

HIGHLIGHTS OF
SKIN DISEASE EDUCATION FOUNDATION'S
41st ANNUAL

Hawaii Dermatology Seminar®

A CONTINUING MEDICAL EDUCATION CONFERENCE

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Target Audience

This journal supplement is intended for dermatologists, pediatricians, family practitioners, internists, nurses, nurse practitioners, physician assistants, and other clinicians who treat patients and practice medical or aesthetic dermatology.

Educational Needs

Expanding knowledge about the biology of skin disease has led to new therapies, updated guidelines, and changes in treatment recommendations. The rapid pace of advancement challenges the clinician's ability to remain current in the management of conditions faced often in practice.

Psoriasis affects about 2% of the population. Three new biologic agents, all interleukin (IL)-17 antagonists, have been approved for the treatment of psoriasis in the last 2 years. At least four IL-23 antagonists are in late-stage development. A biosimilar has been introduced to the US market within the last year. Alternative maintenance regimens have been studied. The new therapies are associated with improved efficacy rates and differing safety profiles with which clinicians must become familiar.

Roughly 20% to 30% of individuals with psoriasis develop psoriatic arthritis (PsA). In addition to the presence of comorbid skin disease, articular manifestations and pathophysiology differentiate PsA from other forms of arthritis. Clinicians would benefit from understanding how to distinguish PsA from rheumatoid arthritis and other rheumatic diseases. Many therapies for psoriasis also are efficacious in PsA.

New guidelines for the treatment of acne highlight the importance of appropriately limited antibiotic use. They also offer recommendations for the therapy of mild, moderate, and severe acne. New topical therapies have been approved for the treatment of this condition. A study about the patient-reported effect of hormonal contraceptives on acne has shed light on this important issue.

Onychomycosis is a common complaint in clinical practice. Laboratory confirmation of diagnosis is a crucial element of successful therapy. New topical therapies offer additional options for patients; an oral therapy is undergoing clinical trials as well. Results acceptable to the patient require persistence with treatment as well as adherence to lifestyle measures intended to reduce the risk of recurrence and reinfection.

The increasing popularity of soft tissue augmentation for aesthetic reasons has been accompanied by reports of accidental injection of filler into facial vasculature. This has resulted in cases of blindness. Along with a thorough knowledge of facial anatomy, certain techniques may reduce the risk of this catastrophic outcome. A protocol for handling complications of injection also is crucial.

Learning Objectives

By reading and studying this supplement, participants should be better able to:

- Explain the mechanisms and roles of currently available biologic agents in the treatment of psoriasis and psoriatic arthritis
- Analyze the investigational biologics for psoriasis
- Distinguish the manifestations of psoriatic arthritis from those of rheumatoid arthritis
- Incorporate recent guideline recommendations into the care of acne
- Demonstrate knowledge of options for laboratory diagnosis of onychomycosis
- Evaluate current and emerging therapy for onychomycosis and acne
- Integrate techniques to prevent serious adverse events, such as blindness, when injecting soft tissue fillers

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 non-profit 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.

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

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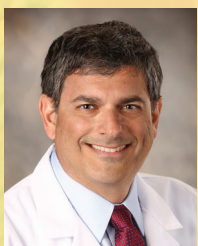
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HIGHLIGHTS OF Skin Disease Education Foundation's 41st Annual Hawaii Dermatology Seminar® Grand Wailea Hotel, Wailea, Maui, Hawaii; January 29–February 3, 2017

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Abstract

New therapies, recent pathophysiological findings, and updated guidelines combined to create compelling presentations at the Skin Disease Education Foundation's 41st Annual Hawaii Dermatology Seminar™. This educational supplement summarizes the highlights of clinical sessions presented during this CME/CE conference.

A growing understanding of the biology of psoriasis has facilitated the development of increasingly efficacious medications. Skin clearance used to be regarded as an impractical goal for psoriasis therapy. Now, some clinical trials of newer medications report more than half of participants attaining Psoriasis Area and Severity Index (PASI) scores of 90. Two leading investigators review the latest findings about the treatment of this condition. Recent evidence demonstrates that psoriasis and psoriatic arthritis share multiple pathological underpinnings. A T helper type 17 (Th17) lymphocyte-based pathogenesis, genes, and microbiome changes have been identified in both conditions. Many therapeutics used in psoriasis care are efficacious in psoriatic arthritis. An expert in psoriatic arthritis updates readers about this condition.

Cutaneous fungal infections, including onychomycosis, pose diagnostic and treatment challenges. New topical therapies and an investigational oral agent offer expanded options for management. The American Academy of Dermatology has issued new guidelines for the treatment of acne. Appropriate antibiotic use is a prominent theme. The US Food and Drug Administration has issued a communication about the risk of unintentional injection of soft tissue fillers into facial blood vessels—including blindness. The lead author of a recent review about this topic discusses how to prevent this serious outcome.

