Update on the Management of Acne and Rosacea from the American Acne and Rosacea Society (AARS)

Coprescription of Isotretinoin and Systemic Corticosteroids for Acne: An Analysis of the National Ambulatory Medical Care Survey

Patient Awareness of Antimicrobial Resistance and Antibiotic Use in Acne Vulgaris

Acquired Ichthyosis in the Setting of Active Pulmonary Tuberculosis

Emerging Authors in Dermatology:
Systemic Psoriasis Therapies and Comorbid Disease in Patients with Psoriasis: A Review of Potential Risks and Benefits

Lymphoplasmacytic Granulomatosis Cheilitis Treated with Cheiloplasty

Topical Imiquimod Induces Severe Weakness and Myalgias After Three Applications: A Case Report

Improvement in Thigh Skin Laxity After Weight Loss with Subcutaneous Radiofrequency Microneedling: A Brief Report

Don’t miss this month’s ONLINE-ONLY EXCLUSIVE:
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Vascular Complications after Facial Filler Injection: A Literature Review and Meta-analysis
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Getting Otezla Gets Even Easier

8 out of 10 commercially insured lives in the US have preferred access with no biologic step required for Otezla.1

Otezla is listed as preferred, with no biologic step requirement, on:

Aetna Prescription Drug Benefit
Cigna Prescription Drug List
CVS Caremark Formularies†
Express Scripts National Preferred Formulary†
OptumRx
Prime Therapeutics
UnitedHealthcare

Indicates no DMARD or biologic step-edit required.

Contact your Otezla representative or visit otezlapro.com for a complete list of plans

*Basic, Standard, and Advanced Control Formularies.
†SafeGuardRx® Program has 1 biologic step for patients on certain Otezla indications.
DMARD, disease-modifying antirheumatic drug.

Please see accompanying Brief Summary of Full Prescribing Information.
Otezla® Study Design
• Evaluated in 2 multicenter, double-blind, placebo-controlled trials of similar design. Patients with moderate to severe plaque psoriasis (N = 1257) were randomized 2:1 to Otezla 30 mg twice daily or placebo for 16 weeks after a 5-day titration.
• Selected inclusion criteria: age ≥18 years, BSA ≥10%, sPGA ≥3, PASI ≥12, candidates for phototherapy or systemic therapy.

INDICATIONS
Otezla® (apremilast) is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Otezla is indicated for the treatment of adult patients with active psoriatic arthritis.

IMPORTANT SAFETY INFORMATION
Contraindications
• Otezla® (apremilast) is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation.

Warnings and Precautions
• Diarrhea, Nausea and Vomiting: Cases of severe diarrhea, nausea, and vomiting have been reported with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

• Depression: Treatment with Otezla is associated with an increase in depression. During clinical trials 1.3% (12/920) of patients reported depression, compared to 0.4% (2/506) on placebo. Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on treatment.

Otezla® (apremilast) significantly increased PASI-75 response (n = 562) at week 16 (primary endpoint) vs placebo (n = 282) (33% vs 5%; P < 0.0001) in ESTEEM 1,2

For patients with moderate to severe plaque psoriasis
RESULTS the way THEY WANT THEM

Otezla has a proven efficacy and safety profile, oral dosing, and no label-required lab monitoring—making it a treatment experience patients can respond to.
Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur.

- **Weight Decrease:** Body weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla and in 5% (19/382) of patients treated with placebo. Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla.

- **Drug Interactions:** Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended.

**Adverse Reactions**

- Adverse reactions reported in ≥5% of patients were (Otezla%, placebo%): diarrhea (17, 6), nausea (17, 7), upper respiratory tract infection (9, 6), tension headache (8, 4), and headache (6, 4).

**Use in Specific Populations**

- **Pregnancy and Nursing Mothers:** Otezla is Pregnancy Category C; it has not been studied in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether apremilast or its metabolites are present in human milk. Caution should be exercised when Otezla is administered to a nursing woman.

- **Renal Impairment:** Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information.

Learn more at OTEZLAPRO.COM

**START** your patients on Otezla today

- Convenient oral dosing
- No required lab monitoring
- Samples available in office
- Bridge program offers 3 years for free
- $0 co-pay

Also approved for the treatment of adults with active psoriatic arthritis

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OTEZLA® (apremilast) tablets, for oral use

The following is a Brief Summary; refer to Full Prescribing Information for complete product information.

INDICATIONS AND USAGE

OTEZLA® (apremilast) is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

CONTRAINdications

OTEZLA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation [see Adverse Reactions (6.1)].

WARNINGS AND PRECAUTIONS

Diarrhea, Nausea, and Vomiting: There have been postmarketing reports of severe diarrhea, nausea, and vomiting associated with the use of OTEZLA. Most patients treated with OTEZLA reported diarrhea, nausea, or vomiting compared to none in placebo-treated patients (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) of patients treated with OTEZLA and 0.2% (1/506) in placebo-treated patients while receiving OTEZLA, compared to 0.2% (2/506) in placebo-treated patients. In the clinical trials, one patient treated with OTEZLA attempted suicide while one who received placebo committed suicide.

Depression: Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur. During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (129/920) of patients treated with OTEZLA reported depression compared to 0.4% (2/506) treated with placebo. During the clinical trials, 0.1% (11/1308) of patients treated with OTEZLA discontinued treatment due to depression compared to none in placebo-treated patients (0/506). Depression was reported as serious in 0.1% (11/1308) of patients exposed to OTEZLA, compared to none in placebo-treated patients (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) of patients while receiving OTEZLA, compared to 0.2% (2/506) in placebo-treated patients. In the clinical trials, one patient treated with OTEZLA attempted suicide while one who received placebo committed suicide.

Weight Decrease: During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (967/848) of patients treated with OTEZLA compared to 5% (19/382) treated with placebo. Weight decrease of ≥10% of body weight occurred in 2% (16/784) of patients treated with OTEZLA compared to none in placebo-treated patients (0/506). The proportion of patients with psoriasis who discontinued treatment due to weight loss of ≥10% of body weight was 0.8% for patients treated with OTEZLA 30 mg twice daily compared to 0.2% (1/506) in placebo-treated patients. No dose adjustment is needed in patients with mild or moderate renal impairment, the dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

Drug Interactions: Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers is not recommended [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

ADVERSE REACTIONS

Clinical Trials Experience in Psoriasis: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial 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. Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.6%), diarrhea (1.9%), and headache (0.8%). The proportion of patients with psoriasis who discontinued treatment due to any adverse reaction was 6.1% for patients treated with OTEZLA 30 mg twice daily and 4.1% for placebo-treated patients.

Table 3: Adverse Reactions Reported in ≥1% of Patients on OTEZLA and With Greater Frequency Than in Patients on Placebo; up to Day 112 (Week 16)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo (N=506) n (%)</th>
<th>OTEZLA 30 mg BID (N=920) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>32 (6)</td>
<td>160 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>35 (7)</td>
<td>155 (17)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>31 (6)</td>
<td>84 (9)</td>
</tr>
<tr>
<td>Tension headache</td>
<td>21 (4)</td>
<td>75 (8)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (4)</td>
<td>55 (6)</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>11 (2)</td>
<td>39 (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (2)</td>
<td>35 (4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (2)</td>
<td>29 (3)</td>
</tr>
<tr>
<td>Decrease appetite</td>
<td>5 (1)</td>
<td>26 (3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (1)</td>
<td>21 (2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (1)</td>
<td>20 (2)</td>
</tr>
<tr>
<td>Migraine</td>
<td>5 (1)</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Frequent bowel movements</td>
<td>1 (0)</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (0)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2 (0)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Tooth abscess</td>
<td>0 (0)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>0 (0)</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Sinus headache</td>
<td>0 (0)</td>
<td>9 (1)</td>
</tr>
</tbody>
</table>

*Two subjects treated with OTEZLA experienced serious adverse reaction of abdominal pain.

Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) patients following discontinuation of treatment with OTEZLA (apremilast).

DIAgRuNCATIONS

Strong CYP 450 Inducers: Apremilast exposure is decreased when OTEZLA is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

USc IN sPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C: OTEZLA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972. Nursing Mothers: It is not known whether OTEZLA or its metabolites are present in human milk. Because many drugs are present in human milk, caution should be exercised when OTEZLA is administered to a nursing woman. Pediatric use: Use: The safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age have not been established. Geriatric use: Of the 1257 patients who enrolled in two placebo-controlled psoriasis trials (PSOR 1 and PSOR 2), a total of 108 psoriasis patients were 65 years of age and older, including 9 patients who were 75 years of age and older. No overall differences were observed in the efficacy and safety in elderly patients 65 years of age and younger adult patients <65 years of age in the clinical trials. Renal Impairment: Apremilast pharmacokinetics were characterized in subjects with mild, moderate, and severe renal impairment as defined by a creatinine clearance of 60-89, 30-59, and less than 30 mL per minute, respectively, by the Cockcroft–Gault equation. While no dose adjustment is needed in patients with mild or moderate renal impairment, the dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

Hepatic Impairment: Apremilast pharmacokinetics were characterized in patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

OVERDOsAGE

In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

Manufactured for: Celgene Corporation, Summit, NJ 07901

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Pat. http://www.celgene.com/therapies

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Based on APRPI.006
Dear Colleagues:

Welcome to the June 2019 issue of *The Journal of Clinical and Aesthetic Dermatology* (JCAD). In this issue, we are pleased to present the article “Update on the Management of Rosacea from the American Acne & Rosacea Society,” by Del Rosso, Tanghetti, Webster, Stein Gold, Thiboutot, and Gallo. This article updates the previously published consensus recommendations from the AARS on the management of rosacea, including discussions of available published data on topical ivermectin, topical oxymetazoline, combination therapy approaches, and physical therapeutic devices for the management of rosacea. Consistent with what many publications on rosacea currently emphasize, the authors encourage clinicians to define the clinical manifestations of rosacea in the patient at presentation and to “select therapies that correlate with the optimal treatment of those manifestations.”

Next, Vasicek et al present the results of their survey analysis in the article titled, “Coprescription of Isotretinoin and Systemic Corticosteroids for Acne: An Analysis of the National Ambulatory Medical Care Survey.” Here, the investigators sought to quantify the estimated frequency of coprescription of isotretinoin and systemic corticosteroids in acne and assess trends as they relate to age, sex, race, insurance, and provider specialty. The results indicate that coprescription of isotretinoin and systemic corticosteroids is very rare, and the authors postulate that this might be because “either many physicians are not experiencing the paradoxical acne flare previously reported in the literature, are initiating low-dose isotretinoin to minimize the risk of a flare, are decreasing the dose of isotretinoin in response to a flare, or are unaware of the utility of the coprescription of systemic corticosteroids with isotretinoin.”

Following this, investigators sought to determine the level of awareness among adult patients with acne vulgaris (AV) and among parents of children/adolescents with AV, with regard to antibiotic resistance. In the article, “Patient Awareness of Antimicrobial Resistance and Antibiotic Use in Acne Vulgaris,” by Del Rosso et al, the authors utilized results of an online survey for their analysis. The analysis revealed that patients with AV and parents of children/adolescents with AV have a general understanding of the risks and potential causes of antibiotic resistance. The majority of those surveyed also indicated that they were not aware of antibiotic-free treatment options for AV, but were open to using them, provided they were effective. The authors close their analysis stating, “This study highlights an existing desire among patients with AV for more information from their clinicians about antibiotic resistance risk and alternative AV therapies.”

Next, in a case report titled, “Acquired Ichthyosis in the Setting of Active Pulmonary Tuberculosis,” by Liang et al, the authors describe a case of a 35-year-old woman with active pulmonary tuberculosis and a history of breast cancer who presented with a several-month history of a widespread, scaly, pruritic skin erosion. The clinical features, diagnostic methods, and treatment modalities of acquired ichthyosis associated with underlying systemic disease, particularly infection, are discussed.

Following this, we are pleased to present four articles as part of our bi-annual “Emerging Authors in Dermatology” series. In a review article titled, “Systemic Psoriasis Therapies and Comorbid Disease in Patients with Psoriasis: A Review of Potential Risks and Benefits,” by Mikhaylov et al, the authors describe and discuss studies of psoriasis treatments and their level of evidence for use in co-occurring diseases. In a case report titled, “Lymphoplasmacytic Granulomatosis Cheilitis Treated with Cheioplasty,” Oiyemhonlan et al present a case of long-standing idiopathic orofacial granulomatous (OFG) in a 65-year-old African-American man. In a case report titled, “Topical Imiquimod Induces Severe Weakness and Myalgias After Three Applications: A Case Report,” by Pasadyn and Cain, the authors describe a patient who developed severe muscle weakness and the inability to walk following use of topical imiquimod 5% cream for three days. And finally, in a case study by Yu et al titled, “Subcutaneous Radiofrequency Microneedling for the Treatment of Thigh Skin laxity Caused by Weight Loss: A Case Study,” the authors evaluate the use of RF in combination with microneedling to nonsurgically improve skin laxity caused by significant weight loss on the thighs of a 39-year-old woman.

Also, don’t miss this month’s Online-only Exclusive article titled, “Vascular Complications after Facial Filler Injection: A Literature Review and Meta-analysis,” by Sito, Manzoni, and Sommariva, which can be accessed here: jcadonline.com/online-only-exclusives. In this article, the investigators present the results of their meta-analysis that explored influential factors on the frequency and severity of vascular complications during filler injections. Results of their analysis revealed that blindness appears to be the main consequence of the vascular complications caused by filler injection, with partial or total recovery in 28 percent of the cases and no improvement in 72 percent of the cases; hyaluronic acid and autologous fat were the two fillers most frequently involved in the cited cases of vascular occlusions. The authors caution that, due to the risk of serious, long-term complications (e.g., blindness caused by vascular occlusion) when injecting facial fillers, physicians performing these procedures should have a proficient knowledge of human anatomy, in particular facial vasculature.

We hope you enjoy this issue of JCAD. As always, we welcome your feedback and submissions.

With regards,

[ photographs of Associate Editor, Editor-in-Chief, and FAAD—Editor-in-Chief, Clinical Dermatology, and FAAD, FAACS—Editor-in-Chief, Aesthetic Dermatology ]
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* Access via website by visiting jcadonline.com/online-only-exclusives/ or via e-Edition by scanning QR code below or visiting jcad.mydigitalpublication.com/publication/?m=54680&l=1

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Take care of sun damage

AMELUZ® [aminolevulinic acid hydrochloride] gel, 10%

BF-RhodoLED®

The only PDT drug approved for field-directed treatment of AK¹

AMELUZ® [aminolevulinic acid hydrochloride] gel, 10% is a porphyrin precursor: It is used in combination with BF-RhodoLED® photodynamic therapy for lesion and field-directed treatment of mild to moderate actinic keratosis on the face and scalp.

Indications And Usage
AMELUZ® gel, in combination with photodynamic therapy (PDT) using the BF-RhodoLED® lamp, a narrowband, red light illumination source, is indicated for lesion-directed and field-directed treatment of actinic keratosis (AK’s) of mild-to-moderate severity on the face and scalp.

Important Safety Information
Most adverse reactions occurred during illumination or shortly afterwards, were generally of mild or moderate intensity, and lasted for 1 to 4 days in most cases; in some cases, however, they persisted for 1 to 2 weeks or even longer. Please see Brief Summary of Full Prescribing Information on following page. You are encouraged to report side effects of Ameluz®. Please contact Biofrontera Inc. at 1-844-829-7434 or FDA at 1-800-332-1088 or www.fda.gov/medwatch.

¹ Ameluz® Prescribing Information. For Ameluz® full Prescribing information visit: https://www.dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=650daa9f-aeeec49ce-95b9-5fa20b988af
AMELUZ® (aminolevulinic acid hydrochloride) gel, 10% with BF-RhodoLED® lamp

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Indications and usage
AMELUZ® gel, in combination with photodynamic therapy using BF-RhodoLED® lamp, is indicated for the visiun-modified and field-directed treatment of actinic keratoses of moderate severity on the face and scalp.

Dosage and administration
AMELUZ®, in conjunction with imiquimod cream, may be administered under the care of a health care provider.
AMELUZ®, containing 10% aminolevulinic acid hydrochloride, is a semiopaque gel for topical use only, not for ophthalmic, oral, or intraluminal use.
Photodynamic therapy with AMELUZ® gel involves preparation of lesions, application of the product, illumination with BF-RhodoLED® lamp. The application area should not exceed 30 cm² and no more than 2 grams of AMELUZ® gel should be used at one time. Lesions that have not completely resolved shall be retreated 5 months after the initial treatment. Refer to BF-RhodoLED® user manual for detailed lamp safety and operating instructions. Both patient and medical personnel contacting the PDT should adhere to all safety instructions.

Contraindications
AMELUZ® is contraindicated in patients with:
- Known hypersensitivity to porphyrins.
- Known hypersensitivity to any of the components of AMELUZ®, which includes sodium phosphate/boric acid.
- Porphyrinas; AMELUZ® use may cause uncontrolled phototoxic effects.
- Photosensitivity. PDT may worsen the photodermatosis or photototoxic reactions.

Warnings and precautions
Transient Anamnic Episodes
Transient episodic episodes have been reported during photodynamic use of AMELUZ® in combination with photodynamic therapy. Inform patients and their caregivers that AMELUZ® in combination with photodynamic therapy may cause transient anamnic episodes. Advise them to contact the health care provider if the patient develops transient anamnic after treatment.

Risk of BF-RhodoLED® Lamp Xenon Light Injury
BF-RhodoLED® lamp may cause eye irritation, glare, or eye injury. Before operating the lamp, personnel must refer to the user manual for specific warnings, cautions, and instructions. Eye exposure to the BF-RhodoLED® light must be prevented. Protective eyewear equipment must be used by personnel, healthcare providers, and anyone present during the treatment. Avoid staring directly at the light source.

Increased Photosensitivity
AMELUZ® increases photosensitivity. Avoid sunlight, prolonged or intense light (e.g., tanning beds, sun lamps) on lesions and surrounding skin treated with AMELUZ® for approximately 48 hours following treatment whether exposed to illumination or not. Concurrent use of AMELUZ® with other known photosensitizing agents may increase the risk of phototoxic reaction to PDT.

Risk of Reactions in Patients with Congenital Disorders
AMELUZ® and BF-RhodoLED® lamp have been tested on patients with inherited or acquired congenital disorders. Special care should be taken to avoid blistering during lesion preparation in such patients. Any blistering should be stopped before application of the gel.

Adverse reactions
The following adverse reactions are discussed in detail in other sections (see Warnings and Precautions).
- Photodynamic Effects. Risk of BF-RhodoLED® lamp-induced Eye Irritation, Increased Photosensitivity, Risk of Bleeding in Patients with Coagulation Disorders, Photodynamic Adverse Reactions, Risk of Muscle Membrane Irritation.

Choice of Treatment Experience
Because clinical trials are conducted under unique and 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 practice.

The clinical trial program for AMELUZ® included three clinical trials and a placebo-controlled clinical trial (Table 1.) in 125 subjects, involving a total of 10 different subjects that were treated with narrow band light. 70% of subjects were adults greater than or equal to 18 years of age, and the majority had Fitzpatrick skin type I or II. No subjects had Fitzpatrick skin type III or IV. Approximately 80% of subjects were male, and 20% subject were Caucasian.

For all adverse reactions, the reactions, severity, and frequency are described as follows: common—occurring in greater than 20% of patients; frequent—occurring in 11-20% of patients; infrequent—occurring in 1-10% of patients; rare—occurring in less than 1% of patients; and very rare—occurring in less than one in 10,000 patients. The most frequent adverse reactions occurring during AMELUZ® treatment (Table 1) are skin irritation, pain, burning, itching, edema, pruritus, erythema, rash, redness, and vesicles. Most adverse reactions occurred during illumination or shortly thereafter, were generally of mild or moderate intensity, and lasted for 3-4 days in most cases. In some cases, however, they persisted for 1 to 2 weeks or even longer. Severe phototolerance occurred in up to 50% of subjects.

There was no evidence that the concomitant use of aminolevulinic acid with 12% healthy subjects, 12% subjects of AMELUZ® development stage demands over continuous exposure for 25 days with doses of aminolevulinic acid that were higher than those normally used in the treatment of AK.

Incidence of Adverse Reactions Ocurring in ≤4% of the AMELUZ Group and More Freemanly than the Vehicle Group in the Actinic Keratosis Trials of the Application Site

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Vehicle n=57</th>
<th>AMELUZ n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>34%</td>
<td>19%</td>
</tr>
<tr>
<td>Pain/Rash</td>
<td>26%</td>
<td>19%</td>
</tr>
<tr>
<td>Irritation</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Erythema</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Desquamation</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Scar</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Flushing</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Lesion</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Vesicles</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Headache</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Itching</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Common: 1%< Common adverse reactions not at the application site for AMELUZ were headache, skin exhibition, chills, and nausea.

Less common (≤0.8%): Other adverse reactions at the application site for AMELUZ were hives and swelling. The adverse reactions are not at the application site were fever, feeling hot, pruritus, perioral, rash, numbness, pain, palpitation, rash, redness, skin erosion, and sodium. In a phase II study designed to investigate the safety and efficacy of aminolevulinic acid at 2% with 12% healthy subjects, 12% subjects of AMELUZ® development stage demands over continuous exposure for 25 days with doses of aminolevulinic acid that were higher than those normally used in the treatment of AK.

Photodynamic Experience
The following adverse reactions have been reported during postapproval use of AMELUZ®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: application site inflammation, application site eczematous.
Eye disorders: eye irritation, photophobia, dryness, photophobia, blurred vision.
General disorders and administration site conditions: fatigue.
Nervous system disorders: dizziness, transient amnestic episodes.

Drug Interactions
There have been no formal studies of the interaction of AMELUZ® with other drugs. It is possible that concurrent use of other light-sensitizing agents such as St. John’s Wort, griseofulvin, thalidomide, salicylates, phenazone, salicylates, quinolones, and intravenous may enhance the phototoxic reaction to PDT.

Use in specific populations
Pediatrics
There are no adequate and well-controlled studies on AMELUZ use in pregnant women to inform a drug-associated risk. Animal reproduction studies were conducted with aminolevulinic acid. Systemic absorption of aminolevulinic acid in humans is negligible following topical administration of AMELUZ under maximal clinical use conditions. If it is not expected that moment to use of AMELUZ will result in fetal exposure to the drug.

The animal background of major birth defects and miscarriage for the indicated population is unknown. The U.S. general population, the estimated background rates of risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% for 4% and 5% to 28%, respectively.

Lactation
No data are available regarding the presence of aminolevulinic acid in human milk, the effects of aminolevulinic acid on the breastfed infant or on milk production. However, breastfeeding is not expected to result in exposure of the infant to the drug due to the negligible systemic absorption of aminolevulinic acid is humans. There is limited topical administration of AMELUZ under maximal clinical use conditions (see Clinical Pharmacology (12.3)). The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for AMELUZ and any potential adverse effects on the breastfeeding child from AMELUZ or from the underlying maternal condition.

Pediatric-use
Safety and effectiveness in pediatric patients below the age of 18 have not been established. AMELUZ is not in a dose condition see above in the pediatric population.

Geriatric Use
In the 515 subjects exposed to AMELUZ in randomized, multicenter clinical trials, 56% (291/525) of the subjects were 65 years old or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but generally greater sensitivity of some older individuals cannot be ruled out.

