HIGHLIGHTS OF
SKIN DISEASE EDUCATION FOUNDATION'S

A CME/CE-CERTIFIED SUPPLEMENT TO
Dermatology News®

43rd Annual
Hawaii Dermatology Seminar®

Topical Therapies for Psoriasis: The Revolution in Vehicles, Combinations, and Novel Agents

Cardiovascular Disease and Psoriasis

Atopic Dermatitis: New Research on Disease Course and Treatment

Acne: Step Up the Use of Nonantibiotic Systemic Therapy

Treatments Beyond Localized Skin Surgery for BCC, SCC, and Localized Melanoma

Onychomycosis: The Most Common Misdiagnosis in Nail Disease

Botulinum Toxins: 2019 Update

Guest Editors

Nathaniel J. Jellinek, MD
Assistant Clinical Professor of Dermatology
Warren Alpert Medical School at Brown University
Providence, Rhode Island
Adjunct Assistant Clinical Professor of Dermatology
University of Massachusetts Medical School
Worcester, Massachusetts
Private Practice
East Greenwich, Rhode Island

Michael S. Kaminer, MD
Associate Clinical Professor of Dermatology
Yale Medical School
New Haven, Connecticut
Adjunct Assistant Professor of Dermatology
Warren Alpert Medical School at Brown University
Providence, Rhode Island
Private Practice
Chestnut Hill, Massachusetts

Alan Menter, MD
Clinical Professor of Dermatology
University of Texas Southwestern Medical School
Dallas, Texas

Jonathan I. Silverberg, MD, PhD, MPH
Associate Professor of Dermatology, Medical Social Sciences, and Preventive Medicine
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Linda F. Stein Gold, MD
Director of Dermatology Clinical Research
Henry Ford Health System
Detroit, Michigan

Christopher B. Zachary, MBBS, FRCP
Professor and Chair, Department of Dermatology
University of California, Irvine School of Medicine
Irvine, California

Original Release Date: August 2019 • Expiration Date: August 31, 2021
Estimated Time to Complete Activity: 2.0 hours

Jointly provided by University of Louisville Continuing Medical Education & Professional Development; ACCME Accredited with Commendation; PIM Postgraduate Institute for Medicine; SDEF Skin Disease Education Foundation; Global Academy for Medical Education

Supported by independent educational grants from **Ortho Dermatologics**, **LEO Pharma Inc.**, and **Galderma Laboratories, L.P.**

A CME/CE-CERTIFIED SUPPLEMENT TO
Dermatology News®

HIGHLIGHTS OF SKIN DISEASE EDUCATION FOUNDATION'S
43rd Annual
Hawaii Dermatology Seminar®

Table of Contents

This continuing medical education (CME/CE) supplement was developed from faculty presentations at the Skin Disease Education Foundation's 43rd Annual Hawaii Dermatology Seminar®, February 17, 2019. The Guest Editors/Faculty acknowledge the editorial assistance of Global Academy for Medical Education and Eileen A. McCaffrey, MA, medical writer, in the development of this supplement. The ideas and opinions expressed in this supplement are those of the faculty and do not necessarily reflect the views of the supporters, Global Academy for Medical Education, the University of Louisville, Postgraduate Institute for Medicine, or the Publisher.

Global Academy for Medical Education

Original Release Date: **August 2019**

Expiration Date: **August 31, 2021**

Estimated Time to Complete Activity: **2.0 hours**

Participants should read the activity information, review the activity in its entirety, and complete the online post-test and evaluation. Upon completing this activity as designed and achieving a passing score on the post-test, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail or you may print it out at that time.

The online post-test and evaluation can be accessed at **https://tinyurl.com/HDS19Supp**.

Inquiries about continuing medical education (CME) accreditation may be directed to the University of Louisville Office of Continuing Medical Education & Professional Development (CME & PD) at cmepd@louisville.edu or 502-852-5329.

CME/CE Accreditation Statements

Physicians: This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Louisville School of Medicine and Global Academy for Medical Education, LLC. The University of Louisville School of Medicine is accredited by the ACCME to provide continuing education for physicians.

The University of Louisville School of Medicine designates this enduring activity for a maximum of 2.0 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Joint Provider Accreditation Statement

In support of improving patient care, this activity has been planned and implemented by Postgraduate Institute for Medicine and Global Academy for Medical Education, LLC. Postgraduate Institute for Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the health care team.

Continuing Nursing Education

The maximum number of hours awarded for this Continuing Nursing Education activity is 2.5 contact hours. Designated for 2.4 hours of pharmacotherapy credit for advanced practice nurses.

Target Audience

This journal supplement is intended for dermatologists, nurse practitioners, registered nurses, physician assistants, and other clinicians who practice medical dermatology and aesthetic medicine.

Educational Needs

Dermatologists can benefit from education on recent developments in many areas of clinical practice. In psoriasis treatment, nearly all patients are prescribed topical therapies. New medications using improved vehicles

Introduction

The Skin Disease Education Foundation's 43rd Annual Hawaii Dermatology Seminar® provided updates on the management of a variety of common skin disorders. This educational supplement summarizes the highlights of clinical sessions presented during this CME/CE conference.

Linda F. Stein Gold, MD, reviews new vehicles that have improved the efficacy of topical treatments. She also describes the increased availability of fixed-dose combination therapy as well as promising new topical agents currently in development. Alan Menter, MD, reviews the increasing evidence that psoriasis is a significant cardiovascular risk factor, which may be due to overlapping inflammatory pathways. He includes information he presented at the conference and data presented by Craig L. Leonardi, MD. Jonathan I. Silverberg, MD, PhD, MPH, provides highlights from his presentation and that of Lawrence F. Eichenfield, MD, on atopic dermatitis, noting that recent studies have upended the idea that this disease has a childhood onset only. Dr. Silverberg describes new thinking about the patterns of the lifetime course of atopic dermatitis and new and upcoming treatments. Many efficacious systemic treatments for acne are underutilized even though they can be used safely, as Julie C. Harper, MD, outlined in her presentation, edited here by Linda F. Stein Gold, MD. Christopher B. Zachary, MBBS, FRCP, provides highlights from a presentation by Scott Fosko, MD, on systemic treatments for basal cell carcinoma, squamous cell carcinoma, and localized melanoma. Nathaniel J. Jellinek, MD, summarizes his talk on onychomycosis, reviewing methods for confirming diagnosis and current treatment. Finally, Michael S. Kaminer, MD, provides an update on botulinum toxins for aesthetic use, drawn partly from a conference presentation by Brooke C. Sikora, MD.

We hope that this information provides a valuable update to your clinical practice.

and fixed-dose combinations have become available, and more are in development. New research linking psoriasis and risk of cardiovascular disease has provided a better understanding of the underlying pathological mechanism and the potential benefit of anti-inflammatory treatment. Recent epidemiologic data on atopic dermatitis in adults have important implications for diagnosis and treatment. In acne treatment, several efficacious systemic treatments are underutilized, and education on their risks and benefits may improve clinical practice. In the treatment of skin cancer, dermatologists should consider several systemic treatments in addition to surgery. Finally, a new botulinum toxin became available recently, and others are in development.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Describe recent data on psoriasis treatment, including new vehicles for topical treatments, fixed-dose combination therapies, and investigational topical medications
- Review the relationship between psoriasis and cardiovascular disease (CVD) and the potential effects of psoriasis treatment on CVD risk
- Describe current research on the temporal patterns of atopic dermatitis onset and resolution and the differences in diagnosis and treatment approach for adult and pediatric patients
- Analyze the efficacy and safety of systemic therapies for acne
- Assess the current nonsurgical treatments for basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and localized melanoma
- Review the options for confirming the diagnosis and data on the use of topical and systemic treatments in the management of onychomycosis
- Assess the advantages and disadvantages of available botulinum toxins used to address patient concerns about facial aging

Disclosure Declarations

Individuals in a position to control the content of this educational activity are required to disclose: (1) the existence of any relevant financial relationship with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients with the exemption of nonprofit or government organizations and non–health-care-related companies, within the past 12 months; and (2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

Nathaniel J. Jellinek, MD, has indicated he has nothing to disclose.

Michael S. Kaminer, MD, has indicated he is a Consultant for Artic Fox, Cutera, Cytrellis, Endo, L'Oréal, Soliton, and Zeltiq.

Alan Menter, MD, has indicated he is on the Speakers Bureau for AbbVie, Celgene, Eli Lilly, Janssen, Novartis, and OrthoDoc.

Jonathan I. Silverberg, MD, PhD, MPH, has indicated he is on the Speakers Bureau for Regeneron/Sanofi; is a Consultant, and/or Advisory Board member for AbbVie, AnaptysBio, Asana, Dermavant, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, Kiniksa, LEO, Menlo, Pfizer, Realm, and Regeneron/Sanofi; and has received Grant/Contracted Research Support from GlaxoSmithKline.

Linda F. Stein Gold, MD, has indicated she is on the Speakers Bureau for Galderma, LEO, Mayne, Pfizer, Sanofi/Regeneron, Taro, and Valeant; is a Consultant for Foamix, Galderma, LEO, Mayne, Menlo, Pfizer, Sanofi/Regeneron, Sol-Gel, Taro, and Valeant; and has received Grant/Contracted Research Support from Foamix, Janssen, LEO, Menlo, Pfizer, and Valeant.

Christopher B. Zachary, MBBS, FRCP, has indicated he is a Consultant for Allergan, Candela, Sciton, and Solta.

University of Louisville CME & PD Advisory Board and Staff Disclosures: The University of Louisville CME & PD Advisory Board and office staff have nothing to disclose, with the following Board Member exceptions: Sathya Krishnasamy, MD – Novo Nordisk (Grant Funding); Ashlee Bergin, MD – Merck Pharmaceuticals (Speaking); Michael Sowell, MD – Amgen (Speaking) and Impax Pharmaceuticals (Grant Funding); Rainer Lenhardt, MD – CSL Behring, Mallinckrodt, and Merck (Speaking).

CME/CE Reviewers: Courtney R. Schadt, MD, Assistant Professor of Medicine, Chief of Dermatology, University of Louisville School of Medicine, Louisville, Kentucky, has nothing to disclose.

Postgraduate Institute of Medicine planners and managers have nothing to disclose.

Global Academy for Medical Education Staff: Shirley V. Jones, MBA; Eileen A. McCaffrey, MA; and Margaret McLaughlin, PhD, have nothing to disclose.

Off-Label/Investigational Use Disclosure

This CME/CE activity discusses the off-label use of certain approved medications as well as data from clinical trials on investigational agents. Such material is identified within the text of the articles.

Topical Therapies for Psoriasis: The Revolution in Vehicles, Combinations, and Novel Agents

Linda F. Stein Gold, MD

Biologics have transformed the experience of psoriasis for the minority of patients who require systemic therapy. The universe of topical therapies that serves most patients with psoriasis[1,2] also has changed and improved in recent years.

