CONTINUING EDUCATION: Facial Skin Tightening With Microfocused Ultrasound and Dermal Fillers

- HIFEM in Dermatology
- Re-pigmentation of Hypopigmentation
- MFU-V for Acne Scars
- Topical Treatments for Melasma

Image credit page 1080
MinoLira Tablets bring immediate- and sustained-release minocycline together for the first time ever in functionally scored tablets (105 and 135mg) for broad dosing options and safety similar to placebo.  

**INDICATION AND USAGE**

MINOLIRA is indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

MINOLIRA did not demonstrate any effect on non-inflammatory acne lesions. Safety of MINOLIRA has not been established beyond 12 weeks of use. This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, MINOLIRA should be used only as indicated.

**IMPORTANT SAFETY INFORMATION**

- This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.
- Minocycline, like other tetracycline-class drugs, can cause fetal harm when administered to a pregnant woman.
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- If pseudomembranous colitis occurs, discontinue MINOLIRA.
- If renal impairment exists, MINOLIRA doses may need to be adjusted to avoid accumulations of the drug and possible liver toxicity.
- Minocycline may cause central nervous system side effects, including light-headedness, dizziness, or vertigo.
- Minocycline may cause intracranial hypertension and autoimmune disorders in adults and adolescents. Discontinue MINOLIRA if symptoms occur.
- Minocycline has been associated with anaphylaxis, serious skin reactions, erythema multiforme, and DRESS syndrome. Discontinue MINOLIRA immediately if symptoms occur.
- The most commonly observed adverse reactions are headache, fatigue, dizziness, and pruritus.

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For Full Prescribing Information, please visit www.minolira.com

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Statement of Need

Human facial aging is a gradual and ongoing process involving various factors including photodamage, skin laxity, volume loss of subcutaneous tissue, and bony resorption. As the aging US population is growing, minimally invasive strategies have become the primary treatment modalities for addressing mild to moderate age-related facial changes. The introduction of microfocused ultrasound (MFU) represents a method to produce a deeper wound healing response with increased collagen remodeling and more durable clinical response. MFU-V treatment protocols continue to be refined and use in combination with other minimally invasive strategies including injectable dermal fillers such as diluted calcium hydroxylapatite for skin laxity and appearance of lines in the neck and décolletage has been studied. Need exists for expanded understanding of dermatology providers on the application of microfocused ultrasound in combination with injectable dermal fillers as a treatment approach for lifting skin on the neck and face and for improving lines and wrinkles on the chest.

Educational Objectives

The information and educational goals for this enduring activity are to expand awareness of microfocused ultrasound as an emerging treatment strategy for the effects of normal facial aging and to demonstrate positive outcomes in facial skin tightening strategies utilizing combination treatment including microfocused ultrasound and injectable dermal fillers. Upon completion of this continuing education activity participants should be able to:

- Summarize the mechanism of action of high-resolution ultrasound imaging (MFU-V) for lifting skin on the neck and face, improving lines and wrinkles on the chest and improving collagen synthesis
- Identify patients best suited for treatment with MFU-V in combination with injectable dermal fillers
- Compare features, benefits, and safety profile MFU-V treatment in lifting skin on the neck and face and for improving lines and wrinkles on the chest

Target Audience

This activity is intended for dermatologists, residents, and fellows in dermatology, and physician assistants, nurse practitioners, and other healthcare providers with an interest in aesthetic treatment of patients of all skin types.

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Facial Skin Tightening With Microfocused Ultrasound and Dermal Fillers: Considerations for Patient Selection and Outcomes

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ABSTRACT

Introduction: Microfocused ultrasound (MFU) is a heat technology that is developed from focused ultrasound (FU) used in a high intense mode to generate heat (HIFU). Patient assessment is very complex and involves more than just addressing complaints. It is a challenge to evaluate, decide on options, and give treatments that guarantee the best outcomes. In order to facilitate the process, the authors divided the protocol into five steps: Assess (expectations, features); Decide (which depth to customize); Select (choose a number of lines to achieve the objective); Plan (combination, if needed); Treat (documentation, safety, and comfort).

Methods: The PubMed search engine was used to search all publications from 1900–2019 that mention HIFU. The information collected was then grouped into the five protocol steps.

Discussion: MFU is a focused ultrasound device that, at certain energy levels, produces heat over 55°C at the focal point, which leads to thermal coagulation points (TCPs) in the target tissue. The creation of TCPs leads to a healing cascade, ending with neocollagenesis and neoelastogenesis. At different levels, this can bring about either a lifting effect or skin tightening, depending on the structure targeted. Therefore, the two most important tools for precision and efficacy of treatment are visualization with ultrasound and real-time evaluation of severity and structural changes (such as bone or fat loss).

Conclusion: MFU-V is a well-known and, based on the evidence, an effective tool for non-invasive lifting and skin tightening. The secret to successful use of the device is to assess adequately patient needs and expectations and plan ahead for the combination of other treatment if necessary to achieve the desired outcome.


BACKGROUND

Microfocused ultrasound (MFU) is a technology developed from focused ultrasound (FU) and used in high intensity mode to generate heat (high intensity focused ultrasound; HIFU). Focused ultrasound was discovered by Frank Fry in 1972 and was used to destroy brain cancer cells. HIFU is a modality in which the ultrasound beam is focused precisely on the target to deliver acoustic energy to part of the body in a non-invasive or minimally invasive manner. The purpose of HIFU is to heat a target tissue without affecting the tissue in the ultrasound propagation pathway. HIFU can increase the temperature of a selected area above 55°C, which results in coagulative necrosis and immediate cell death in a specific depth through a focused ultrasound beam.

Because the ultrasound wavelength at megahertz frequencies has a millimeter-scale beam size and the ultrasound probe has a concave shape, the ultrasound beam can be focused into small, clinically relevant volumes of tissue. The energy absorption raises the temperature at the focus point but increases only to non-cytotoxic levels outside the region. Almost 30 years later, noninvasive facial treatment with intense focused ultrasound (MFU) started to be developed, such as Ulthera® System (Merz North America, Raleigh, NC), which also includes ultrasound visualization (DeepSee®; Merz North America, Raleigh, NC), followed by Doblo (Hironic®, Korea), which does not include real-time visualization in some models, and Ultraformer (Cryomed®, Australia), which does not offer visualization (Table1).

During development, some HIFU parameters were adjusted to reach the goal of generating thermal coagulation zones (TCPs). The final prototype transducer had shorter pulse durations of 50–200ms, a higher frequency of 4 to 7 MHz, and a decreased energy of 0.5 to 10J. As a result, more precise energy delivery was achieved with the microfocused ultrasound with visualization (MFU-V) device during aesthetic treatments for facial tissue.

In 2004, the first preclinical trials were started with a prototype device, followed shortly thereafter by several clinical trials. White and colleagues reported the first aesthetic use of focused ultrasonography and its ability to specifically target the
needed for wound healing. These represent the basis for the new connective tissue matrix, serving to close tissue gaps and to restore the mechanical strength of the wound. Subsequently, the synthesis of collagen increases throughout the wound, while the proliferation of fibroblasts declines successively, adjusting to a balance between synthesis and degradation of the ECM.17 The third phase can last from 21 days to 1 year, depending on the scar tissue.

One of the most important factors is sufficient stimulation during the first phase to have enough fibroblasts to produce organized collagen and elastin. Organized collagen formation (scar tissue) is the physiological endpoint of mammalian wound repair. There is some evidence that inflammation during the process of wound healing is directly linked to the extent of scar formation.15,16 First, fetal wound healing, which lacks the typical inflammatory response, is scarless until a certain age.18,19 In addition, scar formation does occur when inflammation is induced in fetal wounds.20 Also, reproductive hormones have been shown to have an influence on inflammation and the formation of scars. Studies show that low estrogen levels in mice resulted in an impaired rate of healing with excessive inflammation and scarring.15,21,22

To summarize, a TCP induces tissue coagulation and necrosis and starts the healing cascade. To achieve the desired quantity and quality of collagen, a certain amount of inflammation is needed under certain basic conditions such as the required levels of mediators, hormones, and cell migration. The aging

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**TABLE 1.**

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<tr>
<th>Device</th>
<th>Brand</th>
<th>Approved</th>
<th>Visualization</th>
<th>Transducers</th>
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<tr>
<td>Ultherapy - MFU</td>
<td>Merz Pharma - Germany</td>
<td>Canada, US, Europe, Asia, Australia, Central and South America</td>
<td>RealTime USG</td>
<td>1.5mm (micro) 3.0mm (micro) 4.5mm (micro)</td>
</tr>
<tr>
<td>Doublo - HIFU</td>
<td>Hironic - Korea</td>
<td>Asia, South America</td>
<td>Not Real Time USG in some versions</td>
<td>1.5mm (micro) 3.0mm (micro) 4.5mm (micro) 13mm (macro)</td>
</tr>
<tr>
<td>Ultraformer - HIFU</td>
<td>Cryomed - Australia</td>
<td>US, Europe, South America, China, Russia, Australia</td>
<td>No Visualization</td>
<td>1.5mm (micro) 2.0mm (micro) 3.0mm (micro) 4.5mm (micro) 6.0mm (macro) 9.0mm (macro) 13.0mm (macro)</td>
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superficial muscular aponeurotic system (SMAS). The current clearance by the FDA for the aesthetic use of MFU-V are browlift, face, and neck lift, and décolleté tightening.2,12

**METHODS**

The PubMed search engine was used to review all publications from 1900–2019 that mention high intensity focused ultrasound, and the information collected was collated into a step by step approach for didactic purposes.

**Mechanism of Action**

As MFU is a focused ultrasound device, at certain energy levels, it produces heat over 55°C at the focal point, which leads to thermal coagulation points (TCPs) in the target tissue. The creation of TCPs leads to a healing cascade, ending with neo-collagenesis and neoelastogenesis. This healing is regulated and described as an “orchestra playing” by Reinke and Song,14 which begins immediately after the first phase of the injury and lasts for 1 to 3 days. This is the most important phase for the purpose of collagen stimulation.15,16 During this very early phase, mediators such as interleukins (IL-1 and IL-6), tumoral necrosis factor (TNF-α), and other factors (FGF-2, IGF-1, TGF-β, and VEGF) lead to the production of new collagen and elastin, as well as neovascularization within the extra cellular matrix (ECM).

The second phase of proliferation lasts for 5-10 days. Under the control of regulating cytokines (IFN-α, TGF-β), fibroblasts synthesize collagen, fibronectin, and other basic substances needed for wound healing. These represent the basis for the new connective tissue matrix, serving to close tissue gaps and to restore the mechanical strength of the wound. Subsequently, the synthesis of collagen increases throughout the wound, while the proliferation of fibroblasts declines successively, adjusting to a balance between synthesis and degradation of the ECM.17 The third phase can last from 21 days to 1 year, depending on the scar tissue.

One of the most important factors is sufficient stimulation during the first phase to have enough fibroblasts to produce organized collagen and elastin. Organized collagen formation (scar tissue) is the physiological endpoint of mammalian wound repair. There is some evidence that inflammation during the process of wound healing is directly linked to the extent of scar formation.15,16 First, fetal wound healing, which lacks the typical inflammatory response, is scarless until a certain age.18,19 In addition, scar formation does occur when inflammation is induced in fetal wounds.20 Also, reproductive hormones have been shown to have an influence on inflammation and the formation of scars. Studies show that low estrogen levels in mice resulted in an impaired rate of healing with excessive inflammation and scarring.15,21,22

To summarize, a TCP induces tissue coagulation and necrosis and starts the healing cascade. To achieve the desired quantity and quality of collagen, a certain amount of inflammation is needed under certain basic conditions such as the required levels of mediators, hormones, and cell migration. The aging
process involves more than just collagen and elastin restoration. We must understand that there are different needs in terms of stimulation. Therefore, patient assessment becomes a key point in understanding whether just one treatment such as MFU-V is enough to induce collagen formation, or if other procedures that up-regulate mediators and cell migration are also needed during the first phases of healing started by MFU. These include calcium hydroxylapatite (CaHa) or poly-L-lactic acid (PLLA), as shown in a recent study where the histology of the skin after combining both procedures on the same day resulted in larger collagen and elastin formation by increasing stimulation during the first phases of the healing cascade.

**The Devices**

Most HIFU devices have more than one transducer depth and size focus (Table 1). Macrofocused transducers are used for fat reduction, and are not safe for collagen stimulation because the TCPs are too large and the pulse duration is usually longer. Microfocused transducers have different frequencies. A MFU-V transducer with a frequency of 4 MHz has a depth of 4.5mm and creates a TCP of 1mm, while a transducer with a frequency of 7 MHz has a 3mm depth and creates a TCP of 0.3mm, and a transducer with a frequency of 10 MHz has a 1.5mm depth and creates a TCP of 0.18mm (Figure 1).

**How to Achieve the Best Results**

Patient assessment is far more complex than just observing the complaints of the patients who arrive at our office. Sometimes it is hard to estimate the number of lines or which procedures should be combined to provide a natural and satisfactory result. For didactic reasons and to try to facilitate a certain procedure on why and when to use a certain number of MFU-V treatment lines and depths, as well as when to combine other treatments, the authors have divided patient assessment into five steps:

1. **Assess** — expectations, features
2. **Decide** — which depth to customize
3. **Select** — choose a number of lines to achieve the objective
4. **Plan** — combination, if needed
5. **Treat** — documentation, safety, and comfort

**1. Assess**

In this step, there are two main goals:

A. **Expectations**

Identify patient expectations based on the MFU procedure alone. A retrospective study showed discordance between physician and patient regarding satisfaction with results. Sometimes, even though the physician graded the result as only mild improvement, the patients were happy and satisfied, but the opposite can also occur. Sobanko et al showed how important psychological aspects are in improving appearance and how patient motivations for the treatment can differ. Also, patient

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**FIGURE 1.** Schematic illustration of different frequencies present in each different transducer and the wave size and TCP sizes.

- Higher Frequency (10MHz)
- Less Penetration
- Smaler TCP

- Bigger Frequency (4 MHz)
- Deeper Penetration
- Bigger TCP
B. Vectors and Severity
Assess the patient's real needs regarding vectors and procedures needed to meet patient expectations. This is the moment where the physician should decide and make clear if, given the level of expectation, the patient is a candidate for a single or combination treatment. In 2005, Marten and Connell described ways of evaluating severity and different patient needs before facelift.

Through different facial positions, the severity of the loss in one specific vector (horizontal, vertical, or projection) needs to be identified to decide if MFU-V alone is the perfect indication as each procedure corrects a different vector (Figures 2 A–C).

One way of assessing involves using the severity scales for face, neck, and chest aging, and other areas such as knees, buttocks, and anterior and posterior thighs. According to patient self-assessment scores, the necessary treatment intensity or frequency, the number of treatment lines, or number of repeated treatments, or if the severity indicates that more than one procedure is indicated, can be discussed (Figures 3 A, B).

FIGURE 2. A patient after MFU-V treatment. (A) 3 months after treatment showing that the displacement occurred in the direction of the tragus area in the face and in the direction of the mandible border in the superior neck, (B) 3 months after injection of dilute CaHa in face showing a more intense displacement in same direction (horizontal) and in vertical manner in superior neck, and (C) 1 month after injection of CaHa as a filler to the zygomatic arch, lower mandible border, and angle of the mandible showing a new displacement more perpendicular to the skin layer represented by the red arrows.

FIGURE 3. Pre-MFU-V (A) and after 3 months (B). Difference in scale score (right side 2, left side 3) showing improvement related to differences in height of mandible and angle of mandible projection. In these cases, not only horizontal correction of the left side would be needed, but also vertical enhancement of the mandible height and angle.
2. Decide

At this point, the MFU-V depth to achieve the desired outcome needs to be decided. There are two possible goals with MFU-V: skin lifting or skin tightening. For a lifting effect, the SMAS or superficial fascia system (SFS) needs to be targeted. The number of TCPs required to create sufficient tightening and to deposit sufficient new collagen and elastin to achieve a lifting effect needs to be determined. Skin tightening can be achieved by making the skin thicker and, therefore, denser and firmer.

To decide the depth of the SMAS and SFS, the physician must master the ability to identify these layers through real-time ultrasound visualization. This is important because a recent study by Casabona et al. showed that the SMAS and SFS can change with age, gender, and body mass index (BMI), and in different areas of the face and body (Figures 4A,B). Another study showed that patients who received a customized transducer selection based on ultrasound visualization were far more satisfied with results after MFU-V alone (Figures 5A–C). In conclusion, if the MFU-V treatment lines are not directed exactly to the appropriate tissue layers, the procedure can be less effective, leading to frustration with the final results.

3. Select

In this step, the physician should check the number of lines needed based on two parameters: the transducer to use and the coverage area provided by each one, according to appearance, severity, and treatment goal. The amount of collagen that MFU-V can produce depends on the number of lines and therefore the linear coverage or density of lines in the same area (Figures 6A,B). A recent study published by Sasaki et al. showed more treatment lines produce better clinical results. It would be logical to conclude that different severities would require different density of lines or even different number of
layers treated to achieve the same endpoint in same vector (horizontal or vertical depending on area). As mentioned before, the recommended protocol of transducers per area needs to be adapted according to SMAS or SFS depth. Therefore, the coverage needed to be adapted to bring the same result once the TCP area of the 4mm/4.5 MHz transducer (1mm³) is much bigger than the 7mm/3.0 MHz (0.3mm³) or 10mm/1.5mm MHz (0.2mm³) transducers. The author developed a table using the ruler provided with some HIFU devices that has an area of 2.5cm x 5cm and is used to mark and distribute the determined number of lines when delivered by a transducer in a certain area of face and body (Table 2). This table might help to convert the number of lines from one transducer to the other if needed. Although, it is important to point out that we do not have data on what is the ideal conversion of one transducer to the other to keep the same clinical result. The authors recommend these corrections when changing transducers: 4/4.5 to 7/3.0–50% more lines of standard protocol, 7/3.0 to 10/1.5–30% more lines of the standard protocol (Figures 7A–C).40

4. Plan
In this step, the most important assessments are the vectors involved in the aging appearance for each patient and each area of complaint. The face, neck, and chest have different ways of aging, and the same layers of skin are disposed differently in these three areas. Also, it is very important to evaluate the patient in dynamic and resting conditions because this will provide a hint about which layer is more important to treat to effectively address the specific patient complaint.

- Face: Only MFU-V can provide correction in a horizontal manner on the face, tightening the skin and SMAS from the corner of the mouth to pre-auricular area (fixed part of the SMAS).39,41
- Neck: Only MFU-V can provide correction in a vertical manner in the neck, recreating the mandible definition by tightening the platysma and skin from its origin (mandible region) and insertion (clavicle).39
- Décolleté: Only MFU-V can provide correction in a vertical manner on the chest as shown in clinical experience.42,43

Other procedures such as biostimulators and fillers can enhance the strength of other vectors such as horizontal or projection on the frame of the face, neck, and chest (Figure 8).44,45 They can be boosters (enhance collagen stimulation same areas) or highlighters (enhancing visual result of MFU-V by restoring the structure of bone and fat creating a stretching effect on the tissue envelope from SFS to epidermis). The more vectors you treat without overtreating one or the other, the more natural results look.

**TABLE 2.**

<table>
<thead>
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</tr>
<tr>
<td><strong>Lines</strong></td>
</tr>
<tr>
<td>240.0</td>
</tr>
<tr>
<td>120.0</td>
</tr>
<tr>
<td>60.0</td>
</tr>
<tr>
<td>30.0</td>
</tr>
<tr>
<td>40.0</td>
</tr>
<tr>
<td>25.0</td>
</tr>
<tr>
<td>15.0</td>
</tr>
</tbody>
</table>
5. Treat

In this step, it is important to ensure patient comfort, that the treatment goes as planned, and that the patient is satisfied. Photography is important to demonstrate that MFU-V was effective with realistic results.35 It also serves as a quality control tool. Currently available 3D cameras that standardize light exposure and facial position can be used for the face, neck, and chest.

Pain control is an important part of the experience. In some publications, patients evaluated the procedure poorly despite good aesthetic improvements because of the treatment-related pain.24,42,51 There are different protocols described for pain control, and very few publications on what is most commonly used (Table 3).39,42,51 Although not mentioned in most publications, in the authors’ opinion, after using the device for 7 years, the most efficient and easy methods of pain control are a topical paste containing lidocaine and tetracaine 7%/7% (Pliaglis®, Galderma Laboratories) applied 40 minutes prior to the procedure, oral ketorolac 10mg applied 10 minutes prior to the procedure, and good conversation and energy adjustment during the procedure.

An important safety factor during treatment with MFU-V is to be sure the gel coat being used is not too thick, thus interfering with ultrasound penetration that could possibly cause a burn injury.52 The distribution of the lines needs to be correct. A certain amount of overlap is acceptable, but stacking treatment lines is not acceptable because it could also cause burns.53 Before every pulse, be sure the transducer is targeting the right layer to guarantee not only efficacy but also safety, and to avoid adverse events such as nerve damage.52,53

Finally, it is important to contact the patient for further evaluation in 3, 6, and 12 months. Published data show that due to lack of estrogen, especially in some older patients, treatment response can be slow, and it is important to be in close contact with the patient to manage expectations and results.20,24

TABLE 3.

<table>
<thead>
<tr>
<th>Pain Control Measures Prior to MFU-V Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Diazepam (2.5–10mg), ibuprofen (400–1,200mg), or acetaminophen (400–1,000mg) administered 30–60 minutes before treatment. Hydrocodone/acetaminophen, 7.5/500mg or 7.5mg/750mg; hydrocodone 7.5mg or 10mg plus diazepam 5mg or lorazepam 2mg.</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>Intramuscular ketorolac tromethamine 60 mg was given 60 minutes prior to treatment.</td>
</tr>
</tbody>
</table>

Also, it is very important in this step to plan if the procedure(s) will be done the same day. Carruthers et al published a consensus on the combination of MFU-V and other procedures with experts recommendations regarding best timing.46 According to this consensus, it is best to treat in single procedures separated by 15 days to allow recovery from possible adverse effects; however, patients may prefer to have several treatments on the same day. Devices such as MFU-V should be used first, followed by injectables such as fillers, biostimulators, and toxins, followed by superficial treatments such as peels, microneedling, and creams.46,47,48 One recent publication by Yutskoskaya (2019) showed that combining MFU-V and CaHa on the same day is superior to other timings for combination treatment.49

CONCLUSION

The aim of this article was to give an updated overview of the history and changes of this procedure as seen through an experienced physician’s eye. Through this review, it has become clear that in last 7 years since use of the first MFU-V device was approved, the treatment assessment and protocols have changed. However, some retrospective studies make it very clear that patient satisfaction is related not only to the result itself but also to the whole experience of physician-patient interaction, especially regarding expectations, pain, and follow-up.

DISCLOSURE

Gabriela Casabona MD is a consultant for Merz Global. Kai Kaye PhD does not have any conflicts.

REFERENCES

6. White WM, Makin IR, Barthe PG, et al. Selective creation of thermal injury...


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AUTHOR CORRESPONDENCE

Gabriela Casabona MD

1082

November 2019  •  Volume 18  •  Issue 11
1. What is HIFU?
   a. It is an ultrasound
   b. It is a focused ultrasound
   c. It is a focused ultrasound with high intensity
   d. All the above

2. What adaptations are needed in FU technology to be finally used as a non-invasive procedure: adequate pulse duration, controlled energy, and depth?
   a. Higher energies, higher frequencies, and better focus
   b. Less focus, lower energy, and lower frequencies
   c. Variable frequencies, higher energy, and higher focus
   d. Variable frequencies, controlled focus, and variable energies

3. What is the main mechanism of action?
   a. Stimulation of collagen through protein shock
   b. Stimulation of fibrotic tissue
   c. Stimulations of extra cellular matrix
   d. Stimulation of collagen and elastin through 2- healing intention cascade

4. What are the 5 steps concerning assessment and treatment suggested in this article?
   a. Assessment, decision, treatment, picture, and post-procedure care
   b. Assess, decide, select, plan, treat
   c. Assess, decide, select, treat, and follow up
   d. Patient conversation and assessment, visualization, treatment, call back

5. Is HIFU treatment always indicated as a single procedure? Can it be combined with other procedures and when should it be combined and indicated?
   a. Yes, only as a single procedure.
   b. It should be combined with fillers and biostimulators when the patient evaluation shows a need for different vector correction or a boost correction in one vector due to severity and it can be done the same day or 15 days apart.
   c. It should be combined with fillers but not biostimulators when the patient evaluation shows a need for different vector correction and it can be done the same day or 15 days apart.
   d. It should be combined with fillers and biostimulators when the patient evaluation shows a need for different vector correction or a boost correction in one vector due to severity and it cannot be done the same day, only 15 days apart.
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CE Post-Test and Answer Key

<table>
<thead>
<tr>
<th>Question 1</th>
<th>Question 2</th>
<th>Question 3</th>
<th>Question 4</th>
<th>Question 5</th>
</tr>
</thead>
</table>

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☐ I participated in the entire activity and claim 1.0 AMA PRA Category 1 Credit(s)™ and ANCC Credit.

Please answer the following questions using the appropriate rating:

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2. The information presented enhanced my current knowledge base.

3. The information presented addressed my most pressing questions.

4. The activity provided new ideas or information I expect to use.

5. The activity addressed competencies identified by my specialty.

6. The activity avoided commercial bias or influence.

<table>
<thead>
<tr>
<th>1 = Strongly Disagree</th>
<th>2 = Disagree</th>
<th>3 = Neutral</th>
<th>4 = Agree</th>
<th>5 = Strongly Agree</th>
</tr>
</thead>
</table>

Impact of the Activity

1. Name one new strategy you learned as a result of completing this activity:

2. Name one thing you intend to change in your practice as a result of completing this activity:

3. Please provide any additional comments on this activity:

4. Please list any topics you would like to see addressed in future educational activities:
Table 2: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6-Month Safety Pool)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPIXENT 200 mg Q2W</th>
<th>DUPIXENT 300 mg Q2W</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=779</td>
<td>N=788</td>
<td>N=282</td>
</tr>
<tr>
<td>Injection site reactions*</td>
<td>111 (14%)</td>
<td>144 (18%)</td>
<td>50 (6%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>13 (2%)</td>
<td>19 (2%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>17 (2%)</td>
<td>16 (2%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

*Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.

Table 3: Adverse Reactions Occurring in 21% of the DUPIXENT Group in CRSwNP Trials 1 and 2 and Greater than Placebo (24 Week Safety Pool)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPIXENT 300 mg Q2W</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=440</td>
<td>N=282</td>
</tr>
<tr>
<td>Injection site reactions*</td>
<td>28 (6%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>7 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Asthreatia</td>
<td>14 (3%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>7 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>5 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Toothache</td>
<td>5 (1%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

*Injection site reactions cluster includes injection site reaction, pain, bruising and swelling.

Table 4: Eosinophil Counts

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Mean Increase</th>
<th>Median Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>150 cells/mcL</td>
<td>50 cells/mcL</td>
</tr>
<tr>
<td>Week 16</td>
<td>250 cells/mcL</td>
<td>100 cells/mcL</td>
</tr>
<tr>
<td>Week 4</td>
<td>130 cells/mcL</td>
<td>10 cells/mcL</td>
</tr>
</tbody>
</table>

7.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the method. Approximately 4% of patients who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab, ~2% exhibited persistent ADA responses, and ~2% neutralizing antibodies. Approximately 9% of patients who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab, ~2% exhibited persistent ADA responses, and ~2% neutralizing antibodies. Approximately 16% of adolescents with atopic dermatitis who received DUPIXENT 300 mg Q2W for 16 weeks developed antibodies to dupilumab, ~3% exhibited persistent ADA responses, and ~5% neutralizing antibodies. Approximately 4% of adolescents with atopic dermatitis in the placebo group were positive for antibodies to DUPIXENT; ~1% exhibited persistent ADA responses, and ~1% had neutralizing antibodies.

7.3 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.
7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup B meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Please contact 1-877-311-8972 or go to https://mothersbabystudy.org/ongoing-study/dupixent/ to enroll in or to obtain information about the registry.

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy (see Clinical Considerations). In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4 receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) (see Data). The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defects and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

In women with poorly or moderately controlled asthma, evidence demonstrates there is an increased risk of preeclampsia in women of childbearing age if asthma is poorly controlled. The safety and effectiveness of DUPIXENT have been established in pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis (see Indications and Usage). Due to the potential for maternal-fetal-fetal transmission of immunoglobulin G (IgG) antibodies, DUPIXENT should be considered along with the mother’s clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

8.4 Pediatric Use

Atopic Dermatitis

The safety and efficacy of DUPIXENT have been established in pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis. A total of 251 adolescents ages 12 to 17 years old with moderate-to-severe atopic dermatitis were enrolled in Trial 6. The safety and efficacy were generally consistent between adolescents and adults (see Adverse Reactions (6.1) and Clinical Studies (14.2) in the full prescribing information). Safety and efficacy in pediatric patients (<12 years of age) with atopic dermatitis have not been established.

Assessment

A total of 107 adolescents aged 12 to 17 years old with moderate to severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=24). Antibody responses to eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) were assessed in patients aged 12 years of age and older receiving dupilumab. Antibody responses were not detected in either the 200 mg (N=13) or 300 mg (N=16) Q2W dose group. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than in adults at the respective dose level which was mainly accounted for by difference in body weight (see Clinical Pharmacology (12.3) in the full prescribing information). The adverse event profile in adolescents was generally similar to the adults (see Adverse Reactions (6.1)).

CRSwNP

CRSwNP does not normally occur in children. Safety and efficacy in pediatric patients (<12 years of age) with CRSwNP have not been established.

8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects (see Clinical Pharmacology (12.3) in the full prescribing information). Of the 1977 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population. Of the 440 subjects with CRSwNP exposed to DUPIXENT, a total of 79 subjects were 65 years or older. Efficacy and safety in this age group were similar to the overall study population.

10 OVERDOSE

There is no specific treatment for DUPIXENT overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

17 PATIENT COUNSELING INFORMATION

Advising the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Encourage participation in the registry (see Use in Specific Populations (8.1)).

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharp disposal recommendations (see Instructions for Use).

Hyperosensitivity

Advise patients to discontinue DUPIXENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions (see Warnings and Precautions (5.1)).

Advising the patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis (see Warnings and Precautions (5.3)).

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT (see Warnings and Precautions (5.4)).

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy (see Warnings and Precautions (5.5)).

Patients with Comorbid Asthma

Advise patients with atopic dermatitis or CRSwNP who have comorbid asthma not to adjust or stop their asthma treatment without talking to their physicians (see Warnings and Precautions (5.6)).
JDD Podcasts present the latest journal content related to advances in drugs, devices and treatment methods in dermatology, in a new convenient audio format. From article abstracts to interviews, JDD Podcasts provide a fresh perspective of the peer reviewed content you have come to rely on from JDD (Journal of Drugs in Dermatology).

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NEW EPISODE - CME AVAILABLE

Picking up on Prescribing Patterns for Psoriasis: A Real Deal Assessment
Drs. Joel Gelfand, Megan Noe and Adam Friedman

We (and our patients) are fortunate to live during a time when we have many safe and effective options to treat a chronic inflammatory skin disease such as Psoriasis. We are reminded of this, nay inundated, with warm and fuzzy headlines in the lay dermatology press that humblebrag said efficacy. However, how does this translate to the real world, when the perfect, neat lines of clinical trials are blurred by practical issues such as access, patient and practitioner perception, and long term use and efficacy? In a JDD Podcast first, we had not one but two investigators share their work and first steps to evaluate just that. Dr. Megan Noe, Instructor of Dermatology at the Brigham and Women’s Hospital and Harvard Medical School, and Dr. Joel Gelfand, Professor of Dermatology and of Epidemiology, Vice Chair for Clinical Research (Dermatology), and Director of the Psoriasis and Phototherapy Treatment Center at the University of Pennsylvania join us to discuss their study Prescribing Patterns Associated With Biologic Therapies for Psoriasis from a United States Medical Records Database from the August 2019 edition of the JDD. Hear how they formulated this big data dive. Learn which biologics did not get an encore with a refill. Discover which scenarios most often lead our colleagues to use combination therapy and with what. And most importantly, digest Dr. Noe and Gelfands’ approach to picking the right biologic for the right patient. All that and more – I (nail) pity the fool who doesn’t check it out.

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Electromagnetic fields are composed of both electric and magnetic fields. Electromagnetic phenomena are defined by the electromagnetic force which in turn includes electricity and magnetism. Electric fields are the result of electric charges, measured in volts per meter (V/m). Magnetic fields arise from the movement of electric charges as in a current and measured in tesla (T) or the gauss (G; 10,000 G = 1 T). While electric fields are shielded by wood and metal, magnetic fields easily pass through most common materials.

There are four basic principles for understanding electromagnetic theory. First, electric charges attract or repel each other with a force that is inversely proportional to the distance between them. Second, magnetic poles attract or repel each other like electric charges and exist in pairs. Third, and importantly, an electric current in a wire generates a circumferential magnetic field surrounding the wire. The direction of the magnetic field is perpendicular to the wire and in the direction of your fingers of your right hand curled around the wire with your thumb pointing in the direction of the current (Figure 1).

Fourth, and conversely, an electric current is induced in a loop of wire when moved towards or away from a magnetic field or a magnet is moved towards or away from it. In the current instance of HIFEM technology, a rapidly varying magnetic field induces an electric current in the target tissue (Figure 2). In the use of HIFEM technologies for muscular sculpting, the rapidly moving magnet in the handpiece generates an electric current in tissue that depolarizes motor nerves resulting in muscular contractions. Magnetic field intensity delivered are up to 2.5 Tesla. Other applications are being investigated, including fat apoptosis and pelvic floor stimulation.

An important safety issue that needs to be addressed is the dosage of electromagnetic field being generated per treatment. The World Health Organization has established potential long-term effects of childhood leukemia from average magnetic field exposures in the 0.3 T range.

As our laser, light, and energy-based device field evolves with new areas of research and treatments using novel applications, we should continue to emphasize the importance of rigorous research and long-term clinical trials.

References
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Re-pigmentation of Hypopigmentation: Fractional Lasers vs Laser-Assisted Delivery of Bimatoprost vs Epidermal Melanocyte Harvesting System

Jill S. Waibel MD, Ashley Rudnick BS, Kristopher L. Arheart EdD, Nicole Nagrani MD, Adrianna Gonzalez MD, Chloe Gianatasio MS

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bDepartment of Public Health Science, University of Miami Miller School of Medicine, Miami, FL
cDepartment of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL

ABSTRACT

Background: Hypopigmentation is a common cutaneous manifestation that frequently poses a therapeutic challenge for dermatologists. Current treatments have varying efficacies and rarely provide patients with long-term results. However, new treatments are emerging, and head-to-head studies comparing these treatments are warranted.

Methods & Materials: In this prospective, Institutional Review Board (IRB)-approved, double-blinded study, 40 subjects with moderate to severe hypopigmentation were randomized into 1 of 4 treatment arms; non-ablative fractional laser, ablative fractional laser, ablative fractional laser with laser-assisted delivered bimatoprost, and an epidermal harvesting system.

Results: All patients in this study showed improvement regardless of the treatment modality. The average improvement score was calculated on a 0 to 4 scale, and Group 3 (fractional ablative laser and bimatoprost) was found to have a significantly higher average improvement than all other treatments, with 76% of the patients exhibiting at least a grade 3 (over 50%) improvement over the treatment course. Group 1 (non-ablative fractional) also had a significantly higher average score compared with group 2 (fractional ablative laser).

Conclusion: New and emerging therapies have shown promise in helping re-pigmentation of cutaneous hypopigmentation. In this head-to-head trial, it was shown that laser-assisted delivery of bimatoprost had a greater statistically significant improvement compared with 3 possible treatment modalities for stimulation of pigment in medical and cosmetic hypopigmentation.


