A DERMATOLOGY FOUNDATION PUBLICATION

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VOL. 37 NO. 1 SPRING 2018

DERMATOLOGY FOCUS™

DF Clinical Symposia: Proceedings 2018–Part I

ADVANCES IN DERMATOLOGY

The Dermatology Foundation presented its annual 3-day cutting-edge CME symposia series in January. Informal Breakfast Roundtables and evening Therapeutics Forums amplify the take-home value. Led by a keynote talk on Contact Dermatitis, 2018 symposia topics were: Inflammatory Disease Updates; Infectious Disease; CPC Session; Emerging Evidence and Emerging Diseases; Dermatologic Surgery and Minor Procedures; Comorbidities and Associations of Skin Diseases; Health Policy; Patient Interactions, Technologies, and Practice Satisfaction; and Cutaneous Oncology. Part II of the Proceedings will appear in the next issue.

KEYNOTE ADDRESS

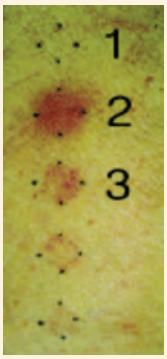
What's Trending in Contact Dermatitis

David E. Cohen, MD, MPH

Introduction. Acute and chronic eczematous contact dermatitis represent delayed-type hypersensitivity to small-molecular-weight chemicals typically encountered in routine activities of daily living and work. Dr. Cohen emphasized that this roster of allergens changes over time. Manufacturers sometimes alter ingredients in a known product; new products appear; preferences evolve. Dermatologists must stay informed and alert. Cohen discussed current trends in preservatives, fragrances, surfactants, and metals—among the most common families of allergens currently causing dermatitis—and their most significant sources of exposure. He presented helpful information and data on the worst offenders, and on patient risk factors for specific allergens.

Current common offenders. "Natural products are increasingly emerging as allergens. Watch out for them, as patients love them." Particularly notable is sheep sebum—the natural skin moisturizer *lanolin*—the 13th most common allergen in North America and extremely prominent in toiletries and personal care products, cosmetics, and lip balm among others. *Bee propolis* (which contains well-known sensitizers and often coreacts with colophony and fragrances) is common in toiletries and skin care products. *Shellac* (secreted by the female lac bug) is used to finish wood products and is in many eye cosmetics. *Fragrances* are "the most dynamic of all the allergen sets," with roughly 3,000 fragrance chemicals routinely used in the U.S. Yet despite dramatic changes in fragrance types preferred

Propylene Glycol: 2018 Allergen of the Year



- Reactions have been described as ICD, ACD, nonimmunologic contact urticaria, subjective or sensory irritation
- Distinction between ACD and ICD has been difficult to discern
- Elicitation thresholds of contact dermatitis have been concentration dependent
- Commonly present in personal care products
  - 8.8% of personal care products of patient presenting for contact allergy testing
  - ≥25% of facial wipes
  - 42.6% of general use personal wipes
- In 1,142 patch-tested children < age 18, 6.8% were reactive to PG
- 22nd most common allergen in North America with 2.18% of 4,859 patients
- Not on TRUE TEST
- Of 166 topical corticosteroids, 128 (3/4)—including all of the creams—contained at least one common allergen, often PG

Reprinted with permission from Y. Horiguchi et al. *Int J Dermatol.* 2005;44:681–3.

(Continued on page 2)

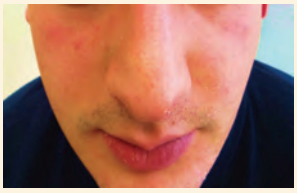
over the years, screening usually relies on the original Fragrance Mixes 1 and 2. They miss half of those who are reactive to essential oils, for example. Cohen discussed fragrances to look out for, including essential oils and other natural products.

Preservatives are increasing in frequency and allergenicity, as the number of products requiring them constantly increases. Cohen discussed *formaldehyde* (2015 Allergen of the Year and 9th most common allergen) and the long list of *formaldehyde releasers*, plus other preservative allergens that do not release formaldehyde (including *parabens* and the little-known but potent *iodopropynyl butylcarbamate*). Detecting the preservative *methylisothiazolinone* (2013 Allergen of the Year), used in personal care products, requires patch testing to higher concentration (0.2%). Cohen discussed reactivity to *paraphenylenediamine*, found in permanent (but not semipermanent) hair dyes. Cohen also provided useful guidance on *metals* (nickel, cobalt, chromium) and surfactants, which enable soaps to foam and facilitate application in thousands of other personal care products.

Keep in mind. *Skin cleansers* frequently contain a menu of offenders. Approximately 50 allergens have been identified as prevalent ingredients, the leaders being formaldehyde-releasing preservatives, surfactants and other foaming agents, and fragrances. Children with atopic dermatitis (AD) are particularly reactive, especially to the surfactant *cocamidopropyl betaine*, to lanolin, and to hydrocortisone.

Surfactants

Amphoteric surfactants are found in thousands of personal care products, eg, shampoos, bath products, eye and facial cleansers, cosmetics, and sunscreens



- **Cocamidopropyl betaine:** 2004 AOY
  - 2016: 1.6% (36th)
  - 2003–2004: 1.8% (32nd)
  - 2001–2002: 2.8% (25th)
- **Oleamidopropyl betaine:** 20th allergen in the NACDG (3.5% of tested individuals)
- **Alkyl glucosides (nonionic surfactants)—2017 AOY**
  - have emulsifying, cleansing, and foaming properties
  - are plant-derived—mainly from palm or coconut oil—and completely biodegradable
  - include decyl, lauryl, cetearyl and coco glucoside (closely related to other surfactants)
  - are widely used in shampoos, liquid skin cleansers, and shower gels; also in leave-on products that include moisturizers, deodorants, and sunscreens

A Goldenberg et al. *Dermatitis.* 2016;27:293–302; JF Fowler. *Dermatitis.* 2004;15:3–4.

Final Comments on Contact Dermatitis

- Surfactants are trending now
- Preservatives continue to remain problematic and are responsible for one of the greatest epidemics of contact dermatitis
- Fragrance allergy is constantly changing and evolving, requiring vigilant observation of ingredients trends
- Natural products can be clandestine sources of allergens

The solvent, emollient, and emulsifier *propylene glycol*—the 2018 Allergen of the Year—is double-edged. It is very important for solubilizing topically applied medications (eg, in a majority of topical steroid creams we prescribe), and similarly in cosmetics, and is a preservative in foods. But it is also a cutaneous irritant and allergen. Cohen provided patch testing guidance.

MINI-SYMPOSIUM: INLAMMATORY DISEASE UPDATES

2018 Updates on Hormonal Treatments for Acne

Kanade Shinkai, MD, PhD

Introduction. Dr. Shinkai described the "vexing patient we all know well"—the adult female with persistent or new-onset adult acne who has failed multiple rounds of standard treatments—and discussed hormonal options, noting that the latest data on oral contraceptive pills (OCPs) support efficacy and reduce concerns. She provided guidance, and also characterized the benefits and risks of adding spironolactone if OCP treatment fails.

OCPs. Shinkai explained the 3-fold action of ethinyl estradiol, noting that the current generation of pills has less than 10% of the estrogen/progesterone content of early OCPs. More-recent progesterone formulations have very low androgenic activity, and the current generation is antiandrogenic. Because estrogen is the component providing the most benefit, current low concentrations make it a disservice to prescribe a low-dose version. Shinkai commented that FDA approval of 3 products for acne is not based on superiority data, and explained her preference for the drospirenone-containing products with higher estrogen content. Current data describe a very low DVT risk that is constant across all formulations. It is markedly lower than during pregnancy/postpartum, and is half that of arterial thrombotic risk. Shinkai noted the risk factors associated with each formulation, and advised when screening is needed. New data show minimally increased risk for breast cancer (13 patients/100,000 users) that increases with duration of use and persists for 5 years after stopping. She discussed counseling patients regarding dosing and potential side effects of OCPs. Shinkai also discussed adding spironolactone for the patient who does not respond to OCPs, and the pros and cons of spironolactone monotherapy. Although the drug is not FDA-approved for this purpose, data suggest some benefit to 50%–80% of these patients, and characterize spironolactone as a very safe therapeutic option. Data do not support an association with cancer. Shinkai discussed side effects and provided monitoring recommendations in very select cases.