Dear Editor:

Tofacitinib is a Janus kinase (JAK) 1/3 inhibitor that has been approved by the United States Food and Drug Administration for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. An increasing number of studies have demonstrated the efficacy of tofacitinib in treatment of alopecia areata (AA).1-4 Treatment duration in these studies ranges from 2 to 18 months. Durability is short, with shedding occurring a mean 8.5 weeks after discontinuation.1 Less is known about extended tofacitinib administration. Here, we update our previous findings with a series of severe AA patients receiving long-term treatment with oral tofacitinib.5

METHODS

The relevant institutional review board approved this retrospective chart review. Investigators searched Cleveland Clinic records for patients with AA treated with tofacitinib from February 2015 to September 2017. Prior to initiation, all other AA therapies were stopped. Patient history and physical examination were obtained before starting treatment. Baseline laboratory evaluation findings, including complete metabolic panel, complete blood count, lipid panel, human immunodeficiency virus screen, hepatitis screen, and quantiferon tuberculosis test, were also obtained before tofacitinib initiation. Because no tofacitinib monitoring guidelines currently exist, laboratory results were collected every 3 to 4 months and quantiferon tuberculosis test findings were collected annually. Women of childbearing potential, barring any contraindication, were recommended to start oral contraception per their primary care providers. Hair loss was measured using the Severity of Alopecia Tool (SALT), which considers the sum of percent hair loss in varying areas of the scalp where a higher score means a greater amount of hair loss. SALT scores were calculated at baseline and each visit by the same physician, at which time standardized photos were also taken. Patients were treated by four different physicians. Tofacitinib was initiated at 5mg twice daily, increased by 5mg per month, and held at

![Figure 1. A 38-year-old woman with severe alopecia areata treated with tofacitinib citrate 10mg twice daily—A) Baseline, B) Month 9, C) Month 12, and D) Month 20.](image)

**TABLE 1. Patient demographics, disease severity and tofacitinib therapy**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at Treatment Initiation</th>
<th>Race</th>
<th>Disease Duration (years)</th>
<th>Last Hair Growth (years)</th>
<th>First Signs of Hair Growth (months)</th>
<th>Therapy Duration (months)</th>
<th>Maintenance Dose (mg/day, split BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>57</td>
<td>Caucasian</td>
<td>25</td>
<td>1</td>
<td>3</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>43</td>
<td>Caucasian</td>
<td>19</td>
<td>4</td>
<td>3</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>22</td>
<td>Caucasian</td>
<td>16</td>
<td>4</td>
<td>3</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>55</td>
<td>African American</td>
<td>26</td>
<td>4</td>
<td>7</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>39</td>
<td>Caucasian</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>0.5</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>56</td>
<td>Caucasian</td>
<td>16</td>
<td>2</td>
<td>10</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>62</td>
<td>Caucasian</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>46</td>
<td>Caucasian</td>
<td>36</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>57</td>
<td>Caucasian</td>
<td>15</td>
<td>1</td>
<td>3</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>37</td>
<td>African American</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>57</td>
<td>Caucasian</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>55</td>
<td>African American</td>
<td>31</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>50</td>
<td>African American</td>
<td>1</td>
<td>0 (disease onset within previous 14 months)</td>
<td>6</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>38</td>
<td>Caucasian</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>56</td>
<td>Caucasian</td>
<td>11</td>
<td>1</td>
<td>2</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>25</td>
<td>Caucasian</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>54</td>
<td>Caucasian</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>56</td>
<td>Caucasian</td>
<td>16</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>49</td>
<td>African American</td>
<td>17</td>
<td>1</td>
<td>8</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>61</td>
<td>Caucasian</td>
<td>44</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>

AA: Alopecia areata; F: Female; M: Male; BID: Twice daily
RESULTS

A retrospective cohort of 20 patients was treated. Patients were mostly female (90%) and more likely to have thyroid disease and atopy, compared to the general population (65% and 40%, respectively, of our cohort). All 20 patients had a diagnosis of alopecia areata—90% had more severe subtypes (70% alopecia universalis, 20% alopecia totalis)—with a mean baseline SALT score of 88 percent. The average length of the current episode of alopecia was 2.4 years.

Twelve patients (60%) received tofacitinib for at least 12 months. Patients were treated for an average of 13 months (range: 0.5–28 months). Maintenance doses ranged from 10 mg to 25 mg, with the majority of patients taking 20 mg in split daily doses.

The average time to regrowth was 3.85 months. Three months after initiating treatment, 70 percent of patients showed regrowth. Regrowth ranged from 1 to 100 percent, with a mean percent regrowth of 42.6 percent and a median of 55 percent. Eleven patients (55%) achieved an improvement in SALT score greater than 50 percent. Twenty-five percent of patients achieved full regrowth (>90% improvement in SALT score) during the study period. Among patients treated for more than 12 months, 91.7 percent had regrowth by the end of the study period. Three patients were nonresponders, with a less than five-percent improvement in SALT score.

Seven patients developed lab abnormalities. Four patients experienced dose-dependent cholesterol, triglycerides, and/or low-density lipoprotein elevation. These resolved with dose decrease or continued treatment, though one patient was started on a statin. Six clinical adverse events (e.g., palpitations, herpes zoster, elevated cholesterol) occurred, each in a different patient. See Tables 1 and 2 for patient characteristics, including demographics, disease, treatment course, and outcomes.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment Initiation SALT Score</th>
<th>Final Data Collection SALT Score</th>
<th>Regrowth (%) at Time of Last Appointment</th>
<th>Lab Abnormality, Associated Dose, and Outcome</th>
<th>Clinical Adverse Event, Associated Dose, and Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>30.8</td>
<td>69.0</td>
<td>Hypercholesterolemia (cholesterol 217, triglyceride 147, LDL 143) at baseline, worsening by Month 8 (cholesterol 250, triglyceride 280, LDL 153), dosage 20 mg; started on atorvastatin by PCP at Month 9 with improvement of cholesterol (151), triglycerides (170) and LDL (68)</td>
<td>Herpes zoster at Month 6; dosage 20 mg; drug discontinued for 10 days, then restart at same dose</td>
</tr>
<tr>
<td>2</td>
<td>78.3</td>
<td>32.2</td>
<td>59.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>50.6</td>
<td>49.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>50.6</td>
<td>49.0</td>
<td>AKI (Cr 1.5 from baseline 1.1) and elevated total cholesterol 270 (150–220), LDL 175 (&lt;130) at Month 4; dosage 30 mg</td>
<td>Metabolic resection and peripheral edema Week 2 after therapy; dosage 20 mg; medication discontinued immediately; edema/resolution resolved within one week after discontinuation</td>
</tr>
<tr>
<td>5</td>
<td>95</td>
<td>44</td>
<td>50.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>95</td>
<td>5.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>95</td>
<td>5.0</td>
<td>NA</td>
<td>URI at Month 2; medication discontinued for 30 days then resumed; no shedding noted at that time; lost to follow-up</td>
</tr>
<tr>
<td>8</td>
<td>79.3</td>
<td>44.2</td>
<td>40.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>76</td>
<td>3</td>
<td>96.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>98</td>
<td>2.0</td>
<td>AST/ALT elevation (AST/ALT4) at Month 6, but 2 months after dose increase to 25 mg (15 mg qAM and 10 mg qPM); medication discontinued but AST remained elevated (49); patient relaunched with 10 mg; with further AST elevation (80); recommendation to discontinue medication</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>100</td>
<td>20</td>
<td>80.0</td>
<td>Elevated cholesterol (217) at Month 6; dosage 20 mg; medication continued; cholesterol normalized by Month 24 without intervention</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
<td>1</td>
<td>99.0</td>
<td>NA</td>
<td>Chest palpitations at Month 6; dosage 10 mg; medication discontinued; patient later found to be on a higher than necessary dose of levothyroxine, which was corrected</td>
</tr>
<tr>
<td>13</td>
<td>95</td>
<td>0</td>
<td>100.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>14</td>
<td>50</td>
<td>0</td>
<td>100.0</td>
<td>Leukopenia (WBC 3.5) at Month 12; dosage 20 mg; dose reduced to 5 mg BID and patient lost hair growth; medication increased back to 10 mg BID with patient informed of risks; WBC normalized to 4.1 by Month 12</td>
<td>NA</td>
</tr>
<tr>
<td>15</td>
<td>71.6</td>
<td>38</td>
<td>47.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>16</td>
<td>100</td>
<td>100</td>
<td>0.0 (scant regrowth on face noted at Month 3; lost to follow-up</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>17</td>
<td>100</td>
<td>50</td>
<td>50.0</td>
<td>Elevated total cholesterol (215), LDL (113) and total bilirubin 1.8 (0–1) at Month 3; dosage 20 mg; dose decreased to 10 mg; LDL and total cholesterol normalized by Month 6; then dose increased to 20 mg without further lab abnormalities; later diagnosed by hepatologist with Gilbert’s syndrome</td>
<td>NA</td>
</tr>
<tr>
<td>18</td>
<td>90</td>
<td>47.2</td>
<td>48.0</td>
<td>NA</td>
<td>Recurrent URIs from initiation through Month 5; dosage 15 mg (10 mg qAM/5 mg qPM); medication stopped then restarted at Month 7 at 10 mg daily without further URI symptoms</td>
</tr>
<tr>
<td>19</td>
<td>50</td>
<td>0</td>
<td>100.0</td>
<td>Elevated AST/ALT (48/51) at Month 10; dosage 10 mg; patient chose to continue medication upon normalization of values</td>
<td>NA</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
<td>100</td>
<td>10.0</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

AA: alopecia areata; F: female; M: male; PCP: primary care provider; LDL: low-density lipoprotein; NA: not applicable; SALT: Severity of Alopecia Tool; AKI: acute kidney injury; AST: aspartate aminotransferase; ALT: alanine aminotransferase; qAM: every morning; qPM: every afternoon; WBC: white blood cells; BD: twice daily; URI: upper respiratory infection.
DISCUSSION
The majority of patients experienced hair regrowth, ranging from less than 5 percent to 100 percent regrowth during the study. This is consistent with other studies, suggesting disease duration might not predict patient response, but rather a pathophysiological mechanism might be involved. For several patients, regrowth differed from their natural hair color and texture (Figure 1). One patient demonstrated female androgenetic alopecia with regrowth, a finding previously observed in male patients.

As this is an off-label use of tofacitinib, this medication was obtained for most patients only after an extensive appeal process with insurance companies. Of the 20 patients treated, six experienced medication interruption—four due to adverse effects and two due to lapses in prescription insurance coverage. Durability among our population was shorter than the 10 to 12 weeks reported in other studies, with hair shedding occurring 4 to 5 weeks after discontinuation, suggesting that a short amount of time is needed for AA inflammatory pathways to reestablish themselves following discontinuation of medication.

Our study is limited by its small sample size, precluding detailed subgroup analyses. Larger, randomized, controlled trials are needed to explore such variations in regrowth. Nevertheless, our results suggest JAK inhibition might serve as an effective treatment modality for AA.

With regard,
SARA HOGAN, MD; SOPHIE WANG, BS; OMER IBRAHIM, MD; MELISSA PILIANG, MD; and WILMA BERGFELD, MD
All authors are with the Department of Dermatology at the Cleveland Clinic Foundation in Cleveland, Ohio.

FUNDING. The authors have no conflicts of interest relevant to the content of this article.

CORRESPONDENCE. Sara Hogan, MD; Email: sara.hogan@gmail.com

REFERENCES

CORRECTION


1. Page 14, Line 2, Section 1.2: “MSC” should be “NMSC.”
2. Page 15, Table 2, heading: “Total Dose Fractions” should be “Time-Dose-Fractionation (TDF) factor.” The numbers below should not be followed by the unit “cGy.”
3. Page 15, Table 2: the superscript “a” should follow “Time-Dose-Fractionation (TDF) factor” not “Therapeutic Dosing Range.”
4. Page 15, Table 3, left column, Line 3: “Therapeutic dosing” should be “Biologically effective dose value.”
5. Page 15, Table 3, left column, Line 4: “TDF” should be “Fraction dose.”
6. Page 16, Section 8.1, Line 11: “Total dose fraction” should be “Time-Dose-Fractionation (TDF) factor.”
7. Page 16, Section 11.2, Line 5: “Biologically effective dose of 3,000 cGy” should be “biologically effective dose value of 3,000 cGy.”
8. Page 16, Section 11.3, Line 3: “healthy skin to SRT of 3,000 cGy” should be “healthy skin to SRT at a BED value of 3,000 cGy.”


The original, uncorrected version of the article is available here: http://jcadonline.com/feb-2019-superficial-radiation-therapy-guidelines/.
A flexible, transparent adhesive that’s strong & protective

CORDRAN® Tape is the only form of flurandrenolide that’s a class 1 high-potency topical steroid. It provides a protective skin barrier through a flexible and transparent adhesive to treat corticosteroid-responsive dermatoses.1-4

INDICATION AND USAGE

CORDRAN® Tape (Flurandrenolide Tape, USP) is a corticosteroid indicated for the relief of the inflammatory and pruritic manifestation of corticosteroid responsive dermatoses, particularly dry, scaling localized lesions.

IMPORTANT SAFETY INFORMATION

Topical corticosteroids are contraindicated in patients with a history of hypersensitivity to any of the components of the product. Use of CORDRAN® Tape is not recommended for lesions exuding serum or in intertriginous areas.

Systemic absorption of potent topical corticosteroids has produced reversible hypothalamic pituitary-adrenal (HPA) axis suppression, manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria in some patients. Use over large surface areas, prolonged use, and the addition of occlusive dressings augment systemic absorption. Pediatric patients may absorb proportionately larger amounts of topical corticosteroids and thus may be more susceptible to systemic toxicity.

HPA axis suppression, Cushing’s syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Patients receiving a large dose to a large surface area should be evaluated periodically for evidence of HPA axis suppression, and therapy should be modified or discontinued as appropriate.

Local adverse reactions may occur more frequently with the use of occlusive dressings. These reactions are listed in approximate decreasing order of occurrence: burning, itching, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis. Reactions that may occur more frequently with occlusive dressings include: maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.


Please see Brief Summary of full Prescribing Information on the adjacent page.
INDICATIONS AND USAGE
For relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, particularly dry, scaling localized lesions.

CONTRAINDICATIONS
Topical corticosteroids are contraindicated in patients with a history of hypersensitivity to any of the components of these preparations. Use of Cordran Tape is not recommended for lesions exuding serum or in intertriginous areas.

PRECAUTIONS
General: Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria in some patients. Conditions that augment systemic absorption include application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using urinary-free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete on discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, so that supplemental systemic corticosteroids are required. Pediatric patients may absorb proportionately larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see Pediatric Use under PRECAUTIONS). If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted. In the presence of dermatologic infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, Cordran Tape should be discontinued until the infection has been adequately controlled.

Laboratory Tests: The following tests may be helpful in evaluating the HPA axis suppression: Urinary-free cortisol test, ACTH stimulation test.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Usage in Pregnancy: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively for pregnant patients or in large amounts or for prolonged periods of time.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use: Pediatric patients may demonstrate greater susceptibility to topical-corticosteroid-induced HPA axis suppression and Cushing’s syndrome than do mature patients because of a larger skin surface area to body weight ratio. Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing’s syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma-cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. Administration of topical corticosteroids to pediatric patients should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of pediatric patients.

ADVERSE REACTIONS
The following local adverse reactions are reported infrequently with topical corticosteroids but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis. The following may occur more frequently with occlusive dressings: maceration of the skin, secondary infection, skin atrophy, striae, miliaria.

OVERDOSAGE
Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).
ABSTRACT

Importance: Previous consensus articles on rosacea from the American Acne and Rosacea Society (AARS) have focused on pathophysiology, clinical assessment based on phenotypic expressions of rosacea, management guidelines, discussions of individual medical therapies, and reviews of physical modalities. Pathophysiologic mechanisms believed to be operative in rosacea have been covered extensively in the literature.

Objective: This article updates the previously published consensus recommendations from the AARS on the management of rosacea, including systematic literature and evidence-based reviews of available therapeutic agents and physical modalities. Observations: This article includes discussions of available published data on topical ivermectin, topical oxymetazoline, combination therapy approaches, and physical devices for the management of rosacea. Consistent with what many publications on rosacea currently emphasize, clinicians are encouraged to define the clinical manifestations present in the patient and to select therapies that correlate with the optimal treatment of those manifestations. There are less data available on how to optimally integrate therapies; however, it appears that rationally selected medical therapies can be utilized concurrently.

Conclusion: Due to the multifactorial pathogenesis of rosacea, its clinical presentation is heterogeneous. Rosacea is a chronic and recurrent inflammatory disorder, and clinical manifestations often vary in nature and severity over time, which might necessitate an adjustment in treatment. As new data become available, rosacea management approaches should be updated.

KEYWORDS: Rosacea, inflammation, erythema, alpha-agonist

CONSENSUS

Update on the Management of Rosacea from the American Acne & Rosacea Society (AARS)

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Recognized as one of the most common and clinically characteristic facial skin disorders, rosacea is an inflammatory dermatosis with a reported prevalence of at least 10 percent among Caucasian adults; it also affects several other racial groups, including Latin-American, African-American, African, and Asian people.1–4 The diagnosis of rosacea is made clinically, based on visible assessment and patient history, after other causes of facial erythema and/or papulopustular skin lesions have been excluded,2,4 including contact dermatitis, seborrheic dermatitis, photodamage, acne vulgaris, cutaneous lupus, and carcinoid syndrome.

The classification of rosacea in both clinical practice and research previously utilized subtype designations as described by Wilkin et al in 2002 from the National Rosacea Society. However, the current recommendations from multiple organizations with interest in the diagnosis and treatment of rosacea suggest characterizing patients with rosacea by individual clinical manifestations and symptoms that are present at the time of examination.2,6–8 As rosacea is a phenotypically heterogeneous disease, this might include central facial erythema without papulopustular (PP) lesions; central facial erythema with PP lesions; the presence of phymatous changes, ocular signs, and symptoms; extensive presence of facial telangiectasias; and marked, persistent, nontransient facial erythema that remains between flares of rosacea and might exhibit severe intermittent flares of acute vasodilation (flushing of rosacea).6,7 Manifestations at

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various time points in a single patient might differ depending on whether the rosacea is flared or quiescent, the age of the patient, the duration of his or her disease, the frequency and magnitude of rosacea flares, and associated symptomatology.\textsuperscript{6,10–13} Previous consenus articles on rosacea from the American Acne & Rosacea Society (AARS) focused on pathophysiology, clinical assessment based on phenotypic expressions of rosacea, management guidelines, discussions of individual medical therapies, and reviews of physical modalities.\textsuperscript{6,10–13} Pathophysiologic mechanisms believed to be operative in rosacea have been covered extensively in the literature.\textsuperscript{14–16} The goal of this article is to update the previously published consensus recommendations from the AARS on the management of rosacea, including a review of therapeutic agents and formulations that have become available since the previous publications and a discussion of newer information on physical modalities.

The hope is that the current management recommendations, based on currently available evidence and clinical experience, can serve as a guide to clinicians. In all of the studies referenced in this article, unless otherwise specified, recognized inclusion criteria, exclusion criteria, washout periods of any previous relevant therapies, and tolerability/safety assessments were incorporated and accepted methods for endpoint evaluations were used (e.g., Investigator Global Assessment [IGA], lesion counts, tolerability/safety assessments).

**ROSACEA MANAGEMENT RECOMMENDATIONS**

**Topical ivermectin.** Ivermectin (IVM) is an avermectin derivative that has been used extensively for many years in human and veterinary medicine due to its antiparasitic activity and anti-inflammatory properties.\textsuperscript{17} The favorable safety profiles of both oral and topical IVM have been correlated with its inability to cross the human blood-brain barrier (BBB) while exhibiting a high affinity for invertebrate neuronal ion channels, allowing for its selective activity against many parasitic organisms.\textsuperscript{17} With regard to rosacea, especially in the presence of PP lesions, the anti-inflammatory properties of IVM that appear to correlate with rosacea pathophysiology are of specific investigative interest. The reduction of Demodex mite proliferation, which appears to have a role as a trigger factor in a subgroup of patients with rosacea, is another targeted area of research.\textsuperscript{18–20} IVM and rosacea pathophysiology. Ivermectin derivatives, including IVM, have been associated with anti-inflammatory effects in multiple \textit{in-vitro} studies; however, the correlation of these effects with rosacea is unknown.\textsuperscript{19,21,22} Recently, a single-center, single-treatment pilot study assessed once-daily application of IVM 1% cream on the facial skin of 20 subjects with papulopustular rosacea (PPR). Over a 12-week treatment period, investigators observed marked clinical improvement through dual mechanisms of action.\textsuperscript{23} In addition to assessing standard clinical parameters, this study utilized real-time polymerase chain reaction (RT-PCR) and immunofluorescence staining to evaluate multiple inflammatory/immune tissue biomarkers; the study also evaluated Demodex mite density via skin surface biopsies. Gene expression levels for multiple biomarkers (e.g., LL-37 [cathelicidin], interleukin [IL]-8, toll-like receptor [TLR]-4, human beta-defensin [HBD]-3) were significantly downregulated following 12 weeks of topical IVM use ($p<0.05$); mean mite density also was significantly reduced ($p<0.001$). All 20 subjects were reported to improve clinically, with 80 percent (16/20) achieving “clear” or “almost clear” results according to Investigator’s Global Assessment (IGA) score.\textsuperscript{23}

**Topical IVM clinical studies.** Once-daily IVM 1% cream (‘Soolantra® Cream, 1%, Galderma Laboratories LP, Fort Worth, Texas) was shown to be significantly more effective than vehicle (n=461) in two pivotal, Phase III, 12-week, double-blind, randomized, controlled trials of adults (n=910) with moderate-to-severe PPR (p<0.001).\textsuperscript{24} In a 16-week, investigator-blinded, randomized, controlled trial of adults with moderate-to-severe PPR, IVM once daily (N=478) demonstrated significant superiority in efficacy compared to metronidazole 0.75% cream applied twice daily (n=484) ($p<0.001$).\textsuperscript{25} An extension assessment of the 16-week study evaluated time to rosacea relapse and maintenance of remission over 36 weeks.\textsuperscript{26} In this extension study, IVM cream once daily (n=399) was compared to metronidazole 0.75% cream twice daily (n=365). Both agents were used intermittently for flares in their respective study groups until subjects achieved an IGA score of “clear” or “almost clear”; if new flares occurred, these treatments were restarted until PPR was controlled again, as described above. Median time to first relapse was significantly longer in the IVM group (115 days) than in the metronidazole group (85 days) ($p=0.0365$; Kaplan–Meier plot analysis), and median days free of treatment was higher with IVM use compared to metronidazole use (196 days vs. 169.5 days; $p=0.026$).\textsuperscript{26}

Favorable tolerability and safety profiles of IVM 1% cream have also been established in a long-term (52-week) safety study, with low reported rates of cutaneous tolerability reactions (<2% overall), comparable skin tolerability rates to those of metronidazole 0.75% cream and vehicle, and no observed systemic safety signals.\textsuperscript{27}

**Clinical application of topical ivermectin in rosacea.** IVM 1% cream has been shown to be an effective, well-tolerated, and safe treatment for PPR in adults in several randomized, controlled trials of subjects with moderate-to-severe disease and in a case series (N=34) from clinical practice.\textsuperscript{24–29} A systematic meta-analysis of 19 randomized, clinical trials reported that IVM 1% cream once daily appears to be more effective than, and at least as tolerable/safe as, other available topical agents used to treat PPR;\textsuperscript{29} however, no true head-to-head comparative studies currently exist, with the exception of studies comparing IVM 1% cream to metronidazole 0.75% cream.\textsuperscript{30} Based on a review of four randomized, controlled trials (N=1,366) comparing IVM 1% cream to metronidazole 0.75% cream, achieving a study endpoint of “clear” based on IGA assessment optimized remission of rosacea; the median time to relapse was greater than eight months in subjects achieving an IGA rating of “clear,” compared with three months for those rated as “almost clear” (p<0.0001).\textsuperscript{31}

Available data support the use of IVM 1% cream as an option for treatment of PPR as a monotherapy, as well as in combination with a topical alpha–agonist for treatment of the persistent nontarget facial erythema component of PPR.\textsuperscript{32–31}

**Topical oxymetazoline.** Oxymetazoline 1% cream, applied once daily, is a topical alpha–agonist that was approved by the United States Food and Drug Administration (FDA) for the treatment of persistent facial erythema of rosacea in adults.\textsuperscript{34} Morning application is recommended to allow for reduction of the
facial erythema during the day; a noticeable onset of effect generally occurs within 1 to 3 hours after application, with a duration of effect usually observed over 8 to 10 hours. In a Phase II, four-week, double-blind, randomized, controlled trial of adult subjects with moderate-to-severe persistent facial erythema due to rosacea (N=356), oxymetazoline HCl cream (Rhofade® Cream, 1%; Aclaris Therapeutics, Inc., Wayne, Pennsylvania) demonstrated optimal dosing at one percent, compared to 0.5-percent and 1.5-percent concentrations, when applied once or twice daily; safety and application-site skin tolerability were considered favorable and were similar among all study groups.15

Topical oxymetazoline clinical studies. Two Phase III, four-week, double-blind, randomized, controlled trials compared oxymetazoline 1% cream to vehicle, both applied once daily, in adult subjects with moderate-to-severe persistent facial erythema due to rosacea at baseline (N=885; 1:1).36,37 In both pivotal studies, oxymetazoline 1% cream demonstrated significant superiority to vehicle in reaching the primary study endpoint—achieving at least a two-grade reduction in erythema—which was rated separately by investigator and patient at the end of the study (p<0.001 in both studies). Digital image analysis evaluating erythema reduction also favored once-daily application of oxymetazoline 1% cream over once-daily application of vehicle (p<0.001).38

A long-term (52 weeks), open-label study evaluated the use of oxymetazoline 1% cream once daily for moderate-to-severe persistent facial erythema of rosacea in adults (N=440).38 Overall, this study demonstrated sustained efficacy, tolerability, and safety over the 52 week duration of the study. Discontinuation of treatment, due mostly to application-site adverse events (AEs), occurred in 3.2 percent of subjects, with no systemic safety signals demonstrated; no clinically relevant changes in skin blanching (i.e., over-whitening), inflammatory (PP) lesions, or telangiectasias were noted.38

The FDA-approved protocol designs used in the pivotal randomized, controlled trials evaluating both brimonidine 0.33% gel and oxymetazoline 1% cream were very similar.39,40 However, the studies evaluating oxymetazoline 1% cream included additional follow-up steps to assess worsening of facial erythema, such as rebound after discontinuation.39–41 Data from the clinical studies and the approved package insert for oxymetazoline 1% cream did not report post-treatment rebound or worsening of facial erythema of rosacea.34–39 AEs reported during treatment phases showed that application-site erythema occurred in one percent of subjects treated with oxymetazoline 1% cream compared to 0.4 percent in vehicle-treated subjects in the pivotal randomized, controlled trials and in two percent of oxymetazoline 1% cream-treated subjects in the long-term study.34–36 These data support that treatment-related worsening of facial erythema (defined as rebound in pivotal clinical studies) noted during active use and/or after discontinuation of once-daily oxymetazoline 1% cream is uncommon.