INTRODUCTION

Hypopigmentation is a common cutaneous manifestation that frequently poses a therapeutic challenge for dermatologists. Hypopigmentation can generally be seen after surgery, laser procedures, trauma, or as a consequence of various inflammatory conditions. The pathogenesis of acquired hypopigmentation has been linked to inflammation, whereby various inflammatory factors cause suppression of pigmentation-related signaling, leading to decreased melanin production.¹

Hypopigmentation can be a significant issue in patients with skin of color. In prior studies, it has been shown that many hypopigmented skin conditions may have inactive melanocytes that may be stimulated by various modalities to produce pigment.² Presumably, the target is stimulation of the human epidermal melanocyte. Melanocytes are melanin-producing neural crest-derived cells located in the stratum basale. Once these cells are stimulated, they synthesize melanin in special organelles called melanosomes, which are transported to keratinocytes to induce pigmentation. The depth of the melanocyte depends on the patient skin site, but ranges from 20 micrometers to 141 micrometers (Table 1).³

Current treatment modalities for hypopigmentation include split thickness skin grafting, excisional surgery, exogenous pigment procedures (such as tattooing), dermabrasion, chemical peels, and laser therapy. However, current treatments have varying efficacies and rarely provide patients with long term results.

In the past decade, it has been shown that laser therapy may demonstrate improvement in hypopigmentation of acne and surgical scars. Fractional lasers were among the many devices studied to help improve hypopigmentation in acne and surgical scars. The mechanism of action is hypothesized to be the repopulation of melanocytes in the hypopigmented areas from surrounding hair follicle stem cells and basal melanocytes.⁴⁻⁷
In 2010, ablative fractional laser (AFXL) was introduced as a new drug delivery-enhancement technique.8-13 The technique is based on fractional photothermolysis, which uses focused laser beams to create an array of very small thermal injuries in the skin.14 Available AFXL systems include the carbon dioxide (CO2, \( \lambda = 10,600 \text{ nm} \)) and erbium-doped yttrium aluminum garnet (Er:YAG, \( \lambda = 2,940 \text{ nm} \)) lasers. These far-infrared lasers vaporize tissue efficiently, creating an array of very small channels cross the skin barrier, providing direct access to viable epidermis and dermis until the channels close by local wound repair, typically within 48 hours, without scarring. Geometrically, the diameter, depth, and number of channels per unit skin area can be independently adjusted to regulate uptake and penetration of topical drugs to specific depths based on target.15

Bimatoprost 0.03% topical solution is a drug that was initially brought to market to treat glaucoma. This drug was then noted to have a side effect which caused periorcular hyperpigmentation due to increased melanogenesis. There appears to be a dose dependent relationship of bimatoprost and the mechanism for increased melanogenesis, and increased transfer of melanosomes with absence of melanocyte atypia. We hypothesize that bimatoprost may induce melanogenesis from dormant melanocytes in hypopigmented conditions.16 In this study, the concept of laser-assisted delivery of bimatoprost was brought to market to treat glaucoma. This drug was then noted to have a side effect which caused periocular hyperpigmentation. Bimatoprost 0.03% topical solution was applied over treatment arm, immediately after fractional ablative laser therapy, topical application with fractional ablative laser is also assessed and all 4 treatment modalities are compared. Throughout the clinical trial there are a variety of conditions treated in each group (Table 2).

### METHODS

#### Subject Population

This prospective, randomized head-to-head comparison studies new and innovative procedures for hypopigmentation, including fractional laser monotherapy (non-ablative and ablative), laser-assisted delivery of bimatoprost, and a novel epidermal melanocyte automated transplant system. The protocol was approved by an IRB, and written informed consent from each patient was obtained. The inclusion criteria for selection of the patient population consisted of healthy individuals ages 18 to 80 years with all Fitzpatrick skin types and moderate to severe hypopigmentation on any body location. Exclusion criteria included pregnancy, breast-feeding, oral retinoids 6 months prior to treatment, active infection, or lesions suspicious for malignancy.

#### Treatment Paradigm

After informed consent was obtained, a visual skin examination and a brief interview on relevant medical history was performed prior to taking photographs of the treatment areas. Patients were then randomly allocated by the clinical coordinator into 1 of 4 groups: Group A – 1550 nm wavelength non-ablative fractional erbium-doped fiber (n=10); Group B – 10,600 nm wavelength fractional ablative laser (n=10); Group C – 10,600 nm wavelength fractional ablative laser followed by topical application with bimatoprost immediately after laser treatment and for 14 days after (n=10); and Group D – epidermal harvesting system with fractional ablative laser to recipient site (n=10) (Figure 1). Laser parameters were kept to a penetration depth of 150 to 300 micrometers. Patients received 3 treatment sessions at 4- to 6-week intervals.

The last modality studied is a novel epidermal harvesting technology. This device performs scar-less and painless epidermal autologous grafting from the donor site. This enables the transfer of autologous epidermis that includes melanocytes to recipient site. This device is Food and Drug Administration (FDA)-approved for wound ulcers and was first used by Anderson et al in Vietnam for children with radiation burns and vitiligo for re-pigmentation.17 18 This emerging technology is currently being used to treat chronic ulcers. To our knowledge, there have been some proofs of concept work done, but no official dermatology studies with this novel epidermal transplant device.

In this study, the efficacies of non-ablative and ablative fractional lasers for the treatment of hypopigmentation are evaluated, along with the combination of fractional ablative laser with bimatoprost, a prostaglandin agonist known to stimulate pigmentation. The epidermal harvesting system in combination with fractional ablative laser is also assessed and all 4 treatment modalities are compared. Throughout the clinical trial there are a variety of conditions treated in each group (Table 2).

<table>
<thead>
<tr>
<th>TABLE 1. Depth of the Melanocyte</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin Site</strong></td>
</tr>
<tr>
<td>Forehead</td>
</tr>
<tr>
<td>Nose</td>
</tr>
<tr>
<td>Med. Cheek</td>
</tr>
<tr>
<td>Lat. Cheek</td>
</tr>
<tr>
<td>Upper Lip</td>
</tr>
<tr>
<td>Lower Lip</td>
</tr>
<tr>
<td>Chin</td>
</tr>
<tr>
<td>Upper Eyelid</td>
</tr>
<tr>
<td>Lower Eyelid</td>
</tr>
</tbody>
</table>
TABLE 2.
Conditions Treated With the Four Treatment Modalities

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Age</th>
<th>Hypopigmentation Condition</th>
<th>Location</th>
<th>Fitzpatrick Skin Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>Idiopathic Guttate Hypomelanosis</td>
<td>Right Arm</td>
<td>III</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>Striae</td>
<td>Right Abdomen</td>
<td>III</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>Hypopigmented Surgical Scar</td>
<td>Right Postauricular</td>
<td>IV</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>Hypopigmented Surgical Scar</td>
<td>Right Lower Abdomen</td>
<td>III</td>
</tr>
<tr>
<td>5</td>
<td>78</td>
<td>Hypopigmented Traumatic Scar</td>
<td>Right Chest</td>
<td>III</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>Idiopathic Guttate Hypomelanosis</td>
<td>Left Back</td>
<td>III</td>
</tr>
<tr>
<td>7</td>
<td>42</td>
<td>Striae</td>
<td>Right Lower Abdomen</td>
<td>IV</td>
</tr>
<tr>
<td>8</td>
<td>38</td>
<td>Striae</td>
<td>Right Inner Thigh</td>
<td>IV</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Inferior Abdomen</td>
<td>V</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>Hypopigmented Surgical Scar</td>
<td>Left Groin</td>
<td>IV</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Age</th>
<th>Hypopigmentation Condition</th>
<th>Location</th>
<th>Fitzpatrick Skin Type</th>
</tr>
</thead>
<tbody>
<tr>
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<td>59</td>
<td>Idiopathic Guttate Hypomelanosis</td>
<td>Right Lower Leg</td>
<td>IV</td>
</tr>
<tr>
<td>12</td>
<td>36</td>
<td>Hypopigmented Traumatic Scar</td>
<td>Right Lower Leg</td>
<td>IV</td>
</tr>
<tr>
<td>13</td>
<td>41</td>
<td>Hypopigmented Surgical Scar</td>
<td>Right Lower Back</td>
<td>IV</td>
</tr>
<tr>
<td>14</td>
<td>45</td>
<td>Hypopigmented Surgical Scar</td>
<td>Mid Chest</td>
<td>III</td>
</tr>
<tr>
<td>15</td>
<td>63</td>
<td>Hypopigmented Traumatic Scar</td>
<td>Upper Back</td>
<td>III</td>
</tr>
<tr>
<td>16</td>
<td>74</td>
<td>Hypopigmented Surgical Scar</td>
<td>Left Arm</td>
<td>II</td>
</tr>
<tr>
<td>17</td>
<td>28</td>
<td>Striae</td>
<td>Right Upper Arm</td>
<td>IV</td>
</tr>
<tr>
<td>18</td>
<td>51</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Right Chest</td>
<td>II</td>
</tr>
<tr>
<td>19</td>
<td>51</td>
<td>Idiopathic Guttate Hypomelanosis</td>
<td>Left Side of Face</td>
<td>III</td>
</tr>
<tr>
<td>20</td>
<td>43</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Mid Upper Chest</td>
<td>IV</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Subject #</th>
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<th>Hypopigmentation Condition</th>
<th>Location</th>
<th>Fitzpatrick Skin Type</th>
</tr>
</thead>
<tbody>
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<td>21</td>
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<td>Hypopigmented Surgical Scar</td>
<td>Left Postauricular</td>
<td>III</td>
</tr>
<tr>
<td>22</td>
<td>31</td>
<td>Striae</td>
<td>Right Abdomen</td>
<td>V</td>
</tr>
<tr>
<td>23</td>
<td>64</td>
<td>Hypopigmented Surgical Scar</td>
<td>Left Back</td>
<td>II</td>
</tr>
<tr>
<td>24</td>
<td>43</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Right Face</td>
<td>V</td>
</tr>
<tr>
<td>25</td>
<td>35</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Right Face</td>
<td>V</td>
</tr>
<tr>
<td>26</td>
<td>13</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Right Shoulder</td>
<td>V</td>
</tr>
<tr>
<td>27</td>
<td>50</td>
<td>Hypopigmented Traumatic Scar</td>
<td>Right Upper Flank</td>
<td>V</td>
</tr>
<tr>
<td>28</td>
<td>86</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Right Neck</td>
<td>V</td>
</tr>
<tr>
<td>29</td>
<td>32</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Right Hand</td>
<td>V</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Left Chest</td>
<td>V</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Age</th>
<th>Hypopigmentation Condition</th>
<th>Location</th>
<th>Fitzpatrick Skin Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>51</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Right Chest</td>
<td>II</td>
</tr>
<tr>
<td>32</td>
<td>51</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Upper Chest</td>
<td>IV</td>
</tr>
<tr>
<td>33</td>
<td>64</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Right Neck</td>
<td>II</td>
</tr>
<tr>
<td>34</td>
<td>17</td>
<td>Vitiligo</td>
<td>Right Knee</td>
<td>IV</td>
</tr>
<tr>
<td>35</td>
<td>38</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Right Upper Lower Leg (Superior)</td>
<td>III</td>
</tr>
<tr>
<td>36</td>
<td>34</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Right Cheek</td>
<td>III</td>
</tr>
<tr>
<td>37</td>
<td>35</td>
<td>Hypopigmented Surgical Scar</td>
<td>Mid Chest</td>
<td>III</td>
</tr>
<tr>
<td>38</td>
<td>35</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Left Jowlie</td>
<td>IV</td>
</tr>
<tr>
<td>39</td>
<td>57</td>
<td>Hypopigmented Surgical Scar</td>
<td>Mid Neck</td>
<td>II</td>
</tr>
<tr>
<td>40</td>
<td>55</td>
<td>Hypopigmented Burn and Traumatic Scar</td>
<td>Left Dorsal Foot</td>
<td>V</td>
</tr>
</tbody>
</table>
areas and gently massaged for approximately 30 seconds to 1 minute. Patients were instructed to apply the medication twice a day for 14 days following the laser treatment.

The epidermal harvesting system technology creates micro suction blisters known as micro-domes by using a combination of vacuum and warmth. This tool allows for epidermal skin grafting in an outpatient setting. The procedure starts with washing of the donor site, which is typically the inner thigh or buttocks due to melanocyte rich areas. Then, the device is applied on the selected area, which raises autologous epidermal micro-blisters in the donor site for 30 minutes. After the initial 30 minutes, there is an assessment to verify that there is sufficient micro-dome formation. Next, preparation for the recipient site is completed and fractional ablative carbon dioxide laser at superficial depth is conducted. Next, the graft acquisition occurs and the ready-to-apply on Tegaderm array of autologous epidermal micro-grafts is transferred to the recipient hypopigmented sites. The donor site is covered for 24 hours post procedure. The recipient site is covered with hypo-fix for 3 to 5 days post procedure.

The primary outcome objective was photographic evaluation showing clinical improvements in scar appearance at 6 months post treatment, as evaluated by 3 blinded independent investigators using the Visual Analogue Scale (VAS). The photographs were ordered as “before” and “after,” and randomly presented to the investigators for comparison (grade 1: <25% improvement, grade 2: 26-50% improvement, grade 3: 51-75% improvement, grade 4: > 75% improvement). For each subject, scores were averaged between the 3 independent investigators to provide a final score. The intra-class correlation coefficient (a measure of inter-rater reliability) was statistically interpreted.

Clinical Assessments
Treatment responses were assessed by comparing pre- and post-treatment clinical photographs. Independent physician evaluators assessed each photograph at 6 months after the last treatment using a quartile grading scale (grade 1, <25% improvement, grade 2, 26-50% improvement, grade 3, 51-75% improvement, grade 4, >75% improvement).

Statistical Analysis
Ordinal logistic regression was used for comparison between baseline and follow-up evaluations.

The data are ordinal with a range of 1 to 4. All time 1 scores were 1; therefore, only time 2 scores were analyzed with a Friedman nonparametric test. First, the scores were ranked within each of the 3 observers. Then a general linear model was used with the ranks as the dependent variable; treatment and observer were the independent variables. Model means and standard errors were reported with P-values for planned comparisons among the 4 treatment groups. The 0.05 alpha level was used to determine statistical significance. SAS 9.4 (SAS Institute, Inc.; Cary, NC) was used for all analyses.

RESULTS
Forty patients with hypopigmentation of various body locations were recruited for participation in this research study. Patients were assigned to 1 of the different treatment groups. All patients tolerated the intervention well with no adverse events. Re-pigmentation was assessed by 3 blinded dermatologists who were randomly presented with 80 photographs taken at baseline and 6 months post-treatment.

All patients in this current study showed improvement in hypopigmentation regardless of the treatment modality (Figure 2 and Table 7). The average improvement score was based on a 0 to 4 scale; and Group 3 (10,600 nm wavelength fractional ablative laser & bimatoprost) was found to have a significantly higher rank than any of the other treatments, with 76% of the patients exhibiting a grade 3 or higher (over 50%) improvement in pigmentation over the treatment course (Table 5). In Table 7, Group 3 with a mean rank score of 29.9 and standard error of 1.7 was significantly higher than Group 1 (21.0 ± 1.8; P=0.001), Group 4 (18.3 ± 1.8; P<0.001), and Group 2 (13.3 ± 1.8; P<0.001). Group 1 was also significantly higher than Group 2 (21.0 ± 1.8 vs 13.3 ± 1.8; P=0.006). Group 1 (1550 nm wavelength non-ablative fractional erbium-doped fiber) also had a significantly higher average score (Table 3) compared with group 2 (10,600 nm wavelength fractional ablative laser) (Table 4). Unfortunately, with all the treatment modalities, many had a decrease of 50% for re-pigmentation (Tables 3-6; Figures 3-8).

TABLE 3.

<table>
<thead>
<tr>
<th>Average Improvement in Pigmentation Score With Non-Ablative Fractional Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graded Improvement in Pigmentation</td>
</tr>
<tr>
<td>1 (&lt;25% Improvement)</td>
</tr>
<tr>
<td>2 (26-50% Improvement)</td>
</tr>
<tr>
<td>3 (51-75% Improvement)</td>
</tr>
<tr>
<td>4 (&gt;75% Improvement)</td>
</tr>
</tbody>
</table>

TABLE 4.

<table>
<thead>
<tr>
<th>Average Improvement in Pigmentation Score With Fractional Ablative Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graded Improvement in Pigmentation</td>
</tr>
<tr>
<td>1 (&lt;25% Improvement)</td>
</tr>
<tr>
<td>2 (26-50% Improvement)</td>
</tr>
<tr>
<td>3 (51-75% Improvement)</td>
</tr>
<tr>
<td>4 (&gt;75% Improvement)</td>
</tr>
</tbody>
</table>
It is still questionable if additional treatment, additional pigmentation, or additional combination therapies address different mechanisms of action for re-pigmentation. In this clinical trial, we hypothesized that skin of color responds to treatment more robustly because the Fitzpatrick skin types in Group 3 are higher on average (Table 2).

### TABLE 5.

<table>
<thead>
<tr>
<th>Graded Improvement in Pigmentation</th>
<th>Percent of Photographs Receiving Each Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt;25% improvement)</td>
<td>9%</td>
</tr>
<tr>
<td>2 (26-50% improvement)</td>
<td>15%</td>
</tr>
<tr>
<td>3 (51-75% improvement)</td>
<td>24%</td>
</tr>
<tr>
<td>4 (&gt;75% improvement)</td>
<td>52%</td>
</tr>
</tbody>
</table>

### TABLE 7.

<table>
<thead>
<tr>
<th>Group</th>
<th>Rank Within OBS</th>
<th>Comparison P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21.0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>13.9</td>
<td>0.006</td>
</tr>
<tr>
<td>3</td>
<td>29.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>18.3</td>
<td>0.085</td>
</tr>
</tbody>
</table>

### FIGURE 2.

All patients in this current study showed improvement in hypopigmentation regardless of the treatment modality.

### FIGURE 3.

(A) Before photo of patient with hypopigmented traumatic scar due to laser complication from hair removal. (B) After photo of the patient in Group 1, 3 treatments of fractional non-ablative laser only in 4 to 6-week intervals.

### FIGURE 4.

(A) Before photo of patient with idiopathic guttate hypomelanosis. (B) After photo of the patient in Group 2, 3 treatments of fractional ablative laser only in 4- to 6-week intervals.

### FIGURE 5.

(A) Before photo of patient with hypopigmented traumatic scar due to face lift approximately 8 years ago. (B) After photo of the patient in Group 1, 3 treatments of fractional non-ablative laser only in 4- to 6-week intervals.

### FIGURE 6.

(A) Before photo of patient with hypopigmented, atrophic burn and traumatic scars due to car accident fire in 2011. (B) After photo of the patient in Group 3, 3 treatments of fractional ablative laser with laser assisted drug delivery of bimatoprost topical solution twice a day for 14 days in 4- to 6-week intervals.

### TABLE 6.

<table>
<thead>
<tr>
<th>Graded Improvement in Pigmentation</th>
<th>Percent of Photographs Receiving Each Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt;25% improvement)</td>
<td>50%</td>
</tr>
<tr>
<td>2 (26-50% improvement)</td>
<td>20%</td>
</tr>
<tr>
<td>3 (51-75% improvement)</td>
<td>17%</td>
</tr>
<tr>
<td>4 (&gt;75% improvement)</td>
<td>13%</td>
</tr>
</tbody>
</table>
The mechanism by which fractional lasers are speculated to work in treating hypopigmentation is through the repopulation of melanocytes from surrounding hair follicles and basal melanocytes, causing an overall increase in pigmentation. This is accomplished through the production of microscopic thermal zones of injury, which induce a molecular cascade that stimulates healing via hundreds of unique biological growth factors, interleukins, adhesion proteins, and differentiated cells in the dermis, which are postulated to help “turn back on” the melanocyte to produce melanosomes.

The ablative fractional resurfacing laser differs from the nonablative fractional laser due to its ability to disrupt the barrier function of the cornified layer of skin by ablating columns extending from the epidermal layers to the deeper dermal layers at a greater depth, allowing for increased stimulation of wound-healing and prolonged effects. However, because the microscopic treatment zones include damage to the epidermis and possibly some focal loss or heating of the melanocyte, the ablative laser causes more aggressive damage with increased recovery time.

Interesting to note in this small study is that the nonablative fractional lasers had better re-pigmentation than the ablative fractional laser. However, the laser-assisted delivery with stimulatory bimatoprost scored the best. This function of ablative lasers has been used for delivery-enhancement purposes, whereby the vertical channels of ablation created by photothermolysis serve as a conduit for deeper penetration to the underlying skin and greater bioavailability of topical medications. Laser assisted delivery has been studied using various medications with favorable outcomes; and it appears that the combination of the 2 modalities have synergistic effects for many indications.

Although bimatoprost is a synthetic prostaglandin originally indicated for the treatment of glaucoma, it has been shown to have the side effect of periocular hyperpigmentation. The mechanism by which this medication causes increased melanogenesis is thought to be due to the induction of dormant melanocytes and through the transfer of melanosomes to basal keratinocytes without melanocyte proliferation, inflammation, or melanocyte atypia. It appears that prostaglandin analogs cause hyperpigmentation in a dose-dependent manner, which becomes more evident with increased contact to the skin.

Based on this principle, studies have shown promising results in the treatment of hypopigmented scars using prostaglandin analogs when combined with fractional lasers. This synergistic effect was first investigated by Massaki et al, who showed that combining the nonablative fractionated laser systems with topical bimatoprost, and tretinoin or pimecrolimus, had significant improvement (>50%) in more than 85% (12/14) of those in the treatment group. This concept was further explored by Siadar et al using the ablative fractional laser, with 11 out of 14 patients demonstrating over 50% improvement in hypopigmentation when treated with the 10,600-nm fractional CO2 laser plus latanoprost 0.005%, an outcome significantly different when compared with placebo over a 6-treatment time course. However, in this study researchers instructed patients to apply topical prostaglandin analog twice a day for 6 months, whereas patients in our current study only applied bimatoprost 0.03% twice a day for 14 days following each laser treatment.

The novel device currently used to perform epidermal grafting procedures is a donor site sparing harvesting system, which enables the transfer of autologous epidermis, including live melanocytes, by creating microsuction blisters known as micromedes using a combination of vacuum and heat. In this procedure, only the epidermal portion of the donor area is grafted, and therefore the graft acquires the characteristics of the recipient site. This has the potential to allow for improved cosmetic outcomes and color matching, without significant donor site morbidities such as scarring. This epidermal harvesting system technology has proven to be effective in the treatment of vitiligo and wounds, yet clinical data are lacking. Additional benefits of this grafting procedure are that it can be performed in the outpatient setting, it requires limited resources and clinical training, and it is more cost-effective when compared with skin grafting. In this study, the ablative fractional laser was
used to prepare the recipient site. This may not be the optimal approach for recipient site preparation, and other methods that may work better include medical sandpaper, microdermabrasion, or liquid nitrogen to create bullae 24 hours prior to optimize engraftment.

**CONCLUSION**

Although lasers have proven to be effective in the treatment of hypopigmentation, comparative studies to determine the most safe and effective method for the treatment of hypopigmented scars are lacking. The results of this study demonstrate that all of the selected laser interventions can potentially improve hypopigmentation, but combining fractionated laser systems with topical bimatoprost appeared to be the most efficacious treatment to accomplish re-pigmentation. In this small comparison, most patients (52%) exhibited over 75% improvement in hypopigmentation within just 3 sessions and without adverse effects. Our data are consistent with previous studies showing the superiority of combination fractional laser with a prostaglandin analog when compared with fractional laser alone. However, this study further compared hypopigmentation improvement outcomes amongst ablative and non-ablative fractional lasers, and also to the novel epidermal harvesting system technique for a more comprehensive evaluation.

In the past 5 years, new technologies are emerging which may give new hope for treatment of hypopigmentation. Among these new technologies, fractional lasers have been demonstrated in early case reports to produce improvement in hypopigmentation. Laser-assisted drug delivery using fractional laser is an evolving modality that may allow for greater precise depth of penetration by existing topical medications to deliver to target cells such as melanocytes. In our study, using bimatoprost solution immediately post ablative fractional laser to increase melanogenesis as well as melanosome transfer to basal keratinocytes increased pigmentation over laser alone.

To our knowledge, this is the first clinical trial performed to compare the efficacy of fractional laser(s), ablative and non-ablative, vs laser-assisted delivery of bimatoprost vs epidermal melanocyte transplantation for the re-pigmentation of hypopigmented areas. The limitations of this study include the lack of objective evaluator assessments for the results and small sample sizes.

**DISCLOSURES**

This research was funded by the ASDS Cutting Edge Research Grant. The fractional ablative laser used in the study was provided to Dr. Jill Waibel by Lumenis with whom she has done another clinical trial. All other authors have nothing to disclose.

**REFERENCES**


**AUTHOR CORRESPONDENCE**

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It’s the power, speed and flexibility you need to put your practice ahead of the rest.

Before
After 2 Txs
Photos courtesy of Vic Ross, M.D.
Simultaneous Changes in Abdominal Adipose and Muscle Tissues Following Treatments by High-Intensity Focused Electromagnetic (HIFEM) Technology-Based Device: Computed Tomography Evaluation

David E. Kent MD, a Carolyn I. Jacob MD b
a Skin Care Physicians of Georgia, Macon, GA
b Chicago Cosmetic Surgery and Dermatology, Chicago IL

ABSTRACT

Objective: This study investigates the effects of high-intensity focused electromagnetic technology for induction of changes in abdominal muscles and abdominal subcutaneous fat.

Methods: 22 male and female subjects (aged 34 to 64, mean BMI, 23.5kg/m2) underwent 8 treatments of the abdomen (2 per week) with a high-intensity focused electromagnetic field device. Subjects were scanned by computed tomography (CT) at baseline and 1 month after the eighth treatment. Sub-umbilical and epi-umbilical slices were used to measure the thickness of subcutaneous fat and abdominal muscles and the abdominal separation. In addition, standardized photographs, weight, and circumference measurements were collected.

Results: While comparing baseline to follow-up measurements, CT data showed on average 17.5% (-3.1±1.9mm) reduction in subcutaneous fat and simultaneous 14.8% (+1.5±0.8mm) thickening of the rectus abdominis muscle. Subjects lost on average 3.9±3.1cm in the waist circumference. Most of the waist reduction effect was achieved after the fourth treatment. The width of abdominal separation decreased by 9.5% (-2.0±1.7mm). All results were highly significant (P<0.01) while weight change was insignificant (P<0.05). Digital photographs showed aesthetic improvement in most subjects. The treatments were painless and without adverse events.

Conclusion: Results suggest that the investigated device is effective for abdominal body sculpting. This technology produced rectus muscle hypertrophy and a reduction in subcutaneous abdominal fat. Data suggests 4 treatments as the ideal protocol delivering 86% of the observed improvement.


INTRODUCTION

Long-term intensive resistance training programs are known to improve isometric strength1–2 and result in muscle hypertrophy,3–4 with accepted hypotheses that the hypertrophic effects are primarily caused by induced muscular micro injury.5,6 Yet studies demonstrate that approximately 50% of people attempting to follow some kind of exercise program drop out due to lack of motivation after several months.7,8 Magnetic stimulation was investigated as an alternative to resistance training and results showed improvement in muscle strength.9,10

Recent studies9–14 reported that intense muscle contractions induced by application of high-intensity focused electromagnetic (HIFEM) technology increased anterior abdominal muscle mass, reduced subcutaneous fat thickness, and reduced the distance between the rectus abdominis muscles. The net result was a reduction in abdominal waist circumference and an improvement in the overall appearance of the abdomen. HIFEM technology is based on a rapidly changing magnetic field generated with a wire coil that, as described by the Faraday’s law of electromagnetic induction, induces a secondary electric current in the underlying tissue.15 The current triggers action potentials in motor neurons which consequently lead to muscle contractions in the area of application.15

Initial HIFEM studies that reported changes in both muscle and fat tissues applied four-treatments. It has been proposed that a higher number of induced muscle contractions will result in more muscle micro injury with resultant increased muscle hypertrophy and fat reduction. However, studies that have investigated this hypothesis are lacking.

This study investigated an extended treatment protocol of a novel device (EMSCULPT, BTL Industries Inc., Boston, MA) utilizing a high-intensity focused electromagnetic (HIFEM) field. The goal of this study is to evaluate the safety and effects of adipose and muscle tissues in the abdomen using computed tomography (CT) and an extended treatment protocol.
MATERIALS AND METHODS

Study Design
Eligible candidates for this study were men or women aged 21-65 years with no weight changes exceeding 5 lbs in the preceding month. For the duration of the study, subjects were instructed to avoid major diet and lifestyle changes. Exclusion criteria for this study ruled out candidates with pregnancy, implanted electronic devices, metal implants (in near proximity to the treatment area, such as hip replacements; shoulder replacements, and/or knee replacements were not considered as exclusion criteria), heart disorders, treatment for active malignancy, and any medical conditions contraindicating the application of an electromagnetic field.

In total, 3 male and 19 female subjects were recruited for the study. The subjects aged from 34 to 65 years (mean age, 47.3±8.5 years) and had a mean BMI of 23.5±3.5 kg/m². Before the treatments, all subjects received informed consent about the treatment procedure and signed written consent. The treatment was applied to the abdomen using the EMSCULPT device (BTL Industries Inc., Boston, MA) based on HIFEM technology. The device consists of a control unit and a cable connecting the unit to a coil applicator, which is applied over the treatment area. The circular coil located in the applicator induces a magnetic field with intensities reaching up to 1.8 T and an active depth of approximately 7cm.

The treatment protocol consisted of 8 sessions kept 2-3 days apart. The protocol was approved by IRB and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The duration of a single treatment was 30 minutes. Subjects were positioned in a supine position, and the treatment was performed by placing the applicator centred over their umbilicus. The applicator was secured by a Velcro belt. During the first session, the intensity of the magnetic stimulation was initially set to low levels of around 10% of the device’s maximum output to allow the subjects experience the sensation felt during the treatment. The intensity was then gradually increased to induce challenging but not painful muscle contractions just below subjects’ tolerance threshold. All subjects reached 100% intensity and were able to maintain this level of stimulation during treatment sessions. During each session and follow up visit the subjects were screened for any adverse events related to the treatment.

Data Collection
Computed tomography (CT) imaging was used to evaluate the outcome of the treatments. Subjects were scanned by a General Electric VCT 64 Slice Lightspeed CT scanner (the body section defined by the T2 and S1 vertebrae) at baseline and 1 month after the last treatment. The sub-umbilical and epi-umbilical slices were extracted from the acquired CT scans and analyzed and measured for the thickness of subcutaneous fat, the thickness of rectus abdominis muscle, and the width of abdominal muscle separation. Measurements were taken at both epi-umbilical and sub-umbilical slices, and their average was recorded.

Waist circumference was measured at baseline and after each treatment by anthropometric tape. The measurements were performed at the upper edge of the umbilicus which served as a standardized point throughout the measurements. Further, standardized photographs and weight measures were taken throughout the study to monitor the subjects’ progress. All data were statistically tested for significance using two-sample paired t-test with the significance level set to 5%.

RESULTS

All 22 subjects completed the full set of treatments and underwent CT imaging at baseline and 1 month after the last treatment. The weight of all subjects was maintained within 5 lbs of the baseline with an average weight change of 1.0 lb (P>0.05). Fat thickness and abdominal separation were reduced, while muscle thickness increased significantly at the 1-month measurements. Waist circumference was gradually decreasing over the course of the treatments. The result summary can be seen in Table 1.

### TABLE 1.

<table>
<thead>
<tr>
<th>Result Summary</th>
<th>Baseline</th>
<th>1 month FU</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectus abdominis thickness [mm]</td>
<td>11.0±2.1</td>
<td>12.5±2.0</td>
<td>1.5±0.8 (P&lt;0.001)</td>
</tr>
<tr>
<td>Subcutaneous fat thickness [mm]</td>
<td>18.3±7.1</td>
<td>15.2±6.5</td>
<td>-3.1±1.9 (P&lt;0.001)</td>
</tr>
<tr>
<td>Abdominal separation [cm]</td>
<td>20.1±9.2</td>
<td>18.1±8.8</td>
<td>-2.0±1.7 (P&lt;0.001)</td>
</tr>
<tr>
<td>Waist circumference [cm]</td>
<td>81.1±7.9</td>
<td>77.2±7.4</td>
<td>-3.9±3.1 (P&lt;0.001)</td>
</tr>
<tr>
<td>Weight [lb]</td>
<td>143.8±23.6</td>
<td>142.8±23.5</td>
<td>-1.0±2.8 (P&gt;0.05)</td>
</tr>
</tbody>
</table>

Evaluation of the CT scans showed a statistically significant increase (P<0.001) of rectus abdominis muscle thickness by an average of 14.8% (1.5±0.8mm). All subjects demonstrated an increase in muscle thickness except subject ID15 who did not show any muscle thickening despite a 14.6% abdominal fat reduction. In 15 subjects the measured muscle thickening exceeded 10%.

Analysis of the subcutaneous adipose tissue revealed a noticeable decrease (P<0.001) in the average fat thickness by 175% (-3.1±1.9mm). In 18 out of the 22 subjects, the measured reduction in subcutaneous fat exceeded 10%, and 12 out of the 22 subjects showed fat reduction higher than 16%. Subject ID8 had an extremely thin fat layer and it
measurements, however, the main descent was observed during the first four sessions (average 3.0±2.52 cm). Additional treatments lead to further circumferential reduction (0.93±1.78 cm) but not to such extent as during the first four treatments. The course of the waist circumference throughout the procedure is documented in Figure 2, where a polynomial curve of a 3rd order was fitted into the data.

The subjects, who experienced muscle contractions induced by the electromagnetic field for the first time, described the initial pulses of the treatment as intense, but quickly adapted to the feeling and further on found the treatments comfortable. Most of them reported intense and strong muscle contractions but no discomfort. None of the subjects reported any pain associated with the treatment. Several subjects reported soreness and muscle fatigue on the day after the treatment, which was comparable to post-workout fatigue. Besides that, no adverse events were observed.

**DISCUSSION**

The results of this study demonstrate that the HIFEM technology effectively induced a dual effect in abdominal fat and skeletal muscles. Increased muscle thickening was accompanied by reduction of the abdominal fat layer and waist circumference in almost all patients. One subject did not show fat reduction and one subject did not show any muscle thickening yet each subject showed improvement in at least 2 out of the 3 conducted measurements. There were no non-responding patients. The degree of fat reduction appears to be independent of the degree of muscle thickening.

The increase in muscle thickness by 14.8% correlates with a study done by Kinney et al who used MRI evaluations of muscle thickness 2 months after the protocol of 4 treatments and found an average reduction of 15.4% (Difference was statistically insignificant 𝑃 < 0.05). Because CT scans were obtained 1 month post-treatment, transient muscle swelling can be ruled out as a reason for the observed hypertrophy, as it typically resolves within 7 to 11 days after muscle micro injury. Comparison of...
was reduced during the first 4 treatments (-3.0±2.52cm), then, sated for the weight of the reduced fat. The waist circumference by the fact that the increased volume of the muscles compen-

sations which can induce stress of endoplasmic reticulum and fat cell apoptosis.

our results with the Kinney et al data is seen in Table 2. Subjects maintained their regular diet and activity level without any modifications. In the absence of other mechanisms of fat reduction, it is likely the observed fat reduction resulted from lipolytic and/or apoptotic actions induced by the intense muscle contractions during the treatment. Intensive resistance training is known to induce lipolysis.17,18 The study by Weiss et al14 found an increased apoptotic index in the porcine model after single HIFEM treatment. They hypothesized that local supramaximal sustained muscle contractions may cause high levels of lipolysis which can induce stress of endoplasmic reticulum and fat cell apoptosis.

Our fat thickness measurements when compared to previous studies of Kinney et al and Katz et al13 (Table 2) had similar fat reduction. Their data demonstrated 18.6% and 19% reduction one month post four treatments, respectively. While not entirely certain, the slightly higher average improvement of Kinney et al might be attributed to the difference in time of the after measurements. Measures performed by Kinney et al were obtained 2 months post-treatment, which were twice as long as our study. Theoretically, skeletal muscles thus had more time to adapt to contractions by muscle growth, and more fat cells could be flushed out of the system when compared to our measurements 1 month post-treatment. The age of the subjects could also play a role. The subject group in the study by Kinney et al was approximately 8 years younger, and younger subjects could, therefore, yield more prominent changes. Similarly, for muscle thickness, the comparison indicates that protocol with more than 4 treatments may not necessarily produce any additional fat reduction.

