous massage to dissolve the obstruction.[13-15] Repeat injections of hyaluronidase is recommended until improvement is noted.[13-15] Additional measures to oxygenate the tissues through vasodilators and/or hyperbaric oxygen, wound care, and bacterial and viral prophylaxis are also recommended.[13-15]

Restore Perfusion

As tissue plasminogen activator is to heart attacks, hyaluronidase is to arterial occlusion following hyaluronic acid injection. Hyaluronidase is a soluble protein enzyme that degrades hyaluronic acid. Hyaluronic acid-based fillers are the most used dermal fillers due to their efficacy and safety. In the past years, hyaluronidase has been used to reverse exogenously injected hyaluronic acid.[16] Some claim the use of hyaluronidase may even be beneficial even if the filler is not a hyaluronic acid. Hyaluronidase will cause temporary dissolution of endogenous hyaluronic acid, which may relieve occlusive pressure.

Hyaluronidase should be readily accessible in any office that performs hyaluronic acid injections. Several commercial formulations of hyaluronidase are available including Hylenex (purified recombinant human hyaluronidase, supplied with 150 units per mL) and Vitrase (purified ovine testicular hyaluronidase, supplied with 200 units per mL). Both products are considered to be pregnancy category C. Hyaluronidase is associated with a low risk of adverse effects, though there have been reports of hypersensitivity reactions.[17] The risk of allergic reaction is significantly reduced with the use of recombinant human hyaluronidase (Hylenex) compared to hyaluronidase from ovine sources (Vitrase). While allergic skin testing may be advocated before using hyaluronidase in non-emergent cases, this is not advocated when vascular occlusion is suspected.

Hyaluronidase does not need to be injected directly into the vasculature as it readily diffuses into the vascular lumen.[14] Administration with one injection for every 3-4cm of skin manifesting necrosis is recommended.[15] Reconstitution of hyaluronidase with lidocaine is recommended by some experts to facilitate vasodilation.[15] Injected hyaluronidase will be partially deactivated by natural anti-hyaluronidase agents and physically diffuse away from the ischemic region. Additional hyaluronidase is often needed to maintain high concentrations sufficient to dissolve the hyaluronic acid quickly.[14]

While small amounts of hyaluronidase (3-20 U) are recommended in treating nodules or asymmetry, experts recommend much higher dosages in the treatment of vascular occlusion.[13-15] There is no consensus on appropriate hyaluronidase dosage and the interval between doses. Cohen et al recommend treating the ischemic area with a minimum of 200 U of hyaluronidase.[15] Retreatment is performed in one hour if there is no improvement. Delorenzi proposes a protocol with much higher initial doses of hyaluronidase with retreatment on an hourly basis until improvement.[14] The amount of hyaluronidase he recommends is based on the volume of ischemic tissue involved. An estimate of 500 U for 1 vascular territory (ie, half an upper lip) and 1,000U for 2 areas (ie, half an upper lip and nasal involvement).[14]

Some hyaluronic acid fillers may require lower volumes of hyaluronidase than other hyaluronic acid fillers based on their composition. Prior studies have shown that degradation of the Restylane family is more sensitive to degradation than the Juvederm family.[18,19] However, these studies used smaller amounts of hyaluronidase than current protocols are recommending. Newer studies using a higher enzyme-substrate ratio show 90% degradation within 6 hours of exposure among both Restylane and Juvederm.[20]

While the exact timeframe for hyaluronidase injection has not been well established, it should be injected as early as possible and is never too late to initiate treatment. Kim et al conducted an experiment using rabbit ears in which hyaluronic acid filler was injected followed by hyaluronidase injected at 4-hour and 24-hour time points.[21] The authors report that there was signifi-

cant reduction in the areas of necrosis when hyaluronidase was administered at the 4-hour time point while no benefit was observed when injected at 24 hours.[21] Despite Kim et al's findings, several case reports have shown improvement after 24 hour time points.[13]

Minimize Clot Formation

Antiplatelet and anticoagulation medications including aspirin or low molecular weight heparin should be initiated to prevent further clot formation. Aspirin 81 BID or Aspirin 325 BID have been recommended.[13-15]

