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STILL AVAILABLE

Issues & Considerations for Optimal Outcomes in Acne Management

JOURNAL-BASED ENDURING CE ACTIVITY

Funded by an educational grant provided by Galderma Laboratories, L.P.
• Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have
may lead to hospitalization or death. Most patients who developed these infections were
Patients treated with CIMZIA are at increased risk for developing serious infections that
SERIOUS INFECTIONS
• CIMZIA is contraindicated in patients with a history of hypersensitivity reaction to
certolizumab pegol or to any of the excipients. Reactions have included angioedema,
Important Safety Information
CONTRAINDICATIONS
• CIMZIA is contraindicated in patients with a history of hypersensitivity reaction to
certolizumab pegol or to any of the excipients. Reactions have included angioedema,

SERIOUS INFECTIONS
Patients treated with CIMZIA are at increased risk for developing serious infections that
may lead to hospitalization or death. Most patients who developed these infections were
taking concomitant immunosuppressants such as methotrexate or corticosteroids.
Discontinue CIMZIA if a patient develops a serious infection or sepsis.
Reported infections include:
• Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have
frequently presented with disseminated or extrapulmonary disease. Test patients for
latent TB before CIMZIA use and during therapy. Initiate treatment for latent TB prior
to CIMZIA use.
• Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiosis,
aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or
other invasive fungal infections may present with disseminated, rather than localized,
disease. Antigen and antibody testing for histoplasmosis may be negative in some
patients with active infection. Consider empiric anti-fungal therapy in patients at risk
for invasive fungal infections who develop severe systemic illness.
• Bacterial, viral, and other infections due to opportunistic pathogens, including
Legionella and Listeria.
Carefully consider the risks and benefits of treatment with CIMZIA prior to initiating
therapy in the following patients: with chronic or recurrent infection; who have been
exposed to TB; with a history of opportunistic infection; who resided in or traveled in
regions where mycoses are endemic; with underlying conditions that may predispose
them to infection. Monitor patients closely for the development of signs and symptoms
of infection during and after treatment with CIMZIA, including the possible development
of TB in patients who tested negative for latent TB infection prior to initiating therapy.
• Do not start CIMZIA during an active infection, including localized infections.
• Patients older than 65 years, patients with co-morbid conditions, and/or patients taking
concomitant immunosuppressants may be at greater risk of infection.
• If an infection develops, monitor carefully and initiate appropriate therapy.

MALIGNANCY
Lymphoma and other malignancies, some fatal, have been reported in children and
adolescent patients treated with TNF blockers, of which CIMZIA is a member. CIMZIA is
not indicated for use in pediatric patients.
• Consider the risks and benefits of CIMZIA treatment prior to initiating or continuing
therapy in a patient with known malignancy.
• In clinical trials, more cases of malignancies were observed among
CIMZIA-treated patients compared to control patients.
• In CIMZIA clinical trials, there was an approximately 2-fold higher rate of lymphoma
than expected in the general U.S. population. Patients with rheumatoid arthritis,
particularly those with highly active disease, are at a higher risk of lymphoma than
the general population.
• Malignancies, some fatal, have been reported among children, adolescents,
and young adults being treated with TNF blockers. Approximately half of the cases
were lymphoma, while the rest were other types of malignancies, including rare
types associated with immunosuppression and malignancies not usually seen in this
patient population.
• Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell
lymphoma, have been reported in patients treated with TNF blockers, including
CIMZIA. These cases have had a very aggressive disease course and have been fatal.
The majority of reported TNF blocker cases have occurred in patients with Crohn’s
disease or ulcerative colitis, and the majority were in adolescent and young adult
males. Almost all of these patients had received treatment with azathioprine
or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis.
Carefully assess the risks and benefits of treating with CIMZIA in these patient types.
MODERATE TO SEVERE PLAQUE PSORIASIS
WHO ARE CANDIDATES FOR SYSTEMIC THERAPY OR PHOTOTherAPY
AND ADULTS WITH ACTIVE PSORIATIC ARTHRITIS

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- Cases of acute and chronic leukemia were reported with TNF blocker use.

HEART FAILURE
- Worsening and new onset congestive heart failure (CHF) have been reported with TNF blockers. Exercise caution and monitor carefully.

HYPERSENSITIVITY
- Angioedema, anaphylaxis, dyspnea, hypotension, rash, serum sickness, and urticaria have been reported following CIMZIA administration. If a serious allergic reaction occurs, stop CIMZIA and institute appropriate therapy. The needle shield inside the removable cap of the CIMZIA prefilled syringe contains a derivative of natural rubber latex which may cause an allergic reaction in individuals sensitive to latex.

HEPATITIS B VIRUS REACTIVATION
- Use of TNF blockers, including CIMZIA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Test patients for HBV infection before initiating treatment with CIMZIA.
- Exercise caution in patients who are carriers of HBV and monitor them before and during CIMZIA treatment.
- Discontinue CIMZIA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming CIMZIA after HBV treatment.

NEUROLOGIC REACTIONS
- TNF blockers, including CIMZIA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, seizure disorder, optic neuritis, peripheral neuropathy, and Guillain–Barré syndrome.

HEMATOLOGIC REACTIONS
- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with CIMZIA.
- Consider stopping CIMZIA if significant hematologic abnormalities occur.

DRUG INTERACTIONS
- Do not use CIMZIA in combination with other biological DMARDS.

AUTOIMMUNITY
- Treatment with CIMZIA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS
- Patients on CIMZIA should not receive live or live-attenuated vaccines.

ADVERSE REACTIONS
- The most common adverse reactions in CIMZIA clinical trials (≥8%) were upper respiratory infections (18%), rash (9%), and urinary tract infections (8%).

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

### WARNINGS

**SERIOUS INFECTIONS**

Patients treated with CIMZIA are at increased risk for developing serious infections that may lead to hospitalization or death [see Warnings and Precautions and Adverse Reactions]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

CIMZIA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before CIMZIA use and during therapy. Treatment for latent infection should be initiated prior to CIMZIA use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens including Legionella and Listeria.

The risks and benefits of treatment with CIMZIA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. [see Warnings and Precautions and Adverse Reactions].

### MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA is a member [see Warnings and Precautions]. CIMZIA is not indicated for use in pediatric patients.

### INDICATIONS AND USAGE

CIMZIA is indicated for reducing signs and symptoms of Crohn’s disease and maintaining clinical response in adults with moderately to severely active disease who have had an inadequate response to conventional therapy. CIMZIA is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA). CIMZIA is indicated for the treatment of adults with active psoriatic arthritis (PsA). CIMZIA is indicated for the treatment of patients with active ankylosing spondylitis (AS). CIMZIA is indicated for the treatment of adults with moderate-to-severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy. CIMZIA is indicated for adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation.

### CONTRAINDICATIONS

CIMZIA is contraindicated in patients with a history of hypersensitivity reaction to certolizumab pegol or to any of the excipients. Reactions have included angioedema, urticaria, anaphylaxis, serum sickness, and urticaria [see Warnings and Precautions].

### WARNINGS AND PRECAUTIONS

**Risk of Serious Infections (see also Boxed Warning)**

Patients treated with CIMZIA are at an increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacteria, mycobacterium, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with CIMZIA should not be initiated in patients with an active infection, including locally important localized infections. Patients greater than 65 years of age, patients with comorbid conditions, and/or patients taking concomitant immunosuppressants (e.g. corticosteroids or methotrexate) may be at a greater risk of infection. The risks and benefits of treatment should be considered in initiating therapy in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis
- with underlying conditions that may predispose them to infection.

### Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving CIMZIA, including patients who have previously or concomitantly received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating CIMZIA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF-blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating CIMZIA, assess if treatment for latent tuberculosis is needed; and consider an induction of 5 mg or greater a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guérin (BCG).

Consider antituberculosis therapy prior to initiation of CIMZIA in patients with a history of latent history of active tuberculosis or in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite previous or concomitant treatment for latent tuberculosis, cases of active tuberculosis have occurred in patients treated with CIMZIA. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with CIMZIA. Consultation with a physician in expertise in the treatment of tuberculosis is recommended to aid in the decision of whether initiating antituberculosis therapy is appropriate for an individual patient. Strongly consider tuberculosis in patients who develop a new infection during CIMZIA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

### Monitoring

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. [see Warnings and Precautions and Adverse Reactions].

### Dermatitis, erythema nodosum, and gastrointestinal disorders:

Cases of active and/or chronic infections, is not fully understood defenses against infections and malignancies. The impact of treatment with TNF blockers on the immune system, which may also contribute to HBV reactivation.

The following symptoms that could be compatible with hypersensitivity reactions:

- Hypersensitivity Reactions

Consider discontinuation of CIMZIA therapy in patients with confirmed tuberculosis infections. Some patients who have been receiving concomitant immunosuppressants may be at a greater risk of infection. These cases were reported postmarketing and are derived from a variety of sources including registries and spontaneous postmarketing reports. CIMZIA is not indicated for use in pediatric patients.

In the controlled trials of clinical trials (placebo-controlled and open label) a total of three cases of lymphoma were observed among 2,367 patients. This is approximately 2-fold higher than expected in the general population. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. In the CIMZIA P0 clinical trials (placebo-controlled and open label) there were one case of Hodgkin’s lymphoma.

Cases in clinical studies for CIMZIA cannot be compared to the rates of clinical trials of other TNF blockers and may not predict the rates observed when CIMZIA is used in a broader patient population. Patients with Crohn’s disease that require chronic exposure to immunosuppressant therapies may be at higher risk than the general population for the development of lymphoma, even in the absence of TNF blocker therapy [see Adverse Reactions]. The potential role of TNF blocker therapy in the development of malignancies in adults is not known.

Postmarketing cases of hepatocellular carcinoma (HCC), a rare type of liver lymphoma that has a very aggressive disease course and is usually fatal, have been reported in patients treated with TNF blockers, including CIMZIA. The majority of reported TNF blocker cases occurred in adolescent and young adult males with Crohn’s disease or ulcerative colitis. Almost all of these patients had received treatment with the immunosuppressants cyclosporine and/or 6-mercaptopurine (6-MP) concomitantly with a TNF blocker. The potential risk of using a TNF blocker in combination with these other immunosuppressants. The potential risk of using a TNF blocker in combination with cyclosporine or 6-MP should be carefully considered.

Cases of autoimmune and/or chronic leukemias have been reported in association with postmarketing TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-6) than the general population for the development of leukemia. Methotrexate and Azathioprine continue to be the most prescribed medications for rheumatoid arthritis and other indications.

### Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including CIMZIA. CIMZIA has not been formally studied in patients with CHF; however, in clinical studies in patients with CHF with another TNF blocker, worsening congestive heart failure (CHF) and increased mortality due to CHF were observed. Exercise caution in patients with heart failure and monitor them carefully [see Adverse Reactions].

### Hypersensitivity Reactions

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, urticaria, dyspepsia, hypertension, rash, serotonin, and urticaria. Some of these reactions occurred after the first administration of CIMZIA. If such reactions occur, discontinue further administration of CIMZIA and institute appropriate therapy. There are no data on the risks of using CIMZIA in patients who have experienced a severe hypersensitivity reaction towards another TNF blocker, in these patients caution is needed [see Adverse Reactions]. The needle should still be removed the removable cap of the CIMZIA prefilled syringe contains a derivatized of natural table factor which may cause an allergic reaction in individuals sensitive to latex.

### Hepatitis B Virus Reactivation

Use of TNF blockers, including CIMZIA, has been associated with reactivation of hepatitis B Virus (HBV) in patients who are chronic carriers of the virus. The same concern is not applicable to patients receiving TNF blocker therapy has been fatal. The majority of reports have been in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation.
Test patients for HIV infection before initiating treatment with CIMZIA. For patients who test positive for HIV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the use of CIMZIA in patients who are carriers of HIV with antiretroviral therapy in conjunction with TNF blocker therapy to prevent HIV reactivation. Patients who are carriers of HIV and require treatment with CIMZIA should be closely monitored for clinical and laboratory signs of active infection throughout therapy and for several months following termination of therapy.

In patients who develop HIV reactivation, discontinue CIMZIA and initiate effective antiretroviral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HIV reactivation is not known. Therefore, exercise caution when considering resumption of CIMZIA therapy in this situation and monitor patients closely.

Neuropsychiatric Reactions
Use of TNF blockers, of which CIMZIA is a member, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, and with peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of CIMZIA in patients with preexisting or reemerging central or peripheral nervous system demyelinating disorders. Rare cases of neuropsychiatric disorders, including seizure disorder, optic neuritis, and peripheral neuropathy have been reported in patients treated with CIMZIA (see Adverse Reactions).

Hematological Reactions
Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Adverse reactions of the hematologic system, including medically significant cytopenias (e.g., leukopenia, pancytopenia, thrombocytopenia) have been infrequently reported with CIMZIA (see Adverse Reactions). The causal relationship of these events to CIMZIA remains unclear.

Although no high risk group has been identified, exercise caution in patients being treated with CIMZIA who have ongoing, or a history of, significant hematologic abnormalities. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, purpura) while on CIMZIA. Consider discontinuation of CIMZIA therapy in patients with confirmed significant hematologic abnormalities.

Use with Biological Disease-Modifying Antirheumatic Drugs (Biological DMARDs)
Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF blocker, etanercept, with no added benefit compared to etanercept alone. A higher risk of serious infections was also observed in combination use of TNF blockers with chloroquine and thalidomide. Because of the nature of the adverse events seen with the combination therapy, similar toxicities may also result from the use of CIMZIA in the combination. Therefore, the use of CIMZIA in combination with other biological DMARD is not recommended (see Drug Interactions).

Autoimmunity
Treatment with CIMZIA may result in the formation of autoantibodies and rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with CIMZIA, discontinue treatment (see Adverse Reactions). Immunizations
Patients treated with CIMZIA may receive vaccinations, except for live or live attenuated vaccines. No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in patients receiving CIMZIA. In a placebo-controlled clinical trial of patients with rheumatoid arthritis, no difference was detected in antibody response to vaccines between CIMZIA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with CIMZIA. Similar proportions of patients developed protective levels of antivaccine antibodies between CIMZIA and placebo treatment groups; however, patients receiving CIMZIA and concomitant methotrexate had a lower humoral response compared to patients receiving CIMZIA alone. The clinical significance of this is unknown.

Immunosuppression
Since TNF modulates inflammation and modulates cellular immune responses, the possibility exists for TNF blockers, including CIMZIA, to affect host defenses against infections and malignancies. The impact of treatment with CIMZIA on the development and course of malignancies, as well as active or chronic infections, is not fully understood (see Warnings and Precautions and Adverse Reactions). The safety and efficacy of CIMZIA in patients with immunosuppression has not been formally evaluated.

ADVERSE REACTIONS
The most serious adverse reactions were:
- Serious infections (see Warnings and Precautions)
- Malignancies (see Warnings and Precautions)
- Heart Failure (see Warnings and Precautions)

Table 1: Adverse Reactions Reported by ≥3% of Patients Treated with CIMZIA Dosed Every Other Week during Placebo-Controlled Period of Rheumatoid Arthritis Studies, with Concomitant Methotrexate.

<table>
<thead>
<tr>
<th>Adverse Reaction (Preferred Term)</th>
<th>Placebo+ MTX* (%)</th>
<th>CIMZIA 200 mg EOW + MTX* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 6</td>
<td>0 0</td>
</tr>
<tr>
<td>Headache</td>
<td>4 5</td>
<td>2 3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 5</td>
<td>1 4</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 5</td>
<td>0 0</td>
</tr>
<tr>
<td>Rash</td>
<td>1 3</td>
<td>1 3</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>1 3</td>
<td>0 0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 3</td>
<td>0 0</td>
</tr>
</tbody>
</table>

**EOW** = Every other Week; **MTX** = Methotrexate.

Hypertensive adverse reactions were observed more frequently in patients receiving CIMZIA than in controls. These adverse reactions occurred more frequently among patients with a baseline history of hypertension and among patients receiving concomitant anticoagulants and non-stereoidal antiinflammatory drugs.

Patients receiving CIMZIA 400 mg as monotherapy every 4 weeks in rheumatoid arthritis controlled clinical trials had similar adverse reactions to those patients receiving CIMZIA 200 mg every other week.

Other Adverse Reactions
Other infrequent adverse reactions (occurring in less than 3% of RA patients) were similar to those seen in Crohn's disease patients.

Psoriatic Arthritis Clinical Study
CIMZIA has been studied in 497 patients with psoriatic arthritis (PsA) in a placebo-controlled trial. The safety profile for patients with PsA treated with CIMZIA was similar to the safety profile seen in patients with RA and previous experience with CIMZIA.

Arthralgic Spinal Disorders Clinical Study
CIMZIA has been studied in 325 patients with axial spondyloarthritis of whom the majority had ankylosing spondylitis (AS) in a placebo-controlled study (US-1). The safety profile treated with CIMZIA was similar to the safety profile seen in patients with RA.

Non-arthropathic Axial Spondyloarthritis Clinical Study
CIMZIA has been studied in 317 patients with non-arthropathic axial spondyloarthritis (nSpA-Qa1). The safety profile for patients with nSpA treated with CIMZIA was similar to the safety profile seen in patients with RA and previous experience with CIMZIA.

Plateau Psoriasis Clinical Studies
In clinical studies, a total of 1172 subjects with plaque psoriasis were treated with CIMZIA. Of these, 779 subjects were exposed for at least 12 months, 551 for 18 months, and 66 for 24 months.

Data from three placebo-controlled studies (Studies PS1, PS2, and PS3) in 1020 subjects (mean age 46 years, 66% male, 94% white) were pooled to evaluate the safety of CIMZIA (see Clinical Studies (14)).

Placebo-Controlled Period (Week 0-16)
In the placebo-controlled period of Studies PS1, PS2, and PS3 in the 400 mg group, adverse events occurred in 63.5% of subjects in the CIMZIA group compared to 61.8% of subjects in the placebo group. The rates of serious adverse events were 4.7% in the CIMZIA group and 4.5% in the placebo group. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the CIMZIA group than in the placebo group.

**Table 2: Adverse Reactions Reported at a Rate of at Least 1% and at a Higher Rate in the CIMZIA Group Than the Placebo Group.**

<table>
<thead>
<tr>
<th>Adverse Reaction (Preferred Term)</th>
<th>Placebo (%)</th>
<th>CIMZIA 400 mg EOW (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Dermatitis, nSpA</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>14</td>
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<tr>
<td>Rash</td>
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<td>Acne</td>
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<td>Fatigue</td>
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<td>Headache</td>
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<tr>
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<tr>
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<tr>
<td>Rash</td>
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<tr>
<td>Acne</td>
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<td>7</td>
</tr>
</tbody>
</table>

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### Table 2: Adverse Reactions Occurring in ≥1% of Subjects in the CIMZIA Treated Group in Placebo-Controlled Periods of the Pivotal Studies PS-1, PS-2, and PS-3

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>CIMZIA 200 mg every other week n (%)</th>
<th>CIMZIA 400 mg every other week n (%)</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infections 1</td>
<td>75 (21.9)</td>
<td>68 (19.4)</td>
<td>33 (21.0)</td>
</tr>
<tr>
<td>Headache 2</td>
<td>13 (3.8)</td>
<td>10 (2.9)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Injection site reactions 3</td>
<td>11 (3.2)</td>
<td>6 (1.7)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Cough</td>
<td>11 (2.2)</td>
<td>8 (1.1)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Herpes infections 4</td>
<td>5 (1.5)</td>
<td>5 (1.4)</td>
<td>2 (1.3)</td>
</tr>
</tbody>
</table>

1. Upper respiratory tract infection includes upper respiratory tract infection, pharyngitis, bronchitis, pharyngitis streptococcal, upper respiratory tract infection viral, upper respiratory tract infection viral, ventricular myocardial infarction, viral pharyngitis, viral sinusitis, and rhinosinusitis.
2. Headache includes headache and tension headache.
3. Injection site reactions include injection site reaction, injection site erythema, injection site bruising, injection site discoloration, injection site pain, and injection site hematoma.
4. Herpes infections include herpes, herpes dermatitis, herpes zoster, and herpes simplex.
5. Subjects received 400 mg of CIMZIA at Weeks 0, 2, and 4, followed by 200 mg every other week.

#### Elevated Liver Enzymes

Elevated liver enzymes were reported more frequently in the CIMZIA-treated subjects (3.5% in the 200 mg group and 3.4% in the 400 mg group) than in the placebo-control and control patients. For some TNF blockers, higher elevation of liver enzymes, two subjects were discontinued from the trial.

In controlled Phase 3 studies of CIMZIA in adults with psO with a controlled duration ranging from 0 to 16 weeks, ALT and AST elevations ≤5×ULN occurred in 4.9% of CIMZIA 200 mg or CIMZIA 400 mg arms and none in placebo arm.

#### Postmarketing Experience

#### Lansing Vacancy: Do not use (including attenuated) vaccines concurrently with CIMZIA

[See Warnings and Precautions (5.1)]
other adverse pregnancy outcomes. However, certolizumab pegol plasma concentrations obtained from two studies of CIMZIA use during the third trimester of pregnancy demonstrated that placental transfer of certolizumab pegol was negligible in most infants at birth, and low in other infants at birth (see Data). There are risks to the mother and fetus associated with active rheumatoid arthritis or Crohn’s disease. The rheumatism of administration of live or live-attenuated vaccines to the infants exposed in utero to CIMZIA should be weighed against the benefits of vaccinations (see Clinical Considerations). No adverse developmental effects were observed in animal reproduction studies during which pregnant rats or rabbits were administered intravenously a rodent antirheumatic TNFα-pagulated Fab’ fragment (cTNF-FP) similar to certolizumab pegol during organogenesis up to 2.4 times the recommended human dose of 400 mg every 4 weeks.

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

Clinical Considerations

Disease-Associated Maternal and/or Fetal/Renal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with rheumatoid arthritis or Crohn’s disease is correlated with maternal disease activity and that active disease increases the risk of adverse pregnancy outcomes, including fetal loss, preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) and small for gestational age birth.

Fetal/Neonatal Adverse Reactions

Due to its inhibition of TNFα, CIMZIA administered during pregnancy could affect immune responses in the in utero exposed newborn and infant. The clinical significance of BCL or low levels is unknown for in utero exposed infants. Additional data available from one exposed infant suggest that CIMZIA may be eliminated at a slower rate in infants than in adults (see Data). The safety of administering live or live-attenuated vaccines in exposed infants is unknown.

Data

Human Data

A limited number of pregnancies have been reported in the ongoing pregnancy exposure registry. Due to the small number of CIMZIA-exposed pregnancies with known outcomes (n=54), no meaningful comparisons between the exposed group and control groups may be conducted to determine an association with CIMZIA and major birth defects or adverse pregnancy outcomes.

A multicenter clinical study was conducted in 16 women treated with CIMZIA at a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks during the third trimester of pregnancy for rheumatological disease or Crohn’s disease. The last dose of CIMZIA was given on average 11 days prior to delivery (range: 1 to 27 days). Certolizumab pegol plasma concentrations were measured in samples from mothers and infants using an assay that can measure certolizumab pegol concentrations at or above 0.032 mcg/mL. Certolizumab pegol plasma concentrations measured in the mothers at delivery (range: 4.9 to 49.4 mcg/mL) were consistent with non-pregnant women’s plasma concentrations in Study R18 (see Clinical Studies). Certolizumab pegol plasma concentrations were not measurable in 13 out of 15 infants at birth. The concentration of certolizumab pegol in one infant was 0.042 mcg/mL at birth (infant/mother plasma ratio of 0.09%). In a second infant, delivered by emergency Caesarean section, the concentration was 0.258 mcg/mL (infant/mother plasma ratio of 0.42%). In Week 4 and Week 8, all 15 infants had no measurable concentrations. Among 16 exposed infants, one serious adverse reaction was reported in a neonate who was treated empirically with intravenous antibiotics due to an increased white blood cell count; blood cultures were negative. The certolizumab pegol plasma concentrations for this infant were not measurable at birth, Week 4, or Week 8.

In another clinical study conducted in 10 pregnant women with Crohn’s disease treated with CIMZIA (400 mg every 4 weeks for every mother), certolizumab pegol plasma concentrations were measured in maternal blood and cord blood obtained at delivery as cord and infant blood at the day of birth with an assay that can measure concentrations at or above 0.41 mcg/mL. The last dose of CIMZIA was given on average 19 days prior to delivery (range: 5 to 42 days). Plasma certolizumab pegol concentrations ranged from not measurable to 1.66 mcg/mL in cord blood and 1.56 mcg/mL in infant blood; and ranged from 1.87 to 59.57 mcg/mL in maternal blood. Plasma certolizumab pegol concentrations were lower (by at least 25%) in the infants than in mothers suggesting lower placental transfer of certolizumab pegol. In one infant, the plasma certolizumab pegol concentration declined from 1.02 to 0.84 mcg/mL over 4 weeks suggesting that certolizumab pegol may be eliminated at a slower rate in infants than adults.

Animal Data

Because certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent antirheumatic TNFα-pagulated Fab’ fragment (cTNF-FP) similar to certolizumab pegol. Animal reproduction studies have been performed in rats during organogenesis at intravenous doses up to 100 mg/kg (about 2.4 times the recommended human dose of 400 mg, the top of the dose range) and have revealed no evidence of harm to the fetus due to cTNF-FP.

Lactation

Risk Summary

In a multicenter clinical study of 17 lactating women treated with CIMZIA at 200 mg every 2 weeks or 400 mg every 4 weeks, minimal certolizumab pegol concentrations were observed in breast milk. No serious adverse reactions were noted in the 17 infants in the study. There are no data on the effects on milk production. In a separate study, certolizumab pegol concentrations were not detected in the plasma of 9 breastfed infants at 4 weeks post-partum (see Data). The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for CIMZIA and any potential adverse effects on the breastfed infant from CIMZIA or from the underlying maternal condition.

Doses of up to 800 mg subcutaneous and 20 mg/kg intravenous have been administered without evidence of dose-limiting toxicities. In cases of overdosage, it is recommended that patients be monitored closely for any adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

PATIENT COUNSELING INFORMATION

See (1.4) approved patient labeling (Medication Guide).

Risk of Serious Infections

Inform patients that CIMZIA may lower the ability of the immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis and reactivation of hepatitis B virus infections. Because caution should be exercised in prescribing CIMZIA to patients with clinically important active infections, advise patients of the importance of informing their health care providers about all aspects of their health (see Warnings and Precautions).

Malignancies

Control patients about the possible risk of lymphoma and other malignancies while receiving CIMZIA (see Warnings and Precautions).

Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions such as heart disease, neurological disease, or autoimmune disorders. Advise patients to report promptly any symptoms suggestive of a myasthenic syndrome such as vision, breathing, or persistent fever (see Warnings and Precautions).

Hyperreactivity Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of severe hypersensitivity reactions. Advise atopic-sensitive patients that the needle shield inside the removable cap of the CIMZIA prefilled syringe contains a derivative of natural rubber latex (see Warnings and Precautions).
PATIENT-FOCUSED SOLUTIONS IN ROSacea MANAGEMENT: TREATMENT CHALLENGES IN SPECIAL PATIENT GROUPS

Release Date: July 1, 2019
Termination Date: June 30, 2020
Estimated Time to Complete This CE Activity: 1.0 hours
Medium or Combination of Media Used: Written article
Method of Physical Participation: Journal article, Journal post-test, web-based post-test, and evaluation
Hardware/Software Requirements: High speed internet connection, any web browser

Statement of Need
Reports show 16 million individuals in the US are affected by rosacea and account for up to 3% of all cases seen in dermatology practice. Recent reports show rosacea is more common in patients with darker skin types than previously recognized and in skin types III-VI, rosacea may be more difficult to distinguish in the early stages; these patients may not seek treatment until their symptoms are quite severe. Rosacea has a considerable psychosocial impact and is the cause of embarrassment, anxiety, and low self-esteem. Men are more likely than women to feel ridiculed for their appearance despite higher disease prevalence in women. Current treatments aid in the management of rosacea signs and symptoms and therapeutic goals and decisions should include individual, patient-identified issues. Current recommendations for achieving optimal treatment results include achieving clear/almost clear skin and improving key patient-reported outcomes. Therefore, there is need for increased medical knowledge on features, benefits, and limits of available treatment modalities, their effect on minimizing rosacea symptoms, and formulation of optimal individualized rosacea treatment plans in special patient groups often not always considered to be at high risk. Dermatology providers of all levels of training and experience require tools to establish ongoing clinician-patient communication relating to the identification of patient-reported disease impact and the burden of the condition on daily life.

Educational Objectives
The overall information and educational goals of this enduring activity are to expand awareness of the impact of rosacea on quality of life of patients of all ages and genders and skin types including those with darker skin, summarize current rosacea treatment strategies and the unique challenges rosacea presents when treating patients with darker skin types, men versus women, and other special patient types, and formulate effective, individualized rosacea treatment regimens that address patients’ self-reported concerns on the impact of their disease on their overall quality of life.

Upon completion of this continuing education activity participants should be able to:

- Recognize the impact of rosacea on various patient populations including skin types III-IV, younger men, and others
- Define rosacea treatment strategies based on individual diagnosis, disease classification, and patients’ self-reported issues
- Identify challenges to early diagnosis and treatment in patients with darker versus lighter skin, male versus female patients, and other select patient types
- Develop and implement ongoing clinician-patient dialogue to assess the impact, extent, and the burden of rosacea on the individual patient to enable better personalized treatment outcomes

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 cutaneous diseases and disorders affecting patients of all skin types.