No changes were observed in the BMI, which can be explained by the fact that the increased volume of the muscles compensated for the weight of the reduced fat. The waist circumference was reduced during the first 4 treatments (-3.0±2.52cm), then, the circumference reduced in a slower pace by additional 0.93±1.78cm. This suggests that 4 treatments may be sufficient for inducing substantial changes in the abdominal skeletal muscle. The reduction of the waist circumference can be caused not only by the fat reduction but also by firmer abdominal muscu-

lature. The waist circumference reduction observed in our study conforms to study by Jacob et al.12 who found a reduction of 3.29±1.9cm after the fourth treatment with HIFEM device and even 4.37±2.63cm reduction during 3-month follow-up.

One of the limitations of the present study is the patient population as the study included 22 subjects. A bigger patient group would provide higher reliability of the statistical analysis and would bring a broader insight on how different patient group react to the treatments and whether the same result would have been seen. Another limitation of the study is that the present study evaluated the subjects 1-month post-treatment. Future studies focusing on longer-term evaluation and follow up regarding the durability of results would be beneficial. Additionally, studies designed to evaluate the role of potential maintenance treatments for sustained improvement would be insightful. Functional parameters that measure isometric strength19 and dynamic endurance19 of abdominal muscles might provide insight into actual physical conditioning.

CONCLUSION

Results show that a HIFEM device is successful for abdominal body sculpting. CT scans documented improvement in both subcutaneous adipose tissue reduction and abdominal skeletal muscle hypertrophy. These results provided pleasing aesthetic improvement. This device also has a very low-risk profile with no thermal effects. Comparison with other studies suggests that treatment protocol including eight sessions does not necessarily bring a significant increment in results compared to 4 treatment protocol results.

DISCLOSURES

David Kent MD and Carolyn I. Jacob are medical advisors for BTL.

ACKNOWLEDGMENT

We would like to thank the Radiology Associates of Macon for performing all CT scans.

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A Randomized, Controlled, Split-Face Study of the Efficacy of a Picosecond Laser in the Treatment of Melasma

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ABSTRACT

INTRODUCTION

Melasma is a common disorder where patients develop hyperpigmented macules and patches on the face and is thought to be the result of sun exposure and hormonal contributions, although the pathogenesis is not completely understood. Lasers have been used for melasma treatment with varying degrees of success.

OBJECTIVES: The objective of this study was to examine the safety and efficacy of a novel picosecond laser for the treatment of melasma.

MATERIALS AND METHODS: Ten subjects received nine weekly laser treatments with a picosecond laser to a randomized half of their face. A lightening cream was applied to the entire face to serve as a control. The primary outcome measure was clinical efficacy measured by a patient-reported outcome survey, the Melasma Quality of Life (MELASQoL) questionnaire, and physician assessment with the Global Aesthetic Improvement Scale (GAIS). The secondary outcome measure was safety, which was assessed by monitoring for adverse events. Photos were taken before every treatment and at a 1-week follow-up.

RESULTS: Ninety percent of subjects rated their melasma as at least slightly better, and 90% percent of subjects would recommend this laser treatment to others with melasma. MELASQoL questionnaire scores improved by an average of 5.7 points after laser treatment. Assessments by two board-certified dermatologists using the GAIS revealed an overall improvement in 80% of patients on the laser treatment side versus 20% on the control side. Side effects, including erythema and discomfort, were minimal and transient post-treatment.

CONCLUSIONS: This study suggests that picosecond laser treatments are a safe and efficacious way to treat melasma.


INTRODUCTION

Melasma is a pigmented disorder in which patients develop symmetric, hyperpigmented macules and patches most commonly on the face. Although the pathogenesis has not been completely elucidated, sun exposure and hormones are thought to contribute to the condition. It occurs most commonly in women and is more prevalent in darker skinned individuals but can occur in all skin types.¹

With more than 5 million Americans affected, melasma is a common reason for dermatology appointments and can negatively impact the quality of life of patients.²³ Despite its widespread prevalence, the treatment of melasma has proven to be difficult. The challenges of treatment are attributed to the chronicity, recurrence rate, and unclear pathogenesis. Many lasers have been used for the treatment of melasma with varying degrees of success. The aim of this study was to investigate the efficacy and safety of a novel picosecond laser for the treatment of melasma.

MATERIALS AND METHODS

This was a randomized, controlled, split-face prospective study. A total of 10 subjects with a previous diagnosis of melasma were recruited from a dermatology office in Beverly Hills, CA. Inclusion criteria included subjects ages 18-65 with a diagnosis of melasma who were able to provide informed consent. Exclusion criteria included subjects under the age of 18 or over the age of 65, those who had used bleaching creams, chemical peels, or laser treatments within the past month prior to enrollment, those who were pregnant or breast feeding, and those who were on oral contraceptive pills.

Informed consent was obtained from subjects who fulfilled the eligibility criteria. Subjects were then randomized to laser treatment on one side of the face and underwent nine weekly picosecond laser treatments using the PiQo4 laser (Lumenis). Subjects were given and instructed to use a topical lightening cream containing .05% tretinoin/3% kojic acid/6% hydroquinone/1% hydrocortisone to their entire face daily for the duration
DISCUSSION

Melasma is a clinical diagnosis and typically falls under the patterns of centrofacial, malar, and mandibular, although extrafacial melasma on the arms, neck, chest, or back has also been described. The centrofacial pattern is the most common presentation and occurs in 50-80% of patients. Melasma has a gender predilection with approximately 90% of affected patients being women. In addition to female gender, risk factors include darker skin type, pregnancy, sun exposure, oral contraceptive pills, and positive family history. The frequency of melasma varies between skin types and ethnicities with Fitzpatrick skin types III and IV most commonly affected. The prevalence of melasma has been studied in many subpopulations with estimates ranging between 9% in Hispanic women in the United States to 41% in India. Melasma also carries a genetic predisposition with 40% of patients having relatives with the disease.

Patient reported outcomes for the treatment of melasma are important as this condition can have a significant negative impact on patient quality of life. The Melasma Quality of Life scale (MELASQOL) is a validated scale to assess the effect of melasma on patient quality of life. Our subjects experienced an average improvement of 5.7 points on their MELASQOL.

The first line therapy for melasma is sun protection and the use of topical lightening agents including hydroquinone and retinoids among others, while second line therapy includes chemical peels. These treatment modalities are often used in combination to optimize management. More recently, oral tranexamic acid has been tried for refractory melasma with promising results.

Laser therapies have become more popular in recent years, especially in patients with refractory disease. Laser treatments for melasma patients can be a challenge as excess heat can cause post-inflammatory hyperpigmentation (PIH) and melasma exacerbation. Q-switched lasers have been used for treating melasma, but PIH is a common pitfall. Similar resultant hyperpigmentation have also been described post-erbium:YAG and CO2 laser treatments. Although fractional resurfacing lasers, which minimize thermal damage to microzones within the skin may mitigate PIH, there are few studies that have shown satisfactory results with these devices. Intense pulsed light (IPL) has also been used with varying degrees of success but requires maintenance treatments and can cause exacerbation of hyperpigmentation if lower wavelengths of light are used.

Because generation of heat is often considered the key factor in post-laser hyperpigmentation, picosecond lasers that deliver energy in exceptionally short pulse durations, minimize photothermal effects and are a promising strategy for treatment of melasma. Indeed, recent studies have supported the use of picosecond lasers for melasma.

39 (77%) Korean patients had greater than 51% improvement in relative lightness values with a combination of daily 2% HQ and 5 weekly laser treatments of dual-wavelength 1064 plus 595 nm on a 750 picosecond laser versus only 3% of subjects on 2% HQ alone. Similarly, Lee et al also successfully treated three Korean patients with treatment resistant melasma with a 755 nm picosecond laser with two patients reporting good improvement and one with fair improvement. In addition, a recent study on thirty female subjects with melasma found that treatment with fractional picosecond 1064 nm laser combined with 4% HQ was superior than 4% HQ alone with a modified melasma area severity index (mMASI) score significantly reduced in the laser group (3.52 ± 1.4 and 4.18 ± 2.03, respectively).

This study emphasizes the utility of using a combination of 955 and 1064 nm on lighter skin phototypes and using 1064 on darker skin phototypes. These picosecond treatment settings offer patients the benefit of little to no downtime in contrast to other laser treatment options which can have significant periods of associated erythema or peeling. In addition, the 1064 nm treatment is safe on darker skin phototypes with no resultant PIH seen in this cohort.

Limitations include a relatively small sample size and the study being limited to female patients. Longer follow-up is needed to assess continued improvement and the durability of treatment. This study also lacked Fitzpatrick skin types V-VI; thus, further studies are needed to assess the safety and efficacy of these laser treatments in African American patients.

In conclusion, picosecond lasers are an efficacious treatment modality for patients with refractory melasma. Nine out of 10 subjects in this study reported an improvement in their melasma and would recommend the treatment to others. MELASQOL scores decreased 5.7 points on average indicating a decreased effect of melasma on patient quality of life. GAIS evaluation by physicians revealed an overall improvement in 80% of patients on the laser treatment side versus 20% on the control side. Side effects were minimal and transient with the laser treatment. This study suggests that picosecond laser treatments are a safe and efficacious way to treat melasma with little down time.

DISCLOSURES

ABL is a sub-investigator for Incyte, Bayer, Unigen Inc., Lenicura, Esteelader, Miragen, Biofrontera. RLM is the medical director of DNA EGF Renewal. JHL has no relevant disclosures.

REFERENCES

of the study. Subjects were also counseled to apply an SPF 30 sunscreen daily to their entire face, which was provided to them at their first visit for consistency. Prior to each treatment, patients were asked about adverse events and side effects, photographs were obtained, and the face was washed with a gentle cleanser. The settings for the first treatment were: wavelength of 1064 nm, pulse duration of 8 nm, fluence of 1 J/cm², and spot size of 9 mm for 3-5 passes. Subsequent treatment settings were: wavelength of 1064 nm, pulse duration of 800 ps, fluence of 1.0 J/cm² (approximately 400 mJ), and spot size of 7 mm. In addition, for patients with Fitzpatrick skin types 1-3, one pass of: wavelength 532 nm, pulse duration of 800 ps, fluence 0.2 J/cm², and spot size of 9 mm was performed at each visit. Subjects completed the Melasma Quality of Life (MELASQOL) questionnaire at their first and last visits. Subjects were asked to rate their change in melasma on the laser treatment side as: “worse”, “no change”, “slightly better”, “better”, or “much better”. They were also asked if they would recommend the treatment to others with melasma. Photographs were evaluated by 2 physicians using the Global Aesthetic Improvement Scale (GAIS) (Table 1).

### TABLE 1. Global Aesthetic Improvement Scale (GAIS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Very Much Improved (Optimal cosmetic result)</td>
</tr>
<tr>
<td>2</td>
<td>Much Improved (Marked improvement in appearance from the initial condition but not completely optimal)</td>
</tr>
<tr>
<td>1</td>
<td>Improved (Obvious improvement in appearance from the initial condition, but a touch up is indicated)</td>
</tr>
<tr>
<td>0</td>
<td>No Change (The appearance is essentially the same as the original condition)</td>
</tr>
</tbody>
</table>

### RESULTS

The average age of subjects enrolled was 42 (range, 26-50) with Fitzpatrick skin phototypes ranging from II-IV. None of the subjects reported a worsening of their melasma. One patient reported her melasma as unchanged, 4 reported it as slightly better, 2 reported it as better, and 3 reported it as much better (Figure 1). The average MELASQOL score improved by 5.7 points from an initial average of 31.8 to a final average of 26.1. Nine out of ten of the subjects said they would recommend this treatment to others with melasma. Assessments by two physicians revealed an overall improvement in 80% (n=8) of patients on the treatment side vs 20% (n=2) on the control side (Table 2, Figure 2).

Side effects included mild discomfort during the treatment and transient erythema that resolved within a couple of hours. Two patients developed petechiae after one of the treatments which resolved after 2-3 days. None of the subjects experienced hyperpigmentation from the treatments.

### TABLE 2. Patient GAIS Scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Treatment side % (n)</th>
<th>Control side % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>10% (1)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>2</td>
<td>30% (3)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>1</td>
<td>40% (4)</td>
<td>20% (2)</td>
</tr>
<tr>
<td>0</td>
<td>20% (2)</td>
<td>80% (8)</td>
</tr>
<tr>
<td>-1</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
</tbody>
</table>

![Figure 1](image1.png)  ![Figure 2](image2.png)


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Safety and Effectiveness of Microfocused Ultrasound With Visualization for the Correction of Moderate to Severe Atrophic Acne Scars

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Objective: To assess the effectiveness of microfocused ultrasound with visualization (MFU-V) for treating moderate to severe atrophic acne scars.

Design: Healthy subjects (N=20) seeking correction of moderate to severe atrophic acne scars on the cheeks and/or temples were enrolled. Scars were predominantly rolling- and boxcar-type, affecting an area ≥5.0cm². Eighteen subjects completed the study.

Intervention: The treatment area was marked with 14mm² and 25mm² squares and treated with four transducers: 7 MHz (3.0mm focal depth) and 10 MHz (1.5mm focal depth), each in 14mm and 25mm widths. During each session, MFU-V treatment lines were applied 2-3mm apart, within each treatment area, with a maximum length of 25mm. Each square received 30 treatment lines at two transducer depths (60 total lines). Subjects received three total treatments, with 30 days between each session. The primary outcome measure was improvement in baseline appearance of scars at 90 and 180 days after the final treatment. Secondary outcome measures included changes in severity using an Acne Scar Improvement Scale (ASIS) and Global Aesthetic Improvement Scale (GAIS) at 60-, 90-, and 180-days post-treatment, and a satisfaction questionnaire at 90-days post-treatment.

Results: Among the 90-day images available for assessments (n=11), 100% were rated as improved by blinded reviewers, and 64% of pre- and post-treatment images were correctly selected. Among 180-day images (n=15), 100% were rated as improved, and 40% of pre- and post-treatment images were correctly selected. Most subjects were determined to have 25-50% improvement in investigator ASIS scores at 60-, 90-, and 180-days post-treatment. All subjects noted some improvement in severity at the 60-day assessment when measured using ASIS. Based on investigator GAIS scores, 100% of subjects were “Improved” or “Much Improved” at 60-, 90-, and 180-days post-treatment. Based on subject GAIS scores, all subjects noted improvement at the 60-day assessment, and 83% and 89% at the 90- and 180-day assessments, respectively. Overall, 17 subjects (94.4%) expressed some degree of satisfaction at 90-days post-treatment.

Conclusions: The results of this study demonstrated that MFU-V therapy is beneficial and well tolerated for the treatment of rolling- and boxcar-type acne scars.


INTRODUCTION

Acne vulgaris is an exceedingly common skin disorder with a reported prevalence ranging from 75%1 to more than 90%2 in adolescents, and this condition often persists into adulthood.3,4 Acne affects both genders equally2 and all racial groups.1,4 The negative impact of acne on patient self-esteem, psychosocial functioning, and overall quality of life is the topic of numerous publications.5-10

An unfortunate long-term consequence of severe acne is scarring. Acne scars have been reported to occur with a frequency as high as 11% in men and 14% in women.11 In one acne study, 1% of patients had scars, and 1 in 7 (14%) scars was considered disfiguring.4 The severity of acne scarring has been correlated with overall acne severity and the duration of untreated acne.12

A delay of up to 3 years between acne onset and adequate treatment corresponded with the final extent of scarring.12 Facial scarring is associated with diminished quality of life13 and negative perceptions by society.14

While the etiology of acne scarring is not well understood, it is thought to result from skin damage during the healing process following active acne.5 Depending on changes in skin collagen, acne scars are classified as atrophic or hypertrophic. Most (80 to 90%) are atrophic scars caused by the loss of collagen.1 Based on morphology, atrophic scars are subclassified as ice pick (60 to 70%), boxcar (20 to 30%), or rolling scars (10 to 15%).3 Histological examination of acne-scar tissue revealed decreased dermal thickness and loss of pilosebaceous units, inflammatory cell infiltrates, and inadequate dense collagen-fiber deposition in the whole dermis.15
Numerous treatments are available for atrophic acne scars including chemical peels, dermabrasion/microdermabrasion, radiofrequency, laser treatment, punch techniques, dermal grafting, subcision, needling, and combined therapies. While all of these techniques have demonstrated varying degrees of effectiveness, the optimal treatment for acne scars remains unknown. The results of a recent Cochrane Review concluded that high-quality evidence regarding the various interventions for treating acne scars is lacking due to poor methodology, underpowered studies, lack of standardized improvement assessments, and different baseline variables. The results of that review did not provide support for the first-line use of any type of intervention for treating acne scars.

A microfocused ultrasound with visualization (MFU-V) device has been developed as a non-invasive aesthetic treatment to lift the eyebrow and lax submental and neck tissue and to improve lines and wrinkles of the décolleté (Ultherapy®; Merz North America, Raleigh, NC). The device is also capable of ultrasound imaging to avoid unwanted target areas such as bone and large blood vessels. Using transducers of varying frequencies and focal depths, the device is designed to focus ultrasound energy to produce small (<1mm³) microcoagulation zones in the mid-to-deep reticular layer of dermis and sub-dermis, while sparing overlying papillary dermal and epidermal layers of skin. The result is immediate contraction of denatured collagen, neocollagenesis, and tissue remodeling.

As neocollagenesis and tissue remodeling are hypothesized to improve the appearance of acne scars, the noninvasive characteristics of this MFU-V device and its ability to produce subcutaneous tissue remodeling make it a good candidate for the treatment of atrophic acne scars. The following open-label pilot study was designed to assess the effectiveness of MFU-V to treat moderate to severe atrophic acne scars.

**METHODS**

**Study Participants**

Healthy male and female subjects, 18 to 70 years of age, who were seeking correction of moderate to severe atrophic acne scars on the cheeks and/or temples were enrolled. Scars were required to be predominantly rolling- and boxcar-type scars, affecting an area ≥5.0cm², with few or no icepick scars present. The majority of scars were distensible with tension applied to the skin. Additional inclusion criteria were the willingness of subjects to: abstain from additional aesthetic therapies in the planned treatment areas; have a history of a stable paper weight; not be willing to use an acceptable method of birth control during the study.

Reasons for exclusion from study participation included the presence of an active systemic or local skin disease that may affect wound healing; severe solar elastosis; excessive subcutaneous fat or skin laxity in the planned treatment areas or significant scarring that could affect outcome assessments; severe or cystic acne on the areas to be treated, defined as >3 active inflammatory acne lesions in either the right or left treatment area; recent or current history of inflammatory skin disease, infection, cancerous/pre-cancerous lesion, or unhealed wound in the planned treatment areas; a history of systemic granulomatous diseases or connective tissue or autoimmune disease; hypertrophic acne scars, any evidence of keloid scarring, or predominantly (>50%) icepick scarring or sinus-tract scars; presence of a metal stent or implant in the treatment area; hypersensitivity to ibuprofen, acetaminophen, lidocaine, or tetracaine; history of chronic drug or alcohol abuse; current or recent smoker within the last 2 years; history of the following cosmetic treatments (timeframe) in the planned treatment areas: skin tightening (12 months); injectable filler including hyaluronic acid (12 months), calcium hydroxyapatite (12 months), poly-L-lactic acid (12 months), cultured fibroblasts (2 years), or permanent fillers (at any time); neurotoxin injections (3 months); microdermabrasion or prescription-level glycolic acid treatments (4 weeks); ablative resurfacing laser treatment (2 years); nonablative, rejuvenative laser or light treatment (6 months); surgical dermabrasion or deep facial peels (2 years); contour threads (at any time); prescription acne medications including isotretinoin or other systemic retinoids (6 months) or topical retinoids (2 weeks); current antiplatelet/anticoagulants including aspirin >82 mg daily; any other concurrent therapy or illness that might jeopardize the objectives of the study; inability to understand the protocol or provide informed consent; or participation in any study involving the use of investigational devices or drugs within the past 30 days.

**Treatment Procedure**

Each subject was pretreated with oral ibuprofen (800mg) 1 hour prior to treatment and a topical anesthetic cream containing 7% lidocaine and 7% tetracaine (Pliaglis® Cream; Galderma Laboratories, LP, Fort Worth, TX) was applied to the treatment area 30 minutes prior to treatment. Standardized images of each subject, using fixed camera and lighting conditions, were obtained prior to treatment (Visia®; Canfield Scientific, Inc., Parsippany, NJ).

For each subject, the area to be treated was identified and the number of squares needed to cover the cheek and temple areas affected by acne scars was determined; 25mm² squares were used for standard transducers and 14mm² squares for narrow transducers, as necessary, to cover the area of scarring. Acetate paper was placed over the area, and the fixed anatomical
landmarks of the tragus, lateral canthi, and mouth corner were marked. The treatment squares were drawn on the acetate paper, which was saved for use during subsequent treatments. Four transducers were available for the application of MFU-V: a 7 MHz transducer with a 3.0mm focal depth and a 10 MHz transducer with a 1.5 mm focal depth, each available as a 25mm or 14mm (narrow) width. After applying ultrasound gel, an ultrasound image was obtained for each proposed treatment area to ensure ultrasound coupling between the transducer and skin (DeepSEE®, Merz North America, Raleigh, NC). Within each treatment area, MFU-V treatment lines were applied 2 to 3mm apart with a maximum length of 25mm. Each treatment line required approximately 3 seconds to complete. Each treatment square received 30 treatment lines per transducer depth, for a total of 60 lines per treatment square, delivered in a crosshatch pattern (Figure 1). Each subject received three MFU-V treatments sessions 30 days apart.

FIGURE 1. Treatment areas. The area to be treated and the number of 25 mm² and 14 mm² squares needed to cover areas affected by acne scars were identified. The treatment squares were drawn on acetate paper placed over the area; paper was saved for use during subsequent treatments.

Primary Endpoint
When compared to images obtained at baseline, improvement in the appearance of acne scars was determined by a blinded, qualitative comparison of facial images obtained 90 and 180 days after the final MFU-V treatment. For each subject, three physicians reviewed pre- and post-treatment images in blinded, randomized order (ie, the reviewers were not aware which images were pre-treatment and which were post-treatment). Each reviewer independently evaluated the images for any improvement in appearance of acne scars or if there was no change. Clinical improvement was recorded using the following scale: exacerbation (-1), no change (0), 1 to 25% improvement (1), 26 to 50% improvement (2), 51 to 75% improvement (3), or 76 to 99% improvement (4). If improvement was assessed, the reviewer was asked choose the correct post-treatment image.

Secondary Endpoint
The principal investigator assessed changes in acne-scar severity using an Acne Scar Improvement Scale (ASIS) and Global Aesthetic Improvement Scale (GAIS) at 60-, 90-, and 180-days post-treatment. Each subject assessed their own overall aesthetic improvement using an ASIS and GAIS at 60-, 90-, and 180-days post-treatment. Subjects also completed a satisfaction questionnaire at the 90-day follow-up visit.

Safety
During the MFU-V treatment procedure, subjects were asked to rate the level of pain they experienced using a validated 11-point (0-10) Numerical Rating Scale (NRS), with 0 denoting no pain and 10 denoting the worst possible pain.23 Pain scores were obtained following the treatment of each area and for each transducer used. Following treatment, the investigator examined each subject for the presence of any acute response, such as erythema or edema.

Statistical Analysis
Available data were summarized for each time point. Subjects with incomplete data were included in summaries for which data were available. Categorical variables were summarized as frequencies and percentages in each category. Continuous and ordinal variables were summarized as the number of subjects (n), means, standard deviations (SD), medians, and ranges (min, max). All programs for data output and analyses were written in SAS® version 9.2 (SAS Institute, Inc., Cary, NC).

The primary effectiveness analysis was performed using subjects who completed the 90- and 180-day assessments. The primary effectiveness assessment was improvement in the appearance of acne scars as determined by a blinded, qualitative assessment of photographs at 90 and 180 days after the final treatment when compared to baseline. Adverse events are presented as the number of subjects reporting each event.
Ethics
Each subject provided signed, informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization prior to participating in any study-related procedures, as well as written consent to be photographed during the study. This study protocol and related materials were approved by a commercial institutional review board (Asentral IRB, Inc., Newburyport, MA). ClinicalTrials.gov Identifier: NCT02145364.

RESULTS

Demographics
Male (n=8) and female (n=12) subjects with a mean (SD) age of 44.5 (11.5) years and mean (SD) body mass index (BMI) of 24.4 (3.9) kg/m² were enrolled. Other subject demographics and baseline characteristics are summarized in Table 1. One subject withdrew consent after the first treatment, and one subject was lost to follow-up.

Primary Endpoint
Pre- and post-treatment images were available for 11 of the 18 subjects completing the 90-day follow-up visit; deficient images were either not obtained during the visit, had inconsistent lighting, or the subject was wearing make-up. Three of the 180-day images were excluded due to inconsistent lighting. Among the 90-day images available for blinded assessments (n=11), all were determined to be improved (100%), and the post-treatment image was correctly selected for 64%. Among the available 180-day images (n=15), all were assessed as improved, and a correct post-treatment image was selected for 40%. Representative pre- and 90-day post-treatment images are shown in Figure 2.

Secondary Endpoint
The 60-, 90-, and 180-day post-treatment investigator and subject ASIS scores are summarized in Table 2. Most subjects were determined to have 25 to 50% improvement. One subject had 75 to 99% improvement at day 180. No subjects had exacerbation in their acne scars, and none showed any change in their skin appearance. The 60-, 90-, and 180-day post-treatment investigator and subject GAIS scores are summarized in Table 3. At each time point, 100% of subjects showed improvement with most rated as Improved or Much Improved.

Safety
As measured using an 11-point (0-10) NRS, the mean pain scores during treatment with the 7 MHz/3.0 mm transducer were 4.2, 5.2, and 5.0 for treatments 1, 2, and 3, respectively. For the 10 MHz/1.5 mm transducer, the mean pain scores were 4.9, 6.2, and 5.9 for treatments 1, 2, and 3, respectively. Scores for both transducers indicate moderate pain severity. Examination of the treatment area revealed no evidence of skin damage or other sequelae such as scarring, burns, or hypo- or hyper-pigmentation.
It should be noted that a potential limitation of this study was the use of blinded evaluations of two-dimensional photographic images, as these images may not accurately capture acne-scar deformities as well as live evaluations of study subjects. The reliability of live assessments in determining improvement surpasses photographic evaluation as evidenced by GIAS and ASIS scores. Future studies will benefit from prioritizing live assessments over photographic evaluations in order to make more definitive statements about effectiveness of the procedure.

Importantly, the improved appearance in acne scars was long lasting based on investigator GIAS, and subject and investigator ASIS scores; the degree of improvement remained essentially unchanged between the 60- and 180-day visits. Nearly 95% of subjects showed up to 50% improvement in ASIS scores at days 60 and 90, which remained approximately 90% at 180 days. Similarly, investigator GIAS scores showed 100% of subjects demonstrated improvement at day 60, and this improvement was maintained through day 180. It is the authors’ clinical experience that the level of improvement observed through 180 days tends to diminish over longer periods of time. Therefore, retreating atrophic acne scars with MFU-V after 12 to 18 months may be helpful for maintaining long-term improvement, but additional studies would be necessary to fully evaluate the benefit. Assessments of treatment efficacy were similar among subjects. Based on subject ASIS scores, 72% of subjects achieved up to 50% improvement in acne-scar appearance at day 60, and this improvement remained at 61% and 56% on days 90 and 180, respectively. Based on subject GIAS scores, nearly 90% continued to note improvement in acne-scar appearance at day 180, and none indicated worsening of scar appearance. Overall, 95% of subjects were satisfied with their treatment results at day 90, of which more than 60% were Satisfied or Extremely Satisfied.

The improvements in acne-scar appearance observed in this study are consistent with the known mechanism of action of MFU-V. Several in vitro and in vivo studies have demonstrated the ability of MFU-V to cause points of thermal injury within the dermis, which results in immediate tissue contraction and leads to neocollagenesis and tissue remodeling. Clinically, the net effect is lifting and tightening of lax skin in various anatomical areas.

A wide range of other treatments have been used for treating atrophic acne scars. Similar to MFU-V, these treatments are also based on increasing collagen formation to reduce scar severity, including subcision, injectable poly-L-acid fillers, microneedling and percutaneous collagen induction, chemical reconstruction, and energy-based devices. While demonstrating varying degrees of effectiveness, all are also associated with various drawbacks, such as the need for repeated treatments, adverse events, or extensive down time. Effectiveness comparisons of these alternate treatments with MFU-V are not possible at this time.

There was no exacerbation of acne scars. Adverse events were reported by two subjects: one underwent surgery for Dupuytren’s contracture, and one reported having the cold/flu. Both events were unrelated to the study procedure.

### DISCUSSION

The results of this study demonstrated that a three-session program of MFU-V applied 30 days apart is beneficial and well tolerated for the treatment of rolling- and boxcar-type acne scars. For most treated subjects (64%), the appearance of acne scars was determined to be improved at the 90-day assessment. It should be noted that a potential limitation of this study was

#### TABLE 2.

<table>
<thead>
<tr>
<th>Acne Scar Improvement Scale (ASIS) Scores</th>
<th>Day 60 (N=18)</th>
<th>Day 90 (N=18)</th>
<th>Day 180 (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigator</strong></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>1% to 25% improvement</td>
<td>5 (27.8)</td>
<td>7 (38.9)</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td>26% to 50% improvement</td>
<td>12 (66.7)</td>
<td>10 (55.6)</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>51% to 75% improvement</td>
<td>1 (5.6)</td>
<td>1 (5.6)</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>76% to 99% improvement</td>
<td>0</td>
<td>0</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Acne scar exacerbation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No change in appearance</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

#### TABLE 3.

<table>
<thead>
<tr>
<th>Global Aesthetic Improvement Scale (GIAS) Scores</th>
<th>Day 60 (N=18)</th>
<th>Day 90 (N=18)</th>
<th>Day 180 (N=18)</th>
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</thead>
<tbody>
<tr>
<td><strong>Investigator</strong></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>1 (Very much improved)</td>
<td>0</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>2 (Much improved)</td>
<td>2 (11)</td>
<td>2 (11)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>3 (Improved)</td>
<td>16 (89)</td>
<td>15 (83)</td>
<td>15 (83)</td>
</tr>
<tr>
<td>4 (No change)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5 (Worse)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any improvement</td>
<td>18 (100)</td>
<td>18 (100)</td>
<td>18 (100)</td>
</tr>
<tr>
<td><strong>Subject</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Very much improved)</td>
<td>0</td>
<td>2 (11)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>2 (Much improved)</td>
<td>7 (39)</td>
<td>5 (28)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>3 (Improved)</td>
<td>11 (61)</td>
<td>8 (44)</td>
<td>7 (39)</td>
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<td>4 (No change)</td>
<td>0</td>
<td>3 (17)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>5 (Worse)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any improvement</td>
<td>18 (100)</td>
<td>15 (83)</td>
<td>16 (89)</td>
</tr>
</tbody>
</table>
CONCLUSION

The results of this study demonstrated that a three-session program of MFU-V applied 30 days apart is beneficial and well tolerated for the treatment of rolling- and boxcar-type acne scars. Furthermore, investigator GAIS, and investigator and subject ASIS scores indicated that the degree of improvement was sustained at 180 days post-treatment. Based on these positive results, MFU-V is a safe and beneficial means for improving the appearance of atrophic acne scars. Further research should be considered in a larger subject population and utilizing a randomized study design to further evaluate the clinical benefits of MFU-V. A study design that includes higher-density treatments for older acne scars, improved subject selection, more standardized study photography processes, live assessments of subjects for primary endpoints, and longer follow-up should be considered.

DISCLOSURES

Authors do not report any conflicts of interests.

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REFERENCES


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Combined 400-600nm and 800-1200nm Intense Pulsed Phototherapy of Facial Acne Vulgaris

J. Matthew Knight MD
Knight Dermatology Institute, Orlando, FL

ABSTRACT

Background and Objective: Laser and light-based therapies are relatively new treatment options for acne vulgaris patients. Intense pulsed light (IPL) is believed to exploit the photosensitivity of P. acnes residing in the pilosebaceous units at lower wavelengths and induce anti-inflammatory effects by influencing cytokine release at higher wavelengths. Our study aimed to assess the clinical safety and efficacy of a novel dual-band “notch” acne filter (400-600nm and 800-1200nm) in improving inflammatory and non-inflammatory lesions in patients presenting with mild-to-moderate acne.

Materials and Methods: The study was designed as a single-site, prospective study of 10 patients with Fitzpatrick skin types II-V presenting with mild to moderate inflammatory facial acne vulgaris. A total of five whole-face light treatments were conducted at 1-2-week intervals with an IPL system (Lumenis M22 System, Lumenis Ltd.) equipped with a dual-band “notch” acne filter (400-600nm and 800-1200nm). Follow-up visits were performed at 1 and 4 weeks following the last treatment session. Acne mean change from baseline was assessed using the 4-point Investigator Global Assessment (IGA) scale. Comprehensive facial photographs were taken, and lesions were counted at screening, treatment 4, and both 1- and 4-week follow-up visits. The investigator and the patients assessed overall improvements in appearance, using the 5-point Likert scale. Subjects also completed the Cardiff Acne Disability Index (CADI) questionnaire and rated their satisfaction from treatment. Subject-reported pain, using the visual analog scale (VAS), and downtime were also recorded.

Results: Treatment impact on overall lesion clearance was most substantial at 4 weeks follow-up, at which 50% of patients showed at least a 50% reduction from baseline of lesion counts (P<0.0001). IGA scores improved throughout the course of the study, and significant improvements in the overall skin condition was noted, with mean 1.63-point and 1.50-point increases from baseline in the acne improvement ratings, at 1- and 4-weeks follow-up, respectively (P=0.0074, 0.0063). Patient-assessed CADI improved throughout the treatment and follow-up visits, peaking at a 3.22-point and 4.9-point average reductions from baseline at 1-week follow-up (P=0.0001) and 1-month follow-up (P<0.0001), respectively. The majority of the patients (80%) rated their acne lesions as improved, much improved, or very much improved at 4-weeks follow-up (P<0.0001). Treatments were well tolerated, with mean per-session VAS scores being ≤3.77, while the mean downtime was negligible (a few hours).

Conclusion: The use of an IPL device equipped with a proprietary “notch” acne filter elicited a significant effect on acne vulgaris. No severe pain, erythema, edema, folliculitis, crusting or exfoliation was noted, emphasizing the safety of our technique.


INTRODUCTION

Acne vulgaris is estimated to affect up to 87% of the population, predominately adolescents and young adults, and is associated with significant, and occasionally permanent, morbidity and psychological burden. Key pathogenic elements include hypercornification of the pilosebaceous unit and increased sebum production, which fosters the colonization of Propionibacterium acne (P. acnes) in the pilosebaceous ducts. In turn, the hair follicles become inflamed, triggering the upregulation of pro-inflammatory mediators.