New Vehicles Increase Potency

Vehicles in topical therapies affect the absorption of the active agent. Delivering the same topical corticosteroid with different vehicles changes its potency, ie, how rapidly the corticosteroid is absorbed. For example, betamethasone dipropionate 0.05% in an ointment is considered a class I super potent steroid, whereas the same ingredient at the same concentration in a spray is a class III steroid. As a lotion, betamethasone dipropionate is a class V mid- or lower-mid-potency steroid.[3] But potency cannot be predicted by the vehicle alone. The effect of the vehicle on potency may vary with the drug; potency depends on the interaction of the agent and the vehicle.

The potency classification system for corticosteroids is based on the vasoconstrictor effect,[4] which assesses how well a medication passes through the stratum corneum, through the epidermis, through the dermis, and deeper into the lower dermis into the systemic circulation. The vasoconstriction test does not measure how well the drug stays in the skin. The measure of potency has become somewhat archaic as it does not capture the mechanism of some newer vehicles, which deposit the therapeutic agent into the epidermis and dermis, at the site of action. For topical medications with these advanced formulations, the measure of potency may underestimate the agent's efficacy.[5] Considering betamethasone dipropionate again, the emollient spray formulation (class III) has demonstrated similar efficacy to that of a super potent formulation (augmented betamethasone dipropionate 0.05% lotion) in patients with psoriasis.[6]

The impact of vehicle on efficacy can also be seen with halobetasol, which is available in a newer enhanced delivery system, a lotion formulation. Halobetasol 0.01% in this new formulation was similar in efficacy to a lotion with 0.05% halobetasol.[7]

Yet another example of changing the vehicle to improve efficacy can be seen with the fixed-dose combination of calcipotriene and betamethasone dipropionate. The ointment contains undissolved crystals, but when 2 propellants, dimethyl ether and butane, are added to create a foam, the medications appear to dissolve and are better able to penetrate the skin. Efficacy was greater with the new foam formulation.[8]

A new proprietary technology for delivering topical products consists of oil droplets containing active agents encapsulated by a thin film of surfactants. Calcipotriene 0.005%/betamethasone dipropionate 0.064% formulated using this technology was developed as a cream with rapid absorption and cosmetic acceptability. A recently completed phase 3 study comparing its efficacy to that of calcipotriene/betamethasone dipropionate topical suspension for mild to moderate psoriasis found greater efficacy with the newer formulation of the encapsulated oil droplets.[9]

Fixed-Dose Combination: Halobetasol Propionate 0.01%/Tazarotene 0.045% (HP/TAZ) Lotion

The US Food and Drug Administration (FDA) recently approved this fixed combination for treatment of psoriasis.[10] In a pooled analysis of two phase 3 trials, HP/TAZ demonstrated efficacy (defined as clear/almost clear and ≥2-grade Investigator's Global Assessment improvement) superior to that of vehicle as early as 2 weeks. About 41% of patients achieved the primary endpoint with HP/TAZ at week 8, compared with 10% of patients randomized to vehicle ($P<0.001$).[11] About one-third of patients treated with HP/TAZ maintained efficacy 4 weeks after treatment cessation (33% vs 9% for vehicle; $P<0.001$).[11]

The combination also demonstrated a synergistic effect in a post hoc analysis of phase 2 trial data, with higher efficacy than that observed with the sum of its individual components.[12] A phase 2 comparison of HP/TAZ with each individual agent as well as with vehicle found that application site reactions (pain, pruritus, erythema) occurred roughly twice as often with tazarotene alone as with the combination product (22.4% [n=13] and 10.2% [n=6], respectively),[13] suggesting that adding the steroid ameliorated the irritation associated with tazarotene.

Investigational Topicals

Aryl Hydrocarbon Receptor (AhR) Agonist

Tapinarof, an AhR transcription factor agonist, has demonstrated multiple actions in experimental studies, suggesting possible benefit in psoriasis and atopic dermatitis. These effects include reduced Th17 cells and increased concentration of skin barrier proteins associated with epidermal differentiation.[14] Evidence suggests that the AhR modulates Th1/Th2 balance.[15]

A phase 2b study evaluated 2 concentrations (0.1% and 0.05%) and 2 dosing regimens (once and twice daily) of tapinarof compared with vehicle controls for 12 weeks of therapy for patients with psoriasis of varying severity.[16] All 4 treatment groups showed significantly higher rates of efficacy than vehicle.

Janus Kinase (JAK) Inhibitor

JAK inhibitors disrupt a number of proinflammatory cytokine pathways. Ruxolitinib (INCB018424), a topical JAK1 and JAK2 inhibitor, is under study for treatment of psoriasis and atopic dermatitis. A small proof-of-concept study evaluated 28 days of therapy for psoriasis with ruxolitinib 1.0% twice daily and 1.5% once or twice daily and found improvement across all cohorts.[17]

Phosphodiesterase (PDE)-4 Inhibitor

The topical PDE-4 inhibitor crisaborole is FDA-approved for the treatment of mild-to-moderate atopic dermatitis.[18] Crisaborole also has been studied in psoriasis (clinicaltrials.gov; ID NCT01300052).

Summary

Innovations in psoriasis therapy have affected topical and systemic therapies. New vehicle technologies are designed to increase skin penetration, absorption, and patient acceptance. Fixed combinations of the agents that have been the mainstays of topical therapy for many years may improve efficacy and adverse event profiles compared with the individual ingredients alone. Investigational topicals for psoriasis include agents with novel mechanisms of action such as an AhR agonist and a JAK1/JAK2 inhibitor.

References on page 14

Cardiovascular Disease and Psoriasis

Alan Menter, MD

The epidemiologic association of psoriasis with cardiovascular (CV) risk is well known.[1] Recent studies have illuminated the pathophysiology underlying this association. Additionally, biologic agents approved by the US Food and Drug Administration for psoriasis therapy have the potential to reduce the risk of CV events in patients with psoriasis.

Cardiovascular disease (CVD), obesity, and psoriasis are all systemic inflammatory disorders. Psoriasis is associated with an elevated risk for obesity[2] and myocardial infarction (MI),[1] as well as with multiple CV risk factors.[2] Severe psoriasis is associated with an increased risk of CV death independent of CV risk factors.[3,4]

Imaging has revealed significantly more vascular inflammation in patients with severe psoriasis (n=4; body surface area >10%) compared with age- and sex-matched controls (n=4). A nested case-control study used [^{18}F]-fluorodeoxyglucose positron emission tomography–computed tomography (FDG-PET/CT) to detect and compare systemic inflammation in the study participants. FDG-PET/CT revealed increased inflammation in multiple aorta segments, including the coronary, hepatic, renal, and femoral arteries compared with controls. The difference remained significant after adjustment for CV risk factors (P<0.001).[5,6]

Chronic inflammation may explain why the Framingham Risk Score underestimated the 10-year incidence of CVD events in patients with psoriatic arthritis. Actual 10-year cumulative incidence of CVD events in a population-based cohort of 126 patients with psoriatic arthritis and no history of CV events was 17% (95% CI, 10-24), nearly twice as high as that predicted by the Framingham Risk Score.[7]

The coronary artery calcium score offers another way to quantify subclinical CV risk. A study measured coronary artery calcium scores in patients with moderate-to-severe psoriasis (n=129) compared with individuals with type 2 diabetes (n=129) and healthy controls (n=100). The prevalence of moderate-to-severe coronary calcification was similar for patients with psoriasis and patients with type 2 diabetes and roughly three times greater than that of controls.[8]

Do Psoriasis Therapies Reduce Risk of CVD?

Because inflammation is central to the pathophysiology of both psoriasis and CVD, investigators have evaluated whether anti-inflammatory psoriasis therapies affect the risk of CVD. Multiple observational studies report a benefit.

Analysis of nationwide databases in Denmark revealed that treatment with biologic agents (80% received tumor necrosis factor-alpha [TNF-α] inhibitors) or methotrexate was associated with lower CVD event rates over a mean follow-up of 18 months compared with patients given other antipsoriatic therapies. Adjusted hazard ratios (HRs) for the composite endpoint of death, MI, and stroke were 0.28 (95% CI, 0.12-0.64) with biologic therapies and 0.65 (95% CI, 0.42-1.00) with methotrexate.[9]

Retrospective cohort studies using claims databases have demonstrated that in patients with psoriasis, TNF-α inhibitor use was associated with:

- Significantly lower risk of MI compared with topical therapy[10]
- Significantly lower risk of major CV events (hospitalization for MI, stroke, transient ischemic attack, unstable angina) compared with methotrexate. Every additional 6 months of TNF-α inhibitor therapy was associated with an 11% reduced risk of a major CV event (P=0.02)[11]
- Significantly lower risk of major CV events compared with phototherapy (adjusted HR, 0.77; P<0.05). As in the study comparing TNF-α inhibitor therapy with methotrexate, longer use of TNF-α inhibitors was associated with increased risk reduction[12]

Crude incidence rates of atrial fibrillation and major adverse cardiovascular events (MACE) were similar with ustekinumab and TNF-α inhibitor use in patients with psoriasis or psoriatic arthritis, according to a retrospective claims data analysis.[13] However, studies examining the relationship between CV events and ustekinumab are mixed. According to a retrospective analysis of clinical trials, the rate of MACE observed with the anti–IL-12/IL-23 agents (ustekinumab and briakinumab) did not differ from that seen with placebo (P=0.12 for risk difference between anti–IL-12/23 agents and placebo). The rate of MACE observed with TNF-α inhibitors also did not differ from that reported with placebo (P=0.94 for the risk difference between anti–TNF-α agents and placebo). MACE was defined as a composite of MI, cerebrovascular accident, or CV death during the placebo-controlled phase of treatment.[14]

In a recent observational study, biologic therapy in a small number of patients with moderate-to-severe psoriasis improved coronary plaque indices. Patients with psoriasis initiating biologic therapy (n=89) and patients who elected not to receive biologic therapy (n=32) were followed prospectively, with total coronary plaque burden and plaque subcomponents measured at baseline and 1 year. Biologic therapy was associated with a small, ie, 6%, reduction in the noncalcified plaque burden (P=0.005 vs baseline), as well as decreases in fibro-fatty burden (P=0.004) and necrotic burden (P=0.03). Fibro-fatty burden increased significantly in the non-biologic therapy group (P=0.004), but no other significant changes were noted in those patients.[15]

Conclusion

A growing body of evidence shows that moderate-to-severe psoriasis is a significant CV risk factor. The mechanisms underlying this relationship are not well defined, but shared inflammatory pathways between psoriasis and atherosclerosis are likely involved.[16] Multiple studies,[10-12,15] although not all,[14] demonstrate that biologic therapy for psoriasis reduces the risk of CV events. Long-term studies, ie, up to 5 years, will be required with a larger number of patients to definitely show that biologic agents can reduce the incidence of CVD in patients with moderate-to-severe psoriasis. New anti-inflammatory agents are currently being developed as treatments for CVD.[17,18]