Credit Statements
Category 1: Creighton University Health Sciences Education designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AAPA accepts AMA Category 1 credit for the PRA from organizations accredited by ACCME.

Nurse CE: Creighton University Health Sciences Continuing Education designates this activity for 1.0 contact hour for nurses. Nurses should claim only credit commensurate with the extent of their participation in the activity.

Accreditation Statement
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Patient-focused Solutions in Rosacea Management: Treatment Challenges in Special Patient Groups

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Skin of Color Center, Mount Sinai West, Icahn School of Medicine at Mount Sinai, New York, NY

ABSTRACT
Rosacea is among the most common facial skin conditions diagnosed by dermatologists. Typical clinical features include erythema, flushing, telangiectasia, papules, and pustules distributed on the central face. While the prevalence of rosacea in populations of Northern European descent is highest among white populations, recent reports have found that rosacea is present in people from a broad range of racial/ethnic backgrounds and skin types. When rosacea presents in darker skin types, the diagnosis is often challenging due to masking of features by increased epidermal melanin. As such, under-diagnosis and under-reporting may contribute to misconceptions about the prevalence of rosacea in skin of color. Recognizing the unique presentations and complications associated with darker skin types is necessary to reduce the disparity in rosacea treatment, especially as the American population continues to become increasingly heterogeneous. Although rosacea is most common in middle-aged females, patients of different demographics may have more negative impacts on quality of life due to their disease. In this article, we review rosacea management with a focus on special patient groups: people with skin of color, and less common forms of rosacea, in order to diminish the physical and psychosocial burden of rosacea in all patient groups. Due to the variability inherent to rosacea, we advocate for an individualized, patient-centered approach to disease management.


INTRODUCTION
Rosacea is a common, chronic facial condition presenting with various combinations of erythema, flushing, telangiectasia, edema, papules, and pustules most often affecting fair-skinned individuals.1,2 Although most prevalent in light-skinned populations with Fitzpatrick skin types I-II, rosacea affects a broad spectrum of populations, including those with skin of color. The prevalence of rosacea in nonwhite racial/ethnic populations is less studied, but recent data suggest that it is more prevalent than previously reported.3 In order to effectively diminish the physical and psychosocial burden of rosacea, considering the diverse populations groups affected by this condition is paramount.

Epidemiology
The prevalence of rosacea is estimated at about 10 percent of predominantly fair-skinned populations and affects approximately 16 million American adults.4,5 The onset of rosacea is often after 30 years of age and displays a female predominance with the exception of phymatous rosacea (Figure 1), which is more common in older males.4 In younger populations with rosacea, this female predilection is amplified.1 Prevalence of rosacea in Germany and Russia based on general population screening found 18% of subjects with rosacea were aged 18-30 years.6 Though more common in adult females, studies evaluating disease severity support the prevalence of more severe disease in subjects of male gender and less than 60 years of age.7

Until recently, rosacea was widely considered to be a disease almost exclusively affecting light-skinned individuals. However, the prevalence of rosacea in skin of color populations is increasingly being recognized. A study analyzing data from the National Ambulatory Medical Care Survey from 1993-2010 to determine racial and ethnic makeup of patients with rosacea found that of all patients diagnosed with rosacea, 2% were black, 2.3% were Asian or Pacific Islander, and 3.9% were Hispanic or Latino.8 These findings challenge the long held belief that rosacea is a disease largely limited to white individuals of Northern European heritage with Fitzpatrick skin types I-III.

The lower prevalence rates of rosacea in non-white populations is likely due to a combination of factors including under-reporting, under-recognition (due to a low index of suspicion and
diagnostic challenges), protective effects of melanin from ultraviolet (UV) radiation, and a lower incidence of genes conferring susceptibility in diverse populations. Recognizing diagnostic challenges posed by masking of clinical features by increased epidermal melanin are necessary to prevent delayed diagnosis, disease progression, and advanced disease, which result in greater morbidity and even disfigurement. 

Pathophysiology
Pathophysiology of rosacea is likely multifactorial, involving abnormal responses to environmental stressors in individuals with genetic predispositions leading to immune and neurovascular dysregulation. Genetically predisposed individuals have an abnormal response to environmental stressors such as UV exposure, temperature changes, microbial antigens (eg, Demodex folliculorum, Helicobacter pylori), and emotional stress that results in Th1/Th17 polarization.

Studies finding increased risk with positive family history, twin studies with high concordance, and genome association studies support the important role of genetics in rosacea. A cohort-based twin study evaluating the role of genetics and environmental factors in rosacea calculated the genetic contribution to rosacea development to be 46%. Genome-wide association studies isolated three human leukocyte antigen (HLA) alleles with known association to autoimmune disease including type 1 DM and celiac disease within a large population of European descent. Additional studies are needed to further elucidate the complex interplay of genetics and environment in rosacea.

Diagnostic and Classification
Rosacea is a clinical diagnosis based on physical exam and history that can have a wide range of presentations. Guidelines from the National Rosacea Society (NRS) published in 2012 pioneered criteria for rosacea diagnosis and categorization defined by the presence of one or more primary features: flushing, persistent erythema, papules, pustules, and telangiectasia with variable presence of secondary features: burning, stinging, erythematous plaques, dryness, edema, ocular manifestations, and phymatous changes. Furthermore, the NRS identified four rosacea subtypes: erythematotelangiectatic (ETR), papulopustular (PPR), phymatous, and ocular, with one variant: granulomatous based on presence of combinations of various primary and secondary disease features. Though this classification of rosacea is still currently in use and enabled the development of significant clinical and therapeutic advancements in rosacea management, it falls short in its failure to accurately address the broader scope of clinical presentations. Oversimplification of the disease into distinct categories overlooks the fact that often features of multiple subtypes are present simultaneously creating a more complex clinical picture and furthermore, there is often progression from one subtype to another over time. These shortcomings were addressed by the global ROSacea CONcensus (ROSCO) consensus panel, which put forth the first set of guidelines for phenotype driven management, which will be further discussed in the management section of this paper.

Overall, ETR is the most common subtype of rosacea, followed by PPR. Important differences in skin of color include higher reported frequency of PPR compared to ETR (likely due to difficulty recognizing features of ETR in dark skin), as well as increased prevalence of the granulomatous subtype (Figure 2). Phymatous changes, most often seen in older males, are frequently observed in combination with ETR or PPR. Ocular rosacea is frequently diagnosed when other features of rosacea are present to aid in the diagnosis, with nearly 50% of patients experiencing onset of cutaneous symptoms prior to ocular symptoms.

Recently, there has been a shift towards a phenotype-led approach, which more accurately reflects patients seen in clinical practice and has important therapeutic implications, further discussed in the treatment portion of this review. This is especially significant in patients with disease not fitting the prototypical descriptions such as those with skin of color who are less likely to be identified as having predominant telangiectasia and erythematous changes in the skin. Additionally, the current classification system perpetuates the lack of evidence-based research and investigation of less prevalent, but high morbidity subtypes such as phymatous and ocular rosacea.

Rosacea remains under recognized in skin of color, however, there are tools readily available to assist with this oftentimes-challenging diagnosis. Patient history can provide vital information that is not obtainable on exam: this can include a description of burning or stinging sensations, a family history of rosacea or mixed heritage, and even a history of acne that failed to respond to standard treatments. On exam, it may be difficult to appreciate features of erythema and telangiectasia due to masking by constitutive skin pigmentation, but other features such as dryness and edema may be visible on the central face or acneiform papular and pustular lesions in
the absence of comedones or acneiform lesions on the body (Figure 3). Furthermore, strategies to further assess erythema and telangiectasia in darker skin include use of dermoscopy, diascopy to test for blanching, and photography against a dark blue background.

Diagnosis of rosacea requires exclusion of differential diagnoses that may present with centrofacial erythema and must be excluded on a case-by-case basis including seborrheic dermatitis, malar rash of acute cutaneous lupus or systemic lupus erythematosus, chronic photodamage, contact dermatitis, carcinoid syndrome, and niacin ingestion. Given the high prevalence of systemic lupus erythematosus and sarcoidosis in individuals of African descent, black patients presenting with central facial erythema sparing the nasolabial folds or edematous plaques should undergo appropriate work up in order to rule out these conditions including serological evaluation (eg, antinuclear antibody or angiotensin converting enzyme, respectively), punch biopsy, and referral to rheumatology or pulmonology colleagues if indicated.

Quality of Life
Rosacea has significant adverse effects on quality of life (QOL). Physical discomfort due to symptoms such as irritation, itching, burning, or stinging understandably affect an individual’s well-being. Psychosocial effects related to skin changes of rosacea that are typically highly visible and have a substantial effect on physical appearance have been shown to cause shame, embarrassment, low self-esteem, low self-confidence, negative body image, and anxiety. Physical appearance has been shown to have a significant impact on a wide variety of social outcomes from personal relationships and mate selection to workplace success. A German study using willingness to pay as a correlate for disease burden found women and those with more extensive facial involvement willing to pay more, and likely to experience greater negative QOL due to their rosacea than their counterparts who are of male gender or have less facial involvement. The associated stigmatization and frustration experienced by patients are well documented, as are increased rates of psychiatric comorbidities such as social anxiety, depression, and social phobia. Notably, males are more susceptible to stigmatization in setting of rosacea, possibly due to more severe phenotypes such as rhinophyma. Increased stigmatization from rosacea has also been associated with higher rates of depression and social avoidance behaviors.

The psychosocial impact on QOL is often underestimated by physicians, likely in part due to the fact that the objective disease severity does not correlate with the magnitude of effect on QOL, with the exception of depression. A web-based cross-sectional study of 600 adults with ETR and PPR cohorts, respectively, found that 45 and 53 percent disagreed that they were satisfied with their appearance due to rosacea, 42 and 27 percent agreed that they “worry how people will react when they see my rosacea,” and 43 and 59 percent strongly agreed that they feel their rosacea is unattractive to others despite more than 90% of both cohorts self-identifying as having mild to moderate disease. Another important finding in the literature is the reversal of psychological symptoms with therapy; though the number of studies evaluating this outcome are limited future studies will likely continue to evaluate these changes as important measures of treatment success.

Management
Diagnosis of rosacea should promptly be followed by education regarding the chronicity and relapsing nature of the disease as well as the importance of gentle skin care, regular photoprotection with sun protection factor 30 or greater, and trigger avoidance. Identification of patient-specific triggers is essential to preventing disease flares. Use of gentle skin cleansers, frequent use of emollients, and avoiding exacerbating factors such as sunlight, temperature changes, and emotional stress, are primary interventions for managing secondary features namely dry, itchy, painful, burning skin. Counseling should be provided in a culturally sensitive manner, taking into account that recommendations may differ significantly from traditional cultural practices in non-white populations such as regular consumption of spicy foods, aggressive exfoliation, or regular use of abrasive skin brightening and lightening products. Many darker skinned individuals report not using sunscreen out of unfamiliarity or cultural discordance and may struggle to find a cosmetically suitable product.
Telangiectasia (moderate quality evidence). The lack of large controlled trials for the treatment of less common phymatous and ocular subtypes is exemplified by the 2015 Cochrane review of rosacea interventions, which found no RCTs for phymatous rosacea and concluded that more studies are warranted to evaluate treatments for ocular rosacea. ROSCO recommends treatment of inflamed phymatous rosacea with lasers, oral doxycycline, or isotretinoin; therapies for non-inflamed phymas can include CO2 lasers, microdermabrasion, and surgical excision based on patient preferences. Initial treatments for ocular rosacea include education on eye care and lid hygiene, use of lubricating drops, and increased dietary intake or supplementation with omega-3 fatty acids. Collaboration with ophthalmology is recommended for more advanced cases.

High quality RCTs in rosacea are increasing and improving our therapeutic arsenal, however there remains a large gap in knowledge in less common subtypes, namely phymatous and ocular rosacea, as well as the spectrum of rosacea in skin of color. The lack of large controlled trials for the treatment of less common phymatous and ocular subtypes is exemplified by the 2015 Cochrane review of rosacea interventions, which found no RCTs for phymatous rosacea and concluded that more studies are warranted to evaluate treatments for ocular rosacea. ROSCO recommends treatment of inflamed phymatous rosacea with lasers, oral doxycycline, or isotretinoin; therapies for non-inflamed phymas can include CO2 lasers, microdermabrasion, and surgical excision based on patient preferences. Initial treatments for ocular rosacea include education on eye care and lid hygiene, use of lubricating drops, and increased dietary intake or supplementation with omega-3 fatty acids. Collaboration with ophthalmology is recommended for more advanced cases.

Treatment approach for rosacea in non-white populations is the same as that used in white populations, with the exception that special consideration must be given to avoid post inflammatory hyperpigmentation. Few rosacea studies have significant numbers of subjects with skin of color as the general dearth of non-white subjects in clinical trials is amplified in rosacea, which is less prevalent in these populations. Individual studies for oral doxycycline and topical oxymetazoline showed equivalent efficacy in subjects with Fitzpatrick skin phototypes I-III and phototypes IV-VI. Vascular lasers are effective in the treatment of vascular components of rosacea in skin of color, however IPL is generally not advised in types IV-VI due to higher risks of dyspigmentation. Use of longer wavelengths and lower fluence in skin of color is advised to minimize the risk of pigmentedary alterations or scarring.

Given the heterogeneity of rosacea, there is no single best therapy, and often multiple treatment modalities including gentle skin care, trigger avoidance, topical agents, oral medications, and laser- or light-based therapies targeting specific disease manifestations are employed in order to achieve desired results. Randomized control trials (RCT) are an integral part of evidence based medicine, and their data support the use of topical azelaic acid, metronidazole, and ivermectin, as well as oral doxycycline for the treatment of mild to moderate PPR and the use of topical ivermectin and oral doxycycline for severe PPR. Inflammatory lesions of PPR, active phyma, and ocular features can be managed with doxycycline 40 mg as an anti-inflammatory at subantimicrobial doses. Effective treatments targeting the erythema of ETR include topical alpha-adrenergics (eg, oxymetazoline, brimonidine), as well as intense pulsed light (IPL), and pulsed-dye laser (PDL) at 585-595 nm. Telangiectasia require physical modalities for eradication such as electrodesiccation, IPL, or laser therapies. Importantly, the 2015 Cochrane review found no difference in efficacy of IPL and PDL for ery-
Rosacea treatment aims to eliminate and maintain clearance of signs and symptoms of the disease in order to eliminate negative effects the condition has on an individual's QOL. Communication with patients is necessary to reveal an individual's personal concerns, goals, and desires, which often differ from what is predicted by clinicians. For example, erythema has been described as the most troublesome symptom, however, these findings come from predominantly fair-skinned populations and it is plausible that erythema is not as bothersome in non-white populations. Alternatively, erythema may not be appreciated by clinicians, but nonetheless can be bothersome to patients, highlighting the need for individually tailored patient care reflecting the patient's wishes. Optimal results and improved patient outcomes are achieved by understanding the patient's subjective disease severity and goals of treatment prior to initiating therapy. Choice of therapy should incorporate patient preferences and values that can include cost of procedural therapies that are typically not covered by health insurance or preference for topical vs oral or frequency of administration.

CONCLUSION

Rosacea is a chronic inflammatory skin condition due to immune and neurovascular dysfunction that has significant effects on QOL. Though more prevalent in patients with fair skin, rosacea occurs in people of all races and ethnicities and until recently has been largely under recognized in nonwhite populations. In order to optimize treatment of rosacea, recognizing more subtle or less typical features in special patient groups is essential. A patient centered approach targeting disease features most bothersome to patients contributes to improved outcomes including QOL. Future studies should continue to evaluate efficacy in diverse populations to accurately reflect the patients in need of treatment.

REFERENCES


AUTHOR CORRESPONDENCE

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1. What is the estimated prevalence of rosacea globally (inclusive of white and non-white populations)?
   a. 1%
   b. 2%
   c. 10%
   d. 20%

2. Which subtype of rosacea has a male predominance?
   a. Erythematotelangiectatic
   b. Papulopustular
   c. Phymatous
   d. Ocular

3. A 36-year-old female with skin type VI presents with an erythematous plaque on the central face, which condition is the least likely diagnosis?
   a. Lupus
   b. Tinea faciei
   c. Rosacea
   d. Sarcoidosis

4. Which treatment option is best for a patient with Fitzpatrick skin type IV requesting treatment for telangiectasia?
   a. Doxycycline
   b. Oxymetazoline
   c. IPL
   d. PDL

5. Which of the following adverse psychosocial effects is correlated with disease severity?
   a. Stigmatization
   b. Anxiety
   c. Depression
   d. Social anxiety disorder

6. Which of the following therapies is contraindicated in a rosacea patient with type IV skin?
   a. Brimonidine
   b. Oxymetazoline
   c. IPL
   d. PDL
Evaluation Form

PATIENT-FOCUSED SOLUTIONS IN ROSACEA MANAGEMENT: TREATMENT CHALLENGES IN SPECIAL PATIENT GROUPS

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1. The information presented was timely and will influence how I practice.
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2. The information presented enhanced my current knowledge base.
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3. The information presented addressed my most pressing questions.
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4. The activity provided new ideas or information I expect to use.
   1  2  3  4  5

5. The activity addressed competencies identified by my specialty.
   1  2  3  4  5

6. The activity avoided commercial bias or influence.
   1  2  3  4  5

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:
The special focus of JDD helps to share knowledge from experienced key opinion leaders to help us better identify the critical differences in management of special patient populations, cosmetic concerns, and therapeutic of women and people of color.

I commend the authors for deciphering between myths and knowledge gaps in aesthetic treatment of patients of color in this special focus issue. The issue is comprehensive in addressing specific concerns of the Black, Hispanic, Latino, and Asian female patients.

Many cultures associate beauty with an even complexion. It has been shown in many reported references, the major cosmetic concern in patients of color is discoloration. This issue addresses discoloration of individuals of color and the use of a multitude of preparations that can blend the complexion. Authors in Asia, Sweden, France, and Brazil discuss the use of injectable deoxycholic acid in non-submental regions and hyaluronic acid for skin boosting, an off-label usage or procedures in the United States. Skin boosting improves hydration and the smoothness of the skin. Additionally, international methods of treating cosmetic patients with multiple modalities are discussed.

The JDD issue also includes an article on rosacea treatments with a focus on darker skin types. Additionally, the supplement addresses a novel treatment for seborrheic keratoses and specifically, reviews the risks related to treating skin of color. The need of prompt diagnosis and treatment of skin cancer reinforces the need to be more aware of the risk factors, the aggressive nature of melanoma, and the need for adequate sun protection.

Further study of how we approach treatment of special population groups, particularly women, in aesthetic areas is merited. We should further understand the emotional impact of a woman when she doesn’t exude a clear complexion. Clarity of the skin and appearance is the precursor to how a woman feels about herself, and we should shine a light on gaining a deeper understanding of the psychology of women in improving treatment regimens. Is a dermatologist simply improving or clearing a woman’s skin, or are we giving her greater power and freedom to live her best life?
Myths and Knowledge Gaps in the Aesthetic Treatment of Patients With Skin of Color

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ABSTRACT

Background: Misperceptions about facial aesthetic treatments in individuals with skin of color (SOC) may influence treatment selection.
Objective: We aimed to identify knowledge gaps and myths concerning facial aesthetic treatment in individuals with SOC.
Methods: A PubMed search identified articles concerning patients with SOC receiving facial aesthetic treatments. The experience of experts in aesthetic treatment of patients with SOC was also considered.
Results: Knowledge gaps included not seeking injectable filler treatment of lips, risk of developing keloids with injectable filler treatment, risk of hyperpigmentation precluding surgical procedures and nonsurgical injectable filler treatment, melasma being a minor cosmetic concern with limited treatments, and racial/ethnic groups being homogeneous with respect to facial characteristics and aesthetic concerns. Dispelled myths included perceptions that: individuals with SOC do not need sunscreen; dermal fillers and neuromodulators are not necessary or useful for patients with darker skin; laser treatments cannot be used on darker skin; facial products are unnecessary; and only medical providers with SOC can understand how to treat patients with SOC.
Conclusions: Knowledge gaps and myths concerning facial aesthetic treatment in individuals with SOC exist. These patients may undergo various facial aesthetic procedures safely and effectively, as long as nuances in treatment approaches are recognized.


INTRODUCTION

The number of surgical and nonsurgical cosmetic procedures performed in the United States increased by more than 30% between 2010 and 2016, with the percentage of procedures performed in non-Caucasians increasing from 19% to 25%. Despite substantial and increasing interest in aesthetic procedures from individuals with SOC, only a few treatment guidelines or recommendations touch on race or ethnicity in discussions of safety and efficacy. Dermatologists and plastic surgeons may thus be hesitant to treat patients with SOC, based on inadequate guidance for that population. A national survey of Australian dermatologists found that 75% were not confident in performing cosmetic procedures for patients with SOC, and a majority expressed a desire for more training on medical conditions and surgical and cosmetic issues in SOC, emphasizing the need for education on treating these patients. Further, widespread and often unsubstantiated anecdotal information regarding treatment preferences and outcomes in people with SOC has encouraged myths about skin care and aesthetic treatment that may prevent this population from receiving the best possible care.

This paper aims to examine knowledge gaps that may exist in the medical community and to dispel patient-held myths associated with skin care and aesthetic treatment in SOC.

METHODS

Based on their clinical experience, the authors, who are experts in the aesthetic treatment of individuals with SOC, identified and reached consensus on myths and knowledge gaps in the aesthetic treatment of individuals with SOC. PubMed searches were conducted on these areas and the results were reviewed for relevance to individuals with SOC.

KNOWLEDGE GAPS IN THE MEDICAL COMMUNITY

Gap: Darker-Skinned Patients of African Descent Do Not Seek Injectable Filler Treatment of the Lips

Response

Darker-skinned patients of African descent may be less likely to undergo enhancement of the lips, but they do request restoration of lip volume lost through aging, generally presenting at an older age than Caucasian patients seeking lip enhancement (Figure 1).
Allergan plc, Dublin, Ireland.

(A) and at 3 months after treatment (B).

Patient is shown before treatment (A) and at 3 months after treatment (B). Reprinted with permission from Allergan plc, Dublin, Ireland.

**FIGURE 1.** Photos of a 74-year-old black female with Fitzpatrick skin phototype VI who received a total of 2.4 mL HYC-24L (Juvéderm Ultra XC) at initial and touch-up treatment in her upper and lower lips, oral commissures, and philtral columns. Patient is shown before treatment (A) and at 3 months after treatment (B). Reprinted with permission from Allergan plc, Dublin, Ireland.

**FIGURE 2.** Melasma in a patient with skin of color before (A) and after (B) combination therapy (chemical peels and hydroquinone 6%). Images published with permission from P. Grimes.

Gap: Melasma Is A Minor Cosmetic Concern With No Effective Treatment Options Beyond Sun Protection and Periodic Use of Hydroquinone®

**Response**

Dyschromia, including post-inflammatory hyperpigmentation (PIH) and melasma (Figure 2), is one of the most common conditions diagnosed in darker-skinned patients and is an important concern in patients with SOC. Dyschromia, including PIH and melasma, was the second-most common condition (19.9% of visits) diagnosed in black individuals in a retrospective chart review of 1412 patient visits at a large dermatology practice specializing in treating patients with SOC. Melasma, which can adversely affect quality of life, is more common in Fitzpatrick skin phototypes IV through VI and in geographic regions that receive more sun exposure. Topical hydroquinone 4% is the standard of care, but other treatments, including azelaic acid, kojic acid, niacinamide, alpha-hydroxy acid products, ascorbic acid, and retinoid topical therapies, are effective if used with appropriate caution. Superficial and medium-depth chemical peels and laser treatment may also be effective but both therapies require further study and should be used with caution, as they themselves are associated with a risk of hyperpigmentation. Deeper peels and (nonfractional) ablative lasers are contraindicated in patients with darker skin, based on the authors’ clinical experience, because of greater risk of scarring and dyspigmentation. It should be emphasized that sunscreen use is an integral, essential component of any treatment regimen for melasma.

**Gap: Patients With SOC Should Not Undergo Surgical Procedures or Even Receive Nonsurgical Injectable Filler Treatment Because There Is a Risk of Developing Hyperpigmentation**

**Response**

In 2016, 1.6 million Hispanics, 1.3 million African Americans, and 1.1 million Asian Americans selected to undergo cosmetic procedures. Patients with SOC are at greater risk of PIH, which can be a sequela of inflammatory dermatoses (eg, acne) or cosmetic and surgical procedures (eg, chemical peel, laser treatment). Hyperpigmentation was reported in one study in approximately 2% to 17% of patients (6% of injection sites) with Fitzpatrick skin phototypes IV through VI receiving hyaluronic acid filler injections for correction of nasolabial folds, but was generally mild and transient. In one study, injection techniques using multiple or serial punctures were associated with an increased risk of hyperpigmentation. Hyperpigmentation may be effectively treated with topical prescription skin-lightening agents or cosmeceuticals. The authors agreed that injecting filler too superficially or too quickly, or using serial epidermal punctures, may increase the risk of hyperpigmentation.

**Gap: Patients With SOC Have a Substantial Risk of Developing Keloids With Injectable Filler Treatment or Surgery**

**Response**

Product labeling for injectable fillers indicates that the safety of these products in patients with known susceptibility to keloid formation has not been evaluated. However, a number of products were not associated with keloid development in clinical trial participants with SOC. The experience of the authors suggests that the development of keloids following treatment with injectable fillers is rare in individuals with SOC. No keloids were reported in patients with SOC in post-approval studies of injectable filler treatments, in a long-term study comparing patients with Fitzpatrick skin phototypes I through III versus IV through VI, or in a case review of 60 patients that included 20 patients with Fitzpatrick skin phototypes IV through VI.

In aesthetic surgery, less invasive options with smaller incisions are generally preferred for patients with SOC. Optimal incision placement, meticulous technique, and closure of surgical wounds with minimal tension are particularly important in patients with SOC to minimize the risk of hypertrophic scarring. Clinical experience suggests that dermal injury from 27-gauge needle puncture does not appear to be associated with significant keloid risk.
among individuals with SOC.37 In National Health and Nutrition Examination Survey data (N=4412), the percentage of respondents who never used sunscreen was greatest for non-Hispanic blacks, followed by Hispanics, then non-Hispanic whites.38 Similarly, the proportion of individuals with SOC in a recent facial aging study (N=4086) who reported never or rarely using sunscreen was substantially greater in respondents with SOC, especially black individuals, compared with Caucasians (Figure 3).39,40

Response
The degree of natural protection across the spectrum of skin types is highly variable; it depends on the size and distribution of melanosomes that, in turn, vary by constitutive melanin pigmentation.41 Photoaging and UVR exposure-mediated skin disorders, including skin cancers, occur in all skin types, albeit at different rates and clinical presentations.42,43 Patients with Fitzpatrick skin phototypes IV, V, or VI can get sunburned (Figure 4).44 Identifying sunburns may be more challenging in darker-skinned individuals; therefore, these individuals may underestimate their photosensitivity. Although nonmelanoma skin cancer is less prevalent in darker skin types, morbidity and mortality is often higher in patients with SOC.43 Patchy dyschromia, including melasma, and isolated dark spots on the skin or diffuse, patchy darkening may occur in SOC if sun protection is not used.36 Sunscreen with a sun protection factor (SPF) of at least 30 should be used to protect against UVR-induced sunburn, skin cancer, photoimmunosuppression, and photoaging of the skin, as well as melasma and photo-induced pigmentation.5,36 UVR exposure can reduce skin elasticity, which contributes to skin sagging; therefore, use of sunscreen may potentially reduce sagging. Sunscreen is also important in the management of PIH and post-therapy care for patients undergoing in-office procedures, such as chemical peels or laser treatments.6,15,19 Patients with SOC who use sunscreen should consider vitamin D supplementation, given the high prevalence of vitamin D deficiency in darker skin types and the importance of vitamin D in maintaining bone health. Low levels of vitamin D are also associated with nonskeletal health conditions, such as diabetes and heart disease.46

MYTHS HELD BY PATIENTS

Myth: Individuals With Darker Skin Do Not Need to Use Sunscreen

Background
The higher melanin content in SOC confers some degree of natural protection against the deleterious effects of ultraviolet radiation (UVR) from the sun; however, all skin types are susceptible to photodamage.29,36 Rates of sunscreen use are lower...
Caucasians.9 In the recent facial aging study, black respondents consequently tend to develop lines and rhytids later in life than significantly greater in patients with SOC versus Caucasians (P ≤.03),

The protection afforded by darker skin may reduce or slow photoaging from UVR.9,31,35 Individuals with darker skin consequently tend to develop lines and rhytids later in life than Caucasians.9 In the recent facial aging study, black respondents showed less severe signs of facial aging compared with Caucasian, Hispanic/Latino, and Asian respondents.39 Individuals with SOC demonstrated a delay in the onset of signs of aging by 10 to 20 years relative to Caucasians.39,40 While lighter-skinned individuals tend to display more lines and wrinkles, darker-skinned individuals display more volume depletion and sagging, with consequent folds.39,40

Response
Patients of all skin types will experience aging effects that may prompt them to seek aesthetic treatment.19 Volume restoration for sagging skin is common for individuals with SOC. Notably, soft-tissue filler treatment and neuromodulator injections are among the most popular minimally invasive aesthetic treatments for individuals with SOC.17 Studies in patients with SOC suggested that such treatment is safe and effective.46,47 In a post hoc analysis comparing the response and safety of abobotulinum toxin type A treatment of glabellar lines in patients with SOC and Caucasians, the response rate after 30 days was significantly greater in patients with SOC versus Caucasians (P≤.03), with similar adverse event rates between groups.47

Myth: As Dark Skin Protects Against Age-related Lines and Wrinkles, Dermal Fillers, and Neuromodulators Are Not Necessary or Useful for Patients With Darker Skin

Background
The greater amount and density of melanin in darker skin can act as a competing chromophore during laser and light-based procedures in SOC, particularly with visible and near-infrared devices.46 Therefore, laser and light-based treatments in patients with SOC are associated with a greater risk of tissue damage and resultant hyper- or hypopigmentation and scarring.46 In addition, post-treatment inflammation from laser or other energy-based devices may induce postinflammatory pigment alteration.