Conclusion. A recent study comparing antibiotic and hormonal therapy found antibiotics ahead at 3 months, but equivalent by 6 months. This justifies Shinkai's conviction that "in this era of antibiotic stewardship, I feel strongly that we should think about hormonal therapy when possible for our adult female patients with acne."

The Bottom Line: OCPs are Still Safe

- Risk of VTE with OCP is still very low (7–10/10,000) and equal across OCP formulations (including drospirenone)
  - Much higher in pregnancy (29/10,000) and postpartum (300/10,000, ie, 60x)
- Highest risk in carriers of genetic hypercoagulability
- Screen/counsel for other risk factors:
  - Family history, blood type (non-O type)
  - Obesity, age, malignancy, trauma, and immobilization

C. Waddington et al. *Open J OB/GYN.* 2017;7:16–30; MV Dragoman. *Best Practice Res Clin Ob Gyn.* 2014;28:825–34.

Spironolactone: Safe, Has Side Effects

(Not FDA approved)

- 8-year safety study in acne: no serious complications
- Main side effects: menstrual irregularities (22%)
  breast tenderness (17%)
- Hyperkalemia (minimal rise in K+ in 13%, no sequelae)
- Mean blood pressure reduction: 5mm Hg SBP, 2.6mm Hg DBP
- TERATOGEN: Category C/D
- Black box warning: benign tumors in animal studies
- No increased cancer risk in 2 large female cohort studies

RJ Biggar et al. *Cancer Epidemiol.* 2013;37:870–5; IS Mackenzie et al. *Br J Clin Pharmacol.* 2017;83:653–63; IS Mackenzie et al. *BMJ.* 2012;345:e4447.

Systemic Therapies in Pediatric Dermatology

Jonathan A. Dyer, MD

Introduction. Other than for propranolol, which revolutionized the treatment of infantile hemangiomas in 2009 and thus has almost a decade of research on long-term effects, there is a serious paucity of data on current systemic therapies used in the pediatric population. Dr. Dyer discussed what little is known for several important drugs that treat inflammatory skin diseases.

Pediatric use of systemic therapies. ***Isotretinoin:*** The changes that Dr. Dyer made in the way he monitors patients on isotretinoin therapy have been validated by two recent studies. Most laboratory abnormalities—primarily elevated lipids—occur within the first 6–8 weeks, and often in patients whose lipids are already high. "With normal initial labs, I get labs only at baseline, then at 2 months." Wound healing is impaired only with "very aggressive dermabrasion." ***Biologic therapies:*** For pediatric psoriasis, Dr. Amy Paller's recent study of *etanercept* use for at least 5 years found no malignancies or deaths, and only 1 serious infectious event. The FDA approved it for psoriasis for ages 4–17. Good data on *ustekinumab* for adolescent psoriasis led to approval for ages 12 and up. *Adalimumab* has European approval for children >age 4, and approval is expected here. Pediatric psoriasis patients on biologics show an increased rate of nonmelanoma skin cancer (primarily SCC), underlining the need for sun protection counseling. With no approved targeted systemic treatments yet for pediatric atopic dermatitis (AD), Dyer relies on methotrexate and mycophenolate mofetil and looks forward to approval for dupilumab. He outlined research implicating a compromised neonatal skin microbiome in the development of AD. Approaches to normalizing it—in progress—may eventually minimize the need for pediatric systemic drugs. ***Propranolol:*** Although it is not directly anti-inflammatory, Dyer included it because of long-term data confirming that children treated as infants a decade ago show no long-term effects.

Conclusion. "We need to encourage the companies making these amazing new drugs to help us get data on their use in children."

Biologics in Pediatric Dermatology

- Etanercept FDA approved for pediatric psoriasis in 11/16
  - 4–17 yo
  - Allows tapering other immunosuppressants (Mtx, CsA)
  - Used for recalcitrant psoriasis at 22 mos
- Ustekinumab in adolescents 12–17 yo
- Adalimumab approved in Europe in 2015 for >4 yo

DW Kress. *J Am Acad Dermatol.* 2006;54:S126–8; G. Fabrizi et al. *Eur J Dermatol.* 2007;17:245; I. Landells et al. *J Am Acad Dermatol.* 2015;73:594–603; D. Kivelevitch et al. *Lancet.* 2017;390:5–6.

DERMATOLOGY FOCUS
A PUBLICATION OF THE DERMATOLOGY FOUNDATION
Sponsored by
Ortho Dermatologics
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Published for the Dermatology Foundation by
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Sheila Sperber Haas, PhD—Managing Editor, Writer

This issue of *Dermatology Focus* is distributed without charge through an educational grant from Ortho Dermatologics.

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MINI-SYMPOSIUM: DERMATOLOGIC SURGERY AND MINOR PROCEDURES

Sentinel Lymph Node Biopsy: Head and Neck

Steven M. Sperry, MD

Background. Dr. Sperry, a head and neck surgeon, noted that lymphadenectomy was first advocated by a British surgeon in the 1890s to attempt preventing distant metastases in melanoma. Prospective randomized trials in the 1970s–'80s highlighted the critical need to accurately identify patients likely to benefit from lymphadenectomy, ie, those with nodal metastasis, which stimulated SLNB development. The first SLNB data were published in 1993 for melanoma patients followed from the 1980s. It replaced primary reliance on lymphadenectomy to gain an accurate staging of regional disease in melanoma, and identifying/assessing the sentinel lymph node in melanoma proved to be a more important prognostic factor than Breslow thickness or ulceration.

SLNB. Sperry summarized the pros and cons. Its primary value is in sparing node-negative melanoma patients from a lymphadenectomy that holds no benefit for them. Identifying occult nodal metastases is a very important prognostic factor that may help guide treatment to improve locoregional control. A negative in the head and neck is that "we deal with the face, including the facial nerves running through the parotid gland." Thus the node-negative patient risks significant disability if the procedure affects smile or eye closure.

(Continued on page 5)

DF Annual Meeting: 2017 Sees Continued Progress

On February 17, Dermatology Foundation President Dr. Kim B. Yancey presided at the annual membership meeting in San Diego. He summarized the past year's accomplishments and challenges and presented the Honorary Awards.

Community Commitment Advances Patient Care

"I've been impressed by the generosity and commitment of so many members of our community," Dr. Yancey said. "Individual dermatologists contributed nearly $2.6 million in 2017 to further the dermatology research that advances patient care." The DF's ability to support advancements in patient care is directly related to our annual fundraising results. In 2017, physician membership contributions accounted for 60% of the DF's total support.

The *Annenberg Circle* welcomed 20 new members, who have raised their commitment to the Dermatology Foundation to $25,000. The many new *AC Sustaining* commitments included those giving an additional annual $5,000 a year, and current *Sustaining* members who have pledged this for additional multiple years. The DF also welcomed 128 new *Leaders Society* members, who contribute $1,500 annually. The 32 *Young Leaders* in this group made this commitment within five years of completing their residency. "These individuals are the future of our specialty," Dr. Yancey emphasized.

