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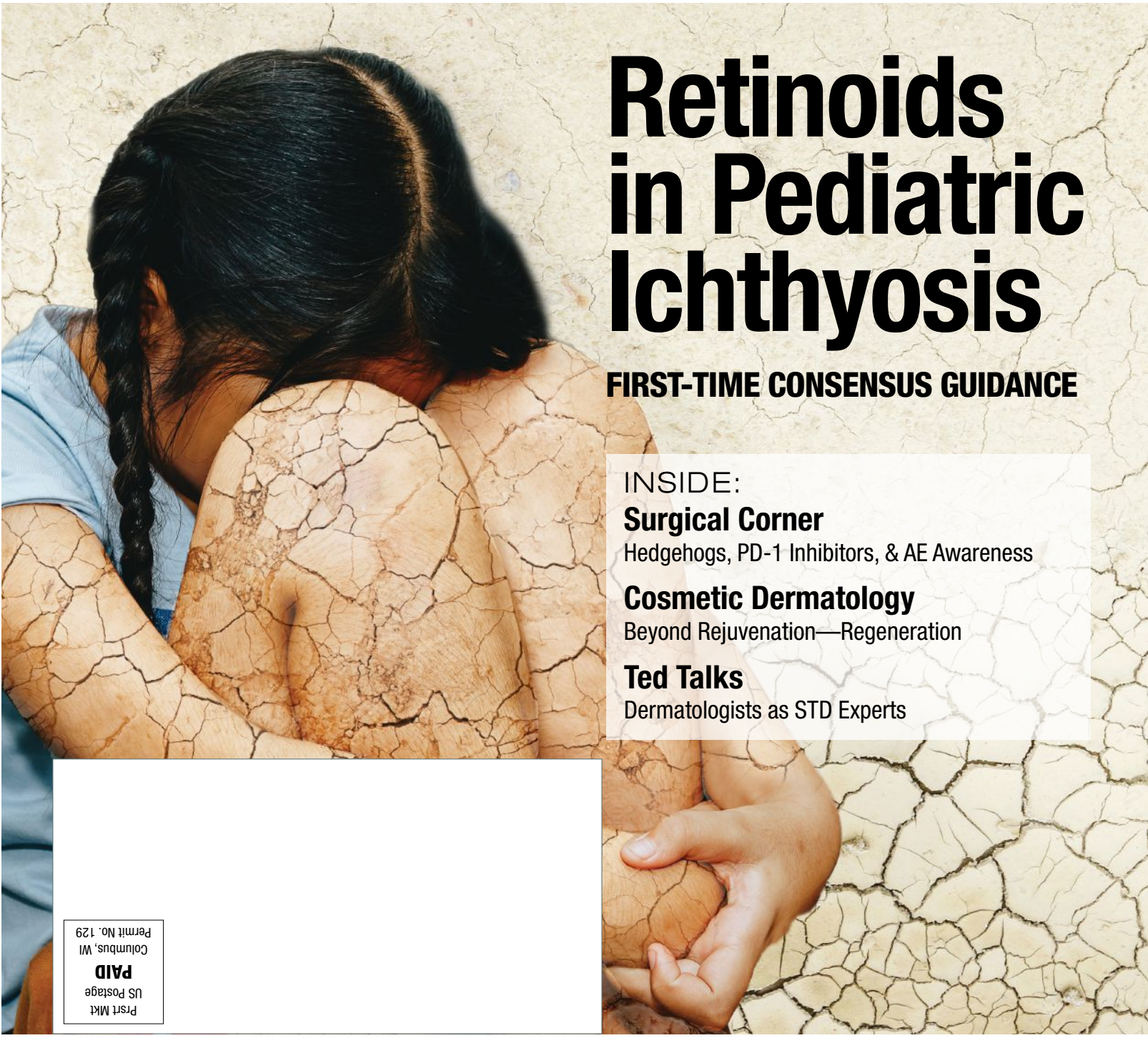
THE Dermatology® Digest

Vol. 2, No. 2 | February 2021



Retinoids in Pediatric Ichthyosis

FIRST-TIME CONSENSUS GUIDANCE

INSIDE:

Surgical Corner
Hedgehogs, PD-1 Inhibitors, & AE Awareness

Cosmetic Dermatology
Beyond Rejuvenation—Regeneration

Ted Talks
Dermatologists as STD Experts

WE WILL CHALLENGE THE STATUS QUO.
WE WILL DELIVER ON OUR PROMISES.

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Contents

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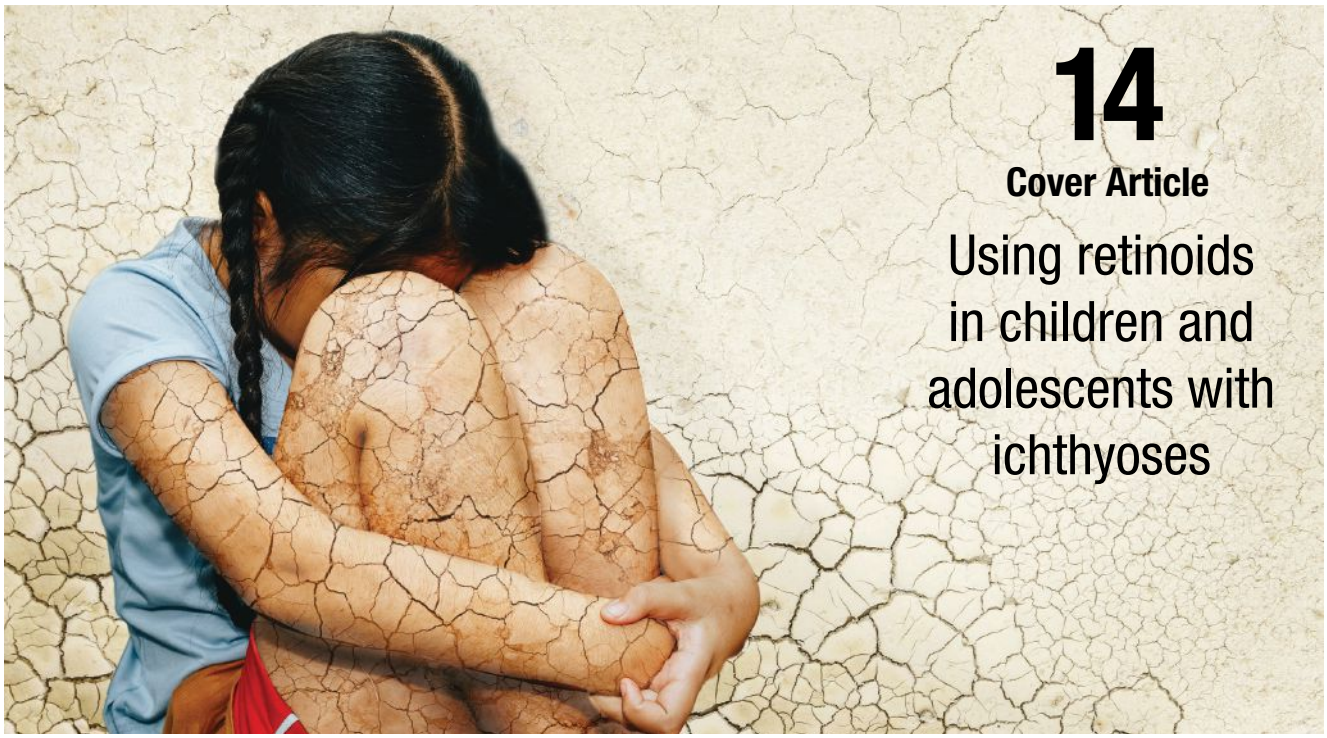
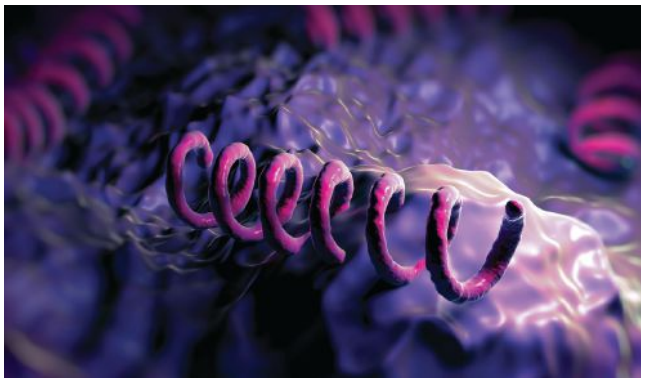
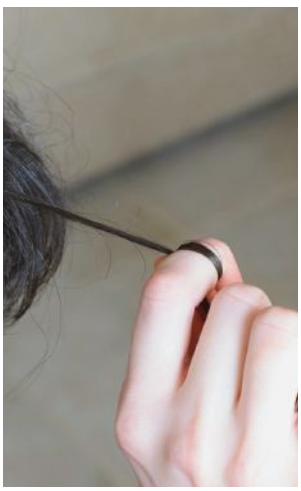
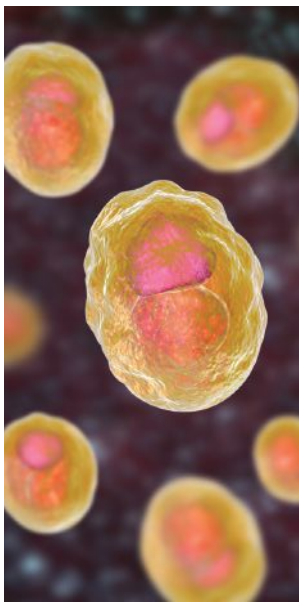








continued on page 3

Ted Talks

"When they met last year, she was the only one with herpes. With the help of her doctor, she's still the only one."

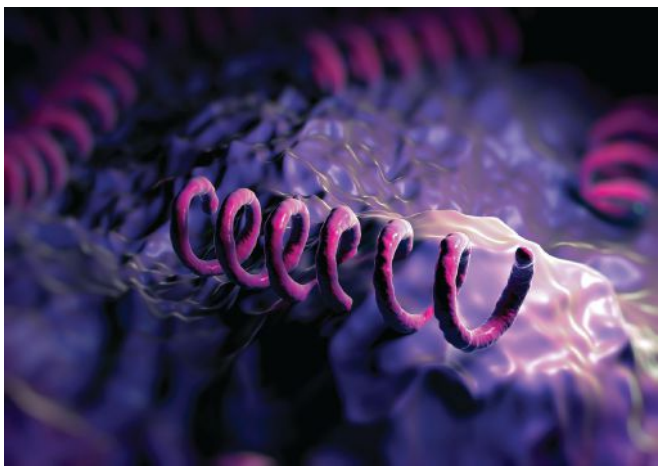
—Burroughs Wellcome Company advertisement, 1986

Ted Rosen, MD, FAAD
Editor-in-Chief

This is Ted's take.
What's yours?
ted.rosen@thedermdigest.com

Be sure to hear Dr. Rosen discuss his recent review article about STDs in the era of COVID at www.thedermdigest.com/ted-talks/literature_update_STDs

Should dermatologists still be experts in sexually transmitted disease? I supervised a night walk-in sexually transmitted disease (STD) clinic for the city of Houston for about 20 years, so this tells you my opinion! Moreover, I am asked to lecture on the subject at conferences and institutional grand rounds worldwide. I answer that rhetorical question in the resounding affirmative. Of course, diagnosing and treating STDs is neither as sexy (pun intended) nor as profitable as, say, administration of fillers and toxins. Still, there are many historical and contemporary reasons why we should strive to be STD authorities. Let's examine a few.



Probably most importantly, consider this: Where do most STDs occur? STDs occur on the *skin* of the anogenital region. While many STDs can affect other organ systems (syphilitic hepatitis, gonococcal tenosynovitis, chlamydial salpingitis, and herpetic encephalitis are some examples), the vast majority of STDs initially present with signs or symptoms involving the cutaneous surface or adjacent mucosa. Are dermatologists not the experts in skin, hair, and nails? Who would (or could) be better at recognizing that patchy, non-scarring alopecia might actually represent secondary syphilis? Who would (or could) be better at distinguishing the condyloma lata of secondary lues from external genital warts? Who better than the dermatologist at determining if an oral mucosal lesion is orolabial herpes, Behcet's disease, or the mucous patch associated with secondary lues? From the perspective of clinical morphology, dermatologists are experts at ascertaining and differentiating genitourinary disease.

What about from a therapeutic standpoint? Again, I maintain that dermatologists are among the most logical practitioners to treat STDs. We know all about imiquimod due to our use of this agent for actinic keratosis; yet, it was originally developed—largely by dermatologists—for the (FDA-approved) treatment of genital warts. We are very familiar with acyclovir and its various analogues because we use them to treat cold sores and shingles; it is not a leap for us to routinely use these agents to manage genital herpes in either an episodic or a suppressive or prophylactic manner. Dermatology providers are also well educated in the use of antibiotics. We are no strangers to doxycycline, the drug of choice for many STDs and the second-tier agent for syphilis.

continued on page 4

Contents continued from page 1

continued from page 2

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> "If American dermatologists totally abandon sexually transmitted diseases, then who will serve as the keepers of that knowledge and experience?"

Historical perspective

There is also the simple historical precedent. A whole series of major dermatological journals signaled, in their various titles, our interest in STDs, especially syphilis. Each of these was once the premier dermatology publication of its time: *American Journal of Syphilology and Dermatology, Journal of Cutaneous and Venereal Diseases, Journal of Cutaneous Diseases and Genitourinary Diseases* and *Archives of Dermatology and Syphilology*. From the late 1800s through 1955, few other than dermatology-oriented journals contained high-quality publications regarding STDs. Many of the leading dermatologists of the day simultaneously practiced venereology and, in fact, much of the best STD research was performed by dermatologists. For example, it was the director of the Dublin Skin Infirmary, often referred to as the father of Irish dermatology, Dr. William Wallace, who proved conclusively that secondary syphilis was a contagious disease. In Europe, to this day, it is expected that dermatologists will be well versed in the diagnosis and management of STDs. Consider the pre-eminent organization the European Academy of Dermatology and Venereology.

It's up to us

The clear question in my mind, therefore, is this: If American dermatologists totally abandon sexually transmitted diseases, then who will serve as the keepers of that knowledge and experience? Infectious disease clinicians are busy enough dealing with the COVID-19 pandemic, multiply-drug-resistant and resurgent tuberculosis, endemic fungal infections, rampant urosepsis, and emerging arboviruses. Gynecologists and urologists are, first and foremost, surgically oriented. Which leaves... whom? By default, dermatologists truly comprise that part of the healthcare community best suited to embrace (pun intended) STDs.

Despite prior optimistic predictions of the demise of syphilis and other STDs, these diseases not only persist but also flourish. From 2014 through 2019, the number of US cases and the rates per 100,000 population of syphilis, chlamydia, and gonorrhea increased dramatically due to the inability of public health officials, health care providers of all types, teachers, parents, clergy, and peer groups to meaningfully alter sexual behaviors. No one could have accurately predicted acceptance of casual sexual encounters popularized in television and movies or the ubiquitous use of sexual imagery in advertising. Nor could anyone have predicted the modern phenomena of "booty calls" and "friends with benefits." Who knew that internet dating sites and cell phone apps would be utilized to almost instantly secure random sexual partners? The paradox is that, while our journals and training programs have steadily de-emphasized STDs, these disorders simply refuse to go away.

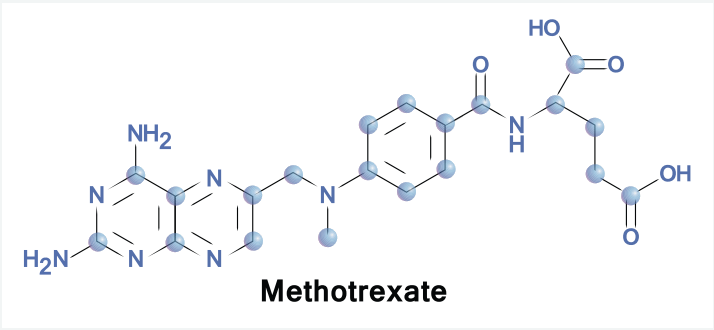
During her 2014 *HeForShe* campaign kick-off presentation, actress Emma Watson famously paraphrased the Jewish scholar Hillel the Elder (110 BC-10 AD) when she asked, "If not me, who? If not now, when?" I would ask the same questions about organized dermatology's diligent attention to and consistent involvement in the realm of STDs. ◈

EDITORIAL BOARD

Off-label Pearl

By Ted Rosen, MD, FAAD, Editor-in-Chief

Patients with **GENERALIZED GRANULOMA ANNULARE** (GA) should be evaluated for glucose intolerance, as generalized GA has been associated with Type 2 diabetes mellitus (DM). Failing to find DM, however, leaves a disorder that may be difficult to treat. The sheer extent may make application of topical steroids impractical, risky, or both. A retrospective study from the Dermatology Department at the University of Connecticut suggests that weekly methotrexate (MTX) may be an effective management tool. Relatively low doses, such as 12.5-15.0 mg once weekly, may suffice. Virtually all patients responded with either complete (43%) or partial (57%) clearance. Potential side effects include gastrointestinal upset and hair loss. The message is that moderate dosages of MTX may clear or improve generalized GA in an otherwise healthy cohort.



Methotrexate

TO READ MORE: Naka F, Strober BE. Methotrexate treatment of generalized granuloma annulare: a retrospective case series. *J Dermatolog Treat*. 2018;29(7):720-724. doi: 10.1080/09546634.2018.1447075.

Literature Lessons

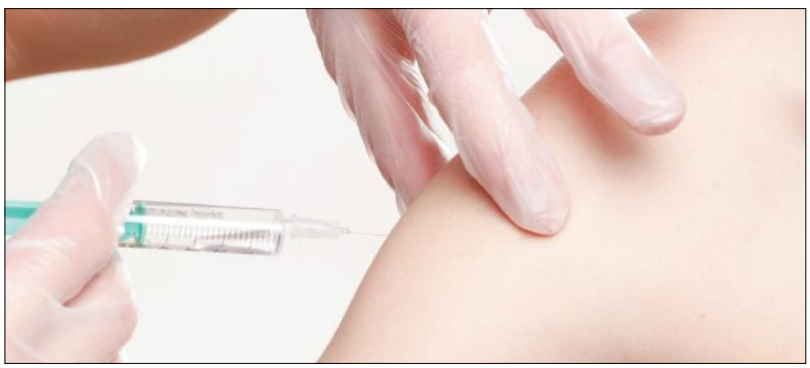
PEDIATRIC DERMATOLOGY

The **MEASLES AND RUBELLA INITIATIVE**, an international consortium, announced on November 12, 2020 that worldwide,

207,5000

MEASLES-RELATED DEATHS OCCURRED IN 2019.

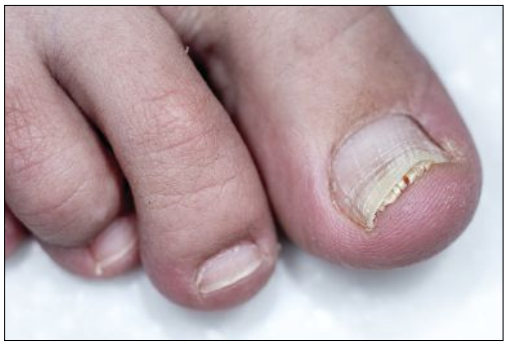
This was due to years of vaccination neglect, significantly worsened by the recent COVID-19 pandemic disrupting pediatric vaccination programs globally.



INFECTIOUS DISEASES

Add **UMBILICAL WART** (HPV types 6 and 11) to the differential of masses found in the naval. The traditional differential diagnosis includes: patent urachus, hypertrophic scar, pyogenic granuloma, endometriosis in women and umbilical metastasis.

TO READ MORE: Villela-Segura U, et al. A case of a reddish umbilical tumor: An uncommon presentation of a viral wart. *Indian J Dermatol Venereol Leprol* 2020;86:709-11.



A recent Turkish study reminds us that **ONYCHODYSTROPHY** does not mean that onychomycosis is the cause. Despite using KOH, culture, and mass spectrometry, fungi could be detected in only 68% of patients with clinical changes consistent with fungal infection.

TO READ MORE: Kara YA. The change of causative pathogens in toenail onychomycosis. *J Cosmet Dermatol* 2020 Nov 3. doi: 10.1111/jocd.13819

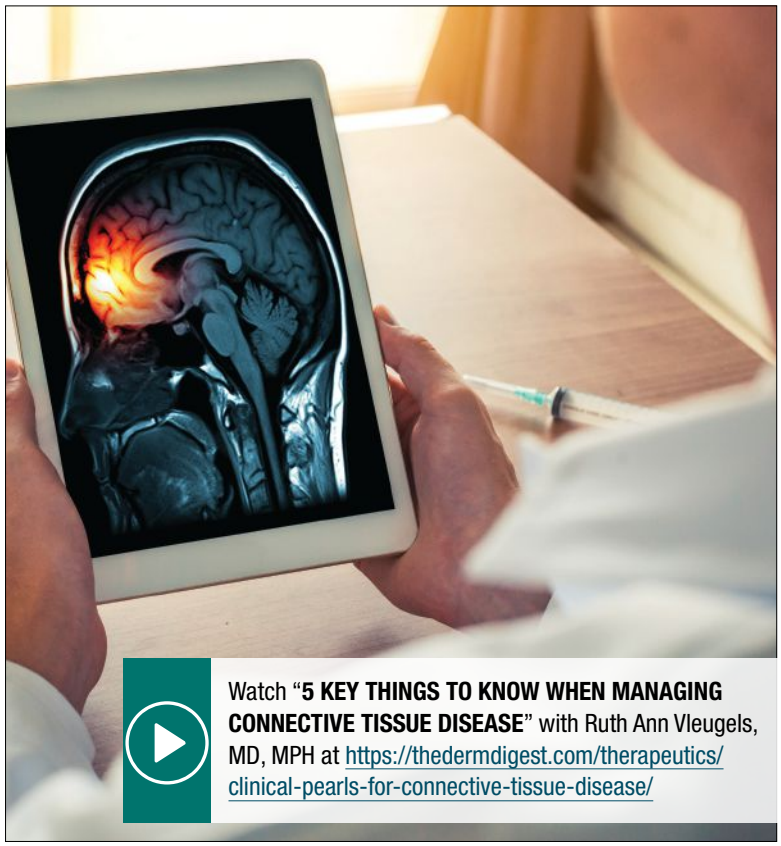
Even extensive **BEDBUG BITES** can be successfully managed by administration of ultrapotent topical steroids and oral non-sedating antihistamines (to tolerance). Eradication of an infestation requires both insecticide and physical modalities.

TO READ MORE: Delaunay P, et al. Bed bug bites. *Dermatol Ther.* 2020 Sep 25. DOI: 10.1111/dth.14341

RHEUMATOLOGIC DISEASES

A single-center, retrospective study of **738** adult patients with **AUTOIMMUNE DISEASE** treated with rituximab disclosed that about **10%** of the cohort developed late-onset neutropenia (absolute neutrophil count less than 1000 cells/ul). In **8.5%** of those with low neutrophil counts also developed sepsis. Filgrastim administration was often successful in reversing neutropenia.

