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DERMATOLOGY FOCUS™

DF Clinical Symposia: Proceedings 2020

ADVANCES IN DERMATOLOGY

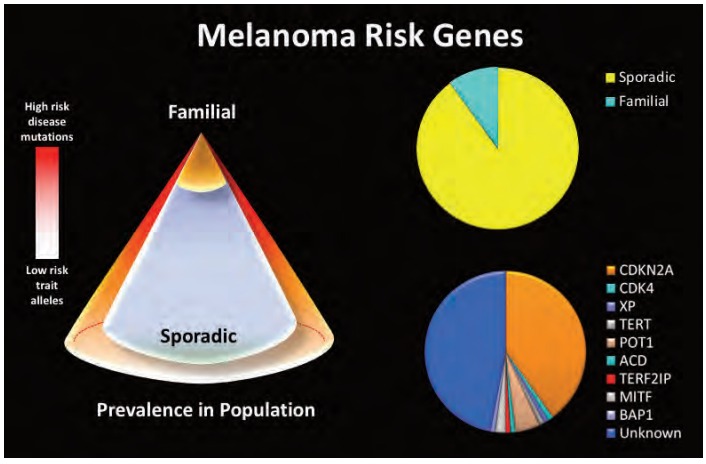
The annual DF Clinical Symposia is a highly regarded 3-day CME event created to share outstanding experts' knowledge in formal plenary talks, Breakfast Roundtables, and interactive evening Therapeutics Forums. The 2020 Clinical Symposia just preceded the rapid rise of Covid-19 in the U.S. We are pleased to present this most recent Clinical Symposia as a double issue of Dermatology Focus *capturing the riches of the plenary talks. The keynote—Melanoma Tumor Syndromes—precedes the 8 symposia: Cancer; Thinking Differently; Therapeutic Updates; Patient Care Pearls; Melanocytic Lesions; Psoriasis; Diagnostics; and Special Populations. Join us for this year's virtual Clinical Symposia—Seaside Chats—coming in April.*

KEYNOTE ADDRESS

New Insights into Melanoma Tumor Syndromes

Hensin Tsao, MD

Introduction. Investigators are using genetic analysis to progress toward several predictive goals in melanoma: identifying patients at high risk for developing dysplastic nevi and/or melanoma, identifying melanoma tumors that risk metastasizing, and identifying a given tumor's drug susceptibility (its "context of vulnerability"). Dr. Tsao focused his talk on the area with the most substantial progress to date: the small number of hereditary gene syndromes so far uncovered that identify high-risk individuals. For each one, he described the function of the healthy gene, the mutation and its effect, and the other cancers also associated with it. He also outlined patient management, and illustrated each tumor syndrome with cases and patient photos.



CDKN2A/CDK4 Tumor Syndrome

- ***CDKN2A/CDK4:*** ***c***yclin ***D***-dependent ***k***inases
- Inactivating mutations in *CDKN2A*
  - Mainly target the p16 transcript
  - Suggests G_1-S restriction is critical in melanoma checkpoint
  - Phenotype replicated by activating *CDK4* mutations
- ***Mutation carriers:*** undergo skin exams 4x/year, pancreatic cancer screening, and stringent sun protection

Known melanoma tumor syndromes. ***FAMM (CDKN2A/CDK4):*** Tsao discussed a patient in his 20s with substantial freckling, large dysplastic nevi and many previous excisions, and more than 15 bona fide melanomas. His brother had had 2 melanomas and their mother had died of pancreatic cancer. The patient turned out to have a p16 mutation (*p16* is a tumor suppressor gene, and *CDKN2A/CDK4* are its cognate partner) that is implicated both in this melanoma tumor syndrome and in pancreatic cancer. Tsao discussed the further increased risk when certain environmental or genomic cofactors are also involved. ***BAP1:*** This mutation, altering a tumor suppressor with a significant role in cell death, is involved in bapomas, cutaneous

(Continued on page 3)

Experience the Best from the Comforts of Home—*Virtually*

Because Covid-19 cancelled our annual live Clinical Symposia this year, the DF is bringing it to you this April—four high-yield educational sessions with live Q&A, each with one of dermatology's renowned experts, on four successive Thursday evenings from 8–9 pm EDT. (Sessions are available to participants online for 90 days.)

After each virtual 30-minute talk on a topic of central interest, gain further from the vital questions that you and your colleagues are eager to have answered.

Apr 8: Jean L. Bolognia, MD
Professor of Dermatology
Yale School of Medicine
Melanoma: The Cutaneous Side Effects of Immune Checkpoint–Blocking Antibodies

Apr 15: Jim R. Treat, MD
Associate Professor of Clinical Pediatrics and Dermatology
Fellowship Director, Pediatric Dermatology
Children's Hospital of Philadelphia
An Update on Atopic Dermatitis

Apr 22: Adewole S. Adamson, MD, MPP
Division of Dermatology
Assistant Professor, Department of Internal Medicine
The University of Texas at Austin
Challenges and Opportunities in Addressing Health Disparities in Skin Cancer in Skin of Color Patients

Apr 29: Jeremy S. Bordeaux, MD, MPH
Director, Dermatologic Surgery and Melanoma Program
University Hospitals of Cleveland
Professor of Dermatology
Case Western Reserve University
When Mohs Surgery Really Matters

Visit dermatologyfoundation.org for registration information.

The Yale School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Yale School of Medicine designates this live activity for a maximum of 4 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

melanomas, and uveal melanomas as well as mesotheliomas and meningiomas and other cancers. ***MITF:*** The culprit SNP in the coding region of this transcription factor initiates the transcription of many more oncogenes. These patients also tend to develop renal cell carcinomas and pheochromocytomas. ***TERT/Shelterin:*** The mutation in the promoter region of the Tert enzyme (TERT is a component of the telomerase enzyme) attracts transcription factors that increase telomerase production and compromise the ability of the Shelterin protein complex to protect the telomere tips from damage. This extends telomere length, creating immortal cancer cells. This tumor syndrome is so rare that there are no clinical guidelines as yet.

BAP1 Tumor Syndrome

- ***BAP1: B***RCA1-***a***ssociated ***p***rotein ***1***
- Key *BAP1*-deficient cancers: cutaneous/ocular melanoma, mesothelioma, and meningioma
  - Lung, breast, kidney, and other cancers do occur
- BAP1-associated lesions are amelanotic, semi-translucent papules, plaques, or nodules
  - Pathologically, they are dermal expansile nodules with large epithelioid cells, and usually BRAF+
- ***Mutation carriers:*** undergo skin exams 2–4x/year; annual eye exam; ? f/u for mesothelioma, kidney cancer, meningioma

MITF Tumor Syndrome

- ***MITF: m***elanocyte-***i***nducing ***t***ranscription ***f***actor
- A functional SNP in the coding region of *MITF* (p. E318K) confers risk for melanoma and renal cell carcinoma (OR=2–5x for melanoma)
  - Low-prevalence variant (~1–3%)
- Suggests that MITF itself—possibly a different isoform—is critical in the biology of renal cell cancer
- ***Mutation carriers:*** undergo skin exam 1–2x/year; referral to kidney specialist for consultation

TERT/Shelterin

- ***TERT: t***elomerase ***r***everse ***t***ranscriptase
- A germline promoter variant increases *TERT* expression by creating an Ets/Tcf binding site
  - TERT promoter mutations are common in melanocytic tumors
  - TERT is amplified in melanomas
- Germline mutations in Shelterin also reported in ~5% of melanoma families (WT *CDKN2A*)
  - Leads to increased telomere length
- ? Delays oncogene-induced senescence
- Rare—no clinical guidelines yet

The unknowns. These melanoma tumor syndromes explain only 50% of melanoma risk due to hereditary gene syndromes (which as a group represents only ~1% of the general population). Tsao is involved in the search for more. He described a study of melanoma families in his clinic that involves exome sequencing, ie, sequencing all of the protein-coding regions in a genome, then counting the mutations gene by gene. They are collaborating with several other groups for a total of 372 melanoma families. The profile involves multiple primary melanomas of early onset, and at least 1 family member with ocular melanoma. Of the 3 genes that stood out, 2 are already known in this context—CDKN2A and BAP1—and one is novel—the tumor suppressor EBF3. "Now we are concentrating on tumors expressing EBF3." Tsao described some of their observations, including a prominent immune signature.

Lessons to date. Tsao described the concept of systemic disease that is emerging regarding melanoma heritability, comparable to the way that psoriasis is now regarded as a systemic disease. "Most of these melanoma syndromes are actually cancer syndromes," he explained. "I want you to think of familial melanoma as a systemic disease in which the other cancers are internal, and thus have to be queried." The melanoma provides a window to the existence of internal risk.

Lessons

- New concepts in melanoma heritability
  - Melanoma/mixed cancer syndromes—melanoma is a window to internal cancer risk
  - New mechanisms of cancer predisposition
    - Gain of expression promoter variants (TERT)
    - Altered ubiquitination (BAP1)
    - Altered epigenetic reprogramming (MITF)
    - Altered telomere metabolism
- *CDKN2A* and *BAP1* are the dominant rare-variant risk loci for cutaneous and uveal melanoma, respectively
- Methodologies for effective rare-variant association studies are still being developed

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John E. Bournas: DF Executive Director *Ushers in a New Era*

Elizabeth I. McBurney, MD, Chair of the Board of Trustees, and DF President Janet A. Fairley, MD, welcomed John E. Bournas, MA, MBA, as the Dermatology Foundation's new Executive Director. He assumed this position at the beginning of September. Mr. Bournas will now be central to a new phase of DF growth and impact—and he is ideally suited to carry out these responsibilities.

Dr. McBurney notes that "John joins the Foundation as it enters into a decade that promises pioneering treatments for patients." He brings a unique and highly relevant range of executive experience in the global healthcare sector, including significant efforts to ameliorate the burden of illness in the patient community. His work throughout has involved identifying core issues and meaningful goals, bringing together people from very different spheres, and facilitating a meeting of the minds and mutual support for resolving problems and reaching goals. Dr. Fairley reflects that "his experience in working with physicians, funding patient-driven programs, and forging strong relationships with industry will cement the DF's standing for all stakeholders."

Mr. Bournas' professional path began with responsibilities in the diplomatic corps, with experience in Chile, Australia, and Japan. His return to the U.S. marked the beginning of his involvement with an interesting variety of medical and healthcare organizations. He began with a small pharmaceutical company focused on hospital-acquired infections that he helped grow to many times its size in just three years. His next focus was the American College of Cardiology (ACC), where he transformed and revitalized their Global Hub, the home for international cardiology professionals within the ACC that includes individual membership, healthcare institutions, and industry support. Their activities are designed to elevate cardiovascular health and patient care worldwide.

Mr. Bournas was recruited to be CEO of the World Federation of Hemophilia (WFH), headquartered in Montreal and dedicated to achieving treatment for all patients with bleeding disorders. Lack of access to diagnosis, medicines, and support were areas of focus for his advocacy work. In addition to strengthening the core of the WFH and helping to establish its research program, Mr. Bournas negotiated one of the largest humanitarian aid donations given by a corporation to a patient-based organization. Close to 1 billion units of treatment factor were committed to be distributed among patients in less-developed countries over a 10-year span. "Bridging that chasm on behalf of the patient community is something I'm exceptionally proud of," he notes. Returning to the U.S., Mr. Bournas was recruited to lead the International Society for Pharmaceutical Engineering, a group working on knowledge sharing and on mitigating drug shortages. Here he built highly effective bridges between academics, regulators such as the FDA and EMA, and industry.

Mr. Bournas' move to the Dermatology Foundation realizes his priorities to engage directly with physicians in working to improve clinical care. "It's a great honor for me to join the Dermatology Foundation. Its history impresses me, and I like the fact that it's focused on funding promising research and science. At the end of the day we're talking about advancing the specialty while alleviating the burden of disease for patients. And that is my passion!"

MINI-SYMPOSIUM: CANCER

Update in the Classification, Pathogenesis, and Treatment of Cutaneous T-Cell Lymphoma

Laura B. Pincus, MD

Classification. The classification statement that has been our guide since 2005 was updated in 2018. One significant change concerns the diagnosis of SMPTCL (primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder), which is no longer considered to meet the clinical criteria for authentic lymphoma, Dr. Pincus explained. This condition typically presents as a solitary lesion (<5 cm) on the head/neck, it does not spread, and patients do not die of it. Assuming the patient meets disease criteria, staging is not required and treatment is now less aggressive. A full body skin exam is required, because if there are multiple lesions or if this lesion is >5 cm, the diagnosis must be reconsidered.

Staging. The basic guide for staging mycosis fungoides (MF) and Sézary syndrome is a 2007 paper. Recently, the staging for folliculotropic MF was modified to reflect recognition that there are indolent (with 96% survival) and aggressive (with 65% survival) forms.

Pathogenesis. "The past 5–10 years have seen an explosion in our understanding of the pathogenesis of cutaneous lymphoma," Pincus noted, enabled by the current ability to sequence the genome to identify genes in play. The mutations Identified alter the normal functions of 5 pathways: apoptosis/DNA repair; T-cell receptor (TCR) signaling; T-cell trafficking; the JAK/STAT pathway; and epigenetic alterations affecting DNA methylation, histone alteration, or

microRNA. Pincus discussed mutations altering TCR signaling (since CTCL is a cancer of T cells) and epigenetics (changes not directly due to DNA modifications of the gene in question).

Treatment. For early-stage MF, skin-directed therapies remain the most effective with the least side-effect concerns. New is that compounding nitrogen mustard is now optional. A prepared gel form is available directly from the company producing it. The many new therapies (mostly IV), some targeted to recently identified mutations, address advanced disease and involve significant side effects. Pincus suggests co-managing these patients with a cutaneous lymphoma center or an appropriate oncologist. She provided an overview of the 2 main categories of new therapies—one targeting mutated genes involved in the pathogenesis (romidepsin), and one targeting cell-surface markers preferentially expressed on cutaneous lymphoma cells (brentuximab vedotin, mogamulizumab).

SMPTCL: Primary Cutaneous CD4+ Small/Medium T-Cell Lymphoproliferative Disorder

- Clinical:
  - Solitary erythematous papule or nodule
  - Rarely multiple lesions
  - Lesions <5 cm in diameter
  - Face, neck, upper trunk

New Staging System for Folliculotropic Mycosis Fungoides

- Indolent and aggressive forms
- Stages predict survival
- More appropriate than BSA used for conventional MF
- **Indolent Stage**
  - Clinical
    - Acneiform lesions
    - Keratosis pilaris–like lesions
  - Histopathology
    - Sparse to moderate perifollicular infiltrates
- **Aggressive Stage**
  - Clinical
    - Indurated/infiltrates plaques, tumors
  - Histopathology
    - Dense infiltrates that extend beyond the follicles

Updates Summary

- **Classification**
  - Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder: from lymphoma to lymphoproliferative disorder
- **Staging**
  - Folliculotropic mycosis fungoides: indolent and aggressive forms have been recognized, with 96% and 65% survival rates, respectively
- **Pathogenesis**
  - Mutations in T-cell receptor signaling genes involved in epigenetics
- **Treatment**
  - Skin-directed therapy best option for early stage disease—gel nitrogen mustard
  - Romidepsin – HDAC inhibitor
  - Brentuximab vedotin – anti-CD30
  - Mogamulizumab – anti-CCR4

Chemotherapy-induced Alopecia: What Every Dermatologist Should Know

Milan Anadkat, MD

Introduction. Dr. Anadkat stressed that fear of hair loss is one of the biggest reasons that patients discontinue chemotherapy, or refuse it altogether. Many women regard losing their hair as worse than the surgery to remove their breasts. He explained why cancer treatments cause hair loss, why hair loss patterns differ depending on the agent, which ones are primarily responsible, and what can help patients to minimize the impact. There is little evidence-based guidance because of the inadequacy of most research in this area.