Industry and Societies Provide Additional Support

Corporate and society fundraising totalled $1.77 million for 2017. The corporations recognized in the Corporate Honor Society (see page 13) each contributed $50,000 or more last year. Dr. Yancey thanked "the many national, regional, and local societies that have provided support to the Research Awards Program," with special appreciation to the American Academy of Dermatology and Women's Dermatologic Society for their individual contributions of $55,000.

Two New Awards Funded

Dr. Yancey was extremely pleased to announce two new uniquely focused research awards. A $1 million gift from Charles and Daneen Stiefel funds the *Stiefel Scholar Award for Skin Cancer Research,* providing $100,000 for each of three years to a mid-career investigator whose research holds substantial promise for improving patient care. The *Diversity Research Supplement Award* "will help to enhance diversity in dermatology," Dr. Yancey explained. These $5,000 awards go to recent Career Development Award recipients to support the participation of an under-represented minority medical student in an ongoing project.

Today's Members Enable Tomorrow's Clinical Innovations

Membership in the Dermatology Foundation is essential for continuing to advance patient care. "We have a base of talented researchers whose work will transform our specialty—*if* we can support them," Dr. Yancey said. **"Tomorrow's clinical innovations are within reach—but only if we all invest in our foundation of research today."** ■

Honorary Award Recipients

Finnerud Award: Kim B. Yancey, MD, **Paul I. Schneiderman, MD,** presenter Kenneth E. Greer, MD

Lifetime Educator: Kim B. Yancey, MD, **Ilona J. Frieden, MD,** presenter Kelly M. Cordoro, MD

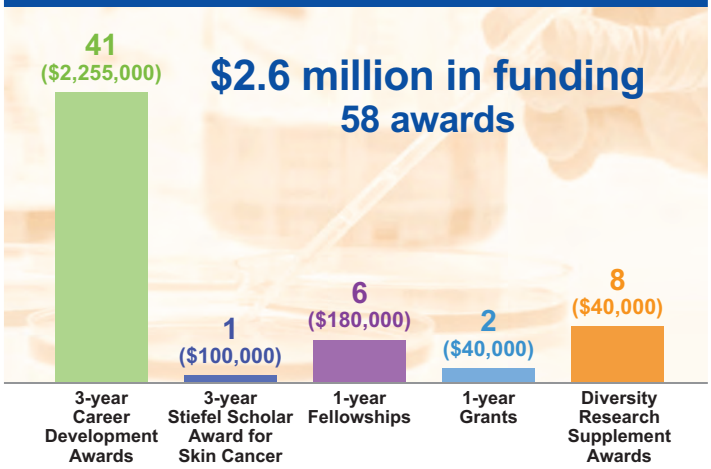
Practitioner of the Year: Kim B. Yancey, MD, **Lisa A. Garner, MD,** presenter Erin E. Boh, MD, PhD

Discovery Award: **Luis A. Diaz, MD, John R. Stanley, MD**

$2.6 Million to Support Research and Innovation

"I am very pleased to announce that $2.6 million in funding was approved for 58 research awards," Dr. Stuart R. Lessin, DF Vice President, told the assembled membership. This includes 41 3-year Career Development Awards, 1 3-year Stiefel Scholar Award for Skin Cancer Research, 6 1-year Fellowships, and 2 1-year Grants. It also includes the 8 newly designated Diversity Research Supplement Awards that total $40,000. "This is a small sum for a worthy goal—furthering diversity in our field—and we look forward to expanding this program's reach in the future," Dr. Lessin explained. He congratulated award recipients. "This is a significant milestone for you, and we all look forward to watching the progress you bring to the specialty."

2018 Research Awards



2018 Leadership Gala

The Annual Leadership Gala is always eagerly anticipated by members of the *Leaders Society*, Annenberg Circle, AC *Sustaining*, and Fitzpatrick Legacy Fund. The DF provides this special thank-you for their strong, ongoing commitment to advancing the knowledge that benefits patient care. This year's Gala, and the Young Leaders Pre-Gala, were held the evening of February 18 at San Diego's colorful, creative The New Children's Museum.

The DF is grateful to the co-sponsors of this memorable event: Amgen Inc.; Lilly USA, LLC; and Ortho Dermatologics (a division of Valeant Pharmaceuticals North America LLC).

Prognostic false positives lead to difficult treatments even though the patient's immune system could have controlled the disease. And the most current trial data do not show overall survival benefit from completion lymphadenectomy after identifying a positive node.

The Future is Interesting, and Unclear…

Discussion in multidisciplinary groups is critical

- Role for completion lymphadenectomy unclear
- Role of adjuvant treatments for higher-risk and surgically treated metastatic melanoma continues to be defined
  - *Targeted inhibitors:* vemurafenib (BRAF), dabrafenib (BRAF), trametinib (MEK)
  - *Checkpoint inhibitors:* nivolumab, pembrolizumab, ipilimumab
  - *Other immunomodulators:* T-VEC, GM-CSF, interferon alpha

In patients with stage IIIA disease (after positive SLNB), the risk of disease recurrence is less than 20% and thus observation should be an option

H&N Melanoma

- 10%–18% of melanomas occur in H&N
- Survival from melanoma in the H&N is worse than for the trunk or extremities
- A +SLN is less common in the H&N than trunk/extremity
- There is a higher false-negative rate for SLNB in the H&N
- H&N melanoma patients with a negative SLN have worse survival than trunk/extremity melanoma patients with negative SLN
- There is a smaller absolute survival difference between +SLN and –SLN H&N melanoma patients—meaning a +SLN has less prognostic value

These facts mean the considerations for performing SLNB for H&N melanoma are different than for other body sites

AM Lachiewicz et al. *Arch Dermatol.* 2008;144:515–21; N Fadaki et al. *Ann Surg Oncol.* 2013;20:3089–97; P. Al Ghazal et al. *Melanoma Res.* 2014;24:158–64; KM McMasters et al. *J Surg Oncol.* 2004;86:212–23; BE Saltman et al. *Head Neck.* 2010;32:1686–92.

Conclusions. Sperry discussed his recommendations for SLNB, relying on it as a staging tool for gaining information but not for improving survival. He emphasized the factors that he brings into his discussions—never easy—with patients. He also discussed the particular challenges of head and neck melanoma, and concluded with a consideration of SLNB for other cutaneous malignancies of the head and neck. "Current evidence is insufficient to know if we can benefit patients by performing this procedure."

Pigmented Lesions: Controversies in Biopsy and Excision of the Primary Lesion

Suzanne M. Olbricht, MD

Introduction. Dr. Olbricht, a dermatologist specializing in Mohs micrographic surgery, drew from her extensive experience and relevant data to provide her particular approach and rationale for handling various aspects of caring for pigmented lesions in the context of "the primary lesion and excision."

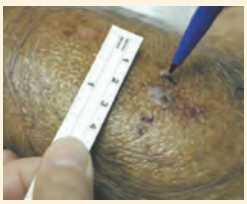
My Practice

- **Atypia present at margin**
  - Mild to moderate atypia* present at margin after entire lesion removed clinically → no re-excision
  - Mild atypia* present at margin with lesion still present → lean to observation
  - Moderate atypia* present at margin with lesion still present → lean to re-excision
- Severe atypia* present at margin → re-excision
- **Malignant melanoma *in situ***
  - fusiform excision, mark 5 mm, take extra depending on ease of closure. Deep margin dictated by needs of closure
- **Lentigo maligna**
  - face: debulk, staged excision with margin control, permanent pathology exam with/without special stains
  - below the neck: fusiform excision, mark 1 cm margins, take if possible

*according to my favorite pathologist.