TO READ MORE: Zonozi R, et al. Incidence, clinical features, and outcomes of late-onset neutropenia from rituximab for autoimmune disease. *Arthritis Rheumatol.* 2020;Sept 6. doi: 10.1002/art.41501



Watch "**5 KEY THINGS TO KNOW WHEN MANAGING CONNECTIVE TISSUE DISEASE**" with Ruth Ann Vleugels, MD, MPH at https://thedermdigest.com/therapeutics/clinical-pearls-for-connective-tissue-disease/

A Mayo Clinic retrospective analysis of 212 patients with autoimmune diseases, including rheumatoid arthritis, psoriasis, and inflammatory bowel disease, revealed that exposure to TNF-alfa inhibitors was associated with **INFLAMMATORY CNS** events. The latter included inflammatory demyelinating (multiple sclerosis and optic neuritis) and nondemyelinating (meningitis, meningoencephalitis, encephalitis, and CNS vasculitis) disorders. This association was, however, much stronger with RA than with psoriasis or psoriatic arthritis.

TO READ MORE: Kunchok A, et al. Association between tumor necrosis factor inhibitor exposure and inflammatory central nervous system events. *JAMA Neurol.* 2020;77:937-946.

HIDRADENITIS SUPPURATIVA

A small German study suggests that **IXEKIZUMAB** might be useful to restore control in hidradenitis suppurativa patients who eventually lose benefit from adalimumab therapy. Hilbring C. EADV 2020. Presentation P0012-629.

The role of **DIET IN HS** has not been adequately explored. A survey of more than 700 HS patients suggests that the following dietary constituents might exacerbate hidradenitis: sugary sweets; bread, rice and pasta; dairy products; and high-fat foods.

TO READ MORE: Fernandez JM, et al. Alleviating and exacerbating foods in hidradenitis suppurativa. *Dermatol Ther.* 2020 Aug 29:e14246. doi: 10.1111/dth.14246

Not surprisingly, when compared to a matched control group, HS patients are at increased risk for **BIPOLAR DISORDERS, DEPRESSION, ANXIETY, PERSONALITY DISORDERS, SUICIDE, SUBSTANCE ABUSE-RELATED DISORDERS, AND ALCOHOL ABUSE**. Thus, it is important for clinicians to adequately manage pain and be on the watch for disorders that may require the assistance of a mental health professional. Phan K, et al. Hidradenitis suppurativa and relationship with psychiatric comorbidities, suicides and substance abuse. P0019, EADV Virtual, 29-31 October 2020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7396254/

A 12 year-long retrospective analysis of nationwide data, disclosed

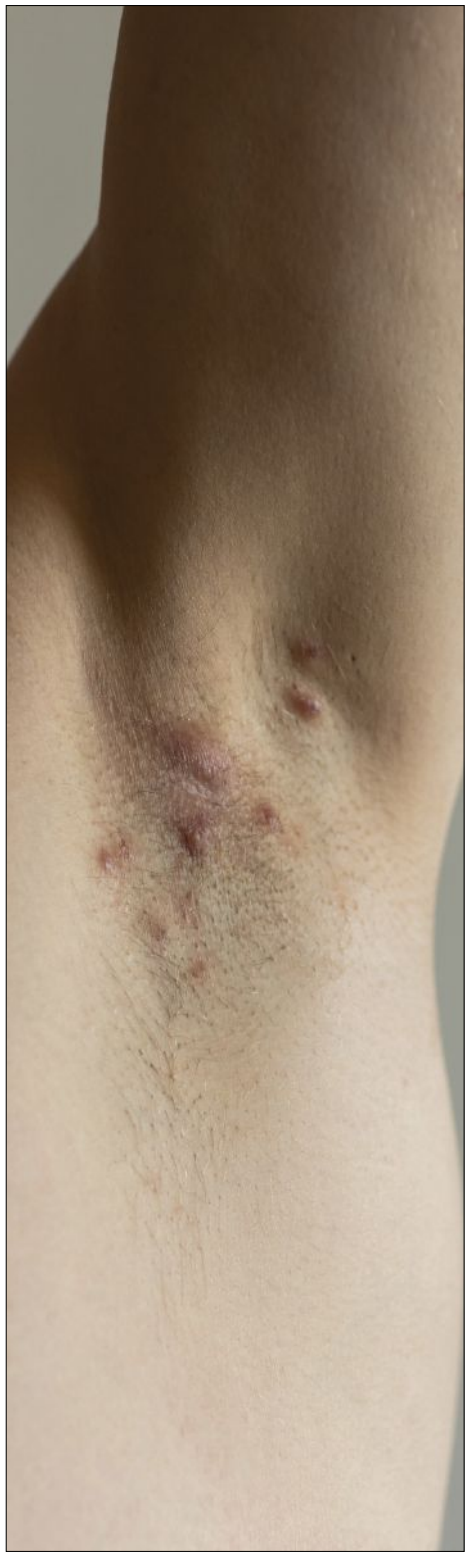
383,000 emergency department (ED) visits for the diagnosis of HS

mostly due to severe pain. Opioid prescriptions were given to 58.3% of patients. Concurrent antibiotics (clindamycin, trimethoprim-sulfamethoxazole HS, and cephalosporins, in that order) were also given in 67% of cases presenting to the ED. Always ask your HS patients if they have recently visited an ED and, if so, what medications they were given (and may still be taking).

TO READ MORE: Taylor MT, et al. Pain severity and management of hidradenitis suppurativa at US emergency department visits. *JAMA Dermatol.* 2020 Nov 18. doi: 10.1001/jamadermatol.2020.4494

Although prior reports have suggested a **FAMILIAL RISK FOR HS**, data has been rather casually collected. Six hundred seventy-six HS patients were enrolled in a registry 2018-2019 at the University of North Carolina Chapel Hill. Questionnaires and detailed in-person interviews disclosed a **57.5% prevalence of HS in first- and second-degree relatives** and a **49.5% prevalence among only first-degree relatives** (parents and siblings). These findings strongly suggest a genetic component to HS.

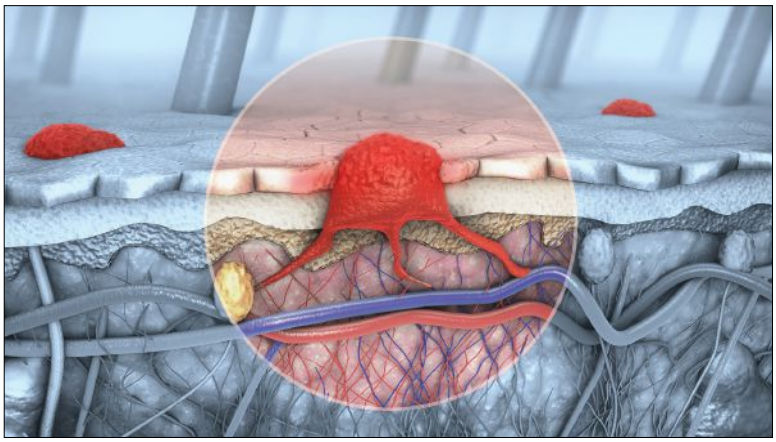
TO READ MORE: Bruinsma RL, et al. Assessment of familial risk in patients with hidradenitis suppurativa. *Br J Dermatol.* 2020 Nov 5. doi: 10.1111/bjd.19664



CUTANEOUS ONCOLOGY

A large US retrospective study demonstrated no advantage to treating **MELANOMA OF THE TRUNK AND EXTREMITIES** with Mohs micrographic surgery compared to the standard intervention of wide local excision.

TO READ MORE: Demer AM, et al. Association of Mohs micrographic surgery vs wide local excision with overall survival outcomes for patients with melanoma of the trunk and extremities. *JAMA Dermatol.* 2020 Oct 21:e203950. doi: 10.1001/jamadermatol.2020.3950



A nicely illustrated Korean case reminds us that hypopigmented MF can precisely mimic **VITILIGO** on a clinical level. Loss of CD7 staining, epidermotropism, and monoclonality may help distinguish the 2 conditions.

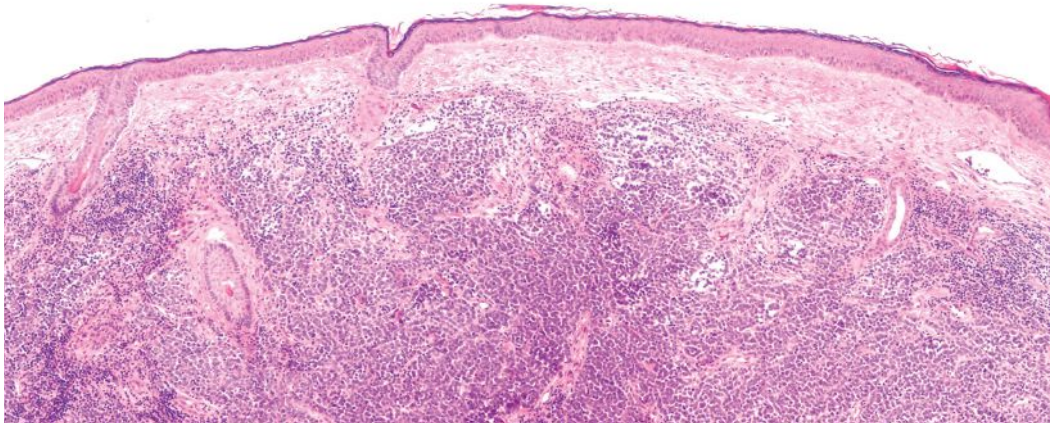
TO READ MORE: Kim JC, Kim YC. Hypopigmented mycosis fungoides mimicking vitiligo. *Am J Dermatopathol.* 2020 Nov 3. doi: 10.1097/DAD.0000000000001750.

About 2% of all cutaneous malignancies arise in the scalp.

These include primary epithelial, melanocytic and adnexal neoplasms, and metastatic tumors. Despite the difficulty due to hair cover, clinicians should attempt a thorough scalp assessment when performing a full body skin examination.

TO READ MORE: Dika E, et al Malignant cutaneous tumours of the scalp: always remember to examine the head. *J Eur Acad Dermatol Venereol.* 2020;34:2208-2215. https://doi.org/10.1111/jdv.16330

Patients with **MERKEL CELL CARCINOMA** with nodal involvement had better regional recurrence-free survival, distant recurrence-free survival, overall disease-free survival ,and disease-specific survival if nodal basin irradiation was part of their management plan. Radiation recipients did better than those who underwent only lymph node dissection. Andruska, N. American Society for Radiation Oncology (ASTRO) Annual Meeting, November, 2020; Abstract 2002



DRUGS AND DEVICES

Due to the persistence and recurrent waves of **COVID-19**, we may experience **SHORTAGES OF CRITICAL GENERIC DERMATOLOGIC DRUGS**. Many of these are manufactured in areas where COVID-19 surges have resulted in factory closures.

TO READ MORE: Egger A, et al. COVID-19 Supply chain considerations for prescription drugs in dermatology. *J Drugs Dermatol.* 2020 Jun 1;19(6):666-667. https://jddonline.com/articles/dermatology/S1545961620P0666X

CHRONIC LIP-LICKING can lead to irritant contact dermatitis, secondary infections, and various forms of cheilitis. The most important suggested preventative maneuver is daily application of a bland lip balm that has minimal amounts of dyes, fragrances, and flavorants, but is rich in ceramides, shea butter, petrolatum, or dimethicone. Cognitive behavioral therapy may also help break the habit of chronic picking at dry lips.

TO READ MORE: Fonseca A, et al. Art of prevention: practical interventions in lip-licking dermatitis. *Int J Womens Dermatol*. 2020;6(5):377-80.

Evidence for the utility of popular **ORAL HAIR GROWTH SUPPLEMENTS** is weak, at best. A recent comprehensive summary summarized: No clinical evidence supports the use of vitamins A, C, and D, biotin, niacin, selenium, ashwagandha, curcumin, and capsaicin; iron supplements should be given when known iron deficiency exists; conflicting data exists for use of zinc in hair loss; weak evidence exists for the use of vitamin E in multiple hair loss conditions; weak evidence exists for pumpkin seed oil and saw palmetto in androgenetic alopecia; horsetail and methylsulfonylmethane supplementation may improve hair health; and marine complexes have exhibited positive effects on hair health.

TO READ MORE: Adelman MJ, et al. Clinical efficacy of popular oral hair growth supplement ingredients. *Int J Dermatol*. 2020 Dec 9. doi: 10.1111/ijd.15344

A retrospective review of 43,000 Swedish patients with **CELIAC DISEASE** showed a higher prevalence of skin disease compared to an age- and sex-matched cohort. Watch for: eczema, psoriasis, urticaria, vitiligo, acne, and alopecia areata.

TO READ MORE: Lebwohl B, et al. Risk of skin disorders in patients with celiac disease: a population-based cohort study. *J Am Acad Dermatol*. 2020 Oct 31. doi: 10.1016/j.jaad.2020.10.079.

Severe, **REFRACTORY ALOPECIA AREATA** can be treated with oral tofacitinib (5mg BID-10mg BID) plus low-dose oral minoxidil (2.5mg QS to BID).

TO READ MORE: Dincer D, et al. Efficacy of systemic minoxidil and tofacitinib combination in treatment-resistant alopecia universalis. *J Cosmet Dermatol*. 2020 Oct 24. doi: 10.1111/jocd.13812.

A retrospective Egyptian study of 1000 healthy men aged 20-35 showed that those who smoke have a higher prevalence and greater severity of **ANDROGENETIC ALOPECIA** (AGA) compared to those who do not smoke. Perhaps we should strongly recommend against smoking for those who already have a known family history of AGA.

TO READ MORE: Salem AH, et al. Implications of cigarette smoking on early-onset androgenetic alopecia: a cross-sectional study. *J Cosmet Dermatol*. 2020, September 18. doi: 10.1111/jocd.13727

COVID-19

In a Brazilian study relying upon a nationally representative internet sampling followed by a "snowball" recruitment, investigators found that **MUCOCUTANEOUS MANIFESTATIONS** occurred frequently in COVID-19, even among patients not sick enough to be hospitalized.

TO READ MORE: Miot HA, et al. Self-reported cutaneous manifestations in 1429 Brazilian COVID-19 patients. *J Eur Acad Dermatol Venereol.* 2020; Nov 2; doi: 10.1111/jdv.17024

Disproportionate to population percentage, in many states, **BLACK INDIVIDUALS** have higher prevalence of COVID-19 infection, hospitalization, and death.

TO READ MORE: Kullar R, et al. Racial disparity of coronavirus disease 2019 in African American communities. *J Infect Dis.* 2020;222:890-93.

A Spanish observational study of more than 11,000 COVID-19-positive individuals who required hospitalization disclosed that **HYPERGLYCEMIA** at the time of admission was a strong predictor of poor outcome. Patients with admission hyperglycemia were more likely to progress from noncritical to critical condition and death, regardless of prior diabetes history.

TO READ MORE: Carrasco-Sanchez FJ, et al. Admission hyperglycemia as a predictor of mortality in patients hospitalized with COVID-19 regardless of diabetes status: data from the Spanish SEMI-COVID-19 Registry. *Annal Med.* Nov 2020. doi: 10.1080/07853890.2020.1836566

Several reports have described a **TRANSVERSE RED-VIOLET NAIL BAND** located just above the normal lunula as a sign of COVID-19 infection.

TO READ MORE: Mendez-Flores S, et al. COVID-19 and nail manifestations: be on the lookout for the red half-moon nail sign. *Int J Dermatol.* 2020;59:1414.

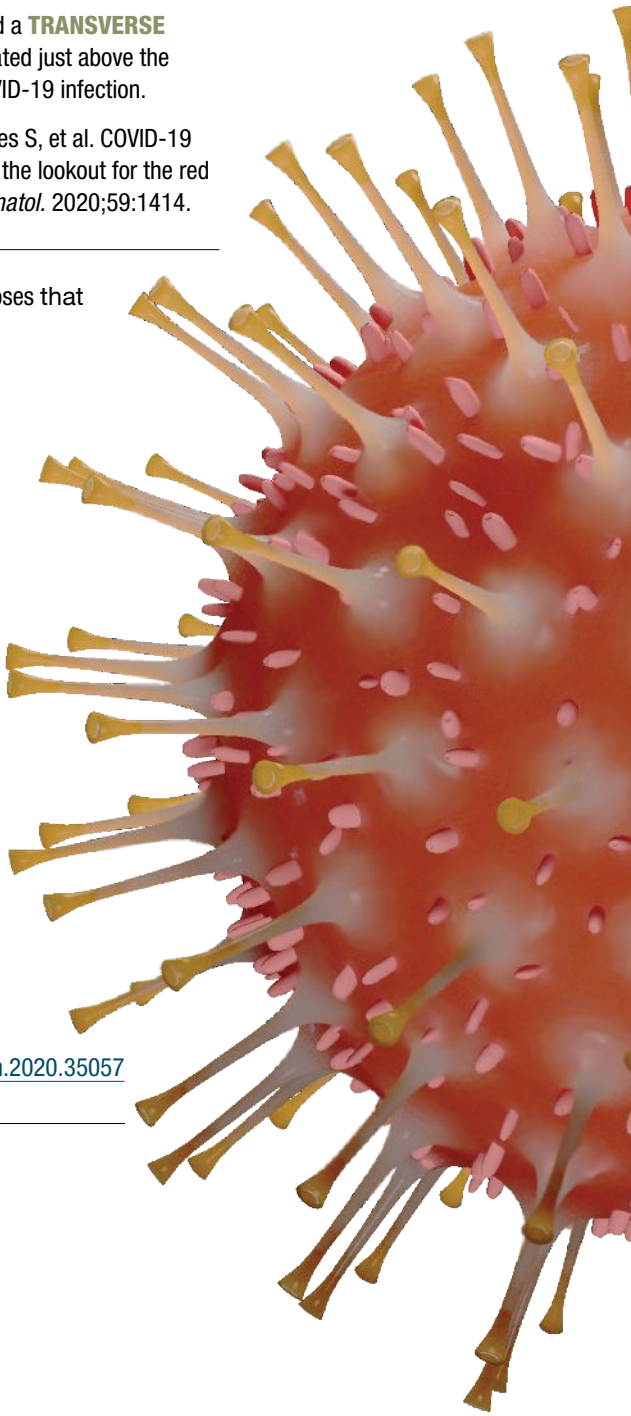
CDC analytical modeling discloses that

59%

OF ALL COVID-19 TRANSMISSION COMES FROM INDIVIDUALS WHO ARE ASYMPTOMATIC. The importance of this finding is that identification and rapid isolation of individuals displaying symptoms of COVID-19 will not stop the persistence of this pandemic.

TO READ MORE: Johansson MA, et al. SARS-CoV-2 transmission from people without COVID-19 symptoms. *JAMA Netw Open.* 2021;4(1): e2035057.

doi:10.1001/jamanetworkopen.2020.35057



COVID-19 HAS BECOME THE LEADING OVERALL CAUSE OF DEATH IN THE US.

HEART DISEASE	**CANCER**	**COVID-19**
about	about	more than
1700	1600	3000
deaths daily	**deaths daily**	**deaths daily**

TO READ MORE: Woolf SH, et al. COVID-19 as the leading cause of death in the United States. *JAMA.* 2020 Dec 17. doi:10.1001/jama.2020.24865

ACNE

CLASCOTERONE, a new topical acne medication, works by blocking androgen receptors. Although it is not specifically approved for this indication, some have suggested it might be an ideal agent to treat female-to-male transgender individuals who develop acne related to their androgen therapy.

TO READ MORE: Marks DH, Mansh MD. Potential role for topical antiandrogens in the management of acne among patients receiving masculinizing hormone therapy. *JAMA Dermatol.* 2020 Nov 4. doi: 10.1001/jamadermatol.2020.4380

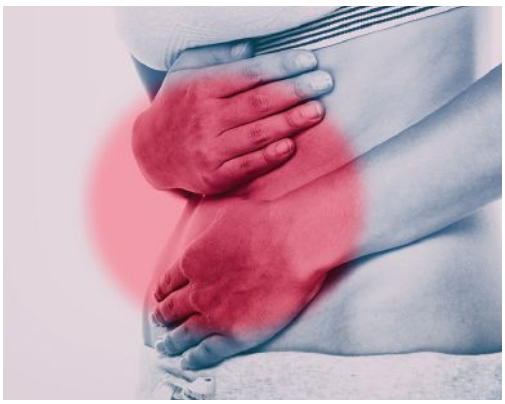
A meta-analysis of 12 randomized controlled and 13 prospective observational studies, including 2445 patients, indicated that acne patients have **LOWER SERUM ZINC LEVELS** than age-matched controls. Oral zinc therapy appears to be beneficial in this analysis of English-language literature. Optimal formulation, dose, and duration of therapy have yet to be determined definitively.

TO READ MORE: Yee BE, et al. Serum zinc levels and efficacy of zinc treatment in acne vulgaris: A systemic review and meta-analysis. *Dermatol Ther.* 2020 Aug 29;e14252. doi: 10.1111/dth.14252

A small, double blind, placebo-controlled Thai study suggests that twice daily application of **KETOCONAZOLE CREAM 2%** may benefit mild adult female acne. Ketoconazole is anti-fungal, but also inherently anti-inflammatory and antiandrogenic; it can also inhibit Cutibacterium acnes lipase activity.

TO READ MORE: Chottawornsak N, et al. Topical 2% ketoconazole cream monotherapy significantly improves adult female acne: a double-blind, randomized placebo-controlled trial. *J Dermatol.* 2019;46(12):1184-1189.

ROSACEA



ULCERATIVE COLITIS AND CROHN'S DISEASE PATIENTS have a 3-fold greater risk of developing rosacea compared to age/sex matched individuals who do not have inflammatory bowel disease.

TO READ MORE: Daou H, et al. Rosacea and the microbiome: a systematic review. *Dermatol Ther (Heidelb).* 2020 Nov 10. doi: 10.1007/s13555-020-00460-1

OCULAR ROSACEA lacks randomized, placebo-controlled trials to guide proper therapy. Topical low-potency steroid combined with an oral tetracycline derivative is the most widely used therapeutic regimen. Though it is often used, little high-quality evidence supports the use of intraocular cyclosporine.

TO READ MORE: Redd TK, Seitzman GD. Ocular rosacea. *Curr Opin Ophthalmol.* 2020; 31(6):503-507.

doi: 10.1097/ICU.0000000000000706

Concurrent daily application of **OXYMETAZOLINE HYDROCHLORIDE 1% CREAM** may enhance the benefit of a wide range of light and laser treatments when utilized for management of persistent facial erythema associated with rosacea.