What happens. Anadkat reviewed the 2 main aspects of the hair unit. The *matrix* contains rapidly dividing cells, and thus is very vulnerable to damage from cytotoxic agents. The *bulge* contains the immortal stem cells, which are typically unaffected and eventually enable the hair to regrow. Maximum hair loss—which can be diffuse or patchy—occurs within 2–3 months after treatment begins. Depending on the treatment, it can produce anagen effluvium (the most likely) or telogen effluvium. Hair should regrow within 1–3 months after stopping treatment, possibly with altered color and/or texture. Permanent—or *persistent*, as Anadkat prefers—hair loss affects roughly 10% of patients, but is not talked about. The biggest offenders are busulfan and the taxanes. The risk, degree, and phenotype of alopecia from targeted biological agents (especially hedgehog inhibitors) vary with the agent and molecular pathway.

Coping. *Wigs* camouflage the loss, and "wig shops are very experienced in helping patients through this." *Scalp cooling*, an important development, is used with solid tumors. The resulting vasoconstrction significantly reduces the dose of chemo reaching the hair. The primitive version uses a cap kept in the freezer and worn during treatment. Scalp cooling machines control dose and fit. Results are most impressive with monotherapy. Side effects are minimal, but protect against cold-induced injury. It is expensive, not yet covered by insurance, and adds time—30 minutes before infusion and 90 minutes afterward.

Final comments. "Hair loss matters to your patients!" It profoundly affects their quality of life. "Our role as dermatologists is to listen to them, and talk with them about the issues. This sounds simplistic, but is actually rare."

Chemotherapy-Induced Alopecia: The Basics

- Maximum hair loss by 2–3 months
- Diffuse or patchy
- Overall incidence estimate = 65%
- Regrowth
  - 1–3 months after chemotherapy discontinuation
  - Often (60%) with altered texture, thickness, and/or color

Not all CIA is the same

- Anagen Effluvium
  - Fully formed hairs
  - Pigmented proximal tip

- Telogen Effluvium
  - Club hairs
  - Proximal tip depigmented
  - Response to stress (cellular coping strategy)

RM Trüeb. *Semin Cutan Med Surg.* 2009;28:11–14; SJ Yun et al. *Dermatol.* 2007;215:36–40.

Anagen Effluvium: Two Patterns

Dystrophic Anagen

- Lower chemotherapy doses
- Less severe follicular damage
- Hair shaft shedding
- "Primary Recovery"
  - Depigmented hair produced in first anagen phase
  - First hair cycle is poor quality
- "Secondary Recovery"
  - Normal pigmented terminal hair produced in subsequent anagen phases
- Takes **longer to fully recover** normal hair growth

Dystrophic Catagen

- Higher doses
- More severe follicular damage
- Hair shaft shedding (more severe chemotherapy insult)
- Skips primary recovery
- Progresses directly to secondary recovery
- Overall **shorter time** to resume normal terminal hair production

R Paus et al. *Am J Pathol.* 1994;144:719–34.

Targeted Agents Most Commonly Causing Alopecia

Different Targets = Different Phenotypes

- EGFR inhibitors (cetuximab)
- Checkpoint inhibitors (ipilimumab)
- Hedgehog inhibitors (vismodegib): highest prevalence (56.9%)
- Proteasome inhibitors (bortezomib): lowest prevalence (2.2%)
- BRAF inhibitors (vemurafenib)

MINI-SYMPOSIUM: THINKING DIFFERENTLY

Thinking Fast and Slow in Dermatology

April W. Armstrong, MD, MPH

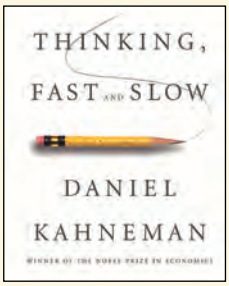
Introduction. Nobelist psychologist-economist Daniel Kahneman's book *Thinking Fast and Slow* characterizes two coexisting, simultaneously operating systems that drive the way we think and make decisions in our daily lives. System 1 is fast and intuitive. System 2 is slower, more deliberate. System 1 is time-efficient, but the lack of deliberation and analysis permits cognitive biases to remain unchallenged and affect decision making. Dr. Armstrong applies this framework to understanding central aspects of decision making as a dermatologist to help minimize mistaken conclusions.

Fast vs slow. First, Armstrong applied this to the process of ***arriving at a diagnosis***, which can occur in as rapidly as .2 seconds. But when this fast thinking is not supplemented with slow thinking, we become vulnerable to two related types of bias that significantly increase the risk of misdiagnoses, which account for 30% of malpractice claims. *Anchoring bias* involves accepting the diagnosis of the referring dermatologist, because it looks correct. The other is that "what we see is what there is." We make the initial diagnosis that seems to fit the facts, and do not consider the other reasonable possibilities—*premature closure*. "This is the single most common cause of misdiagnosis in medicine." To guard against this, deliberately bring some slow thinking into play, where we consider all reasonable differential diagnoses. Then, rank order them and consider relevant diagnostic tests. Armstrong also illustrated the important value of slow thinking when it comes to ***drawing conclusions from*** data—assessing clinical trial outcomes and interpreting results. Then she noted lessons she has learned about "thinking fast and slow in ***the real world***." We all have some patients who will not fit the clinical trial outcomes. Clinical trial data show us specific samples, but the real world includes outliers. "Our patients are much more heterogeneous," and we have to slow down and recognize this in determining treatment.

In summary. Thinking slow may not be as efficient in terms of time, but it can improve your diagnoses and help you evaluate evidence more effectively.

Two Systems That Drive the Way We Think

- **System 1:**
  - fast, intuitive—visual diagnosis
- **System 2:**
  - slower, deliberate—evaluating evidence



"Premature Closure"

- The single most common cause of misdiagnosis
- Occurs when one arrives at an initial diagnosis that *seems* to fit the facts, and then does not consider other reasonable possibilities
- To prevent: rank order all reasonable differential diagnoses (relevance and prevalence)
  - Consider diagnostic tests to discern them

A Clinician's Perspective: Commentaries from the *JAAD*

Warren R. Heymann, MD

Introduction. Dr. Heymann's monthly column in the *JAAD* presents his thoughts precipitated by a paper he finds valuable for improving clinical practice. "I look for what is relevant, and what I want to remember because it might alter the way I practice." He presented a sampling of 7 papers along with his commentaries.

From papers on: *Keratoconus:* The surprising lack of association between this corneal disease and atopic dermatitis (AD) stimulated Heymann to think about the common spectrum of ocular effects found in AD and to emphasize the importance of looking at the whole patient. Consider sending AD patients for a pretreatment baseline eye exam and give urgent attention to existing symptoms. ***Psoriasis due to the CARD14 gene:*** In these familial and sporadic cases, when psoriasis overlaps with pityriasis rubra pilaris (resulting in CAPE: CARD14-associated papulosquamous eruption), ustekinumab is an effective biologic. Unfortunately, biologic choice in the U.S. is not determined by biology but by the patient's insurance company. This must change. ***Granuloma annulare (GA):*** Noting paraneoplastic GA focused Heymann's thoughts on the multifaceted GA-based relationship between dermatologist and oncologist. It goes beyond paraneoplastic disease. Biologic treatments, especially checkpoint

(Continued on page 9)

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- Treatment success* rates were 26% for ARAZLO Lotion vs 13% for vehicle in study 1 and 30% vs 17%, respectively, in study 2 ($P<0.001$ in both studies)[1,4†]
- Most common adverse events (≥1% of patients and greater than vehicle) at application site were pain (5%), dryness (4%), exfoliation (2%), erythema (2%), and pruritus (1%)[1†]

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*Treatment success on the Evaluator's Global Severity Score (EGSS) was defined as at least a 2-grade improvement from baseline and an EGSS score of clear (0) or almost clear (1).[1]

†**Phase 3 study design:** The safety and efficacy of ARAZLO Lotion were assessed in 2 multicenter, randomized, double-blind clinical trials of 1,614 subjects aged 9 years and older with facial acne vulgaris. Subjects had a score of moderate (3) or severe (4) on the EGSS, 20 to 50 inflammatory lesions, 25 to 100 noninflammatory lesions, and 2 or fewer facial nodules.[1]

Indication

ARAZLO™ (tazarotene) Lotion, 0.045% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

Important Safety Information

ARAZLO Lotion is for topical use only. Not for oral, ophthalmic, or intravaginal use.

Contraindication

ARAZLO Lotion is contraindicated in pregnancy due to the potential harm to the fetus.

Warnings and Precautions

Embryofetal Risk Females of childbearing potential should be warned of the potential risk and should use adequate birth-control measures when ARAZLO Lotion is used. A negative result for pregnancy should be obtained within 2 weeks prior to ARAZLO Lotion therapy, and therapy begun during a menstrual period. If the patient becomes pregnant while using ARAZLO Lotion, treatment should be discontinued.

Skin Irritation Patients using ARAZLO Lotion may experience application site pain, dryness, exfoliation, erythema, and pruritus. Depending upon severity, adjust or interrupt dosing as needed, increasing or resuming treatment as tolerated. Avoid application of ARAZLO Lotion to eczematous or sunburned skin.

Photosensitivity and Risk for Sunburn Minimize unprotected exposure to ultraviolet light, including sunlight, sunlamps and tanning beds, during the use of ARAZLO Lotion. Warn patients with high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Instruct patients to use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided.

ARAZLO Lotion should be administered with caution if the patient is taking drugs known to be photosensitizers (eg, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO Lotion.

Adverse Reactions The most common adverse reactions (in ≥1% of patients and greater than vehicle) were: application site pain, dryness, exfoliation, erythema, and pruritus.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

References: 1. ARAZLO Lotion [prescribing information]. Bridgewater, NJ. Bausch Health US, LLC. **2.** Tanghetti EA, Kircik LH, Green LJ, et al. A phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical study to compare the safety and efficacy of a novel tazarotene 0.045% lotion and tazarotene 0.1% cream in the treatment of moderate-to-severe acne vulgaris. *J Drugs Dermatol*. 2019;18(6):542-548. **3.** Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed October 20, 2020. **4.** Data on file.

Ortho Dermatologics

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ARAZLO safely and effectively.
See full Prescribing Information for ARAZLO.

ARAZLO™ (tazarotene) Lotion, 0.045%

For topical use
Initial U.S. Approval: 1997

INDICATIONS AND USAGE

ARAZLO™ (tazarotene) Lotion, 0.045% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

CONTRAINDICATIONS

ARAZLO is contraindicated in pregnancy. ARAZLO may cause fetal harm when administered to a pregnant patient *[see Warnings and Precautions, Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Embryofetal Toxicity Based on data from animal reproduction studies, retinoid pharmacology and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. Safety in pregnant patients has not been established. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, discontinue ARAZLO as soon as pregnancy is recognized.

Tazarotene elicits malformations and developmental effects associated with retinoids after topical and oral administration to pregnant rats and rabbits during organogenesis. However, limited case reports of pregnancy in females enrolled in clinical trials for ARAZLO have not reported a clear association with tazarotene and major birth defects or miscarriage risk *[see Contraindications, Use in Specific Populations]*.

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. In patients treated topically over sufficient body surface area, exposure could be in the same order of magnitude as in orally treated animals. Tazarotene is a teratogenic substance in animals, and it is not known what level of exposure is required for teratogenicity in humans.

Advise pregnant patients of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to ARAZLO therapy. Initiate ARAZLO therapy during a menstrual period. Advise patients of childbearing potential to use effective contraception during treatment with ARAZLO *[see Dosage and Administration in full Prescribing Information, Use in Specific Populations]*.

Skin Irritation Patients using ARAZLO may experience application site pain, dryness, exfoliation, erythema, and pruritus. Depending upon severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of ARAZLO, or discontinue use. Therapy can be resumed, or the frequency of application can be increased, as the patient becomes able to tolerate treatment.

Avoid use of concomitant medications and cosmetics that have a strong drying effect. It is recommended to postpone treatment with ARAZLO until the drying effects of these products subside.

Avoid application of ARAZLO to eczematous or sunburned skin.

Photosensitivity and Risk for Sunburn Because of heightened burning susceptibility, minimize unprotected exposure to ultraviolet light including sunlight and sunlamps during the use of ARAZLO. Warn patients who normally experience high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided. Patients with sunburn should be advised not to use ARAZLO until fully recovered.

ARAZLO should be administered with caution if the patient is taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections:

- Embryofetal toxicity *[see Warnings and Precautions]*
- Photosensitivity and Risk of Sunburn *[see Warnings and Precautions]*

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

In 2 multicenter, randomized, double-blind, vehicle-controlled clinical trials, subjects age 9 years and older applied ARAZLO or vehicle once daily for 12 weeks. The majority of subjects were White (74%) and female (66%). Approximately 22% were Hispanic/Latino and 42% were younger than 18 years of age, fourteen of 779 subjects (1.8%) treated with ARAZLO were between 9 years to less than 12 years of age. Adverse reactions reported by ≥1% of subjects treated with ARAZLO and more frequently than subjects treated with vehicle are summarized in Table 1. Most adverse reactions were mild to moderate in severity. Severe adverse reactions represented 1.3% of the subjects treated. Overall, 2.4% (19/779) of subjects discontinued ARAZLO because of local skin reactions.

Table 1: Adverse Reactions Reported by ≥1% of the ARAZLO Group and More Frequently than the Vehicle Group

Adverse Reactions N (%)		
	ARAZLO Lotion N=779	**Vehicle N=791**
Application site pain[1]	41 (5)	2 (<1)
Application site dryness	30 (4)	1 (<1)
Application site exfoliation	16 (2)	0 (0)
Application site erythema	15 (2)	0 (0)
Application site pruritus	10 (1)	0 (0)

[1]Application site pain defined as application site stinging, burning, or pain

Skin irritation was evaluated by active assessment of erythema, scaling, itching, burning and stinging, with grades for none, mild, moderate, or severe. The maximum severity generally peaked at Week 2 of therapy and decreased thereafter. The percentage of subjects with these signs and symptoms at any post-baseline visit are summarized in Table 2.

Table 2: Incidence of Local Cutaneous Irritation at any Post-Baseline Visit

	ARAZLO Lotion N=774 Mild/Moderate/Severe	**Vehicle Lotion N=789** Mild/Moderate/Severe
Erythema	49%	38%
Scaling	51%	23%
Itching	29%	14%
Burning	30%	6%
Stinging	22%	5%

DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with ARAZLO.

Concomitant use with oxidizing agents, as benzoyl peroxide, may cause degradation of tazarotene and may reduce the clinical efficacy of tazarotene.

In a trial of 27 healthy female subjects, between the ages of 20–55 years, receiving a combination oral contraceptive tablet containing 1 mg norethindrone and 35 mcg ethinyl estradiol, the concomitant use of tazarotene administered as 1.1 mg orally (mean ± SD C_{max} and $AUC_{0\text{-}24}$ of tazarotenic acid were 28.9 ± 9.4 ng/mL and 120.6 ± 28.5 ng•hr/mL, respectively) did not affect the pharmacokinetics of norethindrone and ethinyl estradiol over a complete cycle.