The clinical manifestations of acne range from micro-comedones to inflamed papules, pustules, and nodules, the latter of which can lead to permanent atrophic or hypertrophic scarring. Conventional treatments, such as topical and systemic antimicrobials, anti-inflammatory agents, hormones, and retinoids, have been proven to be effective in targeting the pathogenic factors of acne vulgaris. Although these regimens are standard first-line treatment modalities, they are seldom 100% effective. Additionally, such remedies carry the risk of skin irritation, antibiotic resistance, hematologic abnormalities, and in some cases, teratogenicity. Moreover, obtaining the patients’ long-term compliance can be challenging, thus leading to greater difficulty in treating acne.
Modern technological advancements have provided new options for patients afflicted with acne vulgaris. Laser and light-based therapies, which induce photo-thermal heating of the pilo-sebaceous units, are relatively new treatment alternatives for acne patients. Intense pulsed light (IPL) therapy emits high-intensity, polychromatic, non-coherent visible light at wavelengths ranging from 400-1200 nm, which can safely target specific skin structures across a range of skin types. When used to treat acne, IPL exploits the photosensitivity of P. acnes, rooted in endogenously expressed porphyrins, which absorb best at wavelengths between 410 and 630 nm. Upon photoactivation, highly reactive singlet oxygen is formed, which oxidizes bacterial cell walls, proteins, and lipids, culminating in bacterial destruction. IPL has been proven potent in the treatment of acne, with blue light showing particular effectiveness in lowering lesion counts and destroying bacteria residing in the pilosebaceous unit. On the other hand, red light (620-750 nm) and near-infrared light displays anti-inflammatory effects by inducing cytokine release from macrophages, while increasing synthesis of fibroblast growth factors (FGF) from photoactivated macrophage-like cells. Both the anti-bacterial and anti-inflammatory mechanisms of blue and red light have been demonstrated by Papageorgiou et al. and Goldberg and Russell, who noted a dramatic effect of combined blue-red light phototherapy in acne vulgaris patients.

Our study aimed to assess the clinical safety and efficacy of a novel dual-band “notch” acne filter (400-600 nm and 800-1200 nm) in improving inflammatory and non-inflammatory acne lesions in patients presenting with mild-to-moderate acne.

Materials and Methods

Patients
Healthy patients, aged 15-45, with skin type I-V, presenting with mild to moderate inflammatory facial acne vulgaris, categorized as grade 2-3, as per the Investigator Global Assessment Scale (IGA), and with at least 15 inflammatory papules or pustules, were eligible to participate in this study. Exclusion criteria included the use of oral, topical, or systemic antibiotics within two weeks preceding enrollment, steroid use within 6 months preceding the trial, pregnancy or lactation, and/or a history of photosensitivity. All subjects were instructed to gently cleanse their skin with tepid water, to hydrate with a moisturizer, and to avoid mechanical damage (friction, squeezing) to the skin between treatments. Subjects were instructed to regularly apply sunscreen (SPF≥30).

Light Source
The CE-marked and FDA-cleared M22™ system (Lumenis Ltd., Yokneam, Israel) was equipped with a dual-band “notch” filter to simultaneously deliver 1-3 sub-pulses of non-coherent blue-to-yellow light (400-600 nm) and near-infrared (IR) light (800-1200 nm) over a 15x35 mm spot size, at fluences of 10-32 J/cm². The fluence in the present study ranged from 11-17 J/cm², pulse durations from 4.0-5.0 msec, and interpulse delays from 25-35 msec. Most treatments included a whole-face double pass technique. Test spots were performed and monitored for up to 72 hours. Patients showing an excessive skin reaction were excluded from the study.

Study Design
A total of five whole-face IPL treatments were conducted at 1-2-week intervals. Follow-up visits were performed at 1 and 4 weeks following the last treatment session. Prior to receiving treatment, the patient’s face was gently cleansed to remove all makeup, lipstick/gloss and eyeshadow. Protective ocular safety measures were enforced throughout the treatment sessions. All subjects were instructed to gently cleanse their skin with tepid water, to hydrate with a moisturizer, and to avoid mechanical damage (friction, squeezing) to the skin between treatments. Patients were also asked to refrain from using contraindicated cosmeceuticals and prescription medications throughout the study period and were instructed to avoid sun exposure and to regularly apply sunscreen (SPF≥30).

Clinical Assessments
Comprehensive facial photographs were taken using a professional digital camera system (Omnia, Canfield Imaging Systems, Inc.). Head position, angle, framing, exposure and lighting conditions were standardized for all photographs. Photographs were taken at screening, treatment 4, and at both follow-ups (1 and 4 weeks). Patient evaluation was conducted by counting acne lesions of all types over the entire face. Acne lesions included in the count were comprised of non-inflammatory comedones, inflammatory lesions with surrounding halos and erythema, and deep inflammatory lesions (including nodules and cysts). Lesion and IGA assessments were conducted by the non-blinded principal investigating dermatologist or sub-investigator.

Acne mean change from baseline was assessed using the 4-point IGA scale for acne vulgaris, with “0” indicating clear skin without inflammatory or non-inflammatory lesions and “4” indicating severe acne, with many non-inflammatory and inflammatory lesions but no more than a few nodular lesions. Lesion count and IGA grading were conducted at screening, treatment 4, and at 1- and 4-week follow-ups.

Over the course of treatment, the investigator and patient assessed overall improvements in appearance, using the 5-point Likert scale, with “-1” indicating “worse,” “0” indicating “no change,” “1” indicating improved, “2” indicating much improved, and “3” indicating “very much improved.” Subjects also completed the Cardiff Acne Disability Index (CADI) questionnaire, which evaluates the impact of acne on quality of life, with a maximum score of 15 and a minimum score of 0. The CADI questionnaire was completed at treatment 4, and at the 1- and 4-week follow-ups. Overall satisfaction from treatment was scored by patients at treatment 4, and at 1 week and 4 weeks.
considerable effects recorded 1 week following the full course of treatment, where 50% of patients showed >50% reduction from baseline in lesion counts (Table 2). Overall lesion clearance, which includes non-inflammatory, inflammatory, deep inflammatory, tender and/or painful lesions and inflammatory lesions with surrounding halos or erythema lesions, was most substantial four weeks after completion of the treatment regimen (Table 2). In addition, the mean percentage reduction in lesion counts was found statistically significant ($P < 0.0001$). At the last follow up visit, the average IGA scores improved significantly (2.00 ± 0.67) as compared to baseline (2.85 ± 0.69) (Table 3). Significant improvements in overall skin condition were also observed and the mean improvement increased by 1.63 (±1.06) and 1.50 (±1.35) points from baseline to four weeks following last treatment ($P = 0.0074$, 0.0063). These findings are illustrated in the before and after photographs (Figure 1). Furthermore, patient-reported CADI improved throughout the treatment and follow-up visits, peaking at 3.22 ± 2.82-point and 4.90 ± 1.91-point average reductions from baseline at 1-week follow-up ($P = 0.0001$) and 1-month follow-up ($P < 0.0001$), respectively (Table 4).

**Statistical Methods**

All statistical analyses and data presentations were performed using SAS® version 9.4 (SAS Institute, Cary NC) software. Study data were summarized with descriptive statistics, where continuous variables are presented as a mean (with standard deviation) and discrete variables as a count and percentage. For confidence intervals, the confidence level was 95%. Study variables were modeled using repeated measures analysis of variance (ANOVA), where each variable was modeled individually as a function of its baseline value (when relevant) and visit (as a categorical variable). LSMeans per visit and the differences between visits were estimated from the models and are presented with level of significance. Statistical significance was defined as a $P$-value ≤ 0.05. Nominal $P$-values are presented.

**RESULTS**

A total of 13 patients, of a mean age of 23.5±4.8, primarily female (76.9%), and of skin types II-III (84.7%), were included in this study (Table 1). Ten patients completed the entire course of treatment and follow-up, while the remaining were lost to follow-up. All subjects underwent test-spots prior to initiation of treatment and none required anesthesia.

When assessing treatment impact on inflammatory lesions, a significant and gradual improvement in lesion counts was observed with subsequent treatments and duration of follow-up ($p<0.0001$). A significant effect was observed at 1 week and 4 weeks post-treatment, where 62.5% and 80% of patients showed over 50% improvement, respectively (Table 2). A transient improvement was noted in non-inflammatory lesions, with

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**TABLE 1.**

<table>
<thead>
<tr>
<th>Patient Demographics and Baseline Characteristics</th>
<th>N=13</th>
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<tr>
<td>Age, mean (SD)</td>
<td>23.5 (4.8)</td>
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<tr>
<td>Gender, n (%)</td>
<td></td>
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<tr>
<td>Female</td>
<td>10 (76.9)</td>
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<tr>
<td>Male</td>
<td>3 (23.1)</td>
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<td>Race, n (%)</td>
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<tr>
<td>Caucasian</td>
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<td>Caucasian-Hispanic/Latino</td>
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<td>Skin Type, n (%)</td>
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<tr>
<td>II</td>
<td>4 (30.8)</td>
</tr>
<tr>
<td>III</td>
<td>7 (53.9)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (7.7)</td>
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<td>V</td>
<td>1 (7.7)</td>
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**TABLE 2.**

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<th>Lesion Count and Treatment Success Rates With Treatment Progression</th>
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<tr>
<td>Inflammatory Lesions</td>
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<tr>
<td>Lesion Count</td>
</tr>
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<tr>
<td>Baseline; n=13</td>
</tr>
<tr>
<td>1W FU; n=8</td>
</tr>
<tr>
<td>1M FU; n=10</td>
</tr>
</tbody>
</table>

*Defined as reduction from baseline of ≥50% in lesion count. *Including inflammatory, non-inflammatory, deep inflammatory, tender and/or painful lesions, inflammatory lesions with surrounding halos or erythema.
The majority of patients (80%) rated their acne lesions as “improved” to “very much improved” (Figure 2A-1-month follow-up). Significant changes were noted for skin texture, with 60% of the patients rating their skin as “improved” to “very much improved” (Figure 2B-1-month follow-up). In both follow-up visits, the subject’s self-improvements were statistically significant (for acne lesions: \( P=0.0054 \) and \( P=0.0004 \) at 1- and 4-weeks follow-ups, respectively; for skin texture: \( P=0.0017 \) and \( P=0.0002 \) at 1 and 4 weeks FUs, respectively). In addition, 80% of patients reported an overall skin improvement as “improved” to “very much improved” (mean score \( P=0.0016 \)) at 4 weeks follow-up (Figure 3). Eighty percent of the patients reported some level of satisfaction with treatment outcomes (Figure 4). By the end of the study, 90% of patients viewed their acne condition as a “minor problem” (Figure 5).

Patients found the treatment regimen tolerable (VAS of 3.77±2.00), and no significant differences in pain levels were recorded across the treatment sessions. The mean social downtime associated with treatment was less than a single day in all treated subjects and was considered negligible. Mean redness-related downtime was 3.6 hours. Two patients reported side effects in the form of mild pruritus and mild blistering on the left chin and cheek, both of which self-resolved within one day after the treatment session without sequelae.
FIGURE 2. Improved patient-rated acne lesion scores following dual-band phototherapy of acne vulgaris. Patient categorical ratings of acne lesion (A) and skin texture (B) improvements were recorded before treatment sessions (n=13), and 1 (n=8) and 4 (n=10) weeks following completion of the five-session treatment course. P-values for mean acne lesion scores were 0.0054 and 0.0004 for 1 week and 4 weeks follow-ups, respectively, and 0.0017 and 0.0002 for skin texture at 1 week and 4 weeks follow-ups, respectively. Data shown as % of patients (of total patients at the time of assessment).

FIGURE 3. Overall improvement rating by patients. Overall patient categorical ratings of improvement were recorded before treatment sessions (n=13), and 1 (n=8) and 4 (n=10) weeks following completion of the five-session treatment course. P-values for mean scores: 0.0025 and 0.0016 for 1 week and 4 weeks from baseline values, respectively. Data shown as % of patients (of total patients at the time of assessment).

FIGURE 4. Patients viewing of their acne condition. Subjective assessment of acne condition (CADI) was done at baseline and at 1 week and 4 weeks following last treatment session. Data shown as % of patients (of total patients at the time of assessment).
Several pharmaceutical treatment options for acne demonstrate well-established efficacy and are considered the mainstays of therapy. However, technological advances, coupled with increasing concerns over drug resistance, have led physicians to reevaluate treatment options for this chronic disease. An increasing body of evidence suggests that phototherapy induces marked effects on inflammatory acne lesions with minimal adverse effects. Earlier promising findings regarding the safety and efficacy of combined blue and near-infrared light therapy, thought to address both the inflammatory and bacterial aspects of acne, were corroborated by our study. The results in our study demonstrated a reduction in lesion counts, reaffirmed by improved IGA and CADI scores throughout the one-month follow-up period.

In their comparative assessment of a mixed red-blue light regimen versus blue light only, cool white light, or topical 5% benzoyl peroxide treatments, Papageorgiou et al. found biweekly treatment of mild to severe facial acne vulgaris with alternating 415nm and 633nm light yielded a mean 81% reduction in lesion counts after one treatment session, with significant decreases in lesion counts after five sessions, without eliciting any significant side effects. Of note, a marked (but less potent and more transient) effect of phototherapy on non-inflammatory lesions has been observed by other groups as well. IPL delivers non-coherent, broad-bandwidth, filtered light, which can be easily adjusted to meet desired wavelength, fluence, pulse duration and delay. The light therapy is presumed to evoke a bactericidal effect on P. acnes, by activating its endogenous porphyrins that specifically absorb blue wavelengths. This photoexcitation elevates reactive oxygen species levels, resulting in rapid and selective elimination of bacteria. In contrast, phototherapy with other mid-range wavelengths, eg, PDL, demonstrate little to no impact on P. acnes colonization.

Light therapy with higher wavelengths is also assumed to affect the immunological aspect of acne, in that IPL-triggered photothermal injury induces a wound healing response mediated by an array of inflammatory factors, including upregulation of TGF-ß1 expression, correlating with enhanced nuclear localization of Smad3. These cytokines, reported to derive from laser-induced cellular infiltrates, drive dermal remodeling and inhibit keratinocyte proliferation, which may interfere with micromedone formation.

Taken together, use of the notch acne filter used in our study induces a robust effect, influencing both the bacterial and inflammatory factors underlying acne vulgaris. In our study, no severe pain, erythema, edema, folliculitis, crusting or exfoliation was noted, emphasizing the safety of our technique.

As this study was an open, before-after design, additional randomized and controlled studies are required to support our conclusions. Comparison of the long-term efficacy of IPL treatment in combination with common topical anti-acne agents (ie, real world use) versus IPL treatment alone will be of particular interest. In addition, the present study involved only five treatment sessions, performed at 1-2-week intervals. Further studies will be required to assess whether addition of treatment sessions, and extension of the intersession intervals, can enhance the clinical effect and its longevity.

**DISCLOSURES**

This study was sponsored by Lumenis Ltd. (Yokneam, Israel). Dr. Knight is a consultant, investigator, and speaker for Lumenis Ltd.

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1122

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November 2019 • Volume 18 • Issue 11


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Improper Potency and Impurities in Compounded Polidocanol

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2Dermatology, Laser & Vein Specialists of the Carolinas, Charlotte, NC
3Weill Cornell Vein Treatment Center, New York, NY
4Center for Vein Restoration, Mesa, AZ

ABSTRACT

Polidocanol is an FDA-approved sclerosant indicated for treating uncomplicated spider veins and reticular veins in the lower extremities. Despite restrictions against compounding drugs that are essentially copies of FDA-approved or commercially available products, polidocanol is also available from compounding pharmacies and outsourcing facilities. Compounded drug products are not FDA-approved and have not undergone premarket FDA review for safety, effectiveness, and quality. Seven samples of polidocanol were obtained from three compounding pharmacies and analyzed using high pressure liquid chromatography. None of the samples contained the labeled concentration of polidocanol and five contained excessive levels of impurities. Since the potency and purity of compounded polidocanol injection cannot be assured, physicians who use these products should consider FDA-approved products to ensure optimal safety and efficacy.

INTRODUCTION

Varicose veins are enlarged superficial veins, most commonly found in the lower extremities. Risk factors include family history, advancing age, female gender, pregnancy, obesity and sedentary lifestyle.1 Spider veins are similar, but they are smaller, more superficial and often red or blue. Some varicose veins become symptomatic and require treatment. Symptoms may include burning, throbbing, muscle cramping, itching, and edema. Depending on their size and severity, treatments for varicose veins include compression,2 energy-based radiofrequency3 and laser devices,4 a variety of surgical procedures,5 and sclerotherapy.6 Sclerotherapy involves injecting a sclerosant into the lumen of a vein, resulting in fibrosis and eventual vein ablation.7 Despite the increased popularity of new cutaneous laser devices, sclerotherapy remains the gold standard for treatment of reticular varicose and spider veins,8,9 especially since FDA-approval of sclerosant agents in 2010.10,11

Available FDA-approved liquid sclerosing agents include sodium tetradecyl sulfate and polidocanol.8 Polidocanol was first approved for use as a sclerosing agent in the United States in 2010 (Asclera® Injection, Merz North America, Raleigh NC).9 Specifically, this drug product is indicated to sclerose uncomplicated spider veins (varicose veins ≤1 mm in diameter) and uncomplicated reticular veins (varicose veins 1 to 3 mm in diameter) in the lower extremities. Polidocanol is also an approved sclerosing agent in Europe (Aethoxysklerol®; Chemische Fabrik Kreussler & Co. GmbH, Wiesbaden, Germany). The safety and efficacy of polidocanol as a sclerosant have been demonstrated in large trials.10

Polidocanol is also available from certain compounding pharmacies and outsourcing facilities, despite government restrictions on compounding drugs that are “essentially copies” of FDA-approved or commercially available products.10 Compounded drug products are not FDA-approved and have not undergone FDA premarket review for safety, effectiveness, and quality. Of note, polidocanol is manufactured according to strict FDA regulations for purity and potency throughout the entire manufacturing process. Unlike pharmaceutical companies, compounding pharmacies and outsourcing facilities are not required to report adverse events to the FDA.11 Despite FDA restrictions for compounding drugs, polidocanol remains available from compounding pharmacies and outsourcing facilities, potentially exposing patients to potentially serious health risks.

Previous investigations have demonstrated the inferiority of compounded sclerosants. Among compounded products in one study, three did not contain the labeled drug concentration: two were super-potent, one was sub-potent and all contained impurities.12 These products were believed to be made by diluting the active substance from industrial chemical sources. In another study, five of six samples obtained from three pharmacies did not contain the labeled drug concentration, exceeding it by 20% to 300%, and all six contained impurities.13 In a third study, chemical impurities were measured in eight of nine compounded samples from three pharmacies and some contained unknown particulate matter, while no impurities were detected in the original FDA-approved product.14
As compounded polidocanol for the treatment of varicose veins continues to be available from several pharmacies and outsourcing facilities in the United States, the objective of this study was to obtain and analyze samples of compounded polidocanol for potency and purity.

METHODS
Seven samples of polidocanol were purchased from three compounding pharmacies. Labeled concentrations of polidocanol ranged from 1.5% to 5%. Each sample was analyzed for potency of lauromacrogol 400 (polidocanol) and purity with reversed phase high pressure liquid chromatography (HPLC) with refractive index (RI) detection (Chemische Fabrik Kreussler & Co. GmbH, Wiesbaden, Germany). The results were compared with an FDA-approved polidocanol product (Asclera® Injection, Merz North America, Raleigh NC).

RESULTS
Results of the analysis are summarized in Table 1. Among the seven samples analyzed, six were sub-potent, containing 65.8 to 91.4% of the labeled concentration, and one was super-potent, containing 108.7% of the labeled concentration. Five contained a 10-fold excess of foreign fatty alcohol ethoxylate impurities and four exceeded the limit for unknown impurities. Overall, none of the tested samples were equivalent to the commercially marketed, FDA-approved product (Asclera) with respect to potency and purity.

<table>
<thead>
<tr>
<th>Pharmacy</th>
<th>Labeled Polidocanol Concentration</th>
<th>Actual Polidocanol Concentration</th>
<th>1-Dodecanol</th>
<th>foreign fatty alcohol ethoxylate impurities</th>
<th>Formaldehyde</th>
<th>Acetaldehyde</th>
<th>Unknown Impurities</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>1.5%</td>
<td>16.3 mg/mL (108.7%)</td>
<td>0.63%</td>
<td>0.1%</td>
<td>&lt;0.2 ppm</td>
<td>&lt;0.2 ppm</td>
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<td>5%</td>
<td>45.7 mg/mL (91.4%)</td>
<td>0.66%</td>
<td>0.1%</td>
<td>&lt;0.2 ppm</td>
<td>0.4 ppm</td>
<td>0.04%</td>
</tr>
<tr>
<td>#2</td>
<td>1.5%</td>
<td>13.1 mg/mL (87.3%)</td>
<td>0.50%</td>
<td>26.3%</td>
<td>1.3 ppm</td>
<td>3.7 ppm</td>
<td>0.67%</td>
</tr>
<tr>
<td>#2</td>
<td>3%</td>
<td>19.8 mg/mL (66.0%)</td>
<td>0.67%</td>
<td>27.0%</td>
<td>0.3 ppm</td>
<td>1.1 ppm</td>
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</tr>
<tr>
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<td>5%</td>
<td>32.9 mg/mL (65.8%)</td>
<td>0.74%</td>
<td>27.2%</td>
<td>0.5 ppm</td>
<td>1.7 ppm</td>
<td>0.70%</td>
</tr>
<tr>
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<td>2%</td>
<td>15.3 mg/mL (76.6%)</td>
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<td>22.0%</td>
<td>-/-</td>
<td>-/-</td>
<td>0.30%</td>
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<td>3%</td>
<td>22.8 mg/mL (75.8%)</td>
<td>-/-</td>
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<td>-/-</td>
<td>-/-</td>
<td>0.40%</td>
</tr>
<tr>
<td>#3</td>
<td>0.5%</td>
<td>4.75-5.25 mg/mL (95.0-105.0%)</td>
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<td>22.0%</td>
<td>≤1 ppm</td>
<td>≤2 ppm</td>
<td>≤0.3%</td>
</tr>
<tr>
<td>#3</td>
<td>1%</td>
<td>9.5-10.5 mg/mL (95.0-105.0%)</td>
<td>-/-</td>
<td>22.0%</td>
<td>≤1 ppm</td>
<td>≤5 ppm</td>
<td>≤0.3%</td>
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Discuss
Similar to previous studies,12,13 compounded polidocanol solutions did not deliver the claimed potency in six of seven tested samples and five samples contained excessive contaminants. This inconsistency poses unacceptable risks, most importantly to the patient, but also medicolegal risks to the treating physician. In contrast, clinical trials have demonstrated FDA-approved polidocanol provides effective treatment of chronic venous insufficiency with low toxicity, minimal risk and few complications.21

Contaminants found in the tested compounded polidocanol samples in several publications included foreign fatty C-14 alcohol ethoxylate impurities, excessive formaldehyde and unknown impurities. Other reported contaminants in compounded sclerosants include carbitol,12 tetradecanol, several isomers of 7-ethyl-2-methyl-undec-3/4 ene,14 chlorobutanol (trichloro-2-methyl-2-propanol), benzaldehyde, and benzyl alcohol13 (some samples contained multiple contaminants). Together, these results indicate the lack of purity of the ingredients and/or the absence of sufficient manufacturing controls used to compound these products.

In addition to frequently not meeting the labeled ingredient specifications for potency and purity, there is no requirement for compounded product labeling to include an approved shelf life. If the compounded product is not immediately used, there is no assurance that the product will remain potent and efficacious.

TABLE 1.
Analysis Results of Compounded Polidocanol for Sclerotherapy Injection

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aInsufficient sample size. bPrimarily foreign fatty alcohol ethoxylate impurities. Bold font denotes nonconforming results. cAsclera® Injection, Merz North America, Raleigh NC.
The Federal Food, Drug, and Cosmetic Act requires that all FDA-approved drugs must be safe and effective and manufactured according to current good manufacturing practices (GMPs) to ensure their identity, strength, quality, and purity; however, some pharmacies are compounding drugs that are essentially copies of approved medications and doing so outside of GMPs. According to the FDA, “Compounding is a practice in which a licensed pharmacist, a licensed physician, or in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient.” The FDA has created provisions to allow the practice of compounding for individual patient needs when a drug product is not commercially available. This is common in dermatology practice for therapies such as topical anesthetic (BLT) or an acne cream, but these provisions are not applicable for an injectable product for which the FDA-approved product is medically suitable for a patient. Compounding pharmacies are advertising for physicians to use or switch to compounding sclerosant(s) in lieu of FDA-approved polidocanol, but such promotional statements are prohibited if they are false or misleading, such as baseless statements that compounded products are superior or failing to disclose significant risks associated with unapproved uses that are promoted.

There are numerous cases of injury resulting from various improperly compounded medications. An outbreak of meningitis in 2012 caused by a contaminated steroid injection intended for epidural injection made in a compounding pharmacy affected 753 patients in 20 states with 64 deaths. Subsequently, the United States Congress passed the Drug Quality and Security Act in November, 2013. Among other requirements, the Act stipulates that pharmaceutical compounders are not allowed to essentially copy products that are already FDA-approved and commercially available, unless there is a manufacturing product shortage. Serious patient illness and death associated with poor quality compounded drugs continue to occur. This is also made clear under Section 503A of the Federal Food, Drug, and Cosmetic Act:

“...policies and procedures that are necessary to ensure that the production and distribution of compounding drugs are carried out in a manner that is in compliance with CGMP requirements...”

Since compounded drugs have not undergone FDA review to determine their safety and effectiveness, their potency and purity cannot be assured as demonstrated by the current analysis of several compounded polidocanol products. It has been recognized for many years that physicians who use these products may be at risk legally in the event of an adverse outcome. A physician involved in litigation related to the use of a compounded sclerosant should be prepared to explain why an unapproved agent was used when an FDA-approved agent is available and whether a compounded product was used to increase profit.

CONCLUSION

Compounded drug products have not undergone FDA review to establish safety and efficacy. An analysis of seven samples of compounded polidocanol injection found all of them to be outside the labeled concentration and five had excessive contaminant levels. Physicians who use these products should consider FDA-approved products to ensure optimal treatment outcomes.

ACKNOWLEDGMENT

The authors acknowledge the editorial assistance of Dr. Carl S. Hornfeldt, Apothekon, Inc., during the preparation of this manuscript. This work was funded by Merz North America, Raleigh, NC.

DISCLOSURES

The authors have no further disclosures to report.

REFERENCES


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- 3D cross-polarized lighting (patent pending) improves lesion assessment.
- Accurate body surface area measurements.
- Minimizes photography time and reduces patient anxiety.

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- Psoriasis
- Vitiligo
- Pigmented lesions
- Plastic and reconstructive surgery

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Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris: Impact of Gender and Race on Efficacy and Safety

Edward Lain MD, Doris Day MD, Julie Harper MD, Eric Guenin PharmD PhD MPH

*Austin Institute for Clinical Research, Pflugerville, TX
b Day Dermatology and Aesthetics New York, NY
c University of Alabama at Birmingham Dermatology and Skin Care Center of Birmingham, Birmingham, AL
d Ortho Dermatologics, Bridgewater, NJ

ABSTRACT

**Background:** There has been an increasing interest in gender and racial differences both in the pathogenesis and treatment of acne vulgaris (acne), and postinflammatory hyperpigmentation (PIH) is a major concern in patients of color. Female acne patients report more anxiety and depression with acne improvement positively influencing Quality of Life (QoL) than their male counterparts, and there are differences in acne presentation. The first lotion formulation of tretinoin was developed using novel polymeric emulsion technology to provide an important alternative option to treat these acne patients, especially those who may be sensitive to the irritant effects of other tretinoin formulations.

**Objective:** To determine the impact of gender and race on the efficacy and safety of tretinoin 0.05% lotion in treating moderate or severe acne.

**Methods:** Post hoc analysis of 2 multicenter, randomized, double-blind, vehicle-controlled Phase 3 studies in moderate-to-severe acne. Subjects (aged 9 to 58 years, N=1640) were randomized (1:1) to receive tretinoin 0.05% lotion or vehicle, once-daily for 12 weeks. Efficacy assessments included changes in baseline inflammatory and noninflammatory lesions and treatment success (at least 2-grade reduction in Evaluator’s Global Severity Score [EGSS] and clear/almost clear). Quality of Life was assessed using the validated Acne QoL scale. Safety, adverse events (AEs), cutaneous tolerability, and hypo-/hyper-pigmentation (using a 4-point scale where 0=none and 3=severe) were evaluated at each study visit.

**Results:** At week 12, mean percent reduction in inflammatory lesion counts were 56.9% and 53.4% respectively in female and male patients compared with 47.1% and 39.4% with vehicle (P≤0.001), with females statistically significant to males at week 8 (P=0.026). Mean percent reduction in noninflammatory lesion counts in females and males were 51.7% and 46.1% respectively, compared with 34.9% and 29.7% with vehicle (P=0.001), with females statistically significant to males at week 12 (P=0.035). Treatment success was achieved by 23.6% and 16.1% of female and male patients treated with tretinoin 0.05% lotion by week 12 (P=0.001 vs vehicle) with females statistically significant compared with males (P=0.013). Significant differences in inflammatory lesion count reductions were reported in Caucasian patients from week 8, and Black African/American male patients at week 12. Only male patients reported significant differences in both races in terms of noninflammatory lesions, and only Caucasian patients reported significant differences in treatment success. Female patients treated with tretinoin 0.05% lotion had statistically significant improvements in each Acne QoL domain (except role-social) compared with vehicle. Improvements in QoL in male subjects were only statistically different for acne symptoms. Tretinoin 0.05% lotion was well-tolerated in both genders. There were more treatment-related AEs in the female subpopulation, with a significantly greater incidence of skin dryness (P=0.006), that was more common in the younger Caucasian females.

**Conclusions:** Tretinoin 0.05% lotion has been shown to be effective and well tolerated in moderate-to-severe acne. Treatment was significantly more effective in females than males. Tretinoin 0.05% lotion was well tolerated by both genders, although there was a higher incidence of treatment-related AEs, especially skin dryness, in females. There were racial and gender differences in QoL and beneficial effects on PIH in those patients most at risk.

population. In addition, female acne patients are more likely to develop anxiety and depression and, because of its visibility, it is known to have both psychosocial and functional impacts resulting in poor acne-related Quality of Life (QoL).

However, data are limited on racial differences in the clinical characteristics of acne and its burden on adult females. Women with acne tend to exhibit low QoL and negative self-perceptions. Data on racial differences suggest Caucasian women have higher mean scores on each of the 4 Acne-QoL domains (ie, higher QoL) than non-Caucasian women; but differences were not statistically significant.

Over two-thirds of Black/African American women with acne experience postinflammatory hyperpigmentation (PIH). As a result, strategies that minimize the risk of pigmented abnormalities such as avoiding irritation associated with some topical therapies and reducing inflammation are important treatment considerations. A web-based study showed that, while clearing lesions was important in White females with acne, eliminating PIH was of primary importance in non-White females; supporting other work highlighting the importance of considering race-related characteristics when treating acne.

Recently, clinical efficacy and safety data on a novel tretinoin 0.05% lotion were published. Tretinoin 0.05% lotion was significantly more effective than vehicle in treating moderate or severe acne, with a highly favorable safety and tolerability profile where the incidence of erythema, dryness and skin burning were lower than previously reported with other formulations of tretinoin. Here we present a post hoc analysis of the 2 phase 3 studies in 1640 patients with moderate or severe acne to study the impact of gender and race on efficacy and safety.

**METHODS**

**Study Design**

A post hoc analysis of 2 vehicle-controlled, randomized multicenter, double-blind studies in 1640 patients with moderate or severe acne. Patients were randomized (1:1) to receive tretinoin 0.05% lotion or vehicle applied to the face once-daily for 12 weeks.

**Study Population**

Eligible patients for the post hoc analysis included patients aged 9 to 58 years who presented with 20 to 40 inflammatory lesions (papules, pustules, and nodules), 20 to 100 noninflammatory lesions (open and closed comedones), and 2 nodules or less; and an Evaluator Global Severity Score (EGSS) score of 3 (moderate) or 4 (severe).

The post hoc analysis studied the impact of gender and race on efficacy, safety, and tolerability of tretinoin 0.05% lotion.

**Efficacy Evaluation**

Efficacy evaluations were performed by the investigator and comprised of inflammatory and noninflammatory lesion counts and EGSS assessment at screening, baseline, and subsequent study visits (weeks 4, 8, and 12). Efficacy endpoints included percent change from baseline to week 12 in inflammatory and noninflammatory lesion counts and percent of patients who were treatment successes (ie, those patients who achieved at least a 2-grade reduction from baseline in EGSS and were also ‘clear’ or ‘almost clear’ at the same visit).

Additional assessments included a patient satisfaction score (PSS), and a validated acne-specific quality of life (Acne-QoL) questionnaire (Merck &Co, Inc. Whitehouse NJ). Patients were asked to rate their satisfaction with prior facial acne therapy on a PSS scale of 1 to 10 (where a score of 5 or greater was considered as ‘satisfied’) at baseline, and with study treatment at week 12. Acne-QoL questionnaire scores were grouped into 4 domains (self-perception, role-emotional, role-social, and acne symptoms), where lower scores represented poorer QoL.

**Safety and Cutaneous Tolerability Evaluation**

Adverse events (AEs) were evaluated throughout and summarized by treatment groups, severity, and relationship to study medication. All AEs occurring during the studies were recorded and classified on the basis of medical dictionary for drug regulatory activities terminology (MedDRA Version 18.0) for the safety population. Counts reflected numbers of patients reporting one or more AEs that mapped to MedDRA. At each level of summarization, patients were only counted once under the greatest reported relationship. Treatment-emergent AEs were those with an onset after the first application of study drug. Treatment group comparisons were made by tabulating the frequency of patients with one or more AEs during the study.

Cutaneous safety (erythema and scaling) and tolerability (itching, burning, and stinging) were evaluated using a 4-point scale, where 0 (none), 1 (mild), 2 (moderate), and 3 (severe). Erythema, scaling, hyperpigmentation and hypopigmentation severity were assessed by the investigator at the time of each study visit. Itching, burning, and stinging severity were solicited from the patient as an average of their symptoms during the period since their previous visit.

**RESULTS**

Across the 2 studies, there was a higher proportion of females (N=909) enrolled compared with males (N=731).

**Female Acne Patients**

A high proportion of female patients (N=763, 83.9%) completed the studies with ‘lost to follow-up’ (N=76, 8.4%) and ‘subject request’ (N=43, 4.7%) the main reasons for study discontinuation (Figure 1). Only 4 (0.9%) female patients treated with tretinoin...
0.05% lotion discontinued due to AEs (irritant dermatitis, contact dermatitis, burning face sensation, and facial swelling, erythema, and burning). Mean age (SD) was 22.4 (8.16) years (Table 1). Compared with other acne trials, there was a high proportion of Hispanics (N=412, 45.3%), and in terms of race most (91.4%) female patients were either Caucasians (N=622, 68.4%) or Black/African American (N=209, 23.0%). Completion rates (84.6%) were slightly higher in Caucasian females, with reasons for discontinuation similar to the overall study populations. Three Caucasian females treated with tretinoin 0.05% lotion discontinued due to AEs. At baseline, 92.0% of female patients (N=835) had moderate acne (EGSS=3) and 8.0% (N=73) severe acne (Table 1). Mean inflammatory and noninflammatory lesions counts (SD) were 25.5 (5.10) and 41.1 (17.80) respectively.