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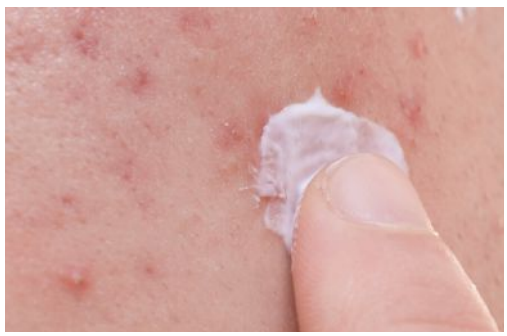

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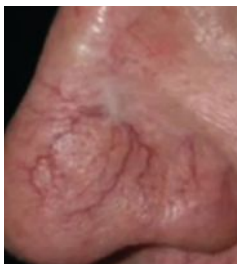
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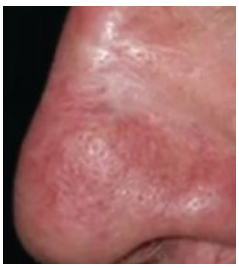
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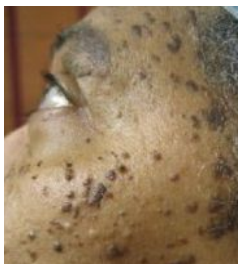
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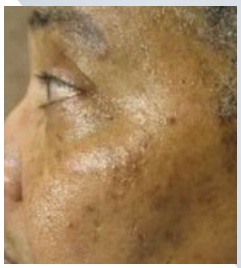
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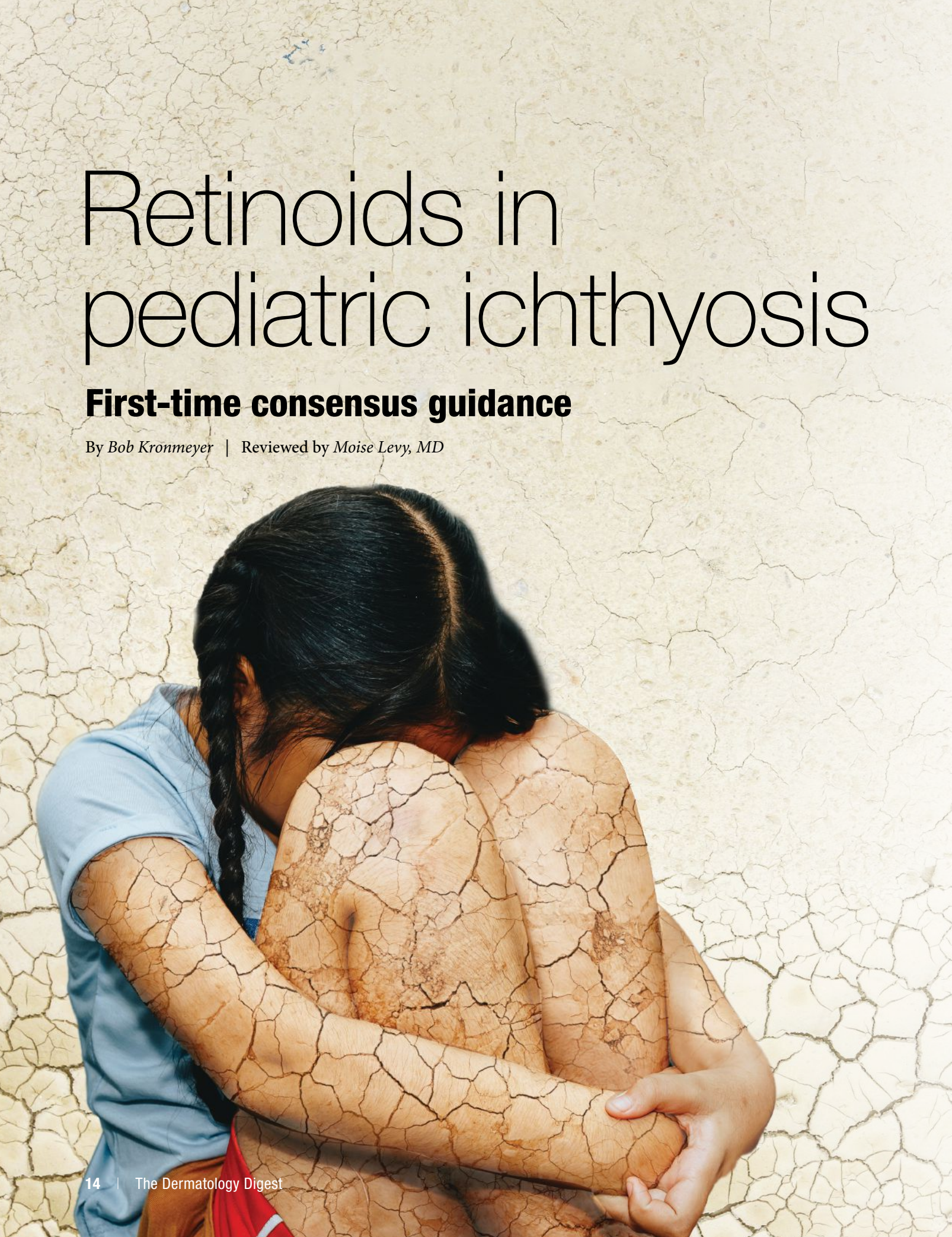
Retinoids in pediatric ichthyosis

First-time consensus guidance

By *Bob Kronmeyer* | Reviewed by *Moise Levy, MD*



Treating ichthyosis and other disorders of cornification in children and adolescents with either topical or systemic retinoids, or both, is not only generally safe, but also can be highly effective in reducing scaling and improving function and appearance, according to consensus recommendations published in November 2020 in the journal *Pediatric Dermatology*.

MOISE LEVY, MD
Professor of Pediatrics and Medicine
Dell Medical School
University of Texas at Austin

"There is lack of a uniform approach to the use of retinoids in childhood cases of ichthyosis," said co-author Moise Levy, MD, a Professor of Pediatrics and Medicine at Dell Medical School, The University of Texas at Austin. "However, these recommendations should not come as a surprise to dermatologists, even though up until now guidance for systemic retinoids has not existed."

The guidance was crafted by a variety of experts in dermatology, ophthalmology, reproductive health, and retinoids, as well as input from the Foundation for Ichthyosis and Related Skin Types (FIRST).

To increase the efficacy of retinoids in this patient population, the dermatologist must "first and foremost engage the patient or family as to what they are seeking in a very basic level from therapy," Dr. Levy said.

Retinoids are known to have an impact on skin turnover. "Because retinoids influence cell development, retinoids have been considered for years as potentially useful in this group of conditions," Dr. Levy said. "What you see as a provider with retinoids is a patient with reduced scaling and thickness of the skin. Such effects are hopefully achieved from use of a topical or a systemic retinoid."

Topical vs systemic

The decision whether to use topical or systemic retinoids depends mostly on the extent of disease. For instance, is therapy specifically for eyelid closure or specifically to lessen thickening of skin on palms and/or soles? Or to improve these sites and also the skin on the torso and extremities?

"If you are trying to treat a very focal area, a topical is clearly the way to go and preferable to a systemic," Dr. Levy said. "But for larger areas of the body impacted by the condition, a systemic retinoid should be considered for use."

For topical therapy, Dr. Levy tends to prescribe tazarotene, despite patient insurance challenges. Retinoid alternatives are tretinoin and

> Because retinoids influence cell development, retinoids have been considered for years as potentially useful in this group of conditions."

adapalene, which fall within the same class as tazarotene.

For systemic therapy, most dermatologists have used either acitretin or isotretinoin, the latter specifically approved for acne; however, acitretin remains in the body for up to 3 years, according to Dr. Levy. "Therefore, acitretin becomes a concern when discussing toxicities, should they develop, or their impact on unborn children," he said. "Instead, we might try isotretinoin, particularly in kids. Compared to acitretin, though, isotretinoin has a much shorter duration of action. For that reason, many physicians favor starting with isotretinoin, if not continuing with the drug, because if any issue develops you can stop the drug and the medication is cleared far more rapidly than with acitretin."

The iPLEDGE program serves as the Risk Evaluation and Mitigation program for isotretinoin, with which all patients and prescribers of isotretinoin must comply. "Adherence to the guidelines, however, can be quite cumbersome, because iPLEDGE was not developed with ichthyosis in mind, which potentially requires years of therapy," Dr. Levy said.

For systemic retinoid dosing, the lowest dose possible to achieve the desired clinical outcome is recommended.

However, duration varies between topical and systemic. "For topicals, there is no specific duration that you need to consider, assuming the patient does not have any side effects from the therapy, such as local irritation," Dr. Levy said. "But for systemic treatment, there are isolated cases of bone toxicity or reproductive concerns among individuals capable of pregnancy and of appropriate age. These considerations might limit duration and timing of therapy."

Side effects and safety

Because all these medications are vitamin A derivatives, systemic retinoids affect bone, and there are isolated reports of closure of the growth plates, particularly in children, and calcification on the soft tissues (tendons and ligaments) around bones. "Retinoids may also cause bony overgrowth along the spine, which can lead to pain," Dr. Levy said. "All these bone issues need to be considered at the onset of therapy. There may also be a family history of such problems."

Furthermore, systemic retinoids may cause dry eye, and to a lesser degree, corneal opacities.

In addition, both isotretinoin and acitretin can occasionally cause elevations in serum lipids or adversely affect liver function. "Nonetheless, we monitor lipid levels and the liver before treatment and at intervals during therapy," Dr. Levy said. "With lipid elevation, there is potential concern about cardiovascular impact from prolonged and elevated levels in the blood."

Psychiatric effects of systemic retinoid therapy also continue to be an area of discussion, particularly for isotretinoin. "These psychiatric changes, though, occur less frequently in the cohort of patients receiving those drugs than occur in the general population," Dr. Levy said. "But we still ask patients about their psychiatric well-being while on these medications. If there is any noted change, we will engage a behaviorist to help."

Patients who could become pregnant and are sexually active should use 2 forms of contraception, including 1 highly effective form, while on any systemic retinoid therapy, either short- or long-term. "There is great risk to an unborn fetus for a multitude of birth defects," Dr. Levy said. "Thus protection from pregnancy is absolutely indicated."

The guidelines underscore that providers must be aware of what is known and unknown about the safety and efficacy of long-term retinoid use. "Risks should be discussed candidly with patients and their families through shared decision-making and recognize that long-term safety data are lacking," Dr. Levy said.

The intention of the guidelines is not to be the final word. "Rather, these recommendations are a platform upon which more data will be delivered," Dr. Levy said. ◈

COMMENTARY

Monitoring and modifications needed

By *Bob Kronmeyer* | Reviewed by *Amy Paller, MD*

None of the recommendations for retinoids in treating ichthyosis and other disorders of cornification in children and adolescents should come as a surprise to dermatologists, according to Amy Paller, MD, a Professor and Chair of Dermatology at Northwestern University in Chicago. "However, there may be monitoring suggestions that are new to clinicians or unmet needs that may resonate," she said.

For patients who require oral retinoids for a long duration, "we prefer to use isotretinoin because it is safer than acitretin, especially among young women," Dr. Paller said. "But the iPLEDGE program still needs to be in place for any use of isotretinoin. Any patient who uses the drug in the long term as a safer retinoid is burdened by the program, including pregnancy testing every month and connecting with the office monthly to receive their next dose. This is a huge obstacle, especially for prescribing [for longer than] 6 months."

Dr. Paller hopes the continuing unmet need of dispensing isotretinoin can be resolved through modifications in the iPLEDGE program. "Our adolescent girls and young adult women have a lifelong disorder that demands responsibility, including pregnancy avoidance while on a retinoid," she said. "Some monitoring is needed, but less often than monthly would be appreciated."

Paller noted that the alternative retinoid, acitretin, has no associated iPLEDGE-like program, but is retained in fat and thus requires a 2- to 3-year period off medication (vs 1 month with isotretinoin) when considering pregnancy.

AMY PALLER, MD

Professor and Chair
of Dermatology
Northwestern University
Chicago

Dr. Paller hopes the continuing unmet need of dispensing isotretinoin can be resolved through modifications in the iPLEDGE program.

In addition, not all disorders of cornification with scaling respond to retinoids. "In fact, some do worse; for example, Netherton syndrome should probably not be considered for retinoids," Dr. Paller said. In contrast, patients with lamellar ichthyosis can greatly benefit from retinoids.

The guidelines for following patients long-term, including ocular and bone monitoring, are valuable. Techniques for administering a retinoid capsule to a child who cannot swallow are also contained in the guidelines.

Dr. Paller added, "Most of these patients carry huge burdens, including the highly visible nature of the disorder, reduced ability to sweat, and the itch and pain associated with their ichthyosis. For many patients, retinoids—whether topical or systemic—can drastically alter their disease course, but only if they are used."

These guidelines for the pediatric population will give dermatologists more confidence in prescribing retinoids, both topically and systemically, for children with disorders of cornification, according to Dr. Paller. "We want clinicians to understand the potential toxicity of retinoids, but risk is minimized by monitoring," she said.

Dr. Paller advocates standardizing monitoring of patients, so that uniform information can be collected for safety.

Habit-reversal training empowers patients

By *Mary Beth Nierengarten* |
Reviewed by *Katlein França, MD, PhD, and Rajani Katta, MD*

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Clinical Assistant Professor
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RAJANI KATTA, MD
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Dermatologists are on the front lines of care for many patients who have conditions involving psychological disorders. Among those that affect the skin are trichotillomania and excoriation disorders, repetitive behavioral disorders classified as types of Obsessive-Compulsive & Related Disorders in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5).[1,2]

The prevalence of these disorders varies, but recent estimates suggest it may be higher than previously known. A 2018 study of nearly 5000 college students found that about 12% met diagnostic criteria for these disorders and almost 60% reported engaging in these behaviors but did not yet meet diagnostic criteria.[3]

Dermatologists are usually the first specialists that patients with these disorders reach out to for help, according to Katlein França, MD, PhD, a Clinical Assistant Professor in the Department

Table 1. Habit-reversal training: core components[2]

Awareness training	Helps patients identify "warning signals" of impending habitual behavior, such as moving a hand toward their head, or emotional cues such as stress or boredom. Patients are given a functional assessment interview in which they describe what happens before, during, and after their habitual behavior.
Competing response training	Patients in collaboration with their clinician choose a competing response to use each time a "warning signal" occurs that is physically incompatible with the habitual behavior. For example, instead of the patient's habitual response to moving their hand toward their head, the patient engages their hands differently, by making a fist, sitting on hands, or putting hands in pockets.
Social support training and contingency management	Training a person close to the patient to provide support and point out warning signs and reinforce competing responses.
Stimulus control	Minimize the environmental influence on repetitive behaviors, such as avoiding situations that trigger emotional states such as stress and boredom or altering triggers, such as covering mirrors.

of Dermatology and Cutaneous Surgery and the Department of Psychiatry and Behavioral Sciences at the University of Miami Miller School of Medicine in Florida. "It is important for dermatologists to be aware of the different treatment approaches and that these patients tend to respond better to integrative treatments," she said.

Among the integrative treatment approaches is habit-reversal training, a behavioral approach that Dr. França has written about extensively and is trained in. It is often used in combination with medications, amino acid supplements, and other psychotherapy methods. Dr. França emphasized that choosing the type of treatment approach will depend on each patient's needs and therefore relies on an individualized treatment strategy.

So what is habit-reversal training, and what do dermatologists need to know about how and when to use it?

Habit-reversal training

The foundation on which habit-reversal training is based is helping patients increase their awareness of their harmful habits and training them to develop neutral habits to replace bad ones, explained Dr. França.

Table 1 lists core components of the treatment, first developed by Azrin in the 1970s.[4]

Although the approach can be used in both children and adults, Dr. França said that it may be challenging to use in children younger than 5 years of age because the technique does require some cognitive awareness and motivation is essential.

Should dermatologists treat or refer?

Although habit-reversal training is a well-established technique, Dr. França emphasized that few practicing dermatologists are aware of it and not many professionals are trained to perform it. Most clinicians practicing it currently are psychologists, she said.

Rajani Katta, MD, a dermatologist on clinical faculty at the Baylor College of Medicine, Houston, Texas, and the McGovern Medical School, Houston, also said that most dermatologists will refer their patients to a trained professional specializing in behavior medicine. "While the technique is considered easy to learn, it does take time to teach and train patients to use, "she said, emphasizing that finding and referring to an expert may also take some time despite the growing number of specialists—particularly at academic med-

In a study of nearly **5000 college students**

12%

met diagnostic criteria for these disorders

60%

reported engaging in these behaviors but did not yet meet diagnostic criteria

> While the technique is considered easy to learn, it does take time to teach and train patients to use it."

ical centers and pediatric hospitals—becoming more aware of the problem.

Underscoring the strong evidence for the benefit of habit-reversal training used in conjunction with standard treatment to treat skin diseases affected by repetitive behaviors, Dr. Katta cited other benefits including its low cost, and low risk, and simplicity. "Importantly, it empowers patients to actively participate in the treatment of their skin disease," she said. Unfortunately, she said, it is an underutilized technique. ◈

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DISCLOSURES

Neither Dr. França nor Dr. Katta reports any relevant financial interests.

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Commentary on page 22

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continued from page 20

COMMENTARY

Changing behavior in two steps

By *Bob Kronmeyer* | Reviewed by *John Koo, MD*

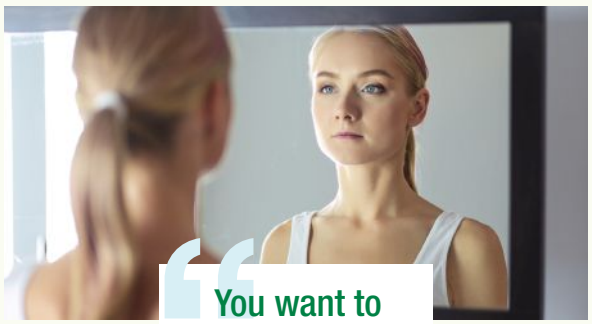
The goal of habit reversal therapy or training is to eradicate a destructive habit, such as trichotillomania (hair pulling) or excoriation disorder (skin picking) in dermatology.

"If the habit is a significant component of the whole behavior, habit reversal therapy can be effective," said John Koo, MD, a professor of dermatology at the University of California, San Francisco, who is board-certified in both psychiatry and dermatology.

JOHN KOO, MD

Professor of Dermatology
University of California,
San Francisco

The first step of reversal therapy is to make the patient more aware of the habit itself. "Many people pick their skin or pull their hair automatically, outside of their awareness," Dr. Koo said. "It is very difficult to reverse a bad habit if the person is not even aware he or she is doing it."



One strategy is for the patient to sit in front of a large mirror and count the number of times he or she engages in the habit. Sometimes, a patient is physically with a therapist who can keep count or the patient can maintain day-to-day diary entries of the behavior.

"You want to make the habit as conscious as possible for the patient," Dr. Koo said.

> "You want to make the habit as conscious as possible for the patient."

The second and final step of reversal therapy is trying to change behavior by introducing a competing response to replace the habit. "This is a deliberate action that is not compatible with carrying out the bad habit, such as forming a fist instead of scratching or picking on the skin," Dr. Koo. "The fist is rigidly kept at the patient's side until that urge to pick disappears."

Another behavioral substitution for scratching or picking skin is simply to rub the affected skin.

"The urge to engage in bad behavior is similar to obsessive compulsive disorder (OCD)," Dr. Koo said. However, by following the 3-minute rule, whereby a patient waits 3 minutes before resuming the bad habit, the patient may be able to extend refraining to 4 minutes than to 5 minutes, "eventually the habit becoming extinct."

Therapy can be extremely effective for the right patient population: those whose habit is outside of their consciousness, whose habit plays a big role in their behavior, and who are highly motivated and dedicated to change their behavior. "This therapy is not as simple as swallowing a pill," said Dr. Koo, who has treated some of his patients with habit reversal for the past 34 years.

Habit reversal initially targeted atopic dermatitis. "After a while, the scratching becomes as much of a habit as a means to counter itchiness," Dr. Koo said. "But getting rid of the original condition is always the most important aspect of therapy."

Therefore, habit reversal is more of a supplemental treatment to conventional therapies like topical steroids, internal oral medications and injectables rather than a replacement treatment.

No formal training is needed for dermatologists to offer habit reversal to their patients, according to Dr. Koo, and is easy to incorporate into practice. "The concept is not that complicated," he said. "The dermatologist can teach him or herself." ◈

STDs in a time of COVID

By *Lisette Hilton* | Reviewed by *Ted Rosen, MD, FAAD, Editor-in-Chief*

Sex happens, even during a pandemic.

TED ROSEN, MD, FAAD
Editor-in-Chief
The Dermatology Digest
Professor of Dermatology
Baylor College of Medicine

Hear Dr. Rosen's essential data update on dermatologists and STDs at https://thedermdigest.com/podcast/ted-talks-literature-update-stds-in-the-covid-19-era/

Sexually transmitted diseases (STDs) persist despite the community containment and social distancing that occur during a pandemic, according to a paper by Italian researchers published December 2020 in the *Journal of Public Health Research*.[1]

The authors documented the case of a 58-year-old man who in late March 2020 was referred to their dermatology clinic with suspected SARS CoV-2 infection. He had a generalized, mildly pruritic exanthematous rash associated with systemic symptoms of 2-week duration, according to the paper.

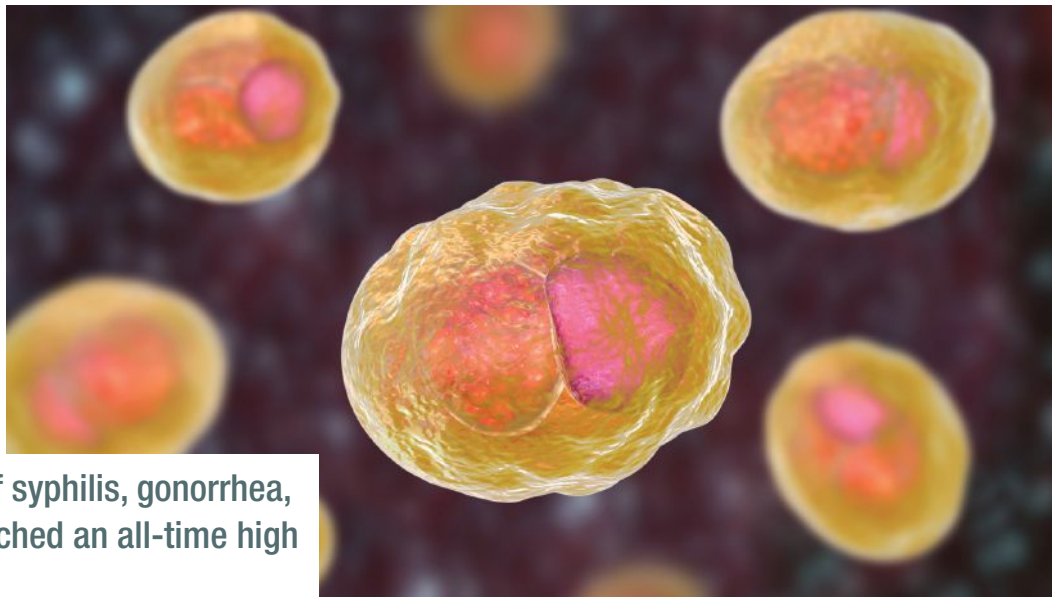
A general practitioner had treated the patient with paracetamol and systemic steroids, which improved his symptoms initially. But the symptoms relapsed, and the skin eruption worsened.

While in the dermatologist's care, the patient referred to a genital rash that spontaneously resolved 2 months earlier. Testing revealed the patient's more generalized rash was related to secondary syphilis. The dermatologist treated the patient with penicillin, which resolved the skin rash.