Clinical application of topical oxymetazoline in rosacea. Oxymetazoline 1% cream may be used for the management of persistent, nontransient, facial erythema of rosacea in adults who present with or without PP lesions.36–38 In patients with PPR, oxymetazoline 1% cream has been successfully utilized for the reduction of persistent facial erythema along with concurrent use of an agent that reduces PP lesions and perilesional erythema (e.g., topical metronidazole, topical azelaic acid, topical IVM, oral doxycycline).38

Topical azelaic acid (AzA). AzA 15% gel (Finacea® Gel, 15%; LEO Pharma Inc., Madison, New Jersey), applied twice daily, is a well-established treatment for PPR.42–45 AzA has been used as a monotherapy, primarily in cases of mild-to-moderate severity, or in combination with oral doxycycline (including sub-antibiotic dose doxycycline) in patients with severe PPR.44,46 More recently, twice-daily AzA 15% foam (Finacea® Foam, 15%; LEO Pharma Inc., Madison, New Jersey) was approved by the FDA for the treatment of PPR in adults, with studies reporting efficacy and safety similar to that observed in the twice-daily AzA 15% gel studies.47–49 The foam vehicle is a lipid-rich, hydrophilic oil-in-water emulsion.47,49

Phase III, 12-week, randomized, controlled trials compared AzA 15% gel and AzA 15% foam, both applied twice daily, to their respective vehicles in adult subjects with facial PPR.49–50 Baseline demographics and disease-related characteristics (i.e., lesion counts, IGAs) were similar in these studies. In the Phase III studies evaluating AzA 15% foam (n=484), application site pain (e.g., stinging, burning) occurred in 3.5 percent and pruritus in 1.4 percent of AzA-treated subjects, all of whom, based on study protocol, were instructed to use gentle skin care products.48–50

In the AzA 15% gel Phase III studies, the most commonly reported treatment-related AEs were burning, stinging, and/or tingling (29%) and pruritus (11%), with no recommendations given regarding skin care during these studies.42 Although there are no comparative head-to-head studies of AzA 15% foam versus AzA 15% gel, these data support the concept that proper skin care is a vital component of rosacea management and that vehicle formulation can play an important role in mitigating application-site AEs.50

Combination topical therapy. When treating patients with PPR, an important clinical consideration is how to optimally integrate a topical alpha-agonist, used to treat persistent facial erythema of rosacea, with a topical agent, used to treat PP lesions and perilesional erythema. This question was investigated in a multicenter, 12-week, double-blind, randomized, controlled trial that evaluated subjects with moderate-to-severe PPR characterized by marked persistent facial erythema and PP lesions (N=190).31 Enrolled subjects were randomized to one of three groups:

• Active group 1 —brimonidine 0.33% gel, applied once daily in the morning (AM) and IVM 1% cream, applied once daily in the evening (PM), both for 12 weeks (n=49)
• Active group 2 —gel vehicle (once daily AM, Weeks 1–4), brimonidine 0.33% gel (once daily AM, Weeks 1–8), and IVM 1% cream (once daily PM, Weeks 1–12) (n=46)
• Vehicle group — gel vehicle (once daily AM) and cream vehicle (once daily PM) for 12 weeks (n=95).

Over the duration of the study, gentle skin care was controlled with a specific cleanser, moisturizer, and sunscreen provided to all subjects. Significantly superior efficacy based on IGA ratings of “clear” or “almost clear” ratings for the reduction in facial erythema and decrease in PP lesions was greatest in the active groups (combined 55.8%) compared to the vehicle group (36.8%) at Week 12 (p=0.007).31 Treatment success was greater in Active Group 1 (IGA “clear” or “almost clear,” 61.2%), which received both active treatments for all 12 weeks,
Compared to Active Group 2 (50%), in which use of brimonidine 0.33% gel was delayed until Week 5. Skin tolerability favorable in all study groups. 33

Clinical relevance of combination therapy

Data. The reductions in facial erythema and PP lesion counts in this topical combination study 33 supports the results of other studies demonstrating the additive therapeutic benefit of combining alpha-agonist therapy with an agent that reduces PP lesions. The best therapeutic outcome was noted when both topical agents were used throughout the study; however, delaying the use of the topical alpha-agonist for the first four weeks of treatment was still associated with marked clinical improvement by Week 12. 21 In addition to parameters assessed by the investigator (e.g., IGA, lesion counts), study subjects in the active groups also reported greater improvements than those in the vehicle group. Lastly, the use of proper skin care appears to be an integral component of successful rosacea management.

Physical modalities (device therapy).

Consensus recommendations from the AARS on use of physical modalities for the treatment of rosacea were reviewed in detail in previous publications. 7,8,10,11,12 An important benefit of device treatment for rosacea is that the therapeutic effects are generally seen over a limited number of treatment sessions, which are in contrast to the need for daily treatment over extended periods of time with topical or oral medication. Once an endpoint of an acceptable therapeutic effect is achieved, the results are typically maintained for a number of years. Concurrent medical therapy is often used to complement device treatments.

Telangiectasias/diffuse facial erythema. Since improvements in telangiectasias and facial erythema of rosacea were reported with use of the pulsed-dye laser (PDL), this laser continues to be an important modality in rosacea treatment. 13 Later generations of PDL have incorporated a different pulse format, which largely eliminated the marked bruising observed after treatment with early PDL devices.

Intense pulsed light (IPL) devices have also been used successfully to treat both the facial erythema and dilated facial vessels associated with rosacea. 14 Studies have demonstrated comparable efficacy between updated PDL and IPL devices. 9,34

Early studies with long-pulsed 532-nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser demonstrated efficacy in treating telangiectasia. 35 More recent studies using a more powerful 532-nm laser reported excellent results when treating telangiectasia and diffuse erythema in patients with rosacea, which were comparable to those seen with PDL devices. 16 Importantly, the use of lasers, IPL devices, and PDLs have shown superior results treating telangiectatic vessels compared to results achieved treating diffuse facial erythema of rosacea, although both have shown response. 37

Electrocautery has been employed for many years at low settings to treat visible dilated blood vessels associated with rosacea. While treatment can be successful when performed carefully using a fine-point tip, there is a risk of nonspecific thermal damage that can produce small linear or punctate scars. 37

PP lesions. Data on the use of lasers and light devices for the treatment of papules and pustules (PP) of rosacea suggest they can be helpful. 21 However, the study methodology used to collect these data failed to capture PP lesion counts or clinical descriptions of rosacea in a controlled manner. Additional well-designed studies evaluating the use of devices for treatment of PPR are needed.

Combination use of a topical alpha-agonist and device therapy. Data are limited on the use of topical alpha-agonist therapy in combination with IPL or specific lasers for the treatment of rosacea. One of the authors of this article (ET), who has extensive experience with the use of devices for rosacea, suggests that the use of a topical alpha-agonist and physical devices are complementary. The natural appearance and the degree of improvement of diffuse facial erythema with use of either topical brimonidine or topical oxymetazoline usually produces a better visible facial appearance than the partial improvement typically seen with devices alone. The partial response achieved when using laser/light devices to treat diffuse facial erythema, combined with the excellent results seen with these devices when treating telangiectasia 51-57 (which are not responsive to the use of a topical alpha-agonist), suggest that a topical alpha-agonist can be initiated after laser and light treatments. There have been some early studies that suggest that the use of an alpha-agonist immediately following treatment with these devices diminishes the pulse treatment erythema that commonly occurs with these devices. 34

Hopefully, further studies will help determine whether use of a topical alpha-agonist will change or compromise the therapeutic effects of the device. Additionally, there are studies in progress that are evaluating the use of alpha-agonists to complement device treatments when used a few days after treatment, as well as literature supporting the potential inhibition of vascular endothelial growth factor with brimonidine, which suggests a potential additive effect of device treatment followed by the use of a topical alpha-agonist. 39 At this point, we do not have sufficient data regarding the complimentary use of these agents with laser and light devices to make evidence-based treatment recommendations.

Adverse effects associated with the use of an ablative device followed directly by the use of a topical alpha-agonist have been observed. 40 Potentially, a treatment with any device that damages the epidermal barrier can result in increased percutaneous absorption of a topically applied alpha-agonist, increasing the risk of hypotension. Studies exploring the safe and complimentary use of devices and topical alpha-agonist therapy are important and much needed.

Microfocused ultrasound and bipolar radiofrequency. There are a number of devices that cause nonselective vascular damage that hold some promise for success in the treatment of rosacea. Microfocused ultrasound with visualization (MFU-V) and bipolar radiofrequency pins have been shown to improve the diffuse facial erythema associated with rosacea. 41 Data from the study evaluating MFU-V technology in patients with rosacea was generated using the same rigorous parameters as those used in the alpha-agonist pivotal clinical trials, which bolsters the investigators’ findings. Moving forward, clinical studies evaluating the efficacy and safety of devices for the treatment of rosacea could generate better quality data by incorporating validated assessment methods, such as the IGA, Clinician’s Erythema Assessment, telangiectasia grading score, inflammatory lesion counts, standardized side effect assessments, and patient efficacy evaluations, especially when the number of study participants is limited or a split-faced study design is being utilized.

CONSENSUS RECOMMENDATIONS FOR THE MANAGEMENT OF ROSACEA

The already published guidelines for rosacea management primarily focus on incorporating medical and/or device therapies that are
correlated with the visible manifestations of rosacea. In all cases, proper skin care, photoprotection, and avoidance of patient-specific rosacea triggers are suggested. How therapies are used, either concurrently or in a staggered fashion, might be considered by some to be more art than science, as clinical studies and outcomes data are currently lacking. However, some combination approaches have been addressed in the literature. These include the initial use of topical metronidazole or topical azelaic acid concurrently with oral doxycycline for treatment of severe PPR with transition to topical therapy alone after adequate response is achieved; topical brimonidine and topical ivermectin for treatment of PPR with diffuse persistent facial erythema of at least moderate severity; and combination treatment with potassium titanyl phosphate laser and topical brimonidine for diffuse persistent facial erythema of rosacea. Table 1 depicts consensus recommendations from the AARS on rosacea management correlated with clinical manifestations observed at the time of presentation.

SUMMARY

This article provides an update to previously published consensus recommendations from the AARS on rosacea management, including discussions of topical ivermectin, topical oxymetazoline, combination therapy approaches, and physical devices. Consistent with what many publications on rosacea currently emphasize, clinicians are encouraged to define the clinical manifestations currently present in each individual patient and to select therapies that correlate with the optimal treatment of those manifestations. There are less data available on how to optimally combine therapies; however, it appears that rationally selected medical therapies can be utilized concurrently. As the pathophysiology of rosacea is multifactorial, the clinical presentation of rosacea is heterogeneous. Rosacea is a chronic and recurrent inflammatory disorder, and clinical manifestations often vary in their nature and severity over time. This might necessitate an adjustment in management. As new data become available, management approaches should be updated.

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REFERENCES

**TABLE 1. American Acne & Rosacea Society recommendations for rosacea management options**

<table>
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<tr>
<th>ROSacea PRESENTATION</th>
<th>MANAGEMENT OPTIONS</th>
<th>QUALITY OF EVIDENCE OF MANAGEMENT OPTIONS (A, B, C)</th>
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| Persistent central facial erythema without papulopustular (PP) lesions | - Topical alpha-agonist (brimonidine, oxyxmetazoline)  
- Intense pulsed light (IPL), potassium titanyl phosphate (KTP) crystal laser, or pulsed-dye laser | B: Systematic review/meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings; lower-quality clinical trial | - More data are needed on optimal use of specific device therapies and topical alpha-agonist therapy in combination |
| Diffuse central facial erythema with PP lesions | - Topical metronidazole  
- Topical azelaic acid  
- Topical ivermectin  
- Oral tetracyclines  
- Topical alpha-agonists  
- Oral isotretinoin | B: Systematic review/meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings; lower-quality clinical trial | - Combination of an oral and topical agent that reduce PP lesions and perilesional erythema based on severity; topical alpha-agonist used for persistent background erythema caused by fixed dilated vasculature |
| Flushing of rosacea (acute/subacute intermittent vasoconstriction) | - Flushing is better prevented than treated via avoidance of known triggers, such as sun exposure and photoprotection  
- Use of low-dose oral drugs with vasoconstrictive properties, including metizaparine, propranolol, or carvediolol(30,31)  
- The use of intradermal botulinum toxin achieved good results in a small group of patients, but there remain limited data(32) | B: Systematic review/meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings; lower-quality clinical trial | - Data are limited on the management of flushing of rosacea(33-35)  
- Limited data exist on topical therapies  
- Some botanicals and natural ingredients might improve facial redness and flushing (niacinamide, parthenolide-free extract of feverfew (Tanacetum parthenium), licorice derivatives, chamomile, green tea) based on preliminary small studies(36,37)  
- An anti-inflammatory cleanser night mask combination was found to markedly reduce facial redness (limited data)(38) |
| Ocular rosacea | - Lid hygiene, sunglasses, eye lubrication formulations(39,40,41,42)  
- Cyclosporin ophthalmic emulsion (3-month, randomized, controlled trial [n=37])(39)  
- Topical metronidazole or ivermectin (blepharitis; applied to external eyelid skin)(43,44,45)  
- Oral doxycycline, erythromycin, or azithromycin(39,46,47)  
| B: Systematic review/meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings; lower-quality clinical trial | - Data are based on clinical experience, case reports, and small studies  
- Topical corticosteroids for short-term therapy but avoid chronic use(48)  
- Oral azithromycin is an alternative option if an oral tetracycline is not effective  
- Oral isotretinoin for refractory disease (transition to intermittent therapy after initial control)  
- Other alternative topical agents include sulfacetamide-sulfur, calcineurin inhibitors, retinoids, and permeatin (limited data available on these agents)(49-51)  
- While the data on the use of IPL, KTP or pulsed-dye laser are limited for PP lesions, these options are useful to treat erythema |
| Granulomatous rosacea | - Oral tetracyclines(52)  
- Topical pimecrolimus (case reports)(53)  
- Oral isotretinoin (0.7mg/kg/day for 6 months)(54)  
- Oral dapson(55)  
- Intense pulsed-dye laser (case)(56)  
- Photodynamic therapy (case)(57)  
- Topical brimonidine(58) | C: Consensus guidelines; usual practice, expert opinion, case series—limited trial data | - No current standard of treatment; limited data based mostly on case reports(58)  
- Oral isotretinoin may produce improvement without recurrence(59) |
| Phymatous rosacea | - Surgical therapy for fully developed phymatous changed (carbon dioxide laser, erbium-doped yttrium aluminum garnet (YAG) laser, electrosurgery, dermabrasion)(56,57) | C: Consensus guidelines; usual practice, expert opinion, case series—limited trial data | - Treatment selection dependent on stage of development (early or fibrotic) and extent of inflammation (active or burnt out)  
- Oral isotretinoin might improve early soft phymatous changes due to sebaceous hyperplasia |

* Reader directed to read body of paper for more details and also to reference specific evidence; management options not listed in any specific order of preference
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40. Mirvaso (brimonidine) topical gel 0.33% [package insert]. Galderma Laboratories, LP, Fort Worth, TX; November 2017.


CONSENSUS

(ePoster). Presented at the American Society for Laser Medicine and Surgery annual meeting; April 5–9, 2017; San Diego, CA.


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Coprescription of Isotretinoin and Systemic Corticosteroids for Acne: An Analysis of the National Ambulatory Medical Care Survey

by BROOKE VASICEK, MD; WILLIAM ADAMS, PhD; LARYN STEADMAN, BFA; JEEAVE RESERVA, MD; and JAMES SWAN, MD

Drs. Vasicek, Reserva, and Swan are with the Division of Dermatology at the Loyola University Medical Center in Hines, Illinois. Dr. Adams is with the Biostatistics Core, Health Sciences Division at the Loyola University Chicago in Chicago, Illinois. Ms. Steadman is with the Indiana University School of Medicine in Indianapolis, Indiana.

Introduction: Isotretinoin treatment has been linked to flares of severe acne, which can be managed by the coadministration of systemic corticosteroids or prevented by beginning with a low dose of isotretinoin. To our knowledge, there are no estimates in the literature on the frequency of coprescription of isotretinoin and systemic corticosteroids. Objectives: We sought to quantify the estimated frequency of coprescription of isotretinoin and systemic corticosteroids and assess trends of the use of isotretinoin with systemic corticosteroids for acne as they relate to age, sex, race, insurance, and provider specialty. Methods: Data from the National Ambulatory Medical Care Survey (NAMCS) from 2003 to 2015, National Hospital Ambulatory Medical Care Survey Hospital Outpatient Departments (NHAMCS-OPD) from 2003 to 2011, and National Hospital Ambulatory Medical Care Survey Hospital Emergency Departments (NHAMCS-ED) from 2003 to 2014 were aggregated for this analysis. The number of prescriptions for isotretinoin and/or systemic corticosteroids was estimated by specialty (for NAMCS) and by survey type (for NHAMCS-OPD and NHAMCS-ED). Results: Among all first visits to a physician for acne (n=18,914,096), approximately 3.9 percent prescribed isotretinoin, 0.24 percent prescribed corticosteroids, and the remaining 96 percent prescribed neither drug. This was comparable to estimates for first visits to a dermatologist for acne (n=13,920,913), where approximately 4.2 percent prescribed isotretinoin, 0.32 percent prescribed corticosteroids, and the remaining 95 percent prescribed neither medication. Conclusion: Currently, isotretinoin and systemic corticosteroids are rarely prescribed together. Keywords: acne, corticosteroids, isotretinoin

ACADEMIC ANTHROPOLOGY

Acne is a common condition treated by dermatologists and other physicians.1,2 Severe acne often requires systemic therapy, such as isotretinoin.3 While isotretinoin is one of the most effective treatments for severely inflamed and nodulocystic acne, acne lesions can, paradoxically, flare or worsen with initiation of isotretinoin treatment.4 Prescribing isotretinoin at a low dose or concurrently prescribing systemic corticosteroids might help prevent these flares.1,4 If a flare in acne due to isotretinoin occurs, the concomitant use of systemic corticosteroids might help improve skin lesions and, although rare, might prevent systemic symptoms associated with acne fulminans.5,6

To our knowledge, there are no estimates in the literature on the frequency of coprescription of isotretinoin and systemic corticosteroids. Given the utility of systemic corticosteroids in decreasing acne flares, this study sought to quantify the estimated frequency of the coprescribing isotretinoin and systemic corticosteroids. We also aimed to assess trends in the use of isotretinoin with systemic corticosteroids for acne as they relate to age, sex, race, insurance, and provider specialty.

METHODS

Data from the National Ambulatory Medical Care Survey (NAMCS) from 2003 to 2015, National Hospital Ambulatory Medical Care Survey Hospital Outpatient Departments (NHAMCS-OPD) from 2003 to 2011, and National Hospital Ambulatory Medical Care Survey Hospital Emergency Departments (NHAMCS-ED) from 2003 to 2014 were aggregated for this analysis. The number of prescriptions for isotretinoin and/or systemic corticosteroids was estimated by specialty (for NAMCS) and by survey type (for NHAMCS-OPD and NHAMCS-ED). Visits were stratified and weighted to reflect their clustered sampling probability as described by the National Center for Healthcare Statistics.7 A visit was considered as being “for acne” if the reason for the visit (or broad reason for the visit) listed “acne or pimples” or if the diagnosis listed “acne varioliformis” or “other acne.”

A multivariable logistic regression model for complex samples was used to estimate the odds of prescribing isotretinoin during a visit for acne as a function of survey year, age at time of visit, sex, race, insurance, and physician specialty. A similar approach was used to estimate the odds of prescribing a corticosteroid, though due to too few visits prescribing corticosteroids, survey year and insurance were not considered as covariates in the model. Regarding specialty, visits in the emergency department and outpatient department datasets were considered as being “nondermatology” visits.

RESULTS

Between 2003 and 2015, a total of 97,996,570 visits for acne occurred. Among visits to
dermatologists for acne (n=58,711,796), approximately 14 percent prescribed isotretinoin, 0.53 percent prescribed corticosteroids, and 0.04 percent prescribed both isotretinoin and corticosteroids (Figure 1). The remaining 85 percent prescribed neither. These estimates differed from visits to nondermatologists for acne (n=39,284,774), where 2.33 percent prescribed isotretinoin, 0.54 percent prescribed corticosteroids, and zero prescribed isotretinoin and corticosteroids. The remaining 97 percent mentioned neither drug.