The impact of tazarotene on the pharmacokinetics of progestin only oral contraceptives (i.e., minipills) has not been evaluated.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary ARAZLO is contraindicated in pregnancy.

There are no available data on ARAZLO use in pregnant patients to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, ARAZLO should be discontinued as soon as pregnancy is recognized.

In animal reproduction studies with pregnant rats, reduced fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at a dose equivalent to the maximum recommended human dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at 15 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavioral delays were observed after oral administration of tazarotene during the period of organogenesis at doses 1 and 30 times, respectively, the MRHD (based on AUC comparison). In pregnant rats, decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 6 times the MRHD (based on AUC comparison) *(see Data)*.

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

Data *Animal Data* In an embryofetal development study in rats, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rats during gestation days 6 through 17. Reduced fetal body weights and reduced skeletal ossification occurred at this dose (equivalent to the MRHD based on AUC comparison). In an embryofetal development study in rabbits, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rabbits during gestation days 6 through 18. Single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were noted at this dose (15 times the MRHD based on AUC comparison).

When tazarotene was given orally to animals, developmental delays were seen in rats; malformations and post-implantation loss were observed in rats and rabbits at doses producing 1 and 30 times, respectively, the MRHD (based on AUC comparison).

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, classic developmental effects of retinoids including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights were observed at this dose (6 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations was observed at this dose.

In a pre- and postnatal development toxicity study, topical administration of a tazarotene gel formulation (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival, but did not affect the reproductive capacity of the offspring. Based on data from another study, the systemic drug exposure in the rat at this dose would be equivalent to the MRHD (based on AUC comparison).

Lactation

Risk Summary There are no data on the presence of tazarotene or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. After single topical doses of a ^{14}C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARAZLO and any potential adverse effects on the breastfed child from ARAZLO.

Clinical Considerations To minimize potential exposure to the breastfed infant via breast milk, use ARAZLO for the shortest duration possible while breastfeeding. Advise breastfeeding patients not to apply ARAZLO directly to the nipple and areola to prevent direct infant exposure.

Females and Males of Reproductive Potential

Pregnancy Testing Pregnancy testing is recommended for patients of childbearing potential within 2 weeks prior to initiating ARAZLO therapy which should begin during a menstrual period.

Contraception Advise patients of childbearing potential to use effective contraception during treatment with ARAZLO.

Pediatric Use Safety and effectiveness of ARAZLO for the topical treatment of acne vulgaris have been established in pediatric patients age 9 years and older based on evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled, 12-week clinical trials and an open-label pharmacokinetic study. A total of 300 pediatric subjects aged 9 to less than 17 years received ARAZLO in the clinical studies *[see Clinical Pharmacology and Clinical Studies in full Prescribing Information]*.

The safety and effectiveness of ARAZLO in pediatric patients below the age of 9 years have not been established.

Geriatric Use Clinical trials of ARAZLO did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

OVERDOSAGE

Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, monitor the patient closely and administer appropriate supportive measures, as necessary.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to the MRHD (based on AUC comparison).

A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposures at the highest dose was 7 times the MRHD (based on AUC comparison).

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in an in vivo mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was equivalent to the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of tazarotene up to 1 mg/kg/day which produced a systemic exposure 4 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose which produced a systemic exposure 6 times the MRHD (based on AUC comparison).

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inhibitors, can cause GA. Additionally, inform the oncologist that subcutaneous GA can resemble metastases on a PET scan. ***Prurigo nodularis:*** This study of subgroups and respective comorbidities highlights the need for the same in-depth workup as for patients with severe chronic pruritus. ***A novel tar product (tapinarof):*** This cream-based, cosmetically elegant version of the ancient treatment enabled 60% of subjects to reach PASI 75. Heymann reflected on our recent molecular understanding of the many ways in which tar works to normalize psoriatic skin. ***HCQ & IGRA:*** 38% of patients with autoimmune skin disease treated with hydroxychloroquine for 1 year had an indeterminate QuantiFERON-TB GOLD response vs only 6% without HCQ. Thus for the HCQ-treated patient who has not improved and is preparing for immunosuppressive therapy, an indeterminate test result for latent TB infection is likely to be false. Get a PPD or infectious disease consult; you will likely proceed with a biologic unless there is high risk for latent disease. Then get a PPD or infectious disease consult. ***Acute inflammatory edema:*** some possibly-cellulitis patients who "flummox" Heymann because they do not sufficiently fit the picture have been recognized as a benign clinical entity with no need for a workup or antibiotics. An important sign is that the observed changes spare the fold completely.

"Tar Smarts" May Have a New Meaning for Atopic Dermatitis and Psoriasis

- "Tar smarts" refers to the immediate burning or stinging sensation when tar-treated sites are exposed to ultraviolet A or sunlight. The benefits of activating AHR (aryl hydrocarbon receptor), an environmental sensor integrating immune responses in health and disease—either by coal tar, tapinarof, or yet-to-be-discovered agents—gives "tar smarts" a new meaning. ***Future studies may demonstrate that the oldest therapeutic approach may be the smartest of all!***

Acute Inflammatory Edema: A Swell Concept

- I have seen such cases and have been flummoxed by trying to render a precise diagnosis. I commend Marchionne et al. for recognizing this entity and providing a precise appellation—***diagnosing AIE should obviate costly evaluations and unfounded antibiotic therapy.***

MINI-SYMPOSIUM: THERAPEUTIC UPDATES

Connective Tissue Disease: Therapeutic Update

Ruth Ann Vleugels, MD, PhD

Introduction. Dr. Vleugels focused on cutaneous lupus. She discussed the visual diagnosis, then her treatment approach. Both comprehensive sun protection and smoking cessation are essential. Potent topical steroids are appropriate for the face when there is risk of scarring from discoid lupus. For systemic treatment, she reviewed her workhorse choices for first-line therapy, most often antimalarials (methotrexate and mycophenolate mofetil), and the additional roster of drugs she relies on for patients who are refractory or respond insufficiently, including the highly effective thalidomide and lenalidomide.

Diagnosis. Vleugels emphasized the unique training and visual skills that enable dermatologists to avoid mistaking the distinctive malar rash of SLE for the facial eruptions seen in rosacea or dermatomyositis. In lupus, the malar rash uniquely spares the nasolabial folds. And because the malar rash indicates active SLE, "you should not let a patient with a true malar rash of lupus leave your office without a workup for systemic involvement. Most important are renal function and urinalysis, as well as a complete blood count investigating for cytopenias."

Antimalarials. Hydroxychloroquine (HCQ) is typically Vleugels' first choice for the treatment of cutaneous lupus. Data show that HCQ is disease modifying in terms of future systemic lupus risk. Dosing should be limited to 5mg/kg actual body weight, and routine ophthalmologic screening is important. The addition of quinacrine can be helpful, although it is challenging to obtain in the U.S.

Beyond antimalarials. "Most experts who see many cutaneous lupus patients rely heavily on methotrexate, mycophenolate mofetil, and thalidomide." Methotrexate (typically dosed at 25 mg/week) and mycophenolate mofetil (2–3 grams daily) are often the first-choice options for antimalarial-refractory patients. Thalidomide and lenalidomide are excellent options in recalcitrant CLE patients and have the advantage of not causing immunosuppression. Patients on thalidomide must be monitored clinically for the development of peripheral neuropathy, whereas those on lenalidomide should have their complete blood and absolute neutrophil counts followed closely. There are some early data to suggest that JAK inhibitors may be beneficial in select patients, although robust studies are lacking.

Therapy: Cutaneous Lupus Erythematosus

- Photoprotection
  - Behavior, sunscreen, protective clothing
  - Consider vitamin D status
- Smoking cessation
- Topicals
  - Corticosteroids, tacrolimus
- Systemic agents
  - Antimalarials—consider in combination
  - Methotrexate, mycophenolate mofetil, thalidomide, lenalidomide, azathioprine, dapsone, acitretin/isotretinoin, IVIG, belimumab, apremilast

Clinical Pearls: JAK Inhibitors

- Rheumatoid arthritis dose: 5 mg PO BID
  - Many skin diseases warrant increase (up to 10 mg PO BID), but consider side effects
  - Kids reach 5 mg PO BID at 40 kg
- Safe to combine with MTX
- Follow: CBC with diff, LFTs, renal function, lipids
- Special considerations:
  - Shingrix in adults; VZV titers in children
  - ? Venous thromboembolism

Vulvar Dermatology Update: What's New Down There?

Rochelle R. Torgerson, MD, PhD

Introduction. Dr. Torgerson focused on lichen sclerosus (LS), as it is one of the most common vulvar diseases seen in the dermatology clinic.

Highlights. Torgerson calls LS a *chronic lymphocytic autoimmune inflammatory disease.* Data support a genetic component. It occurs at any age, not just before puberty and after menopause. Because high

(Continued on page 11)

Key to Autoimmune Disease Prevalence in Women Identified

Sun Pharma Awardee Forges New Research Direction

Autoimmune diseases are extremely challenging to treat, and are among the leading causes of death and disability in the U.S. These high-burden chronic diseases affect more than 50 million Americans—7.5% of the population. "A striking feature is their far greater prevalence in women," Dr. Gudjonsson points out. Women represent 80% of patients with autoimmune diseases, which are the second highest cause of chronic illness in women.

Johann E. Gudjonsson, MD, PhD

Until Dr. Gudjonsson's recent startling discoveries, the underlying cause of this sex bias had remained a mystery. Detection efforts had focused on the logical suspects for sex-biased diseases—hiding somewhere on the X or Y sex chromosome and/or involving the influence of sex hormones. Dr. Gudjonsson recently found the culprit—a previously unknown inflammatory pathway, with no X/Y chromosome or sex hormone connections, that promotes female-biased autoimmunity. Genes in this network are associated with multiple autoimmune diseases, including lupus, scleroderma, and Sjögren's syndrome. "It suggests new avenues for therapeutic development," Dr. Gudjonsson says. And his midcareer Sun Pharma Research Award is enabling him to progress toward this goal.

Dr. Gudjonsson has made significant contributions to the molecular understanding of psoriasis, among other diseases, but he was not focused on psoriasis or on autoimmune disease in women when he made this novel discovery. He was simply doing something he has always loved—following a novel question that has sparked his curiosity to see where it would take him. Dr. Gudjonsson explains that this curiosity has always been an important part of his life. Early on, it fueled his desire to become a physician-investigator when he was a medical student in Iceland. Then it led him to dermatology because of the skin's visual accessibility and ease of sampling. He became fascinated by the immunology and genetics of psoriasis, which became his primary research focus and soon took him to the University of Michigan for their outstanding psoriasis-related training and research capabilities.

Several years ago, Dr. Gudjonsson found himself with data from "a lot of biopsies from healthy skin that we had collected during a psoriasis project," he recalls. "We decided to use this data pool to ask a very simple question—what are the genetic differences between male and female skin?" After identifying these sex-biased genes, "we were surprised to discover that most of them lie outside the X and Y chromosomes, and that women's skin is more immunologically active." These immune-related genes were not random but feed into an immune network that has been implicated in autoimmune diseases.

First, Dr. Gudjonsson and his team determined that expression of these genes is unrelated to the effect of sex hormones. "Then we found the regulator of this gender-biased immune activity, a transcription cofactor called Vestigial-like-3 (VGLL3) that is also more highly expressed in the cells and tissues of women, and may have a role in fine-tuning their immune responses." The profound implications of what Dr. Gudjonsson and his group had discovered were not apparent until they over-expressed this immune regulator in mouse skin. "We were very excited when the mice developed an inflammatory skin phenotype with striking similarities to cutaneous lupus," he notes. "And even more—they developed all of the auto-antibodies associated with systemic lupus (SLE), and with deposition of immune complexes in skin and kidneys. This novel mouse model links together the female factor VGLL3 with autoantibody production," he continues. "And we discovered that TNFSF4 and IL-7—cytokines that are critical to the development and behavior of both T cells and B cells—were both prominently expressed.

(Continued on the back cover)

estrogen levels can mask its severity, during her reproductive years, the patient may be unaware that her vulvar discomfort reflects a condition requiring medical intervention. Visually, LS encompasses a vast spectrum reflecting both individual differences and evolution over time. Torgerson illustrated the tissue alterations and range of architectural changes as structures become obliterated. The patient experiences intense itch unrelieved by scratching, and pain when erosions and fissures develop. There is a risk for squamous cell carcinoma (reduced or eliminated with good control and conscientious maintenance) and autoimmune thyroid disease (screen for function).

Treatment and updates. Testosterone is no longer considered helpful. Torgerson relies heavily on clobetasol ointment (or betamethasone, depending on the patient's insurance coverage). Active treatment to gain control is once or twice daily for 2–8 weeks depending on severity. Maintenance involves application 2–3 nights/week, increasing during flares. If tapering to maintenance is not successful, add tacrolimus (the ointment is better here than pimecrolimus's cream formulation). Mometasone is less than ideal strength, and may require more frequent application. There are rare safety issues with clobetasol use on modified mucous membranes. Patient fear due to inaccurate counseling often leads to underusage, not overusage.

The jury is out. Torgerson advises strong caution for the use of other treatment modalities, as existing data are not reliable. This includes platelet-enriched plasma, fractional microablative CO2 laser, and nonablative Nd:YAG laser.

Lichen Sclerosus Highlights

- All ages
- Itch itch itch…but scratching → minimal relief
- Pain if fissures or erosions
- Architectural alterations
- Increased risk of SCC
  - Reduced with long-term control and ongoing maintenance treatment with topical corticosteroids

Lichen Sclerosus Take-Home

- Testosterone = vehicle only
- Clobetasol ointment = gold standard
  - Active treatment phase (BID 2–8 wks)
  - Maintenance phase (2–3 nights/wk)
  - PRN increase if flare
- Other topical options
  - Tacrolimus (ointment base preferred over pimecrolimus cream)
  - Mometasone furoate ointment
- Maintenance therapy reduces SCC risk
- Slightly higher risk of autoimmune thyroid disease, so check TSH
- Jury is out on PRP and laser

Management of HS: A Practical Toolkit

Ginette A. Okoye, MD

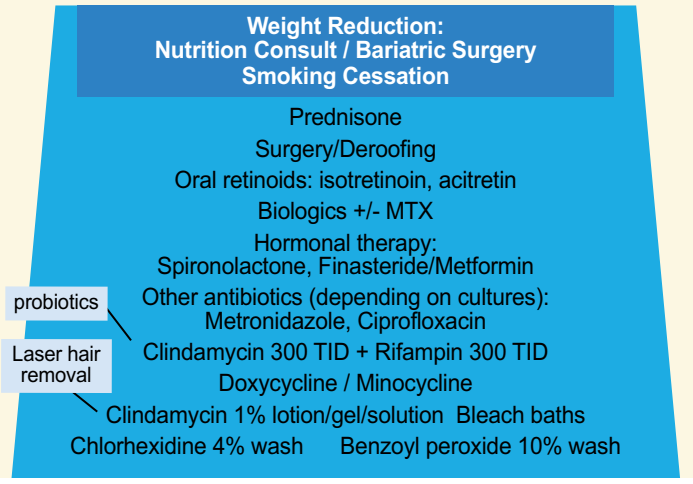
Introduction. Hidradenitis suppurativa (HS) is an intensely impactful inflammatory disorder of the hair follicles belonging to the follicular occlusion tetrad. It affects both patient and family, with high risk for job loss, depression, and divorce. HS is more common in women and in people of African descent, and is associated with obesity, smoking, and low socioeconomic status. Current data indicate 1% prevalence, but those treating it report an increase, especially in adolescents. This systemic inflammatory condition is associated most especially with pyoderma gangrenosum, inflammatory bowel disease, metabolic syndrome, and cardiovascular disease. Management is challenging. Dr. Okoye provided detailed guidance for the therapeutics and procedures she uses.