"… [S]yphilis should never be forgotten," the authors wrote. "As highlighted by present report, the potential impact on public health is substantial, considering that secondary syphilis is a highly contagious generalized bacteremic phase of the disease."

STDs remain a common threat

STDs, in general, are on the rise in the US, according to Ted Rosen, MD, FAAD, Editor-in-Chief of *The Dermatology Digest* and



Combined cases of syphilis, gonorrhea, and chlamydia reached an all-time high nationally in 2018.

Professor of Dermatology at Baylor College of Medicine.

"Between the years 2014 and 2019, there were high double-digit percent increases in STDs across the board in the US. More gonorrhea, more chlamydia, more syphilis. In the first 2 months of 2020, that trend continued," said Dr. Rosen.

Combined cases of syphilis, gonorrhea, and chlamydia reached an all-time high nationally in 2018, according to the annual Sexually Transmitted Disease Surveillance Report released by the CDC in October 2019.[2]

CDC statistics show that from 2017 to 2018, the number of primary and secondary syphilis cases rose 14% to more than 35,000 cases, the highest number reported since 1991. Gonorrhea increased 5% to more than 580,000 cases and chlamydia increased 3% to more than 1.7 million cases. Provisional, unpublished data disclosed by the CDC indicates that these trends continued in 2019, according to Dr. Rosen.

One in 5 people in the US have an STD, according to the CDC.

STD statistics took an interesting turn from March 2020 and after, according to Dr. Rosen. "STDs seemingly took a plunge off a cliff, with a 33% decrease in STDs, including syphilis," he said.

The numbers could reflect declining rates from wearing masks, social distancing, and closing places such as bars, where people might meet casual partners and acquire STDs. Perhaps public health messages stressing things such as self-pleasuring and virtual rather than in-person sex helped to decrease the numbers, according to Dr. Rosen.

But he is not convinced that the numbers reflect STD reality in the age of COVID-19.

"There are good reasons why STDs should have gone up, like a condom shortage. Three of the 4 largest worldwide manufacturers of condoms closed because a lot of their workers acquired COVID-19. So, there was a worldwide shortage of condoms. Among STD clinics in the US, for example, only about 8% have remained open and had normal hours of operation during the pandemic. Two-thirds, more or less, had very curtailed days or hours of operation because STD clinics are not configured for social distancing, for example. Moreover, they don't have enough personal protective equipment."

About a quarter of STD clinics in the US closed completely with the onset of the pandemic, according to Dr. Rosen.

It appears that less testing is being done. CBS News in Denver, for example, reported on January 21, 2021, that Colorado public health agencies had conducted 40% fewer tests for gonorrhea, chlamydia, and syphilis during the COVID-19 pandemic compared to the previous year.

Under those circumstances, one could and should wonder if the numbers are low because STD clinics are either shut down or not functioning properly to capture true numbers. Another potential issue, according to Dr. Rosen, is that many people are afraid to go to dermatologists, primary care physicians, and

1 in 5

people in the US have an STD, according to the CDC.

other doctors for fear of catching COVID-19.

"I honestly believe that the decline in STDs that has been reported is not real," he said.

What we think we know and do not know about STDs and COVID-19

Dr. Rosen coauthored the *SkinMed* August 2020 article "Sexually transmitted diseases in the COVID-19 era", which looked at sexual transmission of COVID-19, as well as STD co-infection with COVID-19.[3]

He said that COVID-19 does not appear to alter facets of STDs.

"HIV causes a change in morphology. It often may institute recurrences of some diseases that tend to recur. And it can alter response to therapy," Dr. Rosen said. "… COVID-19 to date has not caused more recurrence of those diseases that tend to recur like genital herpes or genital warts. It has not altered response to standard treatment protocols, and it has not really altered the morphology of STDs."

Sexual transmission of COVID-19, however, seems a bit of an enigma, according to Dr. Rosen.

Some viruses, such as the Zika virus, can be sexually transmitted and are not considered STDs. Several reports of acutely infected as well as recovering COVID-19 patients have shown no detectable COVID-19 virus in genital secretions, like semen. But researchers in China found in a study of 38 patients that more than 26% of acutely infected and about 9% of recovering COVID-19 patients have some degree of COVID-19 in semen.[4]

"We have yet to determine whether the virus can be transmitted through sexual activity," Dr. Rosen said.

Dermatologists' roles

Dermatologists are STD experts and need to continue to care for STD patients through and after the pandemic, according to Dr. Rosen, who recently wrote an editorial on the topic [Ted Talks: Should dermatologists still be experts in sexually transmitted diseases? – The Dermatology Digest (thedermdigest.com)].[5]

"If you are under the illusion that gynecologists or urologists understand or know STDs other than a very few genital lesions, disabuse yourself of that illusion. They do not. And the infectious disease people—there are not enough of them and they are mostly interested in HIV," Dr. Rosen said.

Dermatologists are ideally trained to treat STDs, most of which occur on the skin.

"If we don't do it, nobody else really will," Dr. Rosen said.

Dermatologists should encourage patients to talk about genital health. Those conversations are particularly important with patients who may be at a high demographic risk, including gay men, bisexual men, those who might be intravenous drug abusers, people who have had past STDs, etc.

"I think this should be part of all of our routines. Whether there is a COVID-19 pandemic or not, it still is an important issue," Dr. Rosen said. "The bottom line is STDs are here, they've been here, they're going to be here, and we need to be aware of them and diagnose and treat them properly and in a timely fashion." ◈

> "I honestly believe that the decline in STDs that has been reported is not real."

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HH and PD-1 inhibitors: watch for adverse events

By *John Jesitus* | Reviewed by *Todd Schlesinger, MD*

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Director, Dermatology and Laser Center of Charleston and the Clinical Research Center of the Carolinas
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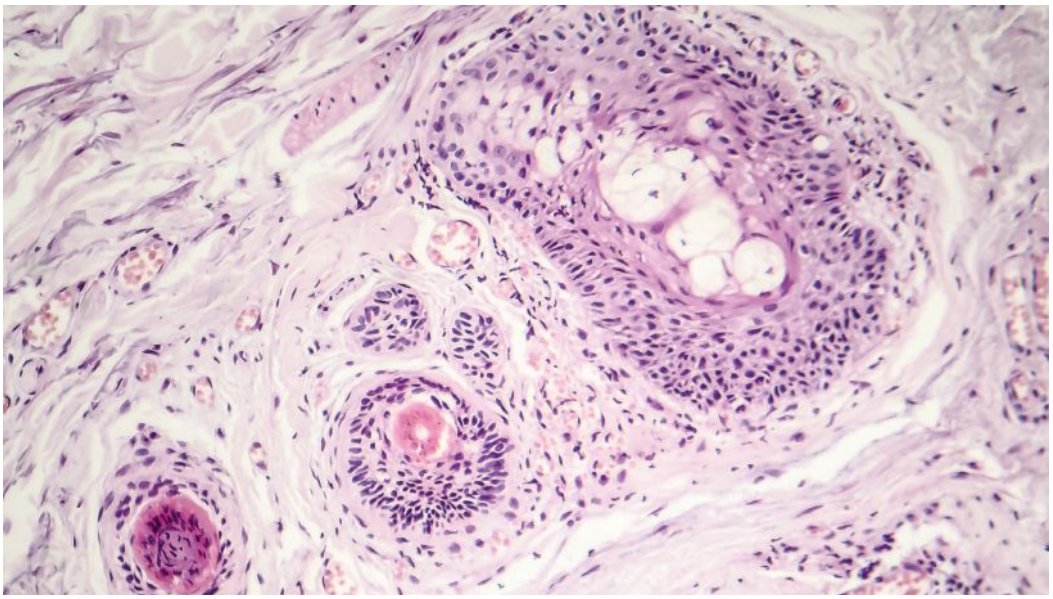
The efficacy of newer medications including inhibitors of hedgehog (HH) and programmed death-1 (PD-1) signaling carries the caveat that prescribers must monitor for multi-systemic adverse events (AEs), which may be severe. Additional considerations with both drug categories include resistance and, for HH inhibitors (HHIs), potential drug interactions.

Checkpoint inhibition

"The difference with PD-1 immune checkpoint inhibitors versus prior medications is that the side effects we see are immune-mediated," said Todd Schlesinger, MD. "Once you activate the immune system to fight the tumor, the immune system can attack other parts of the body as well. It's important to remember that the adverse events from these new immunotherapy medications can affect almost every organ system." Dr. Schlesinger is Director of the Dermatology and Laser Center of Charleston and the Clinical Research Center of the Carolinas, both in Charleston, South Carolina.

Previously, treatment for advanced cutaneous squamous cell carcinoma (CSCC) that was not a candidate for surgery or radiation, including locally advanced (laCSCC) and metastatic tumors (mCSCC), involved cytotoxic and/or platinum-based chemotherapy. Epidermal

Hear the full interview. Todd Schlesinger, MD, provides the latest data on treatments for advanced skin cancers at https://thedermdigest.com/podcast/advanced-skin-cancer-therapies/



growth factor receptor inhibitors such as cetuximab signaled the next evolutionary phase.

The above treatments seek to kill or inhibit growth of the tumor itself. However, Dr. Schlesinger added, these therapies were never FDA-approved for CSCC and provided response rates of around 20%, with significant adverse events (AEs).

Eventually, he said, the discovery of tumor-cell and T-cell receptors proved that CSCC tumors can "cloak" themselves. "They figure out how to protect themselves from the immune system by presenting receptors on their surface that tell the immune system the tumors are part of the body's own tissue." As a result, circulating T cells that are supposed to attack the tumors essentially ignore them.

Unlike prior therapies, the checkpoint inhibitors pembrolizumab (Keytruda, Merck) and cemiplimab (Libtayo, Regeneron and Sanofi Genzyme) can activate cytotoxic immune cells such as CD8 and other cells to infiltrate and destroy CSCCs. "That has shifted the paradigm from attacking the tumor directly toward helping the body's own immune system fight the tumor," said Dr. Schlesinger.

Cemiplimab earned FDA approval in 2018 for patients with mCSCC or laCSCC who are not candidates for curative surgery or radiation. Pembrolizumab earned approval in 2020 for recurrent CSCC or mCSCC not curable by surgery or radiation. In pivotal trials, these drugs achieved overall response rates (ORRs) of 46.1% and 34.3%, respectively.[1,2] With cemiplimab, average time to response was 2.1 months. Duration of response (DOR) lasted at least 6 months in 91% of patients; 99.5% of patients experienced AEs. With pembrolizumab, the 2-month progression-free survival rate was 32.4%, and 66.7% of patients experienced treatment-related AEs.

The systems most commonly impacted by checkpoint-inhibitor AEs include the lungs, gastrointestinal tract, and skin, said Dr. Schlesinger. Fortunately, he added, most of these AEs are mild-to-moderate and easily treatable with medications such as corticosteroids.[1,2,3]

Nevertheless, Dr. Schlesinger said, identifying serious AEs early is crucial, as they require at least temporary (grade 3) or permanent (grade 4) drug discontinuation. In a safety analysis of cemiplimab in basal cell carcinoma (BCC), 17% of patients experienced AEs leading to discontinuation.[3]

"Physicians who are [prescribing] these medications should be attuned to symptoms that that they might otherwise not pay much attention to, such as cough, fatigue, rash, or diarrhea." Additionally, Dr. Schlesinger recommended full laboratory evaluations, including thyroid function and glucose metabolism.

Hedgehog inhibition

FDA-approved in 2012, vismodegib (Erivedge, Genentech) offers ORRs in metastatic BCC (mBCC) and locally advanced BCC (laBCC) of 48.5% and 60.3%, respectively, at 39 months, with DOR lasting 4.8 and 26.2 months, respectively.[4] Sonidegib (Odomzo, Sun Pharma) earned approval in 2015 for locally advanced recurrent BCC or BCC not amenable to surgery or radiation. In pivotal research, sonidegib demonstrated 6-month ORRs of 43% in laBCC and 15% in mBCC.[5] Median DOR was 26.1 months in laBCC, but not evaluable in mBCC.

HHI-related AEs may stem from the presence of the HH pathway in non-tumoral tissues such as taste buds, said Dr. Schlesinger. The most common treatment-emergent AEs for the approved 200-mg sonidegib dose included muscle spasms, alopecia, and dysgeusia, which affected 38% to 49% of patients. Grade 3 and 4 AEs affected 27% and 4% of patients in this cohort, respectively. A subsequent 1215-patient global safety study (STEVIE) showed similar rates of the most common AEs; 31% of patients experienced AEs leading to treatment discontinuation.[6]

Cemiplimab earned FDA approval in 2018 for patients with mCSCC or laCSCC who are not candidates for curative surgery or radiation.

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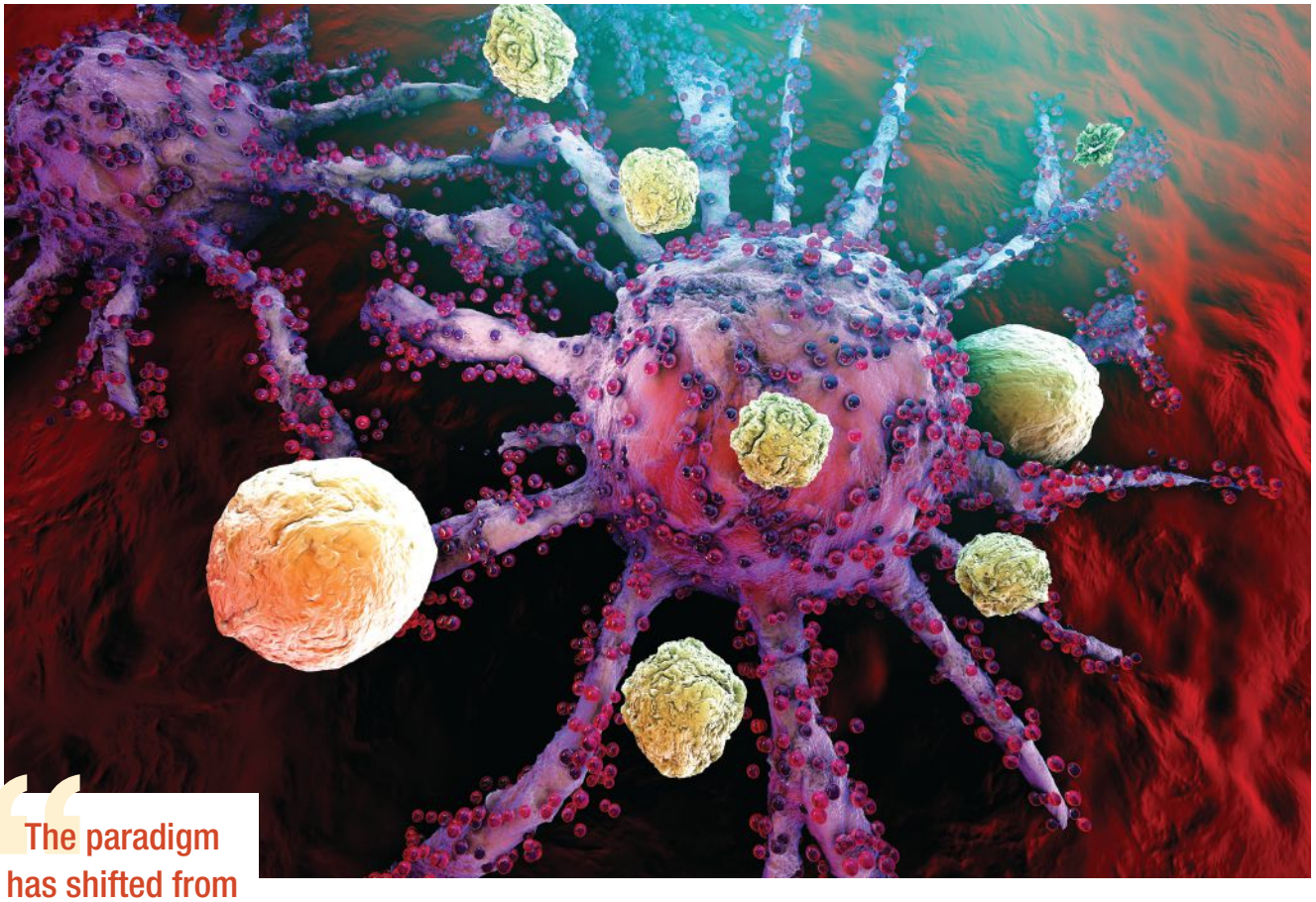

> "The paradigm has shifted from attacking the tumor directly toward helping the body's own immune system fight the tumor."

"Patients were getting side effects from these medications," said Dr. Schlesinger, "so the treatment was being interrupted." Fortunately, he said that with HHIs, tumor response tends to appear before AEs, which provides assurance that these drugs are working.

The STEVIE study moreover showed that most vismodegib side effects decline significantly over time. For example, incidence of muscle spasms dropped from 98% to 4.9% during the trial. "The muscle spasms and hair loss that patients initially experience in the first 12 months of therapy tend to settle down after one year," Dr. Schlesinger said.

The MIKIE trial showed that cycles of 12 or 24 weeks, with an 8-week break between cycles, provided similar efficacy to that seen in pivotal vismodegib studies, with fewer side effects.[7]

"This is a way that you can keep these patients on therapy longer, by using an interrupted dosing schedule," said Dr. Schlesinger.

To temporarily ameliorate HHI side effects, physicians may offer supportive treatments such as minoxidil 5% BID for alopecia and nutritional consults for dysgeusia and/or weight loss.[8] For muscle spasms, options include amlodipine 10 mg daily[8] or levocarnitine. The latter reduced muscle spasm frequency by 48% in a 4-week, double-blinded, randomized placebo-controlled pilot trial.[9]

The potential for drug interactions with sonidegib also warrants consideration. "Patients taking medications that can affect the hepatic metabolism pathway via cytochrome P450 may need a dose adjustment for sonidegib,"[10] said Dr. Schlesinger. That is not the case, he added,

continued on page 30

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continued from page 28

for patients taking sonidegib who experience mild-to-moderate renal impairment or mild hepatic impairment.

Resistance to HHI therapy has driven additional research into adjuvant and co-treatment options. Mutations in the transmembrane protein Smoothened (Smo), HHIs' primary target, account for up to half of advanced BCCs resistant to both vismodegib and sonidegib.[11,12] Researchers have hypothesized that by targeting alternate stages of the HH pathway, drugs such as arsenic trioxide, itraconazole, all-trans retinoic acid, and nicotinamide may bypass or forestall HHI resistance.[13]

"Polychemotherapy could play a role in patients with basal cell carcinoma," says Dr. Schlesinger. Because arsenic trioxide and itraconazole increase QT intervals, he added, these drugs require caution in patients with cardiac disorders and in those taking other drugs that prolong the QT interval.

Regarding CSCC, the FDA recently granted fast-track status to AST-008 (cavrotolimod, Exicure) in combination with anti-PD-1 or anti-programmed death-ligand 1 (PD-L1) therapy for laCSCC or mCSCC refractory to prior anti-PD-1/PD-L1 blockade; and in combination with PD-1 blockade for locally advanced or metastatic Merkel cell carcinoma refractory to prior anti-PD-1 therapy. ◈

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DISCLOSURES

Dr. Schlesinger has been a consultant and researcher for Genentech (vismodegib), Regeneron and Sanofi Genzyme (cemiplimab), and Sun Pharma (sonidegib).

ECZEMA AND COVID-19
What we know and think we know

By *Lisette Hilton* | Reviewed by *Amy S. Paller, MD*

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The COVID-19 pandemic poses concerns for many people with chronic diseases, including eczema. Dermatologists can confidently answer some—but not yet all—of the questions eczema patients commonly ask, including whether eczema or the medications they take to treat it make them more vulnerable to the virus and if it is safe to get the COVID-19 vaccine. *The Dermatology Digest* asked Amy S. Paller, MD, some of the questions that dermatologists may have about eczema and COVID-19.

Does having eczema make people at risk for the virus and severe manifestations of it?

"The important thing about eczema and COVID-19 is that we know that there is not any associated increased risk for those who have eczema, no matter how severe," said Dr. Paller, Chair of Dermatology and Professor of Dermatology and Pediatrics (Dermatology) at Northwestern Medicine, Feinberg School of Medicine, Chicago.

Are patients on systemic medication at increased risk of contracting COVID-19 or having more severe disease?

Theoretically and in practice so far, dermatologists have not seen eczema medications affect COVID-19 risk and disease severity.

However, there are concerns. One is about patients who may be "inappropriately" treated with systemic steroids, according to Dr. Paller.

Reports in the rheumatology literature suggest that systemic steroids are associated with greater COVID-19 severity. This is even though dexamethasone has been used to treat the cytokine storm.

"This is not the time to be treating with systemic steroids when we have other potential therapies," said Dr. Paller.

In short videos on the National Eczema Association's website designed to educate eczema patients about COVID-19 (http://nationaleczema.org - http://nationaleczema.org), Peter Lio, MD, discusses the different tiers of medications that could negatively affect eczema patients' immunity. The first-tier and most powerful immunosuppressive medicines include prednisone or prednisolone, cyclosporin, and possibly methotrexate, according to Dr. Lio, Assistant Professor of Clinical Dermatology and Pediatrics at Northwestern University's Feinberg School of Medicine and the director of the Northwestern University

> This is not the time to be treating with systemic steroids when we have other potential therapies."

Eczema Care and Education Center, Chicago.

Broad-spectrum biologics, including tumor necrosis factor (TNF) inhibitors, carry a modest risk for lowering the immune system response and therefore increasing the potential for disease severity. But dermatologists do not often use TNF inhibitors to treat eczema, according to Dr. Lio.

Third-tier drugs, including dupilumab (Dupixent, Sanofi and Regeneron Pharmaceuticals), appear to be have the least impact on patient immunity, according to Dr. Lio.

"One question is whether it is a problem if you have somebody chronically on dupilumab," Dr. Paller said. "Given its targeting of Th2 immunity, use of dupilumab should not be an issue in handling COVID-19 infection, and I have not heard reports of any issues either."

Should adults with eczema receive the COVID-19 vaccine?

COVID-19 vaccines appear to be safe for eczema patients who are normal immunologically, according to Dr. Paller.

"We encourage everyone with eczema and their families to get the vaccine as soon as it is available for them," she said.

Having eczema will not move someone ahead in line to get the vaccine earlier, she said.

What about eczema patients who have other, sometimes severe, allergic reactions? Might they have an allergic reaction to the vaccine?

More than 20% of adults with atopic dermatitis, or eczema, also have asthma, and they have a 2 to 4 times higher risk for having allergic rhinitis and food allergy, according to the National Eczema Association.

Asthma may put people at risk for infection or having a worse case of COVID-19, according to Dr. Lio.

Eczema patients, in general, do not appear to be at increased risk of an allergic reaction to the vaccine, unless they are allergic to a vaccine component, according to Dr. Paller.