Myth: Laser Treatments Cannot Be Used on Dark Skin

Background
Myths: Individuals With Darker Skin Do Not Need to Use Skin Cleansers or Moisturizers; Oily Skin Is Protective

Background
Sebum secretion may be higher in individuals with SOC versus those with lighter skin,52 although at least 1 study53 found no difference between blacks and Caucasians in skin surface sebum. Studies suggest that facial cleansing practices do vary with ethnicity: In a survey of 423 Californians, Latino respondents had
lower rates of use of both skin cleansers and moisturizers compared with black, white, and Asian respondents. In another study, the proportion of respondents who rarely or never used facial moisturizers was greater in black (43%) and Latino (40%) women than in Caucasian (33%) women.

Response
A balance between facial cleansing and the preservation of skin oil/skin moisture is necessary for optimal aesthetic outcomes. Facial cleansers remove dirt, excess sebum, microorganisms, exfoliated corneum cells, and other foreign substances, such as cosmetics and medications, from the skin surface. Sebum has naturally occurring antioxidant and antimicrobial properties and may potentially contribute to the maintenance of good skin quality attributes, such as smoothness.

Cleansers with an acidic pH, moisturizers, and high rinsability are recommended; those that contain non-ionic/silicone-based surfactants combined with moisturizers may cause the least disruption to the skin barrier and to the normal skin flora. Gentle soap-free cleansers may be an option for some patients. While removal of all oil is not the goal, the removal of excess oil that traps dead skin debris is key, while using a moisturizer to restore the protective barrier. We recommend washing the face and neck at least nightly while considering the use of therapeutic topical agents, such as retinol, at night, and then lightly cleansing or rinsing in the morning to prevent overdrying of the skin. In addition, we recommend gentle cloths and gentle makeup removers for facial cleansing, and daytime moisturizers with an SPF of 30. Moisturizers can maintain skin hydration and restore barrier function that may be disrupted by cleanse use, and may also reduce the dryness of skin in individuals with SOC.

Dermatologists and plastic surgeons consider the use of topical cleansers and moisturizers to be an important component of skin disease management, especially in patients with compromised skin barrier function. However, even among individuals with chronic dermatologic conditions, the use of moisturizers and cleansers is low, suggesting that physicians must clearly communicate their recommendations on the use of facial cleansers and moisturizers.

Myth: Only a Medical Provider With SOC Can Understand the Nuances of Treating Patients With SOC

Background
There is evidence to suggest that black, Hispanic, and Asian patients disproportionately receive care from racially concordant physicians, and that patients who select their physicians are more likely than those assigned to a physician to have a clinician of the same race or ethnicity. In the experience of the authors, this is true of facial aesthetics practices as well. A survey of 1205 black and white residents in Ohio found that black respondents were significantly more likely than white respondents to believe that racially concordant physicians understood their health problems (27% vs 12%) and to anticipate being more at ease with racially concordant physicians (27% vs 20%). In a separate survey of 118 patients from 2 dermatology practices, patient and physician racial concordance did not affect patients’ perception of satisfaction and trust; however, patients with SOC who had Caucasian health care providers indicated issues relating to having all of their questions answered, feeling that the provider had listened to them, and comfort with their treatment plan.

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>Recommended Strategies for the Successful Treatment of Patients With Skin of Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consideration</td>
<td>Recommended Strategy</td>
</tr>
<tr>
<td>Overall</td>
<td>Maintain an up-to-date understanding of issues related to treatment</td>
</tr>
<tr>
<td>Understand patient concerns and expectations in light of ethnic background and physical characteristics</td>
<td></td>
</tr>
<tr>
<td>General skin care</td>
<td>Counsel patients to use sunscreen (SPF of ≥30) and explain the risks associated with not using sunscreen. Recommend vitamin D supplementation in patients who use sunscreen</td>
</tr>
<tr>
<td>Encourage the use of moisturizers and washing the face and neck at least nightly, followed by a light cleanse or rinse in the morning, especially for patients with conditions that may compromise the skin barrier</td>
<td></td>
</tr>
<tr>
<td>Treatment of melasma</td>
<td>Choice of effective pharmaceutical and cosmeceutical agents, although topical hydroquinone 4% remains the standard of care</td>
</tr>
<tr>
<td>Recommend sunscreen use as a component of any treatment regimen for melasma</td>
<td></td>
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<tr>
<td>Collect a thorough medical history to understand the risk of adverse reactions in individual patients</td>
<td></td>
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<tr>
<td>Provide the patient with an accurate understanding of the risks associated with the procedure</td>
<td></td>
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<tr>
<td>When performing laser treatments, consider using longer wavelength lasers, lower fluences, lower treatment densities, and epidermal cooling techniques to prevent tissue damage</td>
<td></td>
</tr>
<tr>
<td>Use test spots before carrying out laser treatments to determine how the skin may respond (strongly recommended for any new laser device acquired by a practice)</td>
<td></td>
</tr>
<tr>
<td>When using dermal fillers, consider adjustments in injection technique (eg, deeper placement of fillers in the dermis, avoiding serial epidermal puncture trauma) that may limit the risk of PIH</td>
<td></td>
</tr>
<tr>
<td>Discuss posttreatment care with the patient and explain how following recommendations may reduce the risk of adverse events</td>
<td></td>
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</table>

PIH, postinflammatory hyperpigmentation; SPF, sun protection factor.
CONCLUSIONS

Both practitioners and patients are concerned about treatment involving SOC. Some concerns are based in fact, such as the risk of PIH, while others are based on broad generalizations that may not be relevant to currently available, minimally invasive treatment options and accepted techniques. Patients with SOC can undergo aesthetic procedures safely and effectively, as long as nuances to the treatment approach are recognized and addressed.

More information is needed in some areas, such as reduction of the risk of dyschromia and more effective treatment for the condition, as are safer and more effective lasers and devices for patients with SOC. Future research on these topics, along with the development of new treatments, such as non-hydroquinone therapies for hyperpigmentation and melasma, will further improve clinicians’ ability to provide safe and effective treatment to all of their patients. The importance of skin care regimens that may help to minimize or delay the need for facial aesthetic treatment, such as the use of sunscreen for the prevention of UVR damage, cannot be underestimated. All clinicians have a responsibility to remain up-to-date in their understanding of issues related to treating patients of any racial/ethnic background or skin type, and to keep their patients informed about the actual risks versus common but unfounded perceptions.

REFERENCES


Understanding the Female Hispanic and Latino American Facial Aesthetic Patient

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Background: Among the growing aesthetic patient population, Hispanic/Latinos represent the largest proportion of non-Caucasians patients. While treatment of Caucasian facial aging patterns are well documented, far less information describes the aesthetic needs of the Hispanic/Latino patient.

Objective: An online study was designed to survey facial aesthetic concerns, treatment priorities, and future treatment considerations among a US-based population of Hispanic/Latino American women.

Materials and Methods: A total of 401 participants ages 30 to 65 years reported their attitudes toward facial aging, current facial conditions, most bothersome facial areas, areas most/least likely to be treated first, awareness of treatment options and their consideration rates, and motives and barriers that factor into consideration of injectable treatments.

Results: Most participants wanted to look good for their age and treatment interests reflected predominant conditions: facial wrinkles, periorbital signs of aging, and uneven skin tone. Most bothersome facial areas included the submental area, periorbital area, and forehead, which were also among the areas most-likely to treat first. The majority of participants would consider injectables. Cost and safety/side effects were cited as frequent concerns.

Conclusion: An understanding of the facial aesthetic concerns and treatment priorities specific to Hispanic/Latino women will enhance the practitioner’s patient-centric treatment approach.

only the structural and cutaneous signs of aging but also the patient’s attitudes toward aging are integral in a patient-centric treatment plan.

The current study aimed to survey the facial aesthetic concerns and treatment priorities among a population of Hispanic/Latino American women who were aesthetically-oriented yet naive to facial injectable treatment use. The data encompassed: 1) attitudes toward signs of facial aging and current facial conditions; 2) facial areas that are most bothersome; 3) facial areas most/least likely considered a priority in a future aesthetic treatment plan; 4) awareness of available aesthetic treatments and their consideration rates, and 5) motives and barriers factoring into consideration of injectable treatments. The data presented here is a subset of a larger study which consisted of 1205 women and also included African American and Asian American participants.12

METHODS

Participants and Study Design
Participants were recruited through online river sampling (banner ads, pop-up ads, instant capture promotions) by the Lieberman Research Worldwide (LRW) agency between March and April 2016. Primary inclusion criteria were: 1) females ages 30 to 65 years old living in the USA; 2) aesthetically-oriented, qualified by level of agreement on an aesthetic orientation screening questionnaire; 3) household annual income >$50,000; 4) naïve to facial injectable treatments; 5) awareness of BOTOX® Cosmetic; and 6) with some discretionary spending flexibility; 4) naïve to facial injectable treatments. The data presented here is a subset of a larger study which consisted of 1205 women and also included African American and Asian American participants.12

Participants identified their ethnic background as one of the following: Mexican, Mexican American, Puerto Rican, Cuban, or “Other Spanish, Hispanic, or Latino.” A questionnaire adapted from the Skin Cancer Foundation website was used to categorize participants by Fitzpatrick Skin Phototype (FSP) I through VI.13,14 The questionnaire took into account eye color, natural hair color, skin color (non-exposed areas, presence/absence of freckles (non-exposed areas), and skin response to ultraviolet radiation (UVR), including the susceptibility of facial and body skin to burn or turn brown (tan) following exposure. Participants also identified their pigmented characteristics by selecting a color most representative of their natural skin tone from a range of 11 skin codes (colors).15

MEASURES AND ANALYSIS

Attitudes Toward Facial Aesthetics and Existing Facial Concerns Questionnaires
Attitudes toward improving facial aesthetics were assessed by the aesthetic orientation screening questionnaire which included a list of options paired with the question “How strongly do you agree with each statement on a scale of 1 (completely disagree) to 6 (completely agree)?” Existing concerns were identified from a list of options paired with the following question: “Would you consider talking to a physician about a treatment for any of the following within the next 2 years?”

Most Bothersome Facial Areas and Treatment Priorities Questionnaires
A 15-point facial diagram and a 6-point Likert scale (1, “not at all bothered” to 6, “very bothered”) were used to assess how bothersome each area was if at all (Figure 1). A Maximum Difference (MaxDiff) ranking methodology, also referred to as “Best/Worst scaling” was then used to generate a rank order of each area as it related to treatment priority.16 Nine different iterations of the facial diagram were shown, each consisting of 3 facial areas at a time until all 15 features were presented. With each iteration, 1 area was selected as the “most likely to be treated first” and 1 area as the “least likely to be treated first.” MaxDiff ranking scores were represented by a “relative importance” value. An average ranking of importance was established among all areas combined. Areas ranking above average represented greater importance and priority relative to those areas ranking close to or below the average.

Awareness of Aesthetic Procedures and Future Treatment Considerations Questionnaires
Treatment procedure awareness and future treatment considerations were identified from a list of options paired with the questions: “Which treatments that are administered in a physician’s office have you ever heard of?” and “Which facial treatments that are administered in a physician’s office would you consider within the next 2 years?”

Motives and Barriers Impacting Consideration Rate of Injectable Treatment Questionnaires
Motives and barriers were identified from a list of options paired with the questions: “Which of the following describes why you would consider a facial injectable treatment for facial lines, wrinkles, and folds in the next 2 years?” and “Which of

FIGURE 1. Diagram used to select most bothersome facial areas and treatment priorities.
FSP III or IV (71%) and a large proportion (46%) self-identified with a Mexican ethnic background (Table 2).

**Attitudes Toward Improving Facial Aesthetics and Existing Facial Concerns**

Most participants agreed with the statement that they wanted their face to look good for their age (84%). A large proportion was interested in treatments that could make them look less tired (72%), and that would address facial lines/wrinkles/signs of aging (63%) as well as hyper/hypo-pigmentation (63%) (Figure 2). Facial wrinkles (56%), dark under-eye circles (55%), uneven skin tone/color (47%), and bags under the eyes (45%) were among the most frequently-reported conditions (Figure 3).

**Most Bothersome Facial Areas**

The most bothersome areas included sagging underneath the chin/double chin (41%), under-eye/tear trough area (37%), crow’s feet lines (CFLs) (37%), and forehead lines (FHLs) (36%). These were followed by glabellar lines (GLs) (31%) and areas of the mid-to-lower face, including nasolabial folds (NLFs) (34%), oral commissures (OCs) (32%), chin (27%), and marionette lines (MLs) (27%; Figure 4). Perioral lines (25%), jawline (23%), lips (22%), cheeks (20%), and temples (16%) were the least bothersome areas.

**Data Analysis**

Max Diff analyses and analysis for correlation between bothersome facial areas and their treatment priorities were conducted by the LRW agency and presented descriptively by percent or by average.

**RESULTS**

**Participants**

The majority of the 401 participants included in the study were 30 to 44 years old (57%), born in the USA (83%), married (83%), with household income > $75,000 (71%), an average spending of < $250/month on facial aesthetic products/services (70%), and had previously spent ≥ $250 on a single medical facial treatment (59%; Table 1). The majority were categorized as FSP III or IV (71%) and a large proportion (46%) self-identified with a Mexican ethnic background (Table 2).

**Attitudes Toward Improving Facial Aesthetics and Existing Facial Concerns**

Most participants agreed with the statement that they wanted their face to look good for their age (84%). A large proportion was interested in treatments that could make them look less tired (72%), and that would address facial lines/wrinkles/signs of aging (68%) as well as hyper/hypo-pigmentation (63%) (Figure 2). Facial wrinkles (56%), dark under-eye circles (55%), uneven skin tone/color (47%), and bags under the eyes (45%) were among the most frequently-reported conditions (Figure 3).
**FIGURE 2.** Attitudes toward improving facial aesthetics.

- I want my face to look good for my age: 84%
- I care about improving my facial appearance: 81%
- I am willing to spend money on my facial appearance: 73%
- I would consider a treatment that makes me look less tired: 72%
- I currently follow a daily skincare regimen: 68%
- I would consider a treatment that addresses my facial lines and wrinkles: 68%
- I would consider a treatment that addresses my hyper/hypo-pigmentation: 63%
- I am bothered by facial lines, wrinkles, and signs of aging: 58%

*Note: Rating of 4, 5, or 6 defined as “agreement”. Rating of 4, 5, or 6 on any statement was considered “aesthetically-oriented”. Survey question: “How strongly do you agree with each statement on a scale of 1 (completely disagree) to 6 (completely agree)?”*

**FIGURE 3.** Existing facial concerns.

- Facial wrinkles: 56%
- Dark circles under the eyes: 55%
- Uneven skin tone or color (dark/light spots): 47%
- Bags under the eyes: 45%
- Large pore size: 43%
- Double chin: 39%
- Facial sun damage: 38%
- Acne scarring: 35%
- Oily skin: 35%
- Sagging facial skin: 30%
- Sagging skin under the brow and above the eyelid: 25%
- Red or rosy facial appearance: 20%
- Broken capillaries on face: 16%

*Survey question: “Would you consider talking to a physician about a treatment for any of the following within the next 2 years?”*

**FIGURE 4.** Most bothersome facial areas.

- Forehead and brow: 41%
- Cheek lines: 37%
- Cheek line in: 37%
- Nasal labial fold: 36%
- Oral commissure: 34%
- Marionette lines: 32%
- Chin: 31%
- Marrowette lines: 30%
- Lip: 27%
- Cheek: 27%
- Neck: 25%
- Earlobe: 23%
- Lower lip: 22%
- Under eye: 20%
- Cheek (full): 16%

*Survey question: “Please indicate how bothered you are, if at all, by the lines, wrinkles, and folds at each area on your face using a scale of 1 (not bothered at all) to 6 (very bothered)?”*
Treatment Priorities

The treatment priorities of each facial area (represented by relative importance scores) ranged from 27 to 77 with treatment priorities tending to correlate with bothersome facial areas (R² = .81, data not shown). In younger participants (ages 30 to 44), areas of the upper face had the highest priorities and included the under-eye/tear trough area (77) and CFLs (75; Figure 5a). Other areas of high importance were FHLs (64), sagging underneath the chin/double chin (64), GLs (56), OCs (55), and NLFs (54). Mid-to-lower facial areas such as chin (44), MLs (43), jawline (38), and cheeks (35) were lower priorities, and perioral lines (32), temples (31), and lips (27) were the least likely to be prioritized for treatment.

For the older participants (ages 45 to 65), under-eye/tear trough area (70) and CFLs (68) remained a top priority but sagging underneath the chin/double chin had increased importance (67; Figure 5b).

Subsequent priorities were NLFs (61), OCs (59), FHLs (59), and GLs (56), followed by MLs (49), jawline (44), and chin (42). Mid-to-lower facial areas such as perioral lines (36) and cheeks (33) were lower priorities, and lips (27) and temples (27) were the lowest priorities.

Awareness of Treatments Options and Future Treatment Consideration Rates

Most participants were aware of the treatments or procedures used to enhance skin quality such as microdermabrasion (89%), laser skin resurfacing (88%), skin tightening procedures (83%), and chemical peels (79%; Figure 6a), and high consideration rates were observed for those treatments within the next 2 years (43 - 64%; Figure 6b). Furthermore, all were aware of neuromodulators (100%), most were aware of under chin fat reduction (79%) and dermal fillers (70%) products, with 69%, 32%, and 35% consideration rates, respectively.

Motives and Barriers Impacting Consideration Rate of Injectable Treatments

Among the 84% (341/401) who would consider an injectable treatment, the most common motives were wanting their face to look good for their age (64%) and to look more youthful (52%; Figure 7). Interestingly, a much smaller proportion agreed with wanting to maintain a competitive edge in the workforce (15%) and to look good for their age (64%) and to look more youthful (52%; Figure 7). These motives are also influenced by an individual’s ethnic background. A high proportion of responders considered treatments that would make them look less tired (72%) and address facial wrinkles and lines (68%) and hyper/hypo-pigmentation (63%); correspondingly, a majority also reported having facial wrinkles (56%), dark circles under the eyes (55%), uneven skin tone/color (47%), and bags under eyes (45%). Although the greater melanin content in more darkly pigmented skin types affords some protection against the immediate effects of UV exposure (eg, sun burn), photodamage still occurs and results in pigmentary changes (eg, freckling, solar lentigo, melasma) and increases an individual’s risk factor for post-inflammatory hyperpigmentation (PIH) following inflammation or injury. Melasma and hyperpigmentation are believed to occur more frequently in Hispanic and Latino ethnicities, with as many as half of all Mexican women reporting melasma associated with pregnancy.

Most Bothersome Facial Areas and Treatment Priorities

Bothersome facial areas correlated somewhat with treatment priorities (R² = .81, data not shown), and any discrepancy (ie, lower importance for short, thinning lashes) might represent areas more easily enhanced by the application of cosmetics versus those that are not. The most bothersome facial areas reported by all were sagging underneath the chin/double chin, under-eye/tear trough, CFLs, and FHLs. While these all translated to areas with high treatment priority, differences between the younger and older age groups were observable. Among the more advanced age group (45 to 65-year-olds) sagging underneath the chin/double chin and areas of the lower face (OCs and NLFs) increased in relative importance in comparison to the younger age group (30 to 44-year-olds). This result is expected since increasing midface ptosis, which accompanies facial aging, can exacerbate grooves and folds in the lower face and displace the importance assigned to areas of the upper face (under-eye/tear trough, CFLs, and FHLs) at a younger age. Also aligned with that reasoning is the change in the importance of the marionette lines (MLs) and the jawline, which were scored as lower priorities by the younger group but increased in importance in the older group.

DISCUSSION

The rate of onset, severity, and pattern of facial aging is influenced by race and ethnicity, while the motives that prompt an individual to seek treatment may be based more on social and cultural ideals of beauty and attitudes about improving their facial aesthetics. In this survey of 401 Hispanic/Latino American women aged 30 to 65, the predominant aesthetic concerns and goals were reported, which may help familiarize practitioners with this patient population and help guide relevant treatment plans.

Attitudes Toward Improving Facial Aesthetics

Participant attitudes about facial aesthetics suggest attitudes about facial aesthetic treatments may stem from current skin and facial conditions, which are also influenced by an individual’s ethnic background. A high proportion of responders considered treatments that would make them look less tired (72%) and address facial wrinkles and lines (68%) and hyper/hypo pigmentation (63%); correspondingly, a majority also reported having facial wrinkles (56%), dark circles under the eyes (55%), uneven skin tone/color (47%), and bags under eyes (45%). Although the greater melanin content in more darkly pigmented skin types affords some protection against the immediate effects of UV exposure (eg, sun burn), photodamage still occurs and results in pigmentary changes (eg, freckling, solar lentigo, and melasma) and increases an individual’s risk factor for post-inflammatory hyperpigmentation (PIH) following inflammation or injury. Melasma and hyperpigmentation are believed to occur more frequently in Hispanic and Latino ethnicities, with as many as half of all Mexican women reporting melasma associated with pregnancy.
**FIGURE 5A AND 5B.** Treatment priorities based on the relative importance of each facial area.

**FIGURE 6A AND 6B.** Awareness of treatments and treatments considered within the next two years.

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**6a) Awareness of Facial Treatments and Procedures**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial plastic surgery</td>
<td>96</td>
</tr>
<tr>
<td>Liposuction</td>
<td>90</td>
</tr>
<tr>
<td>Microdermabrasion</td>
<td>89</td>
</tr>
<tr>
<td>Laser skin resurfacing</td>
<td>88</td>
</tr>
<tr>
<td>Skin tightening procedures</td>
<td>83</td>
</tr>
<tr>
<td>Chemical peels</td>
<td>79</td>
</tr>
<tr>
<td>IPL/Phototheraphy</td>
<td>31</td>
</tr>
<tr>
<td>Neurmodulators</td>
<td>100</td>
</tr>
<tr>
<td>Under chin fat reduction</td>
<td>79</td>
</tr>
<tr>
<td>Dermal fillers</td>
<td>70</td>
</tr>
</tbody>
</table>

**6b) Treatments Considering Next 2 Years**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial plastic surgery</td>
<td>22</td>
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<tr>
<td>Liposuction</td>
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<td>Skin tightening procedures</td>
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<td>Chemical peels</td>
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<td>IPL/Phototheraphy</td>
<td>35</td>
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<tr>
<td>Neurmodulators</td>
<td>69</td>
</tr>
<tr>
<td>Under chin fat reduction</td>
<td>32</td>
</tr>
</tbody>
</table>

Abbrev: IPL, intense pulsed light laser.

Note: Neurmodulators included Onabotulinumtoxin A (BOTOX®), Abobotulinumtoxin A (Dysport®), and Incobotulinumtoxin A (Xeomin®).

Survey question 6a) “Which treatments that are administered in a physician’s office have you ever heard of?”

Survey question 6b) “Which facial treatments that are administered in a physician’s office would you consider within the next 2 years?”
Overall, areas of the upper face (under-eye/tear trough and CFLs) were assigned greater relative importance than the lower face. Although this is expected as areas of the upper face tend to reveal more of the initial signs of aging, it is important to note that participants were not given the option to differentiate between under-eye and tear trough. The cause of dark under-eye circles are multifactorial and could be attributable to periocular inflammation, blood stasis, uneven pigmentation, or may be the result of shadowing caused by tear trough deformity.20,21 With aging, the orbital bone resorption, loss of midface volume, and increasing skin laxity can be associated with increased severity of tear troughs, which are characterized by a concavity separating the lower eyelid from the cheek.22,23 Therefore, this may imply that dark circles under the eyes is a common phenomenon in the Hispanic/Latino population, and may represent key aesthetic concerns for this patient population.

Mestizo or Hispanic individuals with Native American origins share greater craniofacial similarity with Asians than with whites.24 In this light, it should be considered that some His-
panic/Latino patients may also share some of the facial aging patterns observed with the Asian ethnicities. While both Hispanic and Asian facial shape can be characterized as broad (wide bizygomatic and bigonial distance) with heavier malar fat pads, certain Asian ethnicities also tend to have less anteromedial midface projection, which may contribute to the gravitational descent that exposes the tear trough. In another similarity with Asians, aging of the Mestizo face may include an increase in the forehead-glabella supraorbital prominence contributing to superior concavity and shadowing of the forehead. Orbital bone resorption also contributes to descent of the lateral third of the eye brow, and for Mestizo individuals, heaviness of the brow and hooding of the eyelids may also be more pronounced due to a thicker, heavier skin type.

The high importance level and priority assigned to sagging underneath the chin/double chin in both older and younger participants may reflect gravity-induced changes associated with a heavier, thicker skin type in the Hispanic/Latino population. This is in contrast to descent due to increased skin laxity accompanied by jowling that is observed more often in Caucasians. Other anatomical contributors may include a recessed chin position, a facial characteristic observed more often in the Asian and Hispanic/Latino ethnicities that may exacerbate the appearance of the submental fat. It is, however, important to note that participants were not able to differentiate between “sagging underneath the chin” and “double chin.” Body mass index (BMI) can contribute more significantly to the appearance of submental fullness than skin laxity or sagging. As BMI was not measured in this study, we cannot determine if the high prevalence of sagging underneath the chin/double chin in the Hispanic/Latino population may be a consequence of differences in the BMI in this group.

Consideration Rates for Future Treatments Including Injectables
Although there appeared to be a high awareness of injectable treatments involving under chin fat reduction and dermal fillers, they corresponded with lower consideration rates than other minimally-invasive treatments such as microdermabrasion, chemical peels, and laser skin resurfacing. Interestingly, although underneath the chin area was a high priority and 79% of participants were aware of the injectable treatments available for this area, only 35% would consider having this treatment. This observation may reflect a gap in patient knowledge. There was a higher consideration rate for neuromodulators compared with all other minimally-invasive treatment options. This observation agrees with previous studies highlighting the aesthetic preferences of Hispanic/Latino patients and is exemplified by the fact that this population makes up the greatest proportion of ethnic minority patients receiving treatment with neuromodulators.

The strengths of this study include a large participant population, a cross-sectional design, and the use of MaxDiff methodology to minimize scale bias, as compare to using paired comparisons. The data collected and presented here characterizes the priorities and treatment awareness among a diverse population of Hispanic/Latino Americans naive to facial injectable use and helps clinicians to understand this population and to plan treatments accordingly. Two case examples of Hispanic/Latino patients treated by the authors are presented in Figure 9 and Figure 10.

**FIGURE 9.** Facial rejuvenation using injectable treatments with a patient representative of a 30 to 44-year-old age range. Left, pre-treatment. Center, treatment diagram showing placement of hyaluronic acid filler (yellow) (2.1 mL total) for upper and lower eyelids, midface, and onabotulinumtoxinA (45 U total) for glabellar and crow’s feet lines, masseter, depressor anguli oris (DAO), and chin. Right, approximately 2 weeks post-treatment. **Patient photos courtesy of Dr. JR Montes.**

**FIGURE 10.** Facial rejuvenation using injectable treatment with a patient representative of a 45 to 65-year-old age range. Left, pre-treatment. Center, treatment diagram showing placement of hyaluronic acid filler (yellow) (4 mL total) for upper and lower eyelids, temples, midface, marionette lines, and jawline; deoxycholic acid (orange) (2 mL total) for submental region; and onabotulinumtoxinA (52.5 U total) for forehead, glabellar, and crow’s feet lines, oral commissures, depressor anguli oris (DAO), and mentum. Right, approximately 2 months post-treatment. **Patient photos courtesy of Dr. JR Montes.**

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NEW EPISODE
To Treat or Not To Treat: Systemic Therapy Considerations for Psoriasis in the Setting of Malignancy | Dr. David Rosmarin

I’m a biologic girl in a biologic world...or so I think myself and never say out loud when reviewing therapeutic options for moderate to severe psoriasis. We are so fortunate to have so many wonderful options, however certain clinical scenarios may limit our ability to capitalize on said armament mostly due to limited experience and data. Enter previous malignancy – in most phase 3 studies these patients are weeded out or the history of malignancy must be at least 5 years prior to entry. So what to do? Our colleagues at Tufts Medical Center asked this very question. Tune in to hear what Dr. David Rosmarin, Assistant Professor of Dermatology and Residency Program Director learned from performing a retrospective chart review and how his work and his experience guides his clinical decision making when managing psoriasis. Don’t flake (or is it scale?)...check it out.
CONCLUSIONS

Hispanic/Latino Americans are a growing patient population for aesthetic practitioners. As much of the literature pertaining to facial aesthetic rejuvenation is focused on Caucasian women, there is a need to explore the facial aging process among Hispanic/Latino women and identify the attitudes that factor into their consideration of the different treatments. Compared to other racial/ethnic groups, Hispanic/Latino women comprise a diverse racial and ethnic background with signs of facial aging that may share common patterns and characteristic of other racial/ethnic groups, but the practitioner will need to keenly identify them.

