Mycobiome contributes to impaired healing

WHITNEY J. PALMER | Staff Correspondent

Fungus plays a larger role in lingering wounds than previously understood, according to a recent review published in the July issue of Advances in Wound Care. Treating slow-healing wounds solely for bacterial infections could further extend healing time and possibly create additional problems for patients, authors note.

Using next-generation sequencing, such as polymerase chain reaction (PCR) amplification and high-throughput DNA sequencing, can paint a clearer picture of the bacteria and fungi present in the wound microbiome. This knowledge can improve both diagnosis and the way providers treat patients.

In a recent clinical review, the authors determined that high-throughput sequencing is critically important. It can rapidly identify both bacterial and fungal species present in the wound microbiome, helping providers determine the best antimicrobial therapy that will attack both targets. This is vital because current evidence shows fungus is increasingly present, alongside bacteria, providing a protective scaffolding that encourages bacteria to continue to grow. This phenomenon slows down wound healing significantly.

FACTORS IMPACTING HEALING

The researchers reviewed investigations surrounding the wound microbiome to determine what factors could most significantly impede, promote, or have no impact on a patient’s wounds. They specifically looked at non-healing diabetic foot ulcers (DFUs).

BURNOUT NOT A ‘THING’

Studies indicate physicians are fried, but new review says it’s not as bad as it sounds

BOB KRONEMYER | Staff Correspondent

Studies about physician burnout have not used consistent definitions of what is considered burnout nor similar assessment measures; therefore, prevalence estimates vary widely, according to a systemic review that appears in the September 18 edition of JAMA.

“Studies indicate physicians are fried, but new review says it’s not as bad as it sounds. There is no burnout epidemic. Rather, burnout symptoms are endemic among physicians, likely at lower levels than are popularly cited.”

Nonetheless, Dr. Mata believes, like most others, that burnout is an important issue for physicians.

“However, burnout, unlike major depressive order, is not an illness,” he says.

Dr. Mata

THE DATA-DRIVEN STORY

In this review, Dr. Mata, along with first author, Lisa S. Rotenstein, M.D., M.B.A., also of Brigham and Women’s Hospital and several others, synthesized data from 182 studies involving 109,628 physicians in 45 countries published between

BURNOUT CONTINUES ON PAGE 78
**Dermatology Times is guided by a core group of trusted physician experts who provide editorial guidance and expert opinion on issues that affect patients and the practice.**

**Dr. Zoe Diana Draelos**  
Dr. Draelos is a consulting professor of dermatology, Duke University School of Medicine, Durham, N.C.

**Dr. Norman Levine**  
Dr. Levine is a private practitioner in Tucson, Ariz.

**Dr. Elaine Siegfried**  
Dr. Siegfried is professor of pediatrics & dermatology, Saint Louis University Health Sciences Center, St. Louis, Mo.

**Dr. Ronald G. Wheeland**  
Dr. Wheeland is a private practitioner in Tucson, Ariz.
“When was the last time you heard someone was poisoned by hand cream?”

Do we need FDA-approved eye shadow?

by DR. ZOE DIANA DRAELOS
Dr. Draelos is a consulting professor of dermatology, Duke University School of Medicine, Durham, N.C.

Should eye shadow be approved by the US Food and Drug Administration? While at first glance this question may evoke laughter, this question is being debated between regulatory authorities and the cosmetics industry.

There is a movement contending that all cosmetics, skincare products and cleansers should be regulated to protect the health and well being of consumers. Regulation has done much to eliminate mercury-containing skin lightening creams and the ingestion of oral arsenic to achieve pale skin. These are clearly toxic substances used for an appearance benefit with profound risks. We are accustomed to the close regulation of pharmaceuticals. There are clearly defined testing methodologies and regulatory milestones that must be achieved prior to approval of a new drug. The steps involve first, assessing the safety of a given compound, second, evaluating the most effective minimal dose, and finally, determining if certain efficacy goals are reached.

Pharmaceuticals are different than cosmetics in that they must be purchased with a prescription and used under the direction of a skilled physician. There are no prescription cosmetics; they are purchased in the mass market without any professional direction.

Is regulation of cosmetics necessary? This is a question worth considering, since dermatology is the only area of medicine where so many mass products can be purchased that affect the health of the skin, hair and nails.

Indeed, there are a variety of skin and hair care products that are considered over-the-counter drugs. These include acne washes containing benzoyl peroxide or salicylic acid, dandruff shampoos containing zinc pyrithione, and antibacterial cleansers containing benzalkonium chloride. These products contain ingredients that are listed on monographs specifying which ingredients can be used, in which combination, with which concentration, and associated with which claims.

The monograph system has been very effective in allowing the cosmetics industry to create useful consumer products that address common health issues without having to pursue the long and expensive pharmaceutical approval path. This provides medical assistance for mild acne, dandruff, and infection control at an affordable price.

Cosmetics have not been regulated in the past, as they possess substances that only adorn and scent the skin, but both ingredient technology and skin physiology insights have advanced to provide higher efficacy beyond just adornment.

Cleansers were intentionally left without regulation by the federal government as concerns arose in the 1930s that regulation would lead to price increases and reduced ability to purchase cleansers resulting in lower hygiene standards among Americans.

Clean water and cleansers are, in my opinion, the most profound invention of mankind, although others would argue the cell phone is more important. I would argue that it is hard to focus on a cell phone when you are infected with salmonella or shigella. Nevertheless, cleansers are not regulated and there have been few issues with bland soaps and syndets after many years of use.

The push to regulate the cosmetics industry should be based on the introduction of new ingredients. One proposal allows all old ingredients to be grandfathered as approved, the same concept used for all existing pharmaceuticals that were sold when the FDA was created, and only new ingredients would need to go through an IND-type approval process.

The cosmetics industry thrives on new ingredients. Think of the revolution in skin and hair care created by all of the new silicone derivatives that allow superior moisturization without a greasy, sticky film. If new ingredients required approval, it would lead to less innovation, poorer product formulations, longer wait times for new technology, and increased expense. When was the last time you heard someone was poisoned by hand cream? Would the regulation address a problem that exists in the current marketplace?

I can tell you after designing and executing studies with the cosmetics industry for 30 years, the research conducted is extensive. Cosmetic chemists develop carefully designed formulations. Raw materials are assessed for safety and purity. Products and packaging are tested for long term stability on the shelf and after consumer opening. Repeat insult patch testing and 21-day cumulative irritancy testing is performed on finish formulations to insure the absence of irritant and allergic contact dermatitis. Use testing is conducted to insure both safety and efficacy and claim substantiation in normal human use.

Because company reputations are on the line, testing is conducted to be sure problems do not occur and the system appears to be working. How many years have passed since a major cosmetic industry health issue arose in the United States?

I think safety regulation has done much to improve consumer health in the United States. It has set a high bar and an organizational structure for all industries that are not regulated. While it is true that all aspects of life in the United States could be regulated, I am not sure regulation of the cosmetics industry would improve product safety in an environment where there are no present issues.