One specific component that causes some concern is polyethylene glycol (PEG). In an article published January 2021 in *Clinical and Experimental Allergy*, researchers wrote that immediate-type allergy to PEG, which is widely used as an excipient in drugs, cosmetics, and household products, is rare. But the clinical manifestations of PEG allergy are often dramatic.[1]

"If anybody has a concern about PEGs, they should talk with an allergist. And for anybody who does have a history of anaphylaxis of any type, we are advising them to bring epinephrine to the center where the vaccination is being given and sit around an extra half hour to make sure they are ok post-vaccine," Dr. Paller said.

> We encourage everyone with eczema and their families to get the vaccine as soon as it is available for them."

> We are advising people to double-up on their moisturizing."

What about children with eczema? What do dermatologists need to know?

The vaccines have yet to be tested in children, and Dr. Paller said it is not yet clear when children might be vaccinated.

Getting children vaccinated is important, according to Dr. Paller.

"Children are not immune to the morbidity associated with COVID-19, including, at its most severe end, multisystem inflammatory syndrome. And asymptomatic children can certainly transmit COVID-19," she said.

How should dermatologists counsel patients about handwashing and mask wearing?

Dr. Paller has seen many eczema patients with irritant dermatitis on their hands and faces from handwashing and mask wearing.

"We are advising people to double-up on their moisturizing," she said.

She recommended that eczema patients limit or avoid using hand sanitizers, which have a high alcohol content. She also emphasized that gentle or soap-free cleansers are effective, and that antibacterial soap provides no additional benefit. Handwashing for at least 20 seconds is also recommended, but it makes sense for eczema patients to concentrate most on the palms and palmar fingers, where most touching occurs, and less on the tops of the hands, where irritant dermatitis tends to occur. Dr. Paller reminds patients about moisturizing after washing, if possible, and using topical anti-inflammatory medications as needed for dermatitis.

Dr. Lio recommends on http://nationaleczema.org that patients avoid hot water when rinsing their hands and use warm water instead. When it comes to mask wearing, eczema patients should look for masks made of softer materials that still offer some protection but are comfortable and lightweight. ◈

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DISCLOSURES

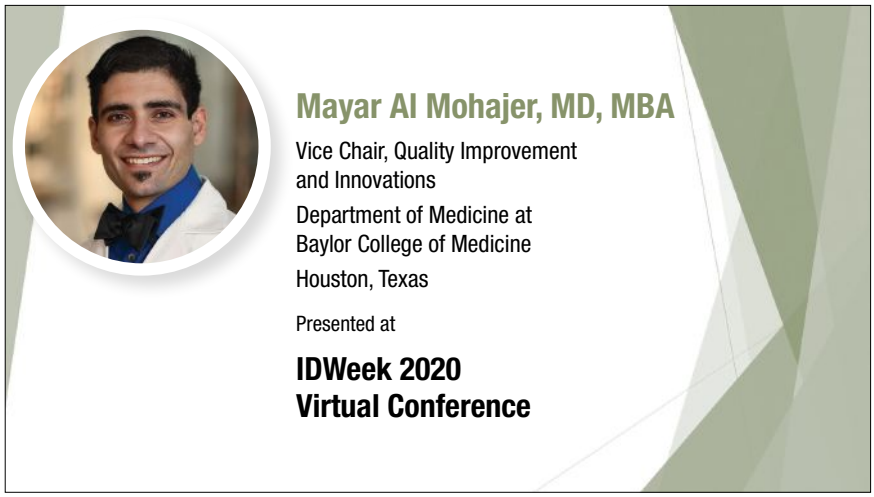
Dr. Paller is an investigator for AbbVie, Eli Lilly, Leo, Janssen, Novartis, Regeneron, and UCB; and a consultant with honorarium for AbbVie, Eli Lilly, Galderma, Janssen, Leo, Novartis, Pfizer, Regeneron, Sanofi-Genzyme, and UCB.

Dr. Lio reports research grants/funding from AbbVie, the National Eczema Association, and Regeneron/Sanofi Genzyme; is on the speaker's bureau for Galderma, L'Oreal, Pfizer, and Regeneron/Sanofi Genzyme; reports consulting/advisory boards for AbbVie, Amyris, AOBiome, Arbonne, Bodewell, Burt's Bees, Dermavant, Dermira, Eli Lilly, Exeltis, Franklin Bioscience/Altus Labs (stock options), Galderma, IntraDerm, Johnson & Johnson, Kiniksa, La Roche Posay/L'Oreal, LEO Pharmaceuticals, Level Ex, Menlo Therapeutics, Micreos (stock options), Pfizer, Pierre-Fabre, Realm Therapeutics, Regeneron/Sanofi Genzyme, Theraplex, TopMD, UCB, Unilever, Verrica, YobeeCare (stock options).

In addition, Dr. Lio has a patent pending for a Theraplex product with royalties paid and is a board member and scientific advisory committee member of the National Eczema Association and an investor at LearnSkin.

Face shield plus mask offers superior COVID-19 protection

By *Lisette Hilton* | Reviewed by *Mayar Al Mohajer, MD, MBA*



SARS CoV-2 infection rates among healthcare workers and hospitalized patients plummeted when one hospital implemented universal masking and face shields, according to data by Baylor College of Medicine researcher Mayar Al Mohajer, MD, MBA.

"We have all seen how COVID-19 has been impacting us across the country—impacting providers in all different specialties, not only their health but also affecting their families. The goal is, what can we do differently to prevent [staff from] getting COVID-19 or bringing this infection home?" said Dr. Mohajer, Vice Chair, Quality Improvement and Innovations, Department of Medicine at Baylor College of Medicine, Houston, Texas.

Dr. Mohajer, who also is Medical Director, Infection Prevention, Diagnostic Stewardship and Antimicrobial Stewardship at Baylor St. Luke's Medical Center, presented the data during the IDWeek 2020 virtual conference. It looks at outcomes from a universal requirement to wear a face shield and mask to reduce the risk of healthcare workers' and patients' COVID-19 exposure, compared to wearing a mask alone.

The findings, he said, support wearing both a face shield and mask as part of a multifaceted approach to prevent SARS CoV-2 infection.

Baylor's experience

Baylor St. Luke's Medical Center implemented several infection prevention measures when the pandemic began. Early on, staff would screen patients for symptoms and elevated temperature. The hospital had a universal masking requirement for healthcare workers, encouraged social distancing, limited meeting sizes, and had a surveillance program regularly testing healthcare workers and patients for COVID-19 infection.

But in May, SARS CoV-2 cases rose sharply in Texas, which was reflected by a steep climb in infection rates among Baylor healthcare workers and hospital-acquired COVID-19 infections among patients.

"We wanted to do something beyond the regular CDC recommendations to limit the transmission to healthcare workers and to our patients," Dr. Mohajer said.

In July Baylor St. Luke's implemented universal face shields, in addition to masks, for all healthcare workers upon entry to the facility. And Dr. Mohajer and his team studied the move's impact using a preintervention and postintervention study design.

"The pre-intervention period was between April 17 and July 1. The intervention period was between July 6 and September 7," he said.

"We tested over 6500 healthcare workers and saw in the pre-intervention period initially—around March—the rates of healthcare workers that were infected was around zero but peaked to close to 12.9% prior to the intervention. Once we started the intervention, the rates of healthcare worker infections went down from around 13% to 2.3%."

"Once we started the intervention, the rates of healthcare worker infections went down from around 13% to 2.3%."

Hospital-acquired infections dropped similarly among hospitalized patients from zero early in the pre-intervention period to 7% at its peak; then to zero early in the intervention period.

Dr. Mohajer also noted a statistically significant drop in hospital-acquired staph infections in the post intervention period, compared to preintervention.

Even Dr. Mohajer said he was surprised by how much of a difference adding face shields appears to make. The findings, he said, support wearing both a face shield and mask as part of a multifaceted approach to prevent SARS CoV-2 infection at any healthcare setting, especially in areas with high transmission

CDC recommends choosing a face shield that wraps around the sides of the face and extends below the chin, or a hooded face shield.

rates. It is a reasonable approach for dermatologists or any providers seeing patients or working in an office, clinic, or hospital.

Implementing face shields

Face shields are an inexpensive way to add a barrier to transmission. The shields can be 3D printed or bought for a few dollars each, according to Dr. Mohajer.

Baylor St. Luke's has implemented a policy in which healthcare workers must wear face masks and shields for not only patient interactions but also staff-to-staff interactions.

"From what we see, a lot of people can get COVID from interactions with colleagues," he said.

Things have not gone without a hitch, however. Some staff have complained about having to wear face shields. The most common complaint is headaches. So, if a healthcare worker is unable to wear a face shield, he or she can wear goggles instead.

Dr. Mohajer is not convinced that goggles provide as much protection as face shields but agrees that face shields may not work for everyone.

"It is key to have our findings replicated by other hospitals, and if these findings are confirmed then hopefully that will lead to changes in guidelines in practices across the country," he said.

There is minimal evidence showing that face shields effectively prevent viral transmission. But one study[1] using cough stimulation found that inhalation risk exposure decreased by 95% immediately after aerosol production, according to a paper published September 25, 2020, in the Journal of Cosmetic Dermatology.[2]

That protection diminished after 30 minutes, according to the researchers.

"Hence, face shields should only be used as an adjunct to other facial protection equipment," the researchers wrote. "[Face shields] should be snugly fit with no gap between the forehead and shield. Good quality material should be used (OHP 150-200 micron) for visual clarity. Full length face shields should be used, and the outer edges should reach the ear. The front of face shield should not be touched, and it should be removed with gloved hands from behind."

CDC (COVID-19: Considerations for Wearing Masks | CDC) recommends choosing a face shield that wraps around the sides of the face and extends below the chin, or a hooded face shield. ◈

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DISCLOSURES

Dr. Mohajer reports no relevant financial interests.

2021 CODING CHANGES: TRIMMING NOTE BLOAT

By *John Jesitus* |
Reviewed by *Mark D. Kaufmann, MD*

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Sweeping changes to evaluation and management (E/M) coding for 2021 will simplify billing-related documentation for dermatologists while likely delivering unintended side effects for payers.

The first major overhaul to American Medical Association (AMA) Current Procedural Terminology (CPT) codes in more than 25 years, the 2021 changes stem from the Patients over Paperwork initiative, launched in 2017 by the US Department of Health and Human Services (HHS).

"They were listening to the complaints of physicians who were saying that the documentation requirements for billing and electronic health record (EHR) notes were becoming so difficult and irrelevant to patient care that they were all complaining of what we lovingly refer to as 'note bloat,'" said Mark D. Kaufmann, MD, an Associate Clinical Professor of Dermatology at Icahn School of Medicine at Mount Sinai, New York, and an advisor to the AAD Relative Value Scale Update Committee (RUC).

Previously, Dr. Kaufmann said, the level of documentation required for Centers for Medicare & Medicaid (CMS) billing meant that perhaps 2/3 of a typical

Incoming AAD President, Mark D. Kaufmann, MD, unpacks the first major overhaul to the AMA's CPT codes in 25 years—impacting how billing changes as a result at https://thedermdigest.com/practice-management/mark-d-kaufmann-md-on-amas-january-1-2021-coding-changes/

> Every patient should have the status of their diagnosis and a plan for the diagnosis, and that basically determines what the code is going to be."

patient chart was irrelevant to patient care. To properly document the physical examination, for example, dermatologists had to examine several body areas—and check off corresponding EHR boxes—unrelated to clinical care. For such reasons, the 2021 changes no longer count a patient's current complaint, history of present illness, review of systems, or examination toward determining the correct E/M code. CMS still expects physicians to do a proper history and physical, said Dr. Kaufmann, but these elements are not required for billing.

Because the new paradigm is based on the type of diagnosis for which a patient is being seen, he said, physicians can do what is medically right and worry less about documentation. In navigating the changes, he added, physicians should consider a 5-column table released by the American Medical Association (AMA) in September 2020 as "the bible" because it is the only written documentation that the AMA has released on the subject.[1] The revisions in this table went into effect on January 1, 2021.

Reading the Medical Decision Making chart

Moving left to right, said Dr. Kaufmann, diagnostic codes chosen for the first column of the table must be supported by information in the 3 main columns (Table 1). The second column from the left reports the level of medical decision-making (MDM) for a particular visit; information in the remaining 3 columns must support the MDM level at which one is billing.

To illustrate proper use of the 3 MDM columns, Dr. Kaufmann offered the example of androgenetic alopecia (AA). In the first MDM column (Number and Complexity of Problems Addressed), AA qualifies for a moderate (level 4) degree of MDM automatically because it is a chronic condition that progresses. "But you need to have something in one of the other columns to go along with it," he said.

If a dermatologist prescribes a medication such as finasteride, he or she can use the third MDM column (Risk of Complications and/or Morbidity or Mortality of Patient Management) to document this fact. "That is an example of moderate medical decision-making in column 3," said

Table 1. CPT E/M Office Revisions
Level of Medical Decision Making (MDM)

Code	Level of MDM (Based on 2 out of 3 Elements of MDM)	Number and Complexity of Problems Addressed
99211	**N/A**	**N/A**
99202 **99212**	**Straightforward**	**Minimal** • 1 self-limited or minor problem
99203 **99213**	**Low**	**Low** • 2 or more self-limited or minor problems; *or* • 1 stable chronic illness; *or* • 1 acute, uncomplicated illness or injury
99204 **99214**	**Moderate**	**Moderate** • 1 or more chronic illnesses with exacerbation, progression, or side effects of treatment; *or* • 2 or more stable chronic illnesses; *or* • 1undiagnosed new problem with uncertain prognosis; *or* • 1 acute illness with systemic symptoms; *or* • 1 acute complicated injury
99205 **99215**	**High**	**High** • 1 or more chronic illnesses with severe exacerbation, progression, or side effects of treatment; *or* • 1 acute or chronic illness or injury that poses a threat to life or bodily function

Revisions effective January 1, 2021: **Note:** this content will not be included in the CPT 2020 code set release

Elements of Medical Decision Making		
	Amount and/or Complexity of Data to be Reviewed and Analyzed *Each unique test, order, or document contributes to the combination of 2 or combination of 3 in Category 1 below.	**Risk of Complications and/or Morbidity or Mortality of Patient Management**
	N/A	**N/A**
	Minimal or none	**Minimal risk of morbidity from additional diagnostic testing or treatment**
	Limited *(Must meet the requirements of at least 1 of the 2 categories)* **Category 1: Tests and documents** • Any combination of 2 from the following: – Review of prior external note(s) from each unique source*; – review of the result(s) of each unique test*; – ordering of each unique test* *or* **Category 2: Assessment requiring an independent historian(s)** *(For the categories of independent interpretation of tests and discussion of management or test interpretation, see moderate or high)*	**Low risk of morbidity from additional diagnostic testing or treatment**
	Moderate *(Must meet the requirements of at least 1 out of 3 categories)* **Category 1: Tests, documents, or independent historian(s)** • Any combination of 3 from the following: – Review of prior external note(s) from each unique source*; – Review of the result(s) of each unique test*; – Ordering of each unique test*; – Assessment requiring an independent historian(s) or **Category 2: Independent interpretation of tests** • Independent interpretation of a test performed by another physician/other qualified health care professional (not separately reported); *or* **Category 3: Discussion of management or test interpretation** • Discussion of management or test interpretation with external physician/other qualified health care professional\appropriate source (not separately reported)	**Moderate risk of morbidity from additional diagnostic testing or treatment** *Examples only:* • Prescription drug management • Decision regarding minor surgery with identified patient or procedure risk factors • Decision regarding elective major surgery without identified patient or procedure risk factors • Diagnosis or treatment significantly limited by social determinants of health
	Extensive *(Must meet the requirements of at least 2 out of 3 categories)* **Category 1: Tests, documents, or independent historian(s)** • Any combination of 3 from the following: – Review of prior external note(s) from each unique source*; – Review of the result(s) of each unique test*; – Ordering of each unique test*; – Assessment requiring an independent historian(s) *or* **Category 2: Independent interpretation of tests** • Independent interpretation of a test performed by another physician/other qualified health care professional (not separately reported); *or* **Category 3: Discussion of management or test interpretation** • Discussion of management or test interpretation with external physician/other qualified health care professional/appropriate source (not separately reported)	**High risk of morbidity from additional diagnostic testing or treatment** *Examples only:* • Drug therapy requiring intensive monitoring for toxicity • Decision regarding elective major surgery with identified patient or procedure risk factors • Decision regarding emergency major surgery • Decision regarding hospitalization • Decision not to resuscitate or to de-escalate care because of poor prognosis

> One of the unintended consequences is that CMS will find that it's going to be easier for many specialties to reach higher reimbursement levels than they ever had before."

Dr. Kaufmann. "At that point, you would have 'moderate' in column 1 and column 3; you could use 99204 or 99214 for the level code for that visit."

Conversely, if a dermatologist recommends an over-the- counter medication such as minoxidil, this qualifies for low-level MDM, making the visit level 3 instead of level 4. Alternatively, counseling a patient without recommending treatment represents straightforward MDM, or a level 2 visit.

"Column 1 is the status of the diagnosis—is it chronic, acute, stable, or flaring? And column 3 is the plan. Every patient should have the status of their diagnosis and a plan for the diagnosis, and that basically determines what the code is going to be." Dermatologists will less frequently use the second (middle) of the 3 MDM columns (Amount and/or Complexity of Data to Be Reviewed and Analyzed), said Dr. Kaufmann.

As of January 1, 2021, the AMA eliminated the 99201 new-patient code because it now qualifies for the same "straightforward" MDM as does code 99202. However, said Dr. Kaufmann, 99211 remains for returning-patient visits handled by clinical staff.

New-patient codes 99202 through 99205 in 2021 apply only to patients who are new to a practice or have not been seen there in the preceding 3 years. While these codes remain unchanged, said Dr. Kaufmann, "the ability of a dermatologist to reach a higher-level code legitimately has increased dramatically with the new paradigm."

Overall, Dr. Kaufmann welcomes the elimination of the "mental gymnastics" formerly required to justify billing codes. "I believe the intent of CMS to make billing easier will be accomplished. However, one of the unintended consequences is that CMS will find that it's going to be easier for many specialties to reach higher reimbursement levels than they ever had before. And that may lead to some second thoughts as far as the payment paradigm is considered."

REFERENCE

1. American Medical Association. CPT evaluation and management (E/M) office or other outpatient (99202-99215) and prolonged services (99354, 99355, 99356, 99XXX) code and guideline changes. https://www.ama-assn.org/system/files/2019-06/cpt-office-prolonged-svs-code-changes.pdf. Published September 1, 2020. Accessed December 20, 2020.

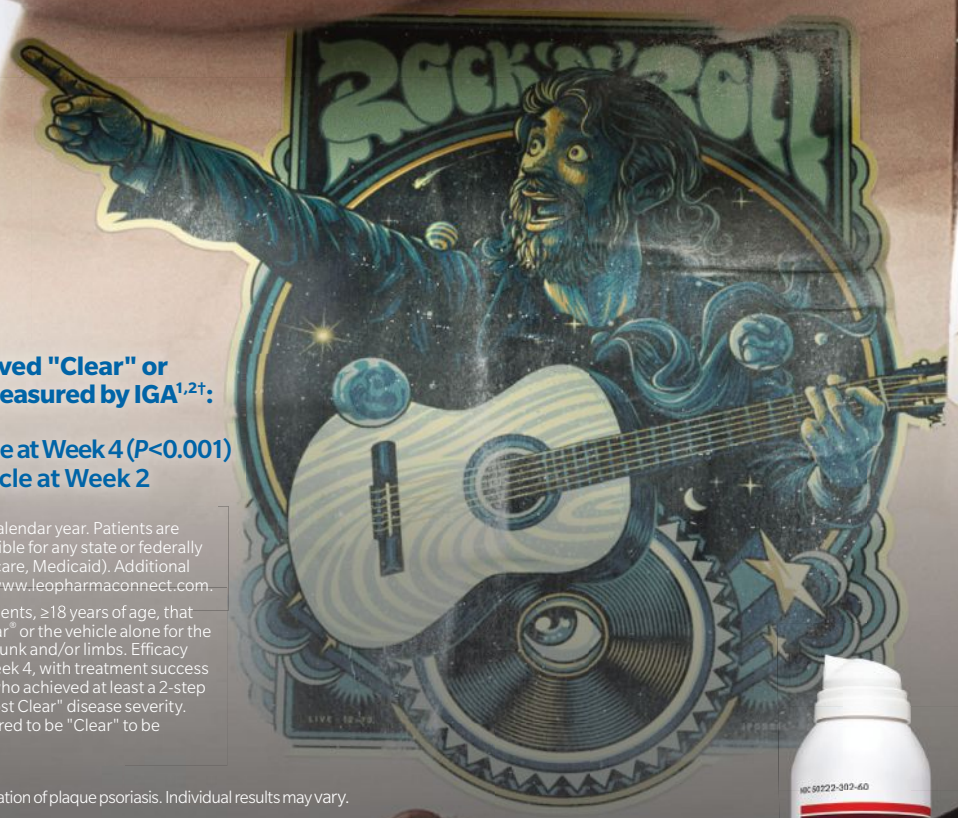
DISCLOSURES

Dr. Kaufmann is advisor to the AAD Relative Value Scale Update Committee.

Most commercially insured patients pay as little as $20*

An experience worth noticing.

With clinical efficacy and safety profile in a once-daily spray foam, choose the Enstilar® Foam experience for your patients with plaque psoriasis.[1]



In adults, patients achieved "Clear" or "Almost Clear" skin as measured by IGA[1,2†]:

- 53.3% vs 4.8% for vehicle at Week 4 ($P<0.001$)
- 26.4% vs 1.9% for vehicle at Week 2

*Valid for up to 12 prescription fills per calendar year. Patients are not eligible if they are enrolled in or eligible for any state or federally funded health care program (eg, Medicare, Medicaid). Additional restrictions and limitations apply; see www.leopharmaconnect.com.

†A randomized clinical trial with 426 patients, ≥18 years of age, that investigated the effectiveness of Enstilar® or the vehicle alone for the treatment of psoriasis vulgaris on the trunk and/or limbs. Efficacy was assessed using a 5-point IGA at Week 4, with treatment success defined as the percentage of patients who achieved at least a 2-step improvement to reach "Clear" or "Almost Clear" disease severity. Patients with "Mild" disease were required to be "Clear" to be considered a treatment success.[1,2]

IGA=Investigator's Global Assessment.

Not an actual patient. Image is a representation of plaque psoriasis. Individual results may vary.

References: 1. Enstilar® [prescribing information]. LEO Pharma Inc. **2.** Leonardi C, Bagel J, Yamauchi P, et al. Efficacy and safety of calcipotriene plus betamethasone dipropionate aerosol foam in patients with psoriasis vulgaris — a randomized phase III study (PSO-FAST). *J Drugs Dermatol*. 2015;14(12):1468-1477.

INDICATION AND USAGE

Enstilar® (calcipotriene and betamethasone dipropionate) Foam is indicated for the topical treatment of plaque psoriasis in patients 12 years and older. Apply Enstilar Foam to affected areas once daily for up to 4 weeks. Discontinue use when control is achieved. Instruct patients not to use more than 60 grams every 4 days.

IMPORTANT SAFETY INFORMATION

For topical use only. Enstilar Foam is not for oral, ophthalmic or intravaginal use and should not be applied on the face, groin or axillae or if skin atrophy is present at the treatment site. Do not use with occlusive dressings. Patients should wash hands after application.