This survey highlighted key aesthetic concerns common among the Hispanic/Latino American women and revealed the most bothersome areas for this population as the under-eye/tear trough area, CFLs, FHLs, and the submentual area. With advancing age, priorities shifted slightly from upper facial areas to include more of the mid and lower facial areas. In addition, the discrepancy between the high level of aesthetic concern for underneath the chin area and low consideration rate for the Injectable treatments for this suggest there may be opportunities to educate patients regarding available treatments that may help them achieve aesthetic goals.

Among participants who would not consider injectables, the main reasons cited were concerns about safety/side effects, concerns about putting a foreign substance into their body, and concern that their face will not look natural. Educating and counseling patients on these barriers may increase patient acceptability of a broader range of treatment options and comfort them in knowing there is a reinforcement on “naturalness” in medical aesthetic treatments. By lessening the barriers to injectables, patients may ultimately achieve a more impactful and longer lasting treatment results. Also, discussing treatment strategies that address existing pigmented issues and minimize the risk of PIH may help strengthen the patient-practitioner bond.

With the observations presented here, this study hopes to contribute to a first step in providing practitioners with a more patient-centric and culturally-competent approach to their treatment of Hispanic/Latino facial aesthetic patients.

DISCLOSURES

S Fabi serves as a consultant, researcher, and advisory board member for Allergan plc. JR Montes serves as a speaker and trainer for Allergan plc. SB Aguilera serves as a speaker and trainer for Allergan plc. V Bucay serves as a speaker and consultant for Allergan plc. S Manson Brown and N Ashourian are employees of Allergan plc and may own stock/options in the company. The opinions expressed in this article are those of the authors. The authors received no honoraria related to the development of this article. This study was funded by Allergan, Inc. Writing and editorial support for this article was provided by Erika von Grote, PhD, Allergan plc, Irvine, CA. The authors would like to thank Garrett T. Shumate of Allergan plc for his invaluable assistance in the interpretation of data and in the development of this manuscript.

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Understanding the Female Asian American Facial Aesthetic Patient

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ABSTRACT

Background: As facial aesthetic procedures have become more widely accepted, the racial and ethnic diversity of aesthetic patient populations has increased. Asian Americans represent a growing segment of this population and have specific aesthetic concerns that should be differentiated from the broader Caucasian population.

Objective: An online study was designed to survey facial aesthetic concerns, treatment priorities, and future treatment considerations among a US-based population of Asian American women.

Materials and Methods: A total of 403 participants ages 30 to 65 years reported perspectives on facial aging, current facial conditions, most bothersome facial areas, most/least likely to be treated first, awareness of treatment options and consideration rates, and motives/barriers impacting the consideration rate of injectable treatments.

Results: Treatment interests reflected predominant issues; uneven skin tone, wrinkles, and sun damage. Most bothersome facial areas included the periorbital area, forehead, and submental area, and also among areas designated as most likely to treat first. The majority of participants would consider injectables. However, safety/side effects, cost, and concerns about not looking natural were primary barriers.

Conclusion: Understanding the aesthetic concerns and priorities specific to Asian American women may help guide treatment plans more aligned with the goals and expectations of this patient population.


INTRODUCTION

As the number of aesthetic procedures increases, it is important for physicians to understand who comprises the expanding population seeking such treatments. In recent years it is clear that as procedures become more widely accepted and commonplace, the patient population seeking them has also grown in terms of its racial, ethnic, and cultural diversity. While many published treatment algorithms in the US are suitable for Caucasian patients, there are far fewer that focus on the aesthetic concerns and needs specific to the Asian patient. In addition, very little data exists focusing on Asian Americans which is a broad community of people representing several countries.

Over the past decade, the total number of Asian patients who received cosmetic procedures in the US increased by 33% with a growing number of younger patients (ie, 18 to 40 years of age) among them.1 A predominance of minimally-invasive facial aesthetic treatments has grown to represent at least 90% of all cosmetic procedures performed in the US in 2017.1 Similar to this trend in aesthetics, Asian patients primarily seek nonsurgical, minimally-invasive treatment modalities, and express concerns for maintaining a natural appearance.3

The descriptor “Asian American” encompasses a diverse population with ethnic origins in East Asia (eg, China, Korea, Japan, Taiwan), South Asia (eg, Bangladesh, Nepal, Pakistan, Sri Lanka), and Southeast Asia (eg, Thailand, Singapore, Indonesia, Philippines). Among this diverse population, there is also a wide range of facial morphologies and Fitzpatrick Skin Phototypes (FSPs).4 Importantly, variations in skin type and underlying structural anatomy impact the rate, pattern, and severity of facial aging among different ethnicities.5,6 However, social and cultural influences ultimately have a defining influence in perceptions of beauty and motivations for seeking treatment.7,8 For the aesthetic physician, understanding not only the structural and cutaneous components of aging
but also the treatment preferences and motivations relevant to Asian American women may help guide treatment plans more aligned with the goals and expectations of this patient population.

The current study surveyed Asian American women who were aesthetically-oriented but naïve to facial injectable treatments with the objective to characterize their aesthetic concerns and treatment priorities. Evaluations included: 1) attitudes toward signs of facial aging and existing facial concerns; 2) facial areas that are most bothersome; 3) facial areas most/least likely to represent a priority in a future aesthetic treatment plan; 4) awareness of available aesthetic treatments and their consideration rates; and 5) motives/barriers factoring into their consideration of injectable treatments. The data presented here is a segment of a larger study consisting of 1205 women which also included African American and Hispanic/Latino American participants.12

**METHODS**

**Participants and Study Design**

Participants living in the US were recruited through online river sampling (banner ads, pop-up ads, instant capture promotions) by the Lieberman Research Worldwide (LRW) agency between March and April 2016. Primary inclusion criteria were 1) females ages 30 to 65 years living in the US; 2) aesthetically-oriented, as determined by level of agreement on an aesthetic orientation questionnaire; 3) household annual income >$50,000 with some discretionary spending flexibility; 4) naïve to facial injectable treatments; 5) aware of BOTOX® Cosmetic; and 6) considering having a medical facial aesthetic treatment within the next 2 years.

Participants identified their most predominant ethnic background as one of the following: Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, American Indian/Alaskan Native, Native Hawaiian, or other Pacific Islander (ie, Samoan, Guamanian, or Chamorro). Participant’s FSP was categorized as I through VI using a questionnaire adapted from the Skin Cancer Foundation website in combination with their selection of a color that most represented their natural skin tone from a range of 11 skin codes (colors).13-15

**Measures and Analysis**

The study design and questionnaire format have been previously described.16 Briefly, attitudes toward improving facial aesthetics and existing concerns were assessed by questionnaire. Most bothersome facial areas and treatment priorities were assessed using a 15-point facial diagram (Figure 1) and a Maximum Difference (MaxDiff) ranking methodology was used to identify the relative importance of each area.17 MaxDiff scores were represented by a “relative importance value.” Areas ranked above average indicated greater importance and were considered a higher treatment priority relative to those areas ranked below the average. Awareness of aesthetic procedures, future treatment considerations, and motives and barriers impacting the consideration rate of injectable treatments were assessed by questionnaire.

**RESULTS**

**Participants**

The majority of the 403 participants included in the study were 30 to 44 years old (57%), born outside of the US (55%), married (82%), with household incomes > $75,000 (74%), an average spending of < $250/month on products or services for facial aesthetics (79%), and had spent ≥ $250 on a single medical facial treatment (55%) (Table 1). The majority were categorized as FSP III or IV (89%) and a large proportion identified with a Southeast Asian (Asian Indian, Filipino, Vietnamese, n = 147) or Chinese (n = 119) ethnic background (Table 2).

**Attitudes Toward Improving Facial Aesthetics and Existing Facial Concerns**

Most agreed with wanting their face to look good for their age (86%), cared about improving their facial appearance (78%), were interested in treatments that addressed hyper/hypo-pigmentation (72%), facial wrinkles and lines (64%) and treatments that would make them look less tired (63%) (Figure 2). Uneven skin tone/color (64%), facial wrinkles (50%), and sun damage (48%) were the most frequently-reported facial concerns (Figure 3).

**Most Bothersome Facial Areas**

Areas of the upper face were the most bothersome and included the under-eye/tear trough area (32%), crow’s feet lines (CFLs)
**TABLE 1.**

<table>
<thead>
<tr>
<th>Characteristic, Statistic</th>
<th>% Total Respondents (N = 403)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>30 - 44</td>
<td>57</td>
</tr>
<tr>
<td>45 - 65</td>
<td>43</td>
</tr>
<tr>
<td><strong>US Region of Current Residence</strong></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>21</td>
</tr>
<tr>
<td>South</td>
<td>20</td>
</tr>
<tr>
<td>Midwest</td>
<td>13</td>
</tr>
<tr>
<td>West</td>
<td>46</td>
</tr>
<tr>
<td>Born in the US</td>
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</tr>
<tr>
<td><strong>Marital Status</strong></td>
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<tr>
<td>Married</td>
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</tr>
<tr>
<td>Single (Never Married)</td>
<td>14</td>
</tr>
<tr>
<td>Separated/Divorced/Widowed</td>
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</tr>
<tr>
<td><strong>Education</strong></td>
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</tr>
<tr>
<td>Some College or College Graduate</td>
<td>64</td>
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<tr>
<td>Post Graduate</td>
<td>35</td>
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<tr>
<td><strong>Household Income</strong></td>
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<tr>
<td>Less than $ 75,000</td>
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<tr>
<td>$ 75,000 - $ 150,000</td>
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<tr>
<td>$ 150,000 or More</td>
<td>27</td>
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<tr>
<td><strong>Monthly Spend on Products and Services for Facial Aesthetics</strong></td>
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<tr>
<td>Less than $ 250</td>
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<tr>
<td>$ 250 or More</td>
<td>20</td>
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<tr>
<td><strong>Maximum Spend on a Single Medical Facial Treatment</strong></td>
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<td>Less than $ 250</td>
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<tr>
<td>$ 250 or More</td>
<td>55</td>
</tr>
</tbody>
</table>

*1% preferred not to answer

**TABLE 2.**

<table>
<thead>
<tr>
<th>Characteristic, Statistic</th>
<th>% Total Respondents (N = 403)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fitzpatrick Skin Phototype</strong></td>
<td></td>
</tr>
<tr>
<td>I - II</td>
<td>3</td>
</tr>
<tr>
<td>III - IV</td>
<td>89</td>
</tr>
<tr>
<td>V - VI</td>
<td>8</td>
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<tr>
<td><strong>Ethnic Background</strong></td>
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<td>Chinese</td>
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<tr>
<td>Japanese</td>
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<tr>
<td>Asian Indian</td>
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</tr>
<tr>
<td>Filipino</td>
<td>14</td>
</tr>
<tr>
<td>Korean</td>
<td>10</td>
</tr>
<tr>
<td>Vietnamese</td>
<td>7</td>
</tr>
<tr>
<td>Other Asian*</td>
<td>7</td>
</tr>
</tbody>
</table>

*Includes American Indian, Alaskan Native, Native Hawaiian or other Pacific Islander (including Samoan, Guamanian, or Chamorro)

**FIGURE 2.** Attitudes toward improving facial aesthetics.

Note: Rating of 4, 5, or 6 defined as "agreement". Rating of 4, 5, or 6 on any statement was considered "aesthetically oriented".

Survey question: "How strongly do you agree with each statement on a scale of 1 (completely disagree) to 6 (completely agree):"
(29%), and forehead lines (FHLs) (29%) (Figure 4). These were followed by sagging underneath the chin/double chin (26%), nasolabial folds (NLFs) (23%), glabellar lines (GLs) (21%), marionette lines (MLs) (20%), and oral commissures (OCs) (18%). Areas selected with less frequency were the chin (16%), cheeks (14%), jawline (13%), perioral lines (12%), temples (11%), and lips (10%).

**Treatment Priorities**

The relative importance ranking of each area ranged from 19 to 77 across the 15 facial areas; overall bothersome facial areas tended to correlate with the treatment priorities ($R^2 = .82$, data not shown). Among the younger group (ages 30 to 44) (Figure 5a), the facial areas of highest priority (represented by relative importance values above the average) included the under-eye/tear trough area (75) and CFLs (75). Other areas of high importance were FHLs (66), sagging underneath the chin/double chin (61), and GLs (59), followed by NLFs (55), and OCs (54). Areas of lower relative importance included MLs (42), chin (37), jawline (36), and cheeks (35). Perioral lines (32), temples (31), and lips (26) were among the least important. Among the older group (ages 45 to 65) (Figure 5b), the under-eye/tear trough area (77) and CFLs (70) were also selected as highest priorities followed by sagging underneath the chin/double chin (62), FHLs (62), and NLFs (61), GLs (56), OCs (56), and MLs (52). Areas of lower relative importance included jawline (39), chin (38), cheeks (34). Perioral lines (29), temples (27), and lips (19).

**Awareness of Treatments Options and Future Treatment Consideration Rates**

A high proportion of participants were aware of surgical procedures (facial plastic surgery and liposuction, 93-95%) (Figure 6a) which corresponded with lower consideration rates compared to minimally-invasive treatments (Figure 6b). A high
**FIGURE 5A AND 5B.** Treatment priorities based on the relative importance of each facial area.

- **5a) Relative Importance Among Ages 30 to 44**
  - 75 Under-eye/tear trough area
  - 75 Crow's feet lines
  - 65 Forehead lines
  - 61 Sagging underneath the chin/double chin
  - 59 Glabellar lines
  - 55 Nasolabial folds
  - 54 Oral commissures
  - 46 Short, thinning lashes
  - 42 Marionette lines
  - 37 Chin
  - 36 Jawline
  - 35 Cheeks
  - 31 Perioral lines
  - 27 Temples
  - 25 Lips
  - 20 (n = 230)

- **5a) Relative Importance Among Ages 45 to 65**
  - 77 Under-eye/tear trough area
  - 70 Crow's feet lines
  - 62 Forehead lines
  - 62 Sagging underneath the chin/double chin
  - 61 Nasolabial folds
  - 56 Glabellar lines
  - 57 Oral commissures
  - 52 Marionette lines
  - 45 Short, thinning lashes
  - 40 Marionette lines
  - 39 Jawline
  - 38 Chin
  - 34 Cheeks
  - 32 Perioral lines
  - 27 Temples
  - 20 Lips
  - 19 (n = 173)

**Note**: Red bar = average performance value. Areas ranking higher than the average designated as having greater relative importance. Survey question: “Please indicate which of the following facial features you would most and least like to have treated first.”

**FIGURE 6A AND 6B.** Awareness of treatments and treatments considered within the next two years.

- **6a) Awareness of Facial Treatments and Procedures**
  - Facial plastic surgery: 95
  - Liposuction: 93
  - Skin tightening procedures: 88
  - Laser skin resurfacing: 87
  - Microdermabrasion: 85
  - Chemical peels: 84
  - IPL/Phototherapy: 41
  - Neuromodulators: 100
  - Under chin fat reduction: 76
  - Dermal fillers: 72

- **6b) Treatments Considering Next 2 Years**
  - (N = 403)

**Abbrev**: IPL, intense pulsed light laser.

**Note**: Neuromodulators included Onabotulinumtoxin A (BOTOX®), Abobotulinumtoxin A (Dysport®), and Incobotulinumtoxin A (Xeomin®).

Survey question 6a) “Which treatments that are administered in a physician’s office have you ever heard of?”

Survey question 6b) “Which facial treatments that are administered in a physician’s office would you consider within the next 2 years?”
proportion were aware of treatments to enhance skin quality such as skin tightening procedures (88%), laser skin resurfacing (87%), microdermabrasion (85%), and chemical peels (84%), which also corresponded with high treatment consideration rates for those kinds of procedures (37 - 64%). Regarding injectable treatments, all or most were aware of neuromodulators (100%), under chin fat reduction (76%) and dermal fillers (72%), and were reflected by future consideration rates of 33%, 20%, and 18%, respectively.

Motives and Barriers Impacting Consideration Rate of Injectable Treatments
Among participants who would consider injectables (74%, 300/403), a high proportion wanted to look good for their age (68%) and look more youthful (55%) (Figure 7). Twenty-three percent agreed that they would consider injectables because they have seen, read, or heard positives things about them and there is more information now available about those treatments (22%). A smaller proportion was motivated by wanting

FIGURE 7. Motives for treatment among those who would consider facial injectables.

FIGURE 8. Barriers to treatment among those who would consider facial injectables.

Survey question: “Which of the following describes why you would consider a facial injectable treatment for facial lines, wrinkles, and folds but have never tried it before?”
to maintain a competitive edge in the workforce (12%) or improve dating prospects or relationships (7%).

The top 3 barriers for not having tried injectable treatments yet cited concerns about safety and side effects (57%), cost (43%), and concerns about their face not looking natural (38%) (Figure 8). Among the 26% who would not consider injectables, the top 3 reasons included 1) concerns about injecting a foreign substance into their body (60%), 2) concerns about safety and side effects (55%), and 3) dislike of needles (32%) (data not shown).

**DISCUSSION**

As facial aging occurs, bone resorption, fat loss, and increasing laxity of soft tissues accentuate the effects of gravity and the appearance of wrinkles and folds. While these elements of aging affect everyone, it is important to keep anatomic differences between races/ethnicities intact so that when corrections are discussed with patients, they are not being made to appear homogenous within the general population. Whether or not signs of facial aging are bothersome to an individual and prompts them to seek treatment is heavily dependent on their social and cultural ideals of beauty and how motivated they are to maintain or improve their facial aesthetics.

**Attitudes Toward Improving Facial Aesthetics**

Not surprisingly, the data showed that attitudes toward facial aesthetics were aligned with facial concerns. Notably, a high proportion would consider treatments for hyper/hypo-pigmentation (72%) which reflected a high incidence of uneven skin tone color (64%) and facial sun damage (48%). This data is expected given that dyschromia has may be more apparent in FSPs III through VI, and the majority of these participants (89%) were in the FSP III and IV categories. An advantage that comes with greater melanin content (primary determinant of pigmentation) is added protection against the immediate effects of UV exposure (eg, sunburn), but photodamage still occurs and is more obvious over time after it has caused pigmenory disorders (eg, freckling, solar lentigo, melasma, and seborrheic keratosis). Greater melanin content also increases an individual's predisposition toward a post-inflammatory hyperpigmentation (PIH) reaction following inflammation or injury. While correcting uneven skin tone may represent a concern for many individuals, a high level of interest among Asian participants, although predominantly younger (57% ages 30 - 44) may also reflect a strong cultural aesthetic standard to preserve and maintain clear and even-toned facial skin.

**Most Bothersome Facial Areas and Treatment Priorities**

Bothersome facial areas tended to correlate with treatment priorities ($R^2 = .82$, data not shown) although some bothersome areas translated to lower priorities (eg, short, thinning lashes). Discrepancies between bothersome areas and treatment priorities might reflect the difference between areas amenable with the application of cosmetics versus those that are more structural. Regardless of age, Asian participants were most bothered by areas of the upper face which included the under-eye/tear trough area, CFLs, and FHLs. While under-eye/tear trough, CFLs, and FHLs were also ranked among the highest treatment priority for both age groups, areas of the mid and lower face (NLFs, OCs, and MLs) were ranked with higher relative importance among the older group. This shift in importance is also expected as it reflects the increasing structural changes and midface ptosis that accompanies facial aging. Furthermore, anatomical characteristics shared by many Asian ethnicities, which include a weaker skeletal facial framework, a wide zygomaticomalar region, less projection of the anteromedial midface, and heavier malar fat pads, provide no support or resistance to the midface ptosis that exposes the tear trough and accentuate redundant skin (folds) in the lower face.

It is important to note that while these observations highlight this as a key treatment area for this patient population, participants were not given the option to differentiate this area specifically as “under-eye”, under-eye bags, and/or “tear trough.” The under-eye area may involve dark circles which includes a vascular or pigmenatory basis, distinct from a tear trough. Malar ptosis can contribute to formation of under-eye bags (orbital...
fat pad pseudo-herniation) and tear trough depression; a result which is further exacerbated by increasing infraorbital skin laxity and orbital bone loss.24,25 Because these fat compartments are no longer forming a smooth plane, surface shadowing becomes more obvious.

Surprisingly, the treatment priority for CFLs was high among the younger group and declined in importance for the older group, although this decline may be the result of shifting priorities as age-related changes in the mid and lower face become increasingly more bothersome. Another reason suggested for this, observed in practice by contributing authors, is that their Asian patients associate a minimal amount of CFLs with a more natural expressive appearance. The initial appearance and severity of CFLs result from dynamic movement of the orbicularis oculi muscle which can also be exacerbated by accumulated photodamage. A classification of CFLs delineates them as upper, lower, and bidirectional, with the bidirectional type usually only becoming more common as people age.26,27 However, in comparisons with a Caucasian population, the presence of bidirectional CFLs has been observed in a higher proportion among Asians beginning at a younger age.26 The high priority for CFLs among the younger group of participants may be aligned with such a predisposition, but more so highlights that CFLs may represent another key treatment area among Asian women regardless of age. Similar to CFLs, a decline in the importance of FHLs among the older group may simply indicate a shift in priorities, as they are displaced by areas of the mid (NLFs) and lower (MLs) facial areas which increased in importance. However, the forehead area is an important aesthetic unit by East Asian beauty standards, and the impact of aging may include an increase in forehead-glabella supraorbital prominence which contributes to superior concavity and shadowing of the forehead.28

A high priority was also given to the treatment of sagging underneath the chin/double chin and was of similar importance among both age groups. While aging of the submental area isn’t defined by race or ethnicity, the effects of aging on the submental area have been suggested to be more pronounced in more heavily pigmented skin types. This is proposed to be due to the gravity-induced descent of a thicker and heavier skin type opposed to descent due to increased skin laxity (accompanied by more jowling) in thinner, less pigmented skin types.29 It may also be due to the fact that initial signs aging for photo-protected skin types are volumetric and structural versus those that are more cutaneous (eg, fine lines and wrinkles) for less pigmented, less protected skin types. Other anatomical contributors may include a more recessed chin position with greater posterior angulation of the lower mentum, a characteristic observable in varying degrees among some Asian ethnicities.30 This lack of skeletal support against tissue descent may exacerbate the appearance of submental fat.30,31 However, it is important to note that participants were not given the option to differentiate between “sagging underneath the chin” and “double chin”. Body mass index likely plays more of a role in the appearance of submental fullness than laxity or sagging. Regardless of the contributing factors, these observations highlight that softening of the cervicomental angle is a strong enough aesthetic concern among Asian women to motivate a desire for treatment and may represent another key treatment area.

The strengths of the study included such factors as a large participant population, a cross-sectional design, and use of the MaxDiff methodology to minimize scale bias versus using paired comparisons. The value in these data is the Asian aesthetic perspective with the potential influence of US or Western cultural standards, as 45% were US-born. As the Asian American population becomes more multicultural, such perspectives may be more relevant than those reporting on traditional aesthetic standards observed by Asians residing in their country of origin. Two case examples of Asian American patients treated by the authors are presented in Figure 9 and Figure 10.

The study questionnaires were designed to suit a racially/ethnically diverse group participants which limited the number of facial areas evaluated to those most common among all. In doing so, several key treatment areas that are predominant in Asia (ie, nose and masseters) where not evaluated in this study. Future studies should include evaluation of these 2 areas in addition to a more granular evaluation of the key treatment areas, under-eye and submental area, highlighted here.

CONCLUSIONS

Asian Americans are a growing segment of the patient population for aesthetic physicians. Since much of the literature and instructional training in injectables has been focused on the aging patterns of Caucasian women, there is a need to evaluate how this process occurs among Asian women of varying ethnicities and in what way it may motivate them to seek treatment. In this survey of 403 Asian American women, aged 30 to 65, the facial areas ranked with the highest importance and priority included the under-eye/tear trough, CFLs, FHLs, and the submental areas with priorities shifting slightly from upper facial lines to mid and lower facial folds and creases with advancing age.

Although awareness of injectable treatments was high, and the majority would consider having them, they were secondary to the skin-focused treatments (eg, skin tightening procedures, laser skin resurfacing, microdermabrasion, and chemical peels). Among participants who would consider injectable treatments but haven’t tried them yet, the greatest barriers were concerns about safety and side effects, cost, and unnatural appearance. Among participants who would not consider injectables, the main reasons cited were concerns about putting a foreign substance into their body, safety and side effects, and a dislike of needles.
Evaluating and counseling patients with these barriers in mind may increase patient acceptability of a broader range of treatment options, which will help them achieve more impactful and longer lasting treatment results, and comfort them in expressing there is a growing reinforcement of maintaining "naturalness" with all medical aesthetic treatments. Ultimately, the practitioner's best approach for introducing new aesthetic treatments may be by starting with primary skin quality concerns using treatment strategies that minimize the risk of PIH and address existing dyschromia and sun damage. This strategy may help strengthen the patient-practitioner bond and overcome barriers with their Asian American patients. This study intends to provide physicians with advice for achieving a more patient-centric approach in their treatment of Asian American facial aesthetic patients.

DISCLOSURE

A Chiu serves as a consultant and clinical investigator for Allergan plc. K Mariwalla has served on an advisory board for Allergan plc. A Hui-Austin serves as a consultant for Allergan plc. V Narurkar has served as a consultant and clinical investigator for Allergan plc. C de la Guardia is an employee of Allergan plc and may own stock/options in the company. The opinions expressed in this article are those of the authors. The authors received no honoraria related to the development of this article. This study was funded by Allergan, Inc. Writing and editorial support for this article was provided by Erika von Grote, PhD, Allergan plc, Irvine, CA. The authors would like to thank Garrett T. Shumate of Allergan plc for his invaluable assistance in the interpretation of data and in the development of this manuscript.

REFERENCES


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

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Icahn School of Medicine at Mount Sinai, New York, NY
Department of Dermatology, George Washington University School of Medicine, Washington, DC
Ortho Dermatologics, Bridgewater, NJ
Bausch Health, Bridgewater, NJ
Bausch Health Americas, Inc., Petaluma, CA

ABSTRACT

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

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

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

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

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

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


INTRODUCTION

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

A key aspect of acne management has been the ongoing evolution of topical treatments that use innovative delivery solutions and optimal formulations to help minimize irritation, without
both efficacy and tolerability. This polymeric emulsion technology provides a more uniform distribution of active and moisturizing excipients at the surface of the skin, which should enhance efficacy and minimize irritation.

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

**METHODS**

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

Patients were enrolled with an Evaluator Global Severity Score (EGSS) score of 3 (moderate) or 4 (severe). Treatments were randomized (2:2:1:1) to tazarotene 0.045% lotion, tazarotene 0.1% cream, and vehicle lotion or cream (to ensure blinding).

Data on vehicle are combined in the result presented here. All patients applied study medication to the face once-daily in the evening for 12 weeks; after being instructed to gently washing their face with a non-medicated cleanser.

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

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

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

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

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

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

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

All statistical analyses were conducted using SAS® version 9.3 or later. Statistical significance was based on 2-tailed tests of the null hypothesis resulting in P-values of 0.05 or less.
All AEs occurring during the studies were recorded and classified on the basis of medical dictionary for drug regulatory activities terminology (MedDRA) for the safety population. The frequency of patients with one or more AEs during the study was tabulated by treatment group.

RESULTS

Baseline Characteristics

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

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

Efficacy

Lesion Counts

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

Median percent change from baseline to week 12 in inflammatory and noninflammatory lesion counts with tazarotene 0.045% lotion was 72.4% and 62.5% versus 66.7% and 56.4% with tazarotene 0.1% cream and 60.0% and 42.3% with vehicle, respectively.
FIGURE 2. Percent change in mean inflammatory lesions from baseline to week 12. (ITT population): Comparison of Tazarotene 0.045% lotion, Tazarotene 0.1% cream, and vehicle.

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

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

Subject Self-Assessment (SSA)
Tazarotene 0.045% lotion showed a greater numerical treatment success (‘clear’ or ‘almost clear’) at week 12 in terms of SSA when compared with tazarotene 0.1% cream ($P=.768$). Treatment success was achieved in 38.5% of patients, compared with 35.9% and 24.6% (tazarotene 0.01% cream and combined vehicle [$P=.096$], respectively).
Patient Satisfaction (PSS) and Quality of Life

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

There were also no statistically significant differences in the improvement between treatment groups based on the mean Acne-QoL assessments in each of the 4 evaluated domains. Improvements in self-perception, role-emotional, and role-social were similar with tazarotene 0.045% lotion and tazarotene 0.1% cream, and markedly greater than those achieved in the combined vehicle groups. In terms of acne symptoms improvement, the absolute change from baseline with tazarotene 0.045% lotion was again greater than that achieved with the combined vehicle, however tazarotene 0.1% cream only demonstrated an improvement similar to that achieved with vehicle.
Safety
A higher proportion of patients treated with tazarotene 0.1% cream (26.8%) reported treatment-emergent AEs compared with tazarotene 0.045% lotion (14.7%) or combined vehicle (13.4%). TEAEs were mostly mild or moderate and unrelated to study drug (Table 2). Treatment-related AEs were more common with tazarotene 0.1% cream. There were two reports of application site pain (2.9%) with tazarotene 0.045% lotion; compared with three reports with tazarotene 0.1% cream (4.2%).