References on page 14

Atopic Dermatitis: New Research on Disease Course and Treatment

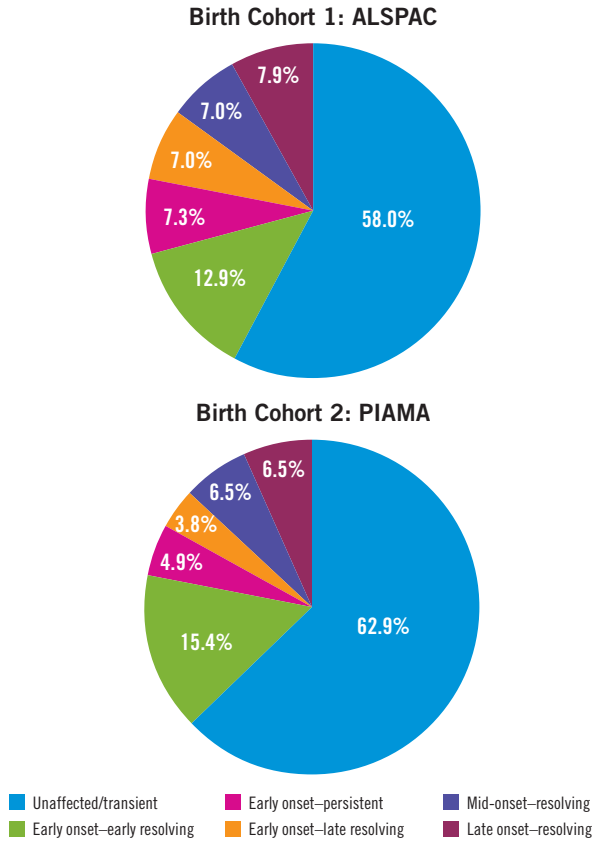
Jonathan I. Silverberg, MD, PhD, MPH

Recent observational findings have upended the conception of atopic dermatitis (AD) as a disease of early childhood onset and late childhood/adolescent resolution marked mostly by cutaneous symptoms and comorbidities. Childhood AD may persist into adulthood, and adult onset is now well established. Novel treatments are also becoming available after years with no new therapies. Crisaborole and dupilumab are now among AD treatment options. Many systemic and topical therapies are in development.

Variable Course of AD

Longitudinal follow-up of 2 large birth cohorts has revealed multiple patterns of AD development. The stereotypical course of early onset–early resolving disease was the most common, but sizable proportions of children who developed the disease followed other patterns (**Figure**).[1] Although many children outgrow AD by or during adolescence, the disease sometimes persists into later adolescence and adulthood. A 25-study meta-analysis reported that roughly 26% cases of AD began in adulthood (≥16 years old).

FIGURE. Diverse Patterns of Atopic Dermatitis Onset and Resolution



ALSPAC, Avon Longitudinal Study of Parents and Children; PIAMA, Prevention and Incidence of Asthma and Mite Allergy.
Source: Paternoster L, et al. *J Allergy Clin Immunol.* 2018;141:964-971.[1]

Pediatric and Adult Prevalence

Two recent US-based surveys yielded almost identical prevalence figures of AD in adults—7.2% and 7.3%—for a total of about 16.5 million adults with AD.[3,4] In the United States, the 12-month AD prevalence is 10.7% in children age 17 years and younger.[5] Diagnosing AD in adults is more difficult than diagnosing AD in children. Identifying AD in adults requires not only awareness of the disorder but evaluation of a larger differential diagnosis than in children, including psoriasis, contact dermatitis, and T-cell lymphoma.

How Often Is AD Moderate or Severe?

About one-third of children with AD have moderate or severe disease.[6] Rates of moderate-to-severe disease were higher in adults with AD, at 47%.[4]

Defining Moderate-to-Severe AD in Clinical Practice

A recent consensus report established criteria for defining moderate-to-severe disease in clinical practice (**Table 1**).[7] Patients with more than 10% of their body surface area affected who have been untreated or undertreated and who respond well to topical therapies may have mild disease.

Treatment

Older Agents

Many commonly used agents, including antimicrobials, antiseptics, and antihistamines, are not approved by the US Food and Drug Administration (FDA) for AD, and no evidence supports their use. Efficacious older therapies include cyclosporine, corticosteroids, and methotrexate. The newest agents are the topical treatment crisaborole and the systemic biologic dupilumab. The most recent American Academy of Dermatology guidelines predate the newest therapies for AD,[8,9] but the Atopic Dermatitis Yardstick attempts to fill the gap by incorporating current treatments into the algorithm.[10]

Crisaborole

Crisaborole, a topical phosphodiesterase-4 inhibitor, was FDA-approved in 2016 for use in AD. Recently it was shown to improve quality of life (QOL) for both patients and their families after 29 days of therapy. The vehicle also improved QOL from baseline, meeting the threshold for a minimal clinically important difference. But improvements with crisaborole significantly exceeded those observed with the vehicle, a petrolatum-based moisturizer.[11]

TABLE 1. Clinical Criteria for Moderate-to-Severe AD[7]

- Involvement of ≥10% BSA
- Regardless of degree of BSA involvement:
  - Individual lesions with moderate-to-severe features
  - Involvement of highly visible areas or areas important for function (eg, neck, face, genitals, palms, and/or soles)
  - Significantly impaired QOL

Clinicians should actively assess the impact of disease on QOL during clinic visits (ie, sleep, pruritus, activities of daily living, and work).

AD, atopic dermatitis; BSA, body surface area; QOL, quality of life.

Dupilumab

Dupilumab, an anti–interleukin (IL)-4, anti–IL-13 injectable biologic agent, has received FDA approval to treat AD in adolescents (age ≥12 years) as well as adults.[12] Phase 3 data showing efficacy in an adolescent population with moderate-to-severe AD were presented recently.[13] Interestingly, roughly half of the patients in this trial had asthma at baseline, and dupilumab is FDA-approved as add-on therapy in asthma for adolescents with an eosinophilic phenotype or dependent on oral corticosteroids.[12] This agent may have multiple benefits in this subset of patients.

New Systemic Therapies

At least 5 compounds are in phase 3 development (**Table 2**) and 15 compounds are in phase 2 development for systemic treatment of AD.

New Topical Therapies

Several new agents are in phase 3 development for use as topical therapies in AD (**Table 3**).[14-16]

Vitamin D Supplementation

Vitamin D deficiency was correlated with AD severity in children, but vitamin D supplementation did not significantly improve disease severity.[17]

Summary

For many patients, AD extends beyond childhood or starts after childhood. Topical crisaborole and the biologic agent dupilumab offer additional treatment options to alleviate the substantial disease burden associated with AD. Additional new topicals and systemic therapies for treating AD are in clinical development.

References

1. Paternoster L, Savenije OEM, Heron J, et al. Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. *J Allergy Clin Immunol.* 2018;141(3):964-971.
2. Lee HH, Patel KR, Singam V, Rastogi S, Silverberg JI. A systematic review and meta-analysis of the prevalence and phenotype of adult-onset atopic dermatitis. *J Am Acad Dermatol.* 2019; 80(6):1526-1532.e7.
3. Hua T, Silverberg JI. Atopic dermatitis in US adults: epidemiology, association with marital status, and atopy. *Ann Allergy Asthma Immunol.* 2018;121(5):622-624.
4. Silverberg JI, Gelfand JM, Margolis DJ, et al. Patient burden and quality of life in atopic dermatitis in US adults: a population-based cross-sectional study. *Ann Allergy Asthma Immunol.* 2018;121(3):340-347.
5. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol.* 2011;131(1):67-73.
6. Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. *Dermatitis.* 2014;25(3):107-114.
7. Boguniewicz M, Alexis AF, Beck LA, et al. Expert perspectives on management of moderate-to-severe atopic dermatitis: a multidisciplinary consensus addressing current and emerging therapies. *J Allergy Clin Immunol Pract.* 2017;5(6):1519-1531.
8. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol.* 2014;71(2):327-349.
9. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014;71(1):116-132.
10. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. *Ann Allergy Asthma Immunol.* 2018;120(1):10-22.e12.
11. Simpson EL, Paller AS, Boguniewicz M, et al. Crisaborole ointment improves quality of life of patients with mild to moderate atopic dermatitis and their families. *Dermatol Ther (Heidelb).* 2018;8(4):605-619.
12. Dupixent [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals; March 2019.
13. Simpson EL, Paller AS, Siegfried EC, et al. Dupilumab efficacy and safety in adolescents with moderate-to-severe atopic dermatitis: results from a multicenter, randomized, placebo-controlled, double-blind, parallel-group, phase 3 study. Presented at: 27th European Academy of Dermatology and Venereology Congress; September 15, 2018; Paris, France. Presentation #4640.
14. Peppers J, Paller AS, Maeda-Chubachi T, et al. A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis. *J Am Acad Dermatol.* 2019;80(1):89-98.e83.
15. Hanifin JM, Ellis CN, Frieden IJ, et al. OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): a phase-II randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol.* 2016;75(2):297-305.
16. Lee YW, Won CH, Jung K, et al. Efficacy and safety of PAC-14028 cream–a novel, topical, nonsteroidal, selective TRPV1 antagonist in patients with mild-to-moderate atopic dermatitis: a phase IIb randomized trial. *Br J Dermatol.* 2019;180(5):1030-1038.
17. Lara-Corrales I, Huang CM, Parkin PC, et al. Vitamin D level and supplementation in pediatric atopic dermatitis: a randomized controlled trial. *J Cutan Med Surg.* 2019;23(1):44-49.

TABLE 2. Targeted Systemic Treatments for AD in Phase 3 Development

Drug	Treatment Type	Target	Trial Identifier
Tralokinumab	Biologic	IL-13	NCT03363854
Baricitinib	Small molecule	JAK1/JAK2	NCT03435081
Abrocitinib (PF-04965842)	Small molecule	JAK1	NCT03796676
Upadacitinib	Small molecule	JAK1	NCT03569293
Tradipitant	Small molecule	NK1 receptor	NCT03568331

AD, atopic dermatitis; IL-13, Interleukin 13; JAK, Janus kinase; NK1, neurokinin1.
Trial identifier: www.clinicaltrials.gov.

TABLE 3. Topical Treatments for AD in or Near Phase 3 Development

Drug	Target	Trial Identifier
Delgocitinib	All JAK	NCT03725722
Ruxolitinib	JAK1/JAK2	NCT03745638 NCT03745651
Tapinarof[14]	Aryl hydrocarbon receptor	—
OPA-15406[15]	PDE-4	NCT03911401
IDP-124	Not reported	NCT03058783
PAC-14028[16]	TRPV1	NCT02965118

AD, atopic dermatitis; JAK, Janus kinase; PDE4, phosphodiesterase 4; TRPV1, transient receptor potential vanilloid subfamily, member 1.
Trial identifier: www.clinicaltrials.gov.

Acne: Step Up the Use of Nonantibiotic Systemic Therapy

Linda F. Stein Gold, MD

Despite acne's high prevalence (~50 million people in the United States[1]), its physical and psychological morbidity during adolescence, and association with lifelong scarring, dermatologists do not always treat it aggressively. The treatment goal should be to have clear or almost clear skin, although not every patient will reach that goal. Greater use of combination oral contraceptives (COCs), spironolactone, and oral isotretinoin in appropriate patients can improve outcomes, reduce the use and duration of oral antibiotics, and lower the risk of inducing antibiotic resistance, in line with the American Academy of Dermatology (AAD) guidelines.[1]

Off-label use of spironolactone for acne in adolescents and adults ages 12 to 40 years increased substantially from 2004 through 2013, based on a retrospective claims data analysis. Use of oral contraceptives (OCs), isotretinoin, and antibiotics did not change substantially during this time period, however.[2] Mean duration of oral antibiotic therapy was about 6 months, double the duration recommended in the AAD guidelines.[1,2]

Research results discussed below debunk some misconceptions about nonantibiotic systemic agents that may limit their use.