Please see Brief Summary of Prescribing Information on following page.

L E O

Enstilar®
(calcipotriene and betamethasone dipropionate) Foam 0.005%/0.064%

ENSTILAR® (calcipotriene and betamethasone dipropionate) foam, for topical use
Rx Only

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

Enstilar® (calcipotriene and betamethasone dipropionate) Foam is indicated for the topical treatment of plaque psoriasis in patients 12 years and older.

DOSAGE AND ADMINISTRATION

Instruct patients to shake can prior to using Enstilar Foam and to wash their hands after applying the product. Apply Enstilar Foam to affected areas once daily for up to 4 weeks. Rub in Enstilar Foam gently. Discontinue Enstilar Foam when control is achieved.

Patients should not use more than 60 grams every 4 days.

Enstilar Foam should **not** be:

- Used with occlusive dressings unless directed by a healthcare provider.
- Used on the face, groin, or axillae, or if skin atrophy is present at the treatment site.

Enstilar Foam is not for oral, ophthalmic, or intravaginal use.

DOSAGE FORMS AND STRENGTHS

Enstilar Foam: 0.005%/0.064% - each gram contains 50 mcg calcipotriene and 0.643 mg of betamethasone dipropionate in a white to off-white opalescent liquid in a pressurized aluminum spray can with a continuous valve and actuator. At administration the product is a white to off-white foam after evaporation of the propellants.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Flammability

The propellants in Enstilar Foam are flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application.

Hypercalcemia and Hypercalciuria

Hypercalcemia and hypercalciuria have been observed with use of Enstilar Foam. If hypercalcemia or hypercalciuria develop, discontinue treatment until parameters of calcium metabolism have normalized. The incidence of hypercalcemia and hypercalciuria following Enstilar Foam treatment of more than 4 weeks has not been evaluated.

Effects on Endocrine System

Hypothalamic-Pituitary-Adrenal Axis Suppression

Systemic absorption of topical corticosteroids can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency steroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age.

Evaluation for HPA axis suppression may be done by using the adrenocorticotropic hormone (ACTH) stimulation test. If HPA axis suppression is documented, gradually withdraw Enstilar Foam, reduce the frequency of application, or substitute with a less potent corticosteroid.

The following trials evaluated the effects of Enstilar Foam on HPA axis suppression:

- In a trial evaluating the effects of Enstilar Foam on the HPA axis, 35 adult subjects applied Enstilar Foam on the body and scalp. Adrenal suppression was not observed in any subjects after 4 weeks of treatment. In another trial, 33 pediatric subjects age 12 to 17 years applied Enstilar Foam on the body and scalp. Adrenal suppression occurred in 3 (9%) of the subjects.

Cushing's Syndrome and Hyperglycemia

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

Additional Considerations for Endocrine Adverse Reactions

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios.

Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.

Allergic Contact Dermatitis

Allergic contact dermatitis has been observed with topical calcipotriene and topical corticosteroids. Allergic contact dermatitis to a topical corticosteroid is usually diagnosed by observing a failure to heal rather than a clinical exacerbation. Corroborate such an observation with appropriate diagnostic patch testing.

Ophthalmic Adverse Reactions

Use of topical corticosteroids, including Enstilar® Foam, may increase the risk of posterior subcapsular cataracts and glaucoma. Cataracts and glaucoma have been reported with the postmarketing use of topical corticosteroid products. Avoid contact with Enstilar Foam with eyes. Enstilar Foam may cause eye irritation. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.

ADVERSE REACTIONS

Clinical Trials Experience

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

Clinical Trials Conducted in Subjects 18 years and older with Psoriasis

The rates of adverse reactions described below were from three randomized, multicenter, vehicle and/or active-controlled clinical trials in adult subjects with plaque psoriasis. Subjects applied study product once daily for 4 weeks, and the median weekly dose of Enstilar Foam was 25 grams. Adverse reactions reported in <1% of adult subjects treated with Enstilar Foam included: application site irritation, application site pruritus, folliculitis, skin hypopigmentation, hypercalcemia, urticaria, and exacerbation of psoriasis.

Clinical Trials Conducted in Subjects 12 to 17 years with Psoriasis

In one uncontrolled clinical trial, 106 subjects aged 12 to 17 years with plaque psoriasis of the scalp and body applied Enstilar Foam once daily for up to 4 weeks. The median weekly dose was 40 grams. Adverse reactions reported in <1% of pediatric subjects treated were acne, erythema, application site pain, and skin reactions.

Postmarketing Experience

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketing reports for local adverse reactions to topical corticosteroids included atrophy, striae, telangiectasia, dryness, perioral dermatitis, secondary infection, and miliaria.

Ophthalmic adverse reactions of cataracts, glaucoma, increased intraocular pressure, and central serous chorioretinopathy have been reported with the use of topical corticosteroids, including topical betamethasone products.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Available data with Enstilar Foam are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriages, or adverse maternal or fetal outcomes. Although there are no available data on use of the calcipotriene component in pregnant women, systemic exposure to calcipotriene after topical administration of Enstilar Foam is likely to be low.

Observational studies suggest an increased risk of having low birth weight infants with the maternal use of potent or super potent topical corticosteroids. Advise pregnant women that Enstilar Foam may increase the potential risk of having a low birth weight infant and to use Enstilar Foam on the smallest area of skin and for the shortest duration possible.

In animal reproduction studies, oral administration of calcipotriene to pregnant rats during the period of organogenesis resulted in an increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs. Oral administration of calcipotriene to pregnant rabbits during the period of organogenesis had no apparent effects on embryo-fetal development. Subcutaneous administration of betamethasone dipropionate to pregnant rats and rabbits during the period of organogenesis resulted in fetal toxicity, including fetal deaths, reduced fetal weight, and fetal malformations (cleft palate and crooked or short tail). The available data do not allow the calculation of relevant comparisons between the systemic exposures of calcipotriene and betamethasone dipropionate observed in animal studies to the systemic exposures that would be expected in humans after topical use of Enstilar® Foam.

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

Data

Human Data

Available observational studies in pregnant women did not identify a drug-associated risk of major birth defects, preterm delivery, or fetal mortality with the use of topical corticosteroids of any potency. However, when the dispensed amount of potent or super potent topical corticosteroids exceeded 300 grams during the entire pregnancy, maternal use was associated with an increased risk of low birth weight in infants.

Animal Data

Embryo-fetal development studies with calcipotriene were performed by the oral route in rats and rabbits. Pregnant rats received dosages of 0, 6, 18, or 54 mcg/kg/day (0, 36, 108, and 324 mcg/m^2/day, respectively) on days 6-15 of gestation (the period of organogenesis). There were no apparent effects on maternal survival, behavior, or body weight gain, no effects on litter parameters, and no effects on the incidence of major malformations in fetuses. Fetuses from dams dosed at 54 mcg/kg/day exhibited a significantly increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs.

Pregnant rabbits were dosed daily with calcipotriene at exposures of 0, 4, 12, or 36 mcg/kg/day (0, 48, 144, and 432 mcg/m^2/day, respectively) on days 6-18 of gestation (the period of organogenesis). Mean maternal body weight gain was reduced in animals dosed at 12 or 36 mcg/kg/day. The incidence of fetal deaths was increased in the group dosed at 36 mcg/kg/day; reduced fetal weight was also observed in this group. The incidence of major malformations among fetuses was not affected. An increase in the incidence of minor skeletal abnormalities, including incomplete ossification of sternebrae, pubic bones, and forelimb phalanges, was observed in the group dosed at 36 mcg/kg/day.

Embryo-fetal development studies with betamethasone dipropionate were performed via subcutaneous injection in mice and rabbits. Pregnant mice were administered doses of 0, 156, 625, or 2500 mcg/kg/day (0, 468, 1875, and 7500 mcg/m^2/day, respectively) on days 7 through 13 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal deaths, reduced fetal weight, malformations (increased incidence of the cleft palate and crooked or short tail), and minor skeletal abnormalities (delayed ossification of vertebra and sternebrae). Fetal toxicity was observed at the lowest exposure that was evaluated (156 mcg/kg/day).

Pregnant rabbits were injected subcutaneously at dosages of 0, 0.625, 2.5, and 10 mcg/kg/day (0, 7.5, 30, and 120 mcg/m^2/day, respectively) on days 6 through 18 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal deaths, reduced fetal weight, external malformations (including malformed ears, cleft palate, umbilical hernia, kinked tail, club foot, and club hand), and skeletal malformations (including absence of phalanges of the first digit and cranial dysplasia) at dosages of 2.5 mcg/kg/day and above.

Calcipotriene was evaluated for effects on peri- and post-natal development when orally administered to pregnant rats at dosages of 0, 6, 18 or 54 mcg/kg/day (0, 36, 108, and 324 mcg/m^2/day, respectively) from gestation day 15 through day 20 postpartum. No remarkable effects were observed on any parameter, including survival, behavior, body weight, litter parameters, or the ability to nurse or rear pups.

Betamethasone dipropionate was evaluated for effects on peri- and post-natal development when orally administered to pregnant rats at dosages of 0, 100, 300, and 1000 mcg/kg/day (0, 600, 1800, and 6000 mcg/m^2/day, respectively) from gestation day 6 through day 20 postpartum. Mean maternal body weight was significantly reduced on gestation day 20 in animals dosed at 300 and 1000 mcg/kg/day. The mean duration of gestation was slightly, but statistically significantly, increased at 100, 300, and 1000 mcg/kg/day. The mean percentage of pups that survived to day 4 was reduced in relation to dosage. On lactation day 5, the percentage of pups with a reflex to right themselves when placed on their back was significantly reduced at 1000 mcg/kg/day. No effects on the ability of pups to learn were observed, and the ability of the offspring of treated rats to reproduce was not affected.

Lactation

Risk Summary

There is no information regarding the presence of topically administered calcipotriene and betamethasone dipropionate in human milk, the effects on the breastfed infant, or the effects on milk production. Concentrations of calcipotriene in plasma are low after topical administration, and therefore, concentrations in human milk are likely to be low. It is not known whether topical administration of large amounts of betamethasone dipropionate could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Enstilar® Foam and any potential adverse effects on the breastfed child from Enstilar Foam or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breast milk, use Enstilar Foam on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply Enstilar Foam directly to the nipple and areola to avoid direct infant exposure.

Pediatric Use

The safety and effectiveness of Enstilar Foam for the treatment of mild to severe plaque psoriasis have been established in pediatric patients age 12 to 17 years. The use of Enstilar Foam for this indication is supported by evidence from adequate and well-controlled trials in adults and from one uncontrolled trial in 106 adolescents age 12 to 17 years with psoriasis of the body and scalp. Calcium metabolism was evaluated in all pediatric subjects and no cases of hypercalcemia or clinically relevant changes in urinary calcium were reported. Hypothalamic pituitary adrenal (HPA) axis suppression was evaluated in a subset of 33 pediatric subjects with moderate plaque psoriasis of the body and scalp (mean body surface area involvement of 16% and mean scalp area involvement of 56%). After 4 weeks of once daily treatment with a mean weekly dose of 47 grams, HPA axis suppression was observed in 3 of 33 subjects (9%).

Because of a higher ratio of skin surface area to body mass, children under the age of 12 years are at particular risk of systemic adverse effects when they are treated with topical corticosteroids. Pediatric patients are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency with the use of topical corticosteroids including Enstilar Foam.

Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients treated with topical corticosteroids.

Local adverse reactions including striae have been reported with use of topical corticosteroids in pediatric patients.

The safety and effectiveness of Enstilar Foam in pediatric patients less than 12 years of age have not been established.

Geriatric Use

Of the total number of subjects in the controlled clinical studies of Enstilar Foam, 97 subjects were 65 years and over, and 21 were 75 and over.

No overall differences in safety or effectiveness of Enstilar Foam were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

When calcipotriene was applied topically to mice for up to 24 months at dosages of 3, 10, and 30 mcg/kg/day (9, 30, and 90 mcg/m^2/day, respectively), no significant changes in tumor incidence were observed when compared to control.

A 104-week oral carcinogenicity study was conducted with calcipotriene in male and female rats at doses of 1, 5, and 15 mcg/kg/day (6, 30, and 90 mcg/m^2/day, respectively). Beginning week 71, the dosage for high-dose animals of both genders was reduced to 10 mcg/kg/day (60 mcg/m^2/day). A treatment-related increase in benign C-cell adenomas was observed in the thyroid of females that received 15 mcg/kg/day. A treatment-related increase in benign pheochromocytomas was observed in the adrenal glands of males that received 15 mcg/kg/day. No other statistically significant differences in tumor incidence were observed when compared to control. The relevance of these findings to patients is unknown.

When betamethasone dipropionate was applied topically to CD-1 mice for up to 24 months at dosages approximating 1.3, 4.2, and 8.5 mcg/kg/day in females, and 1.3, 4.2, and 12.9 mcg/kg/day in males (up to 26 mcg/m^2/day and 39 mcg/m^2/day, in females and males, respectively), no significant changes in tumor incidence were observed when compared to control.

When betamethasone dipropionate was administered via oral gavage to male and female Sprague Dawley rats for up to 24 months at dosages of 20, 60, and 200 mcg/kg/day (120, 360, and 1200 mcg/m^2/day, respectively), no significant changes in tumor incidence were observed when compared to control.

Calcipotriene did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Betamethasone dipropionate did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, or in the rat micronucleus test.

Studies in rats with oral doses of up to 54 mcg/kg/day (324 mcg/m^2/day) of calcipotriene indicated no impairment of fertility or general reproductive performance. Studies in male rats at oral doses of up to 200 mcg/kg/day (1200 mcg/m^2/day), and in female rats at oral doses of up to 1000 mcg/kg/day (6000 mcg/m^2/day), of betamethasone dipropionate indicated no impairment of fertility.

PATIENT COUNSELING INFORMATION

Flammability

Instruct patients that Enstilar Foam is flammable; avoid heat, flame, or smoking when applying this medication.

Administration Instructions

- Shake before use and spray the foam by holding the can in any orientation except horizontally.
- Do not use more than 60 grams every 4 days.
- Discontinue therapy when control is achieved unless directed otherwise by the healthcare provider.
- Avoid use of Enstilar Foam on the face, underarms, groin or eyes. If this medicine gets on face or in mouth or eyes, wash area right away.
- Do not occlude the treatment area with a bandage or other covering unless directed by the healthcare provider. Instruct the patients not to use other products containing calcipotriene or a corticosteroid with Enstilar Foam without first talking to the healthcare provider.
- Wash hands after application.

Local Reactions and Skin Atrophy

Advise patients that local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids.

Hypercalcemia and Hypercalciuria

Advise patients that hypercalcemia and hypercalciuria have been observed with the use of Enstilar Foam.

HPA Axis Suppression, Cushing's Syndrome, and Hyperglycemia

Advise patients that Enstilar Foam can cause HPA axis suppression, Cushing's syndrome, and/or hyperglycemia.

Ophthalmic Adverse Reactions

Advise patients to avoid contact of Enstilar Foam with eyes and to report any visual symptoms.

Pregnancy and Lactation

- Advise pregnant women that Enstilar® Foam may increase the potential risk of having a low birth weight infant and to use Enstilar Foam on the smallest area of skin and for the shortest duration possible.
- Advise breastfeeding women not to apply Enstilar Foam directly to the nipple and areola to avoid direct infant exposure.

Manufactured by: LEO Laboratories Ltd., 285 Cashel Road, Dublin 12, Ireland

or

Colep Laupheim GmbH & Co. KG, Fockestraße 12, 88471 Laupheim, Germany (DE)

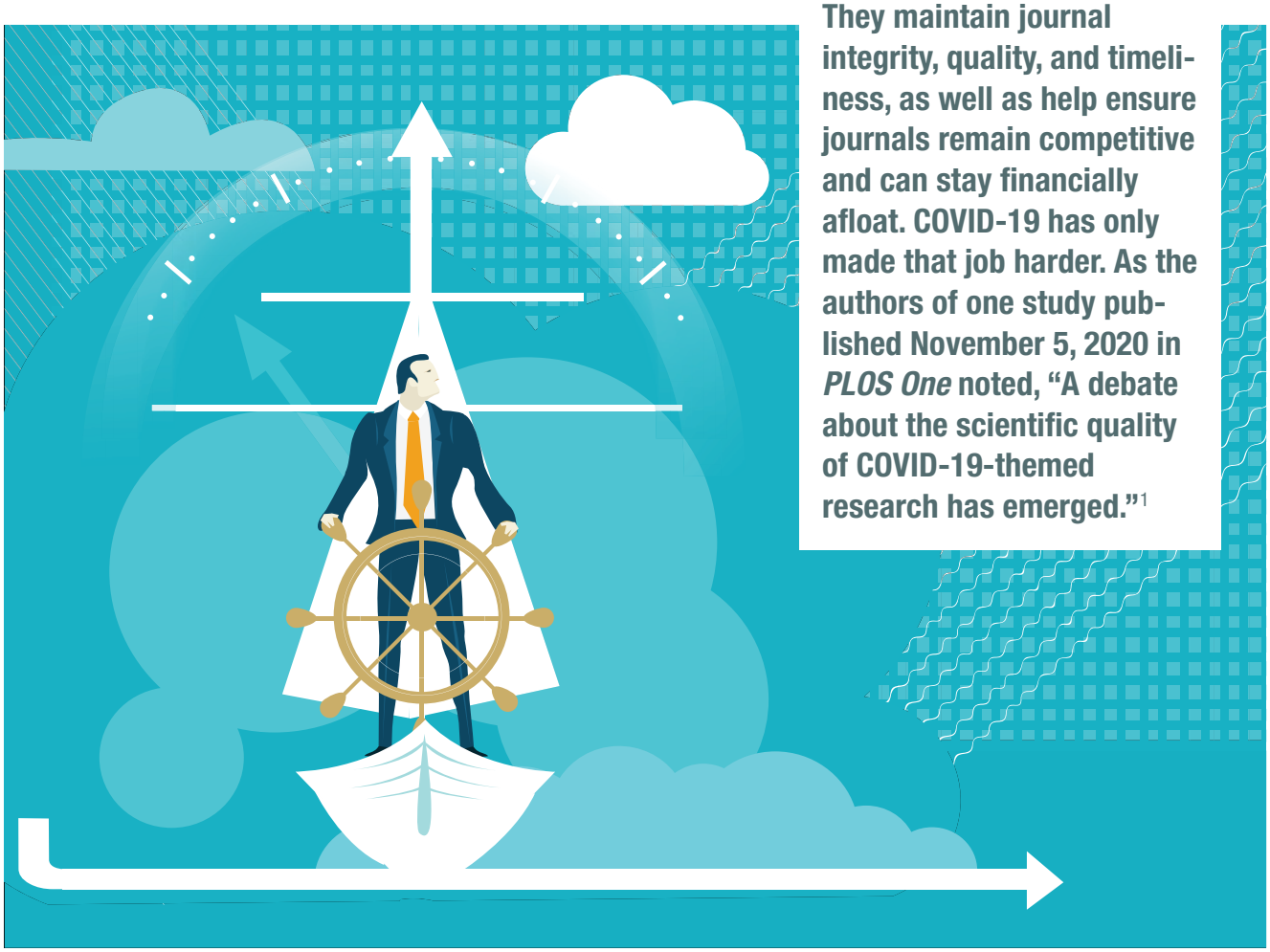
Distributed by: LEO Pharma Inc., Madison, NJ 07940, USA

MAT-32588 March 2020

KEEPING QUALITY HIGH DURING COVID

Dermatology journal editors share insight on maintaining scientific integrity and relevance

By Lisette Hilton



Peer-reviewed journal editors have a tough job. They maintain journal integrity, quality, and timeliness, as well as help ensure journals remain competitive and can stay financially afloat. COVID-19 has only made that job harder. As the authors of one study published November 5, 2020 in *PLOS One* noted, "A debate about the scientific quality of COVID-19-themed research has emerged."[1]

The authors searched the PubMed Database from March 12 to April 12, 2020 and found that indeed the quality of publications concerning COVID-19 in the 3 highest-ranked scientific medical journals—the *New England Journal of Medicine, Journal of the American Medical Association,* and *The Lancet*—was below the quality average of these journals.

The Dermatology Digest asked editors of 2 respected peer-reviewed dermatology journals how they maintain scientific integrity, stay relevant, and navigate the added challenges brought on by the pandemic.

REMARKS BY:

Dermatologist
DIRK M. ELSTON, MD, FAAD,
Editor of the *Journal of the American Academy of Dermatology (JAAD).*

THE DERMATOLOGY DIGEST: Dr. Elston, talk with me about the integrity of *JAAD*. What do readers need to know?

DR. ELSTON: Credibility is any journal's greatest asset. We need to ensure that published data are credible.

THE DERMATOLOGY DIGEST: What was your policy during the pandemic, when time-to-publish was of the essence? Were you concerned about quality? Did you have regrets? Did you have to withdraw any articles post-publication and, on a positive note, what did you learn?

DR. ELSTON: We offered rapid review and publication of COVID-related articles but did not relax our standards. No regrets. It worked well and was the correct approach.

THE DERMATOLOGY DIGEST: How does one balance the rush to publish with maintaining integrity?

DR. ELSTON: We have a pool of reliable reviewers willing to do expedited review. Standards remain the same.

THE DERMATOLOGY DIGEST: Some say the current peer-review process is flawed. What do you think and why?

> "The biggest change going forward will be selective prepublication determined by federal funding agencies."

Are there things that need to change?

DR. ELSTON: It has been said that democracy is the worst form of government—except for all the others. Similarly, peer review is not perfect, but anything else is worse. The biggest change going forward will be selective prepublication determined by federal funding agencies. For select topics like the human genome project it allows information to be available as soon as possible.

THE DERMATOLOGY DIGEST: Do you have specific goals for *JAAD*? What are they?

DR. ELSTON: *JAAD*'s mission is to help dermatologists achieve better patient outcomes. We take that mission seriously and are launching many new features to help readers interpret and apply the literature to their practices. "This month in *JAAD*" summarizes key findings in each journal that influence daily practice. The journal is always evolving and will incorporate new features and technologies to make reading more interesting, relevant, and efficient for busy dermatologists. We know they invest precious time in a journal, and we want to help them get the most out of their investment.

THE DERMATOLOGY DIGEST: Finally, *JAAD* has high impact in the specialty. As a reporter, I often refer to important studies and papers in the journal. What do you think is the journal's niche, edge, and place in the peer-reviewed lineup for dermatologist and other readers?

NOTE: *JAAD* ranked first among dermatology journals, according to the 2019 impact factor rankings published by the *Journal Citation Reports (JCR)* Web of Science Group.

"A journal's impact factor reflects how often the average article in that journal has been cited in a given time period, which for *JCR* is 2 years. *JAAD*'s 2019 impact factor of 8.277 is a 16.5% increase over its previous ranking. This places *JAAD* in the No. 1 position among 68 dermatology journals ranked by *JCR*," according to the American Academy of Dermatology.