For all first visits to a physician for acne, including dermatologists, (n=18,914,096), approximately 3.9 percent prescribed isotretinoin, 0.24 percent prescribed corticosteroids, and the remaining 96 percent mentioned neither drug. Among first visits to a dermatologist for acne (n=13,920,913), approximately 4.2 percent prescribed isotretinoin, 0.32 percent prescribed corticosteroids, and the remaining 95 percent mentioned neither medication. In this sample of data, age (p=0.24), race (p=0.39), sex (p=0.71), and physician specialty (p=0.90) were not associated with the use of a corticosteroid during a visit for acne (Table 1). Similarly, insurance was not associated with the use of isotretinoin.

Visits to dermatologists were 7.73 times more likely to prescribe isotretinoin than visits to non-dermatologists (p<0.001) even after controlling for survey year, age, race, sex, and insurance (95% confidence interval [CI]: 4.38–13.66). Controlling for all other variables in the model, patients between the ages of 20 and 35 years were 1.93 times more likely to be prescribed isotretinoin compared with patients older than 35 years (95% CI: 1.27–2.91, p=0.002), as were patients younger than 20 years of age (OR: 2.75, 95% CI: 1.81–4.18, p<0.001). Controlling for all other variables in the model, those who identified as white were more likely than those who did not identify as white to receive a prescription for isotretinoin (OR: 1.65, 95% CI: 1.08–2.53; p=0.01), as were men (OR: 1.50, 95% CI: 1.10–2.04; p=0.01).

LIMITATIONS

The NAMCS does not include medication dosages, acne type, or acne severity, which limits inferences in prescribing patterns. Also, there might have been other disorders for which the corticosteroid was prescribed at these visits.

CONCLUSION

The coprescription of isotretinoin and systemic corticosteroids is very rare. These results suggest that either many physicians are not experiencing the paradoxical acne flare previously reported in the literature, are initiating low-dose isotretinoin to minimize the risk of a flare, are decreasing the dose of isotretinoin in response to a flare, or are unaware of the utility of the coprescription of systemic corticosteroids with isotretinoin. Dermatologists are more likely than other specialties to prescribe isotretinoin, which might be attributed to the greater severity of acne seen by dermatologists and the level of comfort of isotretinoin use developed during specialty training.

REFERENCES

MinoLira Tablets bring immediate- and sustained-release minocycline together for the first time ever in functionally scored tablets (105 and 135mg) for broad dosing options and safety similar to placebo. It’s the active ingredient you know – redefined.

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

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• This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.
• Minocycline, like other tetracycline-class drugs, can cause fetal harm when administered to a pregnant woman.

To learn more, please visit www.minolira.com

Patient Awareness of Antimicrobial Resistance and Antibiotic Use in Acne Vulgaris

**ABSTRACT**

**Background:** Antibiotic resistance presents a threat to public health. In dermatology, antibiotics are used extensively for the treatment of acne, sometimes for extended periods. Thus, awareness of antibiotic resistance among dermatology patients is relevant in clinical practice. **Methods:** An online survey assessed antibiotic resistance awareness in adults with acne (n=809) and the parents of adolescents with acne (n=210). **Results:** More than 80 percent of subjects said that they were “somewhat familiar” or “very familiar” with antibiotic resistance. Overall, 86 percent of the survey respondents identified the correct definition of antibiotic resistance, with parents more likely than their children to choose the proper definition of resistance, as follows: “When antibiotics and/or antibacterials are used for a period of time, the infectious organism adapts to them and becomes immune, resulting in less effective treatment” (95% confidence interval). Among subjects who might have been prescribed antibiotic treatment for their acne, including individuals that reported antibiotic treatment and individuals that were not sure, 76.9 percent reported that they would be very or extremely likely to use effective antibiotic-free options if given the opportunity. More than 90 percent of people with acne and their parents agreed that healthcare providers should do more to educate patients about antibiotics and antibiotic resistance. **Conclusions:** This survey indicated that patients with acne and their parents think more should be done to educate the public about the potential risks associated with antibiotic use and the availability of antibiotic-free treatment options. Discussions with patients about antibiotic therapies, antibiotic resistance, and alternative therapies represent areas of opportunity for healthcare providers in dermatology.

**KEYWORDS:** Acne, antibiotic resistance, antibiotics

**FUNDING:** This study was funded by Galderma Laboratories, LP.

**DISCLOSURES:** Drs. Del Rosso, Rosen, and Palceski are consultants and investigators for Galderma. Dr. Del Rosso has served as a research investigator and speaker for Galderma. Dr. Del Rosso and Dr. Rosen are employees of Galderma at the time this article was written.

**CORRESPONDENCE:** James Q Del Rosso, DO; Email: jqdelrosso@yahoo.com
Furthermore, increased antimicrobial peptide levels have been observed in AV, which might be the result of C. acnes proliferation or C. acnes–induced changes in sebum levels and composition. 

Alterations in sebum and C. acnes within the pilosebaceous unit also appear to contribute to hyperkeratinization and comedone formation. 

Increased antibiotic use is one of many steps that can be taken to foster the development of resistance. 

Additionally, bacterial resistance is not the only inevitable consequence associated with the clinical use of antibiotics. Both topical and oral antibiotics have been associated with changes in the human microbiome (the vast array of commensal, symbiotic, opportunistic, and pathogenic microorganisms that reside on and within the human body). 

Topical antibiotics alter the cutaneous microbiota, leading to resistance patterns, even at anatomical sites distal to the site of application. For example, alterations in bacterial flora within the anterior nares and at remote cutaneous sites have been observed following topical application of antibiotics. 

Likewise, oral antibiotics can lead to changes in the gastrointestinal (GI) microbiome. This can lead to alterations in commensal competition and flora balance, as well as to the creation of reservoirs of antibiotic resistance within specific microbiota. Systemic antibiotic treatment can also result in opportunistic infection by Clostridium difficile (C. difficile) and contribute to GI-related adverse events.

The impact of antibiotic use and misuse on the emergence of antibiotic resistance, both in the US and worldwide, has led the US Centers for Disease Control and Prevention (CDC) to focus on educational and public awareness measures to support antibiotic stewardship. Among the resistant organisms that can result from antibiotic therapy, carbapenem-resistant Enterobacteriaceae, drug-resistant Neisseria gonorrhoeae (N. gonorrhoeae) (over half of which display resistance to tetracycline), multidrug-resistant Pseudomonas aeruginosa, MRSA, and C. difficile have been identified as urgent threats by the CDC. Worldwide, many common bacteria, such as Escherichia coli (E. coli) and Klebsiella pneumoniae (K. pneumoniae), are exhibiting high rates of resistance, negatively impacting available treatments for common infections, including urinary tract infections and pneumonia.

The current study measured the attitudes toward and awareness of antibiotic resistance among adults with AV and the parents of children/adolescents with AV. Among respondents, this study assessed their experience with antibiotics and antibiotic-free acne treatments, awareness of and experience with superbugs (i.e., strains of bacteria resistant to antibiotics), and agreement with potential actions to limit the future impact of antibiotic resistance.

METHODS

Subjects. The study included survey data from 1,019 subjects. Respondents belonged to one of two groups: 1) People aged 17 to 40 years who had received a prescription treatment (oral or topical) for AV in the previous year (n=809); and 2) parents of children or adolescents (aged 9–17 years) who had received a prescription for AV in the past year (n=210). All subjects were US residents. Participants were required to agree to release contact information in the case of adverse events and/or product-quality complaints. Respondents were obtained from a propriety American Consumer Opinion Panel (Decision Analyst, Arlington, Texas). From the panel, 183,037 panelists were invited to undergo screening, 14,224 completed the screening, and 1,019 qualified and completed the full survey. Patients who met inclusion criteria were informed that individual responses would be anonymous and confidential and were invited to complete the survey by clicking continue.

Survey design. Subjects were surveyed online through Decision Analyst, and included a nationally representative (US, including Alaska and Hawaii) sample of patients with AV, as well as parents of adolescent patients with AV. The survey sections utilized in this study included three main categories of questioning:

1. Demographic questions (employment status, marital status, household income, ethnic background, and educational level; five questions)
2. Study eligibility determination (age, sex, recent diagnoses, and treatments prescribed; 12 questions, some with multiple parts)
3. Assessment of awareness of antibiotic resistance and superbugs, experiences with antibiotic and antibiotic-free therapies for AV, emotional impact of AV, and agreement with potential actions to increase awareness and limit the impact of antibiotic resistance (29 questions, some with multiple parts).

The survey included a combination of free-response and aided (prompted, recognition-
TABLE 1. Study subject demographics (N=1,019)

<table>
<thead>
<tr>
<th>DEMOGRAPHIC</th>
<th>PATIENTS, % (n=809)</th>
<th>PARENTS OF PATIENTS, % (n=210)</th>
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</thead>
<tbody>
<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Male</td>
<td>34.2</td>
<td>23.8</td>
</tr>
<tr>
<td>Female</td>
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<td>76.2</td>
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<td>Age (years)</td>
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<td>17–24</td>
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<td>25–29</td>
<td>27.4</td>
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<tr>
<td>30–34</td>
<td>22.4</td>
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<td>35–39</td>
<td>15.8</td>
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<tr>
<td>Geographical region</td>
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<tr>
<td>South</td>
<td>37.8</td>
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<tr>
<td>Midwest</td>
<td>22.4</td>
<td>16.2</td>
</tr>
<tr>
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<td>20.5</td>
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<tr>
<td>West</td>
<td>18.9</td>
<td>22.9</td>
</tr>
<tr>
<td>Race/ethnicity</td>
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<td></td>
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<td>Hispanic or Latin American</td>
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<td>9.5</td>
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</tr>
<tr>
<td>American Indian, Eskimo, or Aleut</td>
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<td>0.5</td>
</tr>
<tr>
<td>Other ethnic background</td>
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<tr>
<td>Household income</td>
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<tr>
<td>Under $10,000</td>
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<td>3.3</td>
</tr>
<tr>
<td>$200,000 or more</td>
<td>1.5</td>
<td>2.9</td>
</tr>
</tbody>
</table>

*Age of children/adolescent patients represented by parents

RESULTS

Subject demographics. Subject demographics are presented in Table 1. The majority of respondents were women (65.8% of adult patient respondents and 76.2% of parent respondents) and identified as Caucasian or white (59.6% of adult patients and 79.5% of parents). The mean household income of adult patient respondents was $65,200, and the mean household income of parent respondents was $78,900. Respondents resided throughout the US.

Respondent understanding of antibiotic overuse and efficacy. The majority of respondents had a basic understanding of antibiotic resistance, with parents more likely than adult patients to correctly define antibiotic resistance as “when antibiotics and/or antibacterials are used for a period of time, the infectious organism adapts to them and becomes immune, resulting in less effective treatment.” This response was chosen by 91.4 percent of parents versus 85.4 percent of adult patients (significantly different at 95% confidence interval (CI); Figure 1).

More than 80 percent of respondents said that they were at least somewhat familiar with the topic of antibiotic resistance (Figure 2A). Antibiotic resistance awareness was high among both sexes, although some differences and trends were seen in response rates. A greater percentage of male patients with AV, compared to female patients (significant at 95% CI), and a greater percentage of female parents, compared to male parents (not significant [NS]), indicated that they were very or somewhat familiar with antibiotic resistance (Figure 2B). Antibiotic resistance awareness was high among all age groups, with self-reported awareness among patients with AV increasing with age (Figure 2C). Among both patients and parents, the most frequently reported first source of antibiotic resistance information was a physician or medical professional. In contrast, less common sources of “first awareness,” including the news media or online sources, were reported at different rates between the two groups of respondents (Table 2).

Familiarity and concerns around oral versus topical antibiotics. Overall familiarity with the risk of antibiotic resistance resulting from the use oral antibiotics was high. More than 84 percent of respondents agreed that one can develop antibiotic resistance from oral antibiotics. Agreement was similar among patients (83.8%) and parents (86.5%). Agreement that one can develop antibiotic resistance from topical antibiotics was lower, at an average of 62.1 percent of patients (62.7% patients, 59.9% parents). There was a significant difference (at the 95% CI) in respondent knowledge concerning the consequences of antibiotic overuse when patients and parents were compared: 36.7 percent of patients versus 21.4 percent of parents responded that they “did not know overuse of antibiotics could increase (my) risk for an antibiotic-resistant infection.” Men (both patients and parents) were more likely to agree with this statement than women (significantly different at 95% CI).

The majority (56.2%) of respondents somewhat or completely agreed with the assertion that oral antibiotics are more likely to cause antibiotic resistance when compared to topical antibiotics used for the treatment of skin disorders. Only 31.2 percent of respondents agreed with the opposing statement, that topical antibiotics are more likely to cause antibiotic resistance when compared to oral antibiotics used for the treatment of skin conditions such as AV and rosacea.

Perceptions of antibiotic efficacy in acne. A very small percentage of respondents (5.4%) agreed with the assertion that AV can only be treated by antibiotics, with a significantly greater percent of patients than parents thinking this to be true (6.1% vs. 2.9%, respectively, significant at 95% CI). Interestingly and surprisingly, the majority (74.2%) of respondents somewhat or completely agreed with the statement: “for acne, I would prefer to use (or have my children use) an effective antibiotic-free prescription treatment instead of a full-dose antibiotic.”

More than half (53.9%) of study subjects responded that they (or their children) were prescribed an antibiotic for AV during (approximately) the past year. Only 31.7 percent of antibiotics users (or those who were not sure whether they were prescribed an antibiotic)
TABLE 2. Source of first awareness of antibiotic resistance (N=1,019)

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>PATIENTS, % (n=809)</th>
<th>PARENTS OF PATIENTS, % (n=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician/ medical professional</td>
<td>23.3</td>
<td>31.4*</td>
</tr>
<tr>
<td>Dermatologist</td>
<td>9.8*</td>
<td>3.4</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>4.4</td>
<td>17.4*</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>5.3*</td>
<td>1.9</td>
</tr>
<tr>
<td>News/media</td>
<td>13.2</td>
<td>21.3*</td>
</tr>
<tr>
<td>Online</td>
<td>12.4*</td>
<td>4.8</td>
</tr>
<tr>
<td>Friends/family/ neighbors (WOM)</td>
<td>11.1*</td>
<td>6.8</td>
</tr>
<tr>
<td>School/college</td>
<td>9.3*</td>
<td>1.9</td>
</tr>
<tr>
<td>Social media</td>
<td>2.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Other</td>
<td>1.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Don’t recall</td>
<td>6.7</td>
<td>6.3</td>
</tr>
</tbody>
</table>

WOM: Word of mouth
*Significantly higher than the other group at the 95% confidence interval

FIGURE 1. Percent responses to the question “What does antibiotic resistance mean to you?” broken down by aided definitions (95% confidence interval)

FIGURE 2. Respondent self-reported familiarity with antibiotic resistance (95% CI)—A) Familiarity with antibiotic resistance, all respondents (N=1,019); B) Patients vs. parents and male vs. female reporting “Very Familiar” or “Somewhat Familiar” with antibiotic resistance; C) Patients reporting “Very Familiar” or “Somewhat Familiar with antibiotic resistance by age (n=809)
were aware of antibiotic-free prescription options. There was less awareness of antibiotic-free treatment options among parents than among patients (16.2% vs. 35.4%, respectively; Figure 3A). Among this population, 76.9 percent (75.4% patients, 83.1% parents, significantly different at 95% CI) said they would be very or extremely likely to use an antibiotic-free prescription treatment for AV if they were aware of the existence of effective, antibiotic-free therapeutic options (Figure 3B).

In the open-ended response to “what specific role do antibiotics play in treating acne?”, the greatest proportion of responses (43.7%) were associated with the role of antibiotics in the treatment of bacteria or infection (Figure 3C). In contrast, a minority of respondents (18.4%) indicated a belief that AV is an infectious disease, with this belief significantly more prevalent among patients than among parent respondents (19.9% vs. 12.9%, respectively, significant at 95% CI). An additional 17.2 percent of subjects indicated they were undecided concerning the infectiousness of AV. Among antibiotic users, the primary reason reported for choosing this treatment option was that the respondents felt it would be more effective than antibiotic-free prescription treatment options (43%). Other top responses included treatment duration (23.9%) and a lack of awareness of antibiotic-free prescription treatment options (22.8%). Among subjects who were prescribed antibiotic-free treatments, the top reasons reported for the use of an antibiotic-free treatment option were: 1) “felt it would be just as/more effective than antibiotics” (43.3%); 2) “concerns about potential risk of antibiotic resistance” (26.9%); and 3) “relative ease of treatment/application” (26.5%).

**Emotional impact of acne.** The majority of respondents reported that acne had an emotional impact on themselves or their children (Figure 4A), with 54.1 percent of respondents giving the impact a score of eight points or more on a 10-point scale, where 10=“affects me greatly” and 1=“does not affect me.” A greater proportion of women reported that AV had a major emotional impact in that 60.3 percent of women versus 43.0 percent of men ranked emotional impact with a score of 8 or higher (Figure 4B). Overall, 43.5 percent of those surveyed agreed with the statement, “I care more about the emotional impact of my acne today than about the potential long-term impact of antibiotic resistance.” When compared to parents, a greater percentage of patients with AV (46.7% vs. 31.0%) somewhat or completely agreed with this statement (significant at 95% CI). The difference between the two groups was driven by a low proportion of female parents displaying agreement (25.0%). A significantly greater proportion of patients, both male and female, as well as male parents agreed that the emotional impact of AV outweighs the risk of antibiotic resistance (significant at 95% CI). Of all parents surveyed, 65.7 percent reported that they had suffered from AV as a child or young adult. Of these, 47.8 percent ranked the emotional impact of AV as 8 or higher on a 10-point scale.

**Conversations with dermatologists about antibiotic resistance related to acne.** Of all respondents surveyed, only 35.3 percent had discussed the possible risks of antibiotic use as part of their AV treatment during recent conversations with their healthcare provider. These discussions were most often initiated by the doctor (65.6% of all reported discussions). Patients were more likely to report having discussed antibiotic risks with their doctor.
than parents were (Figure 5), and male patients were significantly more likely to report these discussions than female patients (46.9% vs. 31.6%, respectively, significant at 95% CI). Few antibiotic users (including those unsure whether they had been prescribed an antibiotic) reported having discussed antibiotic-free AV treatment options with their prescriber (27.7%). Discussions concerning antibiotic-free treatment options were significantly more likely to occur among patients than parents (Figure 5; significant at 95% CI) and significantly more likely to occur among male patients than female patients (42.6% vs. 23.8%, respectively, significant at 95% CI).

**Risks and actions related to antibiotic resistance.** More than half of respondents (61.5%) reported that they had heard the term superbug, with 56 percent of all respondents reporting that they were aware of the risk and impact of superbugs. Parents were significantly more likely to report an awareness of superbugs compared to patients (72.9% vs. 58.6%, respectively, significant at 95% CI). A slightly higher percentage of female patients reported an awareness of superbugs compared to male patients (60.7% vs. 54.5%, respectively). The percentages of respondents who stated they were aware of specific health risks and costs (aided response question) associated with superbugs are presented in Table 3. Significant differences between the proportion of male and female patients and between patients and parents who correctly identified superbug-related risks were observed (significant at 95% CI). The respondents perceived a myriad of contributing factors to the propagation of superbugs, with overprescribing or unnecessary prescribing of antibiotics among the most commonly selected reasons for superbugs. In general, parents were more aware of causal factors than were current patients with AV (Table 4). A significantly greater percentage of female respondents were aware of causal factors related to antibiotic resistance compared to male respondents, including overprescribing of antibiotics, unnecessary prescribing of antibiotics, and not taking the complete course or duration of any prescribed antibiotic (significant at 95% CI). A significantly greater percentage of male respondents identified poor hygiene as a contributing factor leading to the propagation of superbugs (significant at 95% CI), compared to female respondents.

Subject agreement with a number of potential actions targeting antibiotic resistance was collected. The greatest proportion (>90%) of subjects agreed that doctors and other healthcare professionals should educate patients on antibiotic use and resistance (Figure 6). Parents were more likely than patients to agree with the proposed actions around antibiotic use, and female patients were more likely than male patients to agree with the proposed actions (significant at 95% CI, Table 5).

**DISCUSSION**

This study reports the results of a survey of adults with AV and the parents of adolescents with AV. The survey assessed attitudes toward and awareness of antibiotic resistance and antibiotic use in AV. According to the results of this survey, adult patients with AV and parents of children/adolescents with AV have a basic grasp of antibiotic resistance, yet they underestimate many of the potential associated risks. Increased awareness was associated with increasing age within the surveyed population. Therefore, it might be important to focus on increasing awareness among younger patients with AV and to spend more time discussing the potential resistance-related risks of antibiotics with this population. Regarding the relative risk of antibiotic resistance, survey respondents...
perceived the use of oral antibiotics as a greater risk than the use of topical agents. Only a minority of respondents were aware of healthcare cost-related risks associated with superbugs, so education around the potential economic burden of superbugs (Table 3) is an area of opportunity.

The high emotional impact of AV increases the importance of efficacy in treatment decisions; however, consumers in this survey were clearly found to be open to or even prefer antibiotic-free options if the antibiotic-free treatment is effective. The results of this study demonstrate that patients with AV and parents of younger patients with AV feel that more should be done to combat antibiotic resistance, with most respondents placing the onus on healthcare professionals to educate patients on the topic. Antibiotics are a very important part of the AV therapeutic armamentarium. However, it is important that clinicians educate patients on antibiotic use and risks and incorporate exit plans when treating disorders such as AV when antibiotic therapy is prescribed.

**Education surrounding antibiotic use: what more needs to be done?**
Dermatological disorders, including AV and rosacea, frequently have a powerful psychosocial impact. Psychosocial consequences and negative changes in emotional and psychological health and well-being have been widely reported in the literature. Furthermore, patients with AV can also develop scars, post-inflammatory hyperpigmentation, and erythema. These sequelae can persist for months or years after the active AV lesion that triggered them has resolved. In the present study, more than 70 percent of respondents reported that AV had a high emotional impact. A greater proportion of women than men reported that the disease had a high emotional impact. However, this patient population was also more likely to agree with statements of action regarding antibiotic resistance. Therefore, despite the need and desire for efficacious treatments for AV, survey respondents indicated that they would like more information about antibiotic-free treatment options and agreed that more should be done to raise awareness of issues related to antibiotic resistance.

Nearly 90 percent of those surveyed agreed that antibiotic prescriptions should be clearly labeled with information on the risks of antibiotic resistance. Additionally, more than 80 percent of subjects agreed that government agencies should do more to raise awareness about antibiotic resistance. The CDC has taken up this call through their “Get Smart about Antibiotics Week” initiative. This annual event aims to increase awareness and education concerning antibiotic use and antibiotic resistance. Similar programs are in place throughout the industrialized world.