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

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

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

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

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

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

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

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REFERENCES


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A Survey-Based Comparison of Sun Safety Practices in a Representative Cohort of the General Public Versus Attendees of a Skin Cancer Screening

Emily C. Murphy BS, Stephanie Kao BA, Huan Wang MS, Dechang Chen PhD, Hong Nguyen MD MPH, Adam J. Friedman MD

A large proportion of data on photoprotective practices is yielded from free skin cancer screenings. However, the sun safety practices of populations who seek these skin cancer screenings may differ from the general public. To examine differences in skin cancer prevention practices and risk factors, we surveyed pedestrians at six locations in Washington, DC (public group, n=285) and attendees of a free skin cancer screening (screening group, n=144) using an IRB-approved survey. The screening group was older and included more individuals with fair skin than the public group. Respondents from the screening group were significantly more likely to always wear sunscreen, always seek shade, and always or sometimes wear sun-protective clothing than the public group (P<0.05). To examine whether younger and non-white participants, who were less likely to attend our free screening, have different practices and risk factors than older and white participants, respectively, we compared survey answers for all participants by age and race. White participants were more likely to always or sometimes wear sunscreen and sun-protective clothing than non-white participants (P<0.05). Patients over 61 years were more likely to always seek shade and wear sun-protective clothing than those younger than 31 years (P<0.05). Therefore, free skin cancer screenings need to be better popularized among non-white and younger populations or more effective educational vehicles are needed.

INTRODUCTION

Proper photoprotective practices are critical for the prevention of melanoma and non-melanoma skin cancers. A significant proportion of data on these practices is yielded from intake forms for free skin cancer screenings, such as through the American Academy of Dermatology’s SPOTme program. This program was started in 1985 and is one of the largest cancer screening programs. The project, care access, and examination results of SPOTme’s screening population from 1986 to 2014 was recently examined by Okhovat et al. Nearly two million screenings were reviewed, which showed that the SPOTme program detected thousands of skin cancers that may have gone undetected given 52% of those screened would not have seen a doctor otherwise. Compared to the general United States (US) population, the screening sample was older (only 8.9% of participants were 15 to 29 years old) and included more white individuals (90.3% of the sample was Caucasian). The screening population also included only 37.7% men, and the percentage of men attending screenings decreased over time. Given melanoma deaths are higher among men than women, the authors stated that men, especially white men, are a critical group to screen for skin cancer.

However, it is possible that the knowledge and perceptions of populations who seek skin cancer screenings may differ from the general public, leading to different photoprotective practices among these populations. This is especially relevant in the US where the demographics of our largest skin cancer screening program was not representative of the general population. The SPOTme program is clearly valuable as it has identified over 20,000 melanomas, 32,000 squamous cell carcinomas, and 129,000 basal cell carcinomas, but the data gathered from this program includes only patients who self-select to attend free screenings.
We sought to examine the differences between the population who chooses to attend screenings and the general population by surveying pedestrians in a major city and attendees of a free skin cancer screening. By examining differences in demographics, photoprotective practices, and skin cancer risk factors, this study highlights future directions needed for skin cancer prevention efforts.

**METHODS**

An IRB-approved survey was randomly administered at six locations in Washington, DC (public group, n=285) and to attendees of a free skin cancer screening at George Washington University School of Medicine and Health Sciences (screening group, n=144). The survey included eight questions on demographics (Table 1) as well as sun protective practices and risk factors for skin cancer (Table 2). Based on the Centers for Disease Control and Prevention (CDC) definition of sun-protective behaviors, the participants were asked about their sunscreen use, shade-seeking practices to avoid peak sun, and use of sun-protective clothing to cover up from sun exposure. Further, the survey assessed two risk factors associated with an increased risk of skin cancer: number of sunburns and indoor tanning practices. Statistical analysis was performed using GraphPad Prism, version 7.0 (GraphPad Software Inc.). Chi-square tests were used to compare answers between the public group and survey group. Additionally, survey answers from the public and screening groups were combined to compare answers by age and race.

**TABLE 1.** Demographics of Survey Respondents in the Screening Group and Public Group

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Screening Group % of Respondents</th>
<th>Public Group % of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>69.8</td>
<td>64.5</td>
</tr>
<tr>
<td>Male</td>
<td>30.2</td>
<td>35.5</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;31 years</td>
<td>15.5</td>
<td>47.0</td>
</tr>
<tr>
<td>31 – 60 years</td>
<td>40.4</td>
<td>40.0</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>44.1</td>
<td>13.0</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>73.0</td>
<td>48.2</td>
</tr>
<tr>
<td>Black</td>
<td>13.9</td>
<td>28.7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7.3</td>
<td>5.7</td>
</tr>
<tr>
<td>Asian</td>
<td>2.9</td>
<td>12.4</td>
</tr>
<tr>
<td>Mixed/Other</td>
<td>2.9</td>
<td>5.0</td>
</tr>
</tbody>
</table>

**TABLE 2.** Responses to Survey Questions Regarding Photoprotective Practices and Skin Cancer Risk Factors for the Screening (n=144) and Public (n=285) Groups

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>% of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you use sunscreen?*</td>
<td>Always</td>
<td>34.3</td>
</tr>
<tr>
<td>Screening Group</td>
<td>Sometimes</td>
<td>43.3</td>
</tr>
<tr>
<td>Public Group</td>
<td>Rarely</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td>7.5</td>
</tr>
<tr>
<td>2. Do you seek shade when possible?*</td>
<td>Always</td>
<td>51.5</td>
</tr>
<tr>
<td>Screening Group</td>
<td>Sometimes</td>
<td>36.6</td>
</tr>
<tr>
<td>Public Group</td>
<td>Rarely</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td>3.0</td>
</tr>
<tr>
<td>3. Do you wear sun-protective clothing?*</td>
<td>Always</td>
<td>16.4</td>
</tr>
<tr>
<td>Screening Group</td>
<td>Sometimes</td>
<td>56.7</td>
</tr>
<tr>
<td>Public Group</td>
<td>Rarely</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td>11.9</td>
</tr>
<tr>
<td>4. How many blistering sunburns did you have prior to age 20?</td>
<td>0 to 3</td>
<td>70.0</td>
</tr>
<tr>
<td>Screening Group</td>
<td>4 to 6</td>
<td>16.2</td>
</tr>
<tr>
<td>Public Group</td>
<td>7 to 10</td>
<td>9.2</td>
</tr>
<tr>
<td>5. Approximately how many times over your lifetime have you used indoor tanning equipment?</td>
<td>0</td>
<td>82.0</td>
</tr>
<tr>
<td>Screening Group</td>
<td>1 to 10</td>
<td>10.2</td>
</tr>
<tr>
<td>Public Group</td>
<td>11 to 20</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>21 or more</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*Indicates significant differences between the screening and public groups (P<0.05).
RESULTS

Table 1 presents the demographics for the screening group and public group. The gender distribution did not significantly differ between the two groups, although there was a larger percentage of female participants in both groups (69.8% female for screening group, 64.5% female for public group). The screening group was older with 44.1% being over 60 years old compared to 13.0% of the public group ($P<0.0001$). A higher percentage of the screening group was white compared to the public group (73.0% white in screening group versus 48.2% white in public group; $P<0.0001$).

The survey responses for the screening and public groups regarding sun safety practices and risk factors are presented in Table 2. More respondents from the screening group always wear sunscreen ($P=0.001$), always seek shade ($P=0.002$), and always or sometimes wear sun-protective clothing ($P=0.002$) compared to the public group. Responses between the groups did not differ for the number of blistering sunburns prior to age 20 and the number of indoor tanning uses, suggesting equal risk for both groups.

Given the screening group was older and included more white participants than the public group, these demographic populations may have superior photoprotective practices compared to younger and non-white populations, respectively. To examine this, we combined all the survey responses for the screening and public groups and compared the answers by white versus non-white participants and for three age groups (<31 years, 31-60 years, and >60 years). White participants were more likely to always or sometimes wear sunscreen (84.2% for white versus 52.2% for non-white; $P<0.0001$) and sun-protective clothing (67.5% for white versus 55.4% for non-white; $P=0.012$) than non-white participants (Figure 1). Shade-seeking practices did not vary by race. Patients over 60 years old were more likely to always seek shade (53.2% for >60 years versus 24.0% for <31 years; $P<0.0001$) and wear sun-protective clothing (17.0% for >60 years versus 9.7% for <31 years; $P=0.018$) than those younger than 31 years (Figure 2). Sunscreen use did not vary by age. These age- and race-based relationships reinforce the need to target non-white and younger populations for sun safety education, who were less likely to attend our skin cancer screening.

Alternatively, white participants reported more blistering sunburns than non-white participants (40.3% with ≥4 sunburns for white versus 12.0% with ≥4 sunburns for non-white; $P<0.0001$). Therefore, sun sensitivity in fair-skinned individuals may encourage proper sun safety practices. White respondents also reported more indoor tanning uses (18.7% ≥5 uses for white versus 3.8% ≥5 uses for non-white; $P<0.0001$) than non-white respondents. The number of blistering sunburns and indoor tanning uses did not differ by age.

DISCUSSION

Together, these data show that those who attend skin cancer screenings are more likely to wear sunscreen, seek shade, and wear sun-protective clothing than a randomly sampled population. These photoprotective behaviors defined by the CDC can reduce patients’ sun exposure and therefore, their risk of squamous cell carcinoma, basal cell carcinoma, and melanoma. For melanoma specifically, exposure to ultraviolet radiation accounts for more than 90% of the cases in the US. Indoor tanning use is considered a risk factor for melanoma due to its association with UV exposure. This study reinforces the importance of promoting sun safety education and sun protection practices among different age and race groups, particularly non-white and younger populations, who may be more susceptible to skin cancer.

FIGURE 1. Responses to survey questions for all participants (screening and public groups combined) regarding photoprotective practices, separated by white (n=228) versus non-white (n=184) respondents. *Indicates significant differences between white and non-white individuals ($P<0.05$).

FIGURE 2. Responses to survey questions for all participants (screening and public groups combined) regarding photoprotective practices, separated by age: <31 years (n=154), 31-60 years (n=165), and >60 (n=94). *Indicates significant differences between age groups ($P<0.05$).
tanning use was equal among the screening and public groups, meaning that all patients need to be educated on indoor tanning risks, especially fair-skinned individuals who reported higher use in this survey.

The screening group was older and included more individuals with fair skin, highlighting the need to target younger and non-white populations for sun safety education. Despite the US Preventive Services Task Force (USPSTF) recommendation to target fair-skinned individuals for skin cancer prevention counseling, survival from melanoma is significantly lower for non-white groups, making these critical populations to reach. Prior research has demonstrated that many individuals with darker skin types believe that they are not at risk for skin cancer and that their dark skin provides more sun protection than lighter skin. Tailored sun safety education may be useful for individuals with dark skin to alter their perceptions that skin cancer is not a risk and to encourage good photoprotective practices among patients of all skin colors. In terms of age, while the incidence of melanoma increases with age, sunburns at an early age are associated with a later risk of melanoma. Therefore, encouraging sun safety in younger populations will decrease the risk of skin cancer for patients now and in later in their lives.

That said, educating populations who seek skin cancer screenings is still important given 22% of our screening cohort reported rarely or never wearing sunscreen, underscoring this program’s value. However, a comprehensive skin cancer prevention program should offer more than total body skin examinations. To prevent skin cancer though increased sunscreen use and reduced sunburns, the Community Preventive Services Task Force recommends multicomponent, community-wide interventions, including school-based interventions. An example of such a program is Australia’s SunSmart skin cancer prevention program. This comprehensive campaign includes school- and workplace-based programs, practitioner education, media campaigns, and resource dissemination. From 1988 to 2003, SunSmart was estimated to prevent 9,000 new melanoma cases and 1,000 melanoma deaths in the state of Victoria. Furthermore, the program saved $2.30 for every $1 spent. Based on this program and the doubling of the incidence of melanoma in the US from 1982 to 2011, the CDC estimated that a comprehensive skin cancer prevention program could prevent 20% of melanoma cases and reduce spending on new melanomas by $2.7 billion from 2020 to 2030. A multicomponent, multiple-setting program in the US would likely reach broader demographic populations than skin cancer screenings alone.

Limitations of this study include a small sample size and possible selection bias given the sampling for the public group was done near a university, which may include a more educated population. Thus, it is unknown whether our public group is truly representative of the general public. In addition, the dichotomous categorization of race (white versus non-white) could have overlooked other race-based mediators of sun-protective behaviors, such as differences in cultural practices. Future larger studies should delve further into race-based differences in photoprotective behaviors.

Despite these limitations, this survey-study highlights the need to tailor future skin cancer prevention programs to younger and non-white populations, who we are missing with free skin cancer screenings, which comprise the majority of our current efforts. A more comprehensive skin cancer prevention program could reach a more diverse population, with the goal of reducing new skin cancers among all patient populations.

DISCLOSURES

The authors have no conflict of interest to declare.

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cessed February 17, 2019.


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Non-CE journal-based enduring activity
Topical Ozenoxacin Cream 1% for Impetigo: A Review

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ABSTRACT

Background: Impetigo, a bacterial infection that is highly contagious, involves the superficial skin. Topical treatment for impetigo includes amongst other bacitracin, gentamycin, mupirocin, retapamulin, and more recently, ozenoxacin 1% cream. For more severe conditions systemic antibiotics are prescribed and may be combined with a topical treatment. The current review explored the challenges in treating impetigo in pediatric and adult populations and examined the role of ozenoxacin 1% cream as a safe and effective treatment option.

Methods: We performed PubMed and Google Scholar searches of the English-language literature (2010-2018) using the terms impetigo, bullous impetigo, non-bullous impetigo, antimicrobial and antibiotic resistance, mupirocin, retapamulin, and ozenoxacin. The selected publications were manually reviewed for additional resources.

Results: Although guidelines were updated regularly, the recommended treatments have not changed much since 2014. Emerging antimicrobial resistance is a growing concern in dermatology and pediatrics. Impetigo therapy choices should consider the resistance pattern of S. aureus. Ozenoxacin 1% cream is a prescription medicine for topical treatment of impetigo in adults and children 2 months or older. Ozenoxacin has a low probability of selecting spontaneous resistant mutants in quinolone-susceptible or quinolone-resistant bacterial strains and has shown to be active against MRSA isolates. Ozenoxacin 1% cream has potent bactericidal activity and was shown to be effective and safe for the treatment of impetigo in two well-controlled Phase 3 trials.

Conclusions: Resistance patterns in a wide range of pathogens against oral or topical antibiotics and antiseptics used for the treatment of dermatological conditions, such as impetigo have been observed. When making treatment decisions for impetigo MRSA and other antimicrobial resistance has to be taken into account. Ozenoxacin 1% cream offers a potent bactericidal activity and has demonstrated clinical efficacy and safety. Combined with its favorable features, such as a low dosing frequency and a 5 days treatment regimen, ozenoxacin 1% cream is an important option for the treatment of impetigo for pediatric and adult populations.


INTRODUCTION

Impetigo is a highly contagious bacterial infection involving the superficial skin, primarily due to S. aureus, less frequently S. pyogenes, or both. It occurs most frequently in children ages two to six year but may affect younger and older children and adults as well. Self-inoculation and small family or communities outbreaks are common. There are more than 3 million cases of impetigo in the United States every year.1 Impetigo may be classified as a primary (direct bacterial invasion of an intact skin) or secondary infection of pre-existing skin disease or traumatized skin (atopic dermatitis, scabies, cuts, abrasions, insect bites, and chickenpox). Secondary impetigo is sometimes referred to as “impetiginization.”

Two clinical forms of impetigo are recognized: (1) nonbullous and (2) bullous. The nonbullous type (also known as impetigo contagiosa) is the most common and accounts for around 70% of cases and in the industrialized world is caused by mainly by S. aureus.2 However, S. pyogenes remains a common cause of nonbullous impetigo in developing nations. Clinically, nonbullous impetigo presents as erythematous pustules or vesicles (red sores) that quickly evolve into superficial erosions with a characteristic “honey-colored” crusts. Lesions usually involve the face, around the nose and mouth, but can be seen on extremities and trunk. The lesions are often smaller than 2 cm, not or minimally painful and without erythema or constitutional symptoms, although regional adenopathy may be present.1,2 More severe forms of impetigo may be associated with pruritus, erythema, crusted erosions, fissures, and odor. Bullous impetigo is less common, usually intertriginous areas, and is caused by strains of S. aureus that produce exfoliative
toxin A, a toxin that causes cleavage of very superficial epidermal layers by targeting the protein desmoglein. Lesions are usually large, transparent superficial flaccid bullae before rupturing, leaving round erosions that become crusted often with erythematous plaques. Bullous impetigo occurs frequently in intertriginous areas and is exclusively caused by *S. aureus* which is often colonized from the nose. The skin infection does not penetrate below the epidermal-dermal junction and is to be distinguished from eg herpes simplex infections, *Pseudomonas aeruginosa* infections, scabies, thermal injury, and allergic contact dermatitis. Impetigo typically resolves within two to three weeks without scarring and complications. Complications of non-bullous impetigo are rare but local and systemic spread of infection can occur that may result in cellulitis, lymphangitis, or septicemia. Non-infectious complications of *S. pyogenes* infection include scarlet fever, guttate psoriasis, and post-streptococcal glomerulonephritis.

Treatment options include topical antibiotics such as mupirocin, retapamulin or oral antibiotic therapy eg, amoxicillin/clavulanate, dicloxacillin, cephalexin, clindamycin, doxycycline, minocycline, trimethoprim/ sulfamethoxazole, and macrolides. There are increasing concerns about antibiotic and antiseptic resistance, especially those that are applied topically.

**METHODS**

The target group of this review included dermatologists, pediatricians and general practitioners involved in impetigo treatment. To explore challenges in treating impetigo, particularly in a pediatric population, and to review the role of ozenoxacin 1% cream, we performed PubMed and Google Scholar searches of the English-language literature (2010-2018) using the terms impetigo, bullous impetigo, non-bullous impetigo, antimicrobial resistance, antibiotic resistance, mupirocin, retapamulin, and ozenoxacin. Relevant publications were manually reviewed for additional resources.

**Therapeutic Options for Impetigo**

Both mild- to- moderate non-bullous and bullous types of impetigo typically resolve within two to three weeks without scarring and complications. Severe disease, however, can result in cellulitis, osteomyelitis, or septicemia.

Therapeutics recommended in guidelines and from a meta-analysis have been updated regularly but did not change much since 2014. Cleansing and crust removal is a part of the treatment of impetigo. Previously FDA-approved topical therapies included mupirocin and retapamulin. Other topical therapies for treating impetigo include bacitracin, polymyxin, erythromycin, neomycin, gentamycin, mupirocin, retapamulin, and more recently, ozenoxacin (Table 1). Oral treatment options for antibiotic therapy include amoxicillin/clavulanate, dicloxacillin, cephalexin, clindamycin, doxycycline, minocycline, trimethoprim/ sulfamethoxazole, and macrolides (Table 2).

**Antibiotic and Antiseptic Resistance in Skin Infections**

The World Health Organization (WHO) recognizes antimicrobial resistance (AR) as “rapidly evolving health issue extending far beyond the human health sector.” Antimicrobial stewardship is critical to optimizing the use of antibiotics while preventing the development of resistance and improving patient outcomes. Antimicrobial stewardship has been defined

---

**TABLE 1.**

<table>
<thead>
<tr>
<th>Current Topical Antibiotics for Impetigo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Treatment</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Frequency and period of application</strong></td>
</tr>
</tbody>
</table>

**TABLE 2.**

<table>
<thead>
<tr>
<th>Current Oral Antibiotics for Impetigo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not MRSA infection</strong></td>
</tr>
<tr>
<td><strong>Extensive Infection: Oral Antibiotics</strong></td>
</tr>
<tr>
<td>Dicloxacillin 250 mg 4 times daily for 1 week</td>
</tr>
<tr>
<td>Cephalexin 250 mg 4 times daily for 1 week</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanate 875 mg/125 mg PO BID for 7 days</td>
</tr>
<tr>
<td>Tetracycline 500 mg 4 times daily for 7 days</td>
</tr>
<tr>
<td>Linezolid</td>
</tr>
</tbody>
</table>

|Methicillin-resistant *Staphylococcus aureus* (MRSA)|
|Daptomycin|
as “the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance.”

The authors of the current review noted that dermatologists are among the most frequent prescribers of topical antibiotics. Resistance patterns in a wide range of pathogens against oral or topical antibiotics and antiseptics used for the treatment of dermatological conditions, such as atopic dermatitis, acne, and impetigo have been observed. AR such as in methicillin-resistant *Staphylococcus aureus* (MRSA) is threatening to compromise the effectiveness of crucial medical treatments. *S. aureus* resistance against erythromycin and cloxacinil treatment has moved towards first-generation cephalosporins and/or topical antimicrobials. Moreover, there is an increase in resistance against clindamycin, its susceptibility decreased from 90% to 83%. Retapamulin is indicated for the topical treatment of impetigo due to *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes* in patients aged 9 months or older.

Topical mupirocin was frequently used for the treatment of impetigo and has been an important component in MRSA prevention, however; reports of increasing mupirocin resistance are of serious concern. A retrospective study evaluated 358 *S. aureus* isolates taken between May 2012 and September 2013, from 249 children who visited an outpatient dermatology clinic. At the time of the first culture, 19.3% had mupirocin-resistant *S. aureus isolates*, 22.1% of subjects presenting with an *S. aureus* infection had a mupirocin-resistant isolate and 31.3% of all collected *S. aureus* isolates showed resistance to mupirocin. Prior mupirocin impetigo treatment the children had received was strongly correlated (odds ratio [OR]26.5; *P*<0.001) with mupirocin resistance.

A cross-sectional study of children and adults evaluated samples of those diagnosed with atopic dermatitis and *S. aureus* colonization. A total of 91 subjects were included and 100 *S. aureus* isolates were analyzed. All strains were methicillin-susceptible *S. aureus*. The study showed a prevalence of mupirocin resistance of 5.9%, fusidic acid resistance of 1.1%, and high levels of neomycin and bacitracin resistance (42.6% and 100%, respectively). Fusidic acid resistance was found to be associated with more severe atopic dermatitis.

Topical agents that are effective in treating skin infections caused by resistant strains are developed that may help to avoid resistance and adverse effects from the use of antibiotics. Moreover, topical formulations deliver treatment directly to the site of infection with low systemic absorption compared to oral medications. Therefore, these topical treatments are preferred for localized mild-to-moderate impetigo.

### Ozenoxacin Cream 1%: Efficacy and Safety

Ozenoxacin (XepitM, Cutanea Life Sciences) 1% cream is the only FDA approved non-fluorinated quinolone for the topical treatment of impetigo in adults and children 2 months or older. Ozenoxacin acts as a potent selective inhibitor of DNA replication, blocking the bacterial DNA gyrase A and the topoisomerase IV enzymes, which are critical enzymes for the transcription and replication processes of bacterial DNA. The 1% cream has been shown to have potent bactericidal activity against Gram-positive pathogens associated with skin infections.

A multicenter, randomized, placebo-controlled, parallel, blinded study compared ozenoxacin 1% cream with its vehicle ( placebo) and retapamulin 1% ointment. In this trial, retapamulin was included as an internal validity control. Treatments were applied twice daily for 5 days and assessments during follow-up visits were carried out at 3-4 days, 6-7 days, and 10-13 days. The 335 included pediatric patients of 2 years of age and older had non-bullous (368 (79.3%)) and bullous (96 (20.7%)) impetigo. Clinical success was defined as a total Skin Infection Rating Scale (SIRS) score 0 for exudates/pus, crust, tissue warmth and pain, and no more than 1 for each for erythema/inflammation, tissue edema, and itching. No additional antimicrobial therapy of the baseline affected areas necessary. The clinical success rate defined as clinical cure for ozenoxacin 1% cream was significantly superior to placebo (success rate 54 (34.8%) versus 30 (19.2%); *P=0.003*. Expanded criteria for clinical success including clinical cure and improvement were also assessed as a post hoc analysis. Clinical cure was defined as clinical cure and improvement were also assessed as a post hoc analysis. (Figure 1). Microbiological success after 3-4 days was 109 (70.8%) for ozenoxacin 1% cream and 58 (38.2%) for placebo and 122 (79.2%) for ozenoxacin 1% cream versus 86 (56.6%) for placebo after 6-7 days (Figure 2). Moreover, ozenoxacin 1% cream application resulted in a more rapid microbiological clearance than retapamulin. Rosen et al conducted a randomized clinical trial evaluating and comparing clinical efficacy and safety of ozenoxacin 1% cream and placebo in 139 adults and 272 children with non-bullous and bullous impetigo. Ozenoxacin 1% cream or placebo was applied twice daily for 5 days. Cure/clinical success was defined as a total Skin Infection Rating Scale (SIRS) score 0 for exudates/pus, crust, tissue warmth and pain, and no more than 1 for each for erythema/inflammation, tissue edema, and itching. No additional antimicrobial therapy of the baseline affected areas necessary. Clinical improvement was defined as >10% decrease in total Skin Infection Rating Scale (SIRS) score compared with baseline. Expanded criteria consider clinical success as clinical cure and improvement.

The clinical cure rate for ozenoxacin 1% cream at the 6-7 days assessment was significantly superior to placebo 112 (54.4%)
FIGURE 1. Clinical response at the end of the therapy. Cure/clinical success was defined as a total Skin Infection Rating Scale (SIRS) score 0 for exudates/pus, crusting, tissue warmth and pain, and no more than 1 for each for erythema/inflammation, tissue edema, and itching. No additional antimicrobial therapy of the baseline affected areas necessary. Expanded criteria consider clinical success as clinical cure and improvement. Clinical improvement was not presented and therefore is not comparable to other topical antibiotics where assessment of efficacy also includes clinical improvement.

FIGURE 2. Bacteriological response at day 3-4 and at day 6-7 (end of therapy). Eradication/microbiological success was defined as: The absence of the original pathogen(s) from visit 1 in specimen taken from the baseline affected area (with or without the presence of any new microorganisms). At 3-4 days follow up, \( P < 0.0001 \) for microbiological success: ozenoxacin vs placebo, \( P = 0.0004 \) for retapamulin vs placebo, \( P = 0.0087 \) for ozenoxacin vs retapamulin. At 6-7 days follow up (end of study), \( P \) values for microbiological success: ozenoxacin vs placebo, \( P < 0.0001 \) for retapamulin vs placebo, \( P = 1.0000 \).
FIGURE 3. Clinical response at the end (day 6-7 assessment) of the therapy in ITT population. Cure/clinical success was defined as a total Skin Infection Rating Scale (SIRS) score 0 for exudates/pus, crusting, tissue warmth and pain, and no more than 1 for each for erythema/inflammation, tissue edema, and itching. No additional antimicrobial therapy of the baseline affected areas necessary. For the main outcome, the treatment comparison used only the outcomes of success and clinical failure. Clinical improvement was defined as >10% decrease in total Skin Infection Rating Scale (SIRS) score compared with baseline. Expanded criteria consider clinical success as clinical cure and improvement.

FIGURE 4. Microbiological response at day 3-4 and at day 6-7 (end of therapy) in the ITT population. Overall microbiological success was defined as eradication, a composite of documented eradication (absence of the original pathogen from the posttreatment culture of the specimen obtained from the original site of infection) and presumed eradication (complete resolution of signs and symptoms associated with the absence of culturable material). P values were calculated using the $\chi^2$ test (without continuity correction).
versus 78 (37.9%); P<0.001 (Figure 3). Expanded criteria for clinical success which included clinical cure and improvement were also assessed as a secondary outcome (Figure 3). Microbiological success after 3-4 days was 109 (87.2%) for ozenoxacin 1% cream and 76 (63.9%) for placebo (P<0.002) and 115 (92.0%) for ozenoxacin 1% cream versus 87 (73.1%) for placebo (P<0.005) after 6-7 days (Figure 4).

Overall, the rate of selection of resistant mutants of ozenoxacin is lower than the observed with ciprofloxacin and similar or lower than the observed with levofloxacin in methicillin-sensitive *S. aureus* (MSSA), methicillin-sensitive *S. epidermidis* (MSSE) and MRSA organisms. Ozenoxacin has demonstrated efficacy versus *S. aureus* (including MRSA, Mupirocin-resistant *Staph aureus*, Ciprofloxacin resistant *Staph aureus*) and *S. pyogenes*. The in vitro activity of ozenoxacin against *Pseudomonas aeruginosa* has been shown to be greater than that of nadifloxacin, clindamycin, erythromycin, and gentamicin, but less than that of ofloxacin and levofloxacin. However, the therapeutic efficacy of ozenoxacin against *Pseudomonas aeruginosa* has not been evaluated.

Dermal application studies measuring ozenoxacin levels demonstrated negligible systemic absorption suggesting a safe, favorable safety profile.