The primary lesion and excision. *Best biopsy technique:* A shave or scoop biopsy "can give us a full representation of the histologic picture of *in situ* or invasive melanoma, or a dysplastic nevus." The data show a shave biopsy to be accurate in 97% of cases, with a punch biopsy significantly lower. Olbricht shared her favorite technique for a shave biopsy for an atypical pigmented lesion. *If, after an excisional biopsy, the pathology report says moderately atypical nevus present in the margin:* With mild–moderate atypia and the entire clinically apparent lesion removed, or mild atypia with some lesion remaining, she chooses observation. For moderate atypia with some lesion remaining, she leans to re-excision for complete removal. Severe atypia automatically calls for re-excision. *Margins:* Olbricht always removes a 5 mm margin with a clinically atypical nevus. Lateral margins for melanoma are 5 mm, 1 cm, and 3 cm per the NCCN guidelines, although recent evidence indicates that smaller margins yield the same cure rate and that there is no need for fascial resection. For lentigo maligna she plans a fusiform excision, doing a staged Mohs-type excision if above the neck, and marking 1 cm margins if below the neck. *Orientation of closure:* Olbricht noted the importance of not impairing lymphatic drainage and of using "nice long lines." *BAP1 germline mutations:* In light of the extremely high risk for melanoma and for cancers in other organs, take a full family history, look at close relatives, do a full skin exam twice yearly, and refer patients to other relevant cancer specialists for screening and regular visits.

Planning the Ellipse



- Orientation of closure:
  1. Major skin folds
  2. Minimum skin tension lines
  3. Wrinkle lines
  4. Influence of underlying muscle
  5. Direction of hair growth
  6. Direction of lymphatic drainage
- If orientation of closure on the limbs is circumferential:
  1. Possible dependent edema
  2. Tension is greater
  3. Dog ears require chasing
  4. Re-excision more difficult
  5. Theoretical disadvantage to lymph drainage of malignant cells

How Concomitant Medications Impact Surgical Outcomes

Marta J. Van Beek, MD, MPH

Background. Most patients referred to Dr. Van Beek with high-risk cutaneous squamous cell carcinomas (SCCs) are on medications that have confounding implications for surgery. She discussed the drugs, any existing data, her perspective, and how she handles these patients.

Medications. *Anticoagulants.* Many people take a conventional antithrombotic agent or novel oral anticoagulant, raising concern about bleeding after surgery and impaired healing. Reassuringly, the literature demonstrates that discontinuing this medication for surgery does not statistically decrease bleeding risk, and recommends continuing it. "The risks of managing bleeding during cutaneous surgery are far outweighed by the risk of an embolic event, which would be catastrophic," Van Beek said. Hemostasis and the clotting cascade trigger the first stage of healing. Because anticoagulants disrupt certain coagulation pathways, healing is slower, but not disrupted because redundant pathways upregulate. "I insist that the patient take it easy after surgery—the risk of bleeding is highest in the first 24 hours—and share responsibility for wound care." *Ibrutinib.* This tyrosine kinase inhibitor, which blocks B-cell proliferation, is commonly prescribed to the many CLL (chronic lymphocytic leukemia) patients Van Beek sees. Ibrutinib is associated with bleeding concerns (although risk varies widely due to CLL's heterogeneity). CLL's marked risk of synchronous malignancies includes SCCs, which have a higher recurrence rate than in patients without CLL. Do we continue the drug because it possibly

Anticoagulants in Cutaneous Surgery

Aspirin	Dabigatran (Pradaxa®)
Warfarin (Coumadin®)	Apixaban (Eliquis®)
Clopidogrel (Plavix®)	Rivaroxaban (Xarelto®)

- Literature supports continuing all anticoagulants
  - Bleeding risks are slightly higher
  - Wound healing is impeded (disruption of the clotting cascade /1st phase of wound healing)
- Risks of thromboembolic complications far outweigh the risks of bleeding or impaired healing

C Antia et al. *J Am Acad Dermatol.* 2017;77:967–8.

decreases SCC recurrence via treating the CLL, or discontinue to prevent a serious bleeding event during surgery? Despite the literature's concern with complications, "my practice is to continue ibrutinib. I have a lengthy discussion with the patient and hematologist about the risks of bleeding and extensive bruising." *Ruxolitinib.* This JAK inhibitor (approved for recalcitrant polycythemia vera, myelofibrosis, and other types of myeloproliferative neoplasms) is associated with increased risk for highly aggressive, recurrent SCCs specifically in the myelofibrosis population, but stopping the drug impairs treatment. "Ruxolitinib requires extremely close patient follow-up, with the excision repair modified to permit inspection for tumor recurrence."

Pediatric Procedural Pearls

Jonathan A. Dyer, MD

Introduction. Dr. Dyer shared tips and tricks that he has fine-tuned over his years in practice, beginning with his overall perspective. Although children do not scar as adults do, scarring is inevitable and the goal is to minimize it. Kids are challenging to work on, so finish as quickly as possible. Dyer noted the most likely post-op problems with children and the pre-op planning that helps to avoid or minimize them. "Key is preparing everyone, parents too, on what to expect from the surgery and post-op period."

Pearls. Opt for the simplest procedure and always determine how to minimize the amount of normal skin you remove. Because pediatric skin is so elastic, smaller incisions can often be utilized to create a much smaller scar. Consider staged excisions for very large lesions because removing the lesion in pieces avoids creating a large scar. Dyer discussed the principles for staged excision, cautioning not to wait too long between stages. He discussed the advantages of purse-string closures with children, their role as an adjunct to secondary intention wounds, and the value of staged purse-string closures in an area with sufficient skin stretch. The key to minimizing scar spreading is minimizing tension at the wound edges. Dyer's techniques include multilayered closures that begin with a few deep stitches. Running subcuticular stitches help to prevent track marks. Dyer noted the closures he uses for different anatomic sites. "And the single most important pearl to take home is that I do not close punch biopsies on children." He explained why 1–2 stitches creates an ugly scar. He utilizes gel foam and applies a pressure dressing for rapid, easy healing and the best cosmetic result.

Conclusion. Education of everyone involved is critical. Dyer welcomes questions: DyerJA@health.missouri.edu.

Pediatric Scarring

- Inevitable because children are:
  - Young: thus aggressive healing and inflammatory responses
  - Healthy: with highly elastic dermis and connective tissue
  - Active: they will stress any wound and will give less attention to it
- Higher incidence of track marks
- Higher incidence of scar spreading
- Increased spitting of deep stitches
- Increased risk of dehiscence
- Preventive approach/planning to get the best scar possible
  - **Education**
  - Single or staged
  - Orientation of excision (skin tension lines)
  - Sedated or awake
  - Prepare for post-op!!!
  - **Education**

MINI-SYMPOSIUM: COMORBIDITIES AND ASSOCIATIONS OF SKIN DISEASES

What Every Dermatologist Should Know About Polycystic Ovary Syndrome (PCOS)

Kanade Shinkai, MD, PhD

Introduction. 25% of women diagnosed with PCOS present first to a dermatologist for a skin or hair complaint. Dr. Shinkai works in a multidisciplinary PCOS clinic at UCSF, and combined this clinical experience with published data to discuss the patient that dermatologists commonly encounter. She began with the characteristic skin signs that are reliable disease markers (hirsutism and acanthosis

Diagnostic Workup for PCOS

When? 4 weeks off OCP

Step 1: Endocrine

- Testosterone (free, total)
- 17-hydroxyprogesterone
- trans-vaginal ultrasound
- DHEA-S
- TSH
- prolactin
- androstenedione
- LH: FSH (>3 in 95% PCOS)

Step 2: Metabolic

- BMI
- Blood pressure
- Fasting lipid panel
- Fasting insulin, glucose
- 2 hour glucose challenge
- HgbA1c
- ALT

(Continued on page 10)

DF Honors Excellence in Dermatology

The Dermatology Foundation pays annual tribute to dermatologists whose exemplary capabilities and dedication have helped to make the specialty what it is today. Presentation of the 2017 awards was a highlight of the DF Annual Meeting on Saturday, February 17, in San Diego, CA. The leaders and role models honored by their peers are:

Practitioner of the Year—Lisa A. Garner, MD

Discovery Award—Luis A. Diaz, MD, and John R. Stanley, MD

Clark W. Finnerud Award—Paul I. Schneiderman, MD

Lifetime Career Educator Award—Ilona J. Frieden, MD

(Drs. Frieden and Schneiderman were highlighted in the Winter 2017/18 issue.)