Many cosmetic products, such as hand moisturizers and body lotions, have reduced the incidence of eczematous dermatoses in a more profound way than pharmaceuticals based on the number of units sold. The federal government already regulates the coloring agents used in cosmetics. Do we need FDA approved eye shadow.
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Baseline
3-month follow-up

Rosacea²
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Post 2 treatments

Photos are unretouched. Patient treated with Vbeam Prima; individual results may vary. Photos courtesy of E. Victor Ross, MD.

Photos are unretouched. Patient treated with Vbeam Prima and contact cooling; individual results may vary. Photos courtesy of Konika Patel Schallin, MD.

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¹Auto-calibration on start-up.
²Ross EV. Vbeam Prima before and after photos. Candela, data on file.
Schallin KP. Vbeam Prima before and after photos. Candela, data on file.

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I have pending malpractice lawsuits after opening a medical spa. What are my legal issues?

Medspa ownership liabilities

by DAVID J. GOLDBERG, M.D., J.D.

Dr. Goldberg is director of Skin Laser and Surgery Specialists of New York and New Jersey, past director of Mohs and Laser Research, Icahn School of Medicine at Mt. Sinai; and, adjunct professor of law, Fordham Law School in New York City.

Dr. Broke has been in practice for 20 years. Over the past five years he has experienced a progressive increase in overhead expenses with a corresponding decrease in revenue, despite the fact that he is both a well-respected medical dermatologist and has started performing cosmetic procedures. He has noticed that various types of medical spas are opening around him, which all appear to be successful. Most have limited if any medical supervision, and he works in a jurisdiction that has limited rules relative to supervision. Dr. Broke makes the decision to open his own medical spa a few blocks away from his current office building. He hires medical assistants and aestheticians to perform a variety of energy-based procedures and injectables. Within a year, he has over five medical malpractice lawsuits and three complaints to his local state Board of Medical Examiners. He is now overwhelmed with his legal issues and wonders if he will survive financially and emotionally. What are his legal issues?

Dermatologists or other physicians who become involved in the medical spa industry are lured by the lucrative income and flexible nature of ownership. However, as the popularity of this business model increases, so does the risk for liability.

The number of medical spas in this country is now at a record high. It is true that the number of medical spas decreased drastically during the recession of one decade ago; however, in the last decade the number has increased dramatically over the past decade. Dermatologists, among other core physicians, are opening medical spas or adding medical spa services to existing practices as the demand for non-invasive cosmetic procedures grows. Unfortunately for these physicians, non-core physicians, mid-level practitioners, and entrepreneurs are beginning to outpace core doctors in the medical spa space, according to 2017 Medical Spa State of the Industry Report. Though medical spas offer non-invasive and, what some might suggest are fairly simple medical treatments like neuromodulator injections and laser hair removal, these procedures carry the same risk of litigation as any other medical procedure. Due to the aesthetic nature of the treatments and spa-like setting where most treatments are performed, there is a public perception that medical spa procedures are risk-free. This misconception has contributed, in part, to the recent rise in litigation that has put medical spas in the legal spotlight.

There are several common patient allegations that potentially put dermatologists at risk of losing medical malpractice cases based on negligence or of having a State Medical Board revoke their license to practice medicine.

Negligence lawsuits against a dermatologist are lost when a plaintiff’s attorney can show the dermatologist breached his/her reasonable duty and that there is a nexus between that breach and economic damages. If a dermatologist employee breached that same reasonable duty and it can be shown that there is a nexus between that breach and economic damages, more often than not the dermatologist will also be found liable. Similarly, based on the state jurisdiction, if it can be shown the dermatologist did not provide appropriate supervision, that dermatologist can lose his/her medical license.

In the end, what Dr. Broke needs to be concerned about is that lawsuits are often filed by patients due to allegations of lack of supervision of medical treatments, inadequately trained medical spa personnel, less than optimal results, and lack of informed patient consent. Dermatologists now must be particularly careful when signing on as a “medical director” of a medical spa, offering medical spa treatments or opening a medical spa of their own.
How did you become involved as a judge for the Aspire Higher program?

I was approached by Ortho Dermatologics, and I thought it was a wonderful opportunity. I really liked that they were giving back to the community and that I could help people who want to further their education.

What is your favorite part about being a judge for Aspire Higher?

I really enjoy the whole experience, but two things come to mind: Seeing the impact the scholarships have on the lives of the people who win, and reading their stories.

One of last year’s winners left a voicemail for the judges. I was in the middle of grocery shopping when I heard it, and I started crying because it was so touching. Also, reading about how a problem with a person’s skin impacts each aspect of their life urges us to seek the best possible treatment for our patients even more. I think that what Ortho Dermatologics is doing is exceptionally worthwhile.

It’s so satisfying to see how the Aspire Higher scholarship can change somebody’s life by helping them further their education.

What are your thoughts about Ortho Dermatologics’ commitment to the dermatology community through this scholarship program?

I’m thrilled to be part of it. I’m thrilled to have had the opportunity to hear the patients’ stories, to understand their journey, and to be part of making their educational dreams come true. I think this is a major gift that Ortho Dermatologics gives back to the community, and it’s important to get the word out to our patients that this is available. Ortho Dermatologics really does care about our specialty.
The need for entrepreneurship education in medical school and residency training

by MORGAN NGUYEN, BA; WILLIAM JU, M.D., FAAD; STEVE XU, M.D., FAAD

Ms. Nguyen is a medical student at Northwestern University Feinberg School of Medicine. Dr. JU is co-founder of Advancing Innovation in Dermatology, Inc. and co-founder of the Advancing Innovation in Dermatology Accelerator Fund where Dr. Xu also serves as co-founder. Dr. Xu is an instructor in dermatology at Northwestern University Feinberg School of Medicine and medical director of the Center for Bio-Integrated Electronics at the Simpson Querrey Institute for Bionanotechnology, Northwestern University.

Physicians played a central role in the discovery and development of nearly every transformative medical tool or therapeutic used today (e.g., imatinib, VEGF inhibitors, Herceptin, coronary artery stents, statins). Physicians have created specific initiatives to involve residents in innovation, entrepreneurship, and enhanced adaptability. As of 2016, only thirteen medical schools have acted on that call. Moreover, medical education does not address. As of 2016, only thirteen medical schools have acted on that call. Moreover, medical education does not address.

The challenges facing dermatology and healthcare in general need more physicians that are trained in entrepreneurship. The rapid proliferation of disruptive technologies present imminent challenges to physicians that a traditional basic and clinical sciences education does not address. As of 2016, only thirteen medical schools have acted on that call. Offering entrepreneurship certificates, concentrations and paths of excellence across seven educational themes: innovation, entrepreneurship, technology, leadership, healthcare systems, business of medicine, and enhanced adaptability.

Case Western Reserve University School of Medicine continues the trend, debuting this academic year a Pathway Program in Healthcare Innovation and Entrepreneurship that involves biweekly meetings during preclinical years and a mentored project. Northwestern University Feinberg School of Medicine offers, among others, an interdisciplinary six-month course designed to introduce students to the process of developing medical technologies. Enhancing surgical innovation motivated the creation of University of Michigan’s program. Entrepreneurship education as a tool to train medical students in complex problem solving and solution design is expanding but still represents a small fraction of the broader medical education enterprise.

While medical school offers the opportunity to train an entrepreneurial mind, residency is a time for entrepreneurial action. Residents are on the front lines of patient care, and have the direct clinical exposure necessary to recognize needs and implement changes in healthcare delivery. They understand what clinical problems are worth solving in their specific fields. They enter their respective specialties as new physicians exposed to new problems fresh perspectives and ideas about residents have the unique chance to engage in problem-driven innovation. Tackling problems that affect their patients prompts residents to examine issues that originate in healthcare system, cultivating a broader level of analysis that will make them an asset to any current or future healthcare organization. While residents are in a unique position to see and impact change, they often lack sufficient education, time and funds to develop solutions. Although the Accreditation Council for Graduate Medical Education has formalized some training for residents in quality improvement, a national vision for innovation education has yet to materialize.

Individual specialties and academic institutions have created specific initiatives to involve residents in entrepreneurship education. In dermatology, Advancing Innovation in Dermatology launched an innovation curriculum, virtual Magic WandSM, in March 2017 to instruct residents and trainees in dermatology in key entrepreneurial areas including clinical needs finding, FDA regulation, and intellectual property basics inspired by the original program launched at Massachusetts General Hospital for clinical faculty. Over 90 dermatology residents have attended the Dermatology Innovation Forum, the organization’s annual entrepreneurship conference over the past four years, indicative of strong interest in medical-technical innovation among trainees. Internal medicine residents at Duke can partake in Management and Leadership rotational program, which offers experience in the business of medicine, not entrepreneurship specifically.

Physicians are trained from day one to develop three core abilities — the capacity to learn, the confidence to operate with uncertainty, and domain expertise in an area of healthcare. While these attributes are entrepreneurial in nature, addressing challenges in healthcare will also require creative problem-solving, risk-taking, and technical and business literacy — skills and experience that should be cultivated through education in entrepreneurship early in a trainees journey.

References Cited

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- Pulse Duration: 450 picoseconds
- Repetition Rate: Up to 10 Hz
- Spot Size: Adjustable up to 10 mm

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**EPHINANY DERMATOLOGY PARTNERS WITH SUN CITY DERMATOLOGY**

**EPHINANY DERMATOLOGY**, an Austin, Texas-based practice with offices throughout the South and West, has joined forces with Sun City Dermatology of El Paso, Texas, according to a company news release.

The six-provider group at Sun City, was founded by Adrian Guevara, M.D., in 2006. Dr. Guevara, who was joined by Brett Ozanich, M.D. in Sun City, opened the practice after earning his medical degree at University of Texas Health Sciences Center, San Antonio. Dr. Ozanich received his medical degree from Kansas City University of Medicine, followed by residency at San Antonio Uniformed Services Health Education Consortium.

“I picked Epiphany because they have been committed to the El Paso and Las Cruces market for over two years, and with high patient satisfaction.” Dr. Guevara stated in the news release. “Another factor is that Epiphany is focused on maintaining high standards of care company-wide, so that the dermatological care is excellent at all of their locations.”

Epiphany offers clinical, cosmetic and other dermatologic services in 36 locations in seven states through partnerships with other physicians.

“Through our interactions with Dr. Guevara, we were pleased to learn that he is as committed as we are to delivering excellence in his hometown of El Paso.” Epiphany CEO Gheorghe Pusta said in the news release. “Furthermore, we are delighted to see Dr. Guevara continue his leadership as Epiphany’s El Paso Market medical director.”

The new collaboration will allow for greater access to administrative resources, marketing, IT, human resources and other support services for the practice.

**THE PLASTIC SURGERY FOUNDATION AND MTF BIOLOGICS announced that applications are now being accepted for their Allograft Tissue Research Grant. According to the companies’ joint news release, the program, which began in 2013, funds advancements in tissue transplantation to enhance patient care.**

“To develop new clinical approaches and advance positive patient outcomes in plastic and reconstructive surgery, we need a constant stream of new research in the field,” said Arun Gosain, M.D., president, The Plastic Surgery Foundation. “We are pleased to continue this partnership with MTF Biologics to fund the critical work of clinicians and scientists seeking to uncover new ways that human tissue can advance patient care and results.”

Selected applicants may receive up to $100,000 to support one- to two-year research projects, which must include a strong clinical translation component that incorporates dermal, adipose, placental or other allograft transplant technologies, the companies say.

Previously funded projects have examined such topics as the use of adipose stem cells for the prevention and treatment of diabetic foot ulcers, the impact of adipose derived stem cells on skin improvement in radiation wounds, and tissue-engineered lymph node transplantation for the treatment of lymphedema, as examples.

Applications for the 2019 PSF/MTF Allograft Tissue Research Grant Program will be accepted through December 3, 2018. For more information or to apply, visit www.thepsf.org for more information.

**AVITA BIOMEDICAL NAMES NEW CFO, VP OF BUSINESS DEVELOPMENT**

**AVITA BIOMEDICAL**, a biotech firm that focuses on regenerative medicines, such as stem cell applications, recently named two new members to its senior management team, according to a company news release.

New chief financial officer Scott Burrell joined from CombiMatrix Corporation, where he also was CFO and helped manage that company’s sale.

His background includes 25 years in corporate finance and compliance, working in healthcare, high-tech and biotech fields.

Kevin Green was named AVITA’s vice president of business development. For 10 years at Allergan, he was senior director of business development, overseeing transactions, including the $2.1 billion Kythera acquisition.

“Mr. Burrell and Mr. Green bring decades of B2B, corporate finance and capital raising experience to AVITA. These appointments reflect our plans for further capitalization via investment and partnership,” AVITA Chairman and CEO Hans S. Keirstead, Ph.D., said in a news release.

AVITA, a privately-held company, also recently made hires to support its Root of Skin and Root of Skin MD skincare lines.

**SARECYCLINE APPROVED FOR MODERATE-TO-SEVERE ACNE**

**THE FOOD AND DRUG ADMINISTRATION (FDA)** approved sarecycline (Seyora, Almirall, S.A.) in October for the treatment of non-nodular moderate-to-severe acne vulgaris in patients 9 years of age and older, according to a company news release.

Sarecycline is a first in class tetracycline-derived once-daily oral antibiotic. The approval was based on data from two 12-week multicenter, randomized, double-blind, placebo-controlled efficacy studies. Researchers enrolled 2,002 patients aged 9 years and older and the drug was found to significantly reduced inflammatory lesions as early as 3 weeks after treatment, the company says.

Sarecycline was part of Allergan’s Medical Dermatology portfolio. It was recently acquired by Almirall for the United States and is expected to be launched in January 2019.
**INDICATION**
ALTRENO™ (tretinoin) lotion, 0.05% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

**IMPORTANT SAFETY INFORMATION**
ALTRENO is for topical use only. Not for ophthamlic, oral, or intravaginal use.

**Skin Irritation:** Patients using ALTRENO may experience application site dryness, pain, erythema, irritation, and exfoliation. Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of ALTRENO, or discontinue use. Avoid application of ALTRENO to eczematous or sunburned skin.

**Ultraviolet Light and Environmental Exposure:** Minimize unprotected exposure to ultraviolet light, including sunlight and sunlamps. Warn patients with frequent sun exposure and those with inherent sensitivity to sunlight to exercise caution. Use sunscreen and protective clothing over treated areas when exposure cannot be avoided.

**Fish Allergies:** ALTRENO contains soluble fish proteins. Use with caution in patients with known sensitivity or allergy to fish. Advise patients to contact their healthcare provider if they develop pruritus or urticaria.

**Adverse Reactions:** The most common adverse reactions in clinical trials were application site dryness (4%), pain (3%), erythema (2%), irritation (1%) and exfoliation (1%).

**Nursing Women:** It is not known whether topical administration of tretinoin could result in sufficient systemic absorption to produce detectable concentrations in human milk. The developmental health benefits of breastfeeding should be considered along with the mother's clinical need for ALTRENO and any potential adverse effects on the breastfed child from ALTRENO.

To report SUSPECTED ADVERSE REACTIONS, contact Customer Service at 1-800-321-4576 or the FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see Brief Summary of Prescribing Information on following pages.

**ADVERSE REACTIONS**

**Clinical Trials Experience**

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

In 2 randomized, double-blind, vehicle-controlled trials, subjects age 9 years and older applied ALTRENO or vehicle once daily for 12 weeks. The majority of subjects were White (74%) and female (55%). Approximately 47% were Hispanic/Latino and 45% were 9 years and older applied ALTRENO or vehicle once daily for 12 weeks. The majority of subjects were White (74%) and female (55%). Approximately 47% were Hispanic/Latino and 45% were younger than 18 years of age. Adverse reactions reported by ≥1% of subjects treated with ALTRENO and more frequently than vehicle are summarized in Table 1.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ALTRENO N=767</th>
<th>Vehicle N=783</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site dryness</td>
<td>29 (4)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Application site pain</td>
<td>25 (3)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Application site erythema</td>
<td>12 (2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Application site irritation</td>
<td>7 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Application site exfoliation</td>
<td>6 (1)</td>
<td>3 (&lt;1)</td>
</tr>
</tbody>
</table>

Application site pain defined as application site stinging, burning or pain.

**Skin Irritation**

Patients using ALTRENO may experience application site dryness, pain, erythema, irritation, and exfoliation. Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of ALTRENO, or discontinue use. Avoid application of ALTRENO to eczematous or sunburned skin.

**Ultraviolet Light and Environmental Exposure**

Minimize unprotected exposure to ultraviolet light including sunlight and sunlamps during the use of ALTRENO. 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.

**Fish Allergies**

ALTRENO contains soluble fish proteins. Use with caution in patients with known sensitivity or allergy to fish. Advise patients to contact their healthcare provider if they develop pruritus or urticaria.

**Fish Allergies**

ALTRENO contains soluble fish proteins. Use with caution in patients with known sensitivity or allergy to fish. Advise patients to contact their healthcare provider if they develop pruritus or urticaria.

**Skin Irritation**

Skin irritation was evaluated by active assessment of erythema, scaling, hypopigmentation, hyperpigmentation, itching, burning and stinging. The percentage of subjects who were assessed to have these signs and symptoms at any post baseline visit are summarized in Table 2.

<table>
<thead>
<tr>
<th>Skin irritation</th>
<th>ALTRENO N=760 Mild/Mod/Severe</th>
<th>Vehicle N=782 Mild/Mod/Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>Scaling</td>
<td>49%</td>
<td>30%</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Itching</td>
<td>35%</td>
<td>28%</td>
</tr>
<tr>
<td>Burning</td>
<td>30%</td>
<td>14%</td>
</tr>
<tr>
<td>Stinging</td>
<td>21%</td>
<td>8%</td>
</tr>
</tbody>
</table>

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Available data from published observational studies of topical tretinoin in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no data on ALTRENO use in pregnant women. The systemic levels following topical administration are lower than with administration of oral tretinoin; however, absorption of this product may result in fetal exposure. There are reports of major birth defects similar to those seen in infants exposed to oral retinoids, but these case reports do not establish a pattern or association with tretinoin-related embryopathy (see Data).

Animal reproduction studies have not been conducted with ALTRENO. Topical administration of tretinoin in a different formulation to pregnant rats during organogenesis was associated with malformations (craniofacial abnormalities [hydrocephaly], asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) at doses up to 0.5 mg tretinoin/kg/day, approximately 2 times the maximum recommended human dose (MRHD) based on body surface area (BSA) comparison and assuming 100% absorption. Oral administration of tretinoin to pregnant cynomolgus monkeys during organogenesis was associated with malformations at 10 mg/kg/day (approximately 100 times the MRHD based on BSA comparison and assuming 100% absorption) (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. The background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

**Data**

**Human Data**

While available studies cannot definitively establish the absence of risk, published data from multiple prospective controlled observational
studies on the use of topical tretinoin products during pregnancy have not identified an association with topical tretinoin and major birth defects or miscarriage. The available studies have methodologic limitations, including small sample size and in some cases, lack of physical exam by an expert in birth defects. There are published case reports of infants exposed to topical tretinoin during the first trimester that describe major birth defects similar to those seen in infants exposed to oral retinoids; however, no pattern of malformations has been identified and no causal association has been established in these cases. The significance of these spontaneous reports in terms of risk to the fetus is not known.

**Animal Data**

Tretinoin in a 0.05% gel formulation was topically administered to pregnant rats during organogenesis at doses of 0.1, 0.3 and 1 g/kg/day (0.05, 0.15, 0.5 mg tretinoin/kg/day). Possible tretinoin malformations (craniofacial abnormalities [hydrocephaly], asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) were observed at maternal doses of 0.5 mg tretinoin/kg/day (approximately 2 times the MRHD based on BSA comparison and assuming 100% absorption). These findings were not observed in control animals. Other maternal and reproductive parameters in tretinoin-treated animals were not different from control. For purposes of comparison of the animal exposure to human exposure, the MRHD is defined as 4 g of ALTRENO applied daily to a 60-kg person.

Other topical tretinoin embryofetal development studies have generated equivocal results. There is evidence for malformations (shortened or kinked tail) after topical administration of tretinoin to pregnant Wistar rats during organogenesis at doses greater than 1 mg/kg/day (approximately 5 times the MRHD based on BSA comparison and assuming 100% absorption). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 50 times the MRHD based on BSA comparison and assuming 100% absorption) was topically applied to pregnant rats during organogenesis. Supernumerary ribs have been a consistent finding in rat fetuses when pregnant rats were treated topically or orally with retinoids.

Oral administration of tretinoin during organogenesis has been shown to induce malformations in rats, mice, rabbits, hamsters, and nonhuman primates. Fetal malformations were observed when tretinoin was orally administered to pregnant Wistar rats during organogenesis at doses greater than 1 mg/kg/day (approximately 5 times the MRHD based on BSA comparison). In the cynomolgous monkey, fetal malformations were reported when an oral dose of 10 mg/kg/day was administered to pregnant monkeys during organogenesis (approximately 100 times the MRHD based on BSA comparison). No fetal malformations were observed at an oral dose of 5 mg/kg/day (approximately 50 times the MRHD based on BSA comparison). Increased skeletal variations were observed at all doses in this study and dose-related increases in embryo lethality and abortion were reported in this study. Similar results have also been reported in pigment macaques.

Oral tretinoin has been shown to be fetotoxic in rats when administered at doses 10 times the MRHD based on BSA comparison. Topical tretinoin has been shown to be fetotoxic in rabbits when administered at doses 4 times the MRHD based on BSA comparison.

**Lactation**

Risk Summary

There are no data on the presence of tretinoin or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. It is not known whether topical administration of tretinoin could result in sufficient systemic absorption to produce detectable concentrations in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ALTRENO and any potential adverse effects on the breastfed child from ALTRENO.

**Pediatric Use**

Safety and effectiveness of ALTRENO for the topical treatment of acne vulgaris have been established in pediatric patients age 9 years to less than 17 years based on evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled, 12-week trials and an open-label pharmacokinetic study. A total of 318 pediatric subjects aged 9 to less than 17 years received ALTRENO in the clinical studies (see Clinical Pharmacology and Clinical Studies in full Prescribing Information).

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

**Geriatric Use**

Clinical trials of ALTRENO did not include any subjects age 65 years and older to determine whether they respond differently from younger subjects.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

A 2-year dermal mouse carcinogenicity study was conducted with topical administration of 0.005%, 0.025% and 0.05% of a tretinoin gel formulation. Although no drug-related tumors were observed in surviving animals, the irritating nature of the drug product precluded daily dosing, confounding data interpretation and reducing the biological significance of these results.

Studies in hairless albino mice with a different formulation suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect was confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The genotoxic potential of tretinoin was evaluated in an in vitro bacterial reversion test, an in vitro chromosomal aberration assay in human lymphocytes and an in vivo rat micronucleus assay. All tests were negative.

In dermal fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (approximately 2 times the MRHD based on BSA comparison and assuming 100% absorption), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day and above (approximately the MRHD based on BSA comparison and assuming 100% absorption) were observed.

**PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information).
As a young scientist transitioning from graduate school to a career in the pharmaceutical industry, Matt Davidson, Ph.D., knows how important it is to make a good first impression. But ever since childhood, he struggled with recurring common warts on his hands.

“He was embarrassed to shake other people’s hands,” said Ted White, Verrica’s CEO and president. So, like any scientist, Dr. Davidson began pouring over the science.

“The literature was compelling. I read papers on cantharidin going back to the 1960s. John and William Epstein published a key paper in 1960, but it was a short paper only two pages long that described a study using a 0.7 percent concentration to treat warts on fingers.” Dr. Davidson said. He was able to secure a non-FDA approved version of cantharidin which cleared his skin. His personal success with cantharidin and the existing literature on cantharidin, “got me interested in pursuing this line of research,” he said.

After graduation, Dr. Davidson worked for Applied Immunology (now Precision for Medicine), but at night, he was busy laying the groundwork for Verrica from his garage at his home in the San Francisco Bay Area. Here, he met with mentors and advisors who had successfully launched products or companies: Dennis Brown, Ph.D., of Matrix Pharmaceuticals; Mark de Souza, Ph.D., of Lotus Tissue Repair; and, Glenn Oclassen of Oclassen Pharmaceuticals.

“I had really great mentors who served as advisors early on. They had all founded and successfully ran companies in the dermatology space,” he said.

Now 34, Dr. Davidson is one of the youngest, if not youngest, pharmaceutical company pioneers in the country. As a student, he went through rounds of treatment with liquid nitrogen therapy (a painful procedure in which the lesions shrink but recur). He was eventually treated with cantharidin, which worked. And, so was born his desire to find an effective, affordable treatment with few—if any—side effects.

Headquartered in West Chester, Penn., Verrica specializes in the development of treatment for skin conditions, such as molluscum contagiosum and common warts. The active ingredient for its lead product candidate, VP-102, is the compound cantharidin. It is administered in solution through a single-use, precision applicator and is currently in clinical trials with results of two phase three clinical studies expected early next year.

The company name is based on a blend of the Latin name for warts (verruca) and the word “veracity.” “I like the idea of ‘veracity,’ in doing things the right way and being honest and forthcoming about it,” Dr. Davidson said.

**VERRUCA VULGARIS**

Currently, there is no FDA-approved treatment for verruca vulgaris, despite affecting 10-20 percent of the population.

In some cases, verruca vulgaris heals on its own, but in other cases, it may require cryotherapy, cautery, tissue scraping, laser treatment, electrosurgery, among other treatments.

Cantharidin is the purified active ingredient of cantharides, which is dried, powdered blister beetles (also called Spanish flies). It has been documented in scientific studies as a possible treatment for warts since 1958.

Despite the lack of FDA approval, topical cantharidin has been used by patients for skin conditions, such as common warts, molluscum contagiosum, periungual warts, plantar warts, calluses, cutaneous leishmaniasis, herpes zoster, and acquired perforating dermatosis.

“Mylabris, the dried body of the Chinese blister beetle, has been used medicinally for more than 2,000 years in China and is still used as a folk medicine today in Asia,” according to a 2001 article published in JAMA by Mary Wu Chang, M.D., and colleagues (DOI:10.1001/archderm.137.10.1357).

Cantharidin was first documented in literature in the 1800s and was used by dermatologists to treat molluscum contagiosum and warts, but in 1962, the U.S. Food and Drug Administration changed the rules now requiring clinical trials to support efficacy claims. Today, the FDA tolerates the use of physician or pharmacist-compounded drug products that include cantharidin. The FDA is currently considering adding cantharidin to its bulk drug substance list for pharmacy compounding under Section 503A.

Cantharidin works by being absorbed into the lipid layers of epidermal cell membranes, which activates or releases neutral serine proteases that degenerate desmosomal plaque, “leading to detachment of tonofilaments from desmosomes,” write Dr. Chang and colleagues in JAMA (DOI:10.1001/archderm.137.10.1357).

“This process leads to acantholysis and intraepidermal blistering, and nonspecific lysis of skin. Lesions heal without scarring, as acantholysis is
intraepidermal.”

If used improperly, such as for consumption, it can cause poisoning. But when it’s used as instructed, “complications are exceedingly rare,” they wrote.

Without an FDA-approved cantharidin product, physicians are reluctant to use it in clinic due to the potential of problems associated with reimbursement issues and possible liability, Dr. Davidson said.

“So, we have an unmet need and a product that appears to be a good solution, but there is no mechanism for patients to access the treatment, which is when, in around 2012, I began to develop cantharidin in a quality-controlled manner under good manufacturing conditions,” he said.

In 2015, Dr. Davidson partnered with PBM Capital Group, a Charlottesville, Virginia-based healthcare investment group, to fund Verrica. While common warts is an important indication, we decided that there was a greater need in the treatment of a similar pediatric viral skin disease called molluscum contagiosum,” he said.

“And then it was off to the races. With financing in place, I hired a chief medical officer, a head of clinical operations, got the drug manufactured at scale under good manufacturing conditions and the FDA allowed the start of clinical trials. Within five years, we went from inception to pivotal phase three trials,” he said.

**DRUG DEVELOPMENT**

In developing its cantharidin treatment, Verrica had to address a number of potential problems: access to ingredients, quality control and application. Previous trials, Dr. Davidson said, failed at the point of application. The Verrica team settled on an applicator modeled after a super glue applicator.

“Previous formulations were lacking in a workable, user-friendly formulation. Historically, people would take a jar of cantharidin specially formulated for themselves and then apply the treatment with a toothpick. Plus, they used the same jar repeatedly, which compromised the concentration of the product. It may start as a 0.7 percent solution, but it would very quickly dry out increasing in potency possibly leading to adverse events. Plus, it was frustrating because practitioners didn’t know how much to apply or how long to leave it on the skin,” he said.

The company purified cantharidin to greater than 99 percent, and formulated it in a film-forming solution within a single-use sealed glass ampoule. The clinician simply squeezes the applicator, which causes the glass to break. The solution then descends into the applicator tip, where a filter captures any glass particles.

The solution also includes small amounts of a purple surgical dye. “A faint violet color is placed on each lesion, so the provider knows which lesions has been treated,” White explains.

The first clinical trial of VP-102 for molluscum contagiosum was conducted in collaboration with Steven R. Cohen, M.D., M.P.H., chief if dermatology at the Albert Einstein College of Medicine, Bronx, N.Y. Patients received up to four treatments every three weeks. The treatment was shown to be safe and 44 percent of patients achieved complete lesion clearance by the 12-week endpoint with a mean lesion count reduction of 70 percent.

In a second phase two study with Verrica’s proprietary applicator, 50 percent of patients achieved complete clearance by the 12-week endpoint with the median patient clearing of 98 percent of lesions.

The two ongoing phase three trials compare the product to placebo because there are no FDA-approved treatments. No treatment-related serious adverse events have been reported in any of the company’s clinical studies.

When Verrica went public in June, it raised over $86 million. “We are looking for products that are unique, differentiated, have a patent life and are reimbursed by payers,” White said. “We are also truly excited that our current product is a new chemical entity (NCE) because there are not many NCEs in dermatology. Dermatology tends to be a lot of reformulations, like from a...
Diabetic foot infections

IDSA guidelines require classifying DFUs as infected or noninfected

JOHN JESITUS | Staff Correspondent

While dermatologists are unlikely to treat patients with severe foot infections that require hospitalization, they must be able to diagnose and manage mild-to-moderate infections in diabetic foot ulcers (DFUs), and follow current Infectious Diseases Society of America (IDSA) guidelines regarding antibiotic use, according to Warren S. Joseph, D.P.M., FIDSA, who presented at DERM-foot 2018. He is a consultant, lower extremity infectious diseases, Roxborough Memorial Hospital, Philadelphia, and a co-author of the IDSA guidelines, which appeared in Clinical Infectious Diseases in June 2012.

Dermatologists must be able to distinguish between noninfected DFUs and those that are mildly or moderately infected, he said. The IDSA requirement to classify DFUs as infected or noninfected is a key take-home message because it drives treatment decisions.

“We differentiate the infected from the noninfected by looking for the clinical signs and symptoms of infection such as erythema, heat, swelling, and induration,” Dr. Joseph said. Patients must possess at least two of these criteria, which also include local tenderness or pain and prurulence. Mild infections affect only the skin and subcutaneous tissues, while moderate infections include deeper tissues or erythema greater than 2cm, but no signs of systemic inflammation.

“All mild and most moderate DFUs can be treated on an outpatient basis,” he said. A publication he co-authored applies the IDSA classification scheme to all skin and soft tissue infections (SSTIs). Published in Open Forum Infectious Diseases in January 2017, this article suggests hospitalization and consideration of cultures and surgery for more severe types of moderate SSTIs.

“For years, people would say, ‘These patients don’t respond to infection, and therefore they may not demonstrate the classic signs of inflammation. What about subclinical infection that keeps wounds from healing?’ But I don’t believe there’s particularly good evidence behind this concern.”

IDSA guidelines also advise against cultivating noninfected wounds or treating them with antibiotics.

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We differentiate the infection from the noninfected by looking for the clinical signs and symptoms of infection, such as erythema, heat, swelling and induration.”

Warren S. Joseph, D.P.M., FIDSA, Roxborough Memorial Hospital, Philadelphia

Diabetic foot ulcers should be assessed for infection to determine treatment protocol FROM PAGE 26

you’re going to grow all sorts of bacteria. And none of them are necessarily causing infection.”

According to IDSA guidelines, many of diabetic foot infections can be treated in the outpatient setting. Guideline authors write, “Clinicians can probably use highly bioavailable oral antibiotics alone in most mild, and in many moderate, infections and topical therapy for selected mild superficial infections (strong recommendation, based on moderate evidence).”

With modern antibiotics that are more clinically bioavailable, or bioequivalent to IV antibiotics, “It doesn’t matter whether they’re given IV or PO. You’ve really got the same tissue levels,” said Dr. Joseph. “So there’s no reason to hospitalize patients unless they are septic or medically unstable. That’s not the patient that the average dermatologist deals with.”

Currently, only three antibiotics have FDA approval for diabetic foot infection. Ertapenem, piperacillin/tazobactam and linezolid (the only oral option) had been approved for these indications, he said, until the FDA removed DFUs from its acute bacterial skin and skin structure infection (ABSSSI) clinical-trial guidelines in 2013. Nevertheless, said Dr. Joseph, dermatologists can use any antibiotics off-label if they will be effective against the bacteria present.

A pooled retrospective analysis of two phase three trials involving ABSSSIs showed no difference in efficacy in the use of linezolid and teditzolid whether the infection was in the lower extremity versus other parts of the body, said Dr. Joseph, lead author of the analysis. This publication appeared in the July 2017 edition of the Journal of the American Podiatric Association.

Regarding duration of therapy, “we must move beyond the concept of giving an automatic number of days of antibiotic therapy. You can’t assume that 10 days, or two weeks, is the right number. What happens if the infection looks better in four days? Then you’re giving 10 more days of antibiotics which the patient probably doesn’t need.”

Instead, he suggested basing duration of therapy on clinical response.

“That long ago, the concept of ‘better plus two’ was floated. I believe it’s very valid — treat patients until they are clinically better, plus two more days before discontinuing the antibiotic. The big thrust nowadays in the pharmacy and infectious disease worlds is antimicrobial stewardship — using the narrowest-spectrum antibiotics for the shortest period of time to avoid developing antimicrobial resistance.”

Regarding methicillin-resistant Staphylococcus aureus (MRSA), IDSA guidelines recommend considering initial empirical therapy in three clinical situations:

If the patient has a previous history of MRSA.

If local MRSA prevalence is high. “We left that intentionally vague. But if it’s more likely MRSA than not, it’s worth using empirical MRSA therapy until proven otherwise.”

For severe infections where one cannot afford to be wrong.

“IDSA guidelines differentiate prurulent from non-prurulent cellulitis. In other words, if the patient has pus, one must consider MRSA until proven otherwise. We know MRSA produces more pus than methicillin-susceptible Staphylococcus aureus does.” For mild to moderate infections in patients who have not recently received antibiotic treatment, IDSA guidelines suggest that therapy targeting only aerobic gram-positive cocci may suffice.

Many physicians are concerned about Pseudomonas, he said. “But Pseudomonas is very rarely a pathogen in DFUs. It’s found less than 10 percent of the time because it’s a colonizer — you just find it on wounds. That’s the same even with venous stasis ulcers.” But as with predetermined durations of antibiotic therapy, “We’ve got to get away from assuming that Pseudomonas is actually a pathogen in these wounds — at least in the United States, Canada and Western Europe.” Pseudomonas is much more prevalent in hot, humid climates such as those of the Southern Hemisphere, the Indian Subcontinent and the Far East.

Disclosures: Dr. Joseph is a speaker for Merck, maker of tedizolid.

FOR MORE INFORMATION
Bringing Molluscum Contagiosum to Light

While as many as 1 out of every 5 healthy children contract molluscum contagiosum, this disease and the patients it affects receive very little attention. Quality of life can be negatively affected by a molluscum infection. Children with the disease may become stigmatized and experience teasing, embarrassment, and social isolation. Up to 82% of parents and caregivers express moderate to great concern about molluscum. Lesions may be mostly asymptomatic, but reports indicate that patients do complain about itching, burning, and tenderness.

Although lesions can resolve within 6 to 9 months, patients typically have the infection for 13 months, and some infections can persist for 2 years or more. Treatment at the time of diagnosis provides the best chance of decreasing the number of lesions and spread of the disease.

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Role of protease targets in wound healing uncertain

ILIYA PETROU, MD | Staff Correspondent

Protease modulating therapies are used to assist in venous leg ulcer closure. However, a recent systematic review of the evidence suggests a need to question the biomarker’s importance and further role in the future of targeted chronic wound healing therapies.

Earlier research reported in the literature has suggested that reducing protease levels can improve venous leg ulcer healing beyond the use of first-line treatments, such as compression, according to Maggie Westby, Ph.D., research fellow in the School of Health Sciences at the University of Manchester, UK.

“Whilst protease-modulating (PM) dressings are available to achieve this, in this review we looked upstream to explore what the actual prognosis evidence was for an association between proteases and wound healing,” Dr. Westby said.

Dr. Westby and colleagues conducted a Cochrane systematic review to determine whether protease activity is an independent prognostic factor for the healing of venous leg ulcers. The review included prospective and retrospective longitudinal studies with any follow-up period that recruited people with venous leg ulcers. The authors investigated whether protease activity in wound fluid was associated with future healing of venous leg ulcers.

Eleven studies covering 10 different matrix metalloproteinases (MMPs) and two serine proteases (human neutrophil elastase and urokinase-type plasminogen activators) and consisting of 13 cohorts with 522 participants had data available for the final analysis. Two studies assessed complete healing as the outcome; the remaining studies noted partial healing. A meta-analysis was not performed due to the varied methodologies, protease measurements and treatments. The collective evidence indicated complete uncertainty regarding the association between protease activity and venous leg ulcer healing.

If protease activity is shown to be independently associated with delayed healing, and existing or future treatments are shown to be effective in wounds with high protease levels, this could form part of a personalized medicine approach to wound care and, thus, proteases could be very valuable.

There is still potential for personalized medicine, but according to Dr. Westby, the current evidence base is insufficient to support this approach at the moment.

“We know that compression works, but there is a lot of uncertainty around the effectiveness of dressings in general and PM dressings in particular. As such, the evidence cannot inform whether clinicians should use or should not use protease modulating therapies,” she said.

Currently there is not enough known about the underlying mechanisms affecting delayed healing, and proteases may be only one of many biomarkers involved that can be modified using targeted treatments. The subsequent treatment strategy may differ from person to person.

There is a growing interest in the exploration of biomarkers that, if present in abnormal amounts, may be candidates for targeted treatment to improve outcomes. Biomarker prognosis reviews are new in the wound healing field and, according to Dr. Westby, they may allow the probing of mechanisms and pathways to help further our understanding of delayed healing, upon which targeted treatments could be researched and developed to improve outcomes.

“The protease prognostic factor systematic review highlights extreme uncertainty about the role of protease activity in wound healing. There is very limited research that elevated protease activity is associated with delayed healing. Whilst uncertainty can be frustrating in decision making, it is also important that we acknowledge it and are aware of,” she added.

Protease modulating therapies may be a good future option; however, clinicians should make treatment decisions on the basis of the current evidence, Dr. Westby says, and consider recent multiple-intervention review findings’ patient views, costs and other outcomes data.

“Further research is in progress, and we hope that prognosis research in particular will lead to exciting future approaches in wound care,” Dr. Westby said.

Disclosures: Dr. Westby’s employment at the University of Manchester while completing this work was funded by a National Institute for Health Research (NIHR)-funded Cochrane program grant that focused on high-priority Cochrane Reviews in the prevention and treatment of wounds. This research was co-funded by the NIHR Manchester Biomedical Research Centre.

References


FLARES AREN'T GOING TO PREVENT THEMSELVES

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Wound healing is impaired in both psoriasis and multiple sclerosis, raising the prospect that a better understanding of the process could improve our understanding of the pathophysiology of these two chronic conditions and generate targets for treating them.

The two conditions share a number of characteristics. For example, both diseases demonstrate slight itching, symmetry of the lesions, exacerbation after stopping corticosteroid treatment, and the Koebner phenomenon—provocation of the condition by stress.

The Koebner phenomenon (isomorphic response) was first described in 1876 by the German dermatologist Heinrich Koebner who noted that patients developed psoriasis at sites of excoriations, horse bites, and tattoos. Koebner famously saw a psoriatic plaque develop on the skin of a farmer where his horse, attempting to get to the sugar he kept in his trouser pocket as a treat, had bitten him, noted Vera B. Morhenn of the department of dermatology, San Francisco VA Medical Center, San Francisco, California in a review of the relationship between wound healing, psoriasis and multiple sclerosis published online in Advances in Wound Care.

“Stress has been reported to be a provoking factor for the first and subsequent flares of MS,” she says. “The occurrence of the Koebner phenomenon in psoriasis and MS suggests that the etiology of both of these diseases may relate to defects in the wound healing process.”

Wound healing occurs in four stages: hemostasis, inflammation, proliferation, and maturation.

Keratinocytes and oligodendrocytes play key roles in the process. Keratinocytes are the predominante cell in the epidermis so must be able to respond quickly to repair any damage. They synthesize a large number of cytokines including tumor necrosis factor alpha (TNFα), vascular endothelial growth factor (VEGF), and both the constitutive and inducible forms of nitric oxide synthase, Dr. Morhenn writes.

Oligodendrocytes are non-neural cells of ectodermal origin that form part of the adventitial structure of the central nervous system.

Keratinocytes and oligodendrocytes produce nitric oxide (NO) – a gas that is important in vasodilation and immune and inflammatory responses — and is a vital component of wound healing. NO stimulates keratinocyte proliferation, enhances their expression of VEGF, and activates their production of epidermal growth factor (EGF) receptor ligands. The synthesis of EGF results in an autocrine loop and proliferation of keratinocytes.

In psoriasis, the proliferation of keratinocytes does not stop when the wound has re-epithelialized and in MS repair of the myelin sheath which protects the nerves is not initiated or stops before the wound healing process is completed.

WHAT GOES WRONG IN PSORIASIS

Elevated intracellular calcium ion concentrations in keratinocytes mean that they do not differentiate, significantly increasing the rate of wound healing, according to Dr. Morhenn.

VEGF, a potent stimulator of angiogenesis, and its receptors VEGFR-1 and -2 have been shown to be overexpressed by keratinocytes in the suprabasal layers of the epidermis of psoriatic plaques, as well as, by dermal fibroblasts, implying a dermally derived influence on neovascularization, she writes.

Serum VEGF-A concentrations are also elevated in psoriasis.
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Wound healing insights may help clinicians better understand psoriasis, MS pathophysiology

From Page 32

increased in patients with psoriasis, suggesting it is being overproduced. The synthesis and secretion of VEGF-A is believed to be stimulated by TNFα and EGF in psoriatic keratinocytes, because of an overexpression of receptors for these proteins in psoriatic skin.

Psoriatic lesions of skin that has been traumatized also have increased amounts of nerve growth factor. The increase is evident 24 hours after injury and peaks after two weeks. Cultured keratinocytes taken from nonlesional psoriatic skin have also been shown to have increased levels of nerve growth factor, and these levels increase as keratinocytes proliferation accelerates.

Keratinocytes also express the muscarinic acetylcholine receptor (mACH-R), as well as the nicotinic acetylcholine receptor (nACH-R), and activation of the nACH-R reduces the rate of wound healing. Activation of the nACH-R reduces the rate of wound healing. Activation of the nACH-R reduces the rate of wound healing. Activation of the nACH-R reduces the rate of wound healing. 

“Activation of the mACh-R is needed for maintenance of the epidermal stem cells,” says Dr. Morhenn. “By contrast, in areas of skin that express the psoriatic phenotype, one of the antimicrobial peptides, LL-37, is highly expressed, and, therefore, the wound healing response would likely be initiated.”

There is clearly a relationship between the two conditions, she emphasizes. “Individuals with psoriasis have a significantly higher risk of developing MS and the more severe the psoriasis, the more likely the individual will develop MS,” she writes.

TNFα inhibitors have been used to improve psoriasis, although sometimes they can induce the disease, as well as worsen the symptoms of MS or even induce MS, Dr. Morhenn adds.

“The many similarities in the pathophysiology documented in psoriasis and MS, as well as in wound healing, suggest that further basic research in these two autoimmune diseases may lead to a better understanding of wound healing. Furthermore, these insights may, in turn, suggest novel therapies for psoriasis and MS,” Dr. Morhenn concludes.
Ixekizumab effective in nail psoriasis treatment

WHITNEY J. PALMER | Staff Correspondent

Patients who undergo treatment with ixekizumab (Taltz, Eli Lilly and Company) experience greater nail psoriasis improvement than individuals treated with ustekinumab (Stelara, Janssen Biotech, Inc.), according to data reported at the European Academy of Dermatology & Venereology Congress, Paris, France.

The phase 3b, multi-center, double-blind, head-to-head study, also published in the British Journal of Dermatology, compared treatment results for patients with moderate-to-severe psoriasis randomized to ixekizumab and ustekinumab for nail lesion treatment over 52 weeks.

"The results of the IXORA-S study suggest that Taltz may provide significantly greater clearance of nail psoriasis than ustekinumab," said Lotus Mallbris, M.D., Ph.D., vice president of immunology development, Eli Lilly and Company. "This is significant because nail lesions are a common feature of psoriasis. It is often associated with discomfort, which can lead to functional impairment and distress, further supporting the importance of complete clearance."

Investigators randomized patients to receive ixekizumab or ustekinumab. A total of 136 patients received a 160 mg starting dose of ixekizumab administered as two 80 mg injections. They then received 80 mg injections every two weeks for 12 weeks, followed by 80 mg injections every four weeks. The 166 ustekinumab patients received a 45 mg or 90 mg weight-based dose per label at weeks 0, 4, and every 12 weeks thereafter.

Investigators assessed each fingernail bed for lesions at baseline and at 52 weeks, determining severity with the Nail Psoriasis Severity Index (NAPSI). Scores from 0 with no nail psoriasis to 80 with severe nail psoriasis were combined to obtain total NAPSI scores.

According to results, 61.8% of ixekizumab and 63.3% of ustekinumab patients had nail psoriasis. Mean baseline NAPSI scores were 28.3 (SD: 19.9) and 24.8 (SD: 20.0), respectively. Both groups improved.

At 16 weeks, ixekizumab patients had greater resolution than ustekinumab patients (31% versus 16.2%, p=0.027). At 52 weeks, ixekizumab improvement expanded (61.9% versus 28.6%, p<0.0001). After 52 weeks, the average NAPSI score improvement was significantly larger in ixekizumab patients (-32.3, 95% CI: -30.8, -23.8) than in ustekinumab-treated patients (-15.6, 95% CI: -17.8, -13.4) (p<0.0001).

Despite substantial improvements in ixekizumab patients at one year, researchers stress the need for more lengthy observational studies to determine long-term results.

Reference


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Expert describes true skin emergencies

GALADRIEL BONNEL, PH.D., FNP | Staff Correspondent

Skin emergencies are rare, but when