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Laser-Assisted Delivery of Topical Cidofovir in the Treatment of Plantar Warts

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Duke University School of Medicine, Durham, NC
Duke University Medical Center, Durham, NC

ABSTRACT

Recalcitrant plantar warts pose a therapeutic challenge. Cidofovir is a viral DNA polymerase inhibitor that has been used in treatment of verrucae with greater success than traditional treatments in some cases. Laser-assisted drug delivery enhances drug penetration beyond the epidermis and is particularly well-suited, though under-utilized, to target palmoplantar verrucae. We report the use of an erbium:yttrium-aluminum-garnet (Er:YAG) ablative fractional laser (AFL) followed by topical cidofovir in treating recalcitrant plantar warts. Two patients were treated with a 2940-nm Er:YAG laser at depths of 1.2-1.5 mm followed by topical application of cidofovir 75 mg/mL. Both patients exhibited a significant reduction in lesion size and improvement in symptoms. AFL-assisted delivery of topical cidofovir represents a promising therapeutic option for recalcitrant plantar warts.


INTRODUCTION

The treatment of plantar warts is challenging and current therapies often do not result in satisfactory clearance of verrucae. A large number of plantar warts, particularly those that are large and hyperkeratotic, are recalcitrant to first-line treatments. For instance, cryotherapy and salicylic acid have not demonstrated superiority compared to a wait-and-see approach. Numerous therapeutic modalities have been utilized in the treatment of plantar warts, including topical cantharidin-podophyllotoxin-salicylic acid, topical trichloroacetic acid, topical 5% imiquimod, intralesional mumps, Candida, or Trichophyton antigen, and intralesional 5-fluorouracil. Cidofovir, a nucleotide analogue, is a potent inhibitor of viral DNA polymerase but is nephrotoxic when administered systemically. Local administration of this medication shows significant promise for treating HPV-related verrucous neoplasms. Treatment with intralesional cidofovir has demonstrated complete clearance of plantar warts in up to 98% of patients. Despite recent advances in therapeutic options for plantar warts, patients with symptomatic, large verrucous nodules and tumors remain a therapeutic challenge.

Ablative fractional lasers (AFLs) can be utilized to facilitate drug delivery beyond the stratum corneum and target lesions located within the deeper epidermis and dermis. This technique, known as laser-assisted drug delivery (LAD), has been utilized for various cutaneous applications in treating actinic keratoses, non-melanoma skin cancers, and hypertrophic scars. Several AFLs, including erbium:yttrium-aluminum-garnet (Er:YAG) and carbon dioxide (CO2), are emerging as new treatment options for recalcitrant warts, with clearance rates reported between 47% and 100%. For example, one study showed that treatment with Er:YAG followed by topical podophyllotoxin resulted in complete lesion clearance in 89% of patients with plantar warts. In this report, we describe two cases of refractory plantar verrucae treated with Er:YAG and topical cidofovir.

CASE REPORTS

Patient 1
A 59-year-old male presented with an eight-year history of a gradually enlarging painful verrucous tumor on the right heel that made it difficult to wear closed footwear. A biopsy was consistent with verruca. This lesion had been previously treated with excision, salicylic acid, and cantharidin. He then received three treatments with pulsed dye laser and 40% urea cream; initial improvement was noted, but the lesions exhibited recurrent growth within weeks. A trial of AFL-assisted delivery of topical cidofovir 75mg/mL was proposed. Pre-treatment examination demonstrated a 5.5 x 4 cm yellow hyperkeratotic verrucous tumor on the right posterior heel (Figure 1A). Treatment was initiated with a 2940-nm Er:YAG laser with a 5-mm-spot size, short pulse pattern with a density of 11% and 1.5 mm depth. Following each laser treatment, 1 mL of cidofovir 75mg/mL was applied topically to the treated area and was covered with an occlusive transparent medical dressing for 1 hour (Figure 1B). Following nine serial treatments every two to six weeks, the lesion demonstrated approximately 60% decrease in tumor size with islands of complete clearance and markedly decreased hyperkeratosis; furthermore, the patient was able to resume wearing closed footwear (Figure 1C).
A 44-year-old male presented with a two-year history of plantar warts on the right forefoot and right medial fourth toe associated with pain on ambulation. He had previously received treatment with liquid nitrogen every two weeks for six months without improvement. He then underwent four treatments with a pulsed dye laser without any improvement in lesion size or symptoms. Pre-treatment examination demonstrated numerous verrucous papules coalescing into a plaque on the right plantar forefoot and a six mm verrucous papule on the right plantar fourth toe (Figure 2A). Subsequently, he received five treatments with a 2940-nm Er:YAG laser and 0.5 mL of 75 mg/mL cidofovir as in the same protocol described above. After five treatments, the right forefoot demonstrated 80% clearance and the right fourth toe demonstrated 100% clearance (Figure 2B).

Both patients demonstrated a substantial decrease in the size of their verrucous lesions. Furthermore, there was a significant improvement in symptoms. There was mild localized erythema and edema following each treatment that resolved within 24 hours.

**DISCUSSION**

AFLs are a promising therapeutic option for difficult-to-treat cutaneous lesions, including plantar warts. Topical medications are often ineffective in treating these keratotic neoplasms in large part due to impaired drug delivery to deeper zones of viral replication. The stratum corneum serves as a physical barrier to environmental insults and exposures, including medications; absorption of topical medications is generally less than 5%. Techniques such as paring down the verruca with a scalpel have been used to improve drug delivery. A new approach to increasing drug absorption beyond the stratum corneum is the use of AFLs. AFLs are able to create microthermal zones: multiple vertical cylinders of thermal ablation that penetrate the epidermis. These microthermal zones facilitate drug delivery by allowing increased absorption of topical medications.

Cidofovir, a nucleoside analog, has broad activity against many DNA viruses including all herpes viruses. However, systemic cidofovir has numerous side effects including nephrotoxicity. Topical and intralesional treatment of refractory verruca with cidofovir has shown promising clearance rates in multiple case studies. Local delivery of this antiviral via intralesional injection has shown complete clearance in both immunocompetent and immunocompromised patients. Padilla et al. have reported 80% of patients demonstrating improvement with topical cidofovir alone. We extended this therapeutic concept by utilizing an AFL to further enhance delivery of cidofovir to the target tissue. Our two patients with recalcitrant verruca treated with AFL and topical cidofovir demonstrated a modest to significant reduction in lesion size and improvement in symptoms.

**CONCLUSION**

Plantar warts, particularly large, hyperkeratotic nodules and tumors, are challenging to treat effectively and most conventional treatments yield unsatisfactory results. The use of AFLs to create microthermal zones has been utilized in drug delivery for various dermatological applications. We described two cases of Er:YAG-assisted delivery of topical cidofovir for the treatment of recalcitrant plantar warts with positive results. Although these results are promising, additional studies are needed to further validate this treatment modality and develop a standardized protocol.

**DISCLOSURES**

The authors declare no disclosures.

**REFERENCES**


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A Head-to-Head Comparison of Topical Collagen Powder to Primary Closure for Acute Full-Thickness Punch Biopsy-Induced Human Wounds: An Internally Controlled Pilot Study

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aUniversity of Maryland School of Medicine, Baltimore, MD
bGeorge Washington University School of Medicine and Health Sciences, Washington, DC
cGeorgetown University School of Medicine, Washington, DC
d George Washington Medical Faculty Associates, Washington, DC

ABSTRACT

Background: Collagen-based products have been implemented in wound healing due to collagen’s hemostatic properties, low antigenicity, and poor culture ability.

Objective: To compare the rate and quality of full-thickness wound healing for topical collagen powder and primary closure.

Methods: Eight volunteers received one 4 mm punch biopsy on each thigh. One wound was managed with primary closure while the other received daily collagen powder. Wounds were biopsied at four weeks for histopathological analysis. Subjects rated itch, pain, and treatment preferences at weeks 1, 2, 4, 6, and 12.

Results: Six out of eight collagen-treated wounds were completely healed 4 weeks after initial wounding. Histologic analysis of the wounds revealed epidermal re-epithelization in both groups. More organized granulation tissue was noted in collagen-treated wounds and confirmed using Masson trichrome and CD31 staining for collagen and neoangiogenesis, respectively. Subjects reported similar itch and pain metrics between wounds. Both subjects and blinded dermatologists preferred the early cosmetic appearance of collagen-treated wounds over primarily closed wounds.

Limitations: Small sample size, absence of negative control.

Conclusion: These data suggest that collagen powder is non-inferior to primary closure at the macro- and microscopic levels, while possibly leading to superior early cosmetic outcomes and accelerated histologic wound maturation.

Ethics/Clinical Trials Registration: Study was approved by the George Washington University Institutional Review Board (IRB protocol #121745). ClinicalTrials.gov: NCT03481907.


INTRODUCTION

Collagen, an essential component of the extracellular matrix (ECM), is a triple helical structure composed of three polypeptide chains.1-3 During normal wound healing, collagen acts as a scaffold for cellular ingrowth and organized deposition of new collagen.4,5 Proteases degrade native collagen, releasing polypeptide fragments that act as chemotactic molecules to recruit inflammatory mediators, promote keratinocyte migration, and stimulate the proliferation of fibroblasts and subsequent collagen deposition.4,6 Collagen-based dressings and fractionated collagen powders have been developed for wound therapy as they are thought to replace degraded collagen by bypassing enzymatic breakdown.4,6 Furthermore, powdered collagen supports ECM production and acts as a signaling molecule, recruiting inflammatory cells, fibroblasts, and keratinocytes.7 Collagen has low antigenicity and can be left in wounds without causing irritation or enhancing bacterial growth.8,9 Additionally, collagen promotes thrombosis and hemostasis and has hydrophilic properties useful for absorbing fluid in exuding wounds.10,11 These factors make collagen an ideal wound therapy agent.

Punch biopsies are frequently performed for diagnostic purposes and are often closed primarily with non-absorbable sutures, but may also be left to heal by secondary intention. In a recent survey distributed by the present authors to providers on the Orlando Dermatology Aesthetic and Clinical Conference emailing list, 877 (29.6% response rate) providers completed a survey in which only 5.13% of respondents indicated that they leave a 4mm punch biopsy wound open to heal by secondary intention (data not published). Most respondents were MD/DOs (98.6%), with many being in practice for more than 10 years (38.4%, data not published). While clearly commonly used, it is important...
Each patient received a single 4 mm punch biopsy on the same level of each mid-anterior thigh to provide for internalized controls. One wound was managed with PC, while the other was treated with daily topical collagen powder for up to four weeks. Prior to each biopsy, the areas were cleansed with an alcohol swab and anesthetized using 1 mL of 2% lidocaine with epinephrine. An Integra Miltex 4.0 mm Standard Biopsy Punch instrument was used to create full-thickness wounds and pressure was applied with gauze until hemostasis.

Up to one gram of type 1, 100% bovine collagen powder (Nuvagen™, CPN Biosciences, Inc., Largo, FL) was placed on one wound before covering it with a non-adherent sterile dressing. The other wound underwent PC with two epidermal sutures (4-0 Ethilon Nylon Sutures, Ethicon, Somerville, NJ) and was similarly covered with a sterile dressing after application of petroleum jelly. At the four week follow-up, wounds were re-biopsied following the same procedures.

For home treatment, patients were provided with collagen powder in one-gram containers and dressings along with the following instructions: 1) Irrigate the wound with tap water or saline solution, 2) Dry the wound gently with dry gauze, 3) Apply up to one gram of collagen powder to the wound, and 4) Apply a sterile dressing. This procedure was repeated daily for four weeks after the first biopsy and until wound closure after the second biopsy. For wounds closed primarily, patients were instructed to apply petroleum jelly before covering the wounds with sterile dressings once daily until suture removal (two weeks after placement).

Methods

Patient Selection
Approval for this study (Clinical Trials Registration: NCT03481907) was obtained from the George Washington University Institutional Review Board (Protocol #121745). Eight healthy volunteers 18-75 years old were enrolled after providing informed consent. Inclusion and exclusion criteria are presented in Table 1. Given collagen powder can support ECM development at the wound site without increasing the risk of allergy or infection, management of biopsy wounds with collagen powder may lead to similar or improved healing outcomes compared to PC. Collagen powder also eliminates the need for suture removal, which reduces costs associated with a subsequent clinic visit. This pilot study is the first to compare the utility of topical collagen powder on the rate and quality of full-thickness wound healing compared to the gold standard, PC, through histopathological analysis of healing, and comparison of symptoms and early cosmetic outcomes.

### TABLE 1.

<table>
<thead>
<tr>
<th>Inclusion and Exclusion Criteria Used in Selection of Eight Healthy Participants</th>
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<tbody>
<tr>
<td><strong>Inclusion:</strong></td>
</tr>
<tr>
<td>1. Outpatients</td>
</tr>
<tr>
<td>2. Age 18 to 75 years old</td>
</tr>
<tr>
<td><strong>Exclusion:</strong></td>
</tr>
<tr>
<td>1. Presence of any medical (DM) or skin condition that could impair wound healing</td>
</tr>
<tr>
<td>2. Recent use of systemic immunosuppressive medications (2 months or 5 half-lives)</td>
</tr>
<tr>
<td>3. Recent application of topical steroids to the thigh(s) (2 weeks)</td>
</tr>
<tr>
<td>4. Recent participation in investigational study of a drug or device (4 weeks)</td>
</tr>
<tr>
<td>5. Current use of systemic antimicrobials</td>
</tr>
<tr>
<td>6. History of DM</td>
</tr>
<tr>
<td>7. History of bleeding disorders or concomitant treatment with anticoagulants</td>
</tr>
<tr>
<td>8. History of keloids or hypertrophic scars</td>
</tr>
<tr>
<td>9. Known allergy or sensitivity to any component collagen powder (including bovine products), sutures, or lidocaine and epinephrine</td>
</tr>
<tr>
<td>10. Current or previous use of tobacco products</td>
</tr>
<tr>
<td>11. Recent alcohol or drug abuse</td>
</tr>
<tr>
<td>12. Pregnant females or drug abuse</td>
</tr>
</tbody>
</table>

Mechanical irritation from the suture can also result in pruritus.

Biopsy and Treatment

Up to one gram of type 1, 100% bovine collagen powder (Nuvagen™, CPN Biosciences, Inc., Largo, FL) was placed on one wound before covering it with a non-adherent sterile dressing. The other wound underwent PC with two epidermal sutures (4-0 Ethilon Nylon Sutures, Ethicon, Somerville, NJ) and was similarly covered with a sterile dressing after application of petroleum jelly. At the four week follow-up, wounds were re-biopsied following the same procedures.

For home treatment, patients were provided with collagen powder in one-gram containers and dressings along with the following instructions: 1) Irrigate the wound with tap water or saline solution, 2) Dry the wound gently with dry gauze, 3) Apply up to one gram of collagen powder to the wound, and 4) Apply a sterile dressing. This procedure was repeated daily for four weeks after the first biopsy and until wound closure after the second biopsy. For wounds closed primarily, patients were instructed to apply petroleum jelly before covering the wounds with sterile dressings once daily until suture removal (two weeks after placement).
Histopathology and Outcome Assessments

Immunohistochemical and histopathological processing was performed by HistoWiz, Inc. (Brooklyn, NY) on one baseline sample and both four-week samples, including hematoxylin and eosin (H&E), CD31 (platelet-derived endothelial cell adhesion molecule-1), and Masson trichrome staining. H&E staining was used to examine the quality of the epidermis and collagen bundles as well as to observe the amount of inflammatory granulation tissue. CD31 antibody staining was performed to assess the level of angiogenesis. Staining identified to be artifact, related to large vessels, and outside the wound bed, was excluded. Masson trichrome staining was used to assess collagen deposition. To determine the percent area stained by Masson trichrome, the number of pixels staining above a threshold intensity on images of histopathology slides was calculated using ImageJ 1.48v (National Institutes of Health, Bethesda, MD) and normalized to the total number of pixels. Forty high-power fields (HPF) were reviewed per treatment arm (5 per wound) to tabulate CD31-positive cells.

Photographs of the wounds were taken at 0, 1, 2, 4, 6, and 12 weeks with a ruler in frame to allow ImageJ size calibration. Wound edges were traced and surface areas were calculated using ImageJ. Measurements were performed by two observers and averaged.

Subjects rated itch at 1, 2, 4, 6, and 12 weeks using the Pruritus Numerical Rating Scale (PNRS), a validated and reliable instrument with scores ranging from 1-10 with higher numbers indicating worse itch.19 Itch and pain improvement were also measured using the Patient Overall Assessment Scale, a scale developed for this study which ranges from 1-4 for each symptom with 1 = excellent improvement, 2 = moderate improvement, 3 = no change, and 4 = worsening. After suture removal at weeks 2 and 6, patients rated pain with suture removal on a scale from 0-10, with higher numbers indicating worse pain. Subjects also reported overall wound treatment preference and cosmetic preference at each visit. At the conclusion of the study, subjects were asked about their overall opinions of collagen powder treatment and whether the application process was “annoying” or “difficult.”

Using photographs, three faculty dermatologists blinded to treatment method reported their cosmetic preferences for each wound four weeks after the first biopsy and eight weeks after the second biopsy.

Statistical Analysis

Statistical analysis was performed with Microsoft Excel 2013 and GraphPad Prism, version 7.0. Pain, pruritus, and preference measures were analyzed using data from a single visit or data summed for several visits. Mean values of continuous variables are reported ± the standard error of the mean (SEM). P-values were calculated using the two-sample t-test for equal variances with P-values ≤ 0.05 considered significant.

RESULTS

Patient Population

All eight subjects (mean age: 37, range: 23-59 years) completed the study. Two subjects were female and six were male. One subject was Fitzpatrick Skin Type (FST) I, three were FST II, one was FST III, two were FST III/IV, and one was FST V. All subjects reported no, occasional, or moderate alcohol consumption (1 drink per day for women, 2 drinks per day for men).

Process of Collagen Treatment

Collagen powder was applied daily for four weeks after the first biopsy and for an average of 25.38±3.46 days after the second biopsy until subjective wound closure. In addition to application of pressure and collagen powder after the biopsy, one out of eight patients required hyfrecation for hemostasis, which did not impact the patient’s overall outcome. Three out of eight patients reported that the collagen powder treatment was “annoying” but no patients thought it was “difficult.” Overall, patients felt that treatment with collagen powder was more time intensive than PC, requiring careful placement of powder and dressings over the wounds to prevent spillage.

Wound Closure

Wound size reduced by 28.95±5.09%, 55.76±6.29%, and 95.94±3.53% after 1, 2, and 4 weeks of collagen powder treatment following the initial biopsy, respectively (Figure 1). After the second biopsy, wound size reduced by 75.71±5.63% after 2 weeks (Figure 1). Interestingly, this reduction in wound size was significantly greater than the reduction 2 weeks after the first biopsy (P<0.04). Six out of eight collagen-treated sites were completely healed 4 weeks after the first biopsy, and all wounds were completely healed 8 weeks after the second biopsy. Comparisons of collagen powder- and PC-treated wounds at each study visit are shown in Figure 1 for two representative patients.

Histopathology

Histopathology revealed a well-formed epidermis with some artefactual epidermal/dermal separation for collagen- and PC-treated wounds. However, collagen-treated wounds displayed less inflammatory granulation tissue, and more organized and well-formed collagen bundles on H&E (Figure 2A) and Masson trichrome staining (Figure 2B) compared to PC. Collagen staining intensity was significantly greater in collagen-treated wounds, with a mean staining intensity of 173.40±9.33 versus 125.8±7.31 for PC (Figure 3A; P<0.0001). CD31 staining (Figure 2C) revealed increased neangiogenesis for collagen-treated wounds compared to PC-treated wounds (Figure 3B) (8.55±0.25 versus 4.10±0.17, respectively; P<0.0001).
FIGURE 1. Head-to-head comparison of the wound healing course for two representative patients throughout the study. White scale bar in upper right corner of the first collagen powder wound image is 0.5cm. All images presented are scaled similarly and are in the following sequence from left to right: baseline, week 1, week 2, week 4 prior to second wounding, week 4 after second wounding, week 6, and week 12. The bottom row presents mean (± SEM) percent healing for collagen powder-treated wounds for all patients. Discrepancy in wound size reduction at 2 weeks after first and second biopsies was statistically significant. *P<0.04 SEM: Standard error of the mean.

FIGURE 2. Histopathological assessment of collagen-treated wounds versus primarily closed wounds. Collagen-treated wounds displayed less inflammatory granulation tissue, and more organized and well-formed collagen bundles both on H&E (A), and Masson trichrome staining (B) as compared to PC. CD31 staining (C) revealed increased neoangiogenesis for collagen-treated wounds compared to wounds treated with primary closure.
Pain and Pruritus

No significant differences in pain and pruritus improvement or mean PNRS scores were noted between PC- and collagen-treated sites at visit 2, visits 2-4 combined, or visits 5-6 combined (Table 2). Of note, six out of eight patients commented that reported itch was actually sensed in areas around the adhesive dressings rather than areas treated with collagen powder. Pain with suture removal was reported as an average of 1.06±0.29 out of 10 for all patients.

Cosmetic and Overall Outcomes

Patients significantly preferred the cosmetic outcomes of wounds treated with collagen powder compared to PC, with 4.19±0.23 total cumulative responses preferring collagen powder and only 0.69±0.25 total cumulative responses favoring PC over the course of study (Table 2; *P<0.001). Dermatologist evaluation of the cosmetic appearances of wounds also supported the superiority of collagen-treated wounds, with 72.92% of responses (35/48 wound images) preferring collagen powder versus 27.08% for PC (13/48 wound images; *P<0.0001). Further, overall patient preferences reflected an insignificant favoring of collagen powder treatment over PC (*P=0.22; Table 2).

Adverse Events

Four out of eight patients reported skin irritation including erythema and pruritus from the adhesive dressings overlying collagen-treated sites. No reactions were reported from the collagen powder itself. Three patients reported minor pain after the biopsies, and one patient felt the pain was worse with re-wounding at 4 weeks. No wound dehiscence or infection was noted at either of the treated sites in any subject.

DISCUSSION

Results of this internally-controlled pilot study demonstrate that acute full-thickness wounds treated with collagen powder heal at least as well as those treated with the standard of care, PC, and that collagen powder can be applied safely for at least four weeks. Furthermore, collagen powder treatment leads to

**TABLE 2.** Summary of Patient Reported Outcomes. No significant differences were found between wounds in level of pruritus, pain or pruritus improvement, or overall preferences. Cosmetically, collagen powder treatment was preferred. For cosmetic and overall preferences, mean total cumulative votes per patient were reported. Mean ± SEM scores per patient are presented. SEM: Standard error of mean, POAS: Patient overall assessment scale, PNRS: Pruritus numerical rating scale.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Scale</th>
<th>Visits</th>
<th>Primary Closure (N=8)</th>
<th>Collagen Powder (N=8)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Pain Improvement</td>
<td>POAS</td>
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<td>1.50±0.27</td>
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<td></td>
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<td>2-4</td>
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<td>5-6</td>
<td>4.00±0.69</td>
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<td>Pruritus</td>
<td>POAS</td>
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<td>4.38±0.73</td>
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<td>Pruritus</td>
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<td></td>
<td>2-4</td>
<td>4.63±1.31</td>
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<tr>
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<td>2-6</td>
<td>1.88±0.69</td>
<td>3.13±0.69</td>
<td>0.22</td>
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<tr>
<td>Cosmetic Preference</td>
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<td>0.69±0.25</td>
<td>2.19±0.23</td>
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<td></td>
<td></td>
<td>2-6</td>
<td>0.69±0.25</td>
<td>4.19±0.23</td>
<td>&lt;0.001</td>
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</tbody>
</table>
and sterilize instruments. Indirect costs to the patient, including transportation and sacrificed work time, adds an additional $145,332 to the annual cost of punch biopsies.13 Using collagen powder in 7 of 8 participants. Daily 1 gram doses of collagen powder can be ordered for patients for up to 30 days. Based on the 2019 published fee schedule, Medicare will reimburse $35.66/gram of collagen powder, generally resulting in a net reimbursement of $15-20/gram. Reimbursement rates from private insurances vary. Given its potential reimbursement, the use of collagen powder may be an inexpensive means to close a punch biopsy site.

Histopathology also demonstrated that collagen treatment increased neoangiogenesis, which may create a stronger, more vascularized wound bed that enhances healing. In vitro studies have shown that type I collagen increases endothelial cell proliferation and migration and that fragmented collagen may be more effective at doing so than its intact form.20–22 Collagen can also support the development of capillary-like structures in vitro, possibly due to its ability to suppress cyclic AMP and protein kinase A, leading to the formation of necessary actin stress fibers.20,23 Clinical trials have also demonstrated that collagen can promote angiogenesis.24–26 Compared to untreated wounds, modified collagen gel treatment was shown to contribute to acute inflammatory cell and fibroblast recruitment, collagen deposition, increased endothelial cells, upregulated vascular endothelial growth factor, and improved blood flow.24,25

Our results suggest that collagen powder may be used as an alternative to PC for 4mm punch biopsy wounds. Based on a cost analysis by Christenson et al, the average medical cost per suture placement and removal is $15.13, which amounts to an annual cost of $99,858 for all punch biopsies performed at an academic center.13 This includes both the suture costs as well as physicians’ and nurses’ time for placement and removal. Notably, this does not include the cost to procure, maintain, and sterilize instruments. Indirect costs to the patient, including transportation and sacrificed work time, adds an additional $145,332 to the annual cost of punch biopsies.13 Using collagen powder to manage punch biopsies instead of PC will save time for physicians and nurses and has the potential to increase net reimbursements to clinics. Practitioners can purchase 1 gram packages of collagen powder to assist with hemostasis and to demonstrate the application process to patients following the biopsy. In our study, hemostasis was achieved with pressure and collagen powder in 7 of 8 participants. Daily 1 gram doses of collagen powder can be ordered for patients for up to 30 days. Based on the 2019 published fee schedule, Medicare will reimburse $35.66/gram of collagen powder, generally resulting in a net reimbursement of $15-20/gram. Reimbursement rates from private insurances vary. Given its potential reimbursement, the use of collagen powder may be an inexpensive means to close a punch biopsy site.

Future research elucidating the optimal duration of collagen therapy is needed, as less than four weeks may be sufficient. Shortened treatment courses would decrease the cost and effort required by patients. Future studies should also investigate the efficacy of collagen powder in healing larger wounds and in comparison to healing by secondary intention.

CONCLUSION
This is the first study to compare the use of collagen powder and PC to heal punch biopsy wounds in humans. Using an internally-controlled design, results show that collagen powder is safe when applied daily for four weeks, confers healing capability that is at a minimum non-inferior to PC, may enhance the strength and maturity of the healing wound/scar based on histopathology, and provides superior early cosmetic outcomes compared to PC. Future work should aim to ease the delivery of topical collagen powder while elucidating additional parameters for administration including duration of therapy and candidate wound sizes.

DISCLOSURES
The authors have no relevant conflicts of interest to declare. CPN Biosciences, Inc. provided the support to carry out the study.

REFERENCES


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Patient-focused Solutions in Rosacea Management: Treatment Challenges in Special Patient Groups

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Non-Submental Applications of Injectable Deoxycholic Acid: A Systematic Review

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Natasha Atanaskova Mesinkovska MD PhD

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ABSTRACT

Introduction: Injectable deoxycholic acid (DCA; Kybella; Allergan, Irvine, CA) is currently approved only for treatment of persistent submental fat (SMF). Many cosmetic surgeons use DCA off-label to treat fat tissue in other areas of the body. There is no review summarizing the off-label uses of injectable DCA.

Methods: A systematic literature search was conducted through PubMed, Cochrane, CINAHL, and Web of Science databases using search terms “ATX-101 OR Kybella OR deoxycholic OR deoxycholate NOT amphotericin NOT bile” in accordance to PRISMA guidelines to identify off-label uses for injectable DCA or ATX-101.

Results: Ten pertinent articles were identified for review. Anatomic areas treated include the face, brassiere line, foot, and gluteotrochanteric region. Indications include facial contouring, paradoxical adipose hyperplasia, HIV/HAART-associated buccal fat pad lipodystrophy, and reduction of lipomatous tumors. DCA is efficacious at causing lipolysis and safe with minimal side effects. Most patients treated for cosmetic indications reported high patient satisfaction.

Conclusion: Off-label use of injectable DCA demonstrate a similar safety profile, effectiveness, and overall patient satisfaction compared to FDA-approved use for persistent SMF. DCA appears to be a safe and efficacious alternative to surgical reduction of unwanted adipose tissue in non-submental areas. Larger-scale studies are warranted to explore further cosmetic and potential medical applications.

according to the Cochrane Handbook for Systematic Reviews of Interventions. Rationales for exclusion and article appraisals were recorded at every stage. Final decision on study selection was reached by discussion. References of included and excluded studies were reviewed for potential studies not identified through initial search strategy.

Data Extraction and Analysis
Included studies were summarized using a data extraction form. Studies were graded using the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence.5

RESULTS
Initially, across four literature databases, 8907 non-duplicate articles from the years 1923 to 2018 were identified. After title/abstract screening, 13 articles met criteria for inclusion. These articles were subjected to full-text screen and 10 studies were included in this systematic review as depicted by the PRISMA flow diagram (Figure 1).4 Results of included studies are summarized in Table 1.