Nearly all respondents surveyed agreed that healthcare professionals should be involved in efforts to educate patients about antibiotic resistance, and respondents ranked actions by healthcare professionals as being the most effective. This indicates that there is an opportunity to improve the existing dialogue between clinicians, their staff, patients with AV, and parents of patients that are minors. Notably, the results of the survey indicated a need for improved patient knowledge regarding the specific risks of antibiotic resistance, particularly healthcare cost-associated risks, and knowledge of antibiotic-free treatment options. Because the duration of antibiotic exposure is a critical factor in the propagation of antibiotic resistance, clinicians should be particularly mindful of educating patients with disorders that often require long-term treatment, such as AV. The World Health Organization has recommended that clinicians only prescribe antibiotics when

### TABLE 3. Identification of risks/impacts of superbugs among respondents who reported an awareness of the risk of superbugs (N=1,019)

<table>
<thead>
<tr>
<th>RISK OF SUPERBUGS</th>
<th>PATIENTS, % (n=809)</th>
<th>PARENTS, % (N=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TOTAL</td>
<td>MALE</td>
</tr>
<tr>
<td>Antibiotics will not work when I really need them</td>
<td>79.5</td>
<td>73.0</td>
</tr>
<tr>
<td>Risk of causing more serious illnesses/infections</td>
<td>80.9</td>
<td>73.0</td>
</tr>
<tr>
<td>I or a loved one could be at risk for a hard-to-treat infection</td>
<td>71.6</td>
<td>58.6</td>
</tr>
<tr>
<td>Risk of death</td>
<td>70.0</td>
<td>65.1</td>
</tr>
<tr>
<td>Medications and foods that I consume will become more expensive and harder to find</td>
<td>25.9</td>
<td>32.2*</td>
</tr>
</tbody>
</table>

*Significantly higher than the other group at the 95% CI

### TABLE 4. Perceived causes of superbugs (aided response)

<table>
<thead>
<tr>
<th>PERCEIVED CAUSES OF SUPERBUGS</th>
<th>TOTAL, % (N=1,019)</th>
<th>PATIENTS, % (n=809)</th>
<th>PARENTS OF PATIENTS, % (n=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overprescribing of antibiotics</td>
<td>56.7</td>
<td>54.5</td>
<td>65.2*</td>
</tr>
<tr>
<td>Unnecessary prescribing of antibiotics</td>
<td>47.1</td>
<td>45.4</td>
<td>53.8*</td>
</tr>
<tr>
<td>Inappropriate infection-control procedures in hospitals and medical facilities</td>
<td>35.1</td>
<td>35.0</td>
<td>35.7</td>
</tr>
<tr>
<td>Not taking the complete course or duration of any prescribed antibiotic</td>
<td>33.6</td>
<td>31.9</td>
<td>40.0*</td>
</tr>
<tr>
<td>Poor hygiene</td>
<td>26.0</td>
<td>27.9*</td>
<td>18.6</td>
</tr>
<tr>
<td>Overuse of hand sanitizers</td>
<td>24.7</td>
<td>25.1</td>
<td>23.3</td>
</tr>
<tr>
<td>Other</td>
<td>0.5</td>
<td>0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Don’t know</td>
<td>15.9</td>
<td>16.1</td>
<td>15.2</td>
</tr>
</tbody>
</table>

*Significantly higher than the other group at the 95% confidence level
they are truly needed, utilizing an appropriate agent in the correct dose and for the correct duration of therapy. The latter is not always clearly defined for adequate treatment of AV; however, attempts to limit prolonged oral antibiotic use are recommended. This warrants an exit plan that incorporates topical therapy for long-term control of AV or transition to oral isotretinoin therapy when indicated. An open dialogue between clinicians and/or their staff and patients about the necessity for and alternatives to antibiotic therapies is consistent with the recommendation to limit oral antibiotic prescribing.

**Antibiotic-free treatment options**

Approximately 95 percent of patients and parents surveyed in this study did not think that AV could only be treated with antibiotics, and the majority responded that they would prefer to use an effective, antibiotic-free prescription treatment. Despite this, the awareness of antibiotic-free prescription AV treatments among antibiotic users was quite low. There are a number of effective, safe, antibiotic-free AV treatment options available to patients, and patient education on antibiotic-free treatment options is one avenue for expanding public knowledge and preventing the threat of increasing antibiotic resistance. Antibiotic-free AV treatment options are presented in Table 6.

**Benzoyl peroxide.** In terms of bactericidal action, benzoyl peroxide (BP) provides potent antimicrobial action with no known potential for inducing bacterial resistance. BP is effective at relatively low concentrations, even in the presence of sebum. BP also has keratolytic properties, has been shown to reduce comedones in patients with AV, and might contribute indirectly to anti-inflammatory activity, which can also be beneficial in AV treatment. Due to strong bactericidal action and a lack of resistance induction, some authors have recommended that BP be added to any antibiotic treatment for AV. However, topical BP will not prevent alterations in systemic flora, including the development of antibiotic-resistant bacteria and changes in the GI tract microbiome, resulting from the use of oral antibiotics. Fixed-dose combination products containing BP and either clindamycin or erythromycin have been approved for the treatment of AV. It should be noted that C. acnes resistance to erythromycin is widespread, resistance to clindamycin has been observed, and cross-resistance among C. acnes strains to both antibiotics is common. The incorporation of BP in combination with a topical antibiotic (used as a fixed combination product), such as erythromycin, has been shown to prevent the emergence and proliferation of antibiotic-resistant C. acnes strains, at least at sites where the BP is applied.

**Retinoids.** Retinoids are an effective alternative to antibiotic treatment for AV and are recommended for both initial and maintenance of AV by the American Academy of Dermatology and the Global Alliance to Improve Outcomes in Acne. Retinoids have keratolytic and anti-comedogenic properties, exhibit direct anti-inflammatory activity via downregulation of Toll-like receptor-2 (TLR-2), and might contribute to dermal matrix integrity and acne scar mitigation through the stimulation of collagen production. Fixed-dose combinations of the retinoid adapalene with BP are also available and are an effective antibiotic-free topical option for AV treatment.

**Dapsone.** Topical dapsone might serve as an antibiotic-free option for AV, though whether currently marketed topical dapsone...
formulations exhibit antibiotic activity and/or affects the cutaneous flora remains unknown. In vitro, dapsone demonstrates antimicrobial activity against a wide range of gram-positive bacteria, with several species (including S. aureus, Staphylococcus epidermidis [S. epidermidis], Streptococcus pyogenes [S. pyogenes], and Streptococcus agalactiae [S. agalactiae]) exhibiting a minimum inhibitory concentration (MIC)50 of 128μg/ml or less.73 A topical dapsone 2% nanoemulsion has shown very high (11,963,837.34μg/cm²) local skin concentrations, and therefore, might affect many commensal and pathogenic bacteria.73,74

CONCLUSION

Our survey results suggest that the majority of patients with AV and parents of young patients with AV are aware of and concerned about the impact of antibiotic resistance. Adult patients with AV and parents of younger patients with AV have a general understanding of the risks associated with antibiotic resistance and many of the potential causes of antibiotic resistance; however, they underestimate the role of topical treatments in the development of antibiotic resistance. Most of the respondents were not aware of antibiotic-free treatment options, but the vast majority were open to using an effective, antibiotic-free treatment for AV on themselves or their children. This study highlights an existing desire among patients with AV for more information from their clinicians about antibiotic resistance risk and alternative therapies for AV.

A full understanding of the mechanisms of action of antibiotics in AV is not known; however, the reduction of C. acnes appears to be one factor that correlates with clinical improvement, and its increasing resistance to antibiotics has been associated with reduced efficacy of antibiotic therapy for AV.75–77 Anti-inflammatory properties of some antibiotics (e.g., tetracyclines, macrolides) might also contribute to their therapeutic effects for AV.30,35,50 Moreover, while antibiotic resistance can develop quickly and is widespread, both oral and topical antibiotics are often prescribed for extended periods. This suggests that the anti-inflammatory contribution of antibiotics to AV treatment is significant.73–82 Subantibiotic dosing of oral antibiotics or combining topical antibiotics with BP are two potential approaches to mitigating the risk of antibiotic resistance while harnessing the anti-inflammatory effects of antibiotics.8,10,33,34 Antibiotics are widely prescribed in dermatology; therefore, judicious use of antibiotics in the treatment of noninfectious dermatological diseases (such as AV and rosacea) and increased education of dermatology patients have the potential for great impact in the stewardship of antibiotic therapies.

REFERENCES

### TABLE 6. Antibiotic-free and subantimicrobial AV treatment options

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>THERAPY</th>
<th>APPROVED FOR AV?</th>
<th>AAD RECOMMENDATION STRENGTH</th>
<th>AAD ACNE SEVERITY RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MILD</td>
<td>MODERATE</td>
</tr>
<tr>
<td>Benzoyl Peroxide</td>
<td>Wash and leave-on products in varying concentrations</td>
<td>Yes (OTC, monograph)</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td>Topical retinoids</td>
<td>Adapalene, tazarotene, tretinoin</td>
<td>Yes (adapalene 0.1%, also OTC)</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td>Combination retinoid/benzoyl peroxide</td>
<td>Adapalene 0.3%/BPO 2.5% gel; adapalene 0.1%/BPO 2.5% gel</td>
<td>Yes</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td>Dapsone</td>
<td>5%, 7.5% gel</td>
<td>Approved for female AV; ethinyl estradiol/norgestimate; ethinyl estradiol/norethindrone acetate/ferrous fumarate; ethinyl estradiol/drosiprenone; ethinyl estradiol/drosiprenone/levomefolate</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td>Oral contraceptives (combined estrogen/progestin)</td>
<td>Various formulations, use in women only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelaic acid</td>
<td>20% cream</td>
<td>Yes (20% cream only; other formulations exist)</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Oral isotretinoin</td>
<td></td>
<td>Yes</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Typical doses range from 50–200mg</td>
<td>Yes</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td></td>
<td>Yes (OTC, monograph)</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td></td>
<td></td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Chemical peels</td>
<td>Glycolic acid, salicylic acid peels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td></td>
<td>No</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Intralesional steroids</td>
<td></td>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Subantibiotic dose doxycycline monohydrate once daily</td>
<td>40mg modified-release doxycycline hyclate twice daily</td>
<td>No</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Niacinamide</td>
<td>2%–4% gel</td>
<td>No (OTC)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Laser/light therapy</td>
<td>Blue and red light devices, infrared, pulsed-dye laser, photodynamic therapy, intense pulsed light, photpneumatic therapy, particle assisted photothermolysis</td>
<td>Some (infrared, photopneumatic therapy)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

AAD: American Academy of Dermatology; OTC: over-the-counter; BPO: benzoyl peroxide

Strength of recommendation is as follows: A: Recommendation based on consistent and good-quality evidence; B: Recommendation based on inconsistent or limited-quality evidence; C: Recommendation based on consensus, opinion, case studies, or clinical evidence.


52. Dunn LK, O’Neill JL, Feldman SR. Acne in adolescents: quality of life, self-esteem, mood,
Acquired Ichthyosis in the Setting of Active Pulmonary Tuberculosis

by SYDNEY E. LIANG, MD; GELAREH HOMAYOUNFAR, MD; EDWARD HEILMAN, MD; and TRACEY N. LIEBMAN MD, FAAD


ABSTRACT

Acquired ichthyosis is an uncommon disorder of cornification. It characteristically presents as symmetric scaling of the skin on the trunk and extensor surfaces of the extremities. It is clinically and histologically similar to ichthyosis vulgaris; however, acquired ichthyosis develops later in life and has been associated with various malignancies, infections, medications, autoimmune diseases, metabolic disorders, and malnutrition. We describe a case of a 35-year-old woman with active pulmonary tuberculosis and a history of breast cancer who presented with a several-month history of a widespread, scaly, pruritic skin eruption. Physical examination revealed fine, scaly patches on the extremities with relative sparing of the flexures and larger, scaly, ichthyosiform patches on the chest and back. Skin biopsy revealed orthokeratotic hyperkeratosis and a diminished granular layer, consistent with a diagnosis of acquired ichthyosis. Further evaluation, including positron-emission tomography/computed tomography scan, revealed hypermetabolic infiltrates and cavitation in the lungs, consistent with active pulmonary tuberculosis; there was no evidence of new or recurrent malignancy. The patient was treated with antituberculosis drugs and topical ammonium lactate cream. With incident cases rarely reported in the literature, this case of new-onset ichthyosis in the setting of active pulmonary tuberculosis highlights the distinctive clinical and histologic features of acquired ichthyosis and emphasizes the relationship of acquired ichthyosis with underlying systemic disease, particularly infection.

KEYWORDS: Active pulmonary tuberculosis, acquired ichthyosis, new-onset

Ichthyoses are a group of cutaneous disorders of keratinization that can be congenital or acquired. They are clinically characterized by dry, rough skin with prominent scaling. Acquired ichthyosis, which is nonhereditary and uncommon, typically presents as symmetric scaling of the skin on the trunk and extensor surfaces of the extremities. While clinically and histologically similar to ichthyosis vulgaris, an autosomal dominant hereditary ichthyosis, acquired ichthyosis (AI) develops later in life and is often associated with various conditions, including infections, malnutrition, malignancies, metabolic disorders, and autoimmune diseases. Several medications have also been associated with the development of AI. Here, we present a case of AI in a patient with active pulmonary tuberculosis.

CASE PRESENTATION

A 35-year-old woman with active pulmonary tuberculosis and a history of breast cancer presented with a several-month history of a widespread, scaly, pruritic skin eruption. Upon physical examination, it was noted that there were fine, scaly patches on the bilateral upper and lower extremities, with relative sparing of the flexural areas. Physical examination also revealed larger, scaly, ichthyosiform patches on the chest and back (Figures 1 and 2). There was no organomegaly or lymphadenopathy. Use of over-the-counter emollients provided no improvement. There was no personal or family history of ichthyosis. She had a remote history of breast cancer, which was in complete remission status following radiation and chemotherapy. At the time of presentation, she was being treated for active pulmonary tuberculosis with rifampin, isoniazid, pyrazinamide, and ethambutol. She was not taking any other medications and had no known drug allergies. The patient was human immunodeficiency virus (HIV)-negative. Punch biopsy of the skin revealed orthokeratotic hyperkeratosis and a diminished granular layer (Figure 3), consistent with a diagnosis of AI. Further evaluation, including positron-emission tomography/computed tomography scan, was performed at an outside hospital and showed hypermetabolic infiltrates and cavitation in the lungs, consistent with active pulmonary tuberculosis. There was no evidence of new or recurrent malignancy. The patient was diagnosed with AI in the setting of active pulmonary tuberculosis. In addition to treatment with antituberculosis drugs, she was treated with topical ammonium lactate cream.

Unfortunately, the patient did not follow-up after her tuberculosis treatment was completed. Therefore, it is unknown whether the AI completely resolved.

DISCUSSION

AI most commonly occurs in adulthood and is often a sign of systemic disease. Clinically and...
Histologically similar to the autosomal dominant ichthyosis vulgaris, AI occurs when there is a disruption in the process of cornification, resulting in hyperkeratosis, scaling, and abnormalities of the skin’s barrier function.\(^3,4\) Although the underlying pathophysiologic mechanism remains unclear, low levels of vitamin A, cholesterol deficiency, impaired lipogenesis, increased levels of tumor necrosis factor alpha, and other alterations in the host’s immune system have all been proposed as potential mechanisms of the skin disease.\(^1,4,12,13\)

Clinically, AI classically presents as xerosis with symmetric, prominent scaling.\(^3\) The severity of skin lesions can range from minor roughness and dryness to desquamation of large, plate-like scales.\(^2\) AI primarily affects the trunk and extremities, with relative sparing of the flexural areas, palms, and soles. Histologically, AI characteristically demonstrates compact ortho-subkera inosis, a diminished or absent granular layer, a reduced rete-papilla pattern, and the absence of an inflammatory infiltrate in the dermis.\(^3,11\)

Often a sign of internal disease, AI is most frequently described in the setting of malignancy.\(^3\) Hodgkin’s disease, the first malignancy reported in association with AI, is the most common.\(^3\) Other malignancies, including non-Hodgkin’s lymphoma, leiomyosarcoma, mycosis fungoides, multiple myeloma, Kaposi’s sarcoma, and carcinomas of the breast, lung, and cervix have been reported.\(^4,14,15\) Therefore, a thorough investigation for underlying disease, including malignancy, is critical to perform once AI has been identified. Although the patient in this case had a remote history of breast cancer, her current presentation of AI was not considered to be associated with her previous diagnosis of breast cancer, as she was in complete remission when the ichthyosis initially developed. Furthermore, upon closer investigation, she had no evidence of recurrent or new malignancy.

AI has also been identified in the setting of systemic conditions other than malignancies, such as infections, metabolic disorders, autoimmune diseases, and nutritional disorders.\(^3–5\) However, despite its association with various infections, including leprosy and HIV/acquired immunodeficiency syndrome (AIDS), incident cases of AI in the setting of tuberculosis have been rarely reported in the literature.\(^6–8\) To our knowledge, only two cases of AI secondary to tuberculosis have been described in the modern literature.\(^16,17\) In both
In a third case in South Africa, hydration, and medications. Treatment should be directed at the underlying disease if one is identified upon evaluation. Generally, treatment of the underlying disorder will result in regression of the ichthyotic lesions. However, hydration, lubrication, and keratolysis with topical agents such as urea and salicylic, lactic, and glycolic acids can be useful to help improve xerosis and remove scaling. Additionally, prophylactic measures, such as antisep tic soaps, should also be considered, since patients with AI are predisposed to skin infections secondary to the impaired barrier function of the skin.

Al, an uncommon disorder of cornification, has been rarely reported among patients with tuberculosis in the modern literature. The present case of AI in the setting of active pulmonary tuberculosis augments the current literature on AI and further emphasizes the significance of AI as a cutaneous marker of an underlying internal disease, particularly infection. The relationship of AI with underlying systemic disease should always be considered when evaluating adult patients presenting with new-onset ichthyosis, and given the variety of diseases, medications, and physiologic conditions reported in association with AI, a comprehensive diagnostic investigation for internal disease is essential.

## REFERENCES

While as many as 1 out of every 5 healthy children contract molluscum contagiosum, this disease and the patients it affects receive very little attention.¹ Quality of life can be negatively affected by a molluscum infection.² Children with the disease may become stigmatized and experience teasing, embarrassment, and social isolation. Up to 82% of parents and caregivers express moderate to great concern about molluscum.³ Lesions may be mostly asymptomatic, but reports indicate that patients do complain about itching, burning, and tenderness.³

Although lesions can resolve within 6 to 9 months, patients typically have the infection for 13 months, and some infections can persist for 2 years or more.²,³ Treatment at the time of diagnosis provides the best chance of decreasing the number of lesions and spread of the disease.³

No current FDA-approved treatment option addresses the problem of successfully treating molluscum.

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Our proprietary drug-device combination, VP-102, has recently completed its 2 Phase 3 CAMP trials.

References
Psoriasis is a chronic, immune-mediated, inflammatory, multisystem disease that affects about two percent of the adult population. In addition to its effects on the skin, psoriasis is associated with several comorbidities, including cardiovascular disease (CVD), metabolic syndrome (defined as the combination of obesity, hypertriglyceridemia, reduced high-density lipoprotein [HDL], hypertension, and high fasting glucose), psoriatic arthritis (PsA), depression, Crohn’s disease, ulcerative colitis, drug-induced nephrotoxicity, chronic kidney disease, and nonalcoholic fatty liver disease (NAFLD). Therefore, patients with psoriasis often have higher mortality and hospitalization rates than those of the general population.

Many psoriatic comorbidities have been linked with the chronic inflammatory nature of psoriasis as well as side effects from psoriasis medications. For example, patients with psoriasis often have increased inflammatory mediators in the blood, such as high-sensitivity C-reactive protein, which are predictive of cardiovascular risk. Furthermore, patients...
with psoriasis often have dysregulation of inflammatory and lipid metabolism genes that have been shown to be related to atherosclerotic CVD. In addition, certain psoriasis medications can increase the risk of CVD.

PsA also shares specific immunopathologic and genetic pathways with psoriasis, providing a possible explanation for the frequent co-occurrence of these diseases. Specifically, patients with psoriasis often demonstrate the upregulation of tumor necrosis factor-alpha (TNF-α), a proinflammatory marker that is central to psoriasis pathogenesis. The upregulation of TNF-α results in the infiltration of T-cells and proliferation of keratinocytes in psoriatic plaques. TNF-α is often upregulated in the synovium of PsA patients. Polymorphisms in the TNF-α promoter have been shown to increase susceptibility of both psoriasis and PsA.

Psoriasis-associated metabolic syndrome is also believed to be caused by increased levels of psoriasis proinflammatory factors, including TNF-α. There is evidence suggesting that the psoriasis proinflammatory mediators TNF-α and interleukin (IL)-6 are linked with depression. In addition, inflammatory bowel disease (IBD) most likely co-occurs in patients with psoriasis because it shares many genetic risks and inflammatory pathways with psoriasis. As an example, patients with psoriasis and IBD often have genetic polymorphisms in IL-23R, which lead to changes in the IL-12/23 pathway.

In addition, kidney disease is directly related to risk factors that are common in patients with psoriasis, such as hypertension, diabetes, obesity, dyslipidemia, and metabolic syndrome. Since these risk factors put patients with psoriasis at higher risk for atherosclerosis, these individuals can become predisposed to developing chronic kidney disease and even end-stage renal disease. Several psoriasis medications, such as methotrexate and cyclosporine, are nephotoxic, thus increasing the likelihood of kidney disease or kidney function exacerbation.

NAFLD is another disease associated with psoriasis and ranges from simple steatosis to cirrhosis. It is thought that the chronic inflammation in psoriasis, caused by proinflammatory adipokines or skin-derived cytokines, can trigger NAFLD by increasing insulin resistance and leading to hepatic lipid accumulation.

Systemic therapies that target psoriasis can reduce the risk of systemic comorbidities. These effects are possible because psoriasis shares many of the mechanisms of disease and inflammation with those of its comorbid conditions. In this article, we review United States Food and Drug Administration (FDA)-approved systemic treatments available for psoriasis, with a focus on their multisystem benefits as well as possible exacerbating characteristics. Knowledge about these treatment options for patients with psoriatic comorbidities can help physicians better individualize care for their most complex patients.

**METHODS**

To investigate the systemic effects of FDA-approved psoriasis treatments on well-documented psoriasis comorbidities, we conducted a PubMed search of articles using the term psoriasis combined with each of the following: systemic treatment, comorbidities, cardiovascular disease, metabolic syndrome, depression, psoriatic arthritis, ulcerative colitis, Crohn’s disease, nephrotoxicity, liver disease, methotrexate, acitretin, cyclosporine, apremilast, etanercept, adalimumab, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab, and guselkumab. For each article, the type of study and endpoints were noted. Phase III clinical trials and meta-analyses of randomized, controlled studies were preferentially chosen, but, if none existed, lower-evidence studies, such as cohort studies, case reports, and case-control studies were used. Some additional sources were found by looking at the references of the articles identified during the initial search.

We used the guidelines by Shekelle et al to document the highest level of available evidence for each medication and indication. Level IA indicates evidence for meta-analysis of randomized, controlled trials (RCTs). Level IB represents evidence from at least one RCT. Level IIA represents evidence from at least one controlled study without randomization. Level IIB represents evidence from at least one other type of quasi-experimental study. Level III represents evidence from nonexperimental descriptive studies, including comparative studies, correlation studies, and case-control studies. Lastly, Level IV represents evidence from expert committee reports, opinions, or clinical experience of respected authorities.

**NONBIOLOGIC SYSTEMIC MEDICATIONS**

Nonbiologic systemic medications that are FDA-approved for psoriasis include methotrexate, acitretin, cyclosporine, and apremilast. A summary of these medications and their level of evidence for psoriatic comorbidities can be found in Table 1.