Combination Oral Contraceptives: Risks vs Benefits

Risk of Venous Thromboembolism (VTE)

COCs roughly double the risk of VTE in women of reproductive age compared with non-users of the same age range, from 4 to 5 per 10,000 women per year to 8 to 9 per 10,000 women per year. But these risks are still much lower than the VTE risk associated with a third-trimester pregnancy and puerperium (**Figure**).[3] Therefore, preventing pregnancy in sexually active women reduces the risk of VTE more than COCs raise the risk of VTE. The risk-benefit balance is different in someone who is not sexually active.

Effect on Risk of Cancers

COCs have been shown to reduce the risk of colorectal, endometrial, and ovarian cancer, while increasing the risk of cervical and breast cancer.[4,5]

Interactions With Antibiotics

Rifampin and griseofulvin are the only anti-infectives documented to interact with COCs and reduce their effectiveness.[1,6,7]

Contraindications

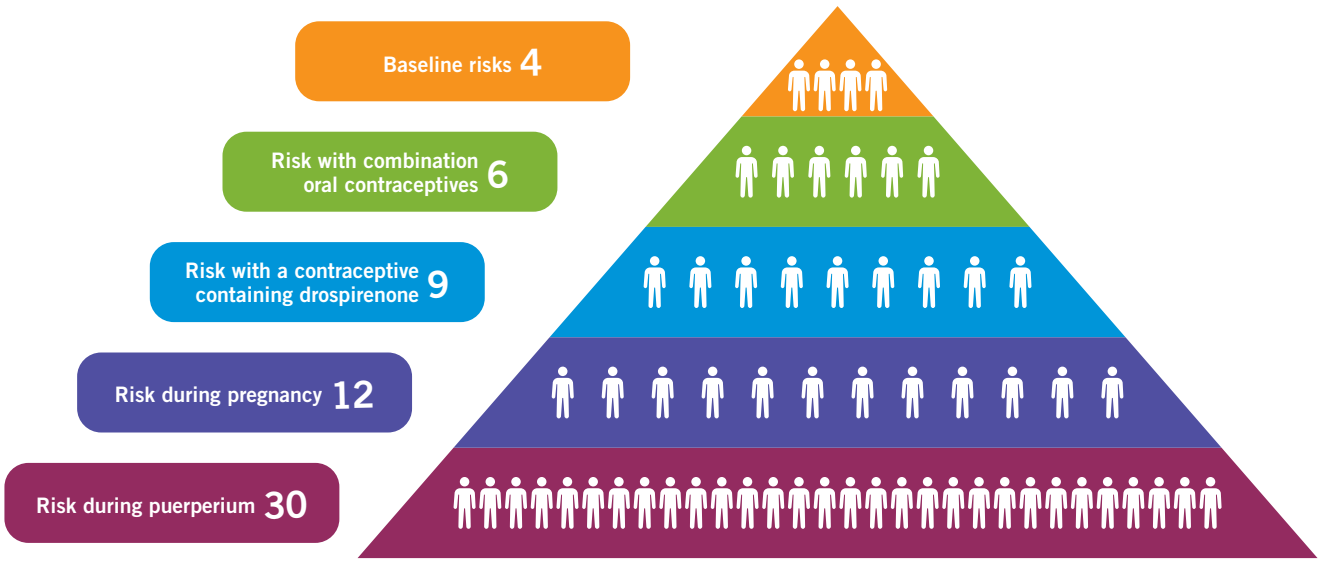
COCs should be avoided for treating acne in patients during pregnancy or less than 6 weeks postpartum. Other contraindications and cautions include smoking, migraines, hypertension, and breast cancer.[8] The risk-benefit ratio may be different for patients seeking acne treatment rather than contraception and should be considered for each individual.

Spironolactone

No Potassium Monitoring Needed in Most Patients With Acne

A retrospective data analysis reported that the rate of hyperkalemia in women (18-45 years old, no cardiovascular disease or renal failure) receiving spironolactone for acne (n=974) was similar to

FIGURE. Approximate Risk of Venous Thromboembolism in Healthy Women of Reproductive Age per 10,000



Source: Reid RL. *J Obstet Gynaecol Can.* 2011;33:1150-1155.[3]

A Topical Therapy for Acne Scars

Scarring is a lifelong reminder of acne for many patients. Treatment for atrophic scars typically involves invasive procedures such as chemical peels, dermabrasion, laser resurfacing, needling, radiofrequency, stem cell therapy, and volumizing fillers.[17] Cost and some patients' desire to avoid invasive measures limit the utility of these options.

The topical retinoid adapalene 0.3% gel alleviated scarring in patients with moderate or severe atrophic acne scars but no active disease.[18] Patients in this recent study applied adapalene 0.3% gel once daily for 4 weeks, then twice daily for another 20 weeks. More than half of the patients completing 6 months of therapy (10/18; 55.6%) demonstrated a 1- or 2-grade improvement from baseline in the full-face global scarring grade. Half the patients demonstrated a 1- or 2-grade improvement after treatment cessation (weeks 48-72). No treatment-related adverse events were reported. Most (88%) patients were satisfied with the gel's effectiveness.[18]

Other studies show that adapalene 0.1% or 0.3% combined with benzoyl peroxide 2.5% reduced scar formation and scar severity compared with vehicle during 6 months of therapy in patients with active inflammatory acne and scarring.[19,20]

the baseline rate in healthy young women not taking this medication (n=1165). The study authors concluded that potassium monitoring is unnecessary in otherwise healthy young women taking spironolactone for acne.[9]

The AAD guidelines advise considering monitoring potassium at baseline, during therapy, and after dose increases in older patients and in patients who are also taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, or digoxin.[1]

Spironolactone is not linked to breast cancer in humans, based on 2 large registry studies (2.3 million women age ≥20 years; ~1.3 million women age >55 years).[10,11]

Pregnancy and Nursing

Spironolactone should not be used during pregnancy, but it is compatible, although rarely used, with breastfeeding.[12]

Isotretinoin

Measure Lipid and Hepatic Panels at Baseline and at 8 Weeks, in the Absence of Abnormalities or Medical History Suggesting the Need for More Frequent Monitoring or Dosing Changes

A 26-study meta-analysis found that the mean changes in laboratory values during isotretinoin therapy did not cross into high-risk levels. Additionally, the proportion of patients with laboratory abnormalities was low.[13] The main concerns are liver function test results and triglyceride levels. Acute pancreatitis associated with elevated triglyceride concentrations generally occurs at levels higher than 1000 mg/dL.[14] To reduce the overall risk, keep triglycerides below 500 mg/dL through lifestyle interventions and isotretinoin dose reduction. If necessary, a triglyceride-lowering agent, such as fenofibrate, can be prescribed.

Isotretinoin Is Not Associated With an Increased Risk of Ulcerative Colitis

A French study of 50 million individuals found no association between isotretinoin and ulcerative colitis but did find a link to a decreased risk of Crohn's disease.[15]

Treatment with mechanical dermabrasion or fully ablative lasers should be delayed in patients being treated with isotretinoin.[16]

Summary

The goal of acne therapy should be achievement of clear or almost clear skin. COCs, spironolactone, and isotretinoin, when used in appropriate patients, are alternatives that minimize the use and duration of systemic antibiotics for acne, as recommended by AAD guidelines.[1]

References

1. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74(5):945-973.e33.
2. Barbieri JS, James WD, Margolis DJ. Trends in prescribing behavior of systemic agents used in the treatment of acne among dermatologists and nondermatologists: a retrospective analysis, 2004-2013. *J Am Acad Dermatol.* 2017;77(3):456-463.e4.
3. Reid RL. Oral contraceptives and venous thromboembolism: pill scares and public health. *J Obstet Gynaecol Can.* 2011;33(11):1150-1155.
4. Gierisch JM, Coeytaux RR, Urrutia RP, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. *Cancer Epidemiol Biomarkers Prev.* 2013;22(11):1931-1943.
5. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet.* 2008;371(9609):303-314.
6. Archer JS, Archer DF. Oral contraceptive efficacy and antibiotic interaction: a myth debunked. *J Am Acad Dermatol.* 2002;46(6):917-923.
7. ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 73: Use of hormonal contraception in women with coexisting medical conditions. *Obstet Gynecol.* 2006; 107(6):1453-1472.
8. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep.* 2016;65(3):1-103.
9. Plovanich M, Weng QY, Mostaghimi A. Low usefulness of potassium monitoring among healthy young women taking spironolactone for acne. *JAMA Dermatol.* 2015;151(9):941-944.
10. Biggar RJ, Andersen EW, Wohlfahrt J, Melbye M. Spironolactone use and the risk of breast and gynecologic cancers. *Cancer Epidemiol.* 2013;37(6):870-875.
11. Mackenzie IS, Macdonald TM, Thompson A, Morant S, Wei L. Spironolactone and risk of incident breast cancer in women older than 55 years: retrospective, matched cohort study. *BMJ.* 2012;345:e4447.
12. Murase JE, Heller MM, Butler DC. Safety of dermatologic medications in pregnancy and lactation: part I. Pregnancy. *J Am Acad Dermatol.* 2014;70(3):401.e1-14.
13. Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G, Kirby JS. Laboratory monitoring during isotretinoin therapy for acne: a systematic review and meta-analysis. *JAMA Dermatol.* 2016;152(1):35-44.
14. Karalis DG. A review of clinical practice guidelines for the management of hypertriglyceridemia: a focus on high dose omega-3 fatty acids. *Adv Ther.* 2017;34(2):300-323.
15. Racine A, Cuerq A, Bijon A, et al. Isotretinoin and risk of inflammatory bowel disease: a French nationwide study. *Am J Gastroenterol.* 2014;109(4):563-569.
16. Spring LK, Krakowski AC, Alam M, et al. Isotretinoin and timing of procedural interventions: a systematic review with consensus recommendations. *JAMA Dermatol.* 2017;153(8):802-809.
17. Zaleski-Larsen LA, Fabi SG, McGraw T, Taylor M. Acne scar treatment: a multimodality approach tailored to scar type. *Dermatol Surg.* 2016;42(suppl 2):S139-149.
18. Loss MJ, Leung S, Chien A, Kerrouche N, Fischer AH, Kang S. Adapalene 0.3% gel shows efficacy for the treatment of atrophic acne scars. *Dermatol Ther (Heidelb).* 2018;8(2):245-257.
19. Dreno B, Bissonnette R, Gagné-Henley A, et al. Prevention and reduction of atrophic acne scars with adapalene 0.3%/benzoyl peroxide 2.5% gel in subjects with moderate or severe facial acne: results of a 6-month randomized, vehicle-controlled trial using intra-individual comparison. *Am J Clin Dermatol.* 2018;19(2):275-286.
20. Dreno B, Tan J, Rivier M, Martel P, Bissonnette R. Adapalene 0.1%/benzoyl peroxide 2.5% gel reduces the risk of atrophic scar formation in moderate inflammatory acne: a split-face randomized controlled trial. *J Eur Acad Dermatol Venereol.* 2017;31(4):737-742.