The volume of new information about pathophysiology, diagnosis, therapy, and safety challenges our ability to keep current while enabling us to improve patient care. We hope that the highlights of this seminar offer you information that can be applied to your busy practices. *Semin Cutan Med Surg* 36(supp3):S51-S59

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Emerging Therapies for the Systemic Treatment of Psoriasis

The efficacy of ustekinumab in treating psoriasis underlined the value of targeting the p40 subunit, shared by interleukin (IL)-12 and IL-23.¹ Pathophysiological evidence suggests that ustekinumab's benefits derive primarily from its effect on IL-23. This cytokine is viewed as the key to psoriasis pathogenesis. IL-23 production leads to T helper type 17 (Th17) cell proliferation in the skin; Th17-derived cytokines such as IL-17A contribute to the pathology of psoriasis.² Recently approved and late-stage investigational therapeutics target the cytokines IL-23 and IL-17A. The most recently introduced therapies display high rates of efficacy, defined as at least a 75% reduction from baseline in the Psoriasis Area and Severity Index score (PASI 75) after 12 or 16 weeks of therapy.

Other developments in psoriasis treatment include the introduction of a biosimilar for the tumor necrosis factor (TNF) inhibitor adalimumab, another TNF inhibitor under study for use in psoriasis, and trials of alternative regimens for approved medications.

IL-17 Antagonists Brodalumab. Approved by the US Food and Drug Administration (FDA) in February 2017, brodalumab is available only through a Risk Evaluation and Mitigation Strategy (REMS) program. It carries a black box warning about the risk of suicide and suicidal ideation and behavior. Six suicides occurred during brodalumab phase III trials, four during psoriasis studies.³ Risk of suicidal ideation and behavior was increased among patients with a history of suicidality or depression.⁴ In contrast to the anti-IL-17A antibodies secukinumab and ixekizumab, brodalumab blocks the IL-17 receptor A (RA) receptor subunit shared by IL-17A and multiple other proinflammatory cytokines in the IL-17 family.⁵

Class efficacy and safety. All three IL-17A antagonists on the US market—secukinumab, ixekizumab, and brodalumab—have produced PASI 75 rates superior to those of an active comparator (etanercept for secukinumab and ixekizumab; ustekinumab for brodalumab) in head-to-head phase III trials. PASI 75 rates at week 12 were as high as 81.6% for secukinumab 300 mg, 89.7% for ixekizumab (q2w), and 86% for brodalumab 210 mg.⁶⁻⁸ All three agents are associated with mild or moderate *Candida* infections, neutropenia (without serious infections), and rare cases of new-onset and/or exacerbations of inflammatory bowel disease (IBD).^{4,6,7,9-11} Brodalumab is contraindicated in patients with Crohn's disease. Patients should be monitored for the onset or (for secukinumab and ixekizumab) exacerbation of IBD, especially if there is a personal or family history of this condition.^{10,11} PASI 75 rates observed with ixekizumab generally were maintained on treatment from week 12 to 60.⁹

IL-23 Antagonists At least four agents that inhibit IL-23 without affecting IL-12 are in development. Clinical data in psoriasis are not available for one, bimekizumab; a phase IIb trial is in progress (ClinicalTrials.gov NCT02905006).

Guselkumab. A phase III study using guselkumab 100 mg (subcutaneous injections week 0, 4, then every 8 weeks) reported significantly higher rates of Investigator Global Assessment scores 0 or 1 and PASI 90 at weeks 16, 24, and 48 as compared with adalimumab (PASI 75, 91.2% at week 16). Rates of overall and serious adverse events (SAEs) were similar across treatment groups. Infections, infections requiring antibiotic treatment, malignancies, and major adverse cardiovascular events (MACE) occurred rarely and at similar rates in the two active

treatment groups.¹² Guselkumab was approved for the treatment of moderate to severe plaque psoriasis on July 13, 2017.¹³

Tildrakizumab. A phase IIb, dose-ranging trial with tildrakizumab (n=355) reported a PASI 75 rate of 74.4% at the highest dose studied (200 mg) after 16 weeks of treatment.¹⁴ Rates of attaining PASI 75 at week 16 (primary end point) were significantly higher with every tildrakizumab dose studied as compared with placebo ($P \leq 0.001$ for each comparison). Most responders (96.4%; 214/222) retained PASI 75 through week 52 of treatment.¹⁴

Risankizumab (previously BI 655066). Following a single dose of this medication, 87% of 31 patients attained PASI 75 at week 12 in a phase I study; 58% reached PASI 90.¹⁵ Response rates remained high at week 24 (71% and 48%, PASI 75 and 90, respectively). Six of the eight patients followed beyond 24 weeks maintained a PASI 100 for 41 to 66 weeks. Laboratory testing on lesional skin of treated individuals revealed reduced levels of proteins and genes associated with the IL-23/IL-17 axis.¹⁵

Preliminary findings from a phase II study comparing risankizumab with ustekinumab reported PASI 90 rates at week 20 of 90% and 76% with the higher and lower dose of risankizumab, respectively, compared with 55% with ustekinumab. Patients received 180 or 90 mg of risankizumab at weeks 0, 4, and 16. Overall AEs were similar between treatments; all SAEs were deemed unrelated to study medication.¹⁶