**Methotrexate.** Methotrexate is an antimetabolite that inhibits the synthesis of deoxyribonucleic acid (DNA) by blocking dihydrofolate reductase and thymidylate reductase. Methotrexate has been shown to have several systemic effects on patients with psoriasis. For example, a large, five-year cohort study showed a decrease in the incidence of cerebrovascular disease and atherosclerosis in patients with psoriasis and rheumatoid arthritis taking a low cumulative dose of methotrexate. Another large cohort study showed that patients with severe psoriasis who were treated with methotrexate had a lower risk of cardiovascular death, myocardial infarction (MI), and stroke as compared to patients treated with topical, phototherapy, and climate therapy. In contrast, a retrospective study showed that methotrexate does not significantly improve metabolic syndrome in patients with PsA. Another study associated methotrexate treatment with an increase in triglycerides and a decrease in HDL in patients with psoriasis. One meta-analysis showed methotrexate’s efficacy in treating PsA, while another demonstrated its benefit in maintaining remission from Crohn’s disease. However, a different meta-analysis revealed no benefit in inducing remission from ulcerative colitis relative to placebo. Methotrexate has also been shown to lead to renal damage and even acute renal failure; therefore, patients should be well hydrated and monitored for drug-drug interactions and creatinine levels while taking methotrexate. Methotrexate has also been shown to decrease renal and creatinine clearance, and thus should be used with caution in patients with renal disease. Patients with NAFLD or any chronic liver disease are at an increased risk for methotrexate-induced hepatotoxicity and hepatic fibrosis. A retrospective case series showed that preexisting liver pathology in patients with psoriasis might be a risk factor for severe hepatotoxicity. In this study, 62.5 percent of the patients with preexisting periportal fibrosis progressed to bridging fibrosis or cirrhosis upon methotrexate treatment. Due to the potential for
acute and chronic hepatotoxicity, the package insert cautions against use of methotrexate in the presence of preexisting chronic liver disease.

**Acitretin.** Acitretin is an oral retinoid that is approved for psoriasis treatment. In addition to its effectiveness in psoriasis, several studies in both humans and animals have shown that retinoids such as acitretin slow atherosclerotic disease progression. However, a cohort study revealed that, in a subset of patients with psoriasis, acitretin was associated with an increased risk of hyperlipidemia. Therefore, these patients should have regular lipid screenings and should be treated for hyperlipidemia to avoid increased CVD risk. More studies are needed to determine the effect of acitretin on CVD risk.

Dermatologists should use caution when prescribing acitretin to patients with obesity and/or high blood lipid levels. Acitretin is considered ineffective for PsA, and the package insert cautions against use in patients with kidney disease. Acitretin is associated with increased risk of hypercholesterolemia and hypertriglyceridemia, but did not show hepatotoxicity on liver biopsy; level III. Should be avoided in NAFLD due to hyperlipidemia. A separate study found that 12 percent of patients with psoriasis treated with cyclosporine developed new-onset hypertension.

**Cyclosporine.** Cyclosporine is an immunosuppressive medication that is approved for psoriasis and has both positive and negative effects on certain psoriatic comorbidities. In a nationwide cohort study, cyclosporine failed to reduce cardiovascular events in patients with psoriasis. Another cohort study showed an association with increased triglyceride levels, increased risk of hypercholesterolemia (odds ratio: 1.34), and increased relative risk for developing arterial hypertension and diabetes (odds ratios: 3.31 and 2.88, respectively) in patients with psoriasis. It is therefore advised that cyclosporine be used only for a short duration, with alternative medications started once the patient’s skin has improved.

A meta-analysis demonstrated that cyclosporine was effective in the treatment of PsA. One meta-analysis showed that high doses or cyclosporine resulted in clinical
improvements in Crohn’s disease, and another showed moderate efficacy of cyclosporine for ulcerative colitis.\textsuperscript{35,36} Cyclosporine should be avoided in patients with renal abnormalities due to nephrotoxicity.\textsuperscript{37} A recent study reported that cyclosporine increased the risk of renal dysfunction in patients with psoriasis and preexisting kidney disease.\textsuperscript{38} According to expert opinion, the length of treatment with cyclosporine correlates with nephrotoxicity. Intermittent treatment with 12-week courses decreases nephrotoxic risk when compared to continuous or long-term therapy.\textsuperscript{39} Additionally, the package insert notes associations with hepatotoxicity and liver injury in some cases, especially in patients with psoriasis and underlying comorbidities.\textsuperscript{33} Specifically, since cyclosporine increases lipid levels, it can potentially exacerbate NAFLD.\textsuperscript{15}

Apremilast. Apremilast is an oral phosphodiesterase-4 inhibitor approved for use in patients with psoriasis and PsA.\textsuperscript{30} It has also been shown to be generally safe in patients with psoriasis and certain comorbidities. A safety analysis that was pooled from two Phase III RCTs showed that patients with psoriasis treated with apremilast for up to 156 weeks did not demonstrate an increased risk of major adverse cardiovascular effects (MACE).\textsuperscript{40} However, additional long-term studies are needed to evaluate the definitive effects on cardiovascular risk reduction in patients with psoriasis.\textsuperscript{35} A meta-analysis showed that apremilast is highly effective in treating PsA.\textsuperscript{41} In regards to kidney disease, one study reported that patients with mild-to-moderate renal impairment did not exhibit changes in renal elimination upon apremilast treatment, while those with severe renal impairment did; therefore, dose reduction is recommended in patients with severe renal dysfunction.\textsuperscript{42} In a Phase III RCT in patients with psoriasis, serum alanine transaminases (ALTs) were elevated three times the upper limit of normal in 0.2 percent of the apremilast group and 0.4 percent of the placebo, and there were no liver-related serious adverse events. Therefore, apremilast might be suitable for patients with psoriasis and comorbid NAFLD.\textsuperscript{43}

TNF-α inhibitors

Etanercept, adalimumab, infliximab, and certolizumab pegol are TNF-α inhibitors that are FDA-approved for psoriasis and PsA. In addition to these indications, adalimumab and infliximab are approved for Crohn’s disease and ulcerative colitis, while certolizumab pegol is approved for Crohn’s disease.\textsuperscript{44} However, with regard to cardiovascular comorbidities, it remains unclear as to whether TNF-α inhibitors significantly reduce the risk of CVD. Some studies have associated TNF-α inhibitors with a decrease in the risks of MI and CVD in patients with psoriasis.\textsuperscript{25,45} In comparison, other studies indicate that TNF-α inhibitors cause no change in MACE.\textsuperscript{46} There is conflicting evidence for individual TNF-α inhibitors, suggesting that additional studies are needed before firm conclusions can be made regarding effects on the cardiovascular system. A summary of these TNF-α inhibitors and their level of evidence for psoriatic comorbidities can be found in Table 2.

Etanercept. There are mixed reports on the effects of etanercept on the cardiovascular system. A retrospective cohort study showed that etanercept decreased the risk of MI, compared to topical agents in patients with psoriasis.\textsuperscript{47} However, a meta-analysis showed no change in the risk of MACE relative to placebo.\textsuperscript{48} A retrospective study reported that etanercept improved metabolic syndrome components (waist circumference, triglycerides, HDL, and glucose) in patients with PsA.\textsuperscript{15} In addition, most studies report that etanercept improves PsA.\textsuperscript{49} However, etanercept does not appear to be effective in treating Crohn’s disease.\textsuperscript{40} A large retrospective study found that etanercept can actually induce or worsen IBD in some patients.\textsuperscript{50} Therefore, physicians should be careful when prescribing etanercept to patients with psoriasis and comorbid IBD.\textsuperscript{4} Etanercept might also help with depression. A Phase III RCT showed that patients with psoriasis who were treated with etanercept had improvements in both depressive symptoms and fatigue as shown on the Hamilton Depression Rating Scale (HAM-D) and Beck’s depression inventory (BDI).\textsuperscript{51} Additionally, a study showed that etanercept treatment for six months did not affect the glomerular filtration rate in patients with psoriasis.\textsuperscript{52} Another study comparing etanercept to phototherapy in patients with psoriasis, NAFLD, and metabolic syndrome found significant reductions ($p<0.05$) in aspartate transaminase to alanine aminotransferase ratio (AST/ALT) and significant increases in insulin sensitivity after 24 weeks of treatment. As insulin resistance is directly correlated with hepatic fibrosis, this study highlights that etanercept seems to be more effective in reducing the risk of hepatic fibrosis than psoralen and ultraviolet A (PUVA) light therapy in patients with psoriasis and NAFLD.\textsuperscript{53}

Adalimumab. There are conflicting findings on the effects of adalimumab on the cardiovascular system. A meta-analysis reported that adalimumab does not appear to cause a change in the risk of MACE.\textsuperscript{46} Another study showed no difference in vascular inflammation in the carotids of patients with psoriasis after 52-week treatment with adalimumab.\textsuperscript{44} However, observational studies have shown reductions in MIs in patients treated with TNF-α inhibitors such as adalimumab. Therefore, further studies are needed to definitively conclude the effect of adalimumab on heart disease in patients with psoriasis.\textsuperscript{55}

A retrospective study showed that adalimumab improved metabolic syndrome components in PsA patients.\textsuperscript{55} Meta-analyses have also shown that adalimumab is effective in both PsA and Crohn’s disease.\textsuperscript{48,56} Furthermore, a meta-analysis demonstrated that adalimumab has a moderate efficacy in ulcerative colitis, but that biologics, such as infliximab, might be more effective.\textsuperscript{57} With regard to depression, an RCT in patients with psoriasis treated with adalimumab showed a significant reduction in depression symptoms, as measured by the Zung Self-rating Depression Scale (ZDS) ($p<0.001$).\textsuperscript{58} Furthermore, another study reported that adalimumab and other TNF-α inhibitors did not have a negative effect on renal function in patients with kidney disease.\textsuperscript{59} A retrospective investigation indicated that, in patients with psoriasis and liver disease who were treated with adalimumab for five years, including three patients with NAFLD, none had progression of liver disease.\textsuperscript{60}

Infliximab. A meta-analysis found no change in the risk of MACE in patients with psoriasis after treatment with infliximab compared to placebo.\textsuperscript{46} However, a pretest–post-test study revealed that infliximab increased body mass index (BMI), as well as HDL and leptin levels, suggesting that lipid profiles and weight should be monitored in patients receiving this treatment.\textsuperscript{61} A meta-analysis showed efficacy in patients with obesity, as infliximab response is independent of BMI, unlike response with other biologics.\textsuperscript{62} Infliximab has been found to benefit patients...
with PsA, ulcerative colitis, and Crohn’s disease. Meta-analyses have demonstrated that infliximab improves PsA, as well as reduces and maintains remission of Crohn’s disease and ulcerative colitis.\(^{46,56,57}\)

Infliximab can also have beneficial effects on psychiatric disorders, although the level of evidence is weak. A case series reported three cases of psoriasis and comorbid depression in which infliximab was effective in stabilizing or symptoms of depression.\(^{63}\)

A separate study showed that infliximab and other TNF-α inhibitors do not have a negative effect on renal function in patients with kidney disease.\(^{59}\) Furthermore, severe liver toxicity is rare in infliximab treatment.\(^{64}\) A case report of a 53-year-old patient with PsA revealed persistent ALT elevations after six infusions of infliximab, as well as chronic hepatitis and mild fibrosis on biopsy.\(^{65}\)

**Certolizumab pegol.** A meta-analysis conducted in patients with rheumatoid arthritis showed that the risk of MACE with certolizumab pegol treatment did not increase with increased drug exposure duration.\(^{44}\) A Phase III RCT in patients with PsA showed improvements in symptoms of PsA upon certolizumab pegol treatment.\(^{58}\) Another Phase III RCT conducted in patients with Crohn’s disease showed modest improvement in response rates, but no significant improvement in remission rates upon certolizumab pegol treatment.\(^{44}\) Certification pegol is currently being investigated in a Phase II clinical trial for its potential use in patients with ulcerative colitis.\(^{60}\)

**OTHER BIOLOGIC MEDICATIONS**

Other biologic medications that are FDA-approved for psoriasis include ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, and tildrakizumab. A summary of these medications and their level of evidence for psoriatic comorbidities can be found in Table 3.

**Ustekinumab.** Ustekinumab is an IL-12/23 inhibitor that offers systemic effects that can be beneficial to patients with psoriasis and certain comorbidities.\(^{29}\) The drug has also been FDA-approved for use in patients with PsA, Crohn’s disease, and ulcerative colitis. However, ustekinumab’s effect on the vascular system is unclear. A meta-analysis showed that patients with psoriasis treated with ustekinumab had no change in the risk of MACE relative to placebo (Table 3).\(^{46}\) Conversely, a recent RCT indicated that ustekinumab might improve myocardial and coronary function in patients with psoriasis,\(^{31}\) while a cohort study reported that its use increased fasting sugar and triglyceride levels.\(^{22}\) However, a separate study reported

<table>
<thead>
<tr>
<th>MEDICATION</th>
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<th>METABOLIC SYNDROME/DIABETES</th>
<th>PSORIATIC ARTHRITIS EFFECTS (ACR 20)</th>
<th>DEPRESSION*</th>
<th>CROHN’S DISEASE</th>
<th>ULCERATIVE COLITIS</th>
<th>DRUG-INDUCED NEPHROTOXICITY/RENAL DISEASE</th>
<th>NAELD OR ANY CHRONIC LIVER DISEASE</th>
</tr>
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<tbody>
<tr>
<td>Etanercept</td>
<td>No change in risk of MACE; level IA(^{46})</td>
<td>Improvement in metabolic syndrome; level III(^{15})</td>
<td>Improved PsA; level IA(^{46}) FDA-approved(^{4})</td>
<td>Decreased depression symptoms and fatigue; level II(^{B})</td>
<td>No efficacy; level IB;(^{4}) potential risk of worsening/induction of Crohn’s disease; level III(^{5})</td>
<td>Potential risk of worsening/induction of ulcerative colitis; level III(^{5})</td>
<td>Treatment for six months did not affect the glomerular filtration rate; level III(^{2})</td>
<td>Reduces AST/ALT ratio and lowers risk for hepatic fibrosis; level III(^{3})</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>No change in risk of MACE; level IA(^{46})</td>
<td>Improvement in metabolic syndrome; level III(^{15})</td>
<td>Improved PsA; level IA(^{46}) FDA-approved(^{4})</td>
<td>Reduced depression symptoms; level II(^{B})</td>
<td>Maintains remission; level IA;(^{46}) FDA-approved(^{4})</td>
<td>Moderate efficacy; level IA;(^{46}) FDA-approved(^{4})</td>
<td>No negative effects on renal function in patients with kidney disease; level III(^{3})</td>
<td>No progression of liver disease in patients with preexisting liver pathology; level III(^{2})</td>
</tr>
<tr>
<td>Infliximab</td>
<td>No change in risk of MACE; level IA(^{46})</td>
<td>Increases BMI, HDL, and leptin levels; level III(^{15})</td>
<td>Infliximab response was same regardless of patients BMI; level IA(^{46})</td>
<td>Improved PsA; level IA;(^{46}) FDA-approved(^{4})</td>
<td>Stabilized or improved manifestations of psychiatric comorbidities; level IV(^{3})</td>
<td>Induced and maintained remission; level IA;(^{46}) FDA-approved(^{4})</td>
<td>Induced and maintained remission; level IA;(^{46}) FDA-approved(^{4})</td>
<td>Persistent ALT elevations after six infusions of infliximab and chronic hepatitis and mild fibrosis on biopsy; level IV(^{3})</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>Risk of MACE with certolizumab pegol did not increase with increased exposure duration; level IA(^{46})</td>
<td><strong>(^{</strong>})</td>
<td>Improved signs and symptoms of PsA; level IB;(^{46}) FDA-approved(^{4})</td>
<td><strong>(^{</strong>})</td>
<td>Modestly improved response rates, but did not significantly improve remission rates; level IB;(^{46}) FDA-approved(^{4})</td>
<td>Currently being investigated in a Phase II clinical trial(^{**})</td>
<td>Currently being investigated in a Phase II clinical trial(^{**})</td>
<td><strong>(^{</strong>})</td>
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**TABLE 2.** FDA-approved TNF-α inhibitors for psoriasis and their level of evidence for psoriatic comorbidities

**Notes:** ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; FDA: United States Food and Drug Administration; HDL: high-density lipoprotein; MACE: major adverse cardiovascular effects; NAELD: nonalcoholic fatty liver disease; MI: myocardial infarction; PsA: psoriatic arthritis

*HADS, HAMS, BDI, and ZDS are different types of depression rating scales

**These medications were either not studied in clinical trials for the noted comorbidity or no significant studies were found during our search.
that ustekinumab did not increase BMI in patients with chronic plaque psoriasis.\textsuperscript{73} These conflicting findings demonstrate the need for further research investigating ustekinumab’s effects on the cardiovascular system.\textsuperscript{75}

A meta-analysis of RCTs showed that ustekinumab is effective in PsA.\textsuperscript{41} Other RCTs have also reported efficacy of ustekinumab use in Crohn’s disease.\textsuperscript{24–26} Ustekinumab has also been demonstrated to help with depression and anxiety in patients with psoriasis. A Phase III RCT that investigated ustekinumab treatment in patients with psoriasis reported significant reductions in the Hospital Anxiety and Depression Scale scores ($p<0.001$ for both depression and anxiety).\textsuperscript{77} According to the package insert, nephrotoxicity has not been reported or formally studied for ustekinumab.\textsuperscript{78} A recent case report described a patient with psoriasis and end-stage renal disease who was on hemodialysis that showed a good clinical response and renal stabilization after ustekinumab treatment.\textsuperscript{79} Furthermore, a retrospective study reported that ustekinumab-induced liver injury was rare and mild in patients with psoriasis, and that ustekinumab is safe for patients with psoriasis and preexisting liver disease.\textsuperscript{80}

**Secukinumab.** Secukinumab is an IL-17A inhibitor that is approved for psoriasis and PsA,\textsuperscript{4} and has been shown to have variable effects on different comorbidities in patients with psoriasis. For example, a meta-analysis showed no difference in the risk of MACE in patients with psoriasis treated with secukinumab compared to placebo.\textsuperscript{83} On the other hand, according to the package insert, clinical trials have reported that a higher percent of patients on secukinumab developed hypercholesterolemia compared to those on placebo.\textsuperscript{82} Another meta-analysis suggested that secukinumab is effective in treating PsA.\textsuperscript{41} Importantly, a Phase II clinical

TABLE 3. Other FDA-approved biologic medications for psoriasis and their level of evidence for psoriatic comorbidities

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<tr>
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<tr>
<td>Ustekinumab</td>
<td>No change in risk of MACE; level IA\textsuperscript{46}</td>
<td>Increased fasting sugar and triglyceride levels; level III\textsuperscript{70} does not increase BMI; level III\textsuperscript{71}</td>
<td>Improved PsA; level IA;\textsuperscript{46} FDA-approved\textsuperscript{82}</td>
<td>Reduced depression and anxiety; level IB\textsuperscript{72}</td>
<td>Strong efficacy; level IB;\textsuperscript{83} FDA-approved\textsuperscript{46}</td>
<td>**</td>
<td>**</td>
<td>Safe for patients with preexisting liver disease; level III\textsuperscript{84}</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>No change in risk of MACE; level IA\textsuperscript{46}</td>
<td>Risk of hypercholesterolemia\textsuperscript{61}</td>
<td>Improved PsA; level IA;\textsuperscript{46} FDA-approved\textsuperscript{82}</td>
<td>**</td>
<td>No efficacy and potential risk of exacerbation; level IB\textsuperscript{72}</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Ikemizumab</td>
<td>No change in risk of MACE; level IA\textsuperscript{46}</td>
<td>No effect on total cholesterol, HDL, triglyceride, fasting glucose level, or blood pressure at 60 weeks; level IA\textsuperscript{46}</td>
<td>Improved PsA; level IB;\textsuperscript{85} FDA-approved\textsuperscript{82}</td>
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<tr>
<td>Brodalumab</td>
<td>No increased cardiovascular risk; level IB\textsuperscript{81}</td>
<td>**</td>
<td>PsA; level IB\textsuperscript{86,87}</td>
<td>Increased risk of suicide in patients with history of depression or suicidality;\textsuperscript{81} no causality between brodalumab and suicidality; level IA\textsuperscript{81}</td>
<td>Exacerbated Crohn’s disease; level IB\textsuperscript{81}</td>
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<td>**</td>
</tr>
<tr>
<td>Guselkumab</td>
<td>No increased risk of MACE; level IB\textsuperscript{81}</td>
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<tr>
<td>Tildrakizumab</td>
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<td>**</td>
<td>**</td>
<td>No new cases or exacerbation of Crohn’s disease; level IA\textsuperscript{81}</td>
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ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; FDA: United States Food and Drug Administration; HDL: high-density lipoprotein; MACE: major adverse cardiovascular effects; NAFLD: nonalcoholic fatty liver disease.

*HADS, HAMS, BDI, and ZDS are different types of depression rating scales.

**These medications were either not studied in clinical trials for the noted comorbidity or no significant studies were found during our search.
trial found that secukinumab exacerbated Crohn’s disease. Therefore, secukinumab should be prescribed with caution in patients with psoriasis and comorbid IBD.

Ixekizumab. Ixekizumab is another IL-17A inhibitor approved for psoriasis and PsA treatment. A meta-analysis showed no difference in the risk of MACE in patients with psoriasis treated with ixekizumab compared to placebo. Similarly, a meta-analysis showed no significant changes between patients with psoriasis treated with ixekizumab or placebo for total cholesterol, HDL, triglyceride, fasting glucose levels or for blood pressure at 60 weeks. However, a Phase III clinical trial suggests that ixekizumab is effective for treating PsA. Brodalumab. Brodalumab, a human immunoglobulin (Ig) G2 monoclonal antibody, inhibits the human IL-17 receptor A and is approved for use in patients with psoriasis. Regarding psoriatic comorbidities, brodalumab was studied in Phase II and III trials and did not appear to increase cardiovascular risk. In addition, multiple Phase II trials have found that brodalumab is effective in patients with PsA. On the other hand, according to the package insert, brodalumab has a suicide and depression warning and should be carefully considered before prescribing to patients with a history of suicidality or depression. However, a recent study that analyzed several psoriasis clinical trials did not find causality between suicide and brodalumab treatment. Thus, more research is needed regarding the safety of brodalumab use in patients with psoriasis and comorbid depression. In addition, a Phase II trial that was conducted for treatment of Crohn’s disease with brodalumab was terminated early because it exacerbated the disease. Therefore, brodalumab is contraindicated in patients with Crohn’s disease.

Guselkumab. Guselkumab is a human IgG1 monoclonal antibody that inhibits the p19 subunit of IL-23, and is approved for use in patients with psoriasis. Phase III trials have shown that guselkumab does not appear to be associated with an increased risk of MACE as compared with placebo.

Tildrakizumab. Tildrakizumab is a humanized IgG1κ monoclonal antibody that inhibits IL-23 p19 and has been recently given FDA approval for use in psoriasis. A recent analysis of three large clinical trials reported that no new cases of IBD or exacerbation of IBD occurred in patients with psoriasis who were taking tildrakizumab.

CONCLUSION
Psoriasis is associated with numerous comorbidities, and selecting the proper treatment can be challenging. Some medications can help with one comorbidity and exacerbate another. Studies of psoriasis medications should continue to explore the effects of study drugs on comorbid disease among patients with psoriasis to help minimize the number of medications required for these patients and to help ensure the application of more personalized therapies that avoid adverse events.