### TABLE 1.
Demographics and Baseline Characteristics by Gender (ITT Population, Pooled Data, N=1640)

<table>
<thead>
<tr>
<th></th>
<th>Female population (N=1640)</th>
<th>Male population (N=1640)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age- Mean years (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tretinoin 0.05% (N=433)</td>
<td>22.4 (8.10)</td>
<td>18.1 (5.10)</td>
</tr>
<tr>
<td>Vehicle (N=476)</td>
<td>22.4 (8.23)</td>
<td>18.1 (5.10)</td>
</tr>
<tr>
<td>Total (N=909)</td>
<td>22.4 (8.16)</td>
<td>18.1 (5.18)</td>
</tr>
<tr>
<td>Tretinoin 0.05% (N=386)</td>
<td>18.1 (5.10)</td>
<td>18.1 (5.27)</td>
</tr>
<tr>
<td>Vehicle (N=345)</td>
<td>18.1 (5.10)</td>
<td>18.1 (5.18)</td>
</tr>
<tr>
<td>Total (N=731)</td>
<td>18.1 (5.18)</td>
<td>18.1 (5.18)</td>
</tr>
<tr>
<td>Ethnicity N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>183 (42.3%)</td>
<td>188 (48.8%)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>250 (57.7%)</td>
<td>166 (41.2%)</td>
</tr>
<tr>
<td>Race N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>3 (0.7%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Asian</td>
<td>18 (4.2%)</td>
<td>9 (2.6%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>111 (25.6%)</td>
<td>99 (13.5%)</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>3 (0.7%)</td>
<td>4 (1.2%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>286 (66.1%)</td>
<td>283 (82.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (2.8%)</td>
<td>13 (3.9%)</td>
</tr>
<tr>
<td>Evaluators’ Global Severity Score N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 – Moderate</td>
<td>400 (92.6%)</td>
<td>337 (87.3%)</td>
</tr>
<tr>
<td>4 – Severe</td>
<td>32 (7.4%)</td>
<td>287 (62.8%)</td>
</tr>
<tr>
<td>Inflammatory Lesion Count- Mean (SD)</td>
<td>25.7 (5.34)</td>
<td>27.0 (5.60)</td>
</tr>
<tr>
<td>Noninflammatory Lesion Count- Mean (SD)</td>
<td>39.7 (17.03)</td>
<td>44.7 (18.71)</td>
</tr>
</tbody>
</table>

One male patient treated with tretinoin did not report ethnicity
One female patient treated with tretinoin did not report severity
Changes in inflammatory and noninflammatory lesions in female patients were significant compared with vehicle from week 8 and week 4 respectively ($P=0.003$ and $P=0.004$). By week 12, the percent change from baseline (LS mean) was 56.9% ($P=0.001$ vs vehicle) and 51.7% ($P<0.001$) respectively, compared with 47.1% and 34.9%, see Figures 2 and 3. Treatment success (at least a 2-grade improvement in EGSS and ‘clear’ or ‘almost clear’) was significant compared with vehicle from week 8 ($P=0.046$), and by week 12, 23.6% of patients were treatment successes (compared with 13.5% on vehicle, $P<0.001$), see Figure 4.

At week 12, inflammatory and noninflammatory lesion count reduction in the Caucasian females (56.3% and 52.6%), compared with 45.4% ($P=0.001$) and 34.9% ($P<0.001$) with vehicle, was similar to the overall population (Figures 5 and 6); and treatment success was achieved in 23.3% of patients (compared with...
12.6% on vehicle, \(P=0.001\)), see Figure 7. Although lesion count reduction was greater in Black/African American female patients treated with tretinoin 0.05% lotion compared with vehicle, differences were not significant. There were no significant differences between Caucasian and Black/African American female patients in terms of inflammatory (56.2% vs 57.3%, \(P=0.879\)) and noninflammatory (52.8% vs 49.3%, \(P=0.238\)) lesion count reduction at week 12; or treatment success (23.3% vs 23.0%, \(P=0.946\)) with tretinoin 0.05% lotion. Patient satisfaction (as assessed by PSS responses) was significantly greater with tretinoin 0.05% lotion at week 12 (72 vs 65, \(P<0.001\)). There was no significant difference between Caucasian and Black/African American females in terms for improvements in patient satisfaction (\(P=0.382\)). Improvements (absolute change from baseline) in all 4 Acne QoL domains with tretinoin 0.05% lotion were also significant compared with vehicle at week 12 (Figure 8), as were improvements...
FIGURE 6. Percent change in noninflammatory lesions from baseline to week 12 by gender and race (ITT population, LS mean).

Caucasian female patients

Caucasian male patients

Black or African American female patients

Black or African American male patients

*P<0.05 versus vehicle  
**P<0.01  
***P<0.001

FIGURE 7. Treatment success. Percent of patients with at least a 2-grade improvement in EGSS and ‘clear’ or ‘almost clear’ at each study visit by gender and race (ITT population pooled data).

Caucasian female patients

Caucasian male patients

Black or African American female patients

Black or African American male patients

*P=0.001 versus vehicle  
**P<0.01  
***P<0.001

*P=0.007 versus vehicle
in Caucasian females with the exception of self-perception ($P=0.051$) and role-social ($P=0.104$). There was no significant difference in Acne QoL domain improvements between female Black/African American or Caucasian patients: self-perception ($P=0.245$), role-emotional ($P=0.205$), role-social ($P=0.101$), and acne symptoms ($P=0.178$).

**Male Acne Patients**

A high proportion of male patients completed the studies (N=618, 84.5%), with ‘lost to follow-up’ (N=58, 7.9%) and ‘subject request’ (N=33, 4.5%) the main reasons for study discontinuation, see Figure 1. Only 2 (0.5%) patients treated with tretinoin 0.05% lotion discontinued due to AEs. Mean age (SD) was 18.1 (5.18) years, see Table 1. Again, there was a high proportion of Hispanics (N=354, 48.5%), and most patients (94.4%) were either Caucasian (N=590, 80.7%) or Black/African American (N=99, 13.5%). Completion rates (84.4%) were similar in the White males, with reasons for discontinuation similar to the overall study populations. Two Caucasian males treated with tretinoin 0.05% lotion discontinued due to AEs. At baseline, 85.4% of male patients (N=624) had moderate acne (EGSS=3) and 14.6% (N=107) severe acne, see Table 1. Mean inflammatory and noninflammatory lesions counts (SD) were 27.2 (5.77) and 45.1 (19.07) respectively.

Changes in inflammatory and noninflammatory lesions were significant compared with vehicle from week 8 and week 4 respectively ($P=0.003$ and $P=0.001$). By week 12, the percent

![FIGURE 8. Improvement in acne QoL from baseline to week 12 by gender (ITT population pooled data).](image)

![FIGURE 9. Investigator assessed cutaneous safety and tolerability (scaling and erythema) from baseline to week 12 by gender (safety population, pooled data, patients treated with tretinoin 0.05% lotion).](image)
change from baseline (LS mean) was 53.4% \((P<0.001\) vs vehicle) and 46.1\% \((P<0.001)\) respectively compared with 39.4\% and 29.7\%, see Figures 2 and 3. Treatment success (at least a 2-grade improvement in EGSS and ‘clear’ or ‘almost clear’) was significant compared with vehicle from week 8 \((P=0.080)\), and at week 12 16.1\% of patients (compared with 7.6\%, \(P=0.001)\) were treatment successes, see Figure 4.

At week 12, lesion count reduction in the Caucasian males (51.9\% and 45.9\% with tretinoin compared with 40.1\% \((P=0.001)\) and 31.4\% \((P<0.001)\) with vehicle) was similar to the overall study population, see Figures 5 and 6; and treatment success was achieved in 15.4\% of patients (compared with 7.7\% in the vehicle group, \(P=0.007\)), see Figure 7. There were no significant differences between active and vehicle in Black/African American patients, and no significant differences between male Caucasian and Black/African American patients in terms of inflammatory \((52.1\% vs 58.2\%, P=0.346)\) and noninflammatory \((45.9\% vs 49.1\%, P=0.522)\) lesion count reduction or treatment success \((15.4\% vs 18.0\%, P=0.668)\) at week 12.

Patient satisfaction (as assessed by PSS responses) was significantly greater with tretinoin 0.05\% lotion at week 12 \((7.3 vs 6.7, P=0.003)\). There was no significant difference between White and Black/African American males in terms for improvements in patient satisfaction \((P=0.641)\).

Improvements (absolute change from baseline) in only one Acne QoL domain with tretinoin 0.05\% lotion (acne symptoms) were significant compared with vehicle at week 12 \((P=0.004)\), see Figure 8.

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**FIGURE 10.** Patient reported cutaneous safety and tolerability (itching, burning, and stinging) from baseline to week 12 by gender (safety population, pooled data, patients treated with tretinoin 0.05\% lotion).

**FIGURE 11.** Investigator assessed cutaneous safety and tolerability (hyperpigmentation) from baseline to week 12 by gender and race (safety population, pooled data).
Improvements in White males were only significant vs vehicle for acne symptoms ($P=0.035$). There was no significant difference in Acne QoL domain improvements between male Black/African American or White patients: self-perception ($P=0.911$), role-emotional ($P=0.606$), role-social ($P=0.490$), and acne symptoms ($P=0.942$).

**Gender Differences**

Overall compliance with tretinoin 0.05% lotion treatment across the 2 studies was slightly better in the female population than the males. Calculated compliance (a patient was considered compliant if they did not miss more than 5 consecutive days dosing and applied 80% to 120% of the expected applications) was 92.0% in males and 94.0% in females. There was a significant difference in terms of inflammatory lesion count reduction between female and male patients, favouring female patients, at week 8 only (46.0% vs 39.4%, $P=0.026$), and a significant difference in terms of noninflammatory lesion count reduction at week 12 (51.7% vs 46.1%, $P=0.035$).

There was a significant difference between female and male patients in terms of treatment success at week 12 (23.6% vs 16.1%, $P=0.013$); and between female and male Caucasian patients in terms of noninflammatory lesion count reduction (52.7% and 46.0%, $P=0.016$) and treatment success (23.3% vs 15.4%, $P=0.024$). There were no significant differences between female and male Caucasian patients in inflammatory lesion count reduction (56.1% and 52.2%, $P=0.129$) at week 12; and no significant differences between female and male Black/African American patients in terms of inflammatory or noninflammatoty lesion count reduction (57.4% and 49.4% vs 58.8% and 49.3% respectively, $P=0.856$ and $P=0.922$) or treatment success (23.0% vs 18.0%, $P=0.501$).

Patient satisfaction with prior facial acne treatment was similar between gender and race, although the differences seen between Caucasian and Black/African American patients was more marked in males (4.9 and 4.3 respectively, compared with 4.5 and 4.6 in females). Treatment satisfaction with tretinoin 0.05% lotion by week 12 (as assessed by PSS responses) was not significantly different between female and male patients treated with tretinoin 0.05% lotion by week 12 (72 vs 73, $P=0.932$), or between Caucasian females and males (72 vs 73, $P=0.444$).

At baseline, Acne-QoL domain scores tended to be higher in the male patients (ie, better QoL) who were subsequently treated with tretinoin 0.05% lotion: self-perception (17.6 vs 12.8 in females), role-emotional (17.2 vs 13.0), role-social (16.2 vs 13.7), and acne symptoms (15.9 vs 13.4). All domain scores increased with treatment, although there were not significant differences between gender in terms of absolute change. In all cases domain scores were higher in male patients at week 12. Similar results were seen in Caucasian and Black/African American patients. In female patients, improvements in Acne-QoL domains were greater in Caucasians than in Black/African Americans in all cases, whereas in males, improvements in each domain score were greater in Black/African Americans.

**Safety and Cutaneous Tolerability**

There was a significant difference in treatment-related AEs between female and male patients (N=43, 10.6% and N=19, 5.2% respectively, $P=0.008$), with a significant difference in terms of application site dryness (N=22, 5.4% and N=6, 1.7% respectively, $P=0.006$), see Table 2. Treatment-related AEs were most prevalent in adolescent females (13.5%), and differences between gender age groups was also significant ($P=0.021$). Application site dryness was also most common in the adolescent (<18 years) females (6.4% vs 4.9% in the adult females). There was also a significant difference in Caucasian females and males (N=29, 10.9% and N=16, 5.5% respectively, $P=0.028$), with a significant difference in terms of application site dryness (N=16, 6.0% and N=5, 1.7% respectively, $P=0.013$). Overall there were 4 reports (2.6%) of application site dryness in Black/African American patients, all in females.

### TABLE 2.

Comparison of Male and Female Subpopulations: Treatment-Emergent and Related Adverse Event (AE) Characteristics through Week 12 (Pooled Data – Safety Population)

<table>
<thead>
<tr>
<th>Relationship to study drug (% by patient)</th>
<th>Male Patients (N=363)</th>
<th>Female Patients (N=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>47 (12.9%)</td>
<td>58 (14.4%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>27 (7.4%)</td>
<td>40 (9.7%)</td>
</tr>
<tr>
<td>Severe</td>
<td>5 (1.4%)</td>
<td>3 (0.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity of AEs reported</th>
<th>Male Patients (N=363)</th>
<th>Female Patients (N=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>19 (5.2%)</td>
<td>43 (10.6%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>60 (16.5%)</td>
<td>58 (14.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Related AEs reported by ≥1% patients*</th>
<th>Male Patients (N=363)</th>
<th>Female Patients (N=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site pain</td>
<td>8 (2.2%)</td>
<td>16 (4.0%)</td>
</tr>
<tr>
<td>Application site dryness</td>
<td>6 (1.7%)</td>
<td>22 (5.4%)</td>
</tr>
<tr>
<td>Application site erythema</td>
<td>4 (1.1%)</td>
<td>7 (1.7%)</td>
</tr>
<tr>
<td>Application site exfoliation</td>
<td>2 (0.6%)</td>
<td>5 (1.2%)</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>1 (0.3%)</td>
<td>6 (1.5%)</td>
</tr>
</tbody>
</table>

*Difference between two groups overall and for dryness was significant ($P=0.008$)
The investigator assessment of scaling and erythema (Figure 9) and patient reports of itching, burning, and stinging (Figure 10) were very similar in female and male patients at baseline. Erythema and itching were the most common, reported in 30% to 40% of patients. Both were markedly reduced in incidence and severity by week 12. There was a slight increase in mild scaling in the male patients treated with tretinoin 0.05% lotion. Hyperpigmentation was more prevalent in Black/African American female patients at baseline, with more reports of moderate (2) or severe (3) severity (Figure 11). Both the incidence and severity of the hyperpigmentation were reduced by week 12. Mean scores reduced from 0.9 to 0.7 (females) and 0.6 to 0.4 (males), where 1=mild.

**DISCUSSION**

Acne is a common disease in adolescents and many adults. Females are more vulnerable to acne across all age groups, with female gender and acne being two independent contributing factors in developing major depression. However, the impact of acne on different genders remains controversial, and poorly studied.

Our post hoc analysis of two large phase 3 studies in patients with moderate or severe acne studied the impact of gender and race on treatment outcomes. Studies have shown that male patients typically are less compliant than females, especially with topical treatments. In these phase 3 studies overall adherence was high, although slightly better in the female population (94% vs 92%). Tretinoin 0.05% lotion was generally more effective in female patients; 23.6% of females were treatment successes vs 92%. Tretinoin 0.05% lotion was generally more effective in women in terms of lesion count reductions; and a previous publication has reported that reduction in noninflammatory lesions was high, although slightly better in the female population (94% vs 92%). Tretinoin 0.05% lotion was generally more effective in female patients; 23.6% of females were treatment successes vs 92%. Tretinoin 0.05% lotion was generally more effective in women in terms of lesion count reductions; and a previous publication has reported that reduction in noninflammatory lesions were very similar in female and male patients at baseline. Erythema and itching were the most common, reported in 30% to 40% of patients. Both were markedly reduced in incidence and severity by week 12. There was a slight increase in mild scaling in the male patients treated with tretinoin 0.05% lotion. Hyperpigmentation was more prevalent in Black/African American female patients at baseline, with more reports of moderate (2) or severe (3) severity (Figure 11). Both the incidence and severity of the hyperpigmentation were reduced by week 12. Mean scores reduced from 0.9 to 0.7 (females) and 0.6 to 0.4 (males), where 1=mild.

**CONCLUSION**

Tretinoin 0.05% lotion has been shown to be highly effective and well tolerated in patients with moderate or severe acne. Efficacy appears greatest in Caucasian females, with significantly more reports of application site dryness than in males that should be easily managed with appropriate use of moisturizers. There were racial and gender differences in QoL and tretinoin 0.05% lotion seemed to have a beneficial effect on PIH in those patients most at risk.

**DISCLOSURES**

Dr Guenin is an employee of Bausch Health. Dr Lain and Dr Harper are advisors and/or investigators with Bausch Health. Dr Day has participated in speaker programs for Bausch Health.

**REFERENCES**

VOTED NEWBEAUTY’S BEST SKIN CARE SYSTEM 9 CONSECUTIVE YEARS!

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A Cohort Study Using a Facial Cleansing Brush With Acne Cleansing Brush Head and a Gel Cleanser in Subjects With Mild-to-Moderate Acne and Acne-Prone Skin

Michael H. Gold MD FAAD, a Glynis R. Ablon MD FAAD, b Anneke Andriessen PhD, c Vivian W. Bucay MD FAAD, d David J. Goldberg MD JD, e Jeremy B. Green MD FAAD, f Deirdre Hooper MD FAAD, g Stephen H. Mandy MD FAAD, h Mark S. Nestor MD PhD, i Arisa Ortiz MD FAAD FACMS j

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cRadboud UMC Nijmegen, Andriessen Consultants, Malden, NL
dBucay Center for Dermatology and Aesthetics, San Antonio, TX
eSkin Laser & Surgery Specialists of NY and NJ, Hackensack, NJ; Icahn School of Medicine at Mt. Sinai, New York, NY
fSKIN Associates of South Florida, Miami, FL
gAudubon Dermatology, New Orleans, LA
hDepartment of Dermatology and Cutaneous Surgery, Miller School of Medicine, University of Miami, Miami FL
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ABSTRACT

Introduction: Acne vulgaris is a highly prevalent skin condition that can adversely affect the quality of life. Acne-predisposed skin is in a state of subclinical inflammation leading to skin barrier dysfunction. A multi-center cohort study was designed to evaluate clinical efficacy and safety of twice daily facial cleansing using an oscillatory sonic brush, acne brush head, and cleansing gel for 4 weeks.

Methods: Subjects with mild-to-moderate acne and acne-prone skin used the cleansing regime after which they applied the skin care products they routinely used. Physician-assessed skin condition comparing baseline versus week 4 using the FDA/IGA scale and subject satisfaction with cleansing efficacy and handling properties of the regime were scored during the last visit.

Results: Forty-six subjects completed the study. Physician-scored skin condition showed a statistically significant improvement in FDA/IGA scores and a significant reduction of inflammatory and non-inflammatory lesions comparing baseline versus 4 weeks. Thirty-five (76.0%) subjects had cleared or almost cleared. Subjects similarly assessed their skin to be improved.

Conclusion: Both the physician and subject scores revealed the gentle cleansing routine using the sonic brush to be effective reducing the number of acne lesions, improving skin condition. No adverse events were reported during the study period. The cleansing regime may offer an attractive, safe option for maintenance and treatment of subjects with mild-to-moderate acne and acne-prone skin.


INTRODUCTION

Acne vulgaris is a highly prevalent skin condition. The common onset of acne is in early adolescence, about 85% of those affected have the condition between the ages 8 and 17 years. Acne affects a substantial number of adults, particularly women, who are more likely to view it as a disorder that requires treatment even when the condition is mild. Compared to adolescent acne, adult acne tends to be more inflammatory with the involvement of the cheeks and lower half of the face. The presence of comedones in adult acne is uncommon.

Acne can adversely affect the quality of life due to psychological and emotional distress, including poor self-esteem, social anxiety, depression, and suicidal ideation. There is an unmet need for acne information, education, and treatments that provide the best patient outcomes.

Acne has a complex, multifactorial pathophysiology. Acne-predisposed skin is in a state of subclinical inflammation, which may be linked to changes in skin surface pH and disturbances of the stratum corneum. Inflammatory events trigger acne lesions and correlate to skin barrier dysfunction.

The impaired skin barrier in acne may benefit from a gentle cleanser used along with other therapeutic measures. Twice daily use of a gentle cleanser in patients with mild-to-moderate acne demonstrated a reduction in acne lesion counts in clinical studies without damage to the skin barrier or sebum overcompensation.
An oscillatory sonic brush uses the skin’s elastic properties by applying an optimal amplitude and frequency range. The sonic brush has been shown to be safe and effective at cleansing the skin for various dermatologic conditions. Effective cleansing clears pores of debris, allowing sebum to leave the skin surface unimpeded. Cleansing and moisturizing help to manage pH levels of the skin, enabling sufficient water retention.

**METHODS**

**Cohort Population**
A multi-center cohort study evaluated the efficacy and safety of a facial cleansing regimen when used twice daily by subjects with mild-to-moderate acne and acne-prone skin as part of a daily skin care routine. Subjects were included in the cohort study with mild-to-moderate facial acne (score 2-3 on the FDA Investigator Global Acne Assessment scale (FDA/IGA), 5-10 inflammatory acne lesions (papules, pustules) and 10 or more non-inflammatory acne lesions (open and closed comedones) (Table 1). Fifty subjects were recruited from 10 centers in the USA, each of the five participating physicians aimed to recruit five subjects.

Regional/local ethical committee approval was obtained for the study. Prior to subject inclusion, the physician informed the subject about the study and obtained the subject’s written consent for participation.

**Study Interventions**
The Clarisonic Mia 2 facial sonic cleansing brush with acne cleansing brush head (Clarisonic Redmond, WA) and Pore and Blemish Gel Cleanser, were used by subjects with mild-to-moderate acne as part of a daily skin care routine.

Depending on the severity of the condition, once/twice daily (morning and bedtime) facial cleansing using the sonic brush and gel was performed by the subject over a 4-week (± 5 days) period. After cleansing, subjects applied the skin care products they routinely used. The sonic brush, brush head, and cleansing gel were provided at the start of the study and were to be used according to the instructions of the manufacturer (Figure 1). Before starting the cohort, the physician demonstrated the use of the sonic brush and cleansing gel to each subject.

Subjects were allowed to use acne medication (topical and systemic) and/or the over-the-counter products they were using at the time of inclusion in the study, except the cleanser. Subjects who have been using acne medication and/or the over-the-counter products for at least two weeks prior to the study start were instructed to continue the same acne medication and/or the over-the-counter products until the end of the study (week 4 (± 5 days)).

**Outcomes**
The purpose of the cohort study was to evaluate clinical efficacy and safety of twice daily facial cleansing using a sonic brush, acne brush head and cleansing gel by subjects with mild-to-moderate acne as part of a daily skin care routine.

The primary objective was physician-assessed skin condition comparing baseline versus day 28 (± 5 days) (end) using the FDA/IGA scale (Clear (0), Almost clear/minimal (1), Mild (2), Moderate (3), Severe (4)).
RESULTS

The multi-center cohort study aimed to include 50 subjects with mild-to-moderate facial acne. Four subjects withdrew consent before the start of the study and forty-six subjects started with the sonic brush cleansing regime after giving informed consent. Subjects had a mean age of 27.55 (± SD 8.02) years, were mainly female: 42 (91.3%) with 4 (8.7%) males.

FDA/IGA acne score at baseline was mild in 28 (60.9%) of the cases, moderate in 14 (30.4%) and severe in 2 (4.3%) of the cases. For 2 (4.3%) cases severity class was not scored (Table 3).

Secondary objectives were subject satisfaction with cleansing efficacy and handling properties of the sonic brush, cleansing head and cleansing gel scored at day 28 (+/- 5 days) during the last visit. The subjects scored their findings on a 5-Point Likert scale: Strongly disagree (1), Disagree (2), Neutral (3), Agree (4), Strongly agree (5).

All unexpected adverse events observed by or reported to the investigators were evaluated. The intensity, duration and causal relationship to the treatment were rated for all adverse events.

Study Design

The cohort had an evaluation duration of 28 days (+/- 5 days) during which the cleansing regime was used. Two or three (depending if screening and baseline assessments could be combined during visit 1) visits were planned during the study period (Table 2).

The sample size for the study was calculated at fifty subjects, which was deemed large enough to collect clinically meaningful data and allowed for a dropout rate of 15%. Subjects used the cleansing regime for a period of 28 days (+/- 5 days). Statistical evaluation was performed using IBM SPSS (IBM Corporation Armonk, New York, NY). A paired T-test or ANOVA was applied to analyze skin condition comparing baseline (day 0) versus day 28 (+/- 5 days) (end) per subject and per group. Where appropriate tests were carried out at the 5% significance level and a confidence interval of 95%.
TABLE 4.  

<table>
<thead>
<tr>
<th>Physician-scored FDA/IGA</th>
<th>0 = none</th>
<th>1 = minimal</th>
<th>2 = mild</th>
<th>3 = moderate</th>
<th>4 = severe</th>
<th>Not scored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline:</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>28.0 (60.9%)</td>
<td>14.0 (30.4%)</td>
<td>2.0 (4.3%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>End of study: at 28 days (+/- 5 days):</td>
<td>6.0 (13.0%)</td>
<td>29.0 (63.0%)</td>
<td>8.0 (17.4%)</td>
<td>1.0 (2.2%)</td>
<td>0 (0%)</td>
<td>2.0 (4.3%)</td>
</tr>
</tbody>
</table>

Comparing baseline versus end results: Mean difference: 1.33 (SD ± 0.68); Two-tailed Paired Samples Test: t(42) = 12.78, P < 0.05 (0.00).  
FDA/IGA scale: 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe  
FDA Investigator Global Acne Assessment scale (FDA/IGA), inflammatory lesions (IL), non-inflammatory lesions (NIL)

Treatments reported at the start of the study that were continued throughout included: benzoyl peroxide and a topical retinoid either alone or in combination (with/without a topical antibiotic) for mild acne and oral antibiotics combined with topical therapy for moderate-to-severe acne. Only two subjects used a non-comedogenic moisturizer to reduce inflammation and/or side effects from treatment, such as skin irritation or dryness.

Forty-four subjects (95.7%) completed the study period and were included in the analysis. Two subjects were lost to follow-up. No adverse events were reported during the study period. At the end of the study physician-scored skin condition revealed that 35 (76.0%) subjects had cleared or almost cleared, 8 (17.4%) had mild acne and 1 (2.2%) had moderate acne (Table 4). The mean improvement in FDA/IGA comparing skin condition at baseline versus 28 days (+/- 5 days) was significant (1.33 (SD ± 0.68)); Two-tailed Paired Samples Test: t(42) = 12.78, P < 0.05 as well as the reduction in the number of physician-scored inflammatory and non-inflammatory lesions (Figure 2).

The subject scored skin condition using a 5-Point scale (Strongly disagree (1), Disagree (2), Neutral (3), Agree (4), Strongly agree (5)) at the end of the study revealed comparable results to the physician scores on improvement of skin condition. When asked if the number of skin imperfections had reduced they scored a mean of 4.13 (SD ± 0.99) (Agree/Strongly agree). The subjects further reported that the excess of sebum was removed (4.31 (SD ± 0.82)), visible blackheads had reduced (4.07 (SD ± 1.00)) as well as redness (4.04 (SD ± 0.93)) providing a more even facial skin complexion (4.08 (SD ± 0.87)). The subjects rated the brush and gel as easy (4.89 (SD ± 0.32)), fast and effective to use (4.84 (SD ± 0.43)), and fitted their skin care regimen (4.77 (SD ± 0.57)). The subjects reported that after using the sonic brush and gel for 4 weeks they felt better about their facial skin (4.61 (SD ± 0.75)) and more confident in their personal (4.39 (SD ± 0.92)) and professional life (4.41 (SD ± 0.95)) (Table 5).

DISCUSSION

Acne affected skin is characterized by inflammation leading to disruption of normal physiological functions of the epidermis, including the stratum corneum. Moreover acne therapies can induce alterations in the epidermis. Enhanced trans-epidermal water loss is reported with benzoyl peroxide, tretinoin, tazarotene, and isotretinoin use. Xerosis and dermatitis commonly result from acne treatment and are very important reasons for non-compliance.

The compromised skin barrier in acne may be improved with a gentle cleansing regime, potentially reducing acne lesion counts and enhancing antimicrobial defenses.
plitude (angular) and frequency (60–90Hz) range to efficiently remove dirt and debris. Moreover the cyclic mechanical stimulation of the sonic brush was shown to increase expression of certain dermal proteins (such as, collagen 4 and 7, procollagen, laminin 5, fibronectin, fibrillin, and decorin) ex-vivo in human skin. The mechanical stimulation of the tissue while using the brush may improve skin condition such as wrinkle presentation when using the brush regularly as part of an anti-aging regime. Clinical studies have shown the use of the oscillatory sonic brush is safe (compared to stand-alone use of a cleanser) and does not cause erythema or other clinical signs of irritation. Other investigations demonstrated safety and efficacy of various cleansers and skin care products for acne in combination with the sonic brush.

The present study demonstrated a significant (mean difference: 1.33 (SD ± 0.68); Two-tailed Paired Samples Test: t(42) = 12.78, \( P < 0.05 \)) improvement in physician scored FDA/IGA scale and subject scored skin condition after 28 days (+/- 5 days) of sonic brush and cleansing gel use. The cleansing regime was easy, fast, and safe, as there were no reported adverse events during the study period.

Four typical cases are shown to illustrate these results (Figures 3–6).

**FIGURE 3.** Case 1. Female 45-year-old presented with mild acne at baseline. After 28 days of sonic brush use (A) Physician-scored acne lesions had almost cleared. (B) Subject-scored skin condition confirmed this result, improving skin radiance, making her feel more confident about her appearance. Handling of the brush was easy and fast and no skin irritation occurred. *Case and photographs courtesy of Dr. M.H. Gold*

**FIGURE 4.** Case 2. Female 37-year-old presented with mild acne at baseline. After 28 days of sonic brush use (A) Physician scored acne lesions had almost cleared. (B) Subject scored skin condition confirmed this result, improving all scored aspects, making her feel better and more confident about her appearance. Handling of the brush was easy and fast and no skin irritation occurred. *Case and photographs courtesy of Dr. M.H. Gold*

**FIGURE 5.** Case 3. Female 30-year-old presented with mild acne at baseline. After 28 days of sonic brush use (A) Physician scored acne lesions had almost cleared. (B) Subject scored skin condition confirmed this result, improving skin complexion and texture, making her feel more confident about her appearance. Handling of the brush was easy and fast and no skin irritation occurred. *Case and photographs courtesy of Dr. M.H. Gold*
FIGURE 6. Case 4. Female 34-year-old presented with mild acne at baseline. After 28 days of sonic brush use (A) Physician-scored acne lesions had cleared. (B) Subject scored skin condition confirmed this result, improving skin condition and self-confidence significantly. Handling of the brush was easy and fast and no skin irritation occurred. Case and photographs courtesy of Dr. M.H. Gold

LIMITATIONS

This study gave a description of practice and did not have a comparator or control group; therefore, cause and effect relationships cannot be inferred. It was beyond the scope of this study to draw any conclusions regarding the possible impact of the evaluated cleansing regime on the underlying disease if it was used as monotherapy; this impact will be explored in future studies. Moreover, the subjects were not on a standardized acne regimen upon entering the trial; therefore, therapeutics added shortly prior to study initiation could represent confounders.

CONCLUSIONS

Cleansing of the face (shown to remove dirt, excess of sebum, and other unwanted debris) may potentially improve skin in mild-to-moderate acne patients. The gentle and effective cleansing routine using the sonic brush reduced significantly ($P<0.05$) the number of physician-scored inflammatory and non-inflammatory lesions in the treated subjects. Subjects similarly assessed their skin to be improved. No adverse events were reported during the study period. The cleansing regime using the sonic brush may offer an attractive, safe option for maintenance and treatment of subjects with mild-to-moderate acne and acne-prone skin.

DISCLOSURES

Dr. Michael Gold is a consultant and has performed research for Clarisonic. All authors contributed to the development, execution of the study, writing, or critical review of the article. The study products used were provided by Clarisonic, who supported a one-day meeting for study protocol development. All authors are registered in ORCID.

REFERENCES


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Efficacy and Tolerability of a Novel Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate or Severe Acne Vulgaris in Adult Females

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ABSTRACT

Background: A novel tretinoin 0.05% lotion formulation has been shown to be efficacious and well-tolerated, and especially effective in adult female acne patients. While it is perhaps counter-intuitive that patients with more severe disease would show clinically significant improvement with topical monotherapy, topical retinoids have been shown to offer realistic treatment options in these patients.

Objective: To evaluate the safety and efficacy of once-daily tretinoin 0.05% lotion in adult females with moderate or severe acne.

Methods: Post hoc analysis of two multicenter, randomized, double-blind, vehicle-controlled phase 3 studies. Adult females (>=18 years of age) with moderate (N=551) and severe (N=55) acne were randomized (1:1) to receive tretinoin 0.05% lotion or vehicle, once-daily for 12 weeks. Efficacy assessments included changes in baseline inflammatory/noninflammatory lesions, treatment success (at least 2-grade reduction in Evaluator's Global Severity Score [EGSS] and clear/almost clear) and quality of life (QoL) using the validated Acne-QoL questionnaire. Safety, adverse events (AEs), and cutaneous tolerability were evaluated throughout.

Results: At week 12, efficacy in adult females with moderate acne (EGSS=3) treated with tretinoin 0.05% lotion was significantly greater than that reported with vehicle. Mean percent reduction in inflammatory and noninflammatory lesion counts was 58.5% and 55.5% respectively compared with 50.3% and 39.8% with vehicle (P=0.039 and P<0.001). Treatment success was achieved by 25.4% of subjects by week 12, compared with 15.4% with vehicle (P=0.006). Tretinoin 0.05% lotion was numerically more effective in adult females with severe acne (EGSS=4). Mean percent reduction in inflammatory and noninflammatory lesion counts was 59.0% and 58.8% respectively (compared with 53.5% and 45.5% with vehicle), and treatment success was achieved by 17.9% of subjects (compared with 4.5% with vehicle), with 46.6% of subjects achieving at least a 2-grade improvement in EGSS by week 12. Quality of life improvements with tretinoin 0.05% lotion were significant compared with vehicle in adult females with moderate acne (except role-social), but not in severe acne (probably due to the group size). The majority of AEs were mild and transient; more frequently reported in the moderate acne population where application site pain (2.9%), and application site dryness (5.0%) were the most common, compared with one report (4.5%) of application site pain and dryness in the severe acne population. Local cutaneous safety and tolerability assessments were generally mild-to-moderate and improved by week 12.

Limitations: The number of severe subjects enrolled in the studies was considerably less than the number of subjects with moderate acne, and the studies were not powered to demonstrate a difference in efficacy based on acne severity.

Conclusions: Tretinoin 0.05% lotion was significantly more effective than vehicle in achieving treatment success and reducing inflammatory and noninflammatory lesions in adult females with moderate acne, with notable improvements in treating adult females with severe acne. It was well-tolerated, and all treatment-related AEs were mild or moderate.


INTRODUCTION

Acne vulgaris (acne) is a common skin disease in adolescence and a growing concern in adult women. However, there are few good prospective studies addressing its severity and response to treatment in this patient population. Treatment considerations include their slow response to therapy, increased likelihood of skin dryness and irritation, and high psychosocial impact. Tolerability is very important in this patient group because topicals are most commonly used and local skin side effects can lead to poor adherence. Also, there are no acne clinical trials exclusively in adult females. Studies with topical therapy in severe acne are limited to combination studies with oral antibiotics, or post hoc analyses of topical fixed combinations in moderate-to-severe acne. Our knowledge on the effectiveness of topical therapy in adult females is also largely restricted to post hoc analyses.
Although topical monotherapy is not recommended for the treatment of severe papulopustular, non-nodulocystic acne, a topical therapy effective enough to improve severe inflammatory acne would address a significant unmet need and might reduce the additional risks of systemic treatments.21

Recently, clinical efficacy and safety data on tretinoin 0.05% lotion that utilize unique polymeric emulsion technology were published.22 Tretinoin 0.05% lotion was significantly more effective than vehicle in treating moderate or severe acne, with a highly favorable safety and tolerability profile where the incidence of erythema, dryness and skin burning were lower than previously reported with other formulations of tretinoin.22 Here we present a post hoc analysis the two phase 3 studies in 606 adult female patients with moderate or severe acne.

**METHODS**

**Study Design**

A post hoc analysis of adult female patients (≥18 years old) from 2 multicenter, randomized, double-blind, vehicle-controlled, parallel group clinical studies in patients with moderate or severe acne was performed. Protocols received approval before patient enrollment from the appropriate institutional review board (IRB) and studies 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 randomized (1:1) to receive tretinoin 0.05% lotion or vehicle applied to the face once-daily for 12 weeks.

**Study Population**

Eligible patients for the post hoc analysis included adult female patients aged 18 to 58 years 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; and an Evaluator Global Severity Score (EGSS) score of 3 (moderate) or 4 (severe).