Treatments Beyond Localized Skin Surgery for BCC, SCC, and Localized Melanoma

Christopher B. Zachary, MBBS, FRCP

Standard treatment for basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and localized melanoma usually includes skin surgery. Several novel treatments that are alternatives to surgery are reviewed briefly here.

Basal Cell Carcinoma

BCC is the most common type of nonmelanoma skin cancer.[1] The Hedgehog (Hh) pathway is an essential regulator of growth and development during embryogenesis. This pathway usually is dormant in adulthood and is activated in several cancers, including BCC. Inhibitors of the Hh pathway have proved beneficial for BCC.[1,2]

Vismodegib

Vismodegib was the first Hh pathway inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of adults with metastatic or locally advanced BCC.[3-5] Vismodegib has also demonstrated efficacy in inhibiting the Hh pathway in patients with basal-cell nevus (Gorlin) syndrome.[6] Toxicity (most commonly grade 1 and 2 dysgeusia, muscle cramps, hair loss, and weight loss) led roughly half the patients to stop a continuous treatment regimen in the phase 2 trial.[6] Two intermittent dosing regimens designed to improve tolerability and safety reduced the number of clinically evident BCC lesions at week 73: 63% fewer BCC lesions with schedule A, 54% fewer BCC lesions with schedule B. Nearly all (95%) patients in the trial developed treatment-related adverse events (AEs), but only 23% discontinued treatment due to AEs.[7]

Sonidegib

Another Hh pathway inhibitor, sonidegib, is FDA-approved for the treatment of adult patients with locally advanced BCC that has recurred after surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.[8,9] In a phase 2 trial, 36% of patients receiving a lower dose and 34% of patients receiving a higher dose had an objective response.[8]

Curettage Without Electrodesiccation

Curettage offers an option to treat small BCC tumors. Nearly all (96% of 302) BCC tumors treated with curettage by one physician showed no recurrence at 5 years. Compared with electrodesiccation, curettage alone was associated with minimal scarring and less hypopigmentation.[10] These findings are of particular interest given the recent *JAMA Dermatology* publication questioning the appropriate-use criteria for superficial BCCs.[11]

Squamous Cell Carcinoma

Approximately 1.5% of patients with cutaneous SCC (cSCC) will die, for an estimated total of between 4000 and 8800 US deaths in 2012.[12] An alternative staging system proposed for cSCC can improve identification of the subset of tumors with a high risk for metastasis and death.[13] Three alternative treatment options for SCC exist: topical fluorouracil (5-FU) and calcitriol,[14] intralesional methotrexate (MTX),[15] and cemiplimab.[16]

Topical 5-FU and Calcitriol

In a randomized trial involving 131 patients, applying topical 5% 5-FU cream plus 0.005% calcipotriol ointment twice daily for 4 days significantly reduced the number of actinic keratoses (mean reduction, 88% vs 26% for Vaseline®; $P<0.0001$). Participants applied the treatment to the face, scalp, and upper extremities.[14] The treatment induced thymic stromal lymphopoietin (TSLP), human leukocyte antigen (HLA) class II, and natural killer cell group 2D (NKG2D) ligand expression in the lesional keratinocytes. These changes were associated with marked CD4+ T-cell infiltration that peaked on days 10 to 11 after treatment, without pain, crusting, or ulceration. The investigators concluded that the synergistic effects of calcipotriol and 5-FU treatment activated CD4+ T-cell–mediated immunity against actinic keratoses.[14]

Intralesional MTX

A 38-case retrospective study and literature review concluded that intralesional MTX is a beneficial nonsurgical treatment option for keratoacanthoma. Resolution occurred in 92% of cases, after a mean of 2.1 injections at a mean of 18 days apart. There were 2 reports of pancytopenia in patients with chronic renal failure.[15]

Cemiplimab

Cemiplimab is a programmed death receptor-1 blocking antibody that is FDA-approved for the treatment of patients with metastatic cSCC or locally advanced cSCC who are not candidates for curative surgery or curative radiation.[16] Results of phase 1 and phase 2 studies (NCT02383212 and NCT02760498) demonstrated response to cemiplimab in about half the patients with advanced cSCC. AEs associated with the study drug occurred in about 15% of the patients in the metastatic-disease cohort of the phase 2 study. These AEs included diarrhea, fatigue, nausea, constipation, and rash; 7% of the patients discontinued treatment because of an AE.[17]

Melanoma

Lentigo maligna is a melanoma subtype with a good prognosis. However, it also has the highest rate of recurrence of all the subtypes when treated by surgical excision alone. Neoadjuvant imiquimod has been used off-label to reduce surgical margins in lentigo maligna.[18,19]

Summary

Although the treatment of BCC, SCC, and localized melanoma traditionally involves skin surgery, several novel alternative treatments are available for BCC, SCC, and localized melanoma.

References

1. Cirrone F, Harris CS. Vismodegib and the hedgehog pathway: a new treatment for basal cell carcinoma. *Clin Ther.* 2012;34(10):2039-2050.
2. Gould SE, Low JA, Marsters JC Jr, et al. Discovery and preclinical development of vismodegib. *Expert Opin Drug Discov.* 2014;9(8):969-984.
3. Erivedge [package insert]. South San Francisco, CA: Genentech, Inc; January 2012.
4. Fosko SW, Chu MB, Mattox AR, Richart JM, Burkemper NM, Slutsky JB. Lichenoid reaction as a potential immune response marker of intratreatment histological response during successful vismodegib treatment for a giant basal cell carcinoma. *Dermatol Ther.* 2015;28(6):359-362.
5. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med.* 2012;366(23):2171-2179.
6. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *N Engl J Med.* 2012;366(23):2180-2188.
7. Dréno B, Kunstfeld R, Hauschild A, et al. Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): a randomised, regimen-controlled, double-blind, phase 2 trial. *Lancet Oncol.* 2017;18(3):404-412.
8. Migden MR, Guminski A, Gutzmer R, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. *Lancet Oncol.* 2015;16(6):716-728.

continued on page 14

Onychomycosis: The Most Common Misdiagnosis in Nail Disease

Nathaniel J. Jellinek, MD

Onychomycosis accounts for up to 50% of all adult nail complaints.[1] It is the most common diagnosis in nail disease, but other nail disorders are often misdiagnosed as onychomycosis and diagnostic accuracy based on clinical examination alone is imperfect.[2] Onychomycosis has an adverse effect on quality of life, causing embarrassment, pain, and fear of being unclean or infectious.

An example of onychomycosis and one of its mimickers are shown in **Figures 1** and **2**, respectively.

Because onychomycosis is misdiagnosed so often, objective laboratory evidence is needed to confirm the diagnosis. Empirical antifungal treatment when no fungus is present can delay the correct diagnosis, allow disease to go untreated, and expose the patient to the cost and risk of adverse effects from unnecessary medication.[3]

Confirming the Diagnosis

Laboratory options commonly used for confirming a diagnosis of onychomycosis have advantages and disadvantages (**Table 1**).[4-8] The combination of potassium hydroxide (KOH) and culture is the current standard for diagnosing onychomycosis.[9] Extensive data support the use of nail clippings for pathology processing and periodic acid–Schiff (PAS) or Grocott-Gomori methenamine silver (GMS) staining that offers improved diagnostic accuracy. However, recent evidence suggests that polymerase chain reaction (PCR) is more sensitive, specific, and faster than either pathologic or culture-based methods.[8]

Pathogens

Dermatophytes are by far the most common cause of onychomycosis in the United States and Canada, with *Trichophyton rubrum* the most common single organism.[10-12] About 14% of onychomycosis cases were caused by nondermatophyte molds (NDM) in a single-center report from Bologna, Italy.[13] In that study, all 59 cases of onychomycosis due to NDM resulted from the following fungi: *Scopulariopsis brevicaulis, Fusarium, Acremonium,* or *Aspergillus.*[13] These same species caused nearly 90% or more cases of NDM onychomycosis identified in a 5-study review (n=151 cases).[14]

Molds can be causative or contaminants in onychomycosis. Some authors suggest confirming an initial positive culture for an NDM with positive cultures from 3 samples taken on a subsequent visit.[15] Mold as the etiologic agent is a negative prognostic factor.[16]

FIGURE 1. Onychomycosis

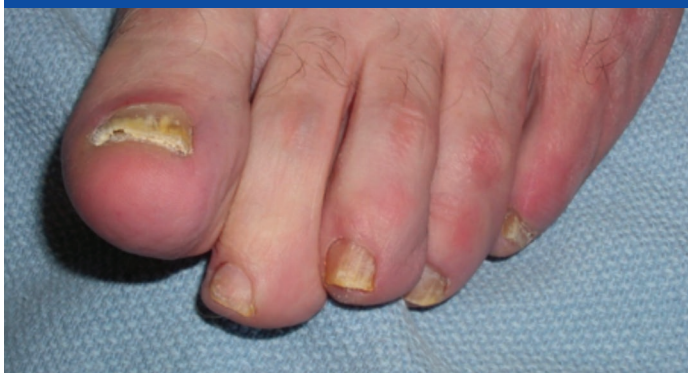


FIGURE 2. Nail Psoriasis
Frequently Misdiagnosed as Onychomycosis

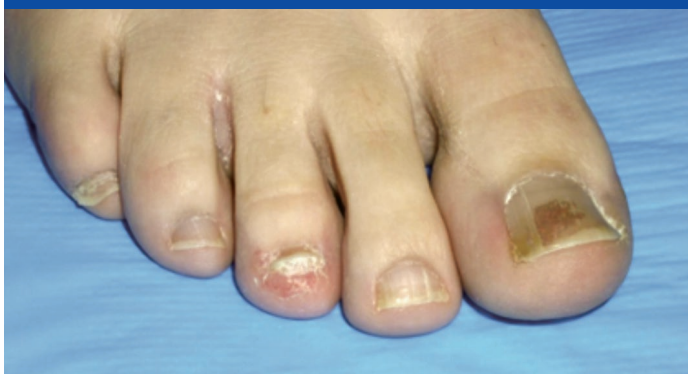


TABLE 1. Laboratory Confirmation of Onychomycosis[4]

Test/Technique	Assess Fungal Viability?	Identify Species?	Time to Results	Comments
Microscopy (KOH/Parker blue-black ink/fluorescent stain)	No	No	Rapid	Low-cost, rapid, in-office test; lower sensitivity than PAS and culture[5,6]
PAS stain	No	No	24 hours	More sensitive than KOH or culture[5,7]; less cost-effective than KOH or culture[6]
PCR, RT-PCR	No	Yes	5 hours to 1 day	More sensitive, accurate, and faster than culture; faster than KOH + culture[8]; 3-4 times less likely than culture to report a false-negative result[9]
Culture (Sabouraud dextrose agar)	Yes	Yes	1-3 weeks	High false-negative rate (~35%)[4]

KOH, potassium hydroxide; PAS, periodic acid–Schiff; PCR, polymerase chain reaction; RT-PCR, real-time polymerase chain reaction.