TNF Inhibitors Certolizumab pegol. An anti-TNF agent approved for use in Crohn's disease, rheumatoid arthritis, and psoriatic arthritis, certolizumab pegol is under study for use in psoriasis. Preliminary reports of two 16-week phase III trials (n=234, n=227) documented PASI 75 rates of 75.8% and 82.6% for patients receiving the higher dose (400 mg every 2 weeks) and 66.5% and 81.4% for those treated with the lower dose (200 mg every 2 weeks) reaching PASI 75. PASI 90 rates were 43.6% and 55.4% with the higher dose, and 35.8% and 52.6% with the lower dose, respectively.¹⁷

Adalimumab biosimilar. Adalimumab-atto (ABP 501) received FDA approval last fall, after demonstrating similar mean PASI percentage improvement to that of adalimumab in a phase III study: 86.6%, 87.6%, and 87.2% for the biosimilar and 88.0%, 88.2%, and 88.1% for adalimumab at weeks 16, 32, and 50, respectively. Rates of immunogenicity and the safety profile also were comparable between the two agents.¹⁸

Adalimumab dose escalation, de-escalation, re-escalation. Some patients do not maintain response to therapy. The open-label extension of the Randomized Controlled Evaluation of Adalimumab (REVEAL) study examined whether dose escalation (from 40 mg every other week to 40 mg weekly) restores response. Raising the dose re-established PASI 75 response in about half of patients (48%; 144/299), after a median of 17 weeks. Those in whom response was restored resumed every-other-week administration. About half (47% [68/144]) of those individuals again stopped responding (ie, fell below PASI 50) after a median of 24 weeks. These patients were again dose escalated and remained on weekly dosing for a median of 44 weeks. The remaining 53% of patients who were dose reduced following initial escalation retained at least a PASI 50 response on every-other-week dosing for a median of 60 weeks. No safety concerns were associated with dose escalation. About a quarter (76/299) of patients who underwent dose escalation retained response after dose reduction back to every-other-week frequency.¹⁹

Extending the Maintenance Dosing Interval A question that

arises in clinical practice is whether patients who are clear or almost clear on biologic therapy would maintain their response with less frequent dosing. The PSTELLAR study evaluated this question with ustekinumab. Following a run-in period using the recommended dosing schedule, responders were randomized to continuation at the recommended maintenance dose (every 12 weeks) or a schedule (n=76) in which ustekinumab was given at intervals based on time to loss of a Physician Global Assessment (PGA) score of at least 2 (n=302). The number of visits at which patients received a static PGA score of 0 or 1 (primary outcome) numerically favored the recommended maintenance schedule, though no statistical comparison was performed: 4.5 visits (95% CI, 3.81-5.21) compared with 4.1 visits (95% CI, 3.72-4.39). The mean number of visits at which patients displayed a PASI 75 response also numerically favored the recommended maintenance schedule, with no statistical comparison performed: 5.8 (SD, 2.31) compared with 5.4 (SD, 2.61) visits (ClinicalTrials.gov NCT01550744).

Conclusions Medications for psoriasis have become increasingly efficacious over the years, with rising proportions of patients achieving PASI 75, 90, and even 100. Relative efficacy should be an important consideration when choosing therapy. The availability of biosimilars and investigation of alternative regimens for older therapies broadens the options for patients. The anti-IL-23 agents in late-stage development will form the next wave of new medications.

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Psoriatic Arthritis: Pathogenesis and Treatment

Psoriatic arthritis (PsA) affects about 20% to 30% of individuals with psoriasis and follows the development of psoriasis in these individuals by about 10 years.¹ This article reviews the pathogenesis of PsA and its relationship to psoriasis and compares features of PsA to those of rheumatoid arthritis (RA). It also reviews how the pathophysiology of PsA translates into treatment response.

Pathogenesis Evidence suggests that the pathogenesis of psoriasis and psoriatic arthritis are overlapping and complex. Interleukin (IL)-12/23 and IL-17 are more important in psoriasis while TNF- α has a more prominent role to play in PsA. In addition, by disturbing the Wnt-Dickkopf (Dkk)-1 pathway, TNF- α results in an imbalance between healing erosion and increasing bony proliferation. Keratinocytes and modified dendritic cells are more important in psoriasis while T cells of various lineages play more significant roles in PsA, particularly with respect to enthesitis.¹

Genetics Genome-wide association scans have identified a number of genes that appear to have a pathogenic role in both PsA and psoriasis. Most of these genes affect skin barrier function, or innate or adaptive immune response.²

Obesity The risk for both psoriasis and PsA rises with body mass index (BMI). Compared with a BMI of 21 to 22.9, the multivariate relative risk of incident plaque psoriasis over 14 years rose with BMI category (25-29.9 and 30-34.9, ≥ 35 ; $P < 0.001$ for trend), in an analysis of data from women in the Nurses Health Study II (n=78,626). Weight gain (from age 18 to follow-up measurement) as well as higher waist circumference, hip circumference, and waist-to-hip ratio were associated with higher risk of incident psoriasis.³ Higher BMI categories also were linked to a greater risk of incident PsA over 5 years among individuals with psoriasis in a UK general population database (n=75,395; $P < 0.001$ for trend).⁴