THE IMPACT FACTOR

In any given year, the 2-year journal impact factor is the ratio of the number of citations received in that year for publications in that journal that were published in the 2 preceding years to the total number of "citable items" published in that journal during the 2 preceding years:[2,3]

$$IF_y = \frac{Citations_y}{Publications_{y-1} + Publications_{y-2}}$$

For example, *Nature* had an impact factor of 41.577 in 2017:[4]

$$IF_{2017} = \frac{Citations_{2017}}{Publications_{2016} + Publications_{2015}} = \frac{74090}{880 + 902} = 41.577$$

DR. ELSTON: Impact factors of all of the key dermatology clinical journals have been rising, which attests to the quality of the content. I am proud of what our specialty has achieved and proud of all of our specialty's journals. ◈

REMARKS BY:

DEBORAH S. SARNOFF, MD, FAAD, FACP,
Co-editor-in-chief of the *Journal of Drugs in Dermatology (JDD)*

THE DERMATOLOGY DIGEST: What would you like colleagues to know about the integrity of *JDD*? How have you built trust among readers?

DR. SARNOFF: As a peer-reviewed medical journal, the *JDD* actively addresses issues involving ethics and potential bias in reporting. The *JDD*, like other top journals in the field, follows the ethical guidelines for scholarly publishing, such as the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations) and COPE (Committee on Publishing Ethics). These guidelines focus on ethics standards, grievance processes and best practices for scholarly publishing.

In addition to following these guidelines, the *JDD* has 20 years of experience in publishing and a robust International Editorial Board of more than 160 renowned experts. Our experience—both in longevity of publishing as well as the combined expertise of our editorial board—provides *JDD* readers with a sense of trust in our content.

THE DERMATOLOGY DIGEST: What was your policy during the pandemic, when time-to-publish was of the essence? Were you concerned about quality? Did you have regrets? Did you have to withdraw any articles post-publication and on a positive note, what did you learn?

DR. SARNOFF: The *JDD* is one of the fastest-to-publish journals in dermatology. Our experience put us in a unique position to be able to use our standard process of delivering priority content quickly without disruption.

Submissions related to the COVID pandemic were given priority over other articles, peer-reviewed expeditiously, and published in the next available issue once they were accepted. The majority of the accepted articles were published within 1 to 3 months of receipt.

Each article was reviewed using our standard process. While that process was expedited, no shortcuts were taken.

The articles were well-received, and we received only positive feedback.

THE DERMATOLOGY DIGEST: How does one balance the rush to publish with maintaining integrity?

DR. SARNOFF: The *JDD*'s standard in developing situations is to disseminate accurate information in a timely manner. While there can be a rush to publish, every article must be

vetted through the same process to ensure integrity.

Just because a process is expedited does not mean it is flawed, provided no shortcuts were taken. This is similar to the recent development of the COVID vaccines and their emergency approval by the FDA.

THE DERMATOLOGY DIGEST: Some say the current peer-review process is flawed. What do you think and why? Are there things that need to change?

DR. SARNOFF: The peer-review process—provided it follows the guidelines—has safeguards to protect the integrity of published research. This process, while it may be expedited, must be maintained even when publishing late-breaking research.

THE DERMATOLOGY DIGEST: Do you have specific goals for the *JDD*? What are they?

DR. SARNOFF: Our goals for the *JDD* are to help educate the dermatology community on recent research and new treatments through all of our publishing channels, and to make our content widely available to anyone who is interested to learn and share knowledge. The *JDD* strives to perpetuate an open exchange of ideas among physicians, researchers, healthcare providers, dermatology businesses, and industry.

To further our educational mission, all US dermatologists, dermatology residents, dermatology nurse practitioners and dermatology physician assistants are eligible for a free *JDD* print and digital subscription.

THE DERMATOLOGY DIGEST: Finally, Dr. Rosen, editor-in-chief of *The Dermatology Digest*, noted that *JDD* doesn't yet have the same impact factor as *JAAD* or JAMA Dermatology. How important is that impact factor for a journal to stay competitive and afloat? What is your niche and place in the peer-reviewed lineup for dermatologists and other readers?

DR. SARNOFF: We receive many high-quality submissions but are able to publish only about 15% of manuscripts received. By focusing our content on the needs of our readers and not on the impact factor, we are better able to serve our audience in a timely manner.

I think it's important to note that the *JDD* is relatively new at 20 years while other journals, such as *JAAD* and *JAMA Dermatology,* have had more time to grow their reputations. Although the *JDD* does not have an impact factor like *JAMA Dermatology* or *JAAD*, our impact has grown, and we rank among the most highly cited dermatology journals on PubMed.

"The peer-review process—provided it follows the guidelines—has safeguards to protect the integrity of published research. This process, while it may be expedited, must be maintained even when publishing late-breaking research."

The *JDD*'s impact has grown both in citations as well as our internal metrics. Submissions have increased, quality has increased, interest has increased according to our site search data, and readership has increased. In 2019, the *JDD*'s impact factor calculation included the most citations to date with 3037 cites.

While this metric served our industry in the past, there are other newer metrics for calculating the "impact" and ranking, such as the Eigenfactor and Google Scholar. With social media, journals are now also looking at better, data-driven "Altmetrics" scores, which measure social media visibility, views, and downloads.

The *JDD* publishes on timely topics with a focus on clinical studies, new aesthetic treatments, anti-aging, and skin health in order to help educate dermatologists and make the best treatments available. The *JDD* is also the official journal of the *Skin of Color Update* and publishes articles on the topic of research and treatments related to skin of color, as well as the effects of aesthetic treatments on patients with skin of color. ◈

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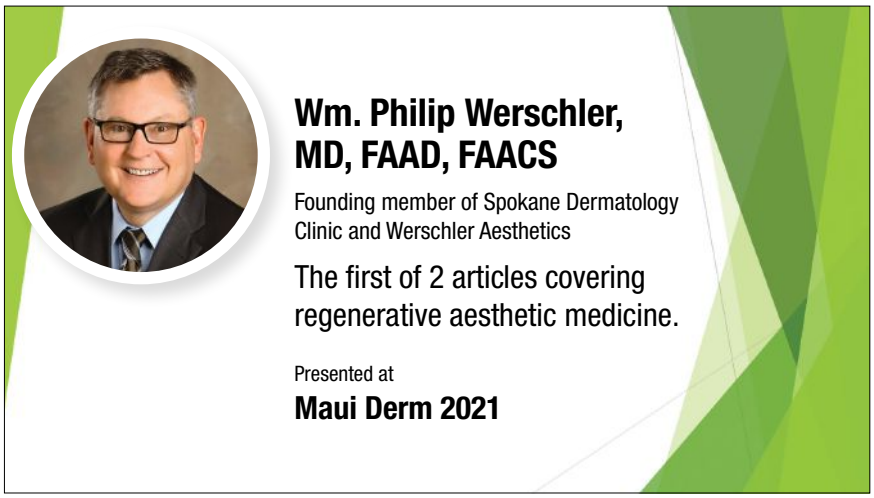
DISCLOSURES *Drs. Elston and Sarnoff report no conflicts of interest.*

REGENERATIVE MEDICINE: Demand in aesthetics expected to surge

By *Lisette Hilton* | Reviewed by Wm. Philip Werschler, MD, FAAD, FAACS



There is plenty of chatter in aesthetic medicine about the potential role regenerative therapies will play.

Wm. Philip Werschler, MD, FAAD, FAACS, revealed at Maui Derm 2021 that regenerative medicine already has taken hold in some aesthetic practices, and with time it will significantly impact what aesthetic providers do and how they do it.

"I think there is a lot of interest, but people don't really understand what the regenerative market is all about. Dermatologists have not been drivers for the most part in regenerative medicine, yet we are the largest potential market," Dr. Werschler said.

Defining things

Regenerative aesthetic medicine (RAM) is simply a branch of regenerative medicine. Regenerative medicine is widely practiced in orthopedics, neurology, and even plastic surgery. In addition to cosmetic surgery, injectables, capital equipment (lasers, energy devices) and medically directed skin care, RAM is considered the "5th Column" of aesthetics, according to Dr. Werschler.

"It has been very slow, next to impossible, to get any kind of reimbursement for regenerative procedures. Insurance does not pay for them. All these stem cell injections into arthritic knees and platelet-rich plasma (PRP) treatments for bad backs, insurance doesn't pay for those," Dr. Werschler said. "The aesthetic

marketplace is the most fertile marketplace to monetize regenerative medicine and hence the term 'regenerative aesthetic medicine.'"

Moving past the word salad to get to the meat

One of the problems is consistency. This area of medicine and aesthetics can best be described as a "word salad," according to Dr. Werschler, of terms and (worse) acronyms, that mean different things to different people, even those who are familiar with this area of medicine.

Dr. Werschler starts with two generally recognized and widely used regenerative aesthetic medicine therapies, PRP and stem cells. "But what does stem cell mean? Most people think that PRP has stem cells. There are no stem cells in PRP. PRP has platelets," Dr. Werschler said. "Even within PRP, you have platelet rich plasma, platelet poor plasma, platelet rich plasma derivatives, platelet rich fibrin, platelet rich fibrin matrix. You take all of those and that is just one technique." Using the term stem cells is as broad as saying something is a "car." There are different kinds of stem cells, including pluripotent, mesenchymal, induced, bone marrow, and adipose-derived. Dermatologists are most likely to use adipose-derived stem cells, according to Dr. Werschler.

Market size, predictions

Lacking concrete numbers defining the regenerative medicine market's size, Dr. Werschler researched and presented global aesthetic market breakdown information from various sources.

"Market reports for aesthetic medicine indicate in pie charts that a big chunk is energy devices, a big chunk is neurotoxins and fillers, both of which probably make up about 75% of the global aesthetics market. Physician dispensed topicals and breast implants account for perhaps another 20%. Emerging therapies, including stem cells, PRP and even suspension sutures account for less than 5%, but the growth rate is very robust, with some sources placing the corporate average growth rate, or CAGR, at 23%. Research reports show massive growth rates predicted for regenerative medicine during this decade," he said. "The relative growth of these procedures, no matter who you talk to or what dataset you look at, is faster relative growth than for established energy-based devices and injectable categories which themselves are quite robust."

The market growth might not be so evident to dermatologists because companies driving the regenerative aesthetics market tend not to be traditional dermatology pharmaceutical brands, although Allergan/Abbvie is listed as one of five global companies involved in consolidation of the market. Others, such as Organogenesis, are in orthopedics and in areas focused on wound care, surgical and sports medicine, while still others are developing 3-D bioprinting (Organovo) essentially growing tissues, organs and more, according to Dr. Werschler.

There also are smaller companies looking to get their share of the growing market and maybe the opportunity to sell to bigger players. One that many dermatologists know, Suneva, maker of Bellafill, is marketing itself as "shaping the future of regenerative medicine" with FDA cleared devices for PRP and fat transfer already on market.

FDA's position: Watch your step

The FDA appears to be learning how to navi-

gate its oversight of regenerative medicine. The FDA does not really say what providers can and cannot do until after the fact, according to Dr. Werschler.

"What the FDA will do is give guidance," he said. "These are guardrails for practitioners and industry to work within and act to some degree as 'safe harbors.'"

"What the FDA will do is give guidance," he said. "These are guardrails for practitioners and industry to work within and act to some degree as 'safe harbors'"

Regenerative medicine falls under the 21st Century Cures Act, signed into law December 13, 2016. The law is designed to accelerate medical product development and innovation. One part of this act is Regenerative Medicine Advanced Therapy, or RMAT.

The FDA considers adipose tissue to be a structural tissue and states that minimal manipulation can be used in patients without FDA premarket approval, but more than "minimal manipulation" requires an approved investigational New Drug Application.

The FDA does not define exactly what minimal manipulation is, according to Dr. Werschler. For example, a provider who takes blood and spins it down to concentrate platelets for PRP ends up with four or five times the normal physiologic concentration. Then, the provider injects platelets into tissue. Even though that provider is altering the physiologic concentration and to some degree the normal function of the platelets, the FDA considers this minimal manipulation.

Doing more than that is where the regulatory trouble starts. Stromal vascular fraction, for example, is a concentrated source of adipose-derived stem cells, pericytes, vascular smooth muscle cells, etc., and is regulated by the FDA as a drug/biological product. This is considered more than "minimal manipulation" by the FDA.

Procedures that fall under the FDA's minimal manipulation guidelines need to be registered with the agency, not approved. These procedures are regulated by FDA section 361: Minimal Manipulation and Homologous Use.

"FDA regulates it from an infectious disease standpoint. In other words, they oversee it to make sure there is no transmission in the handling, in the storage, in the reinjection or the use that puts the patient at risk for transmission of an infectious disease," Dr. Werschler said. "If you manipulate it a little bit more than that, you have to apply for a biologics license…. This more than minimal manipulation is covered under FDA section 351."

Dermatologists need to be aware of the FDA's guidance and realize that when industry representatives tell them that regenerative products and techniques are FDA approved, they are not, according to Dr. Werschler. The problem is that there are decades of precedence when one looks at regular drugs, regular biologics and devices. Regenerative medicine is new. And while the FDA gives guidance in this area of medicine, it has not yet finalized all the rules that impact its use.

So, for now the FDA focuses on safety.

"We (practitioners) decide where the road and guardrails end (guidance), and where the grass starts," Dr. Werschler said. "That's the regulatory side of things. I would say it is somewhere between very muddy and murky water. It is not clear. If I take an antibiotic that is not FDA approved and give it to patients to treat infections, that is black and white. It's not off-label use; it's illegal. I could get fined, lose my license, go to jail. There is very little black and white in the world of regenerative medicine." ◈

STAY TUNED FOR PART 2 of *The Dermatology Digest's* regenerative aesthetic medicine coverage from Maui Derm 2021. Dr. Werschler talks about gateway regenerative aesthetic procedures for dermatology practices, what's new in devices designed for dermatologists, up-and-coming regenerative treatments, and how all this could affect dermatologists for years to come.

Hair-loss supplements: buyer beware

By *John Jesitus*

In the billion-dollar business of oral hair-loss supplements, the evidence for the effectiveness of specific ingredients ranges from promising to nonexistent, according to a recent review.

MADELINE J. ADELMAN, BS
Wayne State University School of Medicine, Detroit

Because OTC hair-growth supplements are easily available, said lead author Madeline J. Adelman, BS, patients with hair loss often turn to these products before consulting physicians. Ms. Adelman is a medical student at Wayne State University School of Medicine, Detroit. The review appeared online December 9, 2020, in the *International Journal of Dermatology*.

Because supplements are marketed as foods, not drugs, Ms. Adelman said, manufacturers need not prove their efficacy and safety before launching them in the marketplace. "There is so much false advertising, misinformation, and capitalization off patient vulnerability," she said. Given this climate, she added, dermatologists must be aware of the safety and utility of these supplements to provide appropriate counseling to their patients. "It's important to know what over-the-counters are out there, what works, and what is a waste of money," she advised.

On a positive note, said Ms. Adelman, evidence for marine-derived formulations as complementary treatments is very promising. "While we don't know exactly why marine-derived collagen affects hair, the clinical-trial data showing that these products have positive impacts on hair health is there," she said. "AminoMar marine complex (Viviscal Limited) has the most data, with clinical trials showing statistically significant beneficial effects on multiple hair-loss conditions."

A proprietary blend of shark and mollusk powder, AminoMar achieved significant improvements in studies of premenopausal women with subclinical hair thinning (n = 96), men with thinning hair (n = 60), and young men with hereditary androgenetic alopecia (n = 40). In the study of premenopausal women, actively treated patients experienced significantly less hair shedding and a statistically significant increase in mean vellus-like hair diameter at 3 months and 6 months. In hereditary androgenetic alopecia, actively treated patients experienced a mean 6-month increase in new non-vellus hair of 38.1%, vs 2.1% in the control group ($P < 0.0001$).

continued on page 60

New biologics on the horizon for psoriasis

By *Bob Kronmeyer* | Reviewed by *Bruce Strober, MD, PhD*

BRUCE STROBER, MD, PhD
Clinical Professor of Dermatology
Yale University

Two biologics in late-stage clinical development are a welcome addition to the armamentarium for treating moderate-to-severe plaque psoriasis: bimekizumab (UCB) and mirikizumab (Eli Lilly and Company).

Bimekizumab

"Bimekizumab has a novel mechanism of action," Bruce Strober, MD, PhD, a Clinical Professor of Dermatology at Yale University, told *The Dermatology Digest*. "The drug inhibits not only interleukin 17A (IL-17A), but also interleukin 17-F (IL-17F), thus becoming the first drug that employs this approach to control psoriasis and psoriatic arthritis. It appears that both isoforms of IL-17 are relevant to psoriasis pathophysiology."

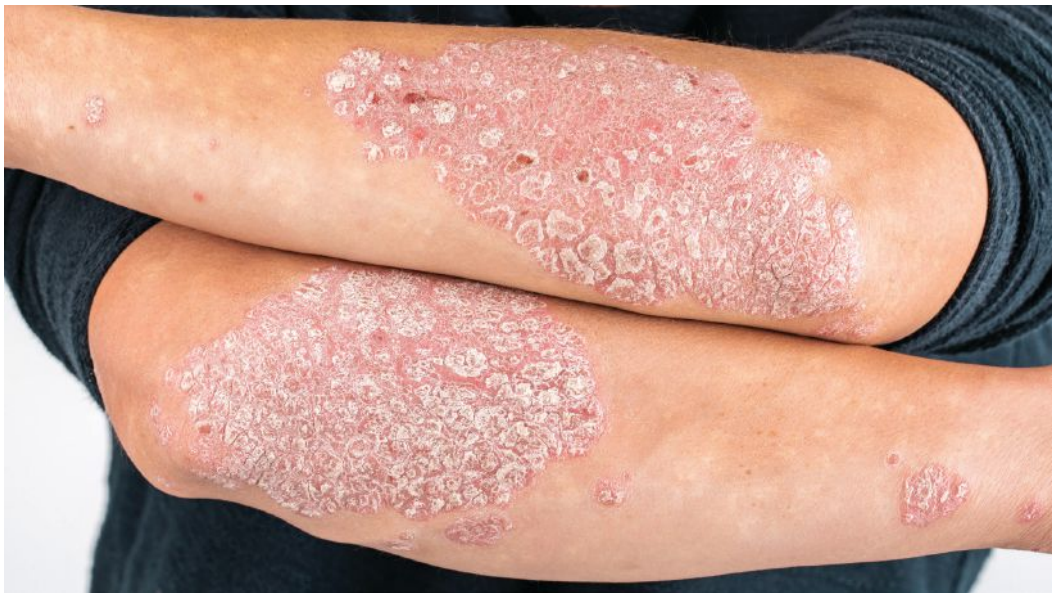
As a result, bimekizumab appears to have greater efficacy than all previous medications used for psoriasis, according to Dr. Strober, who suspects the drug will be FDA-approved by the end of 2021.

Bimekizumab is an investigational humanized monoclonal immunoglobulin G (Ig) antibody (subclass IgG1) that selectively inhibits both IL-17A and IL-17F, which are 2 critical cytokines driving inflammatory processes.

The selective inhibition of both IL-17F and IL-17A suppresses inflammation to a greater degree than IL-17A inhibition alone.

The ideal patient for bimekizumab is with-

> "It appears from phase 2 studies that bimekizumab is very good for the joints and ligaments."



out pre-existing inflammatory bowel disease (IBD), which is a contraindication for all drugs that block the IL-17 pathway. It is also suitable for patients who also have psoriatic arthritis. "It appears from phase 2 studies that bimekizumab is very good for the joints and ligaments," Dr. Strober said.

Separate phase 3 studies of bimekizumab have compared the pending drug to 2 well-established drugs: ustekinumab (Stelara) and adalimumab (Humira Pen). "Not only does bimekizumab achieve profound efficacy in its own right, but it also has significantly better efficacy than these 2 well-known biologics," Dr. Strober said.

Study results

Last June, UCB presented data from the Phase 3 clinical development program of bimekizumab during a virtual session of the American Academy of Dermatology (AAD) 2020 Annual Meeting. The data showed that the drug resulted in skin clearance superior to placebo and ustekinumab at week 16 in adults with moderate-to-severe plaque psoriasis.

The 2 studies also demonstrated rapid response after 1 dose and durability of response up to 1 year.

In BE VIVID, the pivotal Phase 3 study with active comparator ustekinumab, patients treated with bimekizumab 320 mg every 4 weeks achieved significantly superior skin clearance than those receiving placebo or ustekinumab at week 16.

At 16 weeks, 58.6% of bimekizumab patients achieved Psoriasis Area and Severity Index (PASI) 100 versus 20.9% of ustekinumab patients. PASI 90 rates were 85.% for bimekizumab, 49.7% for ustekinumab, and 4.8% for placebo.

In addition, Investigator Global Assessment (IGA) rates of 0 or 1 were 84.1% for bimekizumab, 53.4% for ustekinumab, and 4.8% for placebo.

At week 52, PASI 100 was achieved by

64.2%

OF PATIENTS WHO RECEIVED BIMEKIZUMAB

versus

38%

WITH USTEKINUMAB

> "Bimekizumab should eventually climb toward the top of provider treatment choices ... drugs that block the IL-17 pathway treat not only the skin but also the arthritis component."

For patients who received 1 dose of bimekizumab, 76.9% attained PASI 75 by week 4, compared to only 15.3% of ustekinumab patients and 2.4% of placebo patients.

At week 52, PASI 100 was achieved by 64.2% of patients who received bimekizumab, versus 38% with ustekinumab.

A significantly greater proportion of bimekizumab patients also achieved IGA 0/1 and PASI 90 at week 52 compared to ustekinumab: 77.9% vs. 60.7% and 81.6% vs. 55.8%, respectively ($P < 0.001$).

The most frequently reported adverse events with bimekizumab through week 52 in the study were nasopharyngitis (21.8%), oral candidiasis (15.2%) and upper respiratory tract infections (9.1%).

However, the majority of adverse events were mild to moderate in intensity, and 94.7% of patients continued treatment.

In BE READY, the pivotal Phase 3 randomized withdrawal study, participants were randomized to bimekizumab 320 mg every 4 weeks or placebo for the first 16 weeks.

Bimekizumab was superior to placebo in achieving PASI 90 and IGA 0/1 at week 16. Specifically, 90.8% of the drug group attained PASI 90 compared to 1.2% of the placebo group. Likewise, 92.6% of bimekizumab patients attained IGA 0/1 vs 1.2% of placebo patients, and 68.2% of bimekizumab patients achieved PASI 100 compared to 1.2.% of placebo patients.

Dosing regimens and side effects

In the second phase of the BE READY study, patients who had achieved at least a PASI 90 response at week 16 were re-randomized to receive continuous bimekizumab at 2 different dosing regimens (320 mg every 4 weeks or 320 mg every 8 weeks) or withdrawn from treatment (placebo every 4 weeks).

Maintenance of response was comparable in the 2 bimekizumab treatment arms. Overall, 86.8% of patients who received continuous bimekizumab 320 mg every 4 weeks maintained PASI 90 at week 56, compared to 91% who were switched to bimekizumab 320 mg every 8 weeks and to only 16.2% of patients who were withdrawn.