HS Treatment Continuum

Pathogenesis. Although still under study, all agree that the primary pathogenic event is follicular occlusion caused by a keratin plug at the follicular infundibulum. The follicle eventually ruptures, spilling its intensely inflammatory contents into the dermis. HS patients are unable to resolve this inflammation. It damages large areas of tissue that connect with each other, then with the skin surface, forming tunnels and sinus tracts.

Treating HS. In addition to medical and surgical modalities, also essential are wound care, psychosocial support (for depression, anxiety, possibly suicidality), and lifestyle modifications (eg, smoking cessation, weight loss). Management must be individualized, tied to the patient's—not the physician's—determination of disease severity: one size does not fit all. There are no reliably remittive medications, and thus the choice reflects your patient's perspective on what is most important to minimize/eliminate: drainage, pain, or flares (fewer or briefer). Avoid monotherapy; layer and rotate, "continue to mix it up": biologic + hormonal agent; hormonal agent + burst of antibiotics as needed; surgical intervention + biologic. Okoye discussed 4 treatment options in detail: laser hair removal (Nd:YAG); surgery (deroofing or marsupialization); intralesional steroid injections with triamcinolon (avoid incision and drainage—I&D); biologics. Adalimumab is FDA approved for HS. If not helpful, move to ustekinumab; try infliximab for more-severe patients. Okoye's advice included handling insurance restrictions.

HS Treatment Pyramid



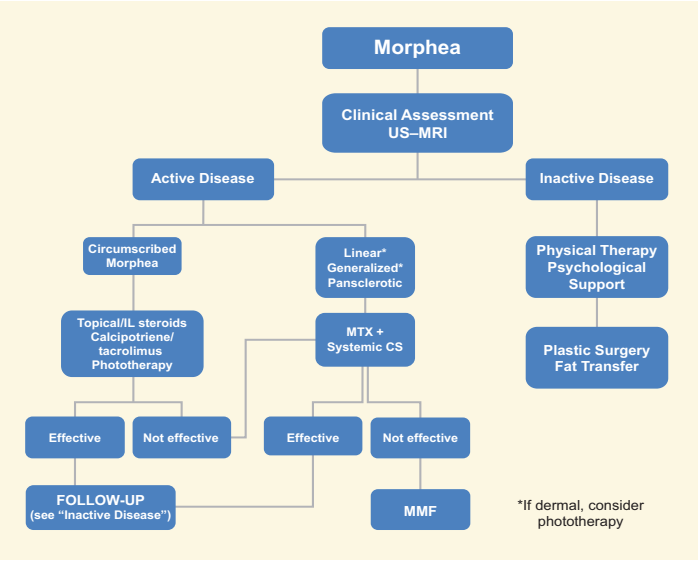
Patient Resources

- Hidradenitis Suppurativa Foundation
  www.hs-foundation.org
- Facebook support groups
- Hope for HS: an in-person support group in SE Michigan
  http://hopeforhs.org

Morphea Update: Lessons From the Morphea in Adults and Children Cohort

Heidi T. Jacobe, MD, MSCS

Introduction. Morphea involves excessive collagen deposition in the dermis and beneath, with admixed inflammation. Dr. Jacobe discussed diagnosis, assessment, and making rational treatment decisions, sharing relevant observations from the Morphea in Adults and Children (MAC) Cohort. She prefaced that examining the sclerosing skin patient is manual, not visual. Palpate the total body skin surface area using 2 fingers to lift up the skin at different body sites, comparing one side with the other. Know what normal skin feels like by palpating your own skin.



Diagnosing and characterizing morphea. A careful history and physical examination, paying close attention to past medical history, demographics, and evolution and cutaneous distribution of lesions, all aid in distinguishing morphea from other conditions in the differential diagnosis. Biopsy can help in this. Common and uncommon morphea mimics to consider include atrophy due to steroid injections, lipodermatosclerosis, breast cancer metastatic to the skin, lupus profundus or panniculitis, and cranial-facial defects. The 3 main morphea subtypes (using her preferred schema) are: *circumscribed* (asymmetrically distributed on the trunk or legs); *generalized* (typically in postmenopausal women, may initially appear as circumscribed but lesion burden eventually expands); *pansclerotic* (most severe form); and *linear* (in children and young adults). Deep disease—involving soft tissue under the skin or dermal involvement alone—can occur with any subtype. After determining subtype, assess the status of *activity* (active inflammation) vs *damage* (post-inflammation alterations). Treating active lesions without delay avoids severe residua from unfettered inflammation (which extends into the dermis, sometimes the subcutis). Jacobe discussed possible neuro-ocular complications in linear disease.

Treatment. Treat activity with agents that suppress inflammation (no reliable treatments for sclerosis exist); damage is treated with supportive care. Circumscribed lesions warrant topicals (steroids, calcipotrienes, tacrolimus) and close follow-up. If progression appears, consider methotrexate (with systemic corticosteroids until it kicks in), and mycophenolate mofetil when methotrexate cannot be used. UVA1 or NBUVB phototherapy may help widely distributed dermal lesions, but avoid for deep lesions or those on the scalp. Supportive care for residual damage includes physical therapy, plastic surgery, and psychological support (the sequelae can be devastating). Cohort data indicate that most patients achieve remission of activity within 1 year, typically by 6 months, with appropriate treatment. Reactivation occurs in ~30–40% of patients, typically within 2 years post-treatment (more likely after UVA1 phototherapy than immunosuppression). Thus all patients require long-term follow up and knowing what to do if they see new activity. Preliminary MAC cohort data indicate that reactivation tends to be less severe.

Summary

- Morphea affects skin and soft tissue
- Characteristic cutaneous distribution of lesions aids risk stratification for extracutaneous disease
- ANA profile and extracutaneous manifestations are different from those of systemic sclerosis
- Key to evaluation—subtype, active vs damage, depth of involvement
- Treatment based on activity and extent

MINI-SYMPOSIUM: PATIENT CARE PEARLS

Clinical Pearls in Medical Dermatology—Observed and Anticipated

Warren R. Heymann, MD

Introduction. Dr. Heymann presented 8 cases that taught him a great deal, 5 in person and 3 from the literature (which he eagerly anticipates encountering in person). For each condition, he described what intrigued him, and what is known about epidemiology, etiology, progression, differential diagnosis, and treatment.

Cases observed. *Prurigo pigmentosa & the keto rash:* A surgical resident came to Heymann with an itchy rash that was slowly improving, wondering if it could be related to the keto diet she had begun 3 weeks earlier. He recognized it as prurigo pigmentosa. Diabetes, dieting, and ketonuria are possible causes. Heymann explained how ketosis could be responsible, noting a case report of a 17-year-old boy with prurigo pigmentosa who had not eaten carbs for a full year. One week of adding carbs generated dramatic improvement. "If you see prurigo pigmentosa, definitely inquire about diet." ***Postherpetic pseudohernia:*** A woman in her early 70s came in shortly after developing a significant bulge in her abdomen. CT scan had been normal. It reflected mononeuropathy—most commonly from herpes zoster (in ~2% of that population)—that weakens the muscle. Manage with mechanical support, PT, pain control. Most gradually improve. ***Carotenemia in the context of macular degeneration:*** A man in his early 80s had been misdiagnosed with pseudoxanthoma elasticum. Carotenemia was obvious from his yellow hands, but his diet was not the culprit. It finally emerged that he had macular degeneration and was taking many supportive supplements with a substantial cumulative carotene content. Because the culprit is age-related—diet with children, and macular degeneration/supplements for older

patients—approach a patient with the age-appropriate question. ***Necrotic carpal tunnel syndrome:*** Heymann described this middle-aged man's hand, with erythema, bullae, distal erosions, and acro-osteolysis distributed in the first 3 digits. This is typically misdiagnosed as scleroderma, but the distribution is key as it reflects ischemia related to the medial nerve. Treatment is surgical decompression. When you see this, insist that carpal tunnel be ruled out—and you will be able to save the patient's hand. ***Annular dermatitis of youth (ADY):*** A young man had multiple annular patches and plaques located predominantly on his flanks and groin. In some they extended to the abdomen, and more rarely to the axillary region or neck. Molecular analysis showed a polyclonal T cell population. Therapy for this periodically relapsing condition involves topical steroids, calcineurin inhibitors, PUVA, and excimer laser.

Cases anticipated. Heymann discussed *acquired erythropoietic protoporphyria, Satoyoshi syndrome,* and *essential syphilitic alopecia.*

Necrotic Carpal Tunnel Syndrome

- Pathophysiology: ischemia of the median nerve from neurovascular compromise resulting in altered autonomic innervation
  - Change in contour
  - Any increase in volume
- Clinical features—remember the distribution of the median nerve!
  - Erythema, bullae, erosions, ulcerations
  - Raynaud, acro-osteolysis
  - Nails: cuticular hyperkeratosis, subungual hyperkeratosis, melanonychia, Beau's lines, onychomadesis
  - Easily misdiagnosed as scleroderma or other connective tissue disease

Essential Syphilitic Alopecia

- The incidence of primary and secondary syphilis from *Treponema pallidum* infection increased from 2.1 cases per 100,000 persons in 2000 to 8.7 cases in 2016, with MSM accounting for 81% of all male cases in 2016
- SA may clinically mimic a wide range of hair disorders, including alopecia areata (AA), trichotillomania, lichen planus pilaris, tinea capitis, telogen effluvium, and androgenetic alopecia. **Thus, the diagnosis may be delayed, especially when SA is the unique manifestation of secondary syphilis and primary syphilis signs are absent or not reported (ie, essential SA)**

H Yeung et al. *JAAD.* 2019;80:591–602; L. Tognetti et al. *Dermatol Pract Concept.* 2017;7:55–9.

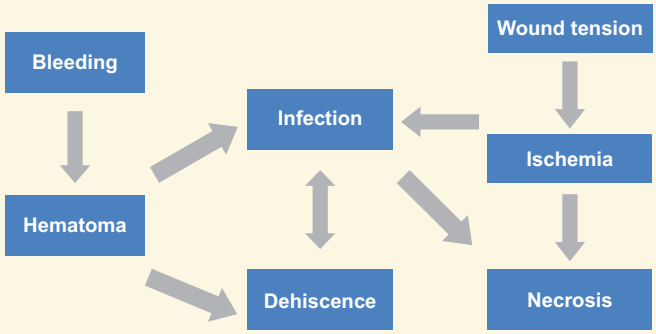
Surgical Complications

Marc D. Brown, MD

Introduction. Surgical complications are unavoidable with even the best technique and expertise. Dr. Brown discussed what he calls The Terrible Tetrad, noting causes, concerns, and how to manage them.

The Tetrad. ***Bleeding*** is the most common complication, typically within the first 48 hours. It potentially occurs in dead space and in more-vascular areas (eg, scalp, nose). Brown noted the typical causes, including the poorly controlled hypertensive patient and those on anticoagulant medication. Because these postoperative bleeding events are not usually serious, continuing anticoagulant therapy is recommended. To decrease the risk of intraoperative bleeding, use meticulous hemostasis. To prevent postoperative bleeding, use deep sutures to minimize dead space and use good pressure dressings. Instruct patients to minimize both activity and alcohol consumption at home. Brown discussed the use of pressure if the patient does develop bleeding. ***Infection:*** One's overall complication rate of infection should be no more than 2–3%. For the individual patient, immune status can be a factor. Brown described the challenge that the ears present, with advice for prevention. He noted the importance of seeing a suspected infection, because of conditions that mimic infection. The data do not support topical antibiotics to prevent infection; use Aquaphor® or petrolatum. He reviewed in-office preventive measures, including topical antibacterial agents such as chlorhexidine. Avoid routine use of prophylactic antibiotics—other than in the few AHA-advised circumstances—as they are not usually needed. ***Dehiscence*** is typically secondary to infection or hematoma, or to the patient's inappropriate activity level at home. Use deep sutures, and instruct patients to be cautious. ***Necrosis*** occurs when tissue ischemia leads to an eschar. Brown noted the situations that promote vascular compromise, and if necrosis does occur, he advised simply leaving it alone. Reassure the patient that the eschar serves as an excellent biological dressing that will spontaneously fall off when ready.

Interrelated Cycle



Critical Caution #1

- **Bleeding—keep patients on anticoagulation therapy**
  - Data show no increased risk for serious post-op events
  - Increased intraoperative bleeding can be controlled
  - Morbid and lethal thrombotic events can occur when anticoagulants are stopped

Critical Caution #2

- **Oral antibiotics—strictly limit prophylactic use**
  - Dangers: allergic reactions, side effects, resistance and superinfection, cost
  - Yet use for surgical visits has *increased* 69%, from 3.92 to 6.65 per 100 visits
  - Concerning, as this may put patients at unnecessary risk
  - Judicious/selective use in Mohs surgery
    - Lower legs
    - Complex nasal reconstruction
    - Tension
    - Lip/ear wedge
    - Poor host defense

Dermatomyositis: Advanced Therapeutic Pearls and Pitfalls

Ruth Ann Vleugels, MD, MPH

Introduction. Dr. Vleugels presented a series of patients illustrating the common diagnostic errors that occur with dermatomyositis (DM), particularly in those with amyopathic or skin-limited disease. As a consequence, existing interstitial lung disease or cancer may go undetected. A diagnosis of DM may be made solely on cutaneous features. Then once diagnosed, clinicians should quickly assess for concomitant pulmonary disease or malignancy. "The skin exam is very often the crucial part of diagnosis, and will allow us to truly make an impact on saving patients' lives."

Diagnosis. A patient admitted to the ICU was treated unsuccessfully for what was thought to be a pulmonary infection. The dermatologist, called in several days later, recognized pink midfacial erythema hugging the nasolabial folds and spreading up to the forehead, pink erythema on the upper eyelids, pink plaques with psoriasiform scale (Gottron papules) over the knuckles, and nailfold capillary changes. The patient was diagnosed with amyopathic DM with fulminant lung disease, and did not survive. Vleugels then described several cases in which patients with skin-limited DM were initially misdiagnosed with lupus, a common occurrence as both present with photosensitive eruptions and a biopsy with vacuolar interface dermatitis. In one patient, the initial misdiagnosis caused metastatic small cell lung cancer to be missed. These cases highlight the crucial need to recognize dermatomyositis based on skin findings alone to avoid missing any associated systemic disease or malignancy. Vleugels reviewed the classic cutaneous phenotype of MDA5 dermatomyositis, which includes ulcerations over the Gottron papules and sign, painful palmar macules and papules, oral ulcers, and nonscarring alopecia. MDA5 carries a high risk of associated interstitial lung disease, including a rapidly progressive variant, yet these patients often lack muscle disease to point the clinician to a DM diagnosis.

- 115 patients with amyopathic DM
- Antimalarials were the most commonly used treatment type
- In the majority (89%), antimalarials were not sufficient to achieve control of skin disease

Only 11% did not need more aggressive therapy

J Pinard et al. *JAMA Dermatol.* 2019;155:494–6.