Microbiome: The Gut and PsA Data increasingly suggest a link between intestinal microbiota, gut inflammation, and spondyloarthropathies (SpAs) such as PsA. Patients with PsA and psoriasis displayed less diverse intestinal microbiota than healthy controls in a small study (n=16 with PsA, 15 with psoriasis, 17 healthy controls). Patients with PsA were diagnosed recently and had not received steroids, disease-modifying agents, or biologic therapy for that condition. The gut microbiota of individuals with PsA had less reportedly beneficial organisms than that of people with psoriasis, and was similar to that of patients with inflammatory bowel disease.⁵

PsA Manifestations A wide range of joint abnormalities is associated with PsA, including synovitis, dactylitis, ankyloses, enthesitis, and arthritis mutilans.^{1,6} The pathology of PsA differs from that of rheumatoid arthritis (RA) in multiple ways, as follows.

Synovio-entheseal complex (SEC). The synovium and enthesitis are closely related, leading authorities to characterize them as a unit called the SEC. One theory suggests that mechanical stress on the enthesitis may lead to an innate immune response and inflammation in the adjacent synovium of patients with PsA.⁷

Synovial histopathology. Studies demonstrate differences between the synovial cellular composition in RA and the SpAs such as PsA. Synovitis in SpA was notable for higher vascularity than that observed in RA, as well as more infiltration with CD163+ macrophages and polymorphonuclear (PMN) leukocytes. Compared with SpA joint tissue, RA synovitis was marked by more lining-layer hyperplasia, lymphoid aggregates, CD1a+ cells, intracellular citrullinated proteins, and major histocompatibility complex–human cartilage glycoprotein-39 (MHC–HC gp39) complexes. Disease activity in SpA was correlated with CD163+ macrophages, PMN leukocytes, and lining-layer hyperplasia.⁸

Bone remodeling. Bone erosion is a hallmark of RA, whereas abnormal bone formation as well as bone erosion occur in PsA. Wnt proteins promote new bone formation in inflammatory arthritis. Dkk-1 and sclerostin inhibit Wnt signaling. TNF- α inhibitors inhibit bone formation by inducing Dkk-1 and sclerostin expression. Dkk-1 levels responded to anti-TNF- α therapy differently in PsA and in RA; Dkk-1 levels were lower in PsA than in RA after 1 year of TNF- α inhibitor treatment. This may contribute to a bone remodeling imbalance favoring bone formation in PsA.⁹

IL-17 in PSA and RA joints. IL-17+CD4+ cells, particularly CD8+ cells, are found at higher levels in the synovial fluid compared with the peripheral blood of patients with PsA but not of those with RA. Levels of IL-17+CD4+ cells have been correlated with a marker for active synovitis in PsA.¹⁰

Pathogenesis and Treatment Efficacy TNF- α inhibitors. About 51% to 59% of patients with PsA responded to TNF- α inhibitors in phase III trials (ie, American College of Rheumatology 20% response [ACR20] at 12 to 14 weeks), depending on the study.^{11,12}

IL-12/23 inhibitor (ustekinumab). At week 24, 43.8% of patients receiving either dose (45 mg or 90 mg) of this agent attained an ACR20 response, in a phase III trial. Response was maintained at week 52 (47.6% achieving ACR20 in combined ustekinumab dose groups).¹³ ACR20 rates were similar in another phase III study (42.4% and 49.5%, 45 mg and 90 mg, respectively, at week 24).¹⁴

Ustekinumab also decreased enthesitis; compared with the placebo group, a lower proportion of those receiving active treatment had residual enthesitis at week 24 ($P < 0.05$).¹³ The agent also reduced radiograph progression compared with placebo at week 24; benefit was maintained at week 52.¹⁵

IL-17 inhibitors (secukinumab, ixekizumab). Roughly half of patients with PsA achieved an ACR20 response at week 24 with secukinumab in phase II (50.0% and 50.5%, 150 mg and 75 mg, respectively) and phase III (54% and 51%, 300 mg and 150 mg, respectively) trials.^{16,17} The phase II study reported reduced radiograph progression with secukinumab, and higher proportions of patients with resolution of dactylitis or enthesitis at week 24, compared with placebo.¹⁷

A matching-adjusted indirect comparison (MAIC), adjusting for differences in patient baseline characteristics, was performed to simulate a head-to-head comparison between data from phase III trials of secukinumab and of adalimumab 40 mg every 2 weeks. Both secukinumab 150 mg and 300 mg had significantly higher mean ACR20 response rates at week 52 than did adalimumab at week 48 (nearest data point), as measured by relative risk and probability of response.¹⁸

Ixekizumab (both doses) and adalimumab 40 mg every 2 weeks produced numerically similar rates of response (ACR20 at week 24) in a head-to-head trial (62.1%, 57.9%, 57.4%; ixekizumab 80 mg every 2 weeks, ixekizumab 80 mg every 4 weeks, adalimumab, respectively). Response rates (ACR20 at week 24) with all active therapies were statistically superior to those observed with placebo (30.2%).¹⁹