2017 Practitioner of the Year: Lisa A. Garner, MD

This annual award recognizes dermatologists for exemplary service as a private practitioner combined with significant contributions to the specialty through leadership and teaching.

"I'm *so* thankful that I had the opportunity to become a dermatologist," Dr. Garner says, "because I enjoy it so much!" Her passionate devotion to the specialty, and to her patients, has helped shape the more than 30 years she has maintained her general medical dermatology practice with special expertise in contact dermatitis. Dr. Garner chose to go into private practice in Garland, Texas, the Dallas-Ft Worth town where she grew up. After completing her residency in 1987, she realized that "there was a real need" with only a single dermatologist in her suburb of 200,000 people.

Dr. Garner began a dermatology elective during medical school at Baylor College of Medicine with no expectations, and finished having found her specialty. The skin fascinated her, the combination of procedural and nonprocedural responsibilities was highly appealing, and the dermatologists she met really enjoyed what they were doing. Dr. Garner's interest in contact dermatitis was sparked when she was preparing for her Boards. She now regularly sees challenging patients from the Dallas area as well as the surrounding states.

Dr. Garner believes strongly in giving back to the specialty she loves. She teaches residents in the pediatric dermatology clinic at the University of Texas Southwestern Medical Center in Dallas, where she is Clinical Professor of dermatology. A colleague who was a resident when she first encountered Dr. Garner says that "Lisa always demonstrates empathy, humility, professionalism, confidence, knowledge, respect for all patients, and passion—and she helps her residents learn to do the same."

In addition, Dr. Garner has always found time to contribute significantly to professional organizations, even as a single parent working full-time with three children to raise. She began as president of the Dallas Dermatological Society in 1994, then held several leadership positions—including the presidency—in the Texas Dermatological Society over the next decade. She has more recently been president of the Women's Dermatologic Society and vice-president of the American Academy of Dermatology, and has served on the Boards of Directors of all of these organizations.

Dr. Garner is "devoted" to the specialty's need for research because it is "required for better treatments and patient outcomes." She makes it clear that while she is not an investigator, she believes it is essential to support those who are beginning their research careers. To help accomplish this, she has been a member of the Dermatology Foundation for 25 years and a tireless volunteer in a variety of leadership roles (including Board membership) for nearly as many.

Caring for her patients remains the heart and soul of Dr. Garner's work. "I always want to be the best dermatologist I can be—I listen and look very carefully. I am dedicated to letting my particularly challenging patients know that I will not give up on them." A colleague sums it up: "Lisa Garner is indeed the Practitioner of the Year—and more!" ■

DF Honors Excellence in Dermatology

2017 Discovery Award:
Luis A. Diaz, MD, and John R. Stanley, MD

This award recognizes significant research accomplishments that have impacted the specialty and its future by: (1) greatly advancing the understanding of cutaneous biology, or (2) identifying a previously unrecognized disease, or (3) developing a revolutionary new therapy.

DF president Dr. Kim Yancey presented the distinguished Discovery Award at the annual meeting in San Diego. "Dr. Luis Diaz and Dr. John Stanley each made a career-long commitment to elucidate the pathophysiology of autoimmune blistering diseases, making discoveries that taught us not only about those diseases, but also a great deal about the biology of skin. They set the stage for interventions and advancements that will carry the specialty forward for years to come," he emphasized. "They were also competitors—fighting for the same discoveries. Their vigorous interaction at scientific meetings energized a wide number of investigators throughout the world to pursue investigative dermatology. Their pursuit of excellence and commitment to discovery over many years earned our deep admiration and respect, and I know that they hold each other in that same regard."

Dr. Diaz and Dr. Stanley knew in medical school that they wanted to combine research and clinical responsibilities. In both cases, an unexpected laboratory encounter with autoimmune blistering diseases ignited their passions and shaped their professional lives.

Dr. Diaz, with a strong interest in autoimmune disease, came to SUNY-Buffalo in 1971 from his native Peru to do his dermatology residency in a department with research expertise in immunology and autoimmune disease. One of his research mentors had recently discovered the autoantibodies in pemphigus and pemphigoid, and lit his own fire "to understand the pathogenesis of these diseases," Dr. Diaz recalls.

After Dr. Stanley had completed his residency at NYU in 1978, he went to the NIH's Dermatology Branch as part of the Visiting Scientist program, hoping to work in cutaneous immunology. The only opening was in a lab exploring the recently discovered basement membrane molecule. Dr. Stanley was asked to determine if antibodies from bullous pemphigoid patients prevented keratinocytes from binding with these molecules. Before long, he realized that the autoimmune blistering diseases were precisely what he wanted to devote himself to.

Diaz and Stanley started their careers at a time when autoimmune disease in general was a mystery and the tools of molecular exploration did not exist. As molecular biology evolved, the seminal contributions of these two investigative dermatologists dovetailed over the years, creating the roadmap in blistering diseases, expanding the understanding of autoimmunity, and opening the way to greatly improved patient care.

Research progress began with the basics. During Dr. Stanley's early tenure at the NIH, he located pemphigoid and pemphigus antigens in cultured human epidermal cells and then published his groundbreaking identification of an autoantigen in bullous pemphigoid—the first of the blistering disease autoantigens to be identified. He went on to identify the autoantigens in pemphigus vulgaris and pemphigus foliaceus. Dr. Diaz and his team began the 10-year period over which they gradually developed the animal models of pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid—essential to progress in exploring the behavior of these diseases.

Dr. Diaz and his team identified and cloned the second bullous pemphgoid autoantigen, BP180, and demonstrated its pathogenicity. Dr. Stanley cloned

(Continued on page 10)

the antigens he had identified and molecularly created antibodies to them, providing tools for research and for ELISA diagnostics. He gradually worked out the molecular pathophysiology of these diseases. Their combined progress eventually led to the use of rituximab, a targeted therapy that has transformed patients' lives. Dr. Diaz has also made substantial progress in unraveling fogo selvagem, a puzzling form of pemphigus foliaceus endemic to an area in Brazil.

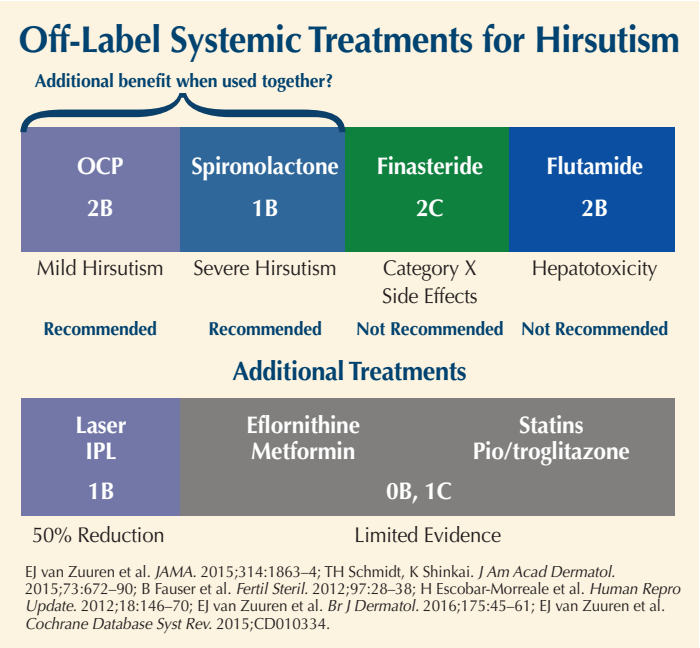
Dr. Diaz became chair of dermatology first at the Medical College of Wisconsin, then at the University of North Carolina, Chapel Hill. Recently partially retired, he remains on the faculty. He is completing several research projects, and continues to probe fogo selvagem. "If I find the cause, I will feel very completed," he says. Dr. Stanley was named chair of dermatology at the University of Pennsylvania. Now retired, he holds a faculty position there and is also a visiting professor at Keio University in Japan. Dr. Stanley is currently analyzing and writing up his last several investigations. Both scientists are deeply appreciative of those who collaborated with them over the years to help hone ideas and carry out the work.