Table 2. Systemic Treatment Efficacy for Onychomycosis[19]

Patients	Regimen	Effective Cure Rate at 72 Weeks[a]
Adults with dermatophyte infection, great toenail, 20%-100% affected	Intermittent terbinafine (n=63)[b]	79%[e]
	Continuous terbinafine (n=40)[c]	66%[e]
	Intermittent itraconazole (n=39)[d]	37%[e]

[a]Simultaneous mycological cure and ≤10% nail involvement.
[b]Daily for 30 days on, 30 days off, then 30 days on.
[c]Daily therapy for 3 months continuously.
[d]Pulse of 200 mg twice daily for 7 days on, 21 days off, 3 pulses given.
[e]*P*<0.001 for intermittent terbinafine vs intermittent itraconazole; *P*=0.02 for continuous terbinafine vs intermittent itraconazole; *P*=NS, continuous vs intermittent terbinafine.
NS, not significant.

Treatment

Terbinafine and itraconazole are each approved by the US Food and Drug Administration for 3 months of daily dosing to treat toenail onychomycosis due to dermatophytes.[17,18] An intermittent approach is also used (**Table 2**),[19] with booster therapy as needed at 6, 9, and 12 months.

Two topical treatments have been introduced within the last several years: efinaconazole 10% and tavaborole 5%. **Table 3** summarizes efficacy results from phase 3 studies.[20,21] These topical agents can be used in superficial or distal subungual onychomycosis, limited to less than 50% of the distal nail, if patients will adhere to the treatment for 1 year.

Both of these newer agents may have a niche in the treatment of onychomycosis caused by NDM. In vitro susceptibility studies show good activity against *Fusarium* and *Aspergillus* species. Against *Fusarium*, efinaconazole showed roughly 8-fold more activity than itraconazole based on the geometric mean minimum inhibitory concentrations (MICs) of both drugs.[22] Another in vitro study showed that efinaconazole was active against *Trichophyton, Microsporum, Epidermophyton, Acremonium, Fusarium, Paecilomyces, Pseudallescheria, Scopulariopsis, Aspergillus, Cryptococcus, Trichosporon,* and *Candida*.[23]

Summary

Clinical diagnosis of onychomycosis should be confirmed with laboratory evidence. PCR offers a good balance of speed, accuracy, and species identification,[9] albeit at increased cost. KOH plus culture is the recommended standard for laboratory confirmation,[4] although this strategy may be evolving as more data on molecular techniques emerge. A laboratory diagnosis of mold as the etiologic agent should always be confirmed.[14,15] The new topical agents efinaconazole and tavaborole demonstrate high in vitro effectiveness against common mold etiologies of onychomycosis.[22,23] Intermittent terbinafine dosing is as effective as continuous dosing and is the study author's preferred regimen.[19]

References

1. Gupta AK, Jain HC, Lynde CW, Macdonald P, Cooper EA, Summerbell RC. Prevalence and epidemiology of onychomycosis in patients visiting physicians' offices: a multicenter Canadian survey of 15,000 patients. *J Am Acad Dermatol.* 2000;43(2 pt 1):244-248.
2. Arrese JE, Piérard-Franchimont C, Piérard GE. Facing up to the diagnostic uncertainty and management of onychomycoses. *Int J Dermatol*. 1999;38(suppl 2):1-6.
3. Gupta AK, Versteeg SG, Shear NH. Confirmatory testing prior to initiating onychomycosis therapy is cost-effective. *J Cutan Med Surg.* 2018;22(2):129-141.
4. Gupta AK, Versteeg SG, Shear NH. Onychomycosis in the 21st century: an update on diagnosis, epidemiology, and treatment. *J Cutan Med Surg.* 2017;21(6):525-539.
5. Wilsmann-Theis D, Sareika F, Bieber T, Schmid-Wendtner MH, Wenzel J. New reasons for histopathological nail-clipping examination in the diagnosis of onychomycosis. *J Eur Acad Dermatol Venereol.* 2011;25(2):235-237.
6. Lilly KK, Koshnick RL, Grill JP, Khalil ZM, Nelson DB, Warshaw EM. Cost-effectiveness of diagnostic tests for toenail onychomycosis: a repeated-measure, single-blinded, cross-sectional evaluation of 7 diagnostic tests. *J Am Acad Dermatol.* 2006;55(4):620-626.
7. Weinberg JM, Koestenblatt EK, Tutrone WD, Tishler HR, Najarian L. Comparison of diagnostic methods in the evaluation of onychomycosis. *J Am Acad Dermatol.* 2003;49(2):193-197.
8. Gupta AK, Zaman M, Singh J. Fast and sensitive detection of *Trichophyton rubrum* DNA from the nail samples of patients with onychomycosis by a double-round polymerase chain reaction-based assay. *Br J Dermatol.* 2007;157(4):698-703.
9. Gupta AK, Nakrieko KA. Onychomycosis infections: do polymerase chain reaction and culture reports agree? *J Am Podiatr Med Assoc.* 2017;107(4):280-286.
10. Gupta AK, Gupta G, Jain HC, et al. The prevalence of unsuspected onychomycosis and its causative organisms in a multicentre Canadian sample of 30 000 patients visiting physicians' offices. *J Eur Acad Dermatol Venereol.* 2016;30(9):1567-1572.
11. Wlodek C, Trickey A, de Berker D, Johnson E. Trends in pediatric laboratory-diagnosed onychomycosis between 2006 and 2014 in the southwest of England. *Pediatr Dermatol.* 2016;33(6):e358-e359.
12. Totri CR, Feldstein S, Admani S, Friedlander SF, Eichenfield LF. Epidemiologic analysis of onychomycosis in the San Diego pediatric population. *Pediatr Dermatol.* 2017;34(1):46-49.
13. Tosti A, Piraccini BM, Lorenzi S. Onychomycosis caused by nondermatophytic molds: clinical features and response to treatment of 59 cases. *J Am Acad Dermatol.* 2000;42(2 pt 1):217-224.
14. Gupta AK, Drummond-Main C, Cooper EA, Brintnell W, Piraccini BM, Tosti A. Systematic review of nondermatophyte mold onychomycosis: diagnosis, clinical types, epidemiology, and treatment. *J Am Acad Dermatol.* 2012;66(3):494-502.
15. Shemer A, Davidovici B, Grunwald MH, Trau H, Amichai B. New criteria for the laboratory diagnosis of nondermatophyte moulds in onychomycosis. *Br J Dermatol.* 2009;160(1):37-39.
16. Carney C, Tosti A, Daniel R, et al. A new classification system for grading the severity of onychomycosis: Onychomycosis Severity Index. *Arch Dermatol.* 2011;147(11):1277-1282.
17. Lamasil [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
18. Sporanox [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2018.
19. Gupta AK, Lynch LE, Kogan N, Cooper EA. The use of an intermittent terbinafine regimen for the treatment of dermatophyte toenail onychomycosis. *J Eur Acad Dermatol Venereol.* 2009;23(3):256-262.
20. Elewski BE, Rich P, Pollak R, et al. Efinaconazole 10% solution in the treatment of toenail onychomycosis: two phase III multicenter, randomized, double-blind studies. *J Am Acad Dermatol.* 2013;68(4):600-608.
21. Elewski BE, Aly R, Baldwin SL, et al. Efficacy and safety of tavaborole topical solution, 5%, a novel boron-based antifungal agent, for the treatment of toenail onychomycosis: results from 2 randomized phase-III studies. *J Am Acad Dermatol.* 2015;73(1):62-69.
22. Tupaki-Sreepurna A, Jishnu BT, Thanneru V, et al. An assessment of in vitro antifungal activities of efinaconazole and itraconazole against common non-dermatophyte fungi causing onychomycosis. *J Fungi (Basel).* 2017;3(2). lc: doi 10.3390/jof3020020.
23. Jo Siu WJ, Tatsumi Y, Senda H, et al. Comparison of in vitro antifungal activities of efinaconazole and currently available antifungal agents against a variety of pathogenic fungi associated with onychomycosis. *Antimicrob Agents Chemother.* 2013;57(4):1610-1616.

Table 3. Topical Treatment Efficacy for Onychomycosis, 52 Weeks of Treatment

Therapy	Patients	Mycological Cure	Complete Cure
Efinaconazole 10%[20] (n=656, 580)[a]	Toenail DLSO with 20%-50% clinical involvement	55%, 53%	18%, 15%
Tavaborole 5%[21] (n=399, 396)[a]	DSO with 20%-60% involvement of a target great toenail	31%, 36%	7%, 9%

[a]Two phase 3 trials.
DLSO, distal lateral subungual onychomycosis; DSO, distal subungual onychomycosis.

Botulinum Toxins: 2019 Update

Michael S. Kaminer, MD

Botulinum toxins have an increasing number of approved indications and off-label uses, not only in aesthetic medicine and neuromuscular disorders, but also in ophthalmologic, urologic, gastrointestinal, hypersecretory, and pain disorders.[1] Several important pharmacological properties contribute to their utility: they are very potent and neurospecific toxins; when injected locally, their diffusion is limited; and their action reverses over time.[2] When used to minimize glabellar frown lines and other facial wrinkles, the full effect develops in about 1 to 2 weeks. Benefit lasts about 4 months, or longer in some cases.[3]

Approved Toxins

Conversion Factor

The first botulinum A toxin (onabotulinumtoxinA) was approved in the United States for cosmetic use in 2002. Three more toxins have been introduced since that time, including 1 in February 2019 (**Table**).[4-10] The dose of incobotulinumtoxinA is equivalent to that of onabotulinumtoxinA in published studies,[11,12] although some clinicians disagree. Multiple studies[12] have reported a dose conversion factor from onabotulinumtoxinA or incobotulinumtoxinA to abobotulinumtoxinA of 1:3; many clinicians use a conversion factor of 1:2.5. Relative potency of the investigational toxin daxibotulinumtoxinA compared with onabotulinumtoxinA has not been established.[13]

Response Rates

The newest agent approved by the US Food and Drug Administration (FDA), prabotulinumtoxinA-xvfs, demonstrated response rates of 68% and 70% at 30 days after a single injection in two phase 3 studies of patients with glabellar lines. Response was defined as at least a 2-point improvement on the 4-point Glabellar Line Scale (GLS) at 30 days.[14] Previous studies of onabotulinumtoxinA reported an 80% response rate at 30 days.[7]

The definition of response varies across clinical trials of these medications, complicating comparisons. Some head-to-head efficacy studies have been performed, however. IncobotulinumtoxinA[6] and prabotulinumtoxinA[9] each has demonstrated noninferiority to onabotulinumtoxinA for the treatment of glabellar lines in separate phase 3 trials. More than half of patients receiving prabotulinumtoxinA or onabotulinumtoxinA demonstrated response at day 2 (54% and 57%, respectively). The agents demonstrated a similar safety profile.[9]

A comparison of incobotulinumtoxinA and onabotulinumtoxinA revealed response rates at 4 weeks of 96% with each product. Response was defined as improvement of at least 1 point on a 4-point facial wrinkle scale at weeks 4 and 12.[6]

Response rates with prabotulinumtoxinA and onabotulinumtoxinA were 87% and 83%, respectively, in a noninferiority trial, in which response was defined as subjects with a GLS score of no lines or mild lines (0 or 1) by investigator assessment at 30 days postinjection.[9]

Investigational Toxins

Several investigational botulinum toxins are expected to be approved by the FDA soon. Injectable daxibotulinumtoxinA, which has completed phase 2 trials, demonstrated greater efficacy and a longer duration of response than onabotulinumtoxinA due to the presence of a stabilizing peptide.[13] In a 24-week dose-ranging study (N=268), 40 U daxibotulinumtoxinA had a significantly greater response rate and longer response duration (24 vs 19 weeks) in the treatment of glabellar lines compared with 20 U onabotulinumtoxinA (P=.03).[13] A phase 3, long-term safety study of daxibotulinumtoxinA for glabellar lines has been completed but results have not been reported (https://clinicaltrials.gov, NCT03004248).