Phosphodiesterase type 4 (PDE4) inhibitor. Apremilast, an oral agent, inhibits PDE4 conversion of cyclic adenosine monophosphate (cAMP) to AMP, thereby downregulating the inflammatory response.²⁰ ACR20 response rates at week 16 with the recommended maintenance dose (30 mg twice daily) were 38%, 32%, and 41% across three phase III studies, significantly higher than the placebo response rates of 19%, 19%, and 18%. Study participants had active disease despite prior or current therapy with a disease-modifying antirheumatic drug or a biologic therapy.²¹

Effects of apremilast on enthesitis or dactylitis were evaluated across the three phase III trials. Enthesitis was measured by the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES). Compared with placebo, apremilast 30 mg twice daily was associated with a significantly greater mean change in MASES and in percentage change in MASES from baseline to week 24. Mean change from baseline in dactylitis count at week 24 was significantly greater with apremilast 30 mg twice daily than with placebo.²²

Summary Several lines of evidence point to links between the pathophysiology of PsA and psoriasis. PsA is distinct from RA in several respects. Many of the same medications that are effective in psoriasis also are beneficial in PsA.

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Onychomycosis and Other Fungi

Onychomycosis is among the most common nail disorders in adults.¹ This article reviews assessment, management, and newer therapies for this disorder.

Confirm the Diagnosis Clinical suspicion of onychomycosis should be verified through laboratory confirmation.^{1,2} Dermatologists often misdiagnosed infections in an interactive case-based survey about superficial mycotic infection. At least half (50% to 60%) of participants correctly identified 8 of 13 cases (61.5%).³ Laboratory testing distinguishes between residual dyschromia or other noninfectious sequelae and persistent infection. Potassium hydroxide (KOH) testing is the least costly, most often available office-based option.⁴ Confirmatory testing was cost-effective prior to efinaconazole but not terbinafine therapy, according to a decision analysis.⁴

Treat All Infection Sites The nail bed can serve as a reservoir of fungal infection that spreads to other parts of the body. Concomitant fungal skin infections, most commonly tinea pedis, were present in 42.8% of 2,716 patients with onychomycosis in one series.⁵ Treating all infection sites may prevent transmission within the individual or to others and may reduce the risk of recurrence.⁶⁻⁸

Oral Therapy Options include terbinafine 250 mg daily for 12 to 16 weeks; itraconazole in a pulse (400 mg daily for 1 week per month for 3 months) or continuous regimen (200 mg once daily for 12 weeks)⁹; off-label fluconazole therapy (150 to 450 mg weekly for 4 to 12 months); and posaconazole (100, 200, or 400 mg once daily for 24 weeks).^{1,10} Efficacy of itraconazole pulse therapy is comparable to that of terbinafine; terbinafine carries a higher rate of adverse events and treatment-related discontinuation.¹¹

An investigational therapy, VT-1161, demonstrated 48-week complete cure rates of 32% to 55% in a phase IIb study, according to a preliminary report. The percentage of nail involvement was reduced by a median of 87%. The rate of adverse events was similar to that observed in the placebo arm. The agent selectively inhibits fungal CYP51.¹²

Topical Therapy Efficacy and safety. Two topical options were introduced in the last few years.^{13,14} Efinaconazole 10%, applied once daily for 48 weeks, has demonstrated mycological cure rates of 55.2% and 53.4% at 52 weeks in two phase III studies. About 45% and 40% of patients in the two trials receiving efinaconazole had ≤10% clinical involvement of the target toenail at 52 weeks.¹⁴ Tavaborole 5%, a boron-based compound applied once daily for 48 weeks, demonstrated mycological cure rates of 31.1% and 35.9% at week 52 in two phase III trials. Clear or almost clear nail (≤10% clinical involvement) was achieved in 26.1% and 27.5% of patients in the two studies.¹³ The rates of adverse events were similar to that of vehicle with both treatments.^{13,14}

Effect of nail polish. Nail penetration with both agents was unaffected by nail polish in ex vivo studies of human nails.^{15,16}

Effect of adjunctive therapy for onychodystrophy. Nail dystrophy and desiccation contribute to onychomycosis. Adjunctive therapy to address nail damage may be beneficial. The polymer poly-urethane forms a waterproof, breathable barrier to protect the nail plate and prevent further damage. Results of in vitro studies with poly-urethane 16%, efinaconazole 10%, and tavaborole 5% suggest that the polymer would not limit the ability of either antifungal agent to access the nail.¹⁷ Findings require clinical confirmation but suggest the possibility of benefit from combining antifungal and anti-dystrophic therapy.