The evolving counterpoint between these two scientists has played a significant role in what they have accomplished. Dr. Diaz reflects that "my life and the life of John have, for some reasons of destiny, become intertwined. John is a great scientist and friend." He recalls—with humor—being asked by a journal to review Dr. Stanley's article on his discovery of the first bullous pemphigoid antigen. "I was amazed at the quality of his work. But it was painful—I was working on the same thing as he was!" Dr. Stanley shares that their early competition had a positive effect. "It made me work harder and look at things more critically. Luis is a wonderful and amazing person," he adds—"and I'm really happy that we *both* received this award." ■

nigricans), outlined the necessary diagnostic evaluation when PCOS is suspected, and concluded with effective treatments (off-label) for the hirsutism.

PCOS basics. It is important to recognize PCOS because, in addition to the substantial impact on quality of life, these women risk significant extracutaneous issues: endocrine, cardiovascular, reproductive, oncologic, and sleep apnea. A cross-sectional study of all of the women referred to Shinkai's clinic and diagnosed with PCOS showed that 92% had at least 1 skin finding, with 2 the average. Most women had acne and/or hirsutism and/or acanthosis nigricans. Although acne on face and trunk was an unreliable marker because there were no systemic associations, hirsutism—commonly found on the trunk and determined with a visual assessment instrument—"proved to be a very specific sign in PCOS." It has very important systemic associations with obesity, dyslipidemia, insulin resistance, and elevations in androgens (especially free testosterone). The rate of hirsutism increases with increasing skin pigment. Shinkai discussed emerging aspects of acanthosis nigricans. (Virilization is not an issue in PCOS, but indicates an androgen-secreting tumor.) Shinkai provided her approach to evaluation, cautioning that if the endocrine assessment cannot be done before the patient has begun an OCP, it must wait until the OCP has been discontinued for 4 weeks. She noted where she differs with the American Society for Reproductive Medicine's recommendations. Shinkai discussed off-label treatments—covering OCPs and systemic treatments for the hirsutism—noting it takes at least 6 months to see benefit.

Conclusion. PCOS is the most common cause of hyperandrogenism, with hirsutism and acanthosis nigricans the best signs. The diagnostic workup should be done before beginning treatment.



EJ van Zuuren et al. *JAMA*. 2015;314:1863–4; TH Schmidt, K Shinkai. *J Am Acad Dermatol*. 2015;73:672–90; B Fauser et al. *Fertil Steril*. 2012;97:28–38; H Escobar-Morreale et al. *Human Repro Update*. 2012;18:146–70; EJ van Zuuren et al. *Br J Dermatol*. 2016;175:45–61; EJ van Zuuren et al. *Cochrane Database Syst Rev*. 2015;CD010334.

Tailoring Psoriasis Therapy to Comorbidities

Kristina Callis Duffin, MD

Introduction. Dr. Duffin reviewed the careful multistep approach to selecting a treatment for the psoriasis patient with moderate-to-severe skin disease. This includes drugs avoided because of a given comorbidity (eg, no methotrexate with coexisting liver disease). And conversely, some therapies can be selected because they are effective for both psoriasis and a comorbid condition. This is widely done for patients with psoriasis and psoriatic arthritis. Duffin devoted the bulk of her talk to the emerging data for several somewhat less common comorbidities.

Two birds with one therapeutic stone. *Inflammatory bowel disease (Crohn's disease, ulcerative colitis):* Patients paradoxically can develop a new onset or flare of psoriasis while on anti-TNF agents for IBD. Ustekinumab (anti-IL-12/anti-IL-23) is an on-label alternative for both diseases. Dr. Duffin recommends working with the patient's

(Continued on page 13)

Ortho | Dermatologics

ALL ABOARD ONEXTON GEL

Efficacy and tolerability matter when it comes to treating acne. In the pivotal trial, ONEXTON GEL was shown to treat both inflammatory and noninflammatory acne, and no patients discontinued due to an adverse event.[1,2]

INSTANT SAVINGS FOR ELIGIBLE PATIENTS AT ORTHORXACCESS.COM
TERMS AND CONDITIONS APPLY

INDICATION

ONEXTON (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75% is indicated for the topical treatment of acne vulgaris in patients 12 years of age or older.

IMPORTANT SAFETY INFORMATION

- ONEXTON Gel is contraindicated in patients with a known hypersensitivity to clindamycin, benzoyl peroxide, any component of the formulation, or lincomycin.
- ONEXTON Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.
- Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. ONEXTON Gel should be discontinued if significant diarrhea occurs.
- Orally and parenterally administered clindamycin has been associated with severe colitis, which may result in death.
- Anaphylaxis, as well as other allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin/benzoyl peroxide. If a patient develops symptoms of an allergic reaction such as swelling and shortness of breath, they should be instructed to discontinue use and contact a physician immediately.
- The most common local adverse reactions experienced by patients in clinical trials were mild and moderate erythema, scaling, itching, burning and stinging.
- ONEXTON Gel should not be used in combination with erythromycin-containing products because of its clindamycin component.
- ONEXTON Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A decision should be made whether to use ONEXTON Gel while nursing, taking into account the importance of the drug to the mother.
- Patients should be advised to avoid contact with the eyes or mucous membranes.
- Patients should minimize exposure to natural and avoid artificial sunlight (tanning beds or UVA/B treatment) while using ONEXTON Gel. To minimize exposure to sunlight, protective clothing should be worn and a sunscreen with SPF 15 rating or higher should be used.

To report SUSPECTED ADVERSE REACTIONS, contact Ortho Dermatologics at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit www.fda.gov/medwatch.

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

References: 1. ONEXTON [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC. **2.** Pariser DM, Rich P, Cook-Bolden FE, Korotzer A. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 3.75% for the once-daily treatment of moderate to severe acne vulgaris. *J Drugs Dermatol*. 2014;13(9):1083-1089.

LEARN MORE AT ONEXTON.COM

ONEXTON®
(clindamycin phosphate and benzoyl peroxide)
Gel, 1.2%/3.75%

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ONEXTON Gel safely and effectively. See full prescribing information for ONEXTON Gel.

ONEXTON™ (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%, for topical use

Initial U.S. Approval: 2000

CONTRAINDICATIONS

Hypersensitivity

ONEXTON Gel is contraindicated in those individuals who have shown hypersensitivity to clindamycin, benzoyl peroxide, any components of the formulation, or lincomycin. Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in postmarketing use with ONEXTON Gel [see Adverse Reactions]

WARNINGS AND PRECAUTIONS

Colitis

Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. If significant diarrhea occurs, ONEXTON Gel should be discontinued.

Severe colitis has occurred following oral and parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.

Studies indicate toxin(s) produced by Clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Stool cultures for Clostridium difficile and stool assay for C. difficile toxin may be helpful diagnostically.

Ultraviolet Light and Environmental Exposure

Minimize sun exposure (including use of tanning beds or sun lamps) following drug application [see Nonclinical Toxicology].