Therapy: Cutaneous Dermatomyositis

- Don't forget to treat pruritus
- Photoprotection
  - Behavior, sunscreens, protective clothing
  - Consider vitamin D status
- Topicals
  - Corticosteroids, tacrolimus
- Systemic agents
  - Antimalarials; consider in combination
  - Methotrexate, mycophenolate mofetil, IVIG, JAK inhibitors, RTX

Treatment. The photosensitivity of DM requires careful photoprotection. The pruritus severity strongly impacts quality of life. Hydroxychloroquine (HCQ) use in these patients is limited by the drug rashes that develop in one-third, and by insufficient benefit (in one study, only 11% of patients did not require more aggressive therapy). Most cutaneous DM patients require additional systemic therapies, typically methotrexate, mycophenolate mofetil, or IVIG (which Vleugels finds to be the most effective therapy for these patients). Other options include JAK inhibitors, which have shown promise for recalcitrant disease, and rituximab. With colleague Dr. Steven Greenberg, Vleugels published on the correlation of the validated skin disease activity score in DM with interferon-ß levels. This initiated development of a new therapeutic for cutaneous DM, which has advanced to an international randomized controlled trial.

Prevention of Infection in Patients With Dermatological Diseases

Brian S. Schwartz, MD

Introduction. Dr. Schwartz focused on the most likely potential infections.

Latent TB infection (LTBI). TB spreads from person to person. A very small % of those exposed develop active disease. For the 95% developing LTBI, adding immunosuppressive therapy significantly risks active infection. PPD and QuantiFERON (an interferon-gamma release assay, or IGRA), which detect LTBI, are commonly indeterminate with previous BCG vaccination or current non-TNF immunosuppressant. Recently, a 34-year-old woman with poorly controlled psoriasis was about to begin a TNF inhibitor. She had received BCG vaccine as a child in Mexico; her QuantiFERON screening results were indeterminate and PPD was not helpful. "How to handle this is one of the most frequent questions from my colleagues." Schwartz takes an extensive TB history covering all possible exposure settings, a chest X-ray checking for evidence of past infection, and often repeats QuantiFERON and PPD. After excluding active infection, he considers treating for latent TB, preferably with weekly isoniazid + rifapentine for 12 weeks.

HBV infection. HBV can reactivate during immunosuppressive therapy and cause life-threatening fulminant liver disease, so test for prior infection. Vaccinate those without infection; treat at-risk patients

Infection Risk Increases With Many Systemic Rx For Dermatological Diseases

- **TB:** TNF inhibitors > steroids
- **HBV (hepatitis B virus):** anti-CD20 > steroids > TNF inhibitors
- **Endemic mycoses:** TNF inhibitors > steroids
- **PJP (pneumocystis jirovecii pneumonia):** steroids + others

Take-Home Points

- **TB:** TNF inhibitors > steroids:
  - Indeterminate IGRA can be challenging
  - Consider shorter Rx regimens for latent TB infection
- **HBV:**
  - Always screen, then consider prophylaxis vs pre-emptive strategy
- **Endemic mycoses:**
  - Reactivation rare, but new infection while on immunosuppressive therapy can be severe
  - Screen for recent infection
  - Educate about preventing new infection
  - Keep in your DDx when these patients are ill
  - Know limitations of diagnostics
- **PJP:**
  - PJP risk often < risk of TMP-SMX complication (3.5%)
  - Consider in those on high-dose steroids and second IS condition

with entecavir. Previously infected patients at highest reactivation risk test positive for the hepatitis B surface antigen and will begin rituximab or prolonged high-dose steroids; TNF inhibitors pose a moderate risk. Rituximab is a moderate risk for patients who are surface-antigen negative, core antibody positive. Schwartz detailed appropriate testing and application of results.

Endemic mycoses. Patients on TNF inhibitors risk more-severe disease from these fungal infections. Before treatment begins, take a travel history (the CDC has a location map for endemic infections); ask about cough, shortness of breath, and other signs and symptoms. Educate patients for avoiding exposure. Keep this in the differential diagnosis in the event of illness. Schwartz provided diagnostic guidance for various contexts.

Pneumocystis. Poor data provide little clear guidance. Patients at possibly concerning risk are on a prolonged high-dose steroid with a second autoimmune condition. Beyond this, the adverse effects of septra prophylaxis are commonly worse than the infection.

Phototherapy in the Age of Biologics

Heidi T. Jacobe, MD, MSCS

Introduction. Dr. Jacobe emphasized phototherapy's continued relevance alongside the progress that biologics have enabled in treating skin diseases. She provided an overview of photobiology and its benefits, discussed equipment, and profiled the expected and unexpected conditions that can benefit.

Phototherapy and skin disease. ***Photobiology:*** Phototherapy modalities, sandwiched between X-rays and infrared, are midway on the electromagnetic spectrum that has gamma rays (ionizing radiation)—short wavelength and high energy—at one end, and radio waves—significantly longer wavelength and lower energy—at the other. Phototherapy uses UVB (290–320 nm), UVA (320–400 nm), and visible light (photodynamic therapy). Longer wavelengths penetrate deeper into the skin (UVA compared to UVB), but their decreased energy can require an increased dose or an accelerant (like psoralen) to get a biological effect. ***Therapeutic impact:*** This wavelength segment exerts inhibitory effects on inflammatory chemokines and cytokines in the skin and maintains crosstalk with various inflammatory cell mediators. In addition, the photoaging effects of UVA—inducing matrix metalloproteinases and collagenases that break down collagen and extracellular matrix—are valuable for treating sclerosing skin conditions. ***Equipment:*** Jacobe discussed options, recommending "the fluorescent lamp cubicle—the real workhorse—for those limited to a single device. Get it in the narrowband UVB range." ***Conditions that benefit:*** Phototherapy remains useful in psoriasis and atopic dermatitis (for those patients who, for various reasons, cannot take the new therapeutic options), vitiligo, and CTCL (where it is still a therapeutic mainstay). Jacobe also uses phototherapy—especially NBUVB—as a go-to 2nd-line therapy, or for recalcitrant patients, or for steroid-sparing benefits, for starters, in the following: lichen planus, chronic idiopathic urticaria, dermatographism, solar urticaria, idiopathic itch, uremic pruritus, immune checkpoint inhibitor–associated dermatitis, lichen sclerosus et atrophicus, and morphea sclerosus (use UVA1). Jacobe provided induction and maintenance guidance.

Final comments. Jacobe explained why some patients burn and how to correct this. She emphasized the lack of proven risk for photocarcinogenesis. And she spoke of the need for validated treatment outcomes for the diseases benefiting from phototherapy, and consistent treatment regimens across treatment centers so that data can be compared.

Phototherapy for Immune Checkpoint Inhibitor Skin Disease

- **Rash/inflammatory dermatitis** (maculopapular rash, pruritus, lichenoid reaction, vitiligo, psoriasis)
- **Bullous diseases** (bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction)
- **Severe cutaneous reactions** (SJS, TEN, acute generalized exanthematous pustulosis, DRESS

Known efficacious treatment for these disorders

Broad mechanism of action

Treats widespread disease

Can be used for maintenance

NBUVB has no skin cancer risk

Biggest reason: It may allow continued treatment with improved life quality!

Other Disorders Responsive to NBUVB Phototherapy

- Lichen planus
- Urticaria—along with an H1 antihistamine
- Pruritus—NBUVB is good, BBUVB is superior
- Prurigo nodularis
- Pityriasis rosea
- Lichen simplex chronicus (including 1 report of vulvar disease)
- PLEVA
- Alopecia areata
- Extragenital lichen sclerosus et atrophicus

Phototherapy is Essential to Dermatologic Therapy

- Even with the advent of newer, targeted therapies, UV therapy remains a therapeutic mainstay
- Many therapeutic challenges can be addressed with phototherapy
- Need for collaborative efforts to determine optimized regimens for efficacy and safety and document cost effectiveness

MINI-SYMPOSIUM: MELANOCYTIC LESIONS

Red, White, and Black: Challenging Nevi in Children

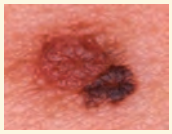
Kelly M. Cordoro, MD

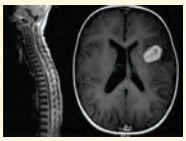
Introduction. Dr. Cordoro discussed "the clinically important aspects of the more challenging nevi in children we see in our offices"—congenital melanocytic nevi (CMN), special site nevi, and Spitz nevi—to help guide clinical decision making. First she emphasized that melanoma in pediatric patients is rare. It takes 600 nevus biopsies to find 1 melanoma, a rate 20 times that in adults. About 2% of *all* melanomas occur before age 20, 90% of which appear in the 15–19-year-old window. "Have a higher threshold for biopsying significantly changing lesions in this age group."

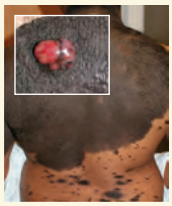
CMN and melanoma risk. Among the greatest risk factors for melanoma in children with large or giant nevi are the presence of satellites, CNS involvement, and 2 or more medium-sized nevi. For children with high-risk CMN, an MRI screening of the brain and spine within the 1st year is recommended. The presence of CNS involvement is a strong predictor of all-site (skin and CNS) melanoma. For small, isolated medium CMN, melanoma risk increases with age and is greatest after puberty. *Red is the new black*, ie, in very young prepubertal children, be wary of amelanotic melanomas that present as persistent, evolving, red, bleeding bumps. They are commonly mistaken for molluscum, pyogenic granuloma, and warts.

Tips for CMN Assessment: *Look and Feel*

- **Small/medium:** conventional changes (ABCD); dermoscopy
  - Change in superficial aspect
  - Risk increases with age
- **Large/giant:** new nodule or lump
  - Change in ***deeper*** tissues; lymphadenopathy
  - Mean age dx/death from CNS or cutan mm ~5 yrs
    - Screening MRI of CNS before age 1

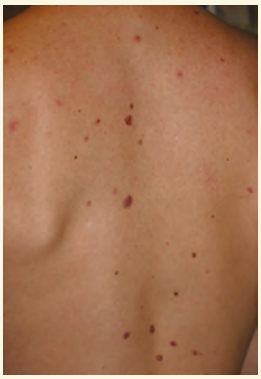


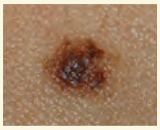




Approach to the "Moley" Child

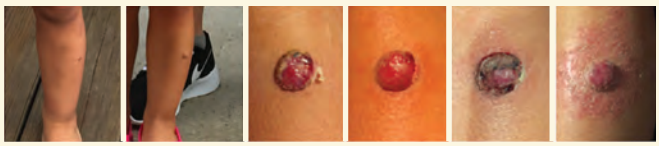
- Age to start FBSE depends on phenotype and risk factors
- Predilection for high nevus count is apparent by age 12; periodic FBSE, dermoscopy, photos
- Identify the "signature nevus"
  - predominant nevus phenotype
  - helps identify outliers





Red is the New Black

- **Amelanotic bleeding nodules are common pediatric presentations of melanoma**
- Conventional ABCDs are less common in younger children
- Biopsy rapidly evolving, suspicious lesions, especially if not typical for common banal entities



3 y/o: melanoma misdiagnosed first as molluscum, then keloid

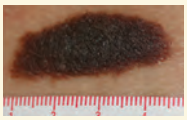
DW Bartenstein et al. *J Pediatr.* 2017;186:205–205e1; K Cordoro et al. *JAAD.* 2013;68:913–25; A Ferrari et al. *Pediatrics.* 2005;115:649–54; MK Melnik et al. *Am Surg.* 1986;52:142–7.

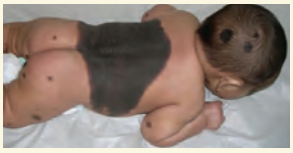
Special site nevi. Scalp, anogenital, acral, and nail matrix/nail unit nevi often look atypical and cause concern clinically and microscopically. Biopsy decisions are individualized, but in general the threshold for children is very high compared to adults, for whom it is very low. If performed, biopsy specimens should be interpreted by dermatopathologists with pediatric histopathology experience.

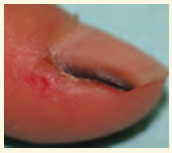
Spitz nevi. These arise mostly within the first 2 decades of life. They can grow very rapidly initially, provoking concern. Spitz nevi occur on a spectrum from benign to intermediate/indeterminate to more clearly melanoma, defined by clinical, histopathologic, and—increasingly—genetic characteristics. There are no clear-cut histopathological features that can reliably and consistently distinguish benign lesions from malignant; thus the standard of care has become molecular analysis for genetic aberration. Use dermoscopy in assessment and followup. "Diagnosis of atypical Spitz nevi has been the Wild West of pigmented lesions; genetic profiling is helping to bring clarity."

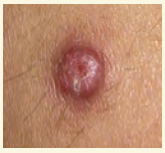
Final Thoughts

- Melanoma is rare
- CMN—size matters
- *Signature nevus* concept
- Conservative approach to *special site* nevi
- Spitz spectrum: diagnostic toolbox is expanding
- Seek expert histopath review for high-stakes lesions
- MM in young children is more likely to be amelanotic









Management of Atypical Pigmented Lesions

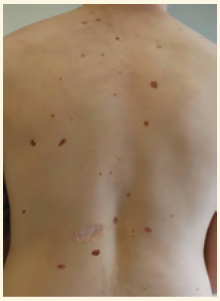
Jennifer A. Stein, MD

Introduction. Dermatologists who care for moley patients regularly face 3 types of decisions about suspicious lesions: (1) When is a biopsy warranted—or not? (2) What is the best way to biopsy it? and (3) When the pathology comes back as atypical/dysplastic, when is re-excision needed? Before discussing her guidelines and supporting data, Dr. Stein described Dr. Jean Bolognia's concept of the *signature nevus* for identifying a moley patient's non-worrisome nevi, and the ugly duckling—the one that doesn't fit this pattern—to identify nevi of potential concern.

Making decisions. *The uncertain nevus:* The lesion that is not clearly either melanoma or benign can be monitored for evidence

Simplified Digital Photography

- Digital dermoscopy with your iPhone into your EMR
- Dedicated SLR camera with dermoscopic lens
- Inexpensive connector to magnetically attach your dermatoscope to a smartphone or iPad



of change. Stein discussed several informative technologies. *Serial dermoscopic monitoring* focuses on the lesion. *Total body photography* (which can be combined with dermoscopy) is excellent in the right patient, and can decrease biopsies 4-fold. The new *pigmented lesion assay* uses *tape stripping* to provide tissue samples for RNA analysis. Melanoma risk is 7% with expression of the LINC gene, 50% with PRAME, and 93% with both together. ***How to biopsy:*** Try to sample the entire lesion, which is easier with a small lesion than a larger one; Stein advises 2 mm around the lesion if possible. ***When to re-excise:*** When pathology notes a dysplastic nevus, the decision to re-excise rests heavily on the degree of atypia and the margin status. Stein outlined her algorithm, though noted it is dependent on the pathologist reading the slides. With *mild atypia*, she leaves it alone and asks the patient to inform her if it repigments. With *moderate atypia*, although there are some data suggesting it is safe not to re-excise (even with positive margins) and simply to watch it, she tends to excise based on her pathologist. Treat *severe atypia* like melanoma *in situ,* re-excising with a 5 mm margin.

Critical. There is much variability from one pathologist to another. Know your pathologist's perspective!