What Constitutes Treatment Success? Treatment success rates in clinical trials may differ from acceptable results in practice. Complete mycological and clinical cure is a common and difficult-to-achieve end point in clinical studies. Yet the patient's goal is typically normal-appearing nails. Cure requires full nail regrowth, which can take more than a year. It is important to educate patients about the time required for full treatment benefit and that the result may not be a normal-looking nail.¹⁸

Lifestyle Measures Onychomycosis is associated with high rates of reinfection and recurrence. Practices that may reduce these risks include^{1,8,19}:

- Discard old shoes or decontaminate shoes and socks with antifungal powder, ozone, or ultraviolet light.
- Avoid walking barefoot in communal facilities such as gyms, hotels, and pools.
- Wear cotton, absorbent socks.
- Clip nails short.
- Avoid sharing nail clippers.
- Avoid frequent manicures and pedicures in nail salons.

Conclusions Laboratory confirmation of the diagnosis, treating any concomitant fungal infection, persisting with therapy, and lifestyle measures to minimize re-exposure all may promote successful therapy of onychomycosis. Topical therapies offer additional options for patients.

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Acne: New Guidelines, New Therapies

The American Academy of Dermatology (AAD) issued new guidelines for the management of acne last year.¹ This article reviews the guidelines as well as new and investigational therapies.

AAD Guidelines Promoting appropriate antibiotic use is one theme of the AAD recommendations.¹ Following are some of the key points.

Limit systemic antibiotic use to the shortest possible duration, typically 3 months.¹ Clinicians often prescribe antibiotics in acne therapy for longer than recommended: a mean of 129 days in one study and 331 days (among patients who later received isotretinoin) in another.^{2,3} While antibiotic use in farm animals has been associated with weight gain, prolonged antibiotic use for acne (median duration, 60 days) was not associated with weight gain in otherwise healthy adolescents.⁴

Reserve systemic therapy for moderate or severe disease. Use of systemic antibiotics other than tetracyclines and macrolides is discouraged.¹

Avoid monotherapy with topical or systemic antibiotics. Benzoyl peroxide (BP) should be added in order to reduce the risk of bacterial resistance. Systemic antibiotic therapy should generally be used with concurrent topical retinoids, and followed by topical maintenance therapy after discontinuation.¹

Oral isotretinoin need not be limited to severe disease but is an alternative for moderate acne that is treatment-resistant and/or associated

with physical scarring or psychological distress.¹

The Figure summarizes AAD guidelines by disease stage.

New Therapies *First over-the-counter (OTC) retinoid.* Adapalene gel 0.1% received US Food and Drug Administration (FDA) approval in July 2016, becoming the first over-the-counter active ingredient approved for acne since the 1980s, and the first OTC topical retinoid.⁵ OTC status may improve access to retinoid therapy.

Once-daily dapsone gel 7.5% received FDA approval in February 2016.⁶ A twice-daily 5% formulation was previously available.

Investigational therapies. A topical small molecule (olumacostat) glasaretil; (DRM 01) designed to affect sebum production is in phase III trials.⁷

SB204, a topical gel containing a nitric-oxide-releasing macromolecule,⁸ was well tolerated in two 12-week-long, phase II trials. Compared with vehicle, it significantly reduced the absolute inflammatory lesion count. It also significantly decreased the noninflammatory lesion count, in the higher of two concentrations tested (4% once daily rather than 2% twice daily).⁹ SB204 1% and 4% twice daily demonstrated significantly greater mean percent reduction in noninflammatory lesions, compared with vehicle; the higher concentration demonstrated significantly greater mean percent reduction in inflammatory lesions.⁸

Hormonal Contraceptives Analysis of patient-reported effects of hormonal contraception on acne indicated that depot injections, subdermal implants, and hormonal intrauterine devices were viewed as worsening acne (n=2,147). The vaginal ring and combined oral contraceptives (COCs) were rated as improving acne. Drospirenone was rated as most beneficial for acne, followed by norgestimate and desogestrel, then levonorgestrel and norethindrone. Triphasic progestin dosage in combined oral contraceptives was associated with a beneficial effect on acne.¹⁰

Milk Consumption of milk, particularly skim milk, has been associated with increased risk of developing moderate to severe acne in a case-control study of patients in dermatology outpatient clinics.¹¹ A prospective cohort study of teenaged boys reported that skim milk, though not whole or low-fat milk, was associated with acne.¹²

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FIGURE American Academy of Dermatology Guidelines for Acne Therapy

*Fixed combination product or separate components.

	Mild	Moderate	Severe
First-Line Treatment	Benzoyl Peroxide (BP) or Topical Retinoid -or- Topical Combination Therapy* BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic	Topical Combination Therapy* BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Antibiotic + Topical Retinoid + BP -or- Oral Antibiotic + Topical Retinoid + BP + Topical Antibiotic	Oral Antibiotic + Topical Combination Therapy* BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Isotretinoin
Alternative Treatment	Add Topical Retinoid or BP (if not on already) -or- Consider Alternate Retinoid -or- Consider Topical Dapsone	Consider Alternate Combination Therapy -or- Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin	Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin

Source: Adapted from: 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.e33.¹