Tissue Oxygenators

Measures to promote vasodilation are recommended including warm compress, topical nitroglycerin, and hyperbaric oxygen. Warm compresses for 5-10 minutes every 30-60 minutes is appropriate. The use of nitroglycerin paste, although controversial, may be applied up to 2-3 times daily.[22,23] Topical nitroglycerin has been shown to induce a local vasodilatory response in dermal vessels. It is often used by physicians in the setting of filler-induced ischemia. It is available in different formulations including sprays, ointments, pastes, and transdermal patches. Some argue against the use of nitroglycerin as it may not improve perfusion and could further disseminate the product into smaller arterioles and capillaries.[23] It is important to prepare the patient for the side effects of nitroglycerin including severe headaches and light-headedness. Hyperbaric oxygen is an additional treatment that can be used in cases of severe necrosis.[24] It is thought to work by a variety of mechanisms: oxygenation of ischemic tissue, reduction of edema, improvement of ischemic/reperfusion injury, promotion of angiogenesis, and collagen maturation.[24] Six total treatments are recommended BID for 90 minutes each.[24]

Wound Care

Sterile pustules, post ischemic erosions, and granulation tissue should be treated with emollients to prevent crusting and minimize bacterial contamination. Frequent gentle wound debridement of necrotic skin is recommended. Re-epithelization may take 1 to 3 weeks. Erythema and textural changes of the skin may last for 3-12 months.[14,15]

Other

Consider prophylactic antibiotic and antiviral therapy for large areas of necrosis: Valcyclovir 500mg BID and Doxycycline 100mg BID. Antihistamine or corticosteroid taper to decrease swelling can also be considered.

Minimizing the Risk of Intra-Arterial Injection

Prevention of intra-arterial injection relies upon sound anatomical knowledge and precise technique. Sound anatomical knowledge includes knowing the location of the vasculature in the various areas of the face as well as common aberrations. Many skilled injectors have "no fly zones" in which the danger is too high to even consider using a filler. Cannulas are also often used among highly skilled injectors. Cannulas are blunt tipped and have a significant smaller chance of penetrating an artery than a needle.[25] In a survey among 52 skilled injectors who experienced vascular occlusion, needles had been used by 83% of respondents and cannulas by 17%.[13] If injecting with a needle, careful aspiration of the syringe is recommended looking for negative flashback before making any filler injection. A red flash would signal inadvertent arterial placement. Slow injection with low pressure reduces the likelihood of a vasoocclusive episode. For a filler to enter the lumen, it must overcome the back pressure of the vessel. For the filler to further embolize, the injection pressure must exceed the arterial pressure causing product to move through the vasculature against the flow of blood until it passes the origin of the central retinal artery.[3]

Staff and patient education are also important. Patients must be made aware of the risk and symptoms to be concerned about so they may alert the physician as early as possible. Staff must not casually dismiss patient calls with concerns following injections. Obtaining a comprehensive written informed consent is also important. Two-thirds of malpractice cases involving filler involve inadequate informed consent.[2]

CONCLUSION

Even the most experienced injector is at risk for vascular occlusion. Injectors need to have thorough knowledge of filler complications and their appropriate management. Identifying the signs of vascular ischemia is paramount to early treatment. Patients who are promptly diagnosed and treated within 2 days have the best outcomes.[26] Delayed treatments are associated with prolonged wound healing and varying degrees of scarring.[13,26]

DISCLOSURE

The authors have no relevant disclosures to report.

REFERENCES

1. American Society of Plastic Surgeons, 2017 Plastic surgery statistics report.
2. Rayess HM, Svider PF, Hanba C, et al. A Cross-sectional analysis of adverse events and litigation for injectable fillers. *JAMA Facial Plast Surg.* 2018;20(3):207–214. doi:10.1001/jamafacial.2017.1888
3. DeLorenzi C. Complications of injectable filler, part 2: vascular complications. *Aesthet Surg J.* 2014;344:584-600.
4. Requena L, Requena C, Christensen L, Zimmermann US, Kutzner H. Adverse reactions to injectable soft tissue fillers. *J Am Acad Dermatol.* 2011;64:1-34.
5. Park T, Seo S, Kim J, Chang C. Clinical experience with hyaluronic acid-filler complications. *J Plast Reconstr Aesthet Surg.* 2011;64:892- 896.
6. Bailey S, Cohen J, Kenkel J. Etiology, prevention, and treatment of dermal filler complications. *Aesthet Surg J.* 2011;31:110-121.
7. Ozturk C, Li Y, Tung R, Parker L, Piliang M, et al. Complications following injection of soft-tissue fillers. *Aesthet Surg J.* 2013;33:862-877.
8. Sung M, Kim H, Woo K, Kim Y. Ocular ischemia and ischemic oculomotor nerve palsy after vascular embolization of injectable calcium hydroxylapatite filler. *Ophthal Plast Reconstr Surg.* 2010;26:289–291.
9. Lazzeri D, Agostini T, Figus M, Nardi M, Pantalone M, Lazzeri S. Blindness following cosmetic injections of the face. *Plast Reconstr Surg.* 2012;129:994–1012.