A botulinum toxin serotype E in the pipeline for treatment of glabellar lines has a rapid onset of action—within 24 hours—yet a response duration of only 2 to 4 weeks.[15] One potential use for such a short-acting toxin may be to reduce scarring after Mohs surgery to achieve better cosmesis. Rapid, short-acting toxins may also be desirable in patients who are toxin-naïve or in individuals who have mild facial asymmetry, such as an elevated eyebrow.[15] The serotype E toxin will be sold in liquid form, so reconstitution will be unnecessary.[15] A liquid form of abobotulinumtoxinA is under study.[16]

Summary

Four toxins are available for facial rejuvenation and contouring beyond the glabellar lines. Pipeline toxins include a toxin A with longer duration than those currently available and a toxin E product with faster onset of action than the serotype A agents.

TABLE. FDA-Approved Botulinum Toxins for Aesthetic Use

Agent	Bacterial Production Strain	Units/Vial (Product Specific)[a]	Noninferiority Studies
AbobotulinumtoxinA[4]	Hall NCTC 2916	125/300/350	—
IncobotulinumtoxinA[5]	Hall ATCC 3502	50/100/200	Noninferior to onabotulinumtoxinA[6]
OnabotulinumtoxinA[7]	Hall-hyper	50/100/200	—
PrabotulinumtoxinA-xvfs[8]	—	100	Noninferior to onabotulinumtoxinA[9]

[a]The potency units of each product are specific to that product and are not interchangeable with those for other products.
ATCC, American Type Culture Collection; FDA, US Food and Drug Administration; NCTC, National Collection of Type Cultures.
Adapted from: Benedetto AV. *Dermatol Clin.* 2019;37(1):117-128.[10]

References

1. Gart MS, Gutowski KA. Overview of botulinum toxins for aesthetic uses. *Clin Plast Surg.* 2016;43(3):459-471.
2. Pirazzini M, Rossetto O, Eleopra R, Montecucco C. Botulinum neurotoxins: biology, pharmacology, and toxicology. *Pharmacol Rev.* 2017;69(2):200-235.
3. Small R. Botulinum toxin injection for facial wrinkles. *Am Fam Physician.* 2014;90(3):168-175.
4. Dysport [package insert]. Fort Worth, TX: Galderma Laboratories, L.P.: July 2016.
5. Xeomin [package insert]. Raleigh, NC; Merz Pharmaceuticals, LLC; July 2018.
6. Sattler G, Callander MJ, Grablowitz D, et al. Noninferiority of incobotulinumtoxinA, free from complexing proteins, compared with another botulinum toxin type A in the treatment of glabellar frown lines. *Dermatol Surg.* 2010;36(suppl 4):2146-2154.
7. Botox Cosmetic [package insert]. Madison, NJ: Allergan USA, Inc; May 2018.
8. Jeuveau [package insert]. Santa Barbara, CA: Evolus Inc; February 2019.
9. Rzany BJ, Ascher B, Avelar RL, et al. A multicenter, randomized, double-blind, placebo-controlled, single-dose, phase III, non-inferiority study comparing prabotulinumtoxinA and onabotulinumtoxinA for the treatment of moderate to severe glabellar lines in adult subjects. *Aesthet Surg J.* 2019 April 5 [Epub ahead of print].
10. Benedetto AV. What's new in cosmetic dermatology. *Dermatol Clin*. 2019;37(1):117-128.
11. Jandhyala R. Relative potency of incobotulinumtoxinA vs onabotulinumtoxinA a meta-analysis of key evidence. *J Drugs Dermatol.* 2012;11(6):731-736.
12. Samizadeh S, De Boulle K. Botulinum neurotoxin formulations: overcoming the confusion. *Clin Cosmet Investig Dermatol.* 2018;11:273-287.
13. Carruthers J, Solish N, Humphrey S, et al. Injectable daxibotulinumtoxinA for the treatment of glabellar lines: a phase 2, randomized, dose-ranging, double-blind, multicenter comparison with onabotulinumtoxinA and placebo. *Dermatol Surg.* 2017;43(11):1321-1331.
14. Beer KR, Shamban AT, Avelar RL, Gross JE, Jonker A. Efficacy and safety of prabotulinumtoxinA for the treatment of glabellar lines in adult subjects: results from 2 identical phase III studies. *Dermatol Surg.* 2019 March 18 [Epub ahead of print].
15. Yoelin SG, Dhawan SS, Vitarella D, Ahmad W, Hasan F, Abushakra S. Safety and efficacy of EB-001, a novel type E botulinum toxin, in subjects with glabellar frown lines: results of a phase 2, randomized, placebo-controlled, ascending-dose study. *Plast Reconstr Surg.* 2018;142(6):847e-855e.
16. Ascher B, Rzany B, Kestemont P, et al. Liquid formulation of abobotulinumtoxinA: a 6-month, phase 3, double-blind, randomized, placebo-controlled study of a single treatment, ready-to-use toxin for moderate-to-severe glabellar lines. *Aesthet Surg J.* 2019 March 20 [Epub ahead of print].

Topical Therapies for Psoriasis: The Revolution in Vehicles, Combinations, and Novel Agents

continued from page 4

References

1. Menter A, Korman NJ, Elmets CA, et al, for the American Academy of Dermatology. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol.* 2009;60(4):643-659.
2. van de Kerkhof PC, Reich K, Kavanaugh A, et al. Physician perspectives in the management of psoriasis and psoriatic arthritis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey. *J Eur Acad Dermatol Venereol.* 2015;29(10):2002-2010.
3. Kircik LH, Bikowski JB, Cohen DE, Draelos ZD, Hebert A. Vehicles matter: formulation development, testing, and approval. Part 1 of 2. *Supplement to Practical Dermatology.* 2010 March:1-16.
4. Humbert P, Guichard A. The topical corticosteroid classification called into question: towards a new approach. *Exp Dermatol.* 2015;24(5):393-395.
5. Basse LH, Olesen M, Lacour JP, Queille-Roussel C. Enhanced in vitro skin penetration and anti-psoriatic effect of fixed combination calcipotriol plus betamethasone dipropionate in an innovative foam vehicle. *J Invest Dermatol.* 2014;134:S33. Abstract 192.
6. Fowler JF Jr, Hebert AA, Sugarman J. DFD-01, a novel medium potency betamethasone dipropionate 0.05% emollient spray, demonstrates similar efficacy to augmented betamethasone dipropionate 0.05% lotion for the treatment of moderate plaque psoriasis. *J Drugs Dermatol.* 2016;15(2):154-162.
7. Kerdel FA, Draelos ZD, Tyring SK, Lin T, Pillai R. A phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical study to compare the safety and efficacy of a halobetasol propionate 0.01% lotion and halobetasol propionate 0.05% cream in the treatment of plaque psoriasis. *J Dermatolog Treat*. 2019;30(4):333-339.
8. Koo J, Tyring S, Werschler WP, et al. Superior efficacy of calcipotriene and betamethasone dipropionate aerosol foam versus ointment in patients with psoriasis vulgaris—a randomized phase II study. *J Dermatolog Treat*. 2016;27(2):120-127.
9. Stein Gold L. What's new in topical therapy. Presented at: 43rd Annual Hawaii Dermatology Seminar; February 17-22, 2019; Waikoloa, HI. Oral presentation.
10. Duobrii [package insert]. Bridgewater, NJ: Bausch Health Americas, Inc; April 2019.
11. Sugarman JL, Weiss J, Tanghetti EA, et al. Safety and efficacy of a fixed combination halobetasol and tazarotene lotion in the treatment of moderate-to-severe plaque psoriasis: a pooled analysis of two phase 3 studies. *J Drugs Dermatol.* 2018;17(8):855-861.
12. Kircik LH, Papp KA, Stein Gold L, Harris S, Pharm TL, Pillai R. Assessing the synergistic effect of a fixed combination halobetasol propionate 0.01% and tazarotene 0.045% lotion in moderate-to-severe plaque psoriasis. *J Drugs Dermatol.* 2019;18(3):279-284.
13. Sugarman JL, Gold LS, Lebwohl MG, Pariser DM, Alexander BJ, Pillai R. A phase 2, multicenter, double-blind, randomized, vehicle controlled clinical study to assess the safety and efficacy of a halobetasol/tazarotene fixed combination in the treatment of plaque psoriasis. *J Drugs Dermatol.* 2017;16(3):197-204.
14. Smith SH, Jayawickreme C, Rickard DJ, et al. Tapinarof is a natural AhR agonist that resolves skin inflammation in mice and humans. *J Invest Dermatol.* 2017;137(10):2110-2119.
15. Negishi T, Kato Y, Ooneda O, et al. Effects of aryl hydrocarbon receptor signaling on the modulation of TH1/TH2 balance. *J Immunol.* 2005;175(11):7348-7356.
16. Robbins K, Bissonnette R, Maeda-Chubachi T, et al. Phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of plaque psoriasis. *J Am Acad Dermatol.* 2019; 80(3):714-721.
17. Punwani N, Burn T, Scherle P, et al. Downmodulation of key inflammatory cell markers with a topical Janus kinase 1/2 inhibitor. *Br J Dermatol*. 2015;173(4):989-997.
18. Eucrisa [package insert]. Palo Alto, CA: Anacor Pharmaceuticals, Inc; October 2017.