Summary

- Goal: reduce unnecessary biopsies and enhance melanoma detection
  - Dermoscopy
  - Total body photos
  - Sequential digital dermoscopic imaging (dermoscopic monitoring)
  - Tape stripping/pigmented lesion assay
- If you do need to biopsy, remove the entire lesion, preferably with a 2 mm margin
- Re-excise severely atypical nevi with a 5 mm margin
- Re-excise moderately atypical nevi based on your pathologist's recommendation
- ***Know your pathologist!***

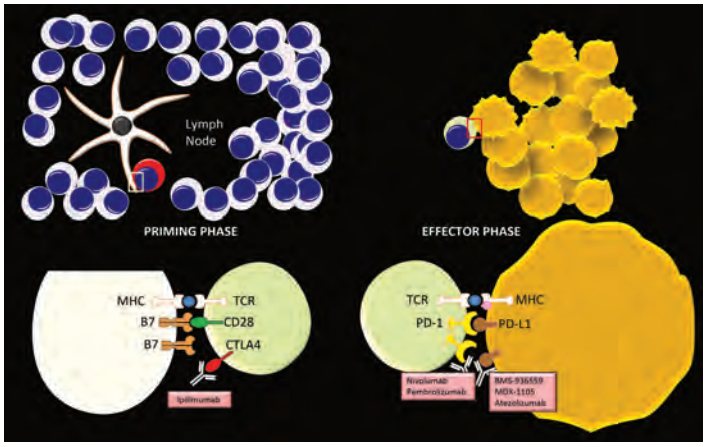
Melanoma 2020: Checking in on Checkpoint Blockade

Hensin Tsao, MD, PhD

Introduction. Dr. Tsao described the molecular mechanics of the *priming* and *effector* phases in mounting an anti-tumor T-cell response. Priming occurs in the lymph node, transforming naïve T cells into killer T cells that recognize an antigen expressed by the melanoma tumor cells. In the effector phase, these primed T cells return to the tumor environment to destroy the tumor. Each phase risks the tumor(s) co-opting a local immune control checkpoint to block this anti-tumor activity—CTLA-4 during priming, and PD-1 in the effector phase. Checkpoint inhibitor drugs—a groundbreaking development in anti-cancer therapy—blockade these checkpoints, liberating the anti-tumor immune response. Tsao presented recent data reflecting their efficacy and reviewed factors enhancing efficacy.

Checkpoint inhibitor efficacy. *Metastatic disease:* The longest follow-up data involve the anti-CTLA-4 inhibitor ipilimumab, with a cure rate of 21%. A cure is likely if one reaches 3 years from treatment initiation. Nivolumab, a PD-L1 inhibitor, "showed tremendous benefit in the earliest studies" for both progression-free and overall survival. When the 2 drugs were tested in combination, affecting both priming and effector phases, 50% of subjects were still alive at 5 years. Complete tumor clearance occurred in ~22% (compared with 19% for nivolumab, 6% for ipilimumab). ***Adjuvant setting:*** The goal is eliminating micrometastases after local spread to the nodes. Pembrolizumab showed the best results, with 75% of patients relapse-free at 1 year. Nivolumab, comparable to pembrolizumab, surpassed ipilimumab in a head-to-head trial. Tsao noted the significant adverse effects that can occur, but emphasized the dramatic progress. "Ten years ago, median survival in stage 4 melanoma was 3–7 months. Now it is up to 52% at 5 years. We can tell our patients that even if they recur, they have a 50% chance of cure. This is extraordinary—and it has all come about in the last 10 years."

Response determinants. Research focuses on identifying the variety of factors that drive and enhance the melanoma patient's response to these agents. Tumor-associated variables to date include high PD-1 expression, heterozygous HLA, and BRAF mutation positivity. Other factors include T cell molecular characteristics and healthy diversity of the gut microbiome.



Melanoma Checkmate?

- Immune checkpoint inhibition is hot!
- Most studies show that anti-PD-1 is superior to single-agent ipilimumab and has a better toxicity profile, but that combination is best
- Immune checkpoint response is "holistic"
  - Tumor mutation burden → neoantigens
  - Antigen presentation: HLA-D and B2M
  - Cytokine response—IFN receptor loss, JAK mutation, etc
  - Molecular state of T cells is important
  - Gut microbiome modulates anti-PD-1 response
- Autoimmune toxicities can be extreme, even lethal

Lentigo Maligna: Challenges

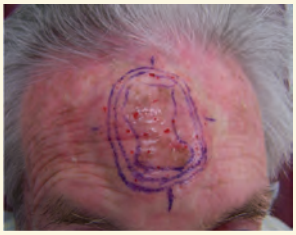
Marc D. Brown, MD

Introduction. Lentigo maligna (LM) is no longer just a geriatric skin cancer, as we see it now among 40–50-year-olds and younger. Dr. Brown discussed the various challenges that LM presents, with guidance for determining the best way to approach and treat this form of melanoma.

The challenges. *Clinical:* Most *in situ* lesions eventually become invasive, but there is no way to predict how slowly/rapidly that will happen. The lesion may extend well beyond the clinical margins. ***Diagnostic:*** Lesions often appear benign, and clinical changes are very slow and subtle. Large lesions risk sampling error. ***Histopathology:*** Detection of atypical melanocytes can be unreliable in frozen sections, producing false positives. Immunostaining avoids this, but its high sensitivity may increase the number of stages with Mohs surgery, and may miss any desmoplastic component.

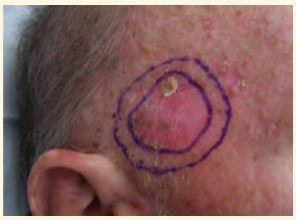
LM: Clinical Challenges

- Unable to predict if and when LM will progress to invasive melanoma
- May extend well beyond ill-defined clinical margins
- Occurs in important facial cosmetic areas
- Lesions can be large



LM: Diagnostic Challenges

- Similar appearance to benign solar lentigo
- Clinical change typically subtle and slow
- Amelanotic variant
- Increasing incidence in younger adults



- Cannot rule out early evolving *in situ* disease

LM: Histopathology Challenge

- Reliability in detecting atypical melanocytes in frozen sections
- Freezing artifact may ➞ false positives
- Immunostains may help diagnosis, but high sensitivity can ➞ extra stages
- May miss desmoplastic melanoma

Surgical guidance, and more. Because of LM's ill-defined and unpredictable nature, the standard of care for melanoma *in situ*—wide local excision (WLE) with 5 mm margin—risks local recurrence because bread loaf sections sample only ~2% of the peripheral margins. Mohs surgery (frozen, slow, or modified) is advised because it involves complete peripheral mapping of the tumor, and the recurrence rate is significantly lower. Brown discussed the types of Mohs surgery, then detailed his own approach. The key is taking adequate peripheral sections so no tumor is missed. Imiquimod is an alternative when surgery cannot be tolerated. Despite shortcomings, "the bottom line is that imiquimod works," with a composite clearance rate of 88%. Brown provided guidance for optimizing effectiveness.

Imiquimod

Disadvantages

- Lower cure rates than surgery
- No margin control
- Reports of recurrence and development of invasive melanoma
- Prolonged treatment times
- Discrepancy between clinical and histologic response

Advantages

- Avoid surgery in elderly or debilitated patients
- Avoid cosmetic disfigurement
- Treat wide areas of subclinical disease
- Well tolerated
- Good cosmesis
- **It works!**

Summary. LM can be a challenge to diagnose clinically and histologically. It has significant subclinical extension, can behave aggressively, and should be treated aggessively. The treatment of choice is surgical excision with complete peripheral mapping. Immunostains have been very helpful. Imiquimod can be used when surgery will not be tolerated.

MINI-SYMPOSIUM: PSORIASIS

The Paradox of Choice: Comparative Effectiveness to Inform Therapeutic Decisions

April W. Armstrong, MD, MPH

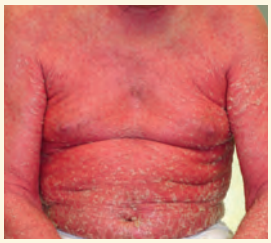
Introduction. Dr. Armstrong's goal was to "sort through the myriad of information we have when it comes to systemic therapy for moderate to severe plaque psoriasis." This included updates on oral therapies, evaluating biologics for efficacy, and the import of the AAD guidelines for treating patients. For each drug, Armstrong detailed efficacy, the baseline labs to be checked and which ones require monitoring during treatment, and contraindications. She made her trove of dosing guidance available afterward.

Subcutaneous Methotrexate

- Better bioavailability, tolerability (less nausea, vomiting, diarrhea), and efficacy than PO methotrexate
- Dose 7.5–25 mg/week
- Classic vial-and-syringe dosage:
  - 25 mg/cc solution
  - Insulin syringes, 1 cc, 25 or 27 gauge, ½" needles
- Single-dose auto-injector:
  - Rasuvo (10 ➞ 25 mg)
  - Otrexup (10 ➞ 25 mg)
  - No refrigeration needed

Cyclosporine: In Whom Do I Use It?

- "Crisis patient": erythrodermic psoriasis; severe pustular psoriasis or plaque psoriasis
- Bridge to other long-term therapies, eg, biologics
- Possibly in pregnant women with severe flare who lack access to phototherapy or biologics



Oral therapies. They have a role. Armstrong uses ***methotrexate*** for patients whose healthcare coverage (or lack of coverage) does not enable access to biologics, and whose renal creatinine clearance is ≥50. It takes at least 6 weeks for improvement to become visible, and ~1/3 of patients will achieve PASI 75 or better by week 16. Subcutaneous methotrexate (7.5–25 mg/week) provides better bioavailability and efficacy than the oral drug, and is also an alternative for the patient intolerant to the oral form. Armstrong discussed the PD4 inhibitor ***apremilast*** and then ***cyclosporine***, which has excellent efficacy. She uses cyclosporine for the patient in crisis (presenting with erythrodermic psoriasis) and as a bridge before another long-term therapy can begin (including pregnant patients), tapering gradually. Armstrong recommends the microemulsion form.

(Continued on page 20)

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Biologics. Armstrong delineated the TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors, and noted that the TNF and IL-17 inhibitors are also effective against both peripheral and axial psoriatic arthritis (PsA). While some IL-23 inhibitors are effective in peripheral PsA, their data in axial disease are still maturing. She discussed limitations in efficacy data where head-to-head trials do not exist. Overall, ixekizumab, brodalumab, risankizumab, guselkumab, and secukinumab have highly robust efficacy against psoriasis. Armstrong delineated her approach to choosing for a given patient. TNF inhibitors (ie, certolizumab) are excellent for peripheral and axial PsA and for the pregnant patient. The IL-17 inhibitors all have "great overall efficacy." The IL-23 inhibitors have "robust efficacy" against psoriasis and require few injections, but more data are needed for axial PsA. If the selelcted biologic has no effect, try dose escalation before switching.

FDA-approved Biologics for Psoriasis

Drug class	Agent	Indication
TNF antagonists	Etanercept (Enbrel)	Psoriasis, PsA
	Infliximab (Remicade)	
	Adalimumab (Humira)	
	Certolizumab (Cimzia)	
p40 IL-12/23 antagonist	Ustekinumab (Stelara)	Psoriasis, PsA
IL-17 antagonists	Ixekizumab (Taltz)	Psoriasis, PsA
	Secukinumab (Cosentyx)	Psoriasis, PsA
	Brodalumab (Siliq)	Psoriasis
IL-23 antagonist	Guselkumab (Tremfya)	Psoriasis
	Tildrakizumab (Ilumya)	
	Risankizumab (Skyrizi)	

FDA, U.S. Food and Drug Administration; PsA, psoriatic arthritis

Choosing a Biologic

TNF inhibitors great in:
- Psoriatic arthritis (peripheral and axial)
- Pregnancy (certolizumab)

Avoid TNF inhibitors in:
- Demyelinating disease
  Hepatitis B

TNF inhibitors not preferred:
- History of latent tuberculosis
- Advanced CHF

IL-17 inhibitors great in:
- Robust psoriasis efficacy
- Psoriatic arthritis (peripheral and axial)

Avoid IL-17 inhibitors:
- Personal history of inflammatory bowel disease

IL-23 inhibitors great in:
- Robust psoriasis efficacy
- Few injections

Avoid IL-23 inhibitors:
- Psoriatic arthritis involving spine

Pediatric Psoriasis: What's New, What's True?

Kelly M. Cordoro, MD

Introduction. The last 10 years have seen a revolution in our understanding of moderate to severe psoriasis in children, sufficient to enable pediatric patients to be included in the official psoriasis guidelines for the first time.* The guidelines comprehensively cover the treatments appropriate for children. Dr. Cordoro discussed what is not addressed there—the critical decision-making process for choosing an appropriate treatment. She has documented the high prevalence of undertreated children, and advises replacing the conventional therapeutic ladder with the imperative to choose the right tool for the job without delay.

The disease burden. ***The psoriasis march:*** Psoriasis in adults is a systemic inflammatory disease that, If not controlled, will eventually result in heart attacks and strokes. Some data from adult studies show reduced risk for cardiovascular disease with systemic treatment. "It is biologically plausible that chronic unchecked inflammation could lead to severe morbidities for our patients as well as they get older. If so, that strongly supports a more aggressive approach to pediatric psoriasis." ***And more:*** Assessment of a child's disease burden extends beyond BSA and systemic inflammatory sequelae. It includes the psychological, emotional, social, and functional burdens of the child who withdraws from all activities that would require exposing affected skin and risk teasing and bullying.

Threshold for use of systemic therapy. Cordoro encouraged replacing the therapeutic ladder—setting biologics as the final option if all else has failed—with the premise: *find the right tool for the job* ***right now.*** Some children need a biologic from the start. Undertreatment impacts self-esteem, mental health, physical health, school performance, and ability to function in society, and produces adults with psychological dysfunction, occupational dysfunction, depression, anxiety, and suicidal potential.

Threshold for Use of Systemic Therapy?

Individualized assessment of *overall disease burden*

- **Kids are undertreated***
  - With medical, psychological, developmental, educational, occupational (life) consequences.
  - **Find the right tool for the job right *now.***

*SA Vogel et al. *Arch Derm.* 2012;148:66–71.

Big Menu of Options— *Which Drug For Which Patient?*

Systemics	Biologics
– Methotrexate	– TNF inhibitors
– Cyclosporine	– IL-12/23 inhibitors
– Acitretin	– IL-17 inhibitors
– Phototherapy	– PDE4 inhibitors

No one "right answer"—*except* with certain comorbidities, contraindications, and genetic variants

- **PsA:** use MTX, all biologics
- **IBD:** avoid IL-17 inhibitors (anti-TNF, IL-12/23 ok)
- **Liver, kidney dz:** avoid MTX, CsA
- **FCBP:** avoid acitretin
- **CAPE:** use anti IL-12/23
- **DIRA:** use IL-1 Ra

Treatment— Important Pediatric Considerations

- Very little existing data, most meds used off-label
- Use holistic approach: ***consider burden beyond the skin***—emotional and psychological reactions to the disease and its treatments
- Individualize: integrate age, disease, comorbidity, preferences
- Kids are undertreated: *medical, psychological, occupational consequences*

SA Vogel et al. *Arch Derm.* 2012;148:66–71.