10. Park S, Woo S, Park K, Huh J, Jung C, Kwon O. Iatrogenic retinal artery occlusion caused by cosmetic facial filler injections. *Am J Ophthalmol.* 2012;154:653–662.
11. Roberts S, Arthurs B. Severe visual loss and orbital infarction following periorbital aesthetic poly-(L)-lactic acid (PLLA) injection. *Ophthalmic Plast Reconstr Surg.* 2012;28:e68–e70.
12. Henderson R, Reilly D, Cooper J. Hyperbaric oxygen for ischemia due to injection of cosmetic fillers: case report and issues. *Plast Reconstr Surg Glob Open.* 2018;6(1):e1618.
13. Goodman G, Roberts S, Callan P. Experience and management of intravascular injection with facial fillers: results of a multinational survey of experienced injectors. *Aesth Plast Surg.* 2016;40:549.
14. DeLorenzi C. New high dose pulsed hyaluronidase protocol for hyaluronic acid filler vascular adverse events. *Aesth Surg J.* 2017; 37(7):814–825.
15. Cohen J, Biesman B, Dayan S, DeLorenzi C, et al. Treatment of hyaluronic acid filler–induced impending necrosis with hyaluronidase: consensus recommendations. *Aesthet Surg J.* 2015;35(7):844–849.
16. Cavallini M, Gazzola R, Metalla M, Valenti L. The role of hyaluronidase in the treatment of complications from huyaluronic acid dermal fillers. *Aesthet Surg J.* 2013;33(8):1167-1174.
17. Raichura N, Alam V, Jaichandran V, Mistry S, Mukherjee B. Hyaluronidase allergy mimicking orbital cellulitis. *Orbit.* 2018;37(2).
18. Sall I, Ferard G. Comparison of the sensitivity of 11 crosslinked hyaluronic acid gels to bovine testis hyaluronidase. *Polymer Degradation and Stability.* 2007;92:915-9.
19. Jones D, Tezel A, Borrel M. In vitro resistance to degradation of hyaluronic acid dermal fillers by ovine testicular hyluronidase. *Dermatol Surg.* 2010;36:804-9.
20. Flynn T, Thompson D, Hyun S. Molecular weight analysis and enzymatic degradation profiles of the soft-tissue fillers Belotero Balance, Restylane and Juvederm Ultra. *Plast Reconstr Surg.* 2013;132:22s-32s.
21. Kim D, Yoon E, Ji Y, Park S, Lee B, et al. Vascular complications of hyaluronic acid fillers and the role of hyaluronidase in management. *J Plast Reconstr Aesthet Surg.* 2011;64:1590-1595.
22. Kleydman K, Cohen J, Marmur E. Nitroglycerin: a review of its use in the treatment of vascular occlusion after soft tissue augmentation. *Dermatol Surg.* 2012;38(12):1889-97.
23. Hwang C, Morgan P, Pimentel A, Sayre J, et al. rethinking the role of nitroglycerin ointment in ischemic vascular filler complications: an animal model with ICG imaging. *Ophthalmic Plast Reconstr Surg.* 2016;32(2):118-22.
24. Henderson R, Reilly D, Cooper J. Hyperbaric oxygen for ischemia due to injection of cosmetic fillers: case report and issues. *Plast Reconstr Surg Glob Open.* 2018 Jan 11;6(1):e1618.
25. Hexsel D, Soirefmann M, Porto M, Siega C, et al. Double-blind, randomized, controlled clinical trial to compare safety and efficacy of a metallic cannula with that of a standard needle for soft tissue augmentation of the nasolabial folds. *Dermatol Surg.* 2012;38(2):207-14.
26. Sun Z, Zhu G, Wang H, Xu X, et al. Clinical outcomes of impending nasal skin necrosis related to nose and nasolabial fold augmentation with hyaluronic acid fillers. *Plast Reconstr Surg.* 2015;136(4):434e-41e.

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