In its initial induction period, bimekizumab will likely be given once every 4 weeks, until week 16, according to Dr. Strober, followed by probably once every 8 weeks. "However, there is a possibility that it will be an every-4-week drug indefinitely," Dr. Strober said. "But this has yet to be decided by the FDA."

Additionally, bimekizumab demonstrates a quick early response. "The drug has a rapid onset of action, so patients will clear perhaps more quickly on bimekizumab than any other previous drug we have used," Dr. Strober said.

> "In contrast to bimekizumab, mirikizumab is not a novel mechanism of action, but rather an interleukin 23 (IL-23) inhibitor."

The best approved drugs for psoriasis have achieved a PASI 90 70% to 75% of the time, according to Dr. Strober, whereas bimekizumab seems to achieve PASI 90 80% to 90% of the time. "At the PASI 90 level, this is roughly a 10% to 15% absolute increase in efficacy over our previous drugs, such as ixekizumab (Taltz) risankizumab (Skyrizi) and guselkumab (Tremfya)," said Dr. Strober.

The 1 known downside of bimekizumab is that approximately 15% to 20% of patients develop candidiasis, mostly of the oral mucosa. "But this adverse event appears to be mild in most patients who experience it," Dr. Strober said. "Most of these patients also stayed in the study and continued to receive medication."

Nonetheless, the candidiasis will sometimes need to be managed by clinicians. "The management of this adverse event is still being defined and characterized," Dr. Strober said. "Ultimately, we are going to learn as a specialty how to successfully manage patients who have this adverse event and keep them on drug the majority of the time. But overall, bimekizumab is a very safe drug," he said.

Still, Dr. Strober anticipates that bimekizumab might not be avidly adopted because of the new mechanism of action and the adverse event of candidiasis. "These concerns could inhibit some prescribers," he said. "Payer restrictions may also play a large role in disallowing this drug to be quickly adopted as a first-line therapy."

Over time, though, Dr. Strober believes bimekizumab will become a popular drug because of its efficacy for both psoriasis and psoriatic arthritis. "The drug should eventually climb toward the top of provider treatment choices," he said. "With bimekizumab, we always need to remember that drugs that block the IL-17 pathway treat not only the skin but also the arthritis component. This might be a major differentiation point when choosing a biologic agent. About one-third of psoriasis patients have both the skin disease and the accompanying joint disease."

Mirikizumab

In contrast to bimekizumab, mirikizumab is not a novel mechanism of action, but rather an interleukin 23 (IL-23) inhibitor. The drug is a humanized IgG4 monoclonal antibody that binds to the p19 subunit of IL-23.

"To my eye, the drug has data that does not make it superior to our current IL-23 inhibitors," Dr. Strober said. "So I am less excited by it."

In addition, mirikizumab dosing likely involves an induction period of every 4 weeks through 16 weeks, followed by dosing every 8 weeks during its maintenance phase, "which is neither novel nor long for an IL-23 inhibitor," he said. "In fact, the IL-23 inhibitor risankizumab is given once every 12 weeks in its maintenance period and may even work better than mirikizumab."

Mirikizumab should become available shortly

after bimekizumab, according to Dr. Strober, either late 2021 or during 2022, and encompasses a similar ideal patient population as bimekizumab.

Last July, Eli Lilly shared results of the multicenter OASIS-2 study that evaluated mirikizumab vs secukinumab (Cosentyx) and placebo in patients with moderate-to-severe plaque psoriasis.

The study randomized 1465 patients in a 4:4:4:1 ratio to 1 of 4 induction and maintenance period treatments: 250 mg mirikizumab at weeks 0, 4, 8, and 12, followed by 250 mg every 8 weeks starting at week 16; 250 mg mirikizumab at weeks 0, 4, 8, and 12, followed by 125 mg every 8 weeks starting at week 16; 300 mg secukinumab at weeks 0, 1, 2, 3, and 4, followed by 300 mg every 4 weeks starting at week 4; and placebo at weeks 0, 4, 8, and 12, followed by 250 mg mirikizumab every 4 weeks starting at week 16 through week 32, followed by every 8 weeks thereafter.

Dosing was via subcutaneous injection for all treatments.

Study results and side effects

The study concluded that mirikizumab was superior to placebo and non-inferior to secukinumab at week 16, as well as being superior to secukinumab at week 52.

The 2 most common treatment-emergent adverse events occurring in at least 5% of patients during the induction period of up to 16 weeks were nasopharyngitis and upper respiratory infections, whereas during the combined induction and maintenance treatment periods of up to 52 weeks, the notable adverse events were nasopharyngitis, upper respiratory tract infections, headache, back pain, and arthralgia.

The frequency of serious adverse events was comparable across treatment arms: less than 2.5% during the induction period and less than 6% during combined induction and maintenance periods up to 52 weeks.

> **"I believe mirikizumab will be a very safe biologic that will work," Dr. Strober said. "However, I do not see the drug altering the treatment landscape, other than adding an additional choice, which is always welcome."**

Despite favorable study results, Dr. Strober currently does not envision many scenarios in which a dermatologist would choose mirikizumab over other drugs in its class, such as risankizumab and guselkumab. One additional influencing factor is payer access.

"I believe mirikizumab will be a very safe biologic that will work," Dr. Strober said. "However, I do not see the drug altering the treatment landscape, other than adding an additional choice, which is always welcome."

Mirikizumab might also treat psoriatic arthritis, "but this effect has yet to be defined," he said.

Dr. Strober noted that the options to treat psoriasis are expanding. "The broad palette of choices, while increasingly complex and confusing for prescribers, is a great benefit to patients who need more options," he said. ◈

DISCLOSURES

Dr. Strober reports the following financial disclosures:

Consultant (honoraria): *AbbVie, Almirall, Amgen, Arcutis, Arena, Aristea, Boehringer Ingelheim, Immunic Therapeutics, Bristol-Myers-Squibb, Connect Biopharma, Dermavant, Dermira, Equillium, Janssen, Leo, Eli Lilly, Meiji Seika Pharma, Mindera, Novartis, Pfizer, GlaxoSmithKline, UCB Pharma, Sun Pharma, Ortho Dermatologics, Regeneron, Sanofi-Genzyme*

Speaker: *AbbVie, Amgen, Eli Lilly, Janssen, Sanofi-Genzyme*

Co-Scientific Director (consulting fee): *Corrona Psoriasis Registry*

Investigator: *Dermavant, AbbVie, Corrona Psoriasis Registry, Dermira, Cara, Novartis*

Editor-in-Chief (honorarium): *Journal of Psoriasis and Psoriatic Arthritis*

Refractory chronic urticaria signals rare disorder

From the files of:

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CASE HISTORY

A 46-year-old Caucasian man presented with a 3-year history of a widespread pruritic evanescent eruption (Figures 1 A-C). He had previously seen dermatologists and allergists who had diagnosed idiopathic chronic spontaneous urticaria. The patient denied any episodes of angioedema and any medication use including OTC supplements. He denied any correlation with temperature changes, exercise, pressure, exposure to sunlight, or water, though he did report a burning sensation during warm-water showers. The personal and family medical history were both unremarkable. Prior treatments included numerous second-generation antihistamines with good response but in the recent several months the eruption had become refractory to therapy. For the past 6 months, the patient had developed bilateral leg weakness, intermittent night sweats, cyclic low-grade fevers (up to 100.8° F), arthralgias, and myalgias. He had responded to pulsed oral prednisone, but in the past 2 months had lost all response to prednisone.

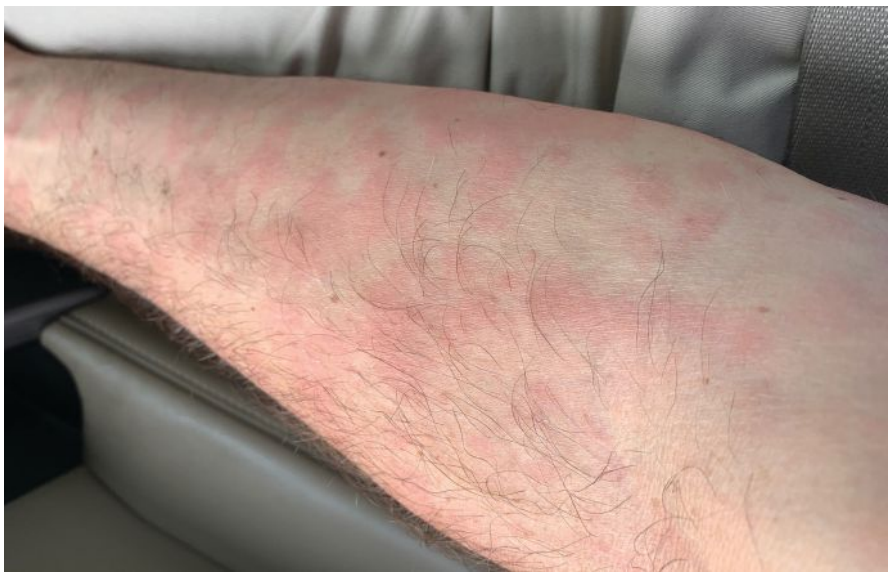

FIGURE 1A.

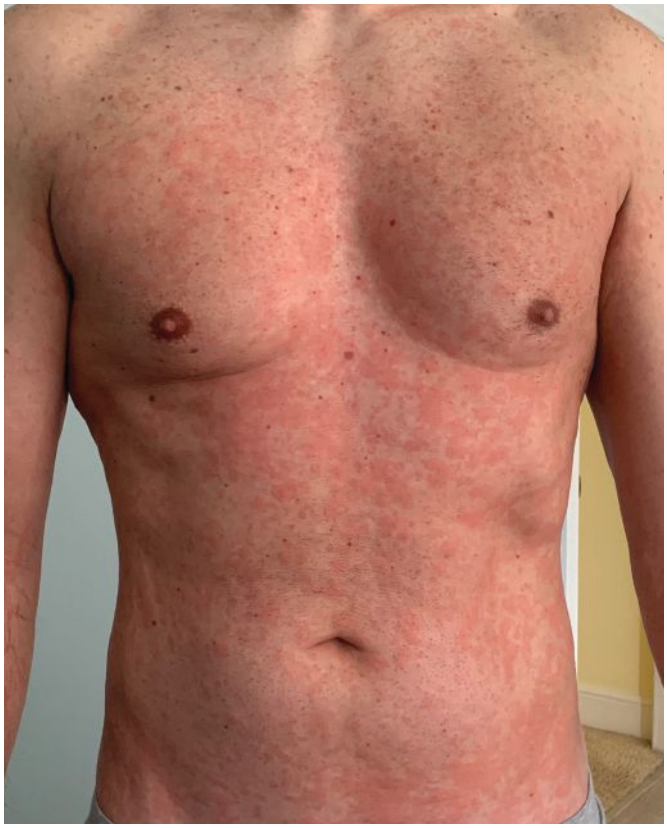

FIGURE 1B.

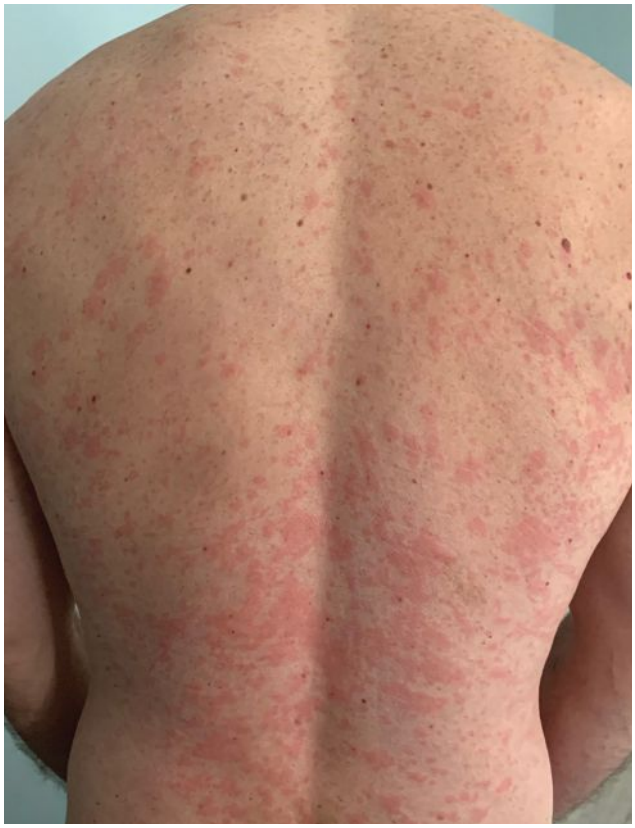

FIGURE 1C.

A skin biopsy performed when the systemic symptoms developed showed perivascular and interstitial neutrophils, perivascular lymphocytes, and scattered eosinophils. Direct immunofluorescence was negative for vasculitis.

Laboratory studies showed lymphopenia and monocytosis, with elevated M-protein, γ globulin, α-1 globulin, α-2 globulin, IgM, C-reactive protein, and erythrocyte sedimentation rate. Liver and renal function tests were normal. Flow cytometry was negative for clonal lymphoid proliferation, and FISH was negative for BCR-ABL translocation.

A bone marrow biopsy showed 1% plasma cells and mildly hypercellular bone marrow with trilineage hematopoiesis and myeloid predominance. Abdominal ultrasound showed only reactive inguinal lymphadenopathy; lymphadenopathy was absent on physical examination. Skeletal CT scan showed mild degenerative changes with no focal bony abnormalities or lytic lesions.

What is your differential diagnosis?

For more on this case, turn to page 58 ▸

continued from page 57

REFRACTORY CHRONIC URTICARIA WITH SYSTEMIC SYMPTOMS

The patient was diagnosed with Schnitzler syndrome using Strasbourg criteria (Table).[1] He was started on off-label treatment with the interleukin-1 (IL-1) receptor antagonist anakinra (Kineret) 100 mg subcutaneous daily. Follow-up is pending.

Table. Strasbourg criteria for definite and probable diagnosis of Schnitzler syndrome*

Definite diagnosis requires both obligate criteria AND at least 2 minor criteria if IgM or 3 minor criteria if IgG
Probable diagnosis requires both obligate criteria AND at least 1 minor criterion if IgM or at least 2 minor criteria if IgG

Obligate criteria	Minor criteria
Chronic urticarial rash*	Recurrent fever (>38 C and unexplained)*
Monoclonal IgM* or IgG spike	Abnormal bone remodeling ± bone pain*
	Biopsy-confirmed neutrophilic dermal infiltrate*
	Leukocytosis and/or elevated CRP*

*Criteria met by this patient

DISCUSSION

The differential diagnosis for chronic spontaneous urticaria is broad. Since most cases are idiopathic, in the absence of history or clinical findings that raise suspicion for another diagnosis a limited initial workup is recommended, and treatment with a second-generation antihistamine is recommended.[2] The refractory nature of the urticaria in this patient combined with the development of systemic symptoms spurred a more intensive diagnostic evaluation.

Entities to consider in the differential diagnosis for treatment-refractory chronic urticaria accompanied by fever, arthralgia, and increased inflammatory parameters include cryopyrin-associated periodic disease (CAPS), adult-onset Still's disease (AOSD), urticarial vasculitis, Sweet syndrome, and Schnitzler syndrome. CAPS develops in childhood, the rash involves the face and is exacerbated by cold, and patients may have hearing loss. AOSD also generally occurs in younger adults and is differentiated by elevated ferritin levels, transaminitis, and pharyngitis. The patient had no morphological or histological evidence of vasculitis.

Schnitzler syndrome

Schnitzler syndrome is a rare, disabling condition that was first described in 1972 by French dermatologist Liliane Schnitzler.[3] Consistent with this patient's history, typical onset is in the fifth decade of life.[4]

Chronic urticaria may be the first clinical sign.[4,5] The eruption typically involves the trunk and limbs and precedes systemic symptoms by several years.[4,5] In addition to unexplained recurrent fevers, arthralgias and myalgia, other common clinical signs include asthenia, unintentional weight loss, axillary or inguinal lymphadenopathy, hepatosplenomegaly, and headache.[5,6]

Schnitzler syndrome generally follows a chronic, non-malignant course. However, 10% to 15% of patients progress to develop a lymphoproliferative disorder, primarily Wäldenstrom macroglobulinemia; median time to development of a malignancy was 8 years in a series of 35 patients.[4]

Etiology and pathophysiology

Schnitzler syndrome is believed to be an autoimmune disorder with an innate immune-mediated mechanism.[5,6] Interleukin-1β (IL-1β) is thought to have a pathogenic role based on the effectiveness of anakinra for inducing remission and considering the finding in some patients of a mosaicism in *NLRP3* in myeloid cell lines, which is a gene associated with increased IL-1 activity in monocytes.[7,8]

Diagnostic work-up

Diagnosis of Schnitzler syndrome is often delayed because chronic urticaria may be the first and only clinical sign for years.[4] Protein electrophoresis to identify a monoclonal gammopathy differentiates Schnitzler syndrome from related inflammatory diseases and should be performed in patients with chronic urticarial rash accompanied by clinical and laboratory signs of systemic inflammation.[5,6] IgM gammopathy is seen more often than IgG gammopathy in patients with Schnitzler syndrome.[6]

Management

As seen in this case, antihistamines are generally ineffective for treating the urticarial rash associated with Schnitzler syndrome, and steroids are only moderately effective.[6] Anti-IL-1 therapy with anakinra is recommended as first-line treatment for Schnitzler syndrome.[1] Because it is highly and rapidly effective for inducing complete remission, some believe that the diagnosis of Schnitzler syndrome should be reconsidered in patients who do not respond to anakinra.[5] Anakinra is not curative, however, and symptoms recur soon after treatment stops.[4]

Efficacy in treating Schnitzler syndrome has also been reported with off-label use of the human IL-1β monoclonal antibody canakinumab (Ilaris).[4] Canakinumab is injected subcutaneously every 4 weeks and is associated with fewer injection-site reactions than is anakinra.[9]

Protein electrophoresis to identify a monoclonal gammopathy differentiates Schnitzler syndrome from related inflammatory diseases and should be performed in patients with chronic urticarial rash ccompanied by clinical and laboratory signs of systemic inflammation.

The effect of anti-IL-1 therapy on the risk for developing a lymphoproliferative disorder is unknown. Bone marrow biopsy in this patient ruled out current hematologic malignancy, but ongoing follow-up with oncology is necessary because a minority of patients may develop a hematologic malignancy. ◈

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continued from page 51

Additional AminoMar studies have demonstrated similar, statistically significant benefits for thinning hair in males and females, alopecia areata (AA) including alopecia totalis, and hereditary androgenetic alopecia.

In small studies, Synergen Complex (Nutrafol, Nutraceutical Wellness Inc.) and Marilex (Nourkrin, Glenmark Pharmaceuticals Ltd.) demonstrated significant improvements for women with self-perceived thinning hair and for men and women with hair loss of varying etiologies, respectively. In the 40-patient Synergen study, treated patients' total, terminal, and vellus hair counts showed significant improvement at 3 months and 6 months. In the 55-patient Nourkrin study, the active group experienced an average hair growth increase of 35.7%, vs 1.5% for placebo. Actively treated patients also reported significantly higher satisfaction with treatment.

> "While we don't know exactly why marine-derived collagen affects hair, the clinical-trial data showing that these products have positive impacts on hair health is there."

All 3 marine-derived supplements contain additional ingredients such as vitamins, minerals, horsetail extract, and ashwagandha. Therefore, authors suggest further investigating individual marine ingredients in larger prospective trials. "Since hair in general takes a long time to grow," said Ms. Adelman, "longer studies with single-ingredient supplements (instead of cocktails) versus placebo would help tell us what actually works, for starters. Plant- and marine-derived bioactive compounds have given us so much already and have great potential. Cytarabine, a chemotherapy drug, was inspired by nucleosides found in marine sponges."

Unlike marine collagen, many ingredients marketed for hair loss have only *in vitro* or animal data—or none at all—behind them. Biotin, for instance, is one of the most heavily advertised hair-loss ingredients. "In just my limited time in dermatology clinics as a medical student," said Ms. Adelman, "I've heard biotin, nutrition, and supplements being asked about so frequently with regard to hair health. Patients are taking and asking about these products. And while taking biotin is harmless, there is no published evidence supporting that oral biotin supplements promote hair growth in the absence of biotin deficiency."

Additionally, no published evidence supports the utility of niacin, vitamin A, or vitamin D in addressing hair loss. Although low vitamin D levels have been associated with AA, telogen effluvium, and female-pattern hair loss, no evidence supports vitamin D monotherapy in treating these conditions.

Oral vitamin C has weak evidence (from animal and *in vitro* human-follicle studies) supporting its use as a hair-growth inducer. Modest evidence suggests that vitamin E can increase hair counts for patients with varying levels of hair loss, and that zinc can increase hair thickness in women with hair loss (although in a separate study, zinc had no impact on AA). Iron supplementation may help patients with possible iron deficiency, but evidence supporting oral use in all hair-loss patients is weak.

While ashwagandha, curcumin, capsaicin, and selenium lack evidence for treating hair loss, some evidence suggests that horsetail and methylsulfonylmethane may be effective complementary or alternative treatments to promote skin and hair health. Similarly, small studies have shown efficacy for saw palmetto (*Serenoa repens*) and pumpkinseed oil, but only in androgenetic alopecia.

Studies of hair growth and supplementation are generally limited by time and compliance. "It is much easier said than done to take a pill every day," Ms. Adelman explained, "and it will take at least 3 to 6 months before there is a noticeable difference in [a patient's] hair." ◈

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DISCLOSURES

Ms. Adelman reports no relevant financial interests.

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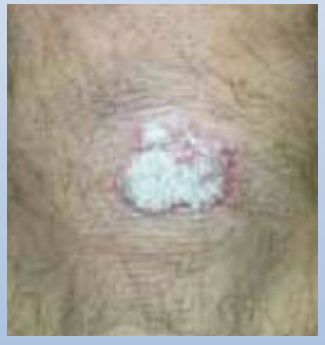
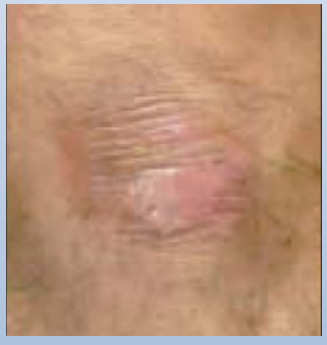
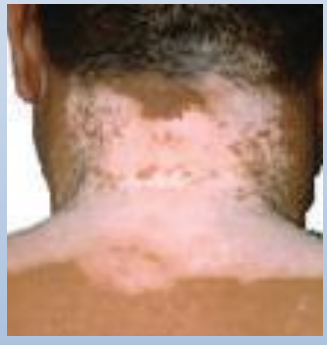


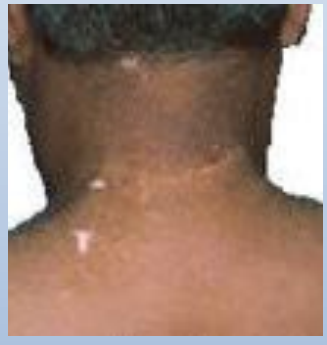
Psoriasis Before UV-B Phototherapy



Psoriasis After UV-B Phototherapy



Vitiligo Before UV-B Phototherapy



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