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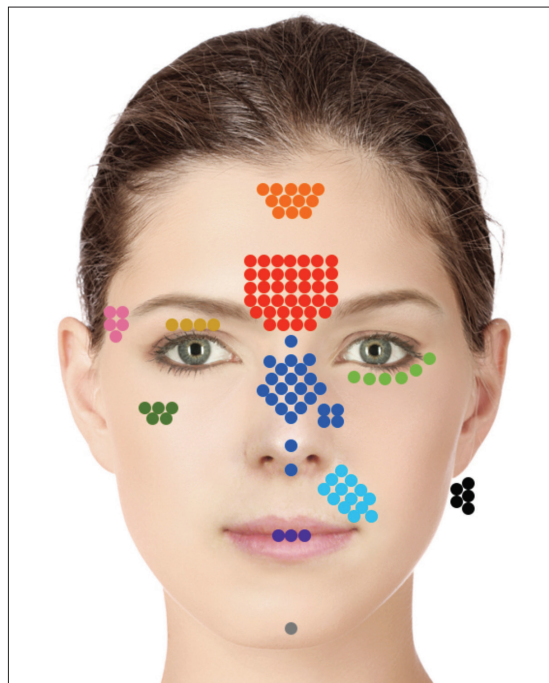
Preventing Blindness When Injecting Soft Tissue Fillers

Reports of complications following soft tissue augmentation appear to have increased as demand for the procedure has risen over the years. Reasons for this may include nonexperts performing injections and a shift toward 3-dimensional facial volume restoration rather than 2-dimensional treatment of discrete wrinkles. Accidental injection of soft tissue fillers into blood vessels can lead to vessel blockage and embolization, resulting in vision changes, blindness, stroke, and skin damage.¹ The US Food and Drug Administration has issued a safety communication about this topic.² A 2015 review identified 98 cases of vision loss associated with filler injections. Understanding facial anatomy is crucial to reduce the risk of negative outcomes. The Figure depicts the injection sites associated with vision loss.¹ Fillers most commonly associated with blindness were autologous fat (47.9%) and hyaluronic acid (HA) (23.5%). Nearly one-quarter of cases (23.5%) also were associated with central nervous system complications.¹

Complete and immediate vision loss is the most common initial symptom of the filler entering a blood vessel. Immediate, sometimes severe ocular pain and headache also are reported frequently. Skin blanching may occur. Nausea and vomiting may develop due to increased intraocular pressure. Ophthalmoplegia and ptosis can manifest within days.^{1,3} These symptoms may ease but vision almost never recovers (2/98 cases, in a recent review).¹

Every office performing soft tissue filler injections should have a protocol for handling complications. If the patient reports eye pain or vision changes, it is important to stop injecting immediately and transfer the patient to an ophthalmologist's office with whom a relationship has been established. Referral to an emergency department often results in long waits to be examined. Delayed care is unacceptable, as retinal damage becomes irreversible after 90 minutes.^{1,3} It is advisable to maintain the names and cell phone numbers for several local ophthalmologists.

FIGURE Injection Sites in Cases of Blindness



A literature search identified 98 cases of vision changes from filler. Injection sites most frequently associated with complications were the glabella (38.8%), nasal region (25.5%), nasolabial fold (13.3%), and forehead (12.2%). Source: Belezny K, Carruthers JD, Humphrey S, Jones D. Avoiding and treating blindness from fillers: a review of the world literature. *Dermatol Surg*. 2015;41(10):1097-1117.¹

If HA filler was used, then hyaluronidase should be injected in and around the treatment location. Retrobulbar injection of hyaluronidase (300-600 units [2-4 cc]) should be considered.¹ Reducing intraocular pressure (eg, by administering acetazolamide, mannitol) is another treatment strategy.^{1,3} The patient's neurologic status should be monitored; consider ordering imaging studies of the brain if visual complications develop.¹

Preventing Complications A thorough knowledge of the anatomy of the area to be injected, including the location of facial blood vessels, is crucial to reduce the risk of adverse events. Aspirating prior to injection can be considered to verify that the needle is not positioned in a blood vessel; the appearance of blood in aspirate should prompt withdrawal and repositioning of the needle.³ Injecting slowly, with minimal pressure and in small increments (≤ 0.1 mL) with a small syringe, while moving the needle tip between injections is important to avoid dispensing more filler than intended and to minimize dispensing filler if a vessel is entered.^{3,4} Using a small needle slows injection speed and, if a vessel is entered, may reduce the risk of vessel occlusion. Use of a blunt, flexible microcannula may reduce the risk of vessel perforation.³

Author: Katie Belezny, MD, FRCPC

References

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2. Unintentional injection of soft tissue filler into blood vessels in the face: FDA Safety Communication. May 28, 2015. <https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm448255.htm>.
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4. DeLorenzi C. Complications of injectable fillers, part I. *Aesthet Surg J*. 2013;33(4):561-575.

Highlights of Skin Disease Education Foundation's 41st Annual Hawaii Dermatology Seminar® Post-Test

FOR NOTES PURPOSES
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Original Release Date: June 2017

Expiration Date: June 30, 2018 • Estimated Time to Complete Activity: 2.0 hours

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

1. This activity discusses at least four agents in clinical development for the treatment of psoriasis. Which of the following is true of them?