(Continued on page 23)

ARAZLO™
(tazarotene) Lotion, 0.045%
REDEFINE WHAT'S POSSIBLE

FOR YOUR PATIENTS WITH ACNE VULGARIS

CRACK THE TAZAROTENE CODE

ARAZLO is the first and only tazarotene lotion, formulated with polymeric emulsion technology, to help deliver the clearance you expect and the tolerability you want[1-3]

- Treatment success* rates were 26% for ARAZLO Lotion vs 13% for vehicle in study 1 and 30% vs 17%, respectively, in study 2 ($P<0.001$ in both studies)[1,4†]
- Most common adverse events (≥1% of patients and greater than vehicle) at application site were pain (5%), dryness (4%), exfoliation (2%), erythema (2%), and pruritus (1%)[1†]

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*Treatment success on the Evaluator's Global Severity Score (EGSS) was defined as at least a 2-grade improvement from baseline and an EGSS score of clear (0) or almost clear (1).[1]

†**Phase 3 study design:** The safety and efficacy of ARAZLO Lotion were assessed in 2 multicenter, randomized, double-blind clinical trials of 1,614 subjects aged 9 years and older with facial acne vulgaris. Subjects had a score of moderate (3) or severe (4) on the EGSS, 20 to 50 inflammatory lesions, 25 to 100 noninflammatory lesions, and 2 or fewer facial nodules.[1]

Indication

ARAZLO™ (tazarotene) Lotion, 0.045% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

Important Safety Information

ARAZLO Lotion is for topical use only. Not for oral, ophthalmic, or intravaginal use.

Contraindication

ARAZLO Lotion is contraindicated in pregnancy due to the potential harm to the fetus.

Warnings and Precautions

Embryofetal Risk Females of childbearing potential should be warned of the potential risk and should use adequate birth-control measures when ARAZLO Lotion is used. A negative result for pregnancy should be obtained within 2 weeks prior to ARAZLO Lotion therapy, and therapy begun during a menstrual period. If the patient becomes pregnant while using ARAZLO Lotion, treatment should be discontinued.

Skin Irritation Patients using ARAZLO Lotion may experience application site pain, dryness, exfoliation, erythema, and pruritus. Depending upon severity, adjust or interrupt dosing as needed, increasing or resuming treatment as tolerated. Avoid application of ARAZLO Lotion to eczematous or sunburned skin.

Photosensitivity and Risk for Sunburn Minimize unprotected exposure to ultraviolet light, including sunlight, sunlamps and tanning beds, during the use of ARAZLO Lotion. Warn patients with high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Instruct patients to use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided.

ARAZLO Lotion should be administered with caution if the patient is taking drugs known to be photosensitizers (eg, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO Lotion.

Adverse Reactions The most common adverse reactions (in ≥1% of patients and greater than vehicle) were: application site pain, dryness, exfoliation, erythema, and pruritus.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

References: 1. ARAZLO Lotion [prescribing information]. Bridgewater, NJ. Bausch Health US, LLC. **2.** Tanghetti EA, Kircik LH, Green LJ, et al. A phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical study to compare the safety and efficacy of a novel tazarotene 0.045% lotion and tazarotene 0.1% cream in the treatment of moderate-to-severe acne vulgaris. *J Drugs Dermatol*. 2019;18(6):542-548. **3.** Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed October 20, 2020. **4.** Data on file.

Ortho Dermatologics

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ARAZLO safely and effectively.
See full Prescribing Information for ARAZLO.

ARAZLO™ (tazarotene) Lotion, 0.045%

For topical use
Initial U.S. Approval: 1997

INDICATIONS AND USAGE

ARAZLO™ (tazarotene) Lotion, 0.045% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

CONTRAINDICATIONS

ARAZLO is contraindicated in pregnancy. ARAZLO may cause fetal harm when administered to a pregnant patient *[see Warnings and Precautions, Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Embryofetal Toxicity Based on data from animal reproduction studies, retinoid pharmacology and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. Safety in pregnant patients has not been established. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, discontinue ARAZLO as soon as pregnancy is recognized.

Tazarotene elicits malformations and developmental effects associated with retinoids after topical and oral administration to pregnant rats and rabbits during organogenesis. However, limited case reports of pregnancy in females enrolled in clinical trials for ARAZLO have not reported a clear association with tazarotene and major birth defects or miscarriage risk *[see Contraindications, Use in Specific Populations]*.

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. In patients treated topically over sufficient body surface area, exposure could be in the same order of magnitude as in orally treated animals. Tazarotene is a teratogenic substance in animals, and it is not known what level of exposure is required for teratogenicity in humans.

Advise pregnant patients of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to ARAZLO therapy. Initiate ARAZLO therapy during a menstrual period. Advise patients of childbearing potential to use effective contraception during treatment with ARAZLO *[see Dosage and Administration in full Prescribing Information, Use in Specific Populations]*.

Skin Irritation Patients using ARAZLO may experience application site pain, dryness, exfoliation, erythema, and pruritus. Depending upon severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of ARAZLO, or discontinue use. Therapy can be resumed, or the frequency of application can be increased, as the patient becomes able to tolerate treatment.

Avoid use of concomitant medications and cosmetics that have a strong drying effect. It is recommended to postpone treatment with ARAZLO until the drying effects of these products subside.

Avoid application of ARAZLO to eczematous or sunburned skin.

Photosensitivity and Risk for Sunburn Because of heightened burning susceptibility, minimize unprotected exposure to ultraviolet light including sunlight and sunlamps during the use of ARAZLO. Warn patients who normally experience high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided. Patients with sunburn should be advised not to use ARAZLO until fully recovered.

ARAZLO should be administered with caution if the patient is taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections:

- Embryofetal toxicity *[see Warnings and Precautions]*
- Photosensitivity and Risk of Sunburn *[see Warnings and Precautions]*

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

In 2 multicenter, randomized, double-blind, vehicle-controlled clinical trials, subjects age 9 years and older applied ARAZLO or vehicle once daily for 12 weeks. The majority of subjects were White (74%) and female (66%). Approximately 22% were Hispanic/Latino and 42% were younger than 18 years of age, fourteen of 779 subjects (1.8%) treated with ARAZLO were between 9 years to less than 12 years of age. Adverse reactions reported by ≥1% of subjects treated with ARAZLO and more frequently than subjects treated with vehicle are summarized in Table 1. Most adverse reactions were mild to moderate in severity. Severe adverse reactions represented 1.3% of the subjects treated. Overall, 2.4% (19/779) of subjects discontinued ARAZLO because of local skin reactions.

Table 1: Adverse Reactions Reported by ≥1% of the ARAZLO Group and More Frequently than the Vehicle Group

Adverse Reactions N (%)		
	ARAZLO Lotion N=779	**Vehicle N=791**
Application site pain[1]	41 (5)	2 (<1)
Application site dryness	30 (4)	1 (<1)
Application site exfoliation	16 (2)	0 (0)
Application site erythema	15 (2)	0 (0)
Application site pruritus	10 (1)	0 (0)

[1]Application site pain defined as application site stinging, burning, or pain

Skin irritation was evaluated by active assessment of erythema, scaling, itching, burning and stinging, with grades for none, mild, moderate, or severe. The maximum severity generally peaked at Week 2 of therapy and decreased thereafter. The percentage of subjects with these signs and symptoms at any post-baseline visit are summarized in Table 2.

Table 2: Incidence of Local Cutaneous Irritation at any Post-Baseline Visit

	ARAZLO Lotion N=774 Mild/Moderate/Severe	**Vehicle Lotion N=789** Mild/Moderate/Severe
Erythema	49%	38%
Scaling	51%	23%
Itching	29%	14%
Burning	30%	6%
Stinging	22%	5%

DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with ARAZLO.

Concomitant use with oxidizing agents, as benzoyl peroxide, may cause degradation of tazarotene and may reduce the clinical efficacy of tazarotene.

In a trial of 27 healthy female subjects, between the ages of 20–55 years, receiving a combination oral contraceptive tablet containing 1 mg norethindrone and 35 mcg ethinyl estradiol, the concomitant use of tazarotene administered as 1.1 mg orally (mean ± SD C_{max} and $AUC_{0\text{-}24}$ of tazarotenic acid were 28.9 ± 9.4 ng/mL and 120.6 ± 28.5 ng•hr/mL, respectively) did not affect the pharmacokinetics of norethindrone and ethinyl estradiol over a complete cycle.

The impact of tazarotene on the pharmacokinetics of progestin only oral contraceptives (i.e., minipills) has not been evaluated.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary ARAZLO is contraindicated in pregnancy.

There are no available data on ARAZLO use in pregnant patients to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, ARAZLO should be discontinued as soon as pregnancy is recognized.

In animal reproduction studies with pregnant rats, reduced fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at a dose equivalent to the maximum recommended human dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at 15 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavioral delays were observed after oral administration of tazarotene during the period of organogenesis at doses 1 and 30 times, respectively, the MRHD (based on AUC comparison). In pregnant rats, decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 6 times the MRHD (based on AUC comparison) *(see Data)*.

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

Data *Animal Data* In an embryofetal development study in rats, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rats during gestation days 6 through 17. Reduced fetal body weights and reduced skeletal ossification occurred at this dose (equivalent to the MRHD based on AUC comparison). In an embryofetal development study in rabbits, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rabbits during gestation days 6 through 18. Single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were noted at this dose (15 times the MRHD based on AUC comparison).

When tazarotene was given orally to animals, developmental delays were seen in rats; malformations and post-implantation loss were observed in rats and rabbits at doses producing 1 and 30 times, respectively, the MRHD (based on AUC comparison).

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, classic developmental effects of retinoids including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights were observed at this dose (6 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations was observed at this dose.

In a pre- and postnatal development toxicity study, topical administration of a tazarotene gel formulation (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival, but did not affect the reproductive capacity of the offspring. Based on data from another study, the systemic drug exposure in the rat at this dose would be equivalent to the MRHD (based on AUC comparison).

Lactation

Risk Summary There are no data on the presence of tazarotene or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. After single topical doses of a ^{14}C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARAZLO and any potential adverse effects on the breastfed child from ARAZLO.

Clinical Considerations To minimize potential exposure to the breastfed infant via breast milk, use ARAZLO for the shortest duration possible while breastfeeding. Advise breastfeeding patients not to apply ARAZLO directly to the nipple and areola to prevent direct infant exposure.

Females and Males of Reproductive Potential

Pregnancy Testing Pregnancy testing is recommended for patients of childbearing potential within 2 weeks prior to initiating ARAZLO therapy which should begin during a menstrual period.

Contraception Advise patients of childbearing potential to use effective contraception during treatment with ARAZLO.

Pediatric Use Safety and effectiveness of ARAZLO for the topical treatment of acne vulgaris have been established in pediatric patients age 9 years and older based on evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled, 12-week clinical trials and an open-label pharmacokinetic study. A total of 300 pediatric subjects aged 9 to less than 17 years received ARAZLO in the clinical studies *[see Clinical Pharmacology and Clinical Studies in full Prescribing Information]*.

The safety and effectiveness of ARAZLO in pediatric patients below the age of 9 years have not been established.

Geriatric Use Clinical trials of ARAZLO did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

OVERDOSAGE

Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, monitor the patient closely and administer appropriate supportive measures, as necessary.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to the MRHD (based on AUC comparison).

A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposures at the highest dose was 7 times the MRHD (based on AUC comparison).

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in an in vivo mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was equivalent to the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of tazarotene up to 1 mg/kg/day which produced a systemic exposure 4 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose which produced a systemic exposure 6 times the MRHD (based on AUC comparison).

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The systemic menu. Most therapies are used off-label. Be conservative in young children and toddlers. In choosing treatment, "there is no one right answer, except for those few cases involving a contraindication." The choice is "more up to nuance." The conventional "oldies but goodies"—methotrexate, cyclosporine, acitretin, phototherapy—are easy to start and stop, and thus excellent for initial disease clearance and for flares. Methotrexate is often combined with a biologic to prevent anti-drug antibodies. Biologics—not good on-and-off drugs—are best reserved for chronic disease.

*A Menter, KM Cordoro et al. "Joint AAD-NPF guidelines of care for the management and treatment of psoriasis in pediatric patients." *JAAD.* 2019;82:161–201.

MINI-SYMPOSIUM: DIAGNOSTICS

Is This Erythroderma Malignant?

Laura B. Pincus, MD

Introduction. Dr. Pincus detailed her systematic approach for accurately determining whether a patient's erythroderma is due to lymphoma or a nonmalignant cause. She used several cases to illustrate the questions that arise and the sequence of steps to achieve an accurate diagnosis. Patients 1 and 2 had Sézary syndrome that had been misdiagnosed and treated as psoriasis. Patient 3 had been misdiagnosed with Sézary syndrome.

The necessary steps. A 54-year-old man had previously reported erythematous scaly patches on his legs that quickly generalized to erythroderma, and a biopsy with just a descriptive diagnosis suggesting psoriasis led to TNF inhibitor therapy. After his plaque partially cleared, then returned, a biopsy revealing abnormal lymphocytes raised the possibility of an erythrodermic form of cutaneous lymphoma, and he was sent to Pincus's clinic. The differential diagnosis for adult erythroderma includes: generalization of a pre-existing dermatosis, malignancy, erythrodermic form of cutaneous lymphoma (Sézary syndrome being the most common), drug hypersensitivity, infection, systemic disease (rare). Pincus reviewed her assessment, with specific blood work (immunophenotyping) ultimately pinpointing Sézary syndrome. The immunosuppressive drug stemming from the psoriasis misdiagnosis had "released the controls that had been holding his Sézary syndrome in check." A 24-year-old woman initially misdiagnosed with poly psoriasis worsened with adalimumab, then etanercept. Her blood evaluation was crucial to her diagnosis of Sézary syndrome with nodular evolution. For a 30-year-old woman with T-cell lymphoma, her blood evaluation contradicted the presumed Sézary syndrome diagnosis and resulted in peripheral T-cell lymphoma not otherwise specified, "the umbrella term for the diagnostic puzzles that don't quite fit anywhere."

Take-home points include. 1. Begin with the skin and thorough clinical exam, do multiple biopsies, and consider a genotypic analysis if the patient is still nondiagnostic. 2. Be cautious with TNF inhibitors and other biologics. If not 100% sure of psoriasis after multiple biopsies, consider a peripheral blood study (flow cytometry and T cell rearrangement studies). 3. Do a CT scan of the lymph nodes. 4. There are multiple types of erythrodermic CTCL in addition to Sézary syndrome.

Evaluation of Erythroderma

- Skin
  - Clinical morphology
  - Skin biopsy: ~60% of cases, biopsy will determine cause
    - Immunophenotyping
    - Genotypic analysis regarding T cell and receptor anomalies, ideally biopsying 2 lesions
- Peripheral blood
  - Light microscopy
  - Immunophenotyping—will detect Sézary cells
  - Genotypic analysis—will detect Sézary cells
- Lymph node
  - Physical exam and imaging to identify abnormal nodes (>1.5 cm)
  - Excisional biopsy if:
    - Abnormal nodes are enlarged via imaging
    - Diagnosis is not clear via blood

Key Take-Home Points

- Evaluation of erythroderma:
  - Skin
    - Clinical examination
    - Biopsy: multiple; genotypic analysis from multiple biopsies
  - Peripheral blood
    - Flow cytometry, genotypic analysis
  - +/– Lymph node
    - CT scan
    - Excisional biopsy if necessary
- Caution with TNF inhibitors
- Multiple types of erythrodermic CTCL
- PD-1 potentially differentiating immunomarker—possibly helpful in differentiating Sézary syndrome from erythrodermic dermatoses

Advanced Therapies in Oral Bullous Disease: What's New in There?

Rochelle R. Torgerson, MD, PhD

Introduction. Dr. Torgerson focused on pemphigus vulgaris and mucous membrane pemphigoid (MMP), both autoatibody-mediated diseases. She outlined the evolution of therapy, then took a brief look at what might be ahead. New therapies are coming.