REFERENCES


Orofacial granulomatosis cheilitis (OFC) is an uncommon clinical disorder characterized by persistent and/or recurrent enlargement of the lips. Labial swelling is seen in 75.5 percent of cases of OFG. It is caused by a T-cell-mediated inflammatory response involving cytokines, such as tumor necrosis factor (TNF). The granulomas found in OFG are found in the lamina propria in association with lymphatic vessels. The pathogenesis of swelling is obstruction of the lymphatic drainage by granulomas. First described in 1985 by Leao et al, the clinical presentation can also include midline or angular fissuring of the lip, fissuring of the tongue, gingival enlargement, cervical lymphadenopathy, paralysis of facial nerves, and mouth ulcers. The age of onset of OFG is typically in young adulthood, having no affinity for particular ethnic backgrounds. In an analysis of more than 42 patients and 220 cases, OFG showed a predilection for women, with a mean age of 33.8 years. The etiology of OFG is unknown; however, it has been associated with other granulomatous diseases, such as Crohn's disease and sarcoidosis. It has been suggested that 10 to 37 percent of patients with OFG have Crohn's disease or oral lesions that precede intestinal involvement. Additionally, 54 percent of patients with endoscopic and histologic intestinal abnormalities have OFG with no gastrointestinal symptoms. While OFG mainly affects the labia of the mouth in 40 percent of patients, it has also been reported to be associated with facial nerve palsy (20%) and fissured tongue (40%) as part of a condition known as Melkersson-Rosenthal syndrome.

**CASE REPORT**

A 65-year-old African-American man presented to a dermatology office with chronic, nonpainful swelling of the lower lip present for seven years. The patient was noted to have a past medical history of anxiety, arthritis, noninsulin-dependent diabetes, hepatitis, hyperthyroidism, and prostate cancer in remission status after radiation therapy. Upon physical examination, the lower lip was noted to have a smooth, shiny surface in addition to being enlarged, hard, and pendulous (Figure 1). There was no facial nerve palsy, fissuring of the tongue or lip, crusting, or open wounds. Histological sections revealed lymphatic vascular ectasia with associated mixed lymphoplasmacytic inflammation and scattered, poorly formed, noncaseating granulomas against a background of dermal edema (Figure 2).
2). Periodic acid-Schiff stain for mycosis fungoides T-cell lymphoma or Whipple disease, acid-fast bacilli stain for tuberculosis, and Fite’s stain for leprosy or norcardia returned negative. There were no vasculitides or malignancies detected on histopathology. Chest radiography was completed to rule out active sarcoidosis or tuberculosis. Complete blood count and chemistry workup were normal.

DISCUSSION

Differential diagnoses. OFG can be distinguished from other pathologies such as mucoceles, salivary gland tumors, caliber-persistent labial artery, and angioedema of the lips. Mucoceles present as soft, blue, asymptomatic cystic lesions and can sometimes interfere with speech and chewing.10 Our patient did not report difficulty with chewing or speech and there was diffuse lip swelling. Salivary gland tumors are almost exclusively found on the upper lip and rarely the lower lip.11 Caliber-persistent labial artery is a vascular tumor that presents as a pulsatile elevation of lip; this was not characteristic of the lesion seen on our patient.12 Hereditary angioedema typically develops during childhood and is characterized by recurrent episodes of severe swelling that can develop on the limbs, face, gastrointestinal tract, and airway.13 Episodes can present with shortness of breath, vomiting, abdominal pain, and nausea. However, this did not correspond with the history reported by our patient.

Diagnostic methods. The diagnosis of OFG is via lesional biopsy and treatment consists of lifestyle changes relating to diet if it is associated with irritable bowel syndrome; topical or systematic steroids for swelling; and immune modulators such as azathioprine, methotrexate, and TNF-α inhibitors, such as infliximab. Surgery can be beneficial for severe permanent swelling.6

Treatment. Our patient had an extensive medical history, so we had to risk stratify many of our treatment options. There have been prior studies that showed successful treatment of OFG with intralesional triamcinolone; however, this requires repeated future injections to prevent recurrence.14,15 Intralesional steroid injections with triamcinolone can be contraindicated in diabetics and individuals with psychiatric illness.14 Clofazamine, an oral phenazine dye used in leprosy, has also been used to treat OFG. Clofazamine has antibacterial, anti-inflammatory, and immunomodulatory properties that can be useful in conditions characterized by granulomas.15 The TNF-α inhibitor infliximab has been used in patients with OFG and Crohn’s disease, but topical immune modulators like clofazamine and infliximab can also be challenging to use in individuals with a history of malignancy postradiation therapy.15 Kruse-Losler et al16 showed that reduction cheiloplasty could be used to manage OFG in individuals with a persistent state of the disease.16

Given our patient’s medical history, surgery was required to provide the best clinical outcome, which involved a lower cheiloplasty under local anesthesia. A large, full-thickness wedge of tissue was removed, maintaining an incision on the inner aspect of the lip (Figure 2). Postoperatively, the lips healed, and there was a significant improvement in size and appearance of the lesion (Figure 3).
Sutures were removed on Day 7. At the three-week postoperative follow-up visit, the swelling had resolved and the patient reported improvement in the appearance of his lower lip and increased self-confidence (Figure 3B). At the one-year postoperative follow-up visit, the patient appeared to be doing well, with no recurrence of the granulomatous cheilitis (Figure 3C).

**CONCLUSION**

OFG is a rare, inflammatory, granulomatous disease. The exact etiology is not clear, though there have been links with other inflammatory and granulomatous conditions, including tuberculosis, sarcoidosis, and Crohn’s disease. Because the etiology is still unclear, the ideal treatment and long-term prognosis of OFG is also unknown. Treatment options range from lifestyle management to surgical intervention. Due to the varying associations and treatments, a clinician should have an understanding of the clinical history and features of this condition so as to provide treatment options to the patient based on medical history.

**ACKNOWLEDGMENTS**

The authors wish to acknowledge Sebastian Fuchs MD, PhD, of the Department of Biomedical Sciences, Western University of Health Sciences College of Osteopathic Medicine in Pomona, California.

**REFERENCES**

ABSTRACT

Imiquimod can be used to treat superficial basal cell carcinoma, actinic keratosis, genital warts, and other skin conditions. The adverse events associated with this topical agent commonly include application site irritation, primarily erythema, as well as headache, myalgia, and fatigue. There are usually minimal systemic symptoms. We report the case of a patient who used topical imiquimod 5% cream on nine basal cell carcinoma lesions daily for three days and developed severe muscle weakness and the inability to walk. He fell twice, went to the emergency department, and was given 125mg injection of methylprednisolone. The imiquimod was then discontinued and he recovered almost back to baseline in 48 hours. We hypothesize the patient’s reaction to the imiquimod was due to an immune etiology, potentially involving TLR7 and NF-κB as precipitators of this myopathy. Overall, this report demonstrates a potential severe and rapid adverse reaction to topical imiquimod administration not previously reported in the literature.

KEYWORDS: Carcinoma, basal cell, imiquimod, myalgia

CASE REPORT

Topical Imiquimod Induces Severe Weakness and Myalgias After Three Applications: A Case Report

by SELENA R. PASADYN, BA and ROBERT CAIN, MD

Ms. Pasadyn and Dr. Cain are with the Cleveland Clinic Lerner College of Medicine in Cleveland, Ohio.


Imiquimod is a topical agent that can be used in the treatment of a variety of skin conditions, such as superficial basal cell carcinoma, actinic keratosis, and genital warts. Its mechanism is through stimulation of the immune system, primarily by way of its agonistic effects on Toll-like receptors (TLR) 7 and 8, along with its activation of nuclear factor kappa B (NF-κB). Imiquimod also promotes the release of cytokines, including interferon-a, interferon-g, and interleukin-12, and provokes a primarily TH1 response in order to induce apoptosis.1,2

Imiquimod has been associated with local skin reactions, primarily erythema, upon application.4 Safety trials have reported that application site reactions, such as itching, can occur in 16 to 62 percent of all imiquimod-treated patients.4 Additionally, headache (29%) and upper respiratory tract infection (14%) are common adverse events observed in other trials.5 In a safety trial where imiquimod was used in 800 patients with actinic keratosis, the most commonly reported systemic symptoms were headache (6.0%), myalgia (2.4%), and fatigue (2.3%).6 We report the case of a patient who developed myalgias and the inability to walk after a three-day course of treatment with imiquimod.

CASE PRESENTATION

An 88-year-old Caucasian man with a past medical history of atrial fibrillation, cerebrovascular accident, diabetes, hypercholesterolemia, hypertension, and pacemaker implantation presented to the emergency department with myalgias, labored breathing, wheezing with a cough and chills, and generalized weakness leading to the inability to walk. He had fallen twice in his home in the hours before arriving at the emergency department. His blood pressure was 132/61, pulse was 77, oral temperature was 99.2°F, and his respirations were 20 per minute. A work-up was completed for influenza and cardiac causes. A computed tomography of the head showed no acute findings. The patient showed no signs of a stroke, although a National Institutes of Health Stroke Scale evaluation was not performed. The patient was continued on aspirin and dipyridamole-aspirin. All other physical exam and laboratory findings were unremarkable.

The patient’s medications included imiquimod, atorvastatin, ferrous sulfate, docusate sodium, sertraline, tamsulosin, lisinopril, metformin, pantoprazole, and bisoprolol-hydrochlorothiazide. Three days prior to admittance to the emergency department, the patient began using topical imiquimod.

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0.625mg for eight basal cell carcinoma lesions on his chest and one on his forehead. On the third day of application, the patient began to experience myalgias, labored breathing, and generalized weakness, which progressively worsened. After four hours, the patient’s wife attempted to wipe off the cream when he began to feel like a “limp rag” and was unable to lift his arms and walk. After falling twice, the patient went to the emergency department, where he was given ipratropium bromide/abuterol sulfate inhalation aerosol and a 125-mg injection of methylprednisolone for his exertional shortness of breath and wheezing. The imiquimod was discontinued. It was hypothesized that the sudden muscle weakness and inability to walk was related to the topical imiquimod. Because of the patient’s compromised ambulation and weakness, it was determined that he should be admitted to the hospital inpatient service for observation. The patient recovered over the next two days and was discharged. The incident exacerbated his underlying gait and balance deficiencies, so he remained in physical therapy for three weeks with an ultimate return to his baseline functioning.

**DISCUSSION**

Other case reports of serious adverse events with topical imiquimod usage have been reported. A 78-year-old man using topical imiquimod 5% cream daily for six weeks for a basal cell carcinoma lost 7kg of weight and developed postural hypotension. A 69-year-old woman developed dizziness, nausea, and severe postural hypotension upon a second course of imiquimod treatment, four months following the first course. Three cases of patients using imiquimod for anogenital warts reported a range of side effects, including flu-like symptoms and rash exacerbations, with one patient progressing to intense headache, fatigue, lumbar pain, generalized myalgia, and locomotor difficulties during the third week of imiquimod treatment. Finally, a 67-year-old man developed fever, myalgias, fatigue, and exacerbation of pityriasis rubra pilaris after using imiquimod three times per week for two weeks on his scalp and cheek.

While the symptoms experienced by our patient (e.g., muscle weakness, myalgia, inability to walk) were consistent with previously reported reactions, our patient’s reaction was more severe with a more rapid onset. Prior patients developed symptoms after several weeks of using imiquimod, whereas our patient experienced a severe systemic reaction after three days.

Given these cases, along with imiquimod’s role in exacerbating autoimmune conditions, an immune etiology is suspected. NF-κB has been shown to play a role in inflammatory myopathy, modulating the immune response, myogenesis, and muscle repair. Additionally, TLR7 has demonstrated involvement in inflammatory responses in myositis and has been expressed in inflammatory myopathic tissues. Thus, it is possible that imiquimod, which stimulates rapid synthesis and release of cytokines, such as TLR7 and NF-κB, could potentially be precipitating this inflammatory myopathy. Potentially, the steroid received at the hospital on the first night our patient arrived could have ameliorated the exaggerated immune response, leading to his myopathy.

Finally, it has been shown that a high-fat diet exacerbates imiquimod-induced reactions in mice and that hyperlipidemia can contribute to inflammation. Given that our patient had hypercholesterolemia, history of cerebrovascular accident, a body mass index of 27.44kg/m², and diabetes, he might have had underlying inflammation, making him more susceptible to such a reaction. Regardless, this clinical picture illustrates a significant and immediate systemic reaction to topical imiquimod not previously described. Clinicians prescribing imiquimod should be aware of this potential immune response.

**REFERENCES**

With the increasing demand for noninvasive skin rejuvenation and body contouring procedures, novel radiofrequency (RF) systems and similar technologies have become some of the fastest-growing areas of aesthetic medicine. RF is a minimally invasive, nonablative technique that is commonly used for body contouring, skin tightening, and cellulite reduction. The electromagnetic technology is based on the use of an oscillating electrical current that generates and delivers thermal energy to the deep dermis and subcutaneous fat that stimulates the production of collagen, elastin, and hyaluronic acid, resulting in skin tightening and lifting, while causing minimal damage to superficial structures of the skin. Several modalities, both invasive and noninvasive, exist for the treatment of skin laxity of the arms and legs. Cosmetic surgery is the classical approach to reducing thigh skin laxity; however, there is a risk for linear surgical scarring using this method that some patients might find aesthetically unpleasing. Ultrasound, RF, and cryolipolysis have emerged as nonsurgical alternatives for the treatment of skin laxity; however, though these modalities require less down time by the patient compared to surgery, typical results using these methods have not yet achieved the same level of efficacy as surgical techniques. RF can be delivered at a frequency ranging from 3GHz to 24GHz using monopolar, bipolar, or unipolar devices, which allows for varying levels of depth penetration. To achieve greater efficacy, a new device that combines fractional RF (a subset of bipolar delivery) with microneedling has been developed as a nonsurgical means to reduce skin laxity, primarily on the face and neck. We present a case in which this new RF microneedling device was successfully used to treat thigh skin laxity, secondary to weight loss, and dimpling in an adult female patient.

CASE PRESENTATION

A 39-year-old woman with Fitzpatrick Skin Type II presented to the dermatological clinic with skin laxity and cellulite of the thighs attributed to significant weight loss. The patient had lost 47.7kg (105lbs) over the previous four years with diet and exercise. The patient previously had been treated by our clinic for alopecia totalis, which was stabilized with 5mg of tofacitinib twice daily. The current visit by
patient was prompted following consultation with the surgery department regarding treatment of her thigh skin laxity and cellulite. Wishing to avoid the risks associated with an invasive cosmetic procedure, including the risk of scarring, the patient requested our consultation regarding alternative nonsurgical treatment modalities for skin laxity and cellulite.

The patient was assessed using the Hexsel and Dal’Forno Severity Scale of Cellulite and the Nürnberger-Müller Classification Scale. Although the Nürnberger-Müller classification is considered the current standard in classification of cellulite, it is less detailed than the newer Hexsel and Dal’Forno Severity Scale of Cellulite. The Hexsel and Dal’Forno Severity Scale of Cellulite uses a 0-to-3 numerical score (0=none, 1=mild, 2=moderate, 3=severe) to rate five categories: number of evident depressions (0 to ≥10 or more); depth of depressions (0=no depressions, 3=deep depressions); morphological appearance of skin surface alterations (0=no raised areas, 3=“orange peel,” “cottage cheese,” or “mattress” appearance); and grade of laxity/flaccidity (0=slight, 3=severe draped appearance). The Hexsel and Dal’Forno Severity Scale of Cellulite also includes the Nürnberger-Müller Classification Scale grade (Grades 0–III). The Nürnberger-Müller Classification Scale designates grades as the following: Grade 0=no alteration of skin surface; Grade I=alterations to skin surface only seen by pinching or contracting the skin; Grade II=“orange peel” or “mattress” appearance evident when standing with no skin manipulation; and Grade III=findings of Grade II plus the presence of raised areas or nodules.

Our patient’s initial score comprised the following: number of evident depressions=3 points; depth of depressions=3 points; morphological appearance of skin surface alterations=3 points; laxity=2 points; and Grade III for the Nürnberger-Müller classification=3 points, for a total score of 14.

Following the assessment, cryolipolysis was ruled out as a treatment method due to the patient’s level of skin laxity. RF microneedling was ultimately selected as the most appropriate nonsurgical treatment for our patient’s thigh skin laxity and cellulite.

Two sessions of subcutaneous RF microneedling (PROFOUND™, formally known as ePrime™ or EvoLastin™; Syneron Medical Ltd., Irvine, California) were performed five months apart on the bilateral medial thighs of the patient. An area of skin laxity measuring 15cm×15cm on each thigh was cleansed and anesthetized with 0.5% lidocaine with epinephrine. RF microneedling was administered in two passes, one vertical and one horizontal, for a total of 235 RF injections at a depth of 5.8mm, with the device set at 67°C, four seconds, and pulses administered 5mm apart at a frequency of 5±460 kHz (Figure 1). The parameters were kept the same for the second session five months later, with 214 RF injections.

Reported side effects included superficial ecchymosis and erythema, which resolved 3 to
Several studies have reported a mean 50-percent reduction in thickness of adipose tissue, measured by ultrasound, suggesting RF’s efficacy in fat reduction. RF combined with microneedling for skin tightening has primarily been used for face and neck skin laxity secondary to aging. In a study evaluating the effectiveness of RF microneedling on skin laxity in 42 patients (mean age 55 years), Alexiades-Armenakas et al \(^8\) reported a 95-percent response rate, with a mean improvement of 24.1 percent, at six months. For this study, the authors used their own rating scale, the Alexiades-Armenakas Rhytid and Laxity Grading Scale, which utilizes 0-to-4 scoring method in half-point increments. \(^10\) Additionally, a randomized, controlled study by Alexiades-Armenakas et al \(^2\) evaluating the effectiveness of RF microneedling on skin laxity of the face and neck reported a 16-percent improvement in 15 female patients (mean age 60 years) compared to a 49-percent improvement in patients who underwent surgical facelifts. \(^2\)

**CONCLUSION**

Although RF microneedling has not yet achieved the same level of efficacy as surgery in the treatment of skin laxity and cellulite, RF provides a safe, noninvasive treatment option for those patients who wish to avoid surgery. Generally, patients undergoing treatment with RF microneedling can expect minimal pain and downtime, no scarring, and only mild, transient bruising, erythema, and edema. \(^3\)

**REFERENCES**

Cloderm® Cream is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The most common adverse events with Cloderm® Cream include burning, itching, irritation, dryness, and folliculitis. Cloderm® Cream is contraindicated in patients who are hypersensitive to any of the ingredients of this product. As with all topical corticosteroids, systemic absorption can produce reversible HPA-axis suppression. Full prescribing information is at www.clodermcream.com.

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- Available in 45 g & 90 g tube and 75 g pump

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Vascular Complications after Facial Filler Injection: A Literature Review and Meta-analysis

by GIUSEPPE SITO, MD, PhD; VERONICA MANZONI, MD; and RAFFAELLA SOMMARIVA, MD

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Abstract

Background: Vascular occlusion during the injection of facial fillers is uncommon, but can result in serious adverse events, including necrosis, blindness, and stroke. Objectives: We explored factors that influence the frequency and severity of vascular complications during filler injections. Methods: This was a meta-analysis that included case reports and case series published during the years 2004 to 2016 describing patients who experienced any type of vascular complication after an aesthetic procedure. In addition to the descriptive analysis of the variables retrieved, a logistic regression for predicting the outcome of the vascular event was performed. Results: The analysis included 93 cases described in 30 articles. Blindness was the main consequence of the vascular complications (n=57; 61%). The reported outcome was partial or total recovery in 24 cases (28%) and no improvement in 61 cases (72%). Hyaluronic acid (HA) and autologous fat were the two fillers most frequently involved in vascular occlusions, with autologous fat showing a stronger trend toward no improvement than HA. Involvement of the ophthalmic and retinal arteries was most frequently associated with no improvement than HA. Injury to ophthalmic and retinal arteries was most frequently associated with no improvement than HA. Conclusion: Injury to ophthalmic and retinal arteries during the injection of facial fillers can result in irreversible serious adverse events. Physicians performing filler injections should have a proficient knowledge of anatomy. Keywords: Dermal fillers, vascular complications, hyaluronic acid, autologous fat, collagen, adverse events

Nonsurgical cosmetic procedures are a growing trend worldwide. Included among these minimally invasive techniques are botulinum toxin and soft-tissue augmentation with fillers, which are used to restore tissue loss and correct aging-related rhytides and folds. In 2011, dermal fillers were used in nearly 1.6 million aesthetic procedures, increasing to 2.3 million in 2013 and 5.5 million in 2014.¹ ²

Hyaluronic acid (HA) fillers are the most commonly used injectable fillers, followed by autologous fat. According to the American Society for Aesthetic Plastic Surgery, nearly 900,000 soft-tissue augmentation procedures were performed with HA in 2004.³ ⁴ Other commonly used filler materials include bovine and human collagen (active for 1–3 months before degradation); poly-L-lactic acid, which stimulates endogenous collagen production for up to 15 months; and calcium hydroxylapatite, which offers up to 2 years of activity.² ³ These fillers can all be used for volume replacement and enhancement, such as cheek and chin augmentation, tear trough valley correction, nose reshaping (rhinoplasty), midface volumization, and lip enhancement.³ ⁵ ⁷ Although these procedures are generally considered safe, some local adverse events, aside from the relatively common site-injection reactions (e.g., swelling, tenderness, pain, bruising), have been observed.⁴ ⁸ ¹⁰ These include edema, erythema, scar formation, hyper- and hypopigmentation, infection, abscess formation, herpetic outbreaks, nodular masses, and paresthesia (if a nerve has been pinched during the procedure). While these adverse reactions are usually transient, the common use of three-dimensional facial volume restoration techniques, where the filler material can be injected at any depth, has brought about infrequent but serious and often irreversible vascular complications caused by symptomatic arterial occlusion.⁶ ¹¹ ¹³ These vascular complications can result in persistent skin necrosis, ophthalmoplegia, permanent unilateral or bilateral vision loss, and stroke.¹ ¹¹ ¹³ Ocular and cerebral embolism occurs when the injected material travels from the distal to proximal retinal and ophthalmic arteries, causing sudden, excruciating pain, persistent blindness, and further tissue necrosis.¹¹ ¹³ In addition to fillers accessing the vessel lumen, vascular occlusion can occur by external compression of the stiff gel bolus deposited in direct contact with the vessel wall.¹⁴ ¹⁵ Based on the available literature, some authors have suggested that the injection technique, site, and substance can have significant influence on the level of risk for an adverse vascular event.² ³ ¹¹ ¹² ¹³ However, most of these reviews were not systematic, and the potential influence of other variables on the incidence of adverse events has not been addressed. Therefore, we reviewed the literature regarding vascular

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complications and performed a meta-analysis of the variables that potentially affect the frequency and severity of adverse events.

**METHODS**

*Literature search and article selection.* This meta-analysis included data from case reports and case series of patients experiencing any type of vascular complication after an aesthetic procedure published during the years 2004 to 2016. The main source for article retrieval was the PubMed. Additional sources included Google Scholar, where the search was restricted to the article title, and a case series by Park et al, which provided details from 19 cases previously published as case reports. The database search, performed on December 2016, combined the term *filler* with the following terms: injection (or injected), blindness, visual loss, ophthalmoplegia, artery occlusion, embolism, ischemia (or ischemic), necrosis, and complication. Only full-text articles written in English were considered for eligibility. To be included in the analysis, cases had to report a vascular event occurring after an aesthetic procedure on the human face.

*Data extraction and management.* Data for the meta-analysis were extracted from each case and transferred to a predefined form containing the following variables: case reference, age, sex, injected product, aesthetic procedure, needle diameter, injected volume, person who injected the product, injection site, blood vessel affected, main consequence(s) of the vascular event, concomitant symptoms, time to symptom onset, intervention performed to treat the vascular complication, and outcome. Additionally, diagnostic tests performed to confirm the occurrence of vascular complications were recorded to address the quality of the articles included in our review. The main consequences of a vascular complication were blindness, visual loss, necrosis, and other. Blindness was only considered when explicitly stated in the text, whereas visual loss included a reduction in visual acuity, the perception of light only, and the perception of hand movement only. Time-to-onset values were grouped into three categories: less than one hour postprocedure, 1 to 24 hours postprocedure, and more than 24 hours postprocedure. The final outcome was categorized as no change, partial recovery, or full recovery based on the progress of the main consequence of the vascular complication.