Cardiovascular Disease and Psoriasis

continued from page 5

References

1. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296(14):1735-1741.
2. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol.* 2006;55(5):829-835.
3. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. *Eur Heart J.* 2010;31(8):1000-1006.
4. Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *J Am Acad Dermatol*. 2019;80(4):1073-1113.
5. Mehta NN, Yu Y, Saboury B, et al. Systemic and vascular inflammation in patients with moderate to severe psoriasis as measured by [^{18}F]-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT): a pilot study. *Arch Dermatol.* 2011;147(9):1031-1039.
6. Kivelevitch D, Schussler JM, Menter A, et al. Coronary plaque characterization in psoriasis. *Circulation*. 2017;136(3):277-280.
7. Ernste FC, Sanchez-Menendez M, Wilton KM, Crowson CS, Matteson EL, Maradit Kremers H. Cardiovascular risk profile at the onset of psoriatic arthritis: a population-based cohort study. *Arthritis Care Res (Hoboken)*. 2015;67(7):1015-1021.
8. Mansouri B, Kivelevitch D, Natarajan B, et al. Comparison of coronary artery calcium scores between patients with psoriasis and type 2 diabetes. *JAMA Dermatol.* 2016;152(11):1244-1253.
9. Ahlehoff O, Skov L, Gislason G, et al. Cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs: a Danish real-world cohort study. *J Intern Med.* 2013;273(2):197-204.
10. Wu JJ, Poon KT, Channual JC, Shen A. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. *Arch Dermatol.* 2012;148(11):1244-1250.
11. Wu JJ, Guerin A, Sundaram M, Dea K, Cloutier M, Mulani P. Cardiovascular event risk assessment in psoriasis patients treated with tumor necrosis factor-alpha inhibitors versus methotrexate. *J Am Acad Dermatol.* 2017;76(1):81-90.
12. Wu JJ, Sundaram M, Cloutier M, et al. The risk of cardiovascular events in psoriasis patients treated with tumor necrosis factor-alpha inhibitors versus phototherapy: an observational cohort study. *J Am Acad Dermatol.* 2018;79(1):60-68.
13. Lee MP, Desai RJ, Jin Y, Brill G, Ogdie A, Kim SC. Association of ustekinumab vs TNF inhibitor therapy with risk of atrial fibrillation and cardiovascular events in patients with psoriasis or psoriatic arthritis. *JAMA Dermatol.* 2019 Mar 27 [Epub ahead of print].
14. Ryan C, Leonardi CL, Krueger JG, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. *JAMA.* 2011;306(8):864-871.
15. Elnabawi YA, Dey AK, Goyal A, et al. Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study. *Cardiovasc Res*. 2019;115(4):721-728.
16. Frieder J, Ryan C. Psoriasis and cardiovascular disorders. *G Ital Dermatol Venereol*. 2016;151(6): 678-693.
17. Ridker PM, Everett BM, Thuren T, et al, for the CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377(12):1119-1131.
18. Zhao TX, Mallat Z. Targeting the immune system in atherosclerosis: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73(13):1691-1706.

Treatments Beyond Localized Skin Surgery for BCC, SCC, and Localized Melanoma

continued from page 10

9. Odomzo [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc; May 2019.
10. Barlow JO, Zalla MJ, Kyle A, DiCaudo DJ, Lim KK, Yiannias JA. Treatment of basal cell carcinoma with curettage alone. *J Am Acad Dermatol.* 2006;54(6):1039-1045.
11 Steinman HK, Dixon A, Zachary CB. Reevaluating Mohs surgery appropriate use criteria for primary superficial basal cell carcinoma. *JAMA Dermatol.* 2018;154(7):755-756.
12. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. *J Am Acad Dermatol.* 2013;68(6):957-966.
13 Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, et al. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. *JAMA Dermatol.* 2013;149(4):402-410.
14. Cunningham TJ, Tabacchi M, Eliane JP, et al. Randomized trial of calcipotriol combined with 5-fluorouracil for skin cancer precursor immunotherapy. *J Clin Invest.* 2017;127(1):106-116.
15. Annest NM, VanBeek MJ, Arpey CJ, Whitaker DC. Intralesional methotrexate treatment for keratoacanthoma tumors: a retrospective study and review of the literature. *J Am Acad Dermatol.* 2007;56(6):989-993.
16. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med.* 2018;379(4):341-351.
17. Libtayo [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; September 2018.
18. Fosko SW, Navarrete-Dechent CP, Nehal KS. Lentigo maligna—challenges, observations, imiquimod, confocal microscopy, and personalized treatment. *JAMA Dermatol.* 2018;154(8):879-881.
19. Donigan JM, Hyde MA, Goldgar DE, Hadley ML, Bowling M, Bowen GM. Rate of recurrence of lentigo maligna treated with off-label neoadjuvant topical imiquimod, 5%, cream prior to conservatively staged excision. *JAMA Dermatol.* 2018;154(8):885-889.

Highlights of Skin Disease Education Foundation's 43rd Annual Hawaii Dermatology Seminar® Post-Test

Original Release Date: August 2019

Expiration Date: August 31, 2021 • Estimated Time to Complete Activity: 2.0 hours

To get instant CME/CE credits online, go to **https://tinyurl.com/HDS19Supp**. Upon successful completion of the online test and evaluation form, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail or you may print it at that time. If you have any questions or difficulties, please contact the Global Academy for Medical Education office at info@globalacademycme.com.

Questions: For each question or incomplete statement, choose the answer or completion that is correct.
Circle the most appropriate response.

1. **A new fixed-combination topical therapy, halobetasol propionate 0.01%/tazarotene 0.045% (HP/TAZ) lotion:**
   A. Has been associated with a lower rate of application site reactions than tazarotene alone
   B. Offers efficacy similar to that of the sum of its components
   C. Led to about one-third of patients achieving clear/almost clear and ≥2-grade IGA improvement after 8 weeks of therapy in phase 3 clinical trials
   D. Was associated with rapidly diminishing benefit after cessation of therapy

2. **The standard system for ranking the potency of a topical corticosteroid is based on a test of**
   A. How long the drug remains in the dermis
   B. How quickly the agent is deposited to the site of action
   C. The interaction of agent and vehicle
   D. The vasoconstrictor effect

3. **A 2015 study examining the Framingham Risk Score (FRS) in patients with psoriatic arthritis (PsA) found that**
   A. The FRS accurately predicted the 10-year cumulative incidence of cardiovascular disease (CVD) events in patients with PsA
   B. The FRS overestimated the 10-year cumulative incidence of CVD events in patients with PsA
   C. The 10-year cumulative incidence of CVD events in patients with PsA was nearly twice the predicted risk
   D. The 10-year cumulative incidence of CVD events in patients with PsA was nearly 10 times the predicted risk

4. **Can spironolactone be used to treat acne during pregnancy and breastfeeding?**
   A. Spironolactone is safe to use during pregnancy and breastfeeding
   B. Spironolactone is NOT safe to use during pregnancy and breastfeeding
   C. Spironolactone is compatible, although rarely used, with pregnancy
   D. Spironolactone is compatible, although rarely used, with breastfeeding

5. **Approximately what percentage of cases of atopic dermatitis begin in adulthood?**
   A. 2%
   B. 10%
   C. 25%
   D. 50%

6. **Which of the following treatments for acne has been shown to reduce the risk of colorectal, endometrial, and ovarian cancer, while increasing the risk of cervical and breast cancer?**
   A. Antibiotics
   B. Combined oral contraceptives
   C. Isotretinoin
   D. Spironolactone

7. **Which of the following agents is approved by the US Food and Drug Administration (FDA) for the treatment of basal cell carcinoma (BCC)?**
   A. Cemiplimab
   B. Neoadjuvant imiquimod
   C. Sonidegib
   D. Topical 5% 5-fluorouracil cream and 0.005% calcipotriol ointment

8. **Which of the following agents is approved by the US FDA for the treatment of cutaneous squamous cell carcinoma (cSCC)?**
   A. Cemiplimab
   B. Neoadjuvant imiquimod
   C. Sonidegib
   D. Vismodegib

9. **Which of the following treatments for onychomycosis has shown in vitro activity against *Trichophyton*, *Microsporum*, *Epidermophyton*, *Acremonium*, *Fusarium*, *Paecilomyces*, *Pseudallescheria*, *Scopulariopsis*, *Aspergillus*, *Cryptococcus*, *Trichosporon*, and *Candida*?**
   A. Efinaconazole
   B. Itraconazole
   C. Tavaborole
   D. Terbinafine

10. **Which of the following has a longer duration of response than onabotulinumtoxinA?**
    A. AbobotulinumtoxinA
    B. DaxibotulinumtoxinA
    C. IncobotulinumtoxinA
    D. PrabotulinumtoxinA-xvfs

Highlights of Skin Disease Education Foundation's 43rd Annual Hawaii Dermatology Seminar® Evaluation Form

Original Release Date: August 2019 • **Expiration Date:** August 31, 2021 • **Estimated Time to Complete Activity:** 2.0 hours

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. CME/CE credit letters and long-term credit retention information will only be issued upon completion of the post-test and evaluation online at: **https://tinyurl.com/HDS19Supp**.

Please indicate your profession/background: *(check one)*

☐ MD/DO ☐ MSN/BSN/RN ☐ PA ☐ APN/NP ☐ PharmD/RPh ☐ Resident/Fellow Researcher ☐ Administrator ☐ Student

☐ Other; specify _____

LEARNING OBJECTIVES: Having completed this activity, you are better able to:	Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
Describe recent data on psoriasis treatment, including new vehicles for topical treatments, fixed-dose combination therapies, and investigational topical medications	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Review the relationship between psoriasis and cardiovascular disease (CVD) and the potential effects of psoriasis treatment on CVD risk	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Describe current research on the temporal patterns of atopic dermatitis onset and resolution and the differences in diagnosis and treatment approach for adult and pediatric patients	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Analyze the efficacy and safety of systemic therapies for acne	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Assess the current nonsurgical treatments for basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and localized melanoma	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Review the options for confirming the diagnosis and data on the use of topical and systemic treatments in the management of onychomycosis	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Assess the advantages and disadvantages of available botulinum toxins used to address patient concerns about facial aging	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

_____

Based on the content of this activity, what will you do differently in the care of your patients/regarding your professional responsibilities? (check one)

☐ Implement a change in my practice/workplace.
☐ Seek additional information on this topic.
☐ Implement a change in my practice/workplace and seek additional information on this topic.
☐ Do nothing differently. Current practice/job responsibilities reflect activity recommendations.
☐ Do nothing differently. Content was not convincing.
☐ Do nothing differently. System barriers prevent me from changing my practice/workplace.

If you anticipate changing 1 or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.

_____

If you plan to change your practice/professional responsibilities, may we contact you in 2 months to see how you are progressing?

☐ Yes ☐ No ☐ I don't plan to make a change.

If you are not able to effectively implement what you learned in this activity, please tell us what the system barriers are (eg, institutional systems, lack of resources, etc).

_____

_____

OVERALL EVALUATION		Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
This education increased my understanding of the subject.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
This education will influence how I do my job.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
This education will help me improve my job performance.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
This education will help me collaborate with other health care professionals.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
This education addressed issues in cultural competency.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
This education was educationally sound and scientifically balanced.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
This education was free of commercial bias or influence.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
This education met my expectations.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Nathaniel J. Jellinek, MD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Michael S. Kaminer, MD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Alan Menter, MD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Jonathan I. Silverberg, MD, PhD, MPH	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Linda F. Stein Gold, MD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Christopher B. Zachary, MBBS, FRCP	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

What issue(s) are you experiencing in your practice/regarding your professional responsibilities that could be addressed in future programming?

_____

_____

Please provide additional comments pertaining to this activity and any suggestions for improvement.

_____

_____

The University of Louisville, Postgraduate Institute for Medicine, and Global Academy for Medical Education thank you for your participation in this CME/CE activity. All information provided improves the scope and purpose of our programs and your patients' care.