ADVERSE REACTIONS

The following adverse reaction is described in more detail in the Warnings and Precautions section of the label:

Colitis [see Warnings and Precautions].

Clinical Trials Experience

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

These adverse reactions occurred in less than 0.5% of subjects treated with ONEXTON Gel: burning sensation (0.4%); contact dermatitis (0.4%); pruritus (0.4%); and rash (0.4%).

During the clinical trial, subjects were assessed for local cutaneous signs and symptoms of erythema, scaling, itching, burning and stinging. Most local skin reactions either were the same as baseline or increased and peaked around week 4 and were near or improved from baseline levels by week 12. The percentage of subjects that had symptoms present before treatment (at baseline), during treatment, and the percent with symptoms present at week 12 are shown in Table 1.

Table 1: Local Skin Reactions - Percent of Subjects with Symptoms Present. Results from the Phase 3 Trial of ONEXTON Gel 1.2%/3.75% (N = 243)

	Before Treatment (Baseline)			Maximum During Treatment			End of Treatment (Week 12)		
	Mild	Mod.*	Severe	Mild	Mod.*	Severe	Mild	Mod.*	Severe
Erythema	20	6	0	28	5	<1	15	2	0
Scaling	10	1	0	19	3	0	10	<1	0
Itching	14	3	<1	15	3	0	7	2	0
Burning	5	<1	<1	7	1	<1	3	<1	0
Stinging	5	<1	0	7	0	<1	3	0	<1

*Mod. = Moderate

Postmarketing Experience

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

Anaphylaxis, as well as allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin phosphate/benzoyl peroxide.

DRUG INTERACTIONS

Erythromycin

Avoid using ONEXTON Gel in combination with topical or oral erythromycin-containing products due to its clindamycin component. In vitro studies have shown antagonism between erythromycin and clindamycin. The clinical significance of this in vitro antagonism is not known.

Concomitant Topical Medications

Concomitant topical acne therapy should be used with caution since a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents. If irritancy or dermatitis occurs, reduce frequency of application or temporarily interrupt treatment and resume once the irritation subsides. Treatment should be discontinued if the irritation persists.

Neuromuscular Blocking Agents

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. ONEXTON Gel should be used with caution in patients receiving such agents.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women treated with ONEXTON Gel. ONEXTON Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproductive/developmental toxicity studies have not been conducted with ONEXTON Gel or benzoyl peroxide. Developmental toxicity studies of clindamycin performed in rats and mice using oral doses of up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of up to 200 mg/kg/day (80 and 40 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

Nursing Mothers

It is not known whether clindamycin is excreted in human milk after topical application of ONEXTON Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to use ONEXTON Gel while nursing, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of ONEXTON Gel in pediatric patients under the age of 12 have not been evaluated.

Geriatric Use

Clinical trials of ONEXTON Gel did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity and impairment of fertility testing of ONEXTON Gel have not been performed.

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered topically twice per week for 20 weeks induced skin tumors in transgenic Tg.AC mice. The clinical significance of this is unknown.

Carcinogenicity studies have been conducted with a gel formulation containing 1% clindamycin and 5% benzoyl peroxide. In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation at doses of 900, 2700, and 15000 mg/kg/day (1.8, 5.4, and 30 times amount of clindamycin and 2.4, 7.2, and 40 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m^2, respectively) did not cause any increase in tumors. However, topical treatment with a different gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900 and 3000 mg/kg/day (1.2, 3.6, and 12 times amount of clindamycin and 1.6, 4.8, and 16 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m^2, respectively) for up to 97 weeks did not cause any increase in tumors. In a 52-week dermal photocarcinogenicity study in hairless mice, (40 weeks of treatment followed by 12 weeks of observation), the median time to onset of skin tumor formation decreased and the number of tumors per mouse increased relative to controls following chronic concurrent topical administration of the higher concentration benzoyl peroxide formulation (5000 and 10000 mg/kg/day, 5 days/week) and exposure to ultraviolet radiation.

Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration assay. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Fertility studies have not been performed with ONEXTON Gel or benzoyl peroxide, but fertility and mating ability have been studied with clindamycin. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g ONEXTON Gel, based on mg/m^2) revealed no effects on fertility or mating ability.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Manufactured for:
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA
By:
Valeant Pharmaceuticals International, Inc.
Laval, Quebec H7L 4A8, Canada
U.S. Patent 8,288,434

Rev 10/2016
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ONX.0075.USA.17

gastroenterologist to determine dosing. The patients Duffin has switched have all done well. Apremilast is emerging as a possible therapy for the psoriasis patient with ulcerative colitis, but more data are needed. *Multiple sclerosis (MS):* Anti-TNF agents must be avoided with MS. Phototherapy and methotrexate can be used. Ustekinumab improves psoriasis without exacerbating MS. Duffin suggested dimethyl fumarate, recently approved for relapsing-remitting MS, as it has efficacy in psoriasis. (Note: it requires monitoring for possible lymphopenia and the rare issue of progressive multifocal leukoencephalopathy.) Secukinumab is another possibility for dual treatment, also being studied in MS. *Cardiometabolic disease:* Conventional wisdom advising a weight-based treatment (eg, infliximab) for better efficacy with the high-BMI patient is not supported by emerging data. Recent data show that a low-calorie diet plus a biologic drug improved PASI scores significantly more than the drug alone, while also addressing the cardiometabolic comorbidities.

Conclusion. Duffin recommends keeping in mind the two-birds-with-one-stone approach for psoriasis patients with comorbidities, and keeping an eye out for the data that will be appearing.

Treatment Selection Based on Comorbidities

Obesity
- Prescribe weight loss/low calorie diet with your biologic
- Weight-based dosed drugs may not make sense

Cardiovascular Disease
- Epidemiologic evidence suggests anti-TNF agents and methotrexate may be protective
- PET-CT doesn't reveal reduction of inflammation at 12 and 52 weeks with adalimumab; more data coming
- Stay tuned for CIRT study: methotrexate in pts with DM or metabolic syndrome post-MI

Crohn's
- Although anti-TNF agents are "first line" biologics for IBD and psoriasis
  - ustekinumab may be the better therapy for patients with both
  - **Caution** with anti-IL17 drugs

Ulcerative Colitis
- Stay tuned for data on apremilast and UC

Multiple Sclerosis
- Consider fumaric acid ester for both MS and Ps
- Anti-IL23 drugs considered safe
- Anti-IL17 data emerging—may be safe and effective
- **Avoid** anti-TNF agents

MINI-SYMPOSIUM: CUTANEOUS ONCOLOGY

High-Risk Cutaneous SCC in the Head and Neck

Steven M. Sperry, MS

Introduction. As a head and neck surgeon, Dr. Sperry treats this extremely common skin cancer exclusively in patients at the highly challenging end of the spectrum. This means cutaneous SCC that is deeply invasive and/or very large, recurrent, treated with radiation, has nodal metastases, etc.—among the poorest-performing nonmelanoma skin cancers, and an extreme source of morbidity when multiple surgical procedures are required. The percentage of patients who die is very small, but the overall number is significant because this cancer is so prevalent. Frustratingly, critical decisions in identifying and then following advanced patients are far from clear-cut.

Challenges. Cutaneous SCC is deemed high-risk when it is judged vulnerable to local recurrence or nodal metastasis, the two conditions associated with mortality. But there is no agreement on prognostic factors. Sperry showed the current list from the American Joint Committee on Cancer (AJCC), adding that "there is also a very long list of recognized factors *not* included in this staging system." Many of these, plus additional factors, are included in the NCCN

(National Comprehensive Cancer Network) guidelines. Current AJCC criteria classify 14% of HNSCC as high-risk, while applying the comprehensive list of other factors places 87% of HNSCC patients in this category. Studies attempting to document relevant prognostic factors have lacked sufficient design comparability to produce a meaningful body of results. Sperry discussed some of the clinical uncertainties all of this produces. One is the difficulty of identifying patients at highest risk for nodal metastases, and then determining how best to monitor them. There are also no guidelines for whether to image, or which type of imaging to choose.