**Efficacy Evaluation**

Efficacy evaluations were comprised of inflammatory, and noninflammatory lesion counts and EGSS assessment at screening, baseline, and subsequent study visits (weeks 4, 8, and 12) were performed. Key efficacy endpoints included changes from baseline in inflammatory and noninflammatory lesion counts and the proportion of patients who were treatment successes (ie, achieved at least a 2-grade reduction from baseline in EGSS and were also considered ‘clear’ or ‘almost clear’ at that same visit). For those adult female patients with severe acne (EGSS=4), treatment success would represent at least a 3-grade reduction in EGSS (ie, from severe to almost clear), and additional data are provided on the number of patients who achieved at least a 2-grade improvement, to mild [EGSS=2].

Additional assessments included a patient satisfaction score (PSS) and validated acne-specific quality of life (Acne-QoL) questionnaire (Merck & Co, Inc. Whitehouse NJ). Patients were asked to rate their satisfaction with prior facial acne therapy on a PSS scale of 1-10 (where a score of 5 or greater was considered as ‘satisfied’) at baseline and following study treatment at week 12.

**Safety Evaluation**

Cutaneous safety (erythema and scaling) and tolerability (itching, burning, and stinging) were evaluated on a 4-point scale from 0 (none) to 3 (severe). The investigator assessed erythema and scaling at the time of the study visit. Itching, burning, and stinging were solicited from the patient as an average of their symptoms during the period since the previous visit. Hyperpigmentation and hypopigmentation severity were assessed by the investigator at each study visit, using the same a 4-point scale. Adverse events (AEs) were evaluated throughout; 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 based on estimation using the Markov Chain Monte Carlo multiple imputation method. No imputations were made for missing safety data.

Reductions in lesion counts were presented as least square means and treatment P-values from an analysis of covariance with factors of treatment and analysis center and the respective baseline lesion count as covariate, values adjusted for multiple imputations. Significance of EGSS reductions were obtained from logistic regression (using Firth’s Penalized Likelihood) with factors of treatment group and analysis center. 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. Treatment group comparisons were made by tabulating the frequency of patients with one or more AEs during the study.

**RESULTS**

**Baseline Characteristics**

A total of 606 adult female acne patients (≥18 years old) were included in the post hoc analysis. Patients had moderate (EGSS=3, N=551) or severe (EGSS=4, N=55) disease. Overall, 494 patients...
Demographic data (Table 1) were also similar across the 2 treatment arms. Patients were predominantly Caucasian (N=400, 66.0%) or Black/African American (N=155, 25.6%). The Asian population was higher in those females with severe disease (10.9% vs 4.5%).

At baseline, the mean number (SD) of inflammatory and non-inflammatory lesions in the severe and moderate acne groups...
was 29.2 (6.30) and 43.5 (21.10), and 25.0 (4.64) and 38.3 (15.25), respectively.

**Efficacy**

**Lesion counts**

In adult females with moderate acne, tretinoin 0.05% lotion resulted in statistically significant reductions in both inflammatory and noninflammatory lesion counts compared with vehicle from week 12 (Figure 2) and week 4 (Figure 3) respectively. At week 12, mean percentage change (LS mean) from baseline in inflammatory and noninflammatory lesion counts was 58.5% and 55.5% respectively compared with 50.3% (P=0.039) and 39.8% with vehicle (P<0.001). Median percent reductions in inflammatory and noninflammatory lesion counts with tretinoin 0.05% lotion were 67.4% and 60.6%, compared with 61.6% and 51.3% with vehicle.

In adult females with severe acne, tretinoin 0.05% lotion resulted in numerically greater reductions in both inflammatory and noninflammatory lesion counts compared with vehicle, but re-

**FIGURE 2.** Percent change in inflammatory lesions from baseline to week 12 by severity (ITT population, LS mean). Adult female [≥18 years] population, pooled data (N=606).

**FIGURE 3.** Percent change in noninflammatory lesions from baseline to week 12 by severity (ITT population, LS mean). Adult female [≥18 years] population, pooled data (N=606).
Results were not significant. At week 12, mean percentage change (LS mean) from baseline in inflammatory and noninflammatory lesion counts was 59.0% and 58.8% respectively, compared with 53.5% and 45.5% with vehicle.

Treatment success
Treatment success was defined as at least a 2-grade improvement in global severity by EGSS and ‘clear’ or ‘almost clear’. By week 12, 25.4% of adult females with moderate acne were treatment successes following treatment with tretinoin 0.05% lotion compared with 15.4% on vehicle (P=0.006), see Figure 4. In the adult females with severe disease, 17.9% achieved treatment success by week 12, compared with 5.4% treated with vehicle (P=0.185). Almost half the adult female patients (46.6%) with severe acne treated with tretinoin 0.05% lotion achieved at least a 2-grade reduction in baseline EGSS by week 12.

Patient satisfaction and quality of life
Patient satisfaction with treatment in those adult female acne patients with moderate disease was significantly greater with tretinoin 0.05% lotion than vehicle by week 12 (P=0.002). Baseline mean scores with tretinoin increased from 4.3 (satisfaction with previous therapy) to 7.3. Patient satisfaction at baseline in the severe acne adult female population was lower (mean score 3.9) and increased greater with treatment to 7.8, although differences to vehicle (mean score 6.7) were not significant, probably

FIGURE 4. Treatment success. Percent of patients with at least a 2-grade improvement in EGSS and ‘clear’ or ‘almost clear’ at each study visit by severity (ITT population pooled data). Adult female [≥18 years] population, pooled data (N=606).

FIGURE 5. Improvement in Acne QoL from baseline to week 12 by severity (ITT population pooled data). Adult female [≥18 years] population, pooled data (N=606).
due to the small sample size.

At baseline, mean score for each Acne-QoL domain (self-perception, role-emotional, role-social, and acne symptoms) in the tretinoin group were much lower in the severe acne population (8.0, 8.9, 9.6, and 9.7 respectively, compared with 11.8, 12.1, 12.9, and 12.6 in the moderate group). When these patients were subsequently treated with tretinoin 0.05% lotion, the QoL improvements (in terms of absolute change from baseline) were also greater in the severe patient population (10.8, 11.5, 7.4, and 8.8 respectively, compared with 9.5, 8.8, 6.3, and 8.5 in the moderate group), see Figure 6. Improvements in Acne-QoL in those adult females with moderate acne were all significant compared with the vehicle group, with the exception of role-social. There were no statistically significant differences in the improvement between treatment groups based on the mean Acne-QoL assessments for each domain in the severe acne population.

Safety
There were a similar proportion of treatment emergent adverse events (TEAEs) in both moderate and severe active treatment groups (Table 2). Most AEs were mild or moderate. There were only 3 (1.3%) severe AEs (in the adult females with moderate acne), with 2 being related to study drug. Seven (2.9%) adult female patients with moderate disease subsequently treated with tretinoin 0.05% lotion discontinued due to TEAEs. Four TEAEs (1.7%) were treatment-related (contact and irritant dermatitis, stinging, burning, and itching), and treatment-related AEs with tretinoin 0.05% lotion were generally uncommon. Application site dryness (5.0%) and pain (2.9%) were reported most frequently in the moderate acne group; one adult female with severe disease reported application site pain and dryness.

### TABLE 2.

<table>
<thead>
<tr>
<th></th>
<th>Tretinoin 0.05% Lotion</th>
<th>Tretinoin 0.05% Lotion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate Adult Female Patients (N=240)</td>
<td>Severe Adult Female Patients (N=22)</td>
</tr>
<tr>
<td>Patients reporting any TEAE</td>
<td>55 (22.9%)</td>
<td>5 (22.7%)</td>
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<tr>
<td>Patients reporting any SAE</td>
<td>4 (1.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Patients who died</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Patients who discontinued due to TEAE</td>
<td>7 (2.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Severity of AEs reported</td>
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<td></td>
</tr>
<tr>
<td>Mild</td>
<td>31 (12.9%)</td>
<td>4 (18.2%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>21 (8.8%)</td>
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</tr>
<tr>
<td>Severe</td>
<td>3 (1.3%)</td>
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<tr>
<td>Relationship to study drug (% by patient)</td>
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<tr>
<td>Related</td>
<td>22 (9.2%)</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Unrelated</td>
<td>33 (13.8%)</td>
<td>4 (18.2%)</td>
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<td>Treatment Related AEs reported by ≥1% patients*</td>
<td></td>
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<tr>
<td>Application site pain</td>
<td>7 (2.9%)</td>
<td>1 (4.5%)</td>
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<tr>
<td>Application site dryness</td>
<td>12 (5.0%)</td>
<td>1 (4.5%)</td>
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<tr>
<td>Application site erythema</td>
<td>4 (1.7%)</td>
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<tr>
<td>Application site exfoliation</td>
<td>3 (1.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>4 (1.7%)</td>
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</tbody>
</table>

**FIGURE 6.** Investigator assessed cutaneous safety and tolerability (scaling and erythema) from baseline to week 12 by severity (safety population, pooled data, adult female [≥18 years] patients treated with tretinoin 0.05% lotion).
Cutaneous Safety and Tolerability

Erythema and scaling were recorded by the investigator and were more common in the severe acne subpopulation. Both improved over the study period, see Figure 6.

Itching, burning, and stinging severity scores were obtained from the patients. About a third of patients reported itching at baseline. Reports of burning and stinging were rare and generally mild. All improved with treatment, see Figure 7.

Hyperpigmentation was generally mild at baseline, and more prevalent in the severe group (mean score=0.8, compared with 0.6 in the moderate group, where 1=mild). There were no increases in mean scores over the 12-week treatment period.

**DISCUSSION**

While it is perhaps counter-intuitive that patients with more severe disease would show clinically significant improvement with topical monotherapy, we were able to report good results with tretinoin 0.05% lotion in adult females with severe acne (EGSS=4). Although the results were not significant vs vehicle, probably due to the small sample size, tretinoin 0.05% lotion achieved almost a 60% reduction in both inflammatory and comedonal lesions by week 12. In addition, almost half the adult female patients (47%) with severe disease treated with tretinoin 0.05% lotion achieved at least a 2-grade reduction in baseline EGSS by week 12.

As expected, satisfaction with prior acne treatment and baseline QoL were much lower in the female patients with severe acne than those with more moderate severity. However, improvements in patient satisfaction and Acne-QoL domain scores following treatment with tretinoin 0.05% lotion were greater, suggesting the improvements in efficacy were clinically relevant. Tolerability was also good in the severe acne population, with only one patient reporting a treatment-related AE (application site dryness and pain). Efficacy and tolerability in adult females with severe acne would warrant a larger study to gain further insights in this increasingly important group of patients.

The data in adult female acne patients with moderate disease (EGSS=3) are also noteworthy, given the limited clinical data and the increased likelihood of skin irritation in adult females treated with retinoids. Previous evaluations of the efficacy and tolerability of retinoids to treat adult female acne are limited to *post hoc* analyses of larger studies of predominantly mild to moderate acne. A small *post hoc* analysis of 2 studies with adapalene 0.3% gel (N=74) reported numerical greater efficacy in reducing inflammatory and noninflammatory lesions (median percent reductions 61.2% and 50.7% respectively) in adult females with moderate acne. While not head to head comparisons, tolerability of adapalene 0.3% gel in the phase 3 study was similar to that reported with adapalene 0.1% gel, with a higher incidence of skin discomfort and dry skin than noted with tretinoin 0.05% lotion.

The only previous study that included tretinoin was a subgroup analysis of the efficacy and safety of clindamycin 1.2%-tretinoin 0.025% gel in adult males and females in comparison to its individual active ingredients and vehicle. Overall, efficacy in reducing inflammatory and noninflammatory lesions with clindamycin 1.2%-tretinoin 0.025% gel from 3 12-week studies was significantly greater vs the comparators in adolescent acne and mild/moderate disease. In patients with more severe disease, clindamycin 1.2%-tretinoin 0.025% gel was not significantly more effective than either individual active ingredient. In the subsequent *post hoc* analysis in adult females, efficacy of tretinoin 0.025% gel was statistically inferior to the fixed combination clindamycin 1.2%-tretinoin 0.025% gel in reducing inflammatory lesions (median percent reductions of 72.4%...
and 63.3% respectively). However, there was no significant difference in reductions in comedonal lesions between the fixed combination and tretinoin monotherapy (median percent reductions of 55.2% and 48.6% respectively). In a condition commonly characterized by both comedones and inflammatory papules, the efficacy observed with tretinoin 0.05% lotion is likely to be important in adult female acne. In addition, although there are no head to head comparisons, the lower incidence of application site reactions than those reported with other tretinoin clinical trials should help patient adherence.

CONCLUSION

Tretinoin 0.05% lotion was significantly more effective than vehicle in achieving treatment success and reducing both inflammatory and comedonal lesions in adult females with moderate acne; with improvements in adult females with severe acne supported through patient reported outcomes. The low potential to cause skin irritation should help compliance in this increasingly important population of acne sufferers.

ACKNOWLEDGMENT

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DISCLOSURES

Drs Harper, Baldwin and Stein Gold are advisors and/or investigators with Ortho Dermatologics. Dr Guenin is an employee of Bausch Health.

REFERENCES

11. Stein Gold L. Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and benzoyl peroxide (3.75%) aqueous gel in moderate and severe acne vulgaris subpopulations. J Drugs Dermatol. 2015;14(8):969-974.

AUTHOR CORRESPONDENCE

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Topical Treatments for Melasma: A Systematic Review of Randomized Controlled Trials

Evan Austin BS, Julie K. Nguyen MD, Jared Jagdeo MD MS

Department of Dermatology, State University of New York, Downstate Medical Center, Brooklyn, NY
Dermatology Service, VA New York Harbor Healthcare System Brooklyn Campus, Brooklyn, NY

ABSTRACT

Background: Melasma is an acquired skin disease characterized by symmetric hyperpigmentation on sun-exposed areas, particularly on the face. Recently, there has been tremendous scientific interest in novel, safe, and effective topical agents to manage melasma. Objective: To evaluate topical treatments for melasma and provide evidence-based recommendations for clinical use and further research. Methods: We performed a systematic review of randomized controlled trials (RCTs) on topical agents for the treatment of melasma on March 4th, 2019 using PRISMA guidelines. Clinical recommendations were based on the American College of Physicians guidelines. Results: After screening, we identified 35 original RCTs using azelaic acid, cysteamine, epidermal growth factor, hydroquinone (liposomal-delivered), lignin peroxidase, mulberry extract, niacinamide, Rumex occidentalis, triple combination therapy, tranexamic acid, 4-n-butylresorcinol, glycolic acid, kojic acid, aloe vera, ascorbic acid, dioic acid, ellagic acid and arbutin, flutamide, parsley, or zinc sulfate for melasma. Conclusions: Cysteamine, triple combination therapy, and tranexamic acid received strong clinical recommendations for the treatment of melasma. Cysteamine has excellent efficacy and is reported to have anti-cancer properties, but has not been directly compared with hydroquinone. Triple combination agents and tranexamic acid are effective, but carry theoretical risks for ochronosis and thrombosis, respectively. Natural compounds are associated with low risk for adverse events, but more research is needed to determine the efficacy, optimal formulation, and appropriate concentration of novel treatments.


INTRODUCTION

Melasma is an acquired skin disease characterized by symmetric patches of hyperpigmentation on sun-exposed areas such as the cheeks, forehead, chin, nose, and upper lips. Histological features may include epidermal and dermal pigmentation, solar elastosis, increased vascularization, and mastocytosis. Although the true incidence of melasma is unknown, melasma has been reported to affect 1% to 50% of the population globally. Melasma is more prevalent in female patients of Asian, Latin American, Middle Eastern, and African descent due to multifactorial causes including increased skin pigmentation, alterations in hormone levels, family history, and sun exposure. Melasma has a tremendous societal and psychosocial impact as patients with melasma report dramatically lower self-esteem, depression, and social isolation.

Therapy for melasma remains a clinical challenge and topical agents are the mainstay. First-line topical treatment options for melasma are hydroquinone (HQ) and triple combination (TC) therapies, which include HQ, a retinoid, and a steroid. Second-line treatments include chemical peels and laser therapies. There have been concerns about the long-term safety and efficacy of HQ. Topical HQ is associated with ochronosis, a bluish-gray discoloration of the skin. In response, HQ has been banned in the European Union as a cosmetic additive, but is available as a prescription medication. Recently, there has been tremendous scientific and general public interest in novel, safe, and effective topical agents to improve melasma. To determine the safety and efficacy of newer topical agents for melasma, we performed a systematic review of randomized controlled trials (RCTs) on topical agents for the treatment of melasma and provided evidence-based recommendations for clinical use and further research.

METHODS

According to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) protocol, we performed a systematic search for novel and currently used topical treatments for melasma on March 4th, 2019 (Figure 1). Included articles were RCTs using topical treatments for melasma published within the
last 15 years (since January 1st, 2003) as this period was considered clinically relevant. Clinical recommendations were based on the American College of Physicians (ACP) guidelines. We excluded studies using proprietary or undescribed active ingredients (as these studies and outcomes would not be verifiable or reproducible by third parties, if desired) and those evaluating non-topical agents (ie, oral medications, bleaching agents, chemical peels, intralesionally administered drugs, laser, and light-based therapies) as stand-alone or combination approaches. Patients were allowed to apply daily sunscreen in the included studies. Non-randomized original reports, literature reviews, conference abstracts, oral presentations, basic science investigations, animal studies, and non-English articles were excluded. We examined the bibliographies of included published original reports and literature reviews to ensure that relevant articles were included in the systematic search.

RESULTS

Our systematic search identified 9,413 articles. After screening titles, abstracts, and full text articles, we identified 35 original RCTs using azelaic acid (2), cysteamine (2), epidermal growth factor (EGF) (1), liposomal hydroquinone (1), lignin peroxidase (1), mulberry extract (1), niacinamide (1), *Rumex occidentalis* (1), tranexamic acid (TXA) (5), TC therapy (5), 4-n-butylresorcinol (3), glycolic acid (2), kojic acid (2), aloe vera (1), ascorbic acid (1), dioic acid (1), ellagic acid and arbutin (1), flutamide (1), parsley (1), or zinc sulfate (2) for melasma. Table 1 provides a detailed summary of the identified studies and highlights study designs, treatment parameters, results, and adverse events (AEs).

![Figure 1. PRISMA Systematic search strategy. We performed a systematic search on March 4th, 2019, according to PRISMA guidelines.](image)

<table>
<thead>
<tr>
<th>Table 1. Summary of Topical Treatments for Melasma</th>
</tr>
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<tbody>
<tr>
<td><strong>Author</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Farshi[11]</td>
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<td></td>
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<td>Mazurek[12]</td>
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### TABLE 1. CONTINUED

**Summary of Topical Treatments for Melasma**

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<th>Author</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Skin Type (Location)</th>
<th>Follow-up</th>
<th>Primary Outcome Measures</th>
<th>Other Outcome Measures</th>
<th>Regimen</th>
<th>Treatment</th>
<th>Baseline</th>
<th>Results</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythema, dryness, itching, burning sensation, and irritation</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Mansouri14</td>
<td>DB, PC</td>
<td>50</td>
<td>III and IV (Iran)</td>
<td>16 weeks</td>
<td>Colorimetry using Mexameter (relative melanin value)</td>
<td>MASI, IGA</td>
<td>Once daily for 16 weeks</td>
<td>5% cysteamine</td>
<td>75.2 ± 37</td>
<td>26.2 ± 16*</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>68.9 ± 31</td>
<td>60.7 ± 27.3</td>
<td>None</td>
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</tr>
<tr>
<td>Farshi15</td>
<td>DB, PC</td>
<td>40</td>
<td>III and IV (Iran)</td>
<td>16 weeks</td>
<td>Colorimetry using Dermacatch (difference between pigmented and normal skin)</td>
<td>MASI, IGA</td>
<td>Once daily for 16 weeks</td>
<td>5% cysteamine</td>
<td>72.3 ± 27.8</td>
<td>23.8 ± 12.9*</td>
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<td>Placebo</td>
<td>52.9 ± 16.4</td>
<td>50 ± 18</td>
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</table>

**Epidermal growth factor**

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<th>Author</th>
<th>Design</th>
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<th>Skin Type (Location)</th>
<th>Follow-up</th>
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<th>Other Outcome Measures</th>
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<th>Treatment</th>
<th>Baseline</th>
<th>Results</th>
<th>Side Effects</th>
</tr>
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<tbody>
<tr>
<td>Lyons17</td>
<td>DB, PC, SF</td>
<td>15</td>
<td>Not reported (California, USA)</td>
<td>8 weeks</td>
<td>Physician GAIS MelasQoL, PSA</td>
<td>Twice daily for 8 weeks</td>
<td>EGF</td>
<td>--</td>
<td>Improvement in 73.4% of patients</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>--</td>
<td>Improvement in 13% of patients</td>
<td>None</td>
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</table>

**Benefits outweigh risks and burden**

**Hydroquinone (Liposome-encapsulated)**

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Skin Type (Location)</th>
<th>Follow-up</th>
<th>Primary Outcome Measures</th>
<th>Other Outcome Measures</th>
<th>Regimen</th>
<th>Treatment</th>
<th>Baseline</th>
<th>Results</th>
<th>Side Effects</th>
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</thead>
<tbody>
<tr>
<td>Taghavi13</td>
<td>DB, SF</td>
<td>20</td>
<td>III and IV (Iran)</td>
<td>16 weeks</td>
<td>MASI</td>
<td>None</td>
<td>Once daily for 12 weeks</td>
<td>4% HQ</td>
<td>10.73 ± 4.7</td>
<td>6.07 ± 3.8</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>4% liposomal HQ</td>
<td>10.73 ± 4.7</td>
<td>6.25 ± 4.0*</td>
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**Lignin Peroxidase**

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<tr>
<th>Author</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Skin Type (Location)</th>
<th>Follow-up</th>
<th>Primary Outcome Measures</th>
<th>Other Outcome Measures</th>
<th>Regimen</th>
<th>Treatment</th>
<th>Baseline</th>
<th>Results</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>Draelos19</td>
<td>SF, SB</td>
<td>30</td>
<td>I-IV (North Carolina, USA)</td>
<td>12 weeks</td>
<td>MASI</td>
<td>Colo-rimetry, dermatospectrophotometer, IGA, PSA</td>
<td>Twice daily for 12 weeks</td>
<td>Lignin peroxidase</td>
<td>Not reported</td>
<td>No difference between groups</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4% HQ</td>
<td>Not reported</td>
<td>--</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Draelos19</td>
<td>SF, SB</td>
<td>30</td>
<td>I-IV (North Carolina, USA)</td>
<td>12 weeks</td>
<td>MASI</td>
<td>Colo-rimetry, dermatospectrophotometer, IGA, PSA</td>
<td>Twice daily for 12 weeks</td>
<td>Lignin peroxidase</td>
<td>Not reported</td>
<td>Significant improvement*</td>
<td>None</td>
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<td></td>
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<td></td>
<td></td>
<td>No treatment</td>
<td>Not reported</td>
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**Mulberry extract**

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<th>Author</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Skin Type (Location)</th>
<th>Follow-up</th>
<th>Primary Outcome Measures</th>
<th>Other Outcome Measures</th>
<th>Regimen</th>
<th>Treatment</th>
<th>Baseline</th>
<th>Results</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvin20</td>
<td>SB, PC</td>
<td>50</td>
<td>III-V (Philippines)</td>
<td>8 weeks</td>
<td>MASI</td>
<td>Colo-rimetry, MelasQoL</td>
<td>Twice daily for 8 weeks</td>
<td>75% mulberry extract oil</td>
<td>4.076 ± 0.24*</td>
<td>2.884 ± 0.25*</td>
<td>Mild itching</td>
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<td></td>
<td></td>
<td>Placebo</td>
<td>3.484 ± 0.52</td>
<td>3.392 ± 0.53</td>
<td>Mild pruritus and erythema</td>
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### TABLE 1. CONTINUED

**Summary of Topical Treatments for Melasma**

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>No. of Patients†</th>
<th>Skin Type (Location)</th>
<th>Follow-up</th>
<th>Primary Outcome</th>
<th>Other Outcome Measures</th>
<th>Regimen</th>
<th>Treatment</th>
<th>Baseline†</th>
<th>Results†</th>
<th>Side Effects</th>
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</thead>
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<tr>
<td>Niacinamide</td>
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<tr>
<td>Navarrete-Solis22</td>
<td>DB, SF</td>
<td>27</td>
<td>III-V (Mexico)</td>
<td>8 weeks</td>
<td>MASI</td>
<td>Chromometer, IGA, infrared thermography, histological sections</td>
<td>Every 3 hours during daytime for 8 weeks</td>
<td>4% niacinamide</td>
<td>3.7 (95% CI: 2.9–4.4)</td>
<td>1.4 (95% CI: 3.3–4.7)†</td>
<td>Erythema, pruritus, and burning</td>
</tr>
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<td></td>
<td></td>
<td>4% HQ</td>
<td>4 (95% CI: 90.9–1.8)</td>
<td>1.2 (95% CI: 0.8–1.6)†</td>
<td>Erythema, pruritus, and burning</td>
</tr>
<tr>
<td>Rumex occidentalis (Western Dock)</td>
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<tr>
<td>Mendoza23</td>
<td>DB, SF</td>
<td>45</td>
<td>Not reported (Philippines)</td>
<td>8 weeks</td>
<td>MASI</td>
<td>Colorimetry, IGA, PSA</td>
<td>Twice daily for 8 weeks</td>
<td>3% <em>R. occidentalis</em> cream</td>
<td>Not reported</td>
<td>0.60 ± 0.86 decrease†</td>
<td>Mild peeling</td>
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<td></td>
<td></td>
<td>4% HQ</td>
<td>Not reported</td>
<td>0.55 ± 0.60 decrease†</td>
<td>None</td>
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<td>Placebo</td>
<td>Not reported</td>
<td>0.09 ± 0.12 decrease</td>
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</tr>
<tr>
<td>Tranexamic acid</td>
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</tr>
<tr>
<td>Atefi26</td>
<td>DB</td>
<td>60</td>
<td>Not reported (Iran)</td>
<td>12 weeks</td>
<td>MASI</td>
<td>Patient satisfaction</td>
<td>Twice daily for 12 weeks</td>
<td>5% TXA</td>
<td>4.80 ± 1.06</td>
<td>2.33 ± 0.71†</td>
<td>None</td>
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<td></td>
<td></td>
<td>2% HQ</td>
<td>4.37 ± 0.93</td>
<td>2.30 ± 0.65†</td>
<td>Erythema and skin irritation</td>
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<td></td>
<td></td>
<td>5% liposomal TXA</td>
<td>14.72 ± 2.2</td>
<td>6.78 ± 2.9†</td>
<td>None</td>
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<td></td>
<td></td>
<td></td>
<td>4% HQ</td>
<td>14.60 ± 2.3</td>
<td>7.60 ± 2.2†</td>
<td>Skin irritation</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>3% TXA</td>
<td>31.68 ± 10.32</td>
<td>10.76 ± 9.43†</td>
<td>Erythema, skin irritation, xerosis, and scaling</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>3% HQ and 0.01% dexamethasone</td>
<td>29.52 ± 11.7</td>
<td>10.48 ± 7.84†</td>
<td>Erythema, skin irritation, dryness of the skin, scaling, hypertrichosis, and inflammation</td>
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<td></td>
<td>3% TXA</td>
<td>Not reported</td>
<td>--</td>
<td>Minor skin irritation</td>
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<td></td>
<td>Vehicle</td>
<td>Not reported</td>
<td>--</td>
<td>Minor skin irritation</td>
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<tr>
<td>Kanechorn Na Ayuthaya25</td>
<td>DB, SF</td>
<td>21</td>
<td>Not reported (Thailand)</td>
<td>12 weeks</td>
<td>MASI</td>
<td>Colorimetry, IGA, PSA</td>
<td>Twice daily for 12 weeks</td>
<td>5% TXA</td>
<td>Not reported</td>
<td>--</td>
<td>Minor skin irritation</td>
</tr>
</tbody>
</table>

* † Baseline and results are reported as mean ± standard deviation unless otherwise noted.
* ‡ Side effects are noted as observed in the study.
* † Results are presented as mean ± standard error of the mean.
### TABLE 1. CONTINUED
Summary of Topical Treatments for Melasma

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Skin Type (Location)</th>
<th>Follow-up</th>
<th>Primary Outcome</th>
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<th>Results</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>Viyoch24</td>
<td>DB, VC</td>
<td>60</td>
<td>IV (Thailand)</td>
<td>8 weeks</td>
<td>Colorimetry using Mexameter® (relative melanin value)</td>
<td>MASI, moisture content, pH, erythema</td>
<td>Twice daily for 8 weeks</td>
<td>6.5% TXA</td>
<td>80.6 ± 19.7</td>
<td>59.4 ± 17.4</td>
<td>Erythema, scaling, burning and/or stinging</td>
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<td>Vehicle</td>
<td>74.4 ± 17.3</td>
<td>75.4 ± 16.3</td>
<td>Erythema, edema, burning and/or stinging</td>
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<tr>
<td>Triple Combination</td>
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<tr>
<td>Ferreira Cestari32</td>
<td>OL</td>
<td>119</td>
<td>II-V (Brazil)</td>
<td>8 weeks</td>
<td>Proportion of patients with complete clearance</td>
<td>IGA, PSA, tolerability</td>
<td>Twice daily for 8 weeks</td>
<td>4% HQ, 0.05% RA, and 0.01% FA</td>
<td>--</td>
<td>35%*</td>
<td>Erythema, burning sensation, desquamation, telangiectasia, and headache</td>
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<tr>
<td>Chan33</td>
<td>SB</td>
<td>242</td>
<td>II-V (East and Southeast Asia)</td>
<td>8 weeks</td>
<td>Global Severity Score (GSS) at 8 weeks</td>
<td>GSS at 4 weeks, MASI, IGA, PSA, patient satisfaction</td>
<td>Once daily for 8 weeks</td>
<td>4% HQ, 0.05% RA, and 0.01% FA</td>
<td>100% of patients with GSS of moderate or severe</td>
<td>64.2% of patients with GSS of none or mild*</td>
<td>Erythema, irritation, exfoliation, and discomfort</td>
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<tr>
<td>Taylor34</td>
<td>SB</td>
<td>6411</td>
<td>I-IV (Multi-center, USA)</td>
<td>8 weeks</td>
<td>Proportion of patients with complete clearance</td>
<td>Proportion of patients with complete or near-complete clearance</td>
<td>Once daily for 8 weeks</td>
<td>0.05% RA and 4% HQ</td>
<td>--</td>
<td>9.5%</td>
<td>Erythema, desquamation, burning, dryness, and pruritus</td>
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<td></td>
<td>0.05% RA and 0.01% FA</td>
<td>--</td>
<td>1.9%</td>
<td>Erythema, desquamation, burning, dryness, and pruritus</td>
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<td></td>
<td>4% hydroquinone and 0.01% FA</td>
<td>--</td>
<td>2.5%</td>
<td>Erythema, desquamation, burning, dryness, atrophy and pruritus</td>
</tr>
<tr>
<td>Author</td>
<td>Design</td>
<td>No. of Patients(^{a})</td>
<td>Skin Type (Location)</td>
<td>Follow-up</td>
<td>Primary Outcome</td>
<td>Other Outcome Measures</td>
<td>Regimen</td>
<td>Treatment</td>
<td>Baseline(^{b})</td>
<td>Results(^{b})</td>
<td>Side Effects</td>
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<td>Gong(^{20})</td>
<td>DB, PC</td>
<td>211</td>
<td>Not reported (China)</td>
<td>8 weeks</td>
<td>Decreased Index of Total Target Score (DITTS)(^{c})</td>
<td>Once daily for 8 weeks</td>
<td>4% HQ, 0.05% RA, and 0.01% FA</td>
<td>--</td>
<td>0.48 ± 0.21(^{d})</td>
<td>Erythema, stabbing pain, peeling, telangiectasia, burning, dry skin, itching, sensation of thin skin, and redness/swelling</td>
<td></td>
</tr>
<tr>
<td>Astaneh(^{21})</td>
<td>DB</td>
<td>32</td>
<td>III-V (Iran)</td>
<td>12 weeks</td>
<td>Investigator’s subjective assessment</td>
<td>Once daily for 12 weeks</td>
<td>4% HQ</td>
<td>Placebo</td>
<td>--</td>
<td>0.10 ± 0.14</td>
<td>Burns, dry skin, tautening, and itching</td>
</tr>
<tr>
<td>Huh(^{38})</td>
<td>DB, SF, VC</td>
<td>20</td>
<td>III-V (South Korea)</td>
<td>8 weeks</td>
<td>Colorimetry using Mexameter(^{e})</td>
<td>Twice daily for 8 weeks</td>
<td>0.1% 4-n-butyresorcinol</td>
<td>206.85 ± 31.60</td>
<td>196.20 ± 28.42(^{e})</td>
<td>Mild erythema and itching</td>
<td></td>
</tr>
<tr>
<td>Huh(^{39})</td>
<td>DB, SF, VC</td>
<td>23</td>
<td>Not reported (South Korea)</td>
<td>8 weeks</td>
<td>Colorimetry using Mexameter(^{e})</td>
<td>Twice daily for 8 weeks</td>
<td>0.1% liposome-encapsulated 4-n-butyresorcinol</td>
<td>200.68 ± 38.24</td>
<td>185.42 ± 38.81(^{f})</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Khemis(^{40})</td>
<td>DB, SF, VC</td>
<td>30</td>
<td>III-V (France)</td>
<td>12 weeks</td>
<td>Clinical pigmentation score</td>
<td>Twice daily for 12 weeks</td>
<td>0.3% 4-n-butyresorcinol</td>
<td>7.5 ± 1.9</td>
<td>6.2 ± 2.3(^{f})</td>
<td>Mild stinging, burning, pruritus, erythema, dryness, peeling and desquamation</td>
<td></td>
</tr>
</tbody>
</table>

### 4-n-butyresorcinol

**| Huh\(^{38}\) | DB, SF, VC | 20 | III-V (South Korea) | 8 weeks | Colorimetry using Mexameter\(^{e}\) | None | Twice daily for 8 weeks | 0.1% 4-n-butyresorcinol | 206.85 ± 31.60 | 196.20 ± 28.42\(^{e}\) | Mild erythema and itching |

**| Huh\(^{39}\) | DB, SF, VC | 23 | Not reported (South Korea) | 8 weeks | Colorimetry using Mexameter\(^{e}\) | PSA | Twice daily for 8 weeks | 0.1% liposome-encapsulated 4-n-butyresorcinol | 200.68 ± 38.24 | 185.42 ± 38.81\(^{f}\) | None |

**| Huh\(^{39}\) | DB, SF, VC | 23 | Not reported (South Korea) | 8 weeks | Colorimetry using Mexameter\(^{e}\) | PSA | Twice daily for 8 weeks | 0.1% liposome-encapsulated 4-n-butyresorcinol | 200.68 ± 38.24 | 185.42 ± 38.81\(^{f}\) | None |

**| Huh\(^{39}\) | DB, SF, VC | 23 | Not reported (South Korea) | 8 weeks | Colorimetry using Mexameter\(^{e}\) | PSA | Twice daily for 8 weeks | 0.1% liposome-encapsulated 4-n-butyresorcinol | 200.68 ± 38.24 | 185.42 ± 38.81\(^{f}\) | None |

### 4-n-butyresorcinol

**| Huh\(^{38}\) | DB, SF, VC | 20 | III-V (South Korea) | 8 weeks | Colorimetry using Mexameter\(^{e}\) | None | Twice daily for 8 weeks | 0.1% 4-n-butyresorcinol | 206.85 ± 31.60 | 196.20 ± 28.42\(^{e}\) | Mild erythema and itching |

---

\(^{a}\) Number of patients

\(^{b}\) Baseline and results are reported as mean ± standard deviation

\(^{c}\) Decreased Index of Total Target Score (DITTS)

\(^{d}\) Significant difference (p < 0.05)