Pemphigus vulgaris. Desmoglein 3 (from the cadherin family) is the primary target for oral disease in pemphigus, which occurs in 50% of pemphigus patients and can be challenging to treat. Therapy involves the induction, then maintenance, of remission. Corticosteroids were discovered to achieve rapid, effective remission, and so were used for maintainance as well. Plasmapheresis and IVIG (both still used as adjuvant therapies) were added with resistant disease. For current perspective, Torgerson presented her most challenging patient. After diagnosing pemphigus and achieving rapid improvement with cortisone, mycophenolate mofetil enabled a reduced cortisone dose after azathioprine had failed. That, along with adjuvant treatments, achieved reasonable maintenance control. In year 3, rituximab became available. This anti-CD20 biologic—approved for pemphigus in 2018—enables a rapid reduction of B cells in circulation and tissues. There are 2 dosing levels: lymphoma dosing, which came first, and later-appearing rheumatology dosing, which is lower. Torgerson counsels patients to accept what their infusion center uses. In sum: Use rituximab (or mycophenolate mofetil if rituximab is not covered) for remission, probably adding a short-term corticosteroid for a fast kick-in. Continue for maintenance. Regarding early rituximab use, the inflammatory bowel disease literature—which is highly relevant—advocates "going in with the biggest gun you have, and go in fast. This may give the best long-term outcome."

MMP. This targets hemidesmosomes in the basement membrane and often also includes the eyes and genitalia. There is huge variability in clinical severity. Dapsone and cyclophosphamide are used for

treatment. Torgerson described a patient whom she diagnosed, then coordinated with ophthalmology for reasonable treatment results. Rituximab (rheumatology dosing) has been looked at in this patient group. "It is too early to be able to bring things together in a synthesized manner, partly because of the variet of antigens in play in MMP.

Mucous Membrane Pemphigoid: Treatments

- Remission: corticosteroids
- Maintenance:
  - Cyclophosphamide
  - Dapsone
  - Azathioprine
  - Mycophenolate mofetil

Take-Home For Pemphigus (and maybe mucous membrane pemphigoid)

- Remission
  - Rituximab + short-term corticosteroid
- Maintenance
  - Rituximab
- New therapies coming soon

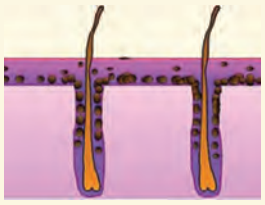
Dermoscopy of Special Sites

Jennifer A. Stein, MD

Introduction. The histology of the face, hands, and feet is unique, and thus the guidance for dermoscopic assessment of nevi on these areas is different than for other sites. Dr. Stein finds dermoscopy especially valuable in these areas because of its ability to identify lesions warranting concern and to avoid unnecessary biopsies, which is particularly important in these areas. She discussed what to look for, liberally illustrating with photos.

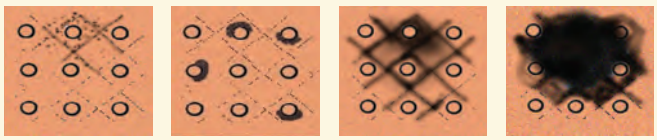
Dermoscopy of Lentigo Maligna (LM)

- LM follows hair follicles
- Thus, dermoscopic features of LM surround the follicles



I. Zalaudek et al. *Arch Dermatol.* 2008;144:1375–9.

Dermoscopic Features in LM



grey dots | asymmetric follicular openings | rhomboidal structures | homogeneous areas

- The circles are hair follicles or other adnexal openings
- Look for linear streaky pigment that makes geometric shapes
- May either spare or obliterate hair follicles

Lentigo maligna (LM) on the face. To the naked eye, LM and pigmented actinic keratoses, solar lentigines, and seborrheic keratoses resemble each other. But the face has unique histologic architectural features—its many adnexal openings, which include hair follicles—that enable dermoscopy to identify LM. Melanocytes follow the course of hair follicles—which look like punched-out holes under the dermatoscope—and produce distinctive patterns associated with them. Stein discussed the 4 core telltale patterns involving these "holes"—grey dots, asymmetric follicular openings, rhomboidal structures (angulated lines, linear streaky pigment), and homogeneous areas. Color is also important. A blue-white veil is bad, and "if you see grey—don't look away."

Hands and feet. Acral skin has dermatoglyphs, ie, ridge-and furrow architecture, which are central to the dermoscope's ability to discriminate between acral nevi and melanoma. "Furrows are fine, ridges are risky." Pigmentation along the narrower furrows of the surface skin markings is characteristic of acral nevi, and thus there is no concern. There are 3 closely related patterns: furrow, lattice-like, and fibrillar. Pigmentation on the wider ridges is highly specific for melanoma, and the lesion must be biopsied. With an unclear pattern, lesions ≤7 mm are considered benign and anything larger must be biopsied. Stein also discussed congenital acral nevi.

Basic Acral Patterns in Acquired Nevi

Benign

- Parallel furrows
- Lattice-like
- Fibrillar

Malignant

- Parallel ridges

MINI-SYMPOSIUM: SPECIAL POPULATIONS

Management of Follicular Disorders in Men of Color

Ginette A. Okoye, MD

Introduction. Dr. Okoye discussed DCS (dissecting cellulitis of the scalp), AKN (acne keloidalis nuchae), and PFB (pseudofolliculitis barbae). They are most common in young African American men, but are seen in other races and also in women. Although these diseases are quite common, we do not hear about them often and research is minimal. "Thus many of my recommendations are based on my clinical experience and that of colleagues." Okoye's discussion of treatments was highly detailed.

DCS. This chronic, inflammatory, scarring alopecia can occur alone or as part of the follicular occlusion tetrad (including HS, acne conglobata, and pilonidal sinus). "We believe that the pathogenesis is follicular occlusion followed by follicular rupture, producing a dense neutrophilic inflammation that causes substantial tissue damage in the dermis." Very painful, suppurative, boggy nodules connect via sinus tracts, with purulent drainage. Disfiguring scarring significantly impacts patients' self-esteem, and may harm job prospects. Query about anabolic steroid use (a significant risk factor). Rule out tinea capitis, a DCS mimic. Because the scar is permanent once a sinus tract forms,

it is critical to initiate aggressive therapy without delay. First-line treatment—isotretinoin (not antibiotics)—achieves complete remission in ~50% of patients when used early—"truly a game changer." (Dosing: 60–80 mg/day through at least 4 months after resolution, then low-dose maintenance.) TNF-α inhibitors are second line: adalimumab > infliximab > ustekinumab+isotretinoin. For everyone: pyrithione zinc 1% shampoo, and a topical steroid 2–3x/week (preferably clobetasol). Avoid shaving the scalp. Avoid I&D. Nd:YAG laser can decrease pain, drainage, and lesion formation.

AKN. This chronic, potentially scarring folliculitis—a marker for metabolic syndrome—involves keloid-like papules and pustules on the occipital scalp and posterior neck. Examine any beard for PFB, which is likely to coexist. *Prevention is key.* Avoid tight stiff collars. Critical is avoiding cutting/shaving hair so closely that it retracts into the skin. (Talk with the patient's barber.) Okoye discussed electric clippers with guards that prevent close contact, and recommended an "even Steven" haircut. If shaving cannot be avoided, moisten hair well, use shave gel, shave gently in the direction of hair growth. After shaving, use a benzoyl peroxide wash plus clindamycin lotion (or combination gel). Prescribe a topical steroid for morning application and a retinoid for night. Okoye advises gently removing ingrown hairs in PFB.

- **Use clippers**
  - No razors
  - Smaller guard size = closer shave
  - Use higher guard numbers
  - If "fade" hairstyle desired, never use clippers without the guard (ie, size 0)

Summary

- Follicular disorders in men of color
  - More research needed; could inform our general understanding of hair follicle biology and perifollicular inflammation
  - Significant, yet underappreciated, impact on QOL
- Dissecting cellulitis of the scalp
  - Painful, disfiguring
  - Rule out tinea capitis
  - Treat early and aggressively: isotretinoin, adalimumab, LHR
  - May decrease the extent of permanent alopecia
- Acne keloidalis nuchae and pseudofolliculitis barbae
  - Common, impactful
  - Prevention and patient education are key

More Than GVHD: When Dermatologists Treat Stem Cell Transplant Recipients

Milan Anadkat, MD

Introduction. Dermatologists working in a cancer setting commonly encounter patients who have received a bone marrow transplant. Dr. Anadkat stressed the need for a perspective that goes beyond GVHD, and includes leukemia cutis (leukemia infiltrating the skin, most commonly with AML—acute myeloid leukemia); chemotherapy-related toxic erythema; drug reaction; and disseminated infection. He used numerous photos of patients (all treated for AML) in discussing these phenotypes and providing treatment guidance.

Cases. *Leukemia cutis:* The patient presented at 4 months post-transplant with spots on her trunk. Examining the oral cavity was critical, because the gingiva become significantly engorged in leukemia cutis. Anadkat discussed *"leukamids"* (cutaneous lesions lacking the presence of leukemic cells), and the poor prognosis if leukemia cutis develops. ***Toxic erythema:*** An erosive, erythematous rash appears in the folds of the axilla and groin at 3–4 weeks post-transplant. It is chemotherapy-induced, with busulfan usually the culprit, and will resolve on its own. ***Drug reaction:*** About 5 weeks after transplant, the patient presented with a rash on sun-exposed areas—the tops of the arms and hands, the neck. It was a phototoxic reaction to the antifungal voriconazole—used preventively in transplant patients, now known to be highly phototoxic. ***Disseminated fungal infection:*** The patient presented at 3 weeks post-transplant with a rash on his hands and feet including dusky purpuric disseminated areas. Anadkat emphasized the critical morphology. ***Acute GVHD:*** The patient presented at 1 month post-transplant with an itchy full-body rash (in early acute GVHD it is often just on the hands, feet, or neck). It lacks the telltale morbilliform eruption of chronic disease. Determining acute and chronic disease "is now based on clinical manifestations, no longer on time since transplant. If the rash looks scleradermoid and the patient had a transplant—it is acute GVHD." ***Chronic GVHD:*** A patient almost 1 year since transplant had a purplish rash with a lichenoid appearance on her face and extremities. "If it looks lichenoid and the patient had a transplant—it's chronic GVHD. Trust your eyes."

Remember…

For patients who have undergone BMT, RASH does *not* always = GVHD

- It could be:
  - leukemia cutis, neutrophilic dermatoses, toxic erythema, drug reaction, disseminated fungal infection

NIH GVHD Guidelines: 2005

- Acute vs chronic—now based on specific clinical manifestations, not the time to onset
- Acute GVHD: classic features of maculopapular rash (face/scalp and palms), nausea, vomiting, anorexia, profuse diarrhea, ileus, or cholestatic hepatitis

Treatment for GVHD

- Lichenoid cGVHD therapy
  - ***Topical steroids***—go big
  - Calcineurin inhibitors
  - Phototherapy
- Sclerodermoid cGVHD therapy: this is a challenge!
  - Topicals
  - Phototherapy: UVA-1, PUVA, NBUVB
  - Photopheresis
  - Traditional immunosuppressants
  - Imatinib
  - JAK inhibitors
  - Rituximab
  - Sirolimus
- And the "little things"
  - Physical therapy
  - Control of pruritus
  - Secondary skin cancers
  - Secondary wound management

Immunizing the Patient With Dermatological Diseases

Brian S. Schwartz, MD

Introduction. Patients on immunosuppressive therapy are at higher risk for infections, and vaccines help to prevent them. Dr. Schwartz explained how to overcome immunosuppressive therapy's attenuation of this protective response. He stressed the risk from live vaccines (those for adults include typhoid, yellow fever, Zostavax for shingles, and the intranasal influenza vaccine) for patients on high-dose steroids, alkylating agents, methotrexate, azathioprine, TNF inhibitors, and other biologics. Avoid them. Schwartz reviewed the 3 most important protective vaccines, and discussed vaccinations within the patient's household.

Timing to maximize efficacy, minimize risk. Immunosuppressive therapies attenuate the response to vaccines. Rituximab and abatacept are the worst offenders, tofacitinib and methotrexate are moderate, and TNF inhibitors and prednisone (depending on dose) have modest impact. Avoid this by vaccinating 2 weeks before beginning immunosuppressive therapy (4 weeks if a live vaccine must be used). If treatment is underway, balance the risk vs benefit of a drug holiday. Withold the agent, vaccinate once it has cleared the patient's system, then restart treatment in 4 weeks.

Family. "Having a well-vaccinated family at home is one of the strongest protective barriers for the patient." Avoid the intranasal influenza vaccine, however, which risks infecting the patient. When an infant receives the rotavirus vaccine, the immunocompromised patient should not change diapers for several weeks afterward.

The essential trio. *Influenza:* With ~43 million cases annually and ~80,000 deaths, ""we must do our best to prevent this infection in our patients." Schwartz suggests the quadrivalent inactivated vaccine. Although high-dose is approved only for >64, data show benefit in younger immunocompromised patients. ***Pneumococcal:*** PCV13 is given first, then PPSV23 after 8 weeks; repeat in 5 years. The final dose occurs after age 65 after the final 5-year interval. ***Varicella zoster:*** There are >1 million cases yearly (lifetime risk of 1/3), potentially with severe consequences. Age and immune status are central risk factors. The inactive vaccine shingrix is accompanied by a highly potent adjuvant. Efficacy and safety data are extremely encouraging. It is not yet approved for people <50. ■

Household Contacts & Vaccines

- Create a barrier of immunity at home!
- Live vaccines OK for household contacts—except:
  - Close contacts should avoid live influenza vaccine
  - Caution about contact with infants post-rotavirus

Take-Home Points

- **Maximize benefit, minimize risk**
  - Plan ahead—vaccinate *before* immunosuppression
  - Consider withholding immunosuppressive before vaccination
- **Influenza**
  - Favor high-dose in >64 yrs, hold MTX for 2 weeks post?
  - If signs and symptoms, PCR for diagnosis + empiric oseltamivir
- **Pneumococcus:** 2 vaccines, algorithm
- **Zoster:** Shingrix data are encouraging for efficacy and safety

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Key to Autoimmune Disease Prevalence in Women

Sun Pharma Award Supports Dr. Johann E. Gudjonsson's Research

(continued from page 10)

It could certainly link overactivity of this female-biased immune network with autoimmune disease."

Dr. Gudjonsson's research strongly implicates VGLL3 as a pivotal orchestrator of sex-biased autoimmunity, and points to TNFSF4 and IL-7 as potential therapeutic targets.

Now his midcareer Sun Pharma Research Award is allowing him to take his preliminary data indicating a fundamental mechanism in autoimmunity and pursue this in depth in his SLE mouse model and in human SLE subjects. **"I'm extremely grateful for this award," Dr. Gudjonsson says. "This research will provide critical insights into autoantibody formation in SLE." He anticipates that these novel insights will potentially apply to other autoantibody-mediated autoimmune diseases as well, and ultimately identify a game-changing therapeutic target.**

The Foundation thanks Sun Pharma for their generous gift of $1 million to fund three midcareer awards for outstanding investigators driving progress in treating challenging inflammatory skin diseases.

Dr. Gudjonsson is Arthur C. Curtis Professor of Skin Molecular Immunology and Associate Professor of Dermatology, University of Michigan. He has received previous research support from the Dermatology Foundation: *2005 Research Fellowship* (Novel Xenotransplantation Model for Psoriasis); ***2008 Research Grant*** (Biological Effects of Genetic Variation in the IL-12B and IL-23R Genes in Psoriasis); ***2010-12 Physician Scientist CDA*** (The Influence of the Cytokine Network in Psoriasis on Clinical Phenotype and Treatment Response)

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