Face
Two case reports described single-patient experiences with injectable PC/DCA in the jowl and lower face, in conjunction with hyaluronic acid (HA) and botulinum toxin type A (BTX-A), as an alternative to surgery.6,7 In one case, a young Asian woman desired non-operative lower facial contouring and underwent 11 injection-only treatments over a 26-month period with PC/DCA lipolysis of the lower jowl, face, and chin, HA augmentation of the chin, cheek, and nose, and BTX-A contouring of the lower face.6 A total of four PC/DCA treatments were given at ten weeks, five months, nine months, and 22.5 months after initial treatment. Her non-operative transformation produced the desired heart-shaped face by slimming the lower cheeks and improving jawline definition.

The second case reported a one-stage, combination jowl rejuvenation procedure in a middle-aged female with BTX-A, HA, and DCA injections to the depressor anguli oris, marionette lines, and the subcutaneous-fat-rich jowl area, respectively.2 Results of the Face-Q, a validated patient-reported outcome instrument, completed 3-months post-treatment indicated significant improvement in facial appearance from baseline (84.5% vs 44%), and an independent standardized wrinkle assessment scale (WAS) assessment (0=no wrinkle, 5=very deep wrinkle) performed by five independent plastic surgeons were consistent, with an average of 2-point improvement from baseline.8,9

Brassiere Line
Two case series (n=7) explored off-label use of DCA injections to the brassiere (bra) line using one to three treatments per site. Six patients received injections to the posterior bra line, and one patient received anterior injections. All seven patients experienced improvement of bra line adiposity and decreased skin thickness.10,11 The first case series described two middle-aged female patients receiving injectable DCA (10mg/ml). One patient received bilateral 2ml (4ml total) injections in the upper back, just above the horizontal bra line, while the other patient received bilateral 1ml (2ml total) injections lateral to both breasts at the axillary tail of Spence. Injections were given in 0.15ml volumes spaced 0.5-1.0cm apart in each treatment area. Both patients required only one treatment session and reported high satisfaction with the gradual reduction of fat bulging based on patient-reported visual self-assessment over a three to nine-month period.

The second case series included five patients treated with DCA injections, over a 12-week period, for persistent posterior-superior bra line liposis.12 Each patient received a total dose of 2mg/cm² bilaterally in 0.2ml injection intervals every four weeks and patients experienced an average 5.2mm reduction in skin pinch thickness of the posterior back and 17-percent reduction in their posterior bra-bulge, similar to Jegasothy's experience.

Gluteotrochanteric/Trochanteric Region
Two larger-scale studies (n=63) reported on the use of DCA-containing injections for aesthetic reduction of the gluteotrochanteric regions.12 One controlled study (n=26) using 10ml 5% PC/4.3% DCA/ethanol subcutaneous injections into the right posterior trochanteric area twice, three weeks apart. Reduction of adipose tissue was evaluated by ultrasound and an optical device (Lipometer®); Moeller Messtechnik, Graz, Styria, Austria) at baseline, 8 weeks, and 20 weeks, and photography at baseline and 20 weeks. At week 20, there was no statistically significant difference between the right and left areas using Lipometer, ultrasound nor qualitative photographic. No patients evaluated the procedure positively, and only two patients (7.7%) opted to receive contralateral injections.

FIGURE 1. PRISMA flow diagram summarizing literature search.
<table>
<thead>
<tr>
<th>Authors; Year</th>
<th>Study Type (Level of Evidence)</th>
<th>Off-label Use</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Adverse Events</th>
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<tbody>
<tr>
<td><strong>Face</strong></td>
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</tr>
<tr>
<td>Wong et al. 2018</td>
<td>Case report (LOE 5)</td>
<td>Lower face and jaw remodeling</td>
<td>20-year-old healthy Asian female</td>
<td>Eleven treatments using (1) botulinum toxin, (2) HA, and (3) PC/DCA (50mg/ml PC, 42mg/ml DCA). A total of four PC/DCA treatments were given at: - 10 weeks (750mg) - 5 months (875mg) - 9 months (937.5mg) - 22.5 months (593mg) - 3155.5mg PCA/DCA total.</td>
<td>Aesthetic enhancement of face shape, jaw contour, and jowl definition. Patient was satisfied with cosmetic result.</td>
<td>None reported.</td>
</tr>
<tr>
<td>Mess 2017</td>
<td>Case report (LOE 5)</td>
<td>Marionette lines and jowls</td>
<td>55-year-old female</td>
<td>Sequential treatment using (1) botulinum toxin, (2) HA, (3) DCA.</td>
<td>Satisfaction with facial appearance at 3 months: 84.5% compared to 44% at baseline (FaceQ).</td>
<td>Self-limited injection-site bruising and edema.</td>
</tr>
<tr>
<td><strong>Brassiere Line</strong></td>
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<tr>
<td>Jegasothy 2018</td>
<td>Case series (LOE 4)</td>
<td>Bra-line lipolysis</td>
<td>Case A: 46-year-old healthy Caucasian female Case B: 47-year-old healthy East Indian female</td>
<td>1 injection of Kybella treatment seated upright: - Case A: 2 ml (20mg) DCA on each side (upper back) - Case B: 1 ml (10mg) DCA on each side (lateral breasts).</td>
<td>Both subjects reported gradual bra line fat decrease beginning at 1 month and continuing until 3- and 9-months post-treatment, respectively; no re-accumulation of fat in treated areas.</td>
<td>Self-limited injection site edema, tenderness, and itching; resolved within 7 days.</td>
</tr>
<tr>
<td>Verma et al. 2018</td>
<td>Case series (LOE 4)</td>
<td>Bra-line lipolysis</td>
<td>5 healthy females</td>
<td>20 mg DCA every 4 weeks.</td>
<td>Average 5.2 mm reduction (4.9 mm) in skin pinch thickness and 17% (10-24%) reduction in posterior bra-bulge from baseline.</td>
<td>Self-resolving injection site pain, swelling/edema, and bruising.</td>
</tr>
<tr>
<td><strong>Gluteotrochanteric/Trochanteric Region</strong></td>
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<tr>
<td>Salti et al. 2007</td>
<td>Double-blind randomized trial (LOE 2)</td>
<td>Gynoid lipodystrophy</td>
<td>37 healthy females</td>
<td>Treatments randomized per side: - One side: 50/25mg/ml PC/NaDC (1000/500mg total) - Other side: 475mg/ml NaDC (475mg total) Given 4 treatments per side, every 8 weeks.</td>
<td>Overall reduction of local fat in 91.9% of patients without significant differences between the treated sides.</td>
<td>Self-resolving pain, bruising, and palpable subcutaneous nodule with both treatments; pain and bruising were more intense with NaDC. Systemic cholinergic effects: dizziness/lightheadedness (n=2, 5.4%), nausea/malaise (n=4, 10.6%), and diarrhea/steatorrhea (n=6, 16.2%) of unknown etiology; resolved within 24 hours.</td>
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### TABLE 1. (CONTINUED)

**Summary of Included Studies**

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<th>Authors; Year</th>
<th>Study Type (Level of Evidence)</th>
<th>Off-label Use</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Adverse Events</th>
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<tr>
<td><strong>Gluteotrochanteric/Trochanteric Region</strong></td>
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<tr>
<td>Kopera 200712</td>
<td>Cohort study (LOE 3)</td>
<td>Trochanteric bulges</td>
<td>26 healthy females</td>
<td>3 treatments with 10ml of 5%PC/4.3%NaDC/ethanol to the right posterior trochanteric region.</td>
<td>No significant decrease in trochanteric bulge between sides. Zero patients evaluated treatment positively.</td>
<td>Not reported.</td>
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</table>

**Feet**

<table>
<thead>
<tr>
<th>Authors; Year</th>
<th>Study Type (Level of Evidence)</th>
<th>Off-label Use</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Adverse Events</th>
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<tbody>
<tr>
<td>Turkmani 201814</td>
<td>Case report (LOE 5)</td>
<td>Piezogenic pedal papules</td>
<td>34-year-old obese (121 kg) woman with intense heel pain for 10 months</td>
<td>0.05ml to 0.1ml of 1% DCA.</td>
<td>Nodules completely disappeared after 2 weeks; no more pain with walking or standing.</td>
<td>None reported.</td>
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</table>

**Paradoxical Adipose Hyperplasia**

<table>
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<th>Authors; Year</th>
<th>Study Type (Level of Evidence)</th>
<th>Off-label Use</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Ward et al. 201815</td>
<td>Case report (LOE 5)</td>
<td>Paradoxical adipose hyperplasia secondary to cryolipolysis at lower abdomen</td>
<td>58-year-old healthy Caucasian female</td>
<td>4 ml 1% DCA 3 times: - Initial: 1.7ml (left), 2.3ml (right) - Remaining: 2ml per side.</td>
<td>Waist circumference decreased from 30.5 inches to 29.5 inches after 3 treatments.</td>
<td>Self-resolving erythema, swelling, and mild tenderness around the injection site within 2-3 days.</td>
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</table>

**Highly Active Antiretroviral Therapy (HAART)-Associated Lipodystrophy of the Buccal Fat Pad**

<table>
<thead>
<tr>
<th>Authors; Year</th>
<th>Study Type (Level of Evidence)</th>
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<th>Subjects</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Adverse Events</th>
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<tr>
<td>Rotunda et al. 201116</td>
<td>Case report (LOE 5)</td>
<td>HIV/HAART-related lipohypertrophy</td>
<td>48-year-old HIV-positive male on HAART with bilateral buccal lipoma-like growths over previous 2 years</td>
<td>1 ml 1% NaDC and 0.25 ml 2% lidocaine; given 3 times.</td>
<td>Both lesions decreased in size and became asymptomatic.</td>
<td>Not reported.</td>
</tr>
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</table>

**Lipoma**

<table>
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<tr>
<th>Authors; Year</th>
<th>Study Type (Level of Evidence)</th>
<th>Off-label Use</th>
<th>Subjects</th>
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<th>Outcomes</th>
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</thead>
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<tr>
<td>Rotunda et al. 200517</td>
<td>Cohort study (LOE 3)</td>
<td>Lipoma</td>
<td>6 patients; 12 lipomas</td>
<td>Injection volumes (ml) equaled half the largest lipoma dimensions.</td>
<td>All lipomas decreased in size [mean area reduction 75% [37-100%]] after an average of 2.2 treatments. Several lipomas fragmented or became softer in addition to decreasing in volume.</td>
<td>2 and 5% DCA associated with burning and prolonged swelling; took up to 6 weeks to resolve. Two patients experienced injection-site cutaneous paresthesia with 5% DCA; took up to 6 weeks to resolve.</td>
</tr>
</tbody>
</table>
A double-blind, self-controlled, randomized study (n=37 females) investigated the use of PC/DCA (50:25mg/ml) versus DCA alone (475mg/ml) in patients with localized gynoid lipodystrophy. Four treatments were administered to the gluteotrochanteric region every eight weeks to allow for post-infiltrative nodular resolution. Each patient received 1000/500mg of PC/DCA on one side and 475mg DCA alone on the contralateral side. After both solutions were diluted in saline, a total of 80 infiltrations (40ml) per side were administered over 1cm intervals during each treatment. Outcome was assessed using thigh circumference at the level of the sub-gluteal fold, ultrasonographic measurement of trochanteric fat pad thickness, and photographs at baseline and eight weeks after the last treatment. Thirty-four patients (91.9%) achieved reduction in thigh circumference and trochanteric fat pad thickness, and photographs at baseline and eight weeks after the last treatment. Thirty-four patients (91.9%) achieved reduction in thigh circumference and trochanteric fat pad thickness without significant difference bilaterally; three patients (8.1%) were non-responders.

**Feet**

One case report described treatment of symptomatic piezogenic pedal papules (pressure-induced papules) on the foot and heel in a 34-year-old obese woman using 0.05-0.1ml (based on papule size) of 1% DCA solution. The patient achieved complete resolution of papules and bilateral heel pain in two weeks.

**Treatment of Paradoxical Adipose Hyperplasia**

One 58-year-old Caucasian female was treated with injectable DCA (10mg/ml) for abdominal paradoxical adipose hyperplasia (PAH) after two prior cryolipolysis treatments. A total of three, 4ml treatments were given at 0, 6, and 16 weeks resulting in gradual reduction of lower abdominal fullness. Positive results were maintained five months after the third treatment despite no change in caloric intake or expenditure. The patient was highly satisfied decreased waist circumference from 30.5 to 29.5 inches.

**Treatment of HIV-Associated Lipodystrophy of the Buccal Fat Pad**

One case of highly active antiretroviral therapy (HAART)-associated buccal fat pad lipodystrophy in a 48-year-old male was treated with three bilateral injections of DCA at baseline, 14 days and 24 days. Each 4cm mass was treated with four intralesionial injections of 1ml 1% DCA. Clinical reduction and magnetic resonance imaging (MRI) assessment three-months after initial treatment confirmed a decrease in maximum buccal fat pad depth from 12-14 to 10mm. At six months, the lesions measured approximately 1cm and regrowth to 1.5cm after one year, and they were reinjected with 1ml of 1% DCA with no further follow-up.

**Treatment of Lipoma**

A small prospective study (n=6) detailed the use of isolated DCA in the treatment of 12 lipomas, ranging from 1cm to 3.5cm in largest dimension, at intervals of 2 to 20 weeks. Patients were injected with DCA at concentrations of 10, 25, or 50mg/ml at volumes equaling half the largest lipoma dimension in centimeters until satisfactory tumor reduction was achieved (one to four treatments). All lipomatous tumors decreased in size with a mean area reduction of 75% (37-100%) after an average 2.2 treatments, while some tumors fragmented and/or became softer after injection. Most importantly, change in lipoma size did not correlate with DCA concentration as patients treated with the lowest dose achieved similar clinical response to those receiving higher doses.

**DISCUSSION**

Minimally invasive cosmetic procedures continue to gain popularity over time, evidenced by a 186% increase in national utilization between 2000 and 2017 (versus a six-percent drop in cosmetic surgical procedures over the same period). Injectable DCA is among several minimally invasive cosmetic procedures popularized by social media, alongside botulinum toxin injections and soft tissue fillers, which prompts further investigation into safety and efficacy as popular interest and indications continue to expand. Cosmetic and medical outcomes of DCA lipidolysis injections achieved desirable results according to patients and providers. The overall high patient satisfaction and minimal side effects associated with non-submental DCA injections mirrors the level of success associated with submental DCA injections and further highlights the potential of less-invasive alternatives to aggressive surgical treatments for adipose tissue removal. For example, combination therapies using injectable DCA in conjunction with HA and BTX-A for lower face contouring may spare future patients from undergoing genioplasty or mandibuloplasty. DCA injections of the jowls and lower face provides an alternative to traditional rhytidectomy or facelift for facial rejuvenation. Notably, patient and physician/evaluator-reported assessments of aesthetic outcomes were concordant in studies on the face, brassiere line, feet, PAH, lipodystrophy and lipomas reported in this article. Future studies may be strengthened by incorporating more patients, utilizing standardized treatments, and using validated tools to measure treatment outcomes, such as the Face-Q or Body-Q, or quantitative measurements with high-resolution ultrasound or MRI. Although DCA injection has unanimously demonstrated superior efficacy in smaller anatomic areas, conflicting evidence reported for DCA injections in reducing gluteotrochanteric and trochanteric fat suggests the need for further research on the efficacy of DCA on larger anatomic areas.

Side effects associated with injectable DCA ranged from no side effects, as seen in treatment of piezogenic pedal papules, to systemic side effects (nausea, dizziness, and diarrhea) potentially associated with large-volume gluteotrochanteric DCA injections. High-volume DCA injections may have several volume-related local effects not seen with smaller-volume DCA injections may cause compression of local structures or increased hydrostatic pressure at the injection site. On a similar note, patients experienced less pain and inflammatory response, without a significant difference in fat reduction using...
a combination PC/DCA.\textsuperscript{13} This therapy may be utilized in areas that experience friction and pressure from functional movements, such as the brassiere line.\textsuperscript{11} Higher concentrations of DCA does not equate to greater clinical fat reduction according to Rotunda et al.'s study which achieved statistically comparable efficacy in terms of lipoma reduction even when using the lowest 1% DCA concentration.\textsuperscript{17} This phenomenon is further supported by findings from Walker et al.'s recent clinical trial.\textsuperscript{23} Further work remains to determine different effects of DCA in neoplastic versus native fat cells and ideal dosing for minimizing side effects in different anatomical areas.

Economic burden associated with DCA injections was found to be a major factor of consideration for patients according to a pooled analysis of four clinical trials of injectable DCA. Patel and Krikel estimated that clinical trial patients receiving injectable DCA incurred an average $6,426 in expenses ($186 of drug per patient), compared to $2,976 as the average cost incurred by patients for liposuction. However, these values may not accurately reflect the charges incurred in clinical practice, as the amount of DCA required can vary drastically based on treated anatomical location. Evaluation of the average number of injections per patient in clinical practice, in addition to characterizing primary payor, is needed to determine the true economic burden of each procedure in the clinical setting.\textsuperscript{24}

Off-label use of injectable DCA is not limited to aesthetic purposes as injectable DCA treats painful piezogenic pedal papules, lipomas, and HAART-associated-lipodystrophy.\textsuperscript{13,14} Given DCAs potential to cause DNA damage through production of reactive oxygen species and modulation of interactions between steroid ligands and their receptors, DCA may possess anti-tumor properties warranting further translational research for treatment of malignant fatty tissue.\textsuperscript{25,26} Despite promising results, the limited literature and number of patients who have undergone non-submental DCA injections should prompt further experimentation of new anatomical applications, indications, and dosages, in addition to establishing safety profiles.

**CONCLUSION**

Most non-submental applications of injectable DCA appear to demonstrate a similar safety profile, efficacy, and patient satisfaction comparable to FDA-approved use for persistent SMF. Current experiences of off-label DCA injection demonstrate favorable cosmetic results and may be a viable alternative to surgical adipose tissue removal, cryolipolysis in PAH-prone patients or patients that cannot receive cryolipolysis, or other non-invasive methods of lipolysis. Larger-scale studies are warranted to explore further cosmetic and potential medical applications.

**DISCLOSURES**

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**REFERENCES**


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Atopic Dermatitis: A Review of Topical Treatment

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

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Effective and Safe Repeated Full-Face Treatments With AbobotulinumtoxinA, Hyaluronic Acid Filler, and Skin Boosting Hyaluronic Acid

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ABSTRACT

Background: It is important to study full-face aesthetic combination treatments to establish well-founded individual treatment plans.

Objective: To evaluate clinical outcome and perception of treatment with either abobotulinumtoxinA (ABO) or hyaluronic acid (HA) filler followed by repeated combined treatment with ABO, HA filler, and Restylane® Skinboosters (RSB).

Methods & Materials: This study was conducted at four sites in Sweden, France, and Brazil and included subjects aged 35-50 years with mild/moderate nasolabial folds and moderate/severe upper facial lines. Monotherapy was ≤125 s.U ABO in at least two upper facial indications with optional touch-up or ≤1 mL HA filler in nasolabial folds/cheeks. At months 6 and 12, both cohorts received ≤125 s.U. ABO in upper facial lines with optional touch-up, ≤2 mL HA filler in nasolabial folds/cheeks (and other facial areas as applicable), and ≤1 mL RSB. Assessments included global facial aesthetic appearance and improvement, first impression, perceived age, wrinkle severity, satisfaction questionnaires, and adverse events.

Results: Repeated full-face treatment with ABO, HA filler, and RSB was associated with better aesthetic outcome and higher levels of satisfaction than treatment with ABO or HA filler alone. However, even modest volumes of HA filler achieved good aesthetic outcomes and high satisfaction. Treatment of several indications was well tolerated.

Conclusion: Aesthetic improvement and subject satisfaction was high and increased with each treatment. All treatments were well tolerated. These data may be used as support when establishing individual treatment plans.


INTRODUCTION

Aesthetic treatment with either botulinum toxin type A (BoNT-A) or hyaluronic acid (HA) filler(s) is generally more common than combination treatment; approximately one-third of patients receive a combination of injectable treatments. Upper facial aesthetic indications of BoNT-A include glabellar lines, lateral canthal lines, and horizontal forehead lines. The marketing authorization for abobotulinumtoxinA (ABO) includes treatment of hyperfunctional facial lines in Brazil and moderate-to-severe glabellar lines and lateral canthal lines in many European countries including France and Sweden.

HA fillers are most commonly used for aesthetic soft-tissue augmentation of the mid and lower face. Restylane® Skinboosters (RSB [Galderma Aesthetics, Sweden]) are used for skin rejuvenation and improved skin quality.

The objective of this study was to collect data on subjects receiving monotherapy with either ABO or HA filler followed by repeated combination treatment with ABO, HA filler, and RSB to provide guidance to practitioners for individual treatment plans. BoNT-A in up to three upper facial indications has not previously been studied in combination with HA filler and RSB.

METHODS

Study Design
This was an 18-month study conducted at four sites in Sweden, France, and Brazil (Figure 1). ABO cohort data up to 6 months have been published. The study protocol was approved by independent Ethics Committees and conformed to the Declaration of Helsinki, Good Clinical Practice, and local regulations.

Eligibility Criteria
Subjects between 35 and 50 years who provided signed in-
formed consent and had mild-to-moderate nasolabial folds and moderate-to-severe upper facial lines at maximum contraction were eligible for the study.

Key exclusion criteria included (1) apparent facial sagging, (2) facial procedures eliciting an active dermal response during the preceding 6 months, or BoNT-A, HA or collagen treatment within the preceding 12 months, (3) treatment with non-collagen or non-HA product, or facial surgery, (4) history of dysphagia, neuromuscular junctional disorders, signs of compensatory frontalis muscle activity or eyelid ptosis, known hypersensitivity to BoNT-A, HA, lidocaine hydrochloride or other amide-type anesthetics, or history of autoimmune disease, (5) inflammation, active skin disease, scarred, or damaged facial skin.

Treatment Procedure
Injections were performed in accordance with the Instructions for Use (HA fillers and RSB) and Summary of Product Characteristics (ABO) that were valid at the time. Local anesthesia was used by decision of the Investigators.

**Monotherapy**

**ABO cohort:** Subjects received up to 125 s.U ABO (Azzalure®/Dysport® [Ipsen Biopharm Limited, UK]) intramuscularly in at least two upper facial indications. Recommended doses were 50 s.U in 5 injection points for glabellar lines, 60 s.U (30 s.U/side) in 3 injection points/side for lateral canthal lines, and 20-60 s.U in 4-6 injection points for forehead lines. Optional touch-up was allowed after 2 weeks.

**HA cohort:** Subjects were injected in nasolabial folds and/or cheeks with ≤1 mL of either OBT™ or NASHA™ fillers (Galderma Aesthetics, Sweden). OBT fillers were Restylane Refyne and/or Restylane Defyne; NASHA fillers were Restylane Lidocaine and/or Restylane Lyft Lidocaine. Needle/cannula and injection method were at the Investigator’s discretion. No touch-up was allowed.

**Combination Treatment**
At months 6 and 12, subjects in both cohorts received up to 125 s.U ABO in at least two upper facial indications, ≤2 mL HA filler in nasolabial folds and/or cheeks (and other areas as applicable), and ≤1 mL Restylane Skinboosters Vital Lidocaine (Europe)/Restylane Skinboosters Vital (Brazil) (Figure 1). Touch-up with ABO was allowed after 2 weeks. Each subject received either OBT or NASHA filler during the study. A second RSB treatment (≤1 mL) was given at month 7.

**Efficacy Assessments**
Subject photographs were taken one month after each treatment (months 1, 7, and 13). Global aesthetic facial appearance was assessed by blinded evaluators by comparing photographs from months 1 and 7, as well as from month 13.

Subject photographs were also used for blinded evaluation of perceived age and first impression regarding social skills, academic performance, dating success, occupational success, attractiveness, financial success, relationship success, and athletic success, using a 10-grade scale. Overall first impression was the sum of the scores from all categories, with a maximum score of 80.

Aesthetic improvement compared to baseline was assessed using the 5-grade Global Aesthetic Improvement Scale (GAIS).
Blinded evaluators used photographs, while subjects and Investigators did the assessment during the medical appointment. Wrinkle severity assessment of upper facial indications at rest and at maximum contraction was assessed by Investigators using a validated 5-grade scale.  

Subject and Investigator satisfaction was assessed using questionnaires.

**Safety Assessment**

Methods for collecting safety data included assessment of adverse events (AEs).

**Statistical Methods**

Two analysis populations were defined for the study. The safety population included all subjects who were injected in at least one nasolabial fold/cheek (HA cohort) or one injection point (ABO cohort). The intention-to-treat population was the primary population for efficacy analyses and included all subjects who were injected in both nasolabial folds/cheeks or at least two upper facial indications.

Statistical analyses and the randomization list were done using SAS® version 9.4. Analyses of global facial aesthetic appearance, wrinkle severity, and GAIS were done using 95% confidence intervals. The aim was to show that global facial aesthetic appearance was superior at month 7 compared to month 1, with the 95% confidence interval above 50%. First impression was presented descriptively and using Wilcoxon signed-rank test. Perceived age assessments were presented descriptively and with paired t-test. Satisfaction questionnaires were analyzed descriptively.

**RESULTS**

Figure 2 shows subject disposition. Sixty-five subjects were randomized to monotherapy with either ABO (n=32) or HA filler (n=33). Table 1 and Table 2 show demographic and baseline data. Injection data are presented in Table 3 to Table 5.

**Efficacy**

**Global Facial Aesthetic Appearance**

One month after first combination treatment (month 7), most subjects (ABO cohort: 67%; HA cohort: 94%) had a superior global facial aesthetic appearance compared with after monotherapy (month 1; Figure 3). When the evaluators compared photographs from months 1, 7, and 13, the best result was obtained at month 13 (one month after the second combination treatment [60% of subjects]), followed by first combination treatment (36%) and monotherapy (4%), both cohorts combined (Figure 4).

---

**FIGURE 2.** Subject disposition. *Nasolabial folds not assessed as mild/moderate (n=3), signs/symptoms of eyelid ptosis/compensatory frontalis muscle activity (n=1), active skin disease, inflammation, or related conditions (n=1). AE (headache). Treatment with prohibited procedure before (n=1) or during (n=1) the study, consent withdrawal (n=1). Safety analyses after first combined treatment did not include subjects withdrawn before month 6. Safety analyses after second combined treatment did not include subjects withdrawn before month 12.
**TABLE 2.**

<table>
<thead>
<tr>
<th>Wrinkle Severity at Baseline</th>
<th>ABO cohort (N=32)</th>
<th>HA cohort (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At rest</strong></td>
<td><strong>At max contraction</strong></td>
<td><strong>At rest</strong></td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>GL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No GL</td>
<td>2 (6.3)</td>
<td>--</td>
</tr>
<tr>
<td>Mild GL</td>
<td>21 (65.6)</td>
<td>--</td>
</tr>
<tr>
<td>Moderate GL</td>
<td>8 (25.0)</td>
<td>14 (43.8)</td>
</tr>
<tr>
<td>Severe GL</td>
<td>1 (3.1)</td>
<td>18 (56.3)</td>
</tr>
<tr>
<td>Very severe GL</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>LCL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No LCL</td>
<td>2 (6.3)</td>
<td>--</td>
</tr>
<tr>
<td>Mild LCL</td>
<td>21 (65.6)</td>
<td>--</td>
</tr>
<tr>
<td>Moderate LCL</td>
<td>8 (25.0)</td>
<td>14 (43.8)</td>
</tr>
<tr>
<td>Severe LCL</td>
<td>1 (3.1)</td>
<td>18 (56.3)</td>
</tr>
<tr>
<td>Very severe LCL</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>FL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No FL</td>
<td>2 (6.3)</td>
<td>--</td>
</tr>
<tr>
<td>Mild FL</td>
<td>21 (65.6)</td>
<td>--</td>
</tr>
<tr>
<td>Moderate FL</td>
<td>8 (25.0)</td>
<td>14 (43.8)</td>
</tr>
<tr>
<td>Severe FL</td>
<td>1 (3.1)</td>
<td>18 (56.3)</td>
</tr>
<tr>
<td>Very severe FL</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

GL: Glabellar lines; LCL: Lateral canthal lines; FL: Forehead lines

**Wrinkle Severity**

Responders to treatment were defined as subjects with at least 1-grade improvement of upper facial lines. In general, more subjects were responders at maximum contraction than at rest, except forehead lines, for which more subjects were responders at rest than at maximum contraction. A majority of subjects were responders at 1 month after each treatment (month 1, month 7, and month 13). Six months after the treatments (month 6, month 12, and month 18), the effect had generally subsided. However, more subjects were responders at month 12 than at month 6, and also at month 18 than at month 12, except for lateral canthal lines at rest (Figure 6).

**First Impression**

Overall first impression was similar between monotherapy and combination treatments; mean scores ranged from 42.4 to 44.6 during the study, both cohorts combined.

**Perceived Age**

Subjects were perceived to look younger after first and second combination treatment compared to after monotherapy, mean difference was -1.3 years ($P<0.007$) and -2.0 years ($P<0.001$), respectively, both cohorts combined. Also, most subjects were assessed as looking younger after the second combination treatment than after the first; mean difference was -0.9 years with $P=0.043$, both cohorts combined.

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**GAIS**

According to blinded evaluators, 70% of subjects in the ABO cohort and 61% in the HA cohort were improved on the GAIS after monotherapy. After first and second combination treatment, 90% and 88% of subjects were improved, respectively, both cohorts combined. GAIS assessments by subjects and investigators showed improvement for 88-100% of subjects after monotherapy and for 94-100% of subjects after both combination treatments (Figure 5).