\(^{e}\) Mexameter

\(^{f}\) Statistical analysis not provided
### TABLE 1. CONTINUED

#### Summary of Topical Treatments for Melasma

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>No. of Patients†</th>
<th>Skin Type (Location)</th>
<th>Follow-up</th>
<th>Primary Outcome Measures</th>
<th>Other Outcome Measures</th>
<th>Regimen</th>
<th>Treatment</th>
<th>Baseline‡</th>
<th>Results‡</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycolic acid</strong></td>
<td></td>
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<tr>
<td>Guevara[^43]</td>
<td>VC, DB</td>
<td>35</td>
<td>III-V (Texas, USA)</td>
<td>12 weeks</td>
<td>MASI and colorimetry using Mexameter[^4]</td>
<td>IGA, PSA</td>
<td>Twice daily for 12 weeks</td>
<td>4% HQ, 10% buffered glycolic acid, vitamins C and E, and sunscreen</td>
<td>Not reported</td>
<td>Significant improvement in MASI and Mexameter score from baseline and between groups</td>
<td>Burning, itching, dryness, peeling, edema, and scaling</td>
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<td></td>
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<td></td>
<td>Vehicle (sunscreen only)</td>
<td>Not reported</td>
<td>–</td>
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</tr>
<tr>
<td>Ibrahim[^44]</td>
<td>SB, PC</td>
<td>100</td>
<td>Not reported (Egypt)</td>
<td>12 weeks</td>
<td>mMASI</td>
<td>IGA, PSA, digital image analysis, dermoscopy</td>
<td>Once daily for 12 weeks</td>
<td>4% HQ</td>
<td>4% HQ and 10% glycolic acid</td>
<td>10.030 ± 2.456</td>
<td>6.060 ± 4.550*</td>
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<td></td>
<td>4% HQ and 0.01% hyaluronic acid</td>
<td>11.600 ± 4.447</td>
<td>4.080 ± 3.041*</td>
<td>Pruritus</td>
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<td></td>
<td></td>
<td>4% HQ, 0.01% hyaluronic, and 10% glycolic acid</td>
<td>12.570 ± 5.522</td>
<td>3.430 ± 3.336*</td>
<td>Pruritus, erythema, scaling, and crusting</td>
</tr>
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<td></td>
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<td></td>
<td>Placebo</td>
<td>10.540 ± 2.699</td>
<td>10.540 ± 2.699</td>
<td>None</td>
</tr>
</tbody>
</table>

**Kojic acid**

| Deo[^45]        | SB     | 80               | IV and V (India)     | 12 weeks  | MASI                     | IGA, PSA, therapeutic response according to ∆MASI | Once daily for 12 weeks | 1% kojic acid | 9.145 ± 7.69 | 3.57 ± 3.04* | Burning |
|                 |        |                  |                      |           |                          |                        |         | 1% kojic acid and 2% HQ | 8.38 ± 4.92 | 2.09 ± 1.62* | Burning |
|                 |        |                  |                      |           |                          |                        |         | 1% kojic acid and 0.1% betamethasone valerate | 11.02 ± 7.33 | 7.58 ± 6.493 | None             |
|                 |        |                  |                      |           |                          |                        |         | 1% kojic acid, 2% HQ, and 0.1% betamethasone valerate | 15.61 ± 9.03 | 7.115 ± 7.03* | Acneiform eruptions |

Benefits closely balanced with risks
### TABLE 1. CONTINUED

#### Summary of Topical Treatments for Melasma

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>No. of Patients*</th>
<th>Skin Type (Location)</th>
<th>Follow-up</th>
<th>Primary Outcome</th>
<th>Other Outcome Measures</th>
<th>Regimen</th>
<th>Treatment</th>
<th>Baseline$^{\dagger}$</th>
<th>Results$^{\dagger}$</th>
<th>Side Effects</th>
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</thead>
<tbody>
<tr>
<td>Monteiro$^{46}$</td>
<td>--</td>
<td>60</td>
<td>Not reported (India)</td>
<td>12 weeks</td>
<td>MASI</td>
<td>None</td>
<td>Twice daily for 12 weeks</td>
<td>0.75% kojic acid cream and 2.5% vitamin C</td>
<td>11.177 ± 6.4817</td>
<td>8.773 ± 5.6743$^{*}$</td>
<td>Erythema and mild burning</td>
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<td></td>
<td></td>
<td>4% HQ</td>
<td>15.613 ± 9.6626</td>
<td>4.334 ± 3.5709$^{**}$</td>
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<tr>
<td>Khosra-van$^{47}$</td>
<td>DB</td>
<td>54</td>
<td>Not reported (Iran)</td>
<td>8 weeks</td>
<td>MASI</td>
<td>None</td>
<td>Once daily for 8 weeks</td>
<td>Parsley (brewed 2.5 g in 125 ml of water) every week</td>
<td>6.66 ± 4.39</td>
<td>4.92 ± 3.07$^{*}$</td>
<td>Redness and itching</td>
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<td></td>
<td>4% HQ</td>
<td>6.68 ± 3.24</td>
<td>5.06 ± 2.66$^{*}$</td>
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<td></td>
<td>Zinc Sulfate</td>
<td>5.7 ± 3.2</td>
<td>5.1 ± 2.9$^{*}$</td>
<td>Not reported</td>
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<td></td>
<td>4% HQ</td>
<td>6.4 ± 3.4</td>
<td>3.3 ± 2.4$^{*}$</td>
<td>Not reported</td>
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<tr>
<td>Iraji$^{48}$</td>
<td>SB</td>
<td>55</td>
<td>Not reported (Iran)</td>
<td>6 months</td>
<td>MASI</td>
<td>PSA</td>
<td>Twice daily for 6 months</td>
<td>10% zinc sulfate solution</td>
<td>5.1 ± 2.0$^{*}$</td>
<td>5.1 ± 2.0$^{*}$</td>
<td>Mild post-inflammatory hyperpigmentation, irritation</td>
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<td></td>
<td>4% HQ</td>
<td>6.3 ± 2.1</td>
<td>3.9 ± 1.4$^{*}$</td>
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<tr>
<td>Yousefi$^{49}$</td>
<td>DB</td>
<td>82</td>
<td>Not reported (Iran)</td>
<td>5 months</td>
<td>MASI</td>
<td>None</td>
<td>Once daily for 2 months</td>
<td>10% zinc sulfate</td>
<td>6.4 ± 1.6</td>
<td>3.9 ± 1.4$^{*}$</td>
<td>Irritation</td>
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<td></td>
<td>4% HQ</td>
<td>6.4 ± 1.6</td>
<td>3.9 ± 1.4$^{*}$</td>
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<tr>
<td>Espinal-Perez$^{51}$</td>
<td>DB</td>
<td>180</td>
<td>IV and V (Mexico)</td>
<td>16 weeks</td>
<td>PSA and colorimetry using DermaSpect$^6$</td>
<td>Digital photograph and regular color slides</td>
<td>Once daily for 16 weeks</td>
<td>5% L-ascorbic acid</td>
<td>15.5 ± 2.4</td>
<td>13.9 ± 2.7</td>
<td>None</td>
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<td>4% HQ</td>
<td>15.0 ± 1.8</td>
<td>10.2 ± 2.0$^{*}$</td>
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<td></td>
<td>Ascorbic Acid</td>
<td>5% L-ascorbic acid</td>
<td>--</td>
<td>Significant subjective improvement on HQ side, no significant difference in colorimetric measures</td>
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<td></td>
<td>4% HQ</td>
<td>--</td>
<td>Irritation</td>
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### TABLE 1. CONTINUED

**Summary of Topical Treatments for Melasma**

<table>
<thead>
<tr>
<th>Author Design</th>
<th>No. of Patients (Location)</th>
<th>Follow-up</th>
<th>Primary Outcome</th>
<th>Other Outcome Measures</th>
<th>Regimen</th>
<th>Treatment</th>
<th>Baseline †</th>
<th>Results ‡</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td><strong>Dioic Acid</strong></td>
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<tr>
<td>Tirado-Sanchez52</td>
<td>OL 96 (Mexico)</td>
<td>12 weeks</td>
<td>MASI</td>
<td>None</td>
<td>Twice daily for 12 weeks</td>
<td>1% dioic acid</td>
<td>14.52 ± 3.4</td>
<td>6.05 ± 1.2*</td>
<td>Erythema, burning, pruritus, and acneiform reaction</td>
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<td></td>
<td></td>
<td>2% HQ</td>
<td>15.22 ± 2.4</td>
<td>6.34 ± 1.3*</td>
<td>Erythema, burning, pruritus, and acneiform reaction</td>
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<td><strong>Ellagic acid and Arbutin</strong></td>
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<tr>
<td>Ertam53</td>
<td>OL 29 (Turkey)</td>
<td>6 months</td>
<td>Colorimetry</td>
<td>None</td>
<td>Twice daily for 6 months</td>
<td>1% arbutin --</td>
<td>Z = -2.803*</td>
<td>None</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>using Mexameter*</td>
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<td>1% synthetic ellagic acid</td>
<td>--</td>
<td>Z = -2.075*</td>
<td>None</td>
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<td>1% natural ellagic acid (plant extract)</td>
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<td>Z = -2.803'</td>
<td>None</td>
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<td><strong>Flutamide</strong></td>
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<td>Adalat-khah54</td>
<td>DB 73 (Iran)</td>
<td>4 months</td>
<td>MASI and</td>
<td>Patient satisfaction</td>
<td>Once daily for 4 months</td>
<td>1% flutamide --</td>
<td>Significant improvement in MASI from baseline for both groups with superior efficacy for flutamide group; no significant difference in colorimetric measures between groups</td>
<td>Not reported</td>
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<td></td>
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<td></td>
<td>colorimetry</td>
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<td>using Mexameter*</td>
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</tr>
</tbody>
</table>

DB: double-blind, DITTS: Decreased Index of Total Target Score, EGF: epidermal growth factor, FA: fluocinolone acetonide, GAIS: Global Aesthetic Improvement Scale, GSS: Global Severity Score, HQ: hydroquinone, IGA: Investigator’s Global Assessment, MASI: Melasma Area and Severity Index, mMASI: Modified Melasma Area and Severity Index, MelasQoL: Melasma Quality of Life scale, OL: open label, PC: placebo-controlled, PSA: Patient’s Self-Assessment, RA: retinoic acid, SB: single-blind, SF: split-face, TXA: tranexamic acid, VC: vehicle-controlled. Asterisks (*) denotes significant improvement from baseline. Hash sign (#) denotes significant improvement compared to other treatment groups. †Sample size is based on per-protocol population (i.e., all patients who completed assigned treatment) unless otherwise specified. ‡Baseline values and results are based on primary outcome measure(s). *Sample size is based on intent-to-treat population (i.e., all patients who were randomized). ‡DITTS > 0.3 indicates improvement.
<table>
<thead>
<tr>
<th>Medication (# of RCTs)</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
<th>Comparison to HQ</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits outweigh risks and burden</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelaic acid (2)</td>
<td>Weak</td>
<td>Moderate</td>
<td>More effective in open-label RCT</td>
<td>Poorly designed RCTs. Reportedly to have anti-cancer effects. May lead to diffuse skin brightening. No long-term adverse event. May have unpleasant smell.</td>
</tr>
<tr>
<td>Cysteamine (2)</td>
<td>Strong</td>
<td>Moderate</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Epidermal growth factor (1)</td>
<td>Weak</td>
<td>Moderate</td>
<td>None</td>
<td>Small sample size.</td>
</tr>
<tr>
<td>Hydroquinone (liposomal-delivered) (1)</td>
<td>Weak</td>
<td>Moderate</td>
<td>Similar</td>
<td>Theoretical enhanced skin penetration.</td>
</tr>
<tr>
<td>Lignin Peroxidase (1)</td>
<td>Weak</td>
<td>Moderate</td>
<td>Similar efficacy and safety profile.</td>
<td>Small sample size.</td>
</tr>
<tr>
<td>Mulberry extract (1)</td>
<td>Weak</td>
<td>Moderate</td>
<td>None</td>
<td>Mild adverse event profile.</td>
</tr>
<tr>
<td>Niacinamide (1)</td>
<td>Weak</td>
<td>Moderate</td>
<td>Similar efficacy with milder adverse events.</td>
<td>Evaluated in one poorly powered study.</td>
</tr>
<tr>
<td>Rumex Occidentalis (1)</td>
<td>Weak</td>
<td>Moderate</td>
<td>None</td>
<td>Mild adverse event profile.</td>
</tr>
<tr>
<td>Tranexamic acid (5)</td>
<td>Strong</td>
<td>High</td>
<td>Similar efficacy with fewer adverse events.</td>
<td>Theoretical risk for thrombosis.</td>
</tr>
<tr>
<td>Triple Combination (5)</td>
<td>Strong</td>
<td>High</td>
<td>Better efficacy with similar adverse event profile.</td>
<td>Risk of ochronosis and theoretical risk for carcinogenesis.</td>
</tr>
<tr>
<td>4-n-butyresorcinol (3)</td>
<td>Weak</td>
<td>High</td>
<td>None</td>
<td>Mild adverse events.</td>
</tr>
<tr>
<td><strong>Benefits closely balanced with risks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycolic acid (2)</td>
<td>Weak</td>
<td>Moderate</td>
<td>Only evaluated in combination with 4% HQ.</td>
<td>Increased risk of skin desquamation.</td>
</tr>
<tr>
<td>Kojic acid (2)</td>
<td>Weak</td>
<td>Moderate</td>
<td>Less effective as stand-alone.</td>
<td>May be combined with 4% HQ for increased efficacy.</td>
</tr>
<tr>
<td><strong>Risks and burden outweigh benefits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parsley (1)</td>
<td>Weak</td>
<td>Moderate</td>
<td>Similar efficacy and adverse events</td>
<td>Formulation needs to be prepared by subjects, which increases burden of treatment.</td>
</tr>
<tr>
<td>Zinc sulfate (2)</td>
<td>Strong</td>
<td>High</td>
<td>Less effective</td>
<td>Risk for PIH.</td>
</tr>
<tr>
<td><strong>Insufficient evidence to determine net benefit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aloe vera (1)</td>
<td>n/a</td>
<td>Moderate</td>
<td>None</td>
<td>No placebo or HQ comparison group. Used safely in pregnant patients.</td>
</tr>
<tr>
<td>Ascorbic Acid (1)</td>
<td>n/a</td>
<td>Moderate</td>
<td>Similar or worse efficacy</td>
<td>Ascorbic acid readily degrades and needs to be combined with other agents.</td>
</tr>
<tr>
<td>Dioic Acid (1)</td>
<td>n/a</td>
<td>Moderate</td>
<td>Similar efficacy</td>
<td>Acneiform reaction from oily vehicle.</td>
</tr>
<tr>
<td>Ellagic acid and arbutin (1)</td>
<td>n/a</td>
<td>Moderate</td>
<td>None</td>
<td>No placebo or HQ comparison group.</td>
</tr>
<tr>
<td>Flutamide (1)</td>
<td>n/a</td>
<td>Moderate</td>
<td>Similar efficacy</td>
<td>Adverse event profile was not provided. Risk of hormonal therapy not evaluated.</td>
</tr>
</tbody>
</table>
TABLE 3. 
Mechanism of Action of Topical Agents

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosinase inhibitor</td>
<td>Hydroquinone, Cysteamine, Kojic acid, Arbutin, Azelaic acid, Ascorbic acid, Ellagic acid, Aloe vera, Rumex occidentalis, 4-n-butylresorcinol, Glycolic acid, EGF</td>
</tr>
<tr>
<td>Dopa oxidase inhibitor</td>
<td>Mulberry extract</td>
</tr>
<tr>
<td>Peroxidase substrates / inhibitors</td>
<td>Hydroquinone, Cysteamine</td>
</tr>
<tr>
<td>Increasing intracellular glutathione</td>
<td>Cysteamine</td>
</tr>
<tr>
<td>Nuclear PPAR receptor agonist</td>
<td>Dioic acid</td>
</tr>
<tr>
<td>Block plasmin pathway</td>
<td>Tranexamic acid</td>
</tr>
<tr>
<td>Prevent Melanosome transfer</td>
<td>Niacinamide, Tretinoin, Dioic acid</td>
</tr>
<tr>
<td>Anti-hormonal</td>
<td>Flutamide</td>
</tr>
<tr>
<td>Increase keratinocyte turnover</td>
<td>Tretinoin, Glycolic acid</td>
</tr>
<tr>
<td>Cytotoxic</td>
<td>Hydroquinone, Azelaic acid</td>
</tr>
<tr>
<td>Unknown</td>
<td>Zinc sulfate, Paralev, Lignin peroxidase</td>
</tr>
</tbody>
</table>

DISCUSSION

Herein, we provided evidence-based recommendations on the safety and efficacy of topical medications for melasma (Table 2). The topical agents are presented below in alphabetical order in categories according to their risk and benefit to patients with melasma. According to ACP guidelines, a strong recommendation may apply to most patients without reservations, whereas a weak recommendation differs according to an individual patient's circumstances. As only RCTs were reviewed, all recommendations were supported by moderate-quality (ie, one or more poorly designed RCT) or high quality of evidence (ie, one or more well designed RCT).

Multiple RCTs used 4% topical HQ as an active ingredient in combination therapies or comparison arms, but most of the literature on 4% HQ as a therapeutic modality was published before 2003. Cysteamine, TC, and TXA received the strongest recommendation of benefit. These medications had greater ef-ficacy and/or milder AE profiles compared with topical HQ. A full description of topical treatments is provided below, and the mechanisms of action are provided in Table 3.

Benefits Outweigh Risks and Burden

**Azelaic acid – weak recommendation**

Two poorly designed RCTs examined the efficacy of azelaic acid. In an open-label study, 29 patients received twice daily 20% azelaic acid or 4% HQ for 8 weeks. 20% azelaic acid was more effective than 4% HQ according to the Melasma Area and Severity Index (MASI) score, but there is a significant bias in this study due to the open-label design. The clinical photographs demonstrated good clinical responses for both treatment arms.

In another open-label RCT, patients received azelaic acid of various concentrations (5%, 10% and 20%) with 3 different supplemental formulations. All 3 azelaic acid formulations improved colorimetric scores after 6 months of twice daily application. The most effective formulation contained 20% azelaic acid with 10% mandelic acid, 5% phytic acid, 5% 4-n-butyl resorcinol, and 2% ferulic acid (Sesderma, Valencia, Spain). No AE profile was provided. Azelaic acid received a weak recommendation due to the poor study design of the included articles. Both studies had an open-label study design and one study compared combination formulations without comparing individual ingredients. The 2 identified studies use different concentrations of azelaic acid (range 5% to 20%), which also confounds results.

**Cysteamine – strong recommendation**

Cysteamine is approved by the U.S. Food and Drug Administration for the treatment of cystinosis and has been shown to inhibit melanogenesis at high concentrations. In 2 well-designed double-blind RCTs, 50 and 40 patients with melasma were treated with 5% cysteamine (Cysteamine®, Scientis Pharma SA, Geneva, Switzerland) or placebo daily for 4 months. In both studies, cysteamine significantly reduced MASI scores compared with placebo. In the second study, significant colorimetric differences were found favoring topical cysteamine compared with the placebo at 2 months and 4 months, and the Investigator’s Global Assessment (IGA) and patient feedback indicated positive efficacy of cysteamine. Patients reported erythema, dryness, itching, burning sensation, and irritation following cysteamine therapy. Side effects were associated with prolonged exposure to the topical agent, and removing the cysteamine by washing may decrease these side effects in patients. Clinical photos demonstrated diffuse skin brightening. Cysteamine has not been directly compared with 4% HQ.

Cysteamine is reported to have anti-cancer and anti-melanoma effects, which may be beneficial compared with HQ. Cysteamine may lead to diffuse skin brightening, and some patients report an unpleasant odor from cysteamine. Cysteamine is widely used in Europe, but is not commercially available in the United States. As a stand-alone agent, cysteamine received a strong recommendation as it has a beneficial efficacy and safety profile.

**Epidermal growth factor – weak recommendation**

The topical application of EGF has been evaluated for the promotion of wound healing and prevention of post-inflammatory hyperpigmentation (PIH) after laser resurfacing of facial skin. In one double-blind, split-face RCT, 50 patients were treated with topical EGF serum (DNARenewal, Beverly Hills, CA) vs placebo on each designated side of the face, twice daily for 8 weeks. According to the Physician Global Aesthetic Improvement Scale,
there was an improvement in the melasma in 73.4% of patients on the EGF-treated side vs 13% on the placebo side. The average Melasma Quality of Life questionnaire score decreased from 42 to 33, with 73% of patients having an improvement in their score. No AEs were reported with use of either treatment.

While the authors concluded that topical EGF is a safe and effective treatment for melasma, additional RCTs with greater power and validated outcome measures are needed to evaluate the efficacy of topical EGF for melasma. Thus, topical EGF received a weak recommendation.

Hydroquinone (Liposomal) – weak recommendation
One double-blind RCT compared once daily treatment with 4% liposomal HQ (prepared by fusion method) to standard formulations of 4% HQ for 12 weeks, and demonstrated similar efficacy between the treatment regimens at week 4 following the end of the treatment course. AEs for liposomal HQ were not reported. As a result, any added benefit of liposomal vehicle is minimal.

Lignin peroxidase – weak recommendation
One split-face RCT compared the efficacy of twice daily lignin peroxidase (elure, Syneron Medical Ltd, Yokneam, Israel) in two cohorts of 30 patients over 12 weeks. In the first cohort, lignin peroxidase significantly improved MASI compared with no treatment. In the second cohort, there was no difference in MASI score between the lignin peroxidase and 4% HQ groups. Investigator grading indicated that lignin peroxidase resulted in improved skin texture. There were no AEs from either treatment. Lignin peroxidase improved patient melasma compared with no treatment.

Mulberry extract – weak recommendation
One single-blind RCT found that twice daily 75% mulberry extract oil for 8 weeks significantly improved patient MASI compared with placebo. Clinical photographs were consistent and showed decreased pigmentation following mulberry extract treatment. Patients treated with mulberry extract reported fewer AEs than the control group. Mulberry extract received a weak recommendation, as additional research is needed to establish the efficacy of mulberry extract for periods greater than 8 weeks and compared with HQ.

Niacinamide – weak recommendation
Niacinamide, also known as vitamin B3, may decrease skin pigmentation by preventing melanosome transfer. One double-blind, split-face RCT of 27 patients compared the efficacy of 4% niacinamide (Nicomide-T Cream 4%, DUSA Pharmaceuticals Inc, Wilmington, MA) with 4% HQ every 3 hours during the daytime for 8 weeks. Both treatments reduced MASI significantly at week 8 compared with baseline. Niacinamide was associated with fewer and milder AEs. Colorimetric measures did not show statistical differences between both sides. However, according to the IGA, good to excellent improvement was observed with niacinamide in 44% of patients compared with 55% with HQ. Niacinamide received a weak recommendation, but there is promising efficacy from a single study.

Rumex occidentalis (Western Dock) – weak recommendation
One double-blind RCT compared the efficacy of twice daily 3% Rumex occidentalis (a perennial herb), 4% HQ, and placebo for 8 weeks in 45 patients. The placebo had no significant effect, while the 3% Rumex occidentalis and 4% HQ significantly decreased MASI scores and colorimetric measures. Patients treated with Rumex occidentalis reported mild peeling. Clinical photographs demonstrated decreased pigmentation and diffuse skin brightening. Rumex occidentalis reduced patient melasma and may be worthy of future research.

Tranexamic acid – strong recommendation
Five RCTs examined the use of topical TXA for patients with melasma. In one study of 60 patients, twice daily treatment with 6.5% TXA (Pazana Laboratory Asia Co., Ltd, Bangkok, Thailand) significantly improved melasma compared with vehicle at week 8. Clinical photographs showed improvement following TXA treatment, but mild pre-treatment severity. However, in another double-blind, split-face RCT, 5% TXA performed no better than the vehicle. Both treatment and control reduced melasma, but there was no difference in efficacy as determined by MASI and colorimetry. In a 60 patient double-blind study, 5% TXA vs 2% HQ twice daily both significantly decreased MASI. 5% TXA was associated with higher patient satisfaction and less skin irritation. In another split-face, double-blind study, 5% liposomal TXA (prepared by fusion method) had similar efficacy in reducing patient MASI score compared with 4% HQ after twice daily treatment for 12 weeks. Skin irritation only occurred in the 4% HQ treated group. In a split-face, double-blind study of twice daily 3% TXA vs 3% HQ and 0.01% dexamethasone, both treatments significantly reduced MASI scores. Photographs showed decreased pigmentation. There was no difference in treatment efficacy between groups, but topical application of 3% HQ and 0.01% dexamethasone was associated with an increased incidence of AEs.

TXA had similar efficacy to HQ with a milder AE profile and received a strong recommendation. The efficacy of TXA is dependent on concentration dose when used as monotherapy. TXA is a lysine analogue and carries a theoretical risk for thrombosis due to the anti-fibrinolytic effects. However, no evidence of increased clotting in low-risk patients was found in a recently published review of the safety and efficacy of oral TXA for melasma. Topical TXA likely has decreased vasculature circulation compared with oral administration, but the theoretical risk of blood clots remains. Clinicians may consider topical TXA as an alternative to HQ in patients without predispositions to thrombotic events.
**Triple combination therapy – strong recommendation**

Five RCTs have examined the efficacy of TC agents. One 211 patient double-blind RCT found that 4% HQ, 0.05% tretinoin, and 0.01% fluocinolone acetonide (FA) (Zhejiang Rishengchang Pharmaceutical Co., Ltd, Zhejiang, China) was more effective than placebo at clearing melasma based on the decreased index of total target score. Another double-blind RCT of 32 patients found that daily 4% HQ, 0.05% tretinoin, and 0.05% dexamethasone had better investigator-rated outcomes than 4% HQ after 12 weeks. Erythema and scaling were more prevalent following TC therapy (87.5% vs 43.7%). An open-label RCT of 119 patients found that once daily TC cream of 4% HQ, 0.05% tretinoin, and 0.01% FA (Tri-Luma®, Galderma, Lausanne, Switzerland) more effectively cleared melasma compared with twice daily 4% HQ, with 35% of patients achieving complete clearance on TC therapy compared with 5.1% in the HQ group. A 242 patient single-blind study evaluating the same treatment regimen similarly demonstrated reduced MASI score compared with 4% HQ. Patient photographs were consistent and showed improvement of melasma. In a single-blind 641 patient RCT, a TC hydrophilic cream containing 4% HQ, 0.05% tretinoin, and 0.01% FA more effectively cleared melasma compared with dual combination regimens of tretinoin plus HQ, tretinoin plus FA, or HQ plus FA. AE of erythema, skin peeling, burning, and stinging sensation were mild and similar among all treatment arms.

TC therapy was superior to 4% HQ with a similar AE profile and received a strong recommendation. TC therapies demonstrate the benefit of synergistic treatments in which HQ decreases melanogenesis, tretinoin increases keratinocyte turnover, and steroids reduce inflammation. Evidence from epidemiological studies and case reports has not revealed an increased risk of cancer but clinicians may consider limiting chronic exposure. If clinical goals have been achieved, a maintenance regimen of once or twice weekly TC therapy may minimize the risk for ochronosis. Relapse has been shown to occur in 50% of patients approximately 190 days following the establishment of a maintenance regimen compared with 58 days following abrupt cessation of therapy. For patients seeking a non-HQ therapeutic approach for the treatment of melasma due to HQ associated safety profile, we recommend against TC.

**4-n-butylresorcinol – weak recommendation**

Three double-blind, split-face RCTs compared the efficacy of 4-n-butylresorcinol 0.1% cream or 0.3% serum with vehicle. In all 3 studies, 4-n-butylresorcinol significantly reduced skin pigmentation compared with vehicle based on colorimetric measures and clinical pigmentation score. In one study, the depigmenting effects of 4-n-butylresorcinol 0.3% serum increased until week 8 and then plateaued. The other two studies only compared the efficacy until week 8. Adverse events were mild in all three studies. Photographs showed improvement following 4-n-butylresorcinol topical therapies.

4-n-butylresorcinol decreased skin pigmentation and may be a useful as a short-term treatment for melasma, but the long-term efficacy beyond 12 weeks is unclear. In vitro studies have indicated that 4-n-butylresorcinol was the most potent inhibitor of tyrosinase compared with HQ, arbutin, and kojic acid. 4-n-butylresorcinol received a weak recommendation, as additional studies are needed to compare the efficacy of 4-n-butylresorcinol to establish the duration of effect greater than 8 to 12 weeks, and comparison studies to 4% HQ may provide additional strength of data.

**Benefits Closely Balanced With Risks and Burden**

**Glycolic acid – weak recommendation**

Glycolic acid is believed to improve melasma by accelerating desquamation. Two RCTs examined the efficacy of combination 10% glycolic acid and 4% HQ for melasma. In a vehicle-controlled, double-blind RCT of 35 patients, twice daily application of a cream containing 10% buffered glycolic acid with 4% HQ, ascorbic acid, vitamin E, and sunscreen (Glyquin, ICN Pharmaceuticals, Costa Mesa, CA) was applied for 12 weeks. The combination 10% glycolic acid product significantly improved melasma compared with sunscreen-only control as determined by MASI and colorimetry. Another single-blind RCT compared daily 4% HQ alone with 4% HQ with 0.01% hyaluronic acid; 4% HQ with 10% glycolic acid; 4% HQ with 0.01% hyaluronic and 10% glycolic acid; or placebo. All 4 topical treatments improved melasma from baseline. The most significant decrease in melasma was measured following 4% HQ with 0.01% hyaluronic acid and 10% glycolic acid. Topical 4% HQ with supplemental glycolic acid was more irritating to skin than HQ alone. Post-treatment photographs showed localized skin brightening around the treatment site.

Glycolic acid is weakly recommended as a supplement to 4% HQ, as the benefits and risk of skin desquamation should be carefully considered for each patient. Additionally, the RCTs do not directly compare the efficacy of glycolic acid alone with HQ alone. Glycolic acid supplementation had greater efficacy and more severe AEs compared with 4% HQ alone. Skin desquamation from glycolic acid may be minimized if patients apply a moisturizing cream concurrently. Glycolic acid appears best suited as adjunct therapy for melasma and not a primary, first-line approach.

**Kojic acid – weak recommendation**

Kojic acid is a tyrosinase inhibitor produced by several fungi species. Two poorly designed RCTs examined the use of kojic acid for melasma. In an 80-patient single-blind RCT, 4 different formulations of 1% kojic acid alone or in combination with 2% HQ and/or 0.1% betamethasone were tested. All 4 treatment groups significantly reduced MASI score after daily treatment for 12 weeks. The authors did not statistically compare intertreatment efficacy but concluded that 1% kojic acid with 2% HQ...
had the best efficacy and 1% kojic acid with 0.1% betamethasone was the least effective. 1% kojic acid, 2% HQ, and 0.1% betamethasone was associated with acneiform eruptions. In another RCT, daily 0.75% kojic acid with 2.5% ascorbic acid for 12 weeks was inferior to 4% HQ.46 Photographs demonstrated minimal efficacy for kojic acid as a stand-alone treatment. Ancillary clinical evidence suggests that compounded 12% HQ with 6% kojic acid may be an effective treatment not associated with diffuse skin brightening, but this formulation has not been studied in an RCT. Based upon the available published literature reviewed, kojic acid received a weak recommendation when combined with other agents, and evidence does not support recommendation as a stand-alone treatment for melasma.

Risks and Burden Outweigh Benefits

Parsley – weak recommendation

In a poorly designed double-blind RCT, patients applied parsley or 4% HQ daily for 8 weeks.47 The patients in the parsley group had to self-brew 2.5 g of parsley in 125 ml of water. Both treatments significantly improved MASI from baseline. AEs in the parsley and 4% HQ group included irritation, redness, and itching. As patients were required to self-prepare parsley extract to prevent treatment expiration, the use of parsley was weakly recommended. Additionally, differences in sample preparation may lead to variability in treatment results.

Zinc sulfate – strong recommendation

Zinc sulfate has been used to treat numerous skin conditions including acne vulgaris and warts. Two RCTs examined the use of once or twice daily 10% zinc sulfate for melasma.48,49 In both studies, topical application of 10% zinc sulfate reduced MASI compared with base-line. Flutamide was more effective than HQ according to MASI and patient satisfaction but there was no difference between treatments when assessed using colorimetric analysis. The AE profile was not provided, and the safety of hormonal therapy should be evaluated before a recommendation can be made.

Insufficient Evidence to Determine Net Benefit

Aloe vera – no strength of recommendation

One double-blind study compared the efficacy of 2 aloe vera formulations (0.5% gel extract or 0.25% liposome-encapsulated gel extract) in 180 pregnant patients with pre-existing melasma.50 After 5 weeks, aloe vera significantly improved patient MASI compared with the standard gel formulation. As there was no placebo or HQ control group, it is difficult to determine the relative efficacy of aloe vera. However, the net risk of AEs is likely low as the treatment was used in pregnant patients. The study did not describe the frequency of aloe vera application.

Ascorbic acid – no strength of recommendation

In a 16 patient, split-face, double-blind RCT, patients were less satisfied with 5% L-ascorbic acid (La Roche-Posay, France) compared with 4% HQ after 16 weeks.51 Colorimetric analysis demonstrated no difference between treatment arms, and HQ was more irritating to the skin. Ascorbic acid is readily oxidized, which limits its use as a stand-alone treatment but may be combined with other topical agents.52

Dioic acid – no strength of recommendation

One open-label RCT of 96 patients compared twice daily 1% dioic acid with 2% HQ for 12 weeks. 1% dioic acid and 2% HQ improved MASI scores from baseline, but there was no significant difference between dioic acid and HQ.52 Patients treated with dioic acid had a higher incidence of acneiform reaction, which the authors attributed to an oily vehicle. An open-label design limited the strength of this study.

Ellagic acid and arbutin – no strength of recommendation

In an open-label RCT involving 29 patients, twice daily treatment with 1% synthetic ellagic acid, 1% arbutin, or plant extract with 1% natural ellagic acid significantly improved skin pigmentation after 6 months without the occurrence of AEs.53 Limitations in the study design included the lack of blinding and lack of a placebo-control. Thus, additional research is needed before conclusions can be drawn about ellagic acid and arbutin therapy for melasma.

Flutamide – no strength of recommendation

One double-blind study compared the efficacy of topical 1% flutamide, an anti-androgenic drug, with 4% HQ over 4 months.54 Both treatments reduced MASI compared with baseline. Flutamide was more effective than HQ according to MASI and patient satisfaction but there was no difference between treatments when assessed using colorimetric analysis. The AE profile was not provided, and the safety of hormonal therapy should be evaluated before a recommendation can be made.

LIMITATIONS

Currently, there is no universally effective treatment for melasma, and some established topical agents carry significant safety risks that may reduce patient compliance and satisfaction. Topical HQ, the basis for many combination therapies, may be less effective in patients with darker skin phenotypes and is associated with ochronosis.55 Other novel agents have shown promising results, but are limited by small sample sizes, poor study design, and limited high quality published RCTs. When evaluating naturally-derived or compounded topical therapies, it is essential to consider the reproducibility of the chemical composition. Differences in treatment concentration or secondary ingredients may have a significant impact on therapeutic efficacy. Additionally, several RCTs used natural agents published in non-English languages. These studies may have added to the literature, but we were unable to evaluate these studies.
CONCLUSION
We performed a systematic review of topical treatments for melasma. Strong evidence-based recommendations include cysteamine, TC, and TXA as first-line treatments for melasma. Cysteamine has excellent efficacy, is reported to have anti-cancer properties, and has no known risk for thrombosis or ochronosis. TC therapies and TXA are effective for melasma but carry theoretical risks for ochronosis or thrombosis, respectively. Natural compounds are associated with low risk for AEs, but more research is needed to determine the efficacy, optimal formulation, and appropriate concentration of novel treatments.

For all topical agents, continued treatment and use of medications is necessary as pigmentation may recur following treatment cessation. Future large RCTs with control arms using standard-of-care treatments (ie, HQ or TC) are necessary to assess the relative risks and benefits of a novel agent. Current topical treatments mostly inhibit melanin formation and transfer, but do not target the vascular components of melasma, inflammation, or underlying disease etiology. We believe that synergistic combination approaches are likely to have greater efficacy than stand-alone treatments. Future mechanistic research on the underlying etiology of melasma may facilitate the development of targeted approaches.