Final points. Sperry discussed perineural invasion, its dangers, and the role of Mohs surgery. He also noted the aggressive, unpredictable tumors in the immunosuppressed patient, and his requests for a sirolimus-based immunosuppression regimen. It may help to control existing cancers and prevent new ones. Sperry also provided his recommendations for using radiation.

CSCC Prognostic Factors

- In AJCC staging:
  - Size
  - Depth of invasion
  - Perineural invasion
  - Bone invasion
  - Node metastasis
  - Extracapsular extension
  - Distant metastasis
- *NOT* in AJCC staging:
  - Histology (poorly differentiated, sarcomatoid/spindle cell, desmoplasia)
  - Anatomic location (ear, temple, cheek, lip)
  - Immunosuppression
  - Overall health/comorbidity
  - Tobacco/alcohol abuse
  - Nutrition
  - Psychosocial functioning

Decision Points for Ordering Imaging in CSCC

- NCCN guidelines: no expert opinion offered on when to order imaging for cN0
- **My take:** anatomic imaging is useful when risk of metastasis is >10%
  - CT with contrast: bone invasion, nodes
  - MRI with/without gadolinium: nerves
  - US of neck and parotid: nodes
- High-risk factors for metastasis:
  - Size
  - Depth of invasion
  - Differentiation
  - Perineural Invasion
  - Location: lip, ear, temple
  - Immunosuppression

Surgical Margins—How Big and For What?

Marta J. Van Beek, MD, MPH

Introduction. Dr. Van Beek discussed the guidelines recently released for nonmelanoma skin cancers. She also explained the decisions that can be made based on the pathologist's assessment of margins, and on classification of dysplastic nevi.

Determining margins. *Biopsy:* After presenting data, Van Beek said that "when a shave or punch removal is not the provider's intent, the pathologist's biopsy margin histology remarks are a poor predictor of whether there will be residual tumor in the excision." *Nonmelanoma skin cancer:* Excellent reviews for BCC and SCC (broken down by low-risk and high-risk) are in the recently released AAD guidelines. Van Beek defined these categories, stressing the importance of Breslow depth in categorizing SCC. *Low-risk* requires a 4 mm margin for BCC, 4–6 mm for SCC, with excisions resulting in an ~95% cure rate. *High-risk* and *recurrent* tumors have much lower cure rates. Mohs surgery should be used because the horizontal sectioning examines the greatest percentage of the margin, providing sufficient confidence for 1–2 mm margins. *Dysplastic nevi:* Recent data support the recommendation that moderately dysplastic nevi with positive biopsy margins that are clinically without pigment can safely be observed. Severely dysplastic nevi may require re-excision. Decisions are complicated by the heterogeneity among pathologists in defining "severe." Van Beek emphasized that dysplastic nevi are a marker of melanoma risk, not precursors of melanoma.

Total (n=235)	POSITIVE Biopsy Margin	Residual Tumor in Excision	NEGATIVE Biopsy Margin	Residual Tumor in Excision
Basal Cell Carcinoma 87 (37%)	78	54 (69%)	9	7 (78%)
Squamous Cell Carcinoma 148 (63%)	136	56 (41%)	12	0 (0%)

BCC
- 69% of POSITIVE bx margins had residual tumor in excision
- 78% of NEGATIVE bx margins had residual tumor in excision

SCC
- 41% of POSITIVE bx margins had residual tumor in excision
- 0% of NEGATIVE bx margins had residual tumor in excision

JE Jackson et al. *J Am Acad Dermatol.* 2012;67:122-7.

Surgical Margins

- Ultimate goal is "clear margins"—whether microns or mm
- Biopsy margins are not predictive of whether there is residual tumor identified in an excision specimen
- Size of margins depends on % of histologic margin examined, sectioning, and inking
  - Larger margin required if a low % of margin was examined
- Recent evidence: mild or moderate dysplastic nevi do not need re-excision regardless of biopsy margins
- Growing evidence: severe dysplastic nevi (SDN) do not need re-excision, but lack of consensus among pathologists on what differentiates an SDN from a melanoma

Bottom line. The ultimate goal is clear margins, whether microns or millimeters. Biopsy margins do not predict whether the excision specimen will contain residual tumor. Margin size is dependent upon the percent of the histologic margin actually examined, which is a function of sectioning and inking. Larger margins are required when this percentage is small or if the tumor is high-risk. Mild or moderate dysplastic nevi do not need re-excision even with a positive margin. Confidence in the growing evidence that severely dysplastic nevi do not require re-excision is weakened by inconsistency in defining "severely dysplastic." ■

2018 DF Clinical Symposia Faculty Disclosures (*Part I*)

David E. Cohen, MD, MPH: Dermira, Ferndale Labs, FIDE, Medimetriks. **Kristina Callis Duffin, MD:** AbbVie, Celgene, Lilly, Novartis, Pfizer, Sienna. **Jonathan A. Dyer, MD:** Allergan, Castle Creek Pharma, Crown Pharmaceuticals, Scioderm. **Suzanne M. Olbricht, MD:** none. **Kanade Shinkai, MD, PhD:** none. **Steven M. Sperry, MD:** none. **Marta J. Van Beek, MD, MPH:** none.

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Stiefel Scholar Award in Skin Cancer: Funding for Groundbreaking Melanoma Treatment

Todd W. Ridky, MD, PhD, Assistant Professor of Dermatology at the University of Pennsylvania, has developed a potential new class of therapeutics for melanoma that synergize with modern anti-PD-1 immunotherapy to cure 50% of melanoma-bearing mice. These dramatic responses—in mice who would have all succumbed to tumor if treated with either drug alone—are permanent. Mice that clear tumors also develop durable immunity that protects them against subsequent tumors when they are reinjected with melanoma cells.

Dr. Ridky's groundbreaking discovery utilizes a synthetic estrogen derivative that makes melanoma cells more differentiated, less proliferative, and more vulnerable to being killed by circulating immune cells. Now his three-year *Stiefel Scholar Award* will enable him to continue the studies needed to move this therapy forward.

Todd W. Ridky, MD, PhD

Dr. Ridky arrived at this potentially transformative melanoma treatment via his patient-oriented approach to research. "My team and I ask questions inspired by clinical observations. Then we follow the arc of scientific discovery to wherever it leads us." Their inspiration was women in his clinic "who note darkening in their skin color during pregnancy—an observation also made by Hippocrates 2,400 years ago." They hoped that identifying what stimulates melanocytes during pregnancy would expand their understanding of normal melanocyte biology. Dr. Ridky and students in his lab connected a series of dots to discover that melanocytes and melanoma are highly responsive to estrogen, and that the effects are not mediated by the traditional estrogen receptor studied extensively in breast cancer. Instead, it is a recently identified alternative estrogen receptor—called G protein-coupled estrogen receptor (GPER)—which activates signaling pathways that are completely different from those initiated by the classic estrogen receptor. He and his students speculate that this explains why women generally have less melanoma, and more favorable outcomes than men. Dr. Ridky's group then determined that a synthetic estrogen derivative that binds only to GPER, acts on normal melanocytes to darken skin when applied topically. When the compound was administered systemically to melanoma-bearing mice, they observed the tremendous survival benefit with immunotherapy and, importantly, saw no systemic toxicity.

Dr. Ridky is grateful to receive the 2018 Stiefel Scholar Award. **"It provides needed research support at a critical time—as we work to expand on our recent findings and move GPER agonists to first-in-human trials for melanoma and other cancers."**

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VOL. 37 NO. 1 SPRING 2018