**Statistical analysis.** Categorical variables were described as frequency and percentage, whereas quantitative variables were described as means and standard deviations (SDs). To assess the factors possibly influencing the outcome of vascular complications, the percentages of cases with no improvement and those showing partial or full recovery were compared using the chi-squared test. For variables showing statistically significant differences, a post-hoc analysis was performed by computing the chi-squared values of the adjusted residuals and applying the Bonferroni correction, as described by Beasley et al. A prediction model (multivariate analysis) for the vascular event outcomes was built using logistic regression. The multivariate analysis included all variables regarding events occurring prior to any vascular complication, which showed

### TABLE 1. Characteristics of cases included in the meta-analysis

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>n</th>
<th>%*</th>
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<tbody>
<tr>
<td><strong>Sex (n=93)</strong></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>84</td>
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<tr>
<td>Male</td>
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<tr>
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<tr>
<td>Other</td>
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<td><strong>Main consequence</strong> (n=93)</td>
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<tr>
<td>Blindness</td>
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<td>Visual loss</td>
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<td><strong>Concomitant symptoms</strong> (n=68)</td>
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<tr>
<td>Pain</td>
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<td><strong>Imaging diagnostic tests</strong> (n=80)</td>
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<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>31</td>
<td>38.8</td>
</tr>
<tr>
<td>OCT</td>
<td>4</td>
<td>5.0</td>
</tr>
<tr>
<td>MRI</td>
<td>52</td>
<td>65.0</td>
</tr>
<tr>
<td>Fundus imaging</td>
<td>15</td>
<td>18.8</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Time to symptoms onset</strong> (n=73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 hour</td>
<td>13</td>
<td>17.8</td>
</tr>
<tr>
<td>1–24 hours</td>
<td>47</td>
<td>64.4</td>
</tr>
<tr>
<td>&gt; 24 hours</td>
<td>12</td>
<td>16.4</td>
</tr>
<tr>
<td><strong>Outcome</strong> (n=85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total or partial recovery</td>
<td>24</td>
<td>28.2</td>
</tr>
<tr>
<td>No improvement</td>
<td>61</td>
<td>71.8</td>
</tr>
</tbody>
</table>

* Percentages are shown based on available cases
** More than one category can apply to each case
significant differences when comparing patients without improvement and those with partial or total recovery. The significant threshold was set at \( \alpha = 0.05 \) and all analyses were performed using the Statistical Package for the Social Sciences version 22.0 for Windows software program (IBM Corp., Armonk, New York).

**RESULTS**

**Study selection.** The initial search (including articles retrieved from additional sources) yielded 143 articles, published during the years 2004 to 2016, on vascular events potentially associated with the use of injected fillers (Figure 1). After removing duplicates and excluding non-English articles and those without full-text availability, 86 were considered eligible. Of these, 56 either reported results at injection sites other than the face or did not report any vascular complication, and thus were discarded. The final selection included 30 full-text articles reporting 93 cases: 22 case reports (i.e., articles containing a full description of one or more cases) and seven case series (i.e., articles containing a tabulated description of various cases with vascular complications), and one observational trial (i.e., an article retrieving data from a cohort of patients, including at least one patient experiencing a vascular complication). Most cases (\( n = 62; 66.7\% \)) were reported in Korea, while 15 (15.1\%) were reported in China, 10 (10.8\%) were reported in the United States, three (3.2\%) were reported in Germany, three (3.2\%) were reported in Taiwan, and one (1.1\%) was reported in Japan.

All cases had information regarding the injection site and main consequences of vascular complications. Other key variables, such as injected substance, outcome, and affected blood vessel were reported in 92 (98.9\%), 85 (91.4\%), and 82 (88.2\%) cases, respectively. In 80 cases (86.0\%), the vascular complication and identity of the affected blood vessel were confirmed by at least one of the following imaging techniques: optical coherence tomography, magnetic resonance imaging, ultrasonography, or fundoscopy. In six cases, the affected vessel was deduced from the signs (e.g., necrosis affecting a skin area clearly irrigated by the facial artery) or the treatment outcome (e.g., prostaglandins injected into a vein, leading to the improvement of signs and symptoms). Conversely, in four cases, the physician failed to identify the affected vessel despite performing imaging diagnostic tests. Needle diameter, injected volume, and the professional who performed the injection were only reported in 11, 17, and 13 cases, respectively; due to their low representation in the study sample, these variables were excluded from analysis.

**Case characteristics.** Table 1 summarizes the main characteristics of the cases described in the selected articles. In most cases (\( n = 57; 61.3\% \)), blindness was the main consequence of vascular complication. In five cases (5.4\%), the patients experienced blindness and skin necrosis simultaneously. Whereas blindness was typically assumed to be a consequence of a vascular embolization of the filler material, necrosis was sometimes attributed to compression (Figure 2). However, none of these cases reported evidence regarding the etiology of skin necrosis, and compression was suggested based on the time-to-onset or necrosis progression. Nine patients (9.7\%) experienced neither necrosis nor visual loss or blindness despite a diagnosis of vascular occlusion. Eight patients (8.6\%) reported mild consequences (e.g., pain, erythema), all of which resolved completely. One patient that was injected with autologous fat in the glabella experienced occlusion of the retinal artery with concomitant brain infarction, which resulted in hemiplegia and death.

Theoretically, multiple blood vessels and nerves can be reached by the needle during filler injection (Figure 3). However, the paths of facial, nasal, temporal, and ophthalmic arteries define anatomical areas with increased risk of injury during filler injection (Figure 4). In the case of the ophthalmic artery, the increased risk included occlusion of one of its most important branches: the retinal artery. In our analysis, the ophthalmic retinal arteries accounted for 79.3 percent of the cases in which the affected blood vessel was reported. In addition to the nasociliary artery, other blood vessels affected by the aesthetic procedure were the choroidal vessels, the internal carotid artery, the middle cerebral artery, and the facial vein and artery. The occlusion of the ophthalmic artery was mostly due to injections in the nose (\( n = 18; 42.9\% \) of all cases affecting the ophthalmic artery). Conversely, the occlusion of the retinal artery was mostly due to injections in the

**FIGURE 1. Flow diagram of study inclusion.**

<table>
<thead>
<tr>
<th>Records identified through PubMed search (n=143)</th>
<th>Additional records identified from other sources (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>146 records after duplicates (n=31) removed</td>
<td></td>
</tr>
<tr>
<td>Records screened (n=146)</td>
<td></td>
</tr>
<tr>
<td>Full-text articles assessed for eligibility (n=86)</td>
<td></td>
</tr>
<tr>
<td>Records excluded (n=60)</td>
<td></td>
</tr>
<tr>
<td>Full-text articles excluded (n=56)</td>
<td></td>
</tr>
<tr>
<td>Full-text articles included in the quantitative analysis (n=30)</td>
<td>Number of cases reported: 93</td>
</tr>
</tbody>
</table>

Table 1 summarizes the main characteristics of the cases described in the selected articles. In most cases (n=57; 61.3%), blindness was the main consequence of vascular complication. In five cases (5.4%), the patients experienced blindness and skin necrosis simultaneously. Whereas blindness was typically assumed to be a consequence of a vascular embolization of the filler material, necrosis was sometimes attributed to compression (Figure 2). However, none of these cases reported evidence regarding the etiology of skin necrosis, and compression was suggested based on the time-to-onset or necrosis progression. Nine patients (9.7%) experienced neither necrosis nor visual loss or blindness despite a diagnosis of vascular occlusion. Eight patients (8.6%) reported mild consequences (e.g., pain, erythema), all of which resolved completely. One patient that was injected with autologous fat in the glabella experienced occlusion of the retinal artery with concomitant brain infarction, which resulted in hemiplegia and death. Theoretically, multiple blood vessels and nerves can be reached by the needle during filler injection (Figure 3). However, the paths of facial, nasal, temporal, and ophthalmic arteries define anatomical areas with increased risk of injury during filler injection (Figure 4). In the case of the ophthalmic artery, the increased risk included occlusion of one of its most important branches: the retinal artery. In our analysis, the ophthalmic retinal arteries accounted for 79.3 percent of the cases in which the affected blood vessel was reported. In addition to the nasociliary artery, other blood vessels affected by the aesthetic procedure were the choroidal vessels, the internal carotid artery, the middle cerebral artery, and the facial vein and artery. The occlusion of the ophthalmic artery was mostly due to injections in the nose (n=18, 42.9% of all cases affecting the ophthalmic artery). Conversely, the occlusion of the retinal artery was mostly due to injections in the
glabella (n=18, 55% of all cases affecting the retinal artery).

In 12 cases (12.9%), vascular occlusion progressed to brain infarction, identified by magnetic resonance imaging. Two of these were associated with ophthalmic artery occlusion, whereas eight were associated with retinal artery occlusion. With the exception of two cases—one leading to the patient’s death and another resulting in neurological sequelae—blindness was the main consequence for all patients affected by brain infarction.

Full recovery was reported in seven cases (8.2%): one case of blindness, one of visual loss, and five cases of vascular occlusion with minor consequences. Temporary blindness was caused by an HA injection in the eyebrow. The patient reported foggy and hazy vision immediately after the filler injection; 10 days later, the filler was successfully removed by irrigation and aspiration after creating a temporal limbal incision in the affected eye. Eight days after removal, visual acuity was restored.

Hyaluronidase was used only in 10 of 40 cases in which HA was the cause of vascular occlusion. The time between symptom onset and hyaluronidase injection exceeded three hours in all cases. The dose of hyaluronidase injected, reported only in five cases, ranged from 1,000 to 9,000 units. In five of these cases, blindness was the main consequence of the vascular event; only one patient experienced partial recovery, whereas the rest remained blind despite attempts to remove the HA obstruction by injecting hyaluronidase.

**Factors influencing outcome.** To explore possible baseline factors influencing the outcome, cases with either visual loss or blindness as the main consequence were grouped into two categories based on the outcome: total or partial recovery and no improvement (Table 2). A chi-squared test revealed significant differences in the injected substance, the affected blood vessel, and the time to symptom onset. The post-hoc analysis of the injected substance showed that both HA and autologous fat were significantly associated with no improvement (p=0.001 for the chi-squared adjusted residuals; the significant threshold after the Bonferroni correction was set at α=0.006). A post-hoc analysis of time-to-onset did not reveal significant differences in any of the three categories.

The injected substance, the affected blood vessel, and the time to symptoms onset were included in a logistic regression analysis. The resulting model explained 22 percent of the outcome’s variance, categorized as “no improvement” and “total or partial recovery” (R²=0.219; p=0.027). However, only the affected blood vessel significantly contributed to the overall model (Table 3).

**DISCUSSION**

In this systematic review and meta-analysis of patients with vascular complications occurring after aesthetic procedures, we found that unilateral blindness was the most frequent vascular adverse event associated with cosmetic fillers for facial tissue augmentation. Of these, autologous fat tended to cause more cases of permanent vascular damage. Among all blood vessels affected, the ophthalmic artery was significantly associated with irreversible blindness.

The risk of vascular complications associated with facial aesthetic procedures has been addressed previously in case reports, case series, and literature reviews. In an attempt to further understand the factors influencing the risks and outcomes of vascular complications, we extracted data from individual cases to provide a quantitative approach. Moreover, considering that the number of products available for soft-tissue augmentation has been progressively and continuously increasing for the last 10 years, our
META-ANALYSIS

A review aimed to present an updated picture of vascular complications associated with these fillers. All analyses based on case reports are constrained by the amount and accuracy of the information published. Eighty-six percent of cases reported using imaging diagnostic techniques to verify the diagnosis of vascular occlusion, and most of them provided details regarding key variables such as the injected substance, the blood vessel affected, the outcome of the vascular complication, and the time to symptom onset.

In terms of clinical correlation, one of the most relevant variables was the filler injected. In our study selection, the absolute number of cases with vascular complications after the use of HA and autologous fat was similar. However, considering that HA is, by far, the most used filler in the world for aesthetic procedures, this observation suggests that autologous fat is more often associated with vascular complications than HA. Regarding the recovery rate of vascular complications, both HA and autologous fat were significantly associated with a lower frequency of improvement, but the latter showed a stronger trend towards more severe outcomes. This result is consistent with that of previous reviews, which concluded that autologous fat is the filler material that most frequently causes permanent blindness. In a previous review by Beleznay et al, autologous fat was responsible for 47.9 percent of cases of unilateral permanent blindness, followed by HA (23.5%), collagen (8.2%), poly-L-lactic acid (3.1%), and calcium hydroxylapatite (2%). The increased risk of major vascular complications associated with autologous fat injections could be explained by its large particle size, enabling it to occlude relatively large vessels, such as the ophthalmic artery.

Regarding safety, one of the advantages of HA is the availability of an effective rescue procedure (i.e., hyaluronidase injection into or around the occluded blood vessel). This is one of the reasons why HA has been claimed as the safest substance indicated for tissue augmentation. However, in our review, the number of cases in which hyaluronidase was administered accounted for only a quarter of all cases in which HA was used (10 vs. 40). Furthermore, although the reduced number of cases limited our statistical analysis, it is worth mentioning that only half of these cases resulted in the total recovery of the main outcome related to vascular occlusion. The low recovery rate despite the use of hyaluronidase could be partially explained by the excessive time gap between symptoms onset and hyaluronidase injection, ranging from 3 to 24 hours, with five over seven cases exceeding the four-hour threshold, below which significant differences are seen. These observations suggest that the safer profile of HA compared with autologous fat might be better explained by the properties of the filler material rather than the availability of a rescue procedure. Due to the different physical properties of each substance, the injector’s ability to inject the filler using the right pressure might become an overriding factor influencing the risk of vascular complications. Rapid injections not only result in greater amounts of filler but also limit the capacity of the injector to identify and amend any vascular occlusion. Furthermore, various authors have proposed that, when exerting too much pressure on the plunger, even during the injection of small amounts of filler, arterial pressure can easily be overcome, with the filler reaching deeper arteries. Of course, injection pressure and rate cannot be monitored.

FIGURE 2. Etiological details of blindness caused by A) direct injection of the filler into the vessel lumen and B) skin necrosis caused by either direct injection or vascular compression

FIGURE 3. A) main vascular and B) nerve structures of the face

FIGURE 4. A) depiction of facial arteries illustrating the primary areas of risk and B) their associated anatomical structure
unless the professional performing the injection uses a motorized injector to deliver the filler; hence, this information could not be included in our analysis. Motorized injectors have been proposed as a means to reduce injection risks, as they provide a comfortable flow rate and allow physicians to keep their attention on the patient.\textsuperscript{49,51}

Considering that shorter onset times are more likely to prompt early interventions, we expected time to symptom onset to influence the outcome. However, no significant differences were found between the times before and after one hour. The importance of the time gap between the vascular complication and the intervention was investigated in animal models by Kim et al.\textsuperscript{47} and Cavallini et al.\textsuperscript{48} who found that rescue procedures performed less than four hours after a filler injection significantly reduced the area of necrotic ear skin. However, these studies were based on hyaluronidase injections as rescue procedures, which were barely used in our case collection. Notwithstanding the lack of correlation with other studies, two important drawbacks limited our analysis of the potential influence of the time-to-onset on symptom recovery. First, our dataset did not include time frames more accurate than a 24-hour interval. Second, most of these cases were reported by ophthalmologists with patients showing sudden blindness concurrent with filler injections; therefore, the time from the aesthetic intervention to the onset of vision loss or blindness was assessed retrospectively.

Our results also showed that the affected blood vessel significantly influenced the outcome of the vascular complication. Based on the statistical analysis, ophthalmic artery occlusion was more frequently associated with no improvement than that of other blood vessels, particularly the nasociliary artery. However, individual case examinations revealed that the most dangerous adverse events (i.e., cerebral infarctions) occurred as an ultimate consequence of retinal artery occlusion. Since the retinal artery is a final branch of the ophthalmic artery, it could be assumed that an occlusion of the retinal artery is not likely to have consequences at more central areas. However, as previously discussed, when the tip of the needle penetrates the artery and pressure is applied to the plunger, the filler can reverse the flow in it, moving as a column proximal to the origin of the retinal artery. If the injector exerts more pressure on the plunger for a longer time, the column can reach the origin

### Table 4. Recommendations for preventing and managing vascular complications associated with filler injections

<table>
<thead>
<tr>
<th>PREVENTIVE STRATEGIES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Practitioner</strong></td>
</tr>
<tr>
<td>Deep knowledge of the vascular anatomy is key for preventing vascular complications. In addition to good anatomical background knowledge, practitioners should consider the following aspects:</td>
</tr>
<tr>
<td>- Possible altered anatomical connections in patients with previous surgeries</td>
</tr>
<tr>
<td>- Possible anatomical variants during the development of some blood vessels; precaution should be taken in all face areas, including the upper lip and the wing of the nose</td>
</tr>
<tr>
<td>- Possible extended vascular anastomoses of the nasal region from the perioral to the periorbital region, which might spread the filler from one area to the other.</td>
</tr>
</tbody>
</table>

| **Filler choice** |
| Use reabsorbable products appropriate for the type of correction and therefore for the implant level. Hyaluronic acid fillers are typically noninflammatory products and have a purely mechanical effect, unlike collagen and autologous fat, which seem to activate the “clotting mechanism.” |

| **Injection technique** |
| - Use a delicate retrograde injection technique. |
| - Use very slow injection rates. |
| - Apply light pressure on the syringe plunger (consider the use of an electronic device). |
| - Distribute the product in various points by injecting small amounts of it (i.e. <0.1 mL). |
| - Use a microcannula for deep injections and very viscous products (strongly recommended). |
| - Use fine needles only for superficial injections. |
| - Always aspirate before injection. |

### MANAGEMENT OF COMPLICATIONS

| Immediate pain and/or bleaching of the area (typically a few seconds after injection) |
| Immediately stop injecting; vigorously massage the area. |

| Possible livedoretiocularis or reactive hyperemia (it may occur up to 10 minutes after injection) |
| Treat immediately to restore the vascular flow. |

| Possible arterial insufficiency (slow capillary reloading with acupressure) |
| Apply warm gauzes, topical paste or patch of nitro-derivatives; inject hyaluronidase (independently from the type of filler injected) and apply a local massage. |

| Dark-blue discoloration of the area (it may occur from ten minutes to hours) |
| Contact your plastic surgeon and consider using systemic antibiotics, steroids, aspirin, low molecular weight heparin, prostaglandin. |

| Blisters and boils after a few days |
| Gently disinfect by swabbing the area; pierce the boils and gently favor the spillage of the serum; leave a gras gauze dressing with antibiotic on the skin for no more than three days, then remove it (with clamp and scissors), gently disinfect with 3% boric acid and medicate with a gras gauze dressing and antibiotic ointment until complete repitilization of the area. |

| Necrosis (can appear after days or weeks) |
| Apply antibiotic ointments until eschar demarcation; after removal of the necrotic tissue, apply products intended to improve tissue regeneration such as hydrocolloids gel, plates or collagen tablets on the loss of residual substance. |

| Ocular complications |
| Contact an eye surgeon immediately. In the meantime, try to reduce eye pressure through ocular massage, timolol drops, acetazolamide/manitol, steroids, haemodilution, oxygen therapy, antiplatelet/anticoagulant, thrombolysis, decompression of the eye anterior chamber. |
of the ophthalmic artery, and part of the filler embolus can access the internal carotid artery and subsequently reach cerebral circulation (Figure 2).6,7,12 The use of motorized devices, which enable accurate pressure control, has been proposed to minimize this risk.10,12,13 We found no differences in the outcome when the occlusion occurred in other blood vessels, particularly the nasociliary and facial arteries. Although this observation is consistent with the larger diameter of these vessels, due to the limited number of cases in which there was occlusion in blood vessels other than the ophthalmic and retinal arteries, no firm conclusions could be reached.

Finally, we addressed the influence of the injection site on the outcome of the vascular event. Previous studies reported the glabella and the forehead as areas more frequently associated with blindness and visual loss than the nose.5,7,11 However, in our analysis, injections in the nose accounted for nearly half of the cases of vascular complications and had a similar frequency to that of injections in the glabella. These observations indicated that the nose might not be a safer injection site than the glabella. Lazzieri et al11 suggested that the dorsal nasal artery (i.e., the second terminal branch of the ophthalmic artery) might be responsible for the transmission of emboli following injections in either the glabella or the area proximal to the nasal root. Other injection sites did not yield significant results upon comparing the outcomes of the vascular procedures. However, it is worth mentioning that our analysis was compromised by the fact that a single patient could be injected at various sites, which precludes the identification of the precise injection responsible for the vascular complication.

Limitations. The fact that our meta-analysis was based mostly on case reports implies some limitations that should not be dismissed. Case reports do not always provide all details of the procedures performed. This was particularly notable for some variables identified as risk factors for vascular complications, such as injection technique, injected volume, pressure applied, and needle diameter, which were omitted in most cases. Some of these factors were investigated by Glogau et al,10 who concluded that low injection pressures (i.e., flow rates of less than 0.3 mL/minute) and small volume injections (i.e., less than 0.5 mL) might prevent retrograde embolization of the filler; the authors also recommended avoiding the fan-like technique, which was identified as the main cause of iatrogenic vascular occlusion. Other variables that could not be analyzed because of data omission, despite their potential interest, include the specialty of the person performing the injection, the characteristics of the device (e.g., needle, cannula), and the concentration of hyaluronidase used in the rescue procedure. In addition to a few poor-quality case reports, some of the cases analyzed were not reported by the physician injecting the filler but rather by the ophthalmologist who treated the complication, thus omitting details of the initial aesthetic procedure. The variables most affected by this lack of data were time-to-onset, initial rescue treatment, and concomitant symptoms, which, in most cases, were retrospectively reported by the physician treating the complication. Another potential source of inaccuracy was the ad-hoc data transformation. The heterogeneity in the way the various case reports reported the data prevented the use of pure, raw data for the analysis, which would have been a factor adding simplicity and clarity to our conclusion.

In addition to presenting an updated and quantitative perspective of vascular complications associated with filler injections, the results obtained in our analysis might serve to support a few recommendations to help clinicians who perform filler augmentation procedures avoid vascular adverse events or minimize their consequences. Table 4 provides a list of key recommendations for preventing and minimizing vascular adverse events when performing filler injections. However, as mentioned before, our analysis has important limitations associated with the accuracy and diversity of data presentation in the source articles. Hence, the recommendations we present in Table 4 should not be interpreted as being strictly supported by the results of our meta-analysis; our recommendations are also based on our own insights gained from our extensive experience as plastic surgeons.

CONCLUSION

This meta-analysis provides an up-to-date overview of vascular complications associated with the injection of facial fillers. Our results support the hypothesis that autologous fat is more likely to cause serious vascular events than HA, irrespective of the use of hyaluronidase to treat the vascular occlusion. In light of the information published in the literature, it seems that accidental injection in the terminal branches of the facial artery, particularly the retinal artery, almost invariably leads to unilateral, and occasionally bilateral, blindness. The incidental occlusion of the retinal artery most frequently occurs when treating the nose, but this artery can also be reached from the glabella. Thus, to prevent vascular adverse effects, it is essential that the physician performing the filler injections has a proficient knowledge of anatomy.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the time and effort of Dr. Patrice Delobel, Dr. Kévin Legent, and Dr. Luana Consolini, who provided scientific advice and helped with laying the groundwork of this research. The authors also thank the i2e3 Biomedical Research Institute team for providing statistical and medical writing assistance.

REFERENCES