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DISCLOSURES
Dr. Jagdeo is a speaker for L’Oréal/Skinceuticals and a consultant for Scientia. Dr. Jagdeo is on the scientific advisory board for Sun Pharma/DUSA Pharmaceuticals, Inc. for the product Levulan® photodynamic therapy. No funding has been received for this article. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the U.S. Department of Veterans Affairs or the United States Government.

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33. Chan R, Park KC, Lee MH, et al. A randomized controlled trial of the efficacy and safety of a fixed triple combination (fluconazole acetone 0.01%, hydroquinone 4%, tretinoin 0.05%) compared with hydroquinone 4%


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Successful Treatment of Porokeratosis With Ablative Fractional Carbon Dioxide Laser and Vitamin C, E, and Ferulic Acid Serum

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ABSTRACT

Porokeratosis is a rare disorder of epidermal keratinization that encompasses several clinical forms, characterized by erythematous, annular plaques with an atrophic center and hyperkeratotic ridge-like border. The histopathological hallmark of porokeratosis is the cornoid lamella, a thin column of parakeratotic corneocytes embedded within the stratum corneum. There is no standard treatment regimen for porokeratosis. Current therapeutic modalities include topical agents, systemic medications, and surgical interventions that have variable efficacy. Here, we report a case of a patient with localized porokeratosis lesions on the face and extremities that resolved after one treatment session with carbon dioxide laser resurfacing combined with topical antioxidant serum containing L-ascorbic acid, alpha tocopherol, and ferulic acid. The diagnosis of porokeratosis was supported by the clinical presentation, dermoscopy, and in vivo skin imaging with optical coherence tomography and reflectance confocal microscopy. This case highlights the utility of using carbon dioxide laser to ablate porokeratosis lesions, as well as the clinical advantages offered by new noninvasive skin imaging modalities to examine, diagnose, and follow up skin pathologies.


INTRODUCTION

Porokeratosis is a disorder of epidermal keratinization that encompasses multiple clinical variants based on different patterns of distribution. It classically manifests as one or more erythematous, annular plaques with an atrophic center and hyperkeratotic ridge-like border.1-3 The primary lesion of classic porokeratosis starts as a small, light brown, scaly papule that spreads in a centrifugal manner and may slowly progress and coalesce into a sharply circumscribed plaque of various sizes and forms.4,5 The lesions are often asymptomatic but may be associated with pruritus.1 Porokeratosis lesions may affect any part of the body, including palmoplantar surfaces and mucous membranes, but are more prevalent on the trunk and extremities.1,2

Porokeratosis may be classified as classic porokeratosis of Mibelli, linear porokeratosis, disseminated porokeratosis, disseminated superficial actinic porokeratosis, punctate porokeratosis, or porokeratosis palmaris et plantaris disseminata.1,3 The histopathological hallmark of porokeratosis is the cornoid lamella, characterized by a thin column of parakeratotic corneocytes embedded within the stratum corneum, forming an indentation within the epidermis.1,3,4 While the exact pathogenesis of porokeratosis remains unclear, it may be acquired or hereditary, and is thought to be due to the clonal expansion of abnormal epidermal keratinocytes.1,4 The proliferation of abnormal clones may be triggered by extrinsic factors such as irradiation, infective agents, mechanical trauma, and immunosuppression.1 The differential diagnosis of porokeratosis includes actinic keratosis, seborrheic keratosis, psoriasis, lichen planus, Bowen’s disease, and squamous cell carcinoma.2,4

The overall prognosis of porokeratosis is favorable. However, a potential complication is an increased risk (estimated to be less than 10%) of malignant transformation of a porokeratosis lesion to a basal or squamous cell carcinoma.1,6 Risk factors include large lesion size, localization on the extremities, older age, and a long period of existence.1

There is no definitive or “gold standard” treatment regimen for porokeratosis, and current therapeutic approaches have variable efficacy and durability. Asymptomatic lesions are often managed conservatively with sun protection, emollients, and clinical surveillance for signs of malignant degeneration.1 Current therapeutic modalities used to improve the signs and symptoms of porokeratosis include many topical, systemic, and surgical treatment options such as: 5-fluorouracil cream, topical vitamin D3 analogs, topical and systemic retinoids (eg, acitretin or isotretinoin), cryotherapy, dermabrasion, laser ablation, imiquimod, ingenol mebutate, topical diclofenac, cantharidin, corticosteroids, topical tacrolimus, phototherapy, and surgical excision.1,4 A systematic review found that no randomized controlled trials have been conducted to assess treatments...
for porokeratosis. Based on a limited number of case reports and cases series available in the literature, porokeratosis of Mibelli shows the best clinical outcomes after treatment with imiquimod cream.

Herein, we report a case of a patient who had multiple lesions consistent with porokeratosis of Mibelli that were each successfully treated with a combination of ablative fractional carbon dioxide (CO₂) laser and topical application of an antioxidant serum.

**CASE REPORT**

A 51-year-old male with Fitzpatrick skin phototype 2 presented to dermatology clinic for evaluation of a chronic rash. He reported the occurrence of focal, red, scaly lesions on his left hand, face, and right arm. The onset of these lesions was unclear, but they remained unchanged despite the use of topical clobetasol. His past medical history included celiac disease and hyperlipidemia, and medications included gemfibrozil. Physical examination revealed three annular, pink, erythematous plaques (approximately 1.0 x 1.0 cm) with a raised scaly border distributed on the left dorsal hand, right forehead superior to the eyebrow, and right dorsal forearm (Figure 1A-C).

The lesion on the forearm was visualized under dermoscopy, optical coherence tomography (OCT), and reflectance confocal microscopy (RCM). Dermoscopy revealed the presence of a peripheral white rim and multiple dotted vessels over an erythematous center and superficial white scales (Figure 2A). OCT (VivoSight, Michelson Diagnostics Ltd, Kent, UK) showed a cornoid lamella (Figure 2B). RCM (VivaScope 3000, Caliber I.D., Rochester, NY) showed an atypical honeycomb pattern and architectural disarray at the corneal level (Figure 2C). Based on the clinical presentation and morphologic features identified on in vivo skin imaging modalities, the diagnosis of porokeratosis of Mibelli was made. A skin biopsy was deferred. Although the lesions were asymptomatic, the patient was concerned about the aesthetic appearance and requested treatment.

The individual lesions were treated with ablative fractional CO₂ laser resurfacing (Fraxel Repair, Solta Medical, Hayward, CA). Two days prior to the procedure, he was started on prophylaxis with valacyclovir (1 g twice daily for 7 days) and cephalexin (500 mg four times daily for 14 days). For each focal site of porokeratosis, the lesion received three passes of the laser at 70 mJ with 35% coverage. An additional pass was performed at 50 mJ with 30% coverage along with feathering at the edges. A topical formulation of 15% L-ascorbic acid, 1% alpha-tocopherol, and 0.5% ferulic acid serum (C E Ferulic, SkinCeuticals Inc, Garland, TX) was applied immediately after the procedure, and the patient was instructed to re-apply it twice daily for two days. At a two months follow-up visit, clinical examination of the affected areas showed complete clearance of the lesions (Figure 1D-F, images not shown).

**DISCUSSION**

There is a paucity of clinical studies evaluating therapeutic modalities for porokeratosis. The use of CO₂ laser ablation for the treatment of porokeratosis has been previously documented in isolated case reports. Successful treatment of porokeratosis of Mibelli with the CO₂ laser has been reported with good clinical and aesthetic outcomes, including histological confirmation of complete resolution of porokeratosis features and no evi-
The use of ablative fractional CO2 laser for the treatment of porokeratosis of Mibelli has several advantages compared to other therapeutic options such as systemic agents or surgical excision, as it is minimally invasive, can be used to treat areas of extensive involvement, and lacks significant side effects. Furthermore, a single treatment session may be sufficient to achieve complete clearance and the potential for post-laser scarring can be minimized as the laser parameters can be customized. Postoperative application of vitamin C, E, and ferulic acid serum has been shown to promote more rapid wound healing after fractional ablative laser treatment.

This case report highlights the clinical utility of using real-time, high-resolution, non-invasive imaging techniques to establish a diagnosis of porokeratosis. In this case, by using OCT to identify the cornoid lamella and using RCM to examine the distinct morphologic features of porokeratosis, we were able to confirm a diagnosis of porokeratosis, avoiding the need for an invasive biopsy for histopathological examination. The hallmark of dermoscopy diagnosis of porokeratosis is the presence of a peripheral white rim, corresponding to the cornoid lamella, which can also be identified on OCT. On RCM imaging of porokeratosis, the presence of sharp demarcation and hyper-refractile border at the level of the corneal layer corresponds in histopathology to the presence of the cornoid lamella.

In conclusion, the use of the CO2 laser in porokeratosis of Mibelli is a therapeutic modality that is minimally invasive, offers fast and durable results, delivers clinical results, and is associated with patient satisfaction. Clinicians should consider the use of ablative fractional CO2 laser to treat focal porokeratosis lesions with consideration of the size of the lesion, anatomical location, and risk of malignant transformation. To date, there are no treatment guidelines or universal consensus on the optimal treatment for porokeratosis, with the therapeutic armamentarium consisting of a variety of topical agents, systemic medications, and surgical modalities. The approach to treatment for porokeratosis should be individualized with consideration of the functional and aesthetic impact and patient preferences.

DISCLOSURE

Dr. Jagdeo is a consultant for SkinCeuticals-L’Oréal.

REFERENCES

INDICATION
ALTRENO™ (tretinoin) lotion, 0.05% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

IMPORTANT SAFETY INFORMATION
ALTRENO is for topical use only. Not for ophthalmic, oral, or intravaginal use.

Skin Irritation: Patients using ALTRENO may experience application site dryness, pain, erythema, irritation, and exfoliation. Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of ALTRENO, or discontinue use. Avoid application of ALTRENO to eczematous or sunburned skin.

Ultraviolet Light and Environmental Exposure: Minimize unprotected exposure to ultraviolet light, including sunlight and sunlamps. Warn patients with frequent sun exposure and those with inherent sensitivity to sunlight to exercise caution. Use sunscreen and protective clothing over treated areas when exposure cannot be avoided.

Fish Allergies: ALTRENO contains soluble fish proteins. Use with caution in patients with known sensitivity or allergy to fish. Advise patients to contact their healthcare provider if they develop pruritus or urticaria.

Adverse Reactions: The most common adverse reactions in clinical trials were application site dryness (4%), pain (3%), erythema (2%), irritation (1%) and exfoliation (1%).

Nursing Women: It is not known whether topical administration of tretinoin could result in sufficient systemic absorption to produce detectable concentrations in human milk. The developmental health benefits of breastfeeding should be considered along with the mother’s clinical need for ALTRENO and any potential adverse effects on the breastfed child from ALTRENO.

To report SUSPECTED ADVERSE REACTIONS, contact Customer Service at 1-800-321-4576 or the FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see Brief Summary of Prescribing Information on preceding pages.


Ortho Dermatologics

ALTRENO™ lotion

the first and only acne treatment that provides the proven efficacy of tretinoin in a hydrating lotion.¹²

See tolerability and efficacy results at ALTRENOHCP.com.
BRIEF SUMMARY OF PRESCRIBING INFORMATION
This Brief Summary does not include all the information needed to use ALTRENO safely and effectively. See full prescribing information for ALTRENO.

ALTRENO™ (tretinoin) lotion, for topical use
Initial U.S. Approval: 1973

INDICATIONS AND USAGE
ALTRENO™ (tretinoin) lotion, 0.05% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Skin Irritation
Patients using ALTRENO may experience application site dryness, pain, erythema, irritation, and exfoliation. Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of ALTRENO, or discontinue use. Avoid application of ALTRENO to eczematous or sunburned skin.

Ultraviolet Light and Environmental Exposure
Minimize unprotected exposure to ultraviolet light including sunlight and sunlamps during the use of ALTRENO. Warn patients who normally experience high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided.

Fish Allergies
ALTRENO contains soluble fish proteins. Use with caution in patients with known sensitivity or allergy to fish. Advise patients to contact their healthcare provider if they develop pruritus or urticaria.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In 2 randomized, double-blind, vehicle-controlled trials, subjects age 9 years and older applied ALTRENO or vehicle once daily for 12 weeks. The majority of subjects were White (74%) and female (55%). Approximately 47% were Hispanic/Latino and 45% were younger than 18 years of age. Adverse reactions reported by ≥1% of subjects treated with ALTRENO and more frequently than vehicle are summarized in Table 1.

Table 1: Adverse Reactions Reported by ≥1% of Subjects Treated with ALTRENO and More Frequently Than Vehicle

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ALTRENO N=767</th>
<th>Vehicle N=783</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site dryness</td>
<td>29 (4)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Application site pain†</td>
<td>25 (3)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Application site erythema</td>
<td>12 (2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Application site irritation</td>
<td>7 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Application site exfoliation</td>
<td>6 (1)</td>
<td>3 (&lt;1)</td>
</tr>
</tbody>
</table>

†Application site pain defined as application site stinging, burning or pain.

Clinical Trials Experience
Skin irritation was evaluated by active assessment of erythema, scaling, hypopigmentation, hyperpigmentation, itching, burning and stinging. The percentage of subjects who were assessed to have these signs and symptoms at any post baseline visit are summarized in Table 2.

Table 2: Application Site Tolerability Reactions at Any Post Baseline Visit

<table>
<thead>
<tr>
<th>Reactions</th>
<th>ALTRENO N=760 Mild/Mod/Severe</th>
<th>Vehicle N=782 Mild/Mod/Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>Scaling</td>
<td>49%</td>
<td>30%</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>35%</td>
<td>30%</td>
</tr>
<tr>
<td>Itching</td>
<td>35%</td>
<td>28%</td>
</tr>
<tr>
<td>Burning</td>
<td>30%</td>
<td>14%</td>
</tr>
<tr>
<td>Stinging</td>
<td>21%</td>
<td>8%</td>
</tr>
</tbody>
</table>

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Available data from published observational studies of topical tretinoin in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no data on ALTRENO use in pregnant women. The systemic levels following topical administration are lower than with administration of oral tretinoin; however, absorption of this product may result in fetal exposure. There are reports of major birth defects similar to those seen in infants exposed to oral retinoids, but these case reports do not establish a pattern or association with tretinoin-related embryopathy (see Data).

Animal reproduction studies have not been conducted with ALTRENO. Topical administration of tretinoin in a different formulation to pregnant rats during organogenesis was associated with malformations (craniofacial abnormalities [hydrocephaly], asymmetrical thyroid, variations in ossification, and increased supernumerary ribs) at doses up to 0.5 mg tretinoin/kg/day, approximately 2 times the maximum recommended human dose (MRHD) based on body surface area (BSA) comparison and assuming 100% absorption. Oral administration of tretinoin to pregnant cynomolgus monkeys during organogenesis was associated with malformations at 10 mg/kg/day (approximately 100 times the MRHD based on BSA comparison and assuming 100% absorption) (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defects, loss, and other adverse outcomes. The background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data
Human Data
While available studies cannot definitively establish the absence of risk, published data from multiple prospective controlled observational studies on the use of topical tretinoin products during pregnancy have
not identified an association with topical tretinoin and major birth defects or miscarriage. The available studies have methodologic limitations, including small sample size and in some cases, lack of physical exam by an expert in birth defects. There are published case reports of infants exposed to topical tretinoin during the first trimester that describe major birth defects similar to those seen in infants exposed to oral retinoids; however, no pattern of malformations has been identified and no causal association has been established in these cases. The significance of these spontaneous reports in terms of risk to the fetus is not known.

**Animal Data**

Tretinoin in a 0.05% gel formulation was topically administered to pregnant rats during organogenesis at doses of 0.1, 0.3 and 1 g/kg/day (0.05, 0.15, 0.5 mg tretinoin/kg/day). Possible tretinoin malformations (craniofacial abnormalities [hydrocephaly], asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) were observed at maternal doses of 0.5 mg tretinoin/kg/day (approximately 2 times the MRHD based on BSA comparison and assuming 100% absorption). These findings were not observed in control animals. Other maternal and reproductive parameters in tretinoin-treated animals were not different from control. For purposes of comparison of the animal exposure to human exposure, the MRHD is defined as 4 g of ALTRENO applied daily to a 60-kg person.

Other topical tretinoin embryofetal development studies have generated equivocal results. There is evidence for malformations (shortened or kinked tail) after topical administration of tretinoin to pregnant Wistar rats during organogenesis at doses greater than 1 mg/kg/day (approximately 5 times the MRHD based on BSA comparison and assuming 100% absorption). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 50 times the MRHD based on BSA comparison and assuming 100% absorption) was topically applied to pregnant rats during organogenesis. Supernumerary ribs have been a consistent finding in rat fetuses when pregnant rats were treated topically or orally with retinoids.

Oral administration of tretinoin during organogenesis has been shown to induce malformations in rats, mice, rabbits, hamsters, and nonhuman primates. Fetal malformations were observed when tretinoin was orally administered to pregnant Wistar rats during organogenesis at doses greater than 1 mg/kg/day (approximately 5 times the MRHD based on BSA comparison). In the cynomolgus monkey, fetal malformations were observed when an oral dose of 10 mg/kg/day was administered to pregnant monkeys during organogenesis (approximately 100 times the MRHD based on BSA comparison and assuming 100% absorption). No fetal malformations were observed at an oral dose of 5 mg/kg/day (approximately 50 times the MRHD based on BSA comparison). Increased skeletal variations were observed at all doses in this study and dose-related increases in embryo lethality and abortion were reported in this study. Similar results have also been reported in pigtail macaques.

Oral tretinoin has been shown to be fetotoxic in rats when administered at doses 10 times the MRHD based on BSA comparison. Topical tretinoin has been shown to be fetotoxic in rabbits when administered at doses 4 times the MRHD based on BSA comparison.

**Lactation**

**Risk Summary**

There are no data on the presence of tretinoin or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. It is not known whether topical administration of tretinoin could result in sufficient systemic absorption to produce detectable concentrations in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ALTRENO and any potential adverse effects on the breastfed child from ALTRENO.

**Pediatric Use**

Safety and effectiveness of ALTRENO for the topical treatment of acne vulgaris have been established in pediatric patients age 9 years to less than 17 years based on evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled, 12-week trials and an open-label pharmacokinetic study. A total of 318 pediatric subjects aged 9 to less than 17 years received ALTRENO in the clinical studies [see Clinical Pharmacology and Clinical Studies in full Prescribing Information].

The safety and effectiveness of ALTRENO in pediatric patients below the age of 9 years have not been established.

**Geriatric Use**

Clinical trials of ALTRENO did not include any subjects age 65 years and older to determine whether they respond differently from younger subjects.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

A 2-year dermal mouse carcinogenicity study was conducted with topical administration of 0.005%, 0.025% and 0.05% of a tretinoin gel formulation. Although no drug-related tumors were observed in surviving animals, the irritating nature of the drug product precluded daily dosing, confounding data interpretation and reducing the biological significance of these results.

Studies in hairless albino mice with a different formulation suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect was confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The genotoxic potential of tretinoin was evaluated in an in vitro bacterial reversion test, an in vitro chromosomal aberration assay in human lymphocytes and an in vivo rat micronucleus assay. All tests were negative.

In dermal fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (approximately 2 times the MRHD based on BSA comparison and assuming 100% absorption), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day and above (approximately the MRHD based on BSA comparison and assuming 100% absorption) were observed.

**PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information).
Successful Treatment of Lower Extremity Telangiectasias Using 585-nm Pulsed-Dye Laser at Low Fluence Combined With Optical Coherence Tomography: A Case Report

Ali Rajabi-Estarabadi MD, Caiwei Zheng BA, Natalie Williams BS, Samuel C. Smith MS, Keyvan Nouri MD, Robert S. Kirsner MD PhD
Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL

ABSTRACT

Background: Significant advances have been made in using lasers and intense pulse light sources to treat common vascular lesions such as telangiectasias. However, the treatment of leg telangiectasia, specifically, is more challenging because it involves the clearing of smaller veins as well as the larger feeding veins. The latest guidelines recommend use of short wavelength pulse-dyed lasers (PDL) as an option to treat telangiectasia cases that are unresponsive to sclerotherapy.

Methods: A 29-year-old white woman presented with persistent telangiectasia, with multiple telangiectasias ranging from 1 cm to 20 cm in size involving the dorsal feet and both ankles and legs, which developed 10 years prior, associated with paresthesia. Test spots were treated with a 585-nm pulsed dye laser with various energy settings, and treatment was performed at 5.5 J/cm² with spot size 10 mm and 0.5ms pulse duration.

Results: Near complete clearance was achieved 1 month after the single treatment without adverse effects. Optical coherence tomography (OCT) imaging demonstrated a reduction of cutaneous blood flow after treatment.

Discussion: We report successful treatment despite using settings that were previously reported to lack efficacy. This treatment resulted in considerable improvement in aesthetics and symptomatology. Also, OCT confirmed decreased vascular flow and bulging.

Conclusion: Our results suggest there is still much to learn about the use of PDL in treating telangiectasias of the lower extremities, and that the ideal parameters warrant further investigation. Moreover, the novel use of OCT in auxiliary imaging for identification of treatment spots, as well as monitoring response at a microvascular level, holds great potential for wider application.


INTRODUCTION

Telangiectasias of the lower extremities are common. Sclerotherapy is the first-line treatment for telangiectasias, but significant advances have been made in using lasers to treat these vascular lesions,1,2 including use of pulsed dye laser (PDL), potassium-titanyl-phosphate (KTP)-lasers, and longer wavelength lasers such as alexandrite lasers, diode lasers (800 nm – 900 nm), and millisecond Nd:YAG lasers (1064 nm). Among these, short wavelength PDL has been viewed as a subpar treatment option for telangiectasia. There is also a perhaps unfounded consensus that longer wavelength PDL with higher fluences is better suited for treating vascular lesions of the lower extremities due to the vessels’ deeper location and larger diameter, respectively.3

In this report, we investigate the use of short wavelength PDL with low fluence levels in treating a patient with telangiectasia of the lower extremities that did not respond favorably to sclerotherapy. Additionally, we employed optical coherence tomography (OCT) imaging to identify the treatment area and monitor treatment response at the microvascular level. We report successful treatment of lower extremity telangiectasia with a single session of 585-nm PDL therapy at low fluences in combination with OCT monitoring, which resulted in considerable improvement in aesthetics and symptomatology.

Case Presentation
A 29-year-old Caucasian woman (Fitzpatrick skin type I) presented with multiple telangiectasias ranging from 1 cm to 20 cm in size, involving the dorsal feet and both dorsal and ventral ankles and legs, which developed 10 years prior, associated with paresthesia. Two biopsies favored the diagnosis of essential telangiectasia. The patient had been previously treated with sclerotherapy, along with gabapentin 200mg nightly for paresthesias of the affected areas; but both provided only limited improvement. She had noted frequent nosebleeds since childhood, but otherwise had no history of weight loss, fatigue, gastrointestinal bleeding, or neurological symptoms. No family history of similar symptoms was reported.
Three spots on the dorsum of the right foot were considered as test spots. Each spot measured approximately 1 cm x 1 cm. These spots were imaged using dynamic OCT to identify dilated vessels and visualize blood flow at different skin depths. The sites were then treated with a 585-nanometer PDL with the energy set to 3.5 J/cm², 4.5 J/cm², and 5.5 J/cm², respectively. A spot size of 10 mm was used due to the large size of the lesions, with a 0.5 ms pulse duration. The patient tolerated the procedure well. Post treatment instructions included sun avoidance and sunscreen use (SPF >30) on the treated areas. The use of gabapentin was unaltered. The patient returned for evaluation 4 weeks later. OCT demonstrated the most substantial decrease in blood flow and number of dilated vessels on the test spot treated with a fluence of 5.5 J/cm². This result was also evident on visual inspection when comparing the 3 test spots.

The patient returned for the treatment of 3 additional area. Each area was treated once, each 1 month apart (Figure 1).

Fluence levels ranged from 4.5 J/cm² to 5.5 J/cm² depending on the location of the lesion, with a spot size of 10 mm and pulse duration of 0.5 ms. The results were documented photographically both before and at 1 month follow-up. As seen in Figures 2a and 2b, near 100% clearance was achieved 1 month after the single treatment with no adverse effects reported. OCT imaging was also employed to compare blood flow of the lesion both before and one month after treatment, as shown in Figure 3. Blood flow data from OCT confirmed effective clearance. An evident drop in blood flow was seen at all measured depths after laser therapy. The highest blood flow was seen at a depth of 0.35 mm both before and after treatment. These data are reported in Figure 4.

Fluence levels ranged from 4.5 J/cm² to 5.5 J/cm² depending on the location of the lesion, with a spot size of 10 mm and pulse duration of 0.5 ms. The results were documented photographically both before and at 1 month follow-up. As seen in Figures 2a and 2b, near 100% clearance was achieved 1 month after the single treatment with no adverse effects reported. OCT imaging was also employed to compare blood flow of the lesion both before and one month after treatment, as shown in Figure 3. Blood flow data from OCT confirmed effective clearance. An evident drop in blood flow was seen at all measured depths after laser therapy. The highest blood flow was seen at a depth of 0.35 mm both before and after treatment. These data are reported in Figure 4.

DISCUSSION
Although sclerotherapy remains the first-line treatment for leg telangiectasias, laser treatment is a promising alternative for those with contraindications, inadequate response, or intolerable side effects such as purpura and hyperpigmentation.4 The use of PDL on lower extremity telangiectasias dates was originally reported in the 1990s; and some consensus had been reached based on previous studies and reports. For example, a shorter wavelength PDL of <600 nm has been recognized to yield the best results for facial telangiectasia because it is more efficacious in treating superficial vessels of small caliber, with diameters no larger than 1.0 mm.4,6 Treatment of telangiectasia of the lower extremities, however, involves vessels that are often larger in size and deeper beneath the thicker adventitial tissues and basal lamina, in addition to smaller more superficial vessels, thus making treatment with a single laser difficult.4,6 Shorter wavelength (<600 nm) modalities such as KTP and LPDL have been reported to be most effective for narrow veins (<1 mm), while longer wavelength modalities such as alexandrite,
of coagulation following intense pulsed light treatment, making telangiectasia, OCT has been reported to provide visualization after a single treatment. However, there was an increase in the favorable outcome, with 585-nm PDL at 1.5 ms and 16-20 J/cm², without consensus. The study by Garden reported perhaps the most 100% clearance was achieved with only a single treatment. In effect, the results prove to be more efficacious compared with previous reports that are more in line with the existing parameter consensus. The study by Garden reported perhaps the most favorable outcome, with 585-nm PDL at 1.5 ms and 16-20 J/cm², having achieved 69±8% clearance after a single treatment. In comparison, our case achieved a higher clearance (nearly 100%) at a lower fluence (5.5 J/cm²).

Positive reports using the 595-nm PDL date back to 1997, when Posner, 2002; 39(6):213-219. In 2003, Tanghetti et al. reported even better results, with over 75% clearance in 50% of treated lesions at 16 J/cm² with a 40 ms pulse duration after a single treatment. However, there was an increase in the incidence of temporary purpura, likely secondary to the use of higher fluences. Compared with the collective results using the 595-nm PDL, our case was able to achieve a greater clearance rate with a much lower fluence and pulse duration, with no notable side effects.

Another unique aspect of this case is the employment of OCT. The use of OCT in dermatology is still novel but has already shown great promise. Recent studies have recommended OCT-based microangiography as a modality to provide high-resolution vascular maps, as well as direct visualization and quantitation of in vivo microvascular changes. Particularly in the treatment of telangiectasia, OCT has been reported to provide visualization of coagulation following intense pulsed light treatment, making OCT an attractive adjunct tool before and after treatment.

In this case, OCT imaging was useful in identifying treatment spots as well as monitoring changes with treatment. OCT was also helpful in identifying small interconnecting vessels surrounding the treatment spots that were otherwise invisible to the naked eye and dermoscopy. Identification and treatment of these accessory vessels are speculated to have greatly reduced the need for multiple treatment sessions.

Our results suggest there is still much to learn about the use of PDL in treating telangiectasias of the lower extremities, and that the ideal parameters warrant further investigation. The excellent outcome achieved in this case was beyond expectation and, as such, necessitates more research in the application of low fluence, shorter wavelength PDL in the treatment of telangiectasias. Furthermore, the novel use of OCT in auxiliary imaging for identification of treatment spots as well as monitoring response at a microvascular level holds great potential for wider application.

DISCLOSURE

The authors have no conflicts of interest.

REFERENCES


The authors have no conflicts of interest.
Do You Know the Most Complete, Targeted Biologic for Psoriasis? The Answer May Surprise You

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The National Rosacea Society (NRS) estimates that approximately 16 million Americans are affected by rosacea. Persistent facial redness (erythema) is cited as the most common sign of rosacea and may resemble a flushing or sunburn that does not go away. Typical triggers include sun exposure, stress, weather, food, and exercise.
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14. Required Notice

A Publication of Ownership for a Requester Publication is required and will be printed in the September 2019 issue of this publication.
BRYHALI™ (halobetasol propionate) Lotion, 0.01% is indicated for the topical treatment of plaque psoriasis in adults.

**INDICATIONS AND USAGE**

BRYHALI™ (halobetasol propionate) Lotion, 0.01% is indicated for the treatment of plaque psoriasis in adults.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

**Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression**

BRYHALI has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Systemic effects of topical corticosteroids may include reversible HPA axis suppression with the potential for glucocorticoid insufficiency. This may occur during treatment or upon withdrawal of treatment with the topical corticosteroid.

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression with BRYHALI was evaluated in a study of 19 adult subjects with moderate to severe plaque psoriasis involving ≥20% of their body surface area (BSA). HPA axis suppression was reported for 1 (5.6%) subject at Week 4 and for 3 (15.8%) subjects at Week 8. All 3 subjects had normal HPA axis suppression at baseline with discontinuation of treatment [see Clinical Pharmacology in full Prescribing Information].

Because of the potential for systemic absorption, use of topical corticosteroids, including BRYHALI, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, over use of topical corticosteroids, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver disease, and young age. An adrenocorticotropic hormone (ACTH) stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, attempt to gradually withdraw the drug, reduce the frequency of application, or substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Systemic effects of topical corticosteroids may also include Cushing’s syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to corticosteroids. Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids due to their larger surface-to-body mass ratios [see Use in Specific Populations].

**Local Adverse Reactions**

Local adverse reactions from topical corticosteroids may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and milia. These may be more likely with occlusive use, prolonged use, or use of higher potency corticosteroids, including BRYHALI. Some local adverse reactions may be irreversible.

**Concomitant Skin Infections**

Use an appropriate antimicrobial agent if a skin infection is present or develops. If a favorable response does not occur promptly, discontinue use of BRYHALI until the infection has been adequately treated.

**Allergic Contact Dermatitis**

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Consider confirmation of a clinical diagnosis of allergic contact dermatitis by appropriate patch testing. Discontinue BRYHALI if allergic contact dermatitis occurs.

**ADVERSE REACTIONS**

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In randomized, double-blind, multicenter, vehicle-controlled clinical trials, 426 adults with plaque psoriasis were treated with BRYHALI and had post-baseline safety data. Subjects applied BRYHALI once daily for up to eight weeks. Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with BRYHALI and more frequently than in vehicle-treated patients.

**Table 1: Adverse Reactions Occurring in ≥1% of the Subjects Treated with BRYHALI through Week 8**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>BRYHALI (N=284)</th>
<th>Vehicle (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
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<tr>
<td>Application Site Dermatitis</td>
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<td>0%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1%</td>
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</tbody>
</table>

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

There are no available data on BRYHALI use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, increased malformations, including cleft palate and omphalocoele, were observed after oral administration of halobetasol propionate during organogenesis to pregnant rats and rabbits. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of BRYHALI.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

**Data**

**Animal Data**

Halobetasol propionate has been shown to cause malformations in rats and rabbits when given orally during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocoele was seen in rats but not in rabbits.

**Lactation**

**Risk Summary**

There are no data on the presence of halobetasol propionate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production after treatment with BRYHALI.

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for BRYHALI and any potential adverse effects of the breastfed child from BRYHALI.

**Clinical Considerations**

Advise breastfeeding women not to apply BRYHALI directly to the nipple and areola to avoid direct infant exposure.

**Pediatric Use**

Safety and effectiveness of BRYHALI in pediatric patients under the age of 18 years have not been evaluated.

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing’s syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children [see Warnings and Precautions].

**Geriatric Use**

Of 284 subjects exposed to BRYHALI in clinical trials, 61 subjects were 65 years or older. Clinical trials of BRYHALI did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

Halobetasol propionate was not genotoxic in the Ames assay, in the sister chromatid exchange test in Chinese hamster somatic cells, in chromosome aberration studies of germinal and somatic cells of rodents, or in a mammalian spot test. Positive mutagenicity effects were observed in a mouse lymphoma gene mutation assay in vitro and in a Chinese hamster micronucleus test.

Studies in rats following oral administration of halobetasol propionate at dose levels up to 0.05 mg/kg/day indicated no impairment of fertility or general reproductive performance.

**PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information).}

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Bridgewater, NJ 08807 USA

By:

Valeant Pharmaceuticals International, Inc.

Laval, Quebec H7L 4A8, Canada

U.S. Patent Numbers: 6,517,847 and 8,809,307

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\(^1\) POTENT TO SUPERPOTENT CLEARANCE\(^1\):

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Significant symptomatic relief as early as week 2\(^2\)

No increased epidermal atrophy observed through 8 weeks of treatment\(^2\)

Local adverse reactions from topical corticosteroids may include atrophy, striae, telangiectasias, hypopigmentation and allergic contact dermatitis. Some local adverse reactions may be irreversible.

STUDY RESULTS: 36.5% of patients in trial 1 and 38.4% in trial 2 achieved treatment success at week 8 (primary endpoint) vs 8.1% and 12.0% of patients with vehicle, respectively \((P < 0.001\) in both trials).\(^1\)

STUDY DESIGN: The safety and efficacy of BRYHALI Lotion were assessed in 2 prospective, multicenter, randomized, double-blind, phase 3 clinical trials in 430 adult patients with moderate-to-severe plaque psoriasis. Patients were treated with BRYHALI Lotion or vehicle lotion, applied once daily. Primary efficacy endpoint was treatment success evaluated at week 8. Secondary efficacy endpoint was treatment success evaluated at weeks 2, 4, 6, and 12(4 weeks post treatment). Tertiary efficacy endpoint was a 2-grade improvement from baseline at each time point for the individual signs of psoriasis (erythema, plaque elevation, and scaling).\(^2\)

\(^\text{b}\) Treatment success was defined as at least a 2-grade improvement from baseline in the Investigator’s Global Assessment score, and a score of “clear” or “almost clear” (primary endpoint) at week 8.\(^1\)


Indication

BRYHALI™ (halobetasol propionate) Lotion, 0.01% is a corticosteroid indicated for the topical treatment of plaque psoriasis in adults.

Important Safety Information

Warnings and Precautions

• BRYHALI Lotion has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis during treatment or upon cessation of treatment; periodic evaluation may be required.

• Systemic effects of topical corticosteroids may also include Cushing’s syndrome, hyperglycemia, and glucosuria.

• Children may be more susceptible to systemic toxicity when treated with topical corticosteroids.

• Local adverse reactions may include atrophy, striae, telangiectasias, hypopigmentation, and allergic contact dermatitis. Some local adverse reactions may be irreversible.

• Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist.

• Use an appropriate antimicrobial agent if a skin infection is present or occurs, and if prompt response is not seen, discontinue use until infection has been adequately treated.

• Discontinue BRYHALI Lotion if allergic contact dermatitis occurs.

Adverse Reactions

• The most common adverse reactions (≥1%) were upper respiratory tract infection, application site dermatitis, and hyperglycemia.

To report SUSPECTED ADVERSE REACTIONS, contact Customer Service at 1-800-321-4576 or FDA at 1-800-FDA-1088.

Please see Brief Summary of full Prescribing Information on following page.