- A. All have demonstrated efficacy superior to that of an active comparator.
- B. All target interleukin (IL)-23 without affecting IL-12.
- C. None have entered phase III trials.
- D. At least one has demonstrated Psoriasis Area and Severity Index (PASI)-100 rates of >95%.

2. Which of the following statements is true about diagnosing onychomycosis?

- A. Onychomycosis is a clinical diagnosis.
- B. Potassium hydroxide testing is not cost-effective prior to initiation of efinaconazole therapy.
- C. Laboratory confirmation is required.
- D. Evidence indicates that dermatologists have a high accuracy rate for clinical diagnosis of superficial mycotic infections.

3. Which of the following statements most accurately describes the results of a matching-adjusted indirect comparison between data for two biologic therapies in psoriatic arthritis (PsA)?

- A. Secukinumab was superior to adalimumab in terms of mean American College of Rheumatology 20% improvement criteria (ACR20) response rates at weeks 52 and 48, respectively.
- B. Ixekizumab was superior to etanercept in terms of mean ACR20 response rates at week 14.
- C. Ustekinumab was superior to infliximab in terms of mean ACR20 response rates at weeks 52 and 48, respectively.
- D. IL-17 inhibitors were superior to tumor necrosis factor (TNF)- α inhibitors in terms of mean ACR20 response rates at weeks 20 and 14, respectively.

4. Which first-line therapy option for mild acne is consistent with the latest American Academy of Dermatology guidelines?

- A. Topical antibiotic therapy
- B. Topical benzoyl peroxide (BP) plus topical antibiotic
- C. Systemic antibiotic therapy with doxycycline plus topical BP
- D. Systemic antibiotic therapy with trimethoprim-sulfamethoxazole plus topical BP

5. Psoriasis therapies sharing which mechanism of action are associated with mild to moderate *Candida* infections, neutropenia, and, rarely, new-onset or exacerbations of inflammatory bowel disease?

- A. IL-17A antagonists

- B. IL-23 antagonists
- C. Anti-TNF inhibitors
- D. Agents targeting the p40 subunit

6. Recommendations to prevent serious adverse events such as blindness during facial injection of soft tissue fillers may include all but which of the following:

- A. A thorough knowledge of facial anatomy, including location of facial blood vessels
- B. Aspirating prior to injection
- C. Use of a blunt, flexible microcannula
- D. Inject quickly, with maximal pressure, to shorten the duration of the procedure

7. Among patients with PsA participating in phase III trials, response (ie, ACR20) rates to TNF- α inhibitors at weeks 12 to 14 are:

- A. 30% to 45%
- B. 51% to 59%
- C. 60% to 75%
- D. >75%

8. Two therapies approved for acne in 2016 are:

- A. A topical over-the-counter retinoid and a higher strength dapsone gel
- B. A topical small molecule designed to affect sebum production
- C. A topical gel containing a nitric-oxide-releasing macromolecule
- D. A new systemic antibiotic approved for long-term (>3 months) use in moderate to severe acne

9. Which of the following characteristics resemble PsA rather than rheumatoid arthritis (RA)?

- A. Bone erosion without bone formation
- B. Abnormal bone formation and bone erosion
- C. Higher levels of CD8+ cells in the synovial fluid than in peripheral blood
- D. Less vascularity in synovial cells of PsA compared with RA

10. Which of the following statements best describes oral therapy for onychomycosis:

- A. Off-label fluconazole and posaconazole are not recommended for the treatment of onychomycosis.
- B. No new systemic therapies for onychomycosis are being evaluated in clinical trials.
- C. Terbinafine is preferred to itraconazole therapy because of its superior safety record.
- D. The efficacy of itraconazole pulse therapy is similar to that of terbinafine.

The University of Louisville and the Postgraduate Institute of Medicine thank you for your participation in this CME/CE activity. All information provided improves the scope and purpose of our programs and your patient care.

Highlights of Skin Disease Education Foundation's 41st Annual Hawaii Dermatology Seminar® Evaluation Form

Original Release Date: June 2017 • **Expiration Date:** June 30, 2018 • **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: <http://tinyurl.com/HISupp2017>

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: <i>Having completed this activity, you are better able to:</i>	Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
Explain the mechanisms and roles of currently available biologic agents in the treatment of psoriasis and psoriatic arthritis.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Analyze the investigational biologics for psoriasis.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Distinguish the manifestations of psoriatic arthritis from those of rheumatoid arthritis.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Incorporate recent guideline recommendations into the care of acne.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Demonstrate knowledge of options for laboratory diagnosis of onychomycosis.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Evaluate current and emerging therapy for onychomycosis and acne.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Integrate techniques to prevent serious adverse events, such as blindness, when injecting soft tissue fillers.	☐ 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 one 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
Katie Belezny, MD, 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
Neal Bhatia, 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
Lawrence F. Eichenfield, 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
Daniel E. Furst, 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
Kenneth B. Gordon, 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
Craig L. Leonardi, 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

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.

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