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GL: Glabellar lines; LCL: Lateral canthal lines; FL: Forehead lines
### TABLE 3.

**Injection Information Baseline**

<table>
<thead>
<tr>
<th></th>
<th>ABO cohort (N=32)</th>
<th>HA cohort (N=33)</th>
<th>Both (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABO dose (s.U), mean (range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GL</td>
<td>Baseline (n=32)</td>
<td>47.5 (30.0-58.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Touch-up (n=11)</td>
<td>16.4 (6.00-26.0)</td>
<td></td>
</tr>
<tr>
<td>LCL</td>
<td>Baseline (n=32)</td>
<td>33.9 (20.0-50.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Touch-up (n=13)</td>
<td>14.5 (1.50-22.0)</td>
<td></td>
</tr>
<tr>
<td>FL</td>
<td>Baseline (n=27)</td>
<td>29.2 (75.0-60.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Touch-up (n=4)</td>
<td>10.6 (1.00-20.0)</td>
<td></td>
</tr>
<tr>
<td><strong>HA filler volume mL, mean (range)</strong></td>
<td>0.87 (0.40-1.00)</td>
<td>0.44 (0.20-0.60)</td>
<td></td>
</tr>
</tbody>
</table>

GL: Glabellar lines; LCL: Lateral canthal lines; FL: Forehead lines

### TABLE 4.

**Injection Information: First Combined Treatment (Month 6)**

<table>
<thead>
<tr>
<th></th>
<th>ABO cohort (N=31)</th>
<th>HA cohort (N=31)</th>
<th>Both (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABO dose (s.U), mean (range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GL</td>
<td>Month 6 (n=31/31(^a))</td>
<td>49.3 (32.0-64.0)</td>
<td>51.5 (40.0-64.0)</td>
</tr>
<tr>
<td></td>
<td>Touch-up (n=12/9(^a))</td>
<td>19.6 (6.00-30.0)</td>
<td>30.2 (18.0-50.0)</td>
</tr>
<tr>
<td>LCL</td>
<td>Month 6 (n=30/31(^a))</td>
<td>38.1 (20.0-56.0)</td>
<td>37.7 (24.0-58.0)</td>
</tr>
<tr>
<td></td>
<td>Touch-up (n=10/9(^a))</td>
<td>17.7 (12.0-30.0)</td>
<td>19.0 (8.0-40.0)</td>
</tr>
<tr>
<td>FL</td>
<td>Month 6 (n=28/23(^b))</td>
<td>28.8 (9.0-54.0)</td>
<td>30.3 (8.0-46.0)</td>
</tr>
<tr>
<td></td>
<td>Touch-up (n=6/5(^b))</td>
<td>23.0 (10.0-40.0)</td>
<td>23.4 (2.0-40.0)</td>
</tr>
<tr>
<td><strong>HA filler volume mL, mean (range)</strong></td>
<td>0.71 (0.40-1.30)</td>
<td>0.61 (0.20-1.20)</td>
<td>0.66 (0.20-1.30)</td>
</tr>
</tbody>
</table>

GL: Glabellar lines; LCL: Lateral canthal lines; FL: Forehead lines

### TABLE 5.

**Injection Information: Second Combined Treatment (Month 12)**

<table>
<thead>
<tr>
<th></th>
<th>ABO cohort (N=31)</th>
<th>HA cohort (N=29)</th>
<th>Both (N=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABO dose (s.U), mean (range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GL</td>
<td>Month 12 (n=30/29(^a))</td>
<td>46.0 (25.0-64.0)</td>
<td>49.2 (32.0-58.0)</td>
</tr>
<tr>
<td></td>
<td>Touch-up (n=11/7(^a))</td>
<td>20.3 (3.0-40.0)</td>
<td>17.1 (10.0-24.0)</td>
</tr>
<tr>
<td>LCL</td>
<td>Month 12 (n=29/29(^a))</td>
<td>41.0 (25.0-60.0)</td>
<td>38.7 (28.0-60.0)</td>
</tr>
<tr>
<td></td>
<td>Touch-up (n=9/7(^a))</td>
<td>14.6 (3.0-16.0)</td>
<td>21.4 (16.0-30.0)</td>
</tr>
<tr>
<td>FL</td>
<td>Month 12 (n=29/26(^b))</td>
<td>29.1 (10.0-40.0)</td>
<td>28.0 (8.0-40.0)</td>
</tr>
<tr>
<td></td>
<td>Touch-up (n=5/5(^b))</td>
<td>24.0 (10.0-40.0)</td>
<td>31.6 (18.0-60.0)</td>
</tr>
<tr>
<td><strong>HA filler volume mL, mean (range)</strong></td>
<td>0.51 (0.20-1.00)</td>
<td>0.50 (0.20-1.00)</td>
<td>0.51 (0.20-1.00)</td>
</tr>
</tbody>
</table>

GL: Glabellar lines; LCL: Lateral canthal lines; FL: Forehead lines

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**FIGURE 3.** Subjects with superior global facial aesthetic appearance after first combination treatment than after monotherapy. Since the confidence interval was above the predetermined limit (50%; dashed line) in the HA cohort and in both cohorts combined, it was shown that with 95% confidence, the majority of subjects in the underlying populations had a superior facial aesthetic appearance after combination treatment than after monotherapy.
FIGURE 5. GAIS score improvement compared to baseline. *Somewhat, much, or very much improved.

FIGURE 4. Subject photographs. Female subject, age 45, with no previous facial procedures. The subject provided signed consent to that photographs of her face could be used publicly for scientific purposes. (A) One month after monotherapy with: 51 + 8 s.U ABO in glabellar lines, 29 + 10 s.U in lateral canthal lines, and 11 s.U in forehead lines. (B) One month after first combination treatment with: 48 s.U ABO in glabellar lines, 23 s.U in lateral canthal lines, and 11 s.U in forehead lines; 1.90 mL HA filler in nasolabial folds, lips, cheeks, nose tip and pre-mental crease; 1 mL RSB in lower face. (C) One month after second combination treatment with: 50 s.U ABO in glabellar lines and 25 s.U in lateral canthal lines; 2.0 mL HA filler in nasolabial folds, cheeks, lips, tear troughs, pre-mental crease and upper eyelids; 1 mL RSB in upper and lower face.

Subject and Investigator Satisfaction Questionnaire
At baseline, approximately one-third of subjects were satisfied with their facial appearance. The proportion of satisfied subjects increased from baseline/month 1 to month 7 and month 13 (Figure 7a). Satisfaction with skin quality parameters improved from baseline to month 7 and month 13 (Figure 7b). At all timepoints, more than 90% of subjects stated they would do the treatment again and recommend treatment to a friend.

Investigator satisfaction with overall facial aesthetic outcome was high after monotherapy (ABO cohort: 84%; HA cohort: 67%) and after both combination treatments (98-100%, both cohorts combined).

Safety
Monotherapy
Ten subjects (15%, both cohorts combined) had 12 treatment-related AEs of mild or moderate intensity. None were serious; most resolved within 2 weeks. Headache was most common in the ABO cohort, affecting 3 subjects, and injection-site bruising in the HA cohort, also affecting 3 subjects.

First combination treatment
Twenty-eight subjects (45%) had 45 treatment-related AEs of mild or moderate intensity; most resolved within 1 week; none were serious. Injection-site bruising after HA filler or RSB injection was most commonly reported, affecting 13 subjects. Headache was most common in the ABO cohort, reported for 2 subjects.
Second combination treatment

Nineteen subjects (31%) had 36 treatment-related AEs of mild or moderate intensity, most resolved within two weeks; none were serious. All but one treatment-related AE were related to HA filler and/or RSB injection. Injection-site bruising was most commonly reported, affecting 14 subjects.

**DISCUSSION**

We previously conducted a study where ABO was administered in glabellar lines only (Cartier et al, accepted for publication Dermatologic Surgery 2019). The present study was designed similarly, but with ABO administered also in lateral canthal lines and forehead lines.

As in our previous study (Cartier et al, accepted for publication Dermatologic Surgery 2019), overall aesthetic outcomes were more beneficial after combination treatment than after monotherapy. The first combination treatment achieved a superior global facial aesthetic appearance over monotherapy in most subjects. Global aesthetic appearance increased further with the second combination treatment. Thus, cumulative treatments over time resulted in better aesthetic outcomes.

Most subjects had GAIS score improvement throughout the study (61-90%) according to blinded evaluators. Subject/Investigator assessments showed improvement for 94-100% of subjects after both combination treatments and after monotherapy with ABO, and for 88-91% of subjects after monotherapy with HA filler.

Combination treatments achieved higher subject and Investigator satisfaction than monotherapy. This is in line with results after combination treatment in another study where higher mean ABO doses and HA filler volumes were injected. It should be noted though, that combination treatments were administered after monotherapy in our study.

The volume of HA filler at monotherapy was restricted to maximum 1 mL to reflect what was considered feasible for the majority of new aesthetic patients. Although the Investigators assessed that most subjects (76%) would have benefited from having additional filler volume, most subjects (64%) in the HA filler cohort were satisfied with the treatment results after monotherapy and Investigators were satisfied with the overall facial aesthetic outcome for 67% of the subjects.

Subject satisfaction with treatment and skin quality improved over time, suggesting that the addition of Skinbooster was effective for improving skin quality, although the assessment could be influenced by all products included in the combination treatments.

The wrinkle severity of upper facial lines improved at least 1-grade 1 month after treatment for a majority of subjects, both at rest and at maximum contraction. Improvement was generally higher at maximum contraction than at rest, except for forehead lines for which improvement at rest was comparatively high, also at six months after treatment. By reducing muscle movement while maintaining some muscle activity, botulinum toxins have potential to reduce also static wrinkles with natural looking results. Wrinkle severity improvement data for glabellar lines were in line with previous results (Cartier et al, accepted for publication Dermatologic Surgery 2019).
Both single and combination treatments were well tolerated. Most treatment-related AEs resolved spontaneously, and all were of mild-to-moderate intensity. The most frequently reported AE was injection-site bruising, an anticipated reaction to the study treatments.

This study was limited by the restricted volumes of HA filler, set to reflect a real-life scenario where subjects often have limited resources. Also, since combination treatments were administered in sequence following monotherapy, potential confounding effects on clinical outcome should be considered.

Efficacy results from this and from our previous study (Cartier et al, accepted for publication Dermatologic Surgery 2019) underline the benefit of establishing treatment plans based on patients’ individual treatment goals.

CONCLUSIONS

Treatment of several indications with HA products and ABO was effective and well tolerated. Combination treatment with ABO, HA filler, and RSB, administered in sequence after monotherapy, resulted in more beneficial aesthetic outcomes than monotherapy alone.

DISCLOSURES

Galderma funded the study and provided the study products. H. Cartier, P. Bergentz, C. Siega, and F. Camozzato have no other conflicts of interest to declare; P. Hedén is a consultant for Al-lergan, Galderma, and Teoxane; D. Hexasl is a consultant for Galderma and Merz; C. Skoglund, C. Edwartz, and M. Norberg are employed by Galderma; P. Kestemont is a consultant for Al-lergan, Filorga, Galderma, Teoxane, Universkin, and Vivacy.

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An Atypical Presentation of PLEVA: Case Report and Review of the Literature

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ABSTRACT
Pityriasis lichenoides et varioliformis acuta (PLEVA) is a rare, self-limited, cutaneous disorder of unknown etiology. Clinically, PLEVA is characterized by the sudden onset of scaly, erythematous macules and papules localized to the trunk and proximal extremities. We report the case of a patient who presented with multiple erythematous papules and plaques on the palms, forearms, and dorsal feet.


REPORT OF A CASE

A 62-year-old woman presented for evaluation of recurrent itchy lesions distributed over her upper and lower extremities including her hands and feet. She reported that the rash had been present for several months, but that she had a similar rash one year before. At her previous evaluation one year before, she reported the lesions had also occurred on the hands and feet but were accompanied by lesions in the mouth. At that time, she was diagnosed with Hand, Foot, and Mouth disease via biopsy and positive coxsackie titers. After treatment with clobetasol 0.05% cream, the lesions resolved, until this current episode.

Physical examination at the time of her current outbreak revealed multiple erythematous and hyperpigmented scaling, 1-3 cm papules and plaques on both palms and forearms, some with a collarette of the scale and others with necrotic changes and excoriations. Also, there were several similar hyperpigmented papules on the dorsal feet and ankles. Oral lesions were absent. Two 4 mm punch biopsy specimens were obtained from the left palm and right wrist.

Histopathologic examination revealed parakeratosis and a brisk lichenoid inflammation with scattered dyskeratotic keratinocytes and erythrocyte extravasation. These histologic findings were consistent with pityriasis lichenoides et varioliformis acuta (PLEVA). The patient tested negatively for syphilis and antinuclear antibody laboratory results were within normal limits.

FIGURE 1. Clinical Image Multiple erythematous and hyperpigmented scaling papules and plaques on both palms and forearms.

FIGURE 2. Histopathologic Image Punch biopsy specimen from the center of a papule on the left palm (hematoxylin-eosin, original magnification ×10).
DISCUSSION

Pityriasis lichenoides is a cutaneous inflammatory disease with unknown etiology. It is considered to be on a spectrum, with both acute and chronic forms. The acute type, called Pityriasis lichenoides et varioliformis acuta (PLEVA), also known as Mucha-Habermann disease, can be found in patients of all ages but is most commonly seen in individuals in their second or third decade of life. Currently, there is no established etiology, though proposed theories include lymphoproliferation, an inflammatory reaction to a viral infection, and possible immune-complex-mediated vasculitis.

Patients with PLEVA often present with erythematous papules, with a light micaceous scale and a central punctum, that progress into necrotic papules. Papules are usually present in several different stages of development, which is a hallmark of diagnosis. Lesions are typically concentrated proximally, with heaviest involvement of the trunk, proximal limbs, and flexor surfaces and are often asymptomatic but can be pruritic or associated with a burning sensation. Involvement of distal appendages is not common, especially as the only location for the disease process.

Previously, the patient was diagnosed with coxsackie virus because of the positive coxsackie titers, though it is not clear if they were germane to the skin eruption. While there were papular lesions in the mouth as well as on the palms, soles of the feet, and gluteal area and biopsy results showed confluent necrosis, parakeratosis and hyperkeratosis, a specific histopathologic diagnosis for the previous rash was not possible due to the superficial nature of the biopsy.

A definitive diagnosis of PLEVA can only be made with histological findings from a skin biopsy. Histologically, there is parakeratosis, spongiosis, exocytosis of lymphocytes and erythrocytes into the epidermis, epidermal necrosis, and an edematous dermis with wedge-shaped lymphohistiocytic perivascular infiltrate. Vasculitis is rare.

In patients with asymptomatic lesions, treatment may be limited to close monitoring without pharmacologic intervention. Systemic antibiotic therapy with tetracyclines or erythromycin and phototherapy are used for the treatment of symptomatic disease. Methotrexate is reserved for the treatment of patients who have failed oral antibiotics and phototherapy. Topical corticosteroids may be useful for improving symptoms and accelerating the resolution of individual lesions.

Uncommon localizations of PLEVA, such as that seen in this case of distal extremity lesions only, pose a diagnostic challenge, which may result in delayed diagnosis. This case highlights an atypical manifestation of PLEVA localized to distal extremities, specifically the forearms, hands, and feet.
Implications of Treatment Vehicles in Effective Topical Therapy

To provide dermatology providers with an educational reference tool exploring the important role of vehicle technology, the advancements in vehicle formulation and the role of vehicles in optimizing therapeutic outcomes in cutaneous diseases including acne vulgaris and plaque psoriasis.

This supplement is funded by an educational grant provided by Mayne Pharma Group Limited.
Treatment of Solitary Keratoacanthoma of the Nose With Intralesional Methotrexate and Review of the Literature

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ABSTRACT
Keratoacanthoma (KA) is a unique clinical pathological entity that is difficult to categorize. Differentiating a KA from a squamous cell carcinoma (SCC) is important for treatment implications but is often challenging. We report a patient with a solitary KA of the skin of the right ala successfully treated with intralesional (IL) injections of methotrexate (MTX). We also provide a review of the literature on IL-MTX as a treatment modality for KA.


INTRODUCTION
Keratoacanthoma (KA) is a unique clinical pathological entity that is difficult to categorize. Differentiating a KA from a squamous cell carcinoma (SCC) is important for treatment implications but is often challenging. Clinically, aggressive SCC may present similarly to KA with rapid growth over weeks. Furthermore, it is often challenging, histologically, to distinguish between KA and SCC without an excisional biopsy.1-3 While some KAs have shown the ability to spontaneously involute,4 others have progressed to high-risk SCC or metastasized.5,6 A malignant course in suspected KA is thought to be more likely the result of diagnostic confusion with SCC rather than malignant transformation.3

We report a patient with a solitary KA of the skin of the right ala successfully treated with intralesional (IL) injections of methotrexate (MTX). We also provide a review of the literature on IL-MTX as a treatment modality for KA.

REPORT OF A CASE
A 53-year-old woman presented with an eight week history of a rapidly enlarging 1cm in diameter nodule on the right nasal ala (Figure 1). Incisional biopsy revealed a squamous cell carcinoma, keratoacanthoma type, with lesional tissue extending to the base of the biopsy. The lesion was injected with 1cc of methotrexate (25 mg methotrexate/mL) three times, with an interval of one week between injections. After each treatment, involution of the lesion was observed (Figure 2, 3). Four weeks after the first treatment, the lesion had completely resolved. No recurrence of the lesion was noted during a follow-up at 6 months (Figure 4).

DISCUSSION
There is a great deal still unknown of the etiology and patho-
FIGURE 4. The tumor has totally resolved 6 months following intralesional methotrexate injection. The skin appears clinically normal without scarring.

physiology of KA. Even classifying it as a malignant versus benign tumor is controversial. With so much uncertainty, there are no clear guidelines to follow in management of KAs.

Etiology
KA is assumed to originate from the hair follicle as it exhibits markers consistent with those in the follicular isthmus and infundibulum.1 The classic KA evolves in 3 clinical stages: proliferative, stabilizing, and regressing. There are several variants of KA including solitary sporadic, solitary iatrogenic, multiple iatrogenic, multiple familial, and centrifugum et marginatum. Ultraviolet exposure is a predominant risk factor for most of these variants.2,5

Clinical Manifestations
Solitary sporadic KA is a rapidly enlarging neoplasm appearing mainly on sun-exposed areas of the skin. Men are affected up to 3 times more frequently than women. The classic lesion presents as a dome-shaped nodule with a central hyperkeratotic plug. There may be associated pain or tenderness. KAs usually enlarge rapidly to full size within 6 to 10 weeks. Most KAs grow to a diameter of 1 to 2 cm and 0.5 cm in thickness. Larger KAs (more than 3 cm) are referred to as Giant KA. Spontaneous involution tends to begin around 8-12 weeks and can take up to 4 to 6 months to totally resolve. The resulting scar is often hypopigmented and atrophic.3

Iatrogenic KA can be induced by medical procedures that create trauma to the skin or in response to systemic chemotherapy. They can be solitary or multiple. Solitary KA along prior excision areas can mimic tumor regrowth.36 Multiple/ERuptive KAs are rapidly growing nodules that can also occur along prior excision areas. Multiple KAs may also be associated with prurigo nodularis, usually on the lower limbs of elderly women with sun-damaged skin.37 There are reports of KAs following esthetic procedures on sun-damaged skin including chemical peels, dermabrasion, and resurfacing laser procedures.13-17 Systemic chemotherapy notably BRAF inhibitors and Hedgehog pathway inhibitors are associated with KAs.18,19

Histology
KAs have a distinct histologic appearance. The distinctive architecture of the tumor shows a central keratin-filled crater surrounded by symmetrical, cup-shaped invaginations of thin atrophic epidermis with overhanging edges. There is a sharp demarcation between tumor and stroma. The cellular component is similar to SCC with well-differentiated keratinocytes with a glassy cytoplasm. Cytologic atypia is minimal. If hyperchromatic nuclei or abnormal mitoses are present, the diagnosis of an invasive SCC is favored. As the lesion regresses, the cup-shaped architecture flattens, and fibrosis develops at the base.20

Discriminating between KA and SCC is difficult when the biopsy transects the base of the lesion. Though it may appear to be a KA, without the base, an invasive SCC cannot be ruled out. Thus, biopsies that are fully representative of the lesion are helpful though not always practical for a large KA or KAs in cosmetically sensitive areas.21 There are no reliable immunohistochemical staining markers used in differentiating KA from SCC.22

Treatment for Solitary KAs
The ambiguity between a KA and SCC creates a dilemma with regard to the management of KAs. Though there is a tendency for spontaneous involution, most do not recommend waiting for the tumor to self-resolve due to the uncertainty of behavior.25 In addition, therapeutic intervention may hasten resolution, limit damage to vital structures and provide an improved cosmetic result. Many treatment modalities have been reported with various success rates and side effects.

Surgical removal is the gold standard regimen when possible. Standard surgical excision with 5 mm margins, Mohs surgery or curettage and electrodesiccation is commonly used in small (<1 cm), solitary KAs.22

Intralesional (IL) chemotherapy may be warranted for solitary large KAs or those adjacent to vital structures that may often require extensive reconstruction. Methotrexate (MTX) is preferred as an intralesional drug, with 5-fluorouracil (5-FU), bleomycin or interferons being other options.23 MTX has an appealing mechanism of action for a rapidly growing KA. It is a folic acid analog that inhibits DNA synthesis in actively dividing cells. KAs treated with IL-MTX show high cure rates of 71-92%.21,23-27

There is no standard protocol for administering IL-MTX injections. Current data show 1-4 injections are generally required with many resolving in 2 injections. Injections are separated by 2 to 3 weeks. The concentrations used per injection show extreme variation from 0.3 to 2.0 mL in a concentration of 25 mg/mL or 12.5 mg/mL.21,23-27 Annest and colleagues showed a 92% cure rate among 38 KAs treated with a mean cumulative dose of IL-MTX of 38.2 mg.25 Small KAs are injected at a single central point at the base of the lesion. Large KAs are injected into 4 quadrants at the central base of the lesion. MTX is injected until an end point of uniform tumor blanching is achieved. Though
rare, there are reports of pancytopenia following a single 25 mg dose of IL-MTX.\textsuperscript{26,29} Both cases occurred in patients with hemodialysis-dependent renal failure. Thus, obtaining a baseline and 1-week post injection complete blood cell count is reasonable, particularly in patients with kidney disease.

IL-5FU has also shown success in treating KAs.\textsuperscript{25,30} Many prefer IL-MTX compared to IL-5FU for practical reasons. IL-5FU often requires pretreatment with local anesthesia while IL-MTX is generally well tolerated without the use of local anesthesia. IL-5FU also requires weekly injections while IL-MTX requires injections performed at 2 to 3-week intervals.\textsuperscript{25}

While cure rates are high, factors that predict when a KA will not respond to IL-MTX are not well established. Rossi and colleagues studied response rates of IL-MTX in solitary KAs of the head and neck.\textsuperscript{21} Potential factors were identified that may be associated with treatment failures. They found that persistent pain and sustained growth post two treatments of IL-MTX may suggest an underlying aggressive SCC. In addition, immunosuppression may also raise concern for a more aggressive SCC tumor. Some Larger KAs have also shown to have poor response. Annest et al found the average tumor diameter for nonresponding lesions was larger than the average tumor for responsive lesions (2.8 vs 1.9 cm).\textsuperscript{36}

IL-MTX is an attractive treatment modality for KA. It is relatively noninvasive, inexpensive, quickly administered, safe, relatively painless, tissue sparing with good cosmetic outcomes. In summary, if the clinical and diagnostic biopsy suggest a diagnosis of KA, approximately 1 mL of MTX in a concentration of either 12.5 or 25 mg/mL is injected directly in the base of the tumor. This should be repeated at 2 week intervals until tumor resolution. If the tumor does not respond after two treatments, surgical treatment should be considered as the diagnosis may be invasive SCC. Monitor for MTX-induced cytopenias in renal failure patients.

**Treatment for Multiple KAs**

Multiple KAs have been managed with systemic retinoids.\textsuperscript{31,32} Patients have a marked response while on the retinoid. When the medication is discontinued however there is frequently regrowth. The dosage varies from 0.5 to 1.0 mg/kg of acitretin at the beginning of treatment and tapered as needed. Smaller doses of 20 to 20 mg/day are often necessary to sustain clinical response. IL corticosteroids are occasionally used with good response either as monotherapy or with systemic retinoids.\textsuperscript{33}

**Conclusion**

While the majority of KAs are benign acting, the diagnostic ambiguity has led to treatment standards toward that used for well-differentiated SCC. The increasing data on the effectiveness of IL-MTX is promising and prevents overtreatment with large excisions and reconstructions that may compromise functional and esthetic outcome. A poor response to IL-MTX indicates a more aggressive entity and must be re-evaluated.

**REFERENCES**


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A Giant Cutaneous Horn: One of the Largest Recorded

Dillon Nussbaum BSc, Julia Schwartz MD, Adam Friedman MD FAAD
George Washington University School of Medicine and Health Sciences, Washington, DC

ABSTRACT

We present a case of one of the largest cutaneous horns recorded in the known literature as an opportunity to explore diagnostic considerations and treatment options. Cutaneous horns are common exophytic neoplasms composed of dense keratin that are always secondary to primary lesions, which can be benign or malignant. Due to the variance of the primary lesion, diagnostic biopsies are necessary to rule out a malignant origin. Several case reports of giant cutaneous horns may suggest that a larger size indicates a verrucous origin, although a biopsy is necessary as this association has only been noted in very few cases. If the primary lesion is found to be malignant and extending to the biopsy margins, further treatment is required, whereas a benign origin usually requires no further treatment.


MANUSCRIPT

A 65-year-old African American female presented to an outpatient dermatology clinic with an occasionally pruritic and painful “abnormal skin growth” on her back for 22 years. On the mid back was a 22-centimeter tan-brown, horn shaped growth, with a well vascularized base, attached to a pedunculated flesh colored plaque. A shave biopsy was performed below the base of the lesion. Pathology revealed an acanthotic endophytic cellular pattern with protruding columns of parakeratosis, consistent with a cutaneous horn arising from a verruca. Cutaneous horns are compact growths of keratin usually arising from either a verruca, an actinic keratosis, or more concerning, squamous or basal cell carcinoma. In fact, 23% of cutaneous horns develop from malignant cutaneous neoplasms underscoring the importance of histologic analysis and appropriate follow up. Fortunately, the margins on the biopsy specimen were negative/clear and the patient has yet to return with recurrence.

A literature search of various synonyms of the words “giant cutaneous horn” suggests that this reported case of a 22-centimeter horn is possibly the largest to ever be described. In looking at similar cases, it appears that cutaneous horns of such a considerable size tend to be secondary to verruca rather than the more dangerous malignant neoplasms. Although no genetic analysis was performed on this biopsy, one previous case was found to have extensive horn like growths induced by human papillomavirus type two. It can be hypothesized that such large horns, and such extensive growth are result of verrucae that may have a genetic predilection in their viral DNA to tremendous angiogenic and proliferative abilities. Cutaneous horns secondary to malignant neoplasms tend to grow in a much more disordered pattern, as would be expected with malignant cells, compared to horns secondary to verrucae.
Cutaneous horns, or “cornu cutaneum” in Latin, are described first in the 16th century, those with horns at the time were used for show. Horns are common among various animals; the main distinction of animal horns and cutaneous horns are animal horns tend to grow off bones giving them strength and cutaneous horns have no bony structure. Similarly, animal horns tend to be common among a species and the same cannot be said for cutaneous horns in humans. All human cutaneous horns are pathologic in nature and require a diagnostic biopsy. Again, the differential diagnosis consists of a cutaneous horn secondary to a verruca, squamous or basal cell carcinoma, or actinic keratosis. Further treatment may be required if the origin is malignant and extending to the margins of the biopsy or if the initial biopsy does not resolve an underlying verruca or actinic keratosis. Previous literature may indicate that the larger and more structured a cutaneous horn appears may point to a verrucous, rather than malignant origin but more inquiry needs to be conducted to affirm such an association.

**DISCLOSURES**

The authors have no conflicts of interest to declare.

**REFERENCES**

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This brief summary does not include all the information needed to use BRYHALI safely and effectively. See full prescribing information for BRYHALI.

BRYHALI (halobetasol propionate) lotion, 0.01% for topical use
Initial U.S. Approval: 1990

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression

Halobetasol propionate 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 glucocorticosteroid 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 test 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, use over large surface areas, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, 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 Cushings 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>Upper Respiratory Tract Infection</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Application Site Dermatitis</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1%</td>
<td>0%</td>
</tr>
</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 on 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 Cushings 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].

HPA axis suppression, Cushings syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema [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 mutagenic 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:
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CHART A COURSE TO
SYMPTOMATIC RELIEF

The efficacy of Class 1 halobetasol with safety proven for up to 8 weeks of dosing1,2

A NEW POTENCY CLASS OF STEROID LOTION

2 PIVOTAL PHASE 3 TRIALS

POTENT TO SUPERPOTENT CLEARANCE1:

Continued results 4 weeks post treatment1

Significant symptomatic relief as early as week 22

No increased epidermal atrophy observed through 8 weeks of treatment2

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: 38.5% 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).2

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

*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).


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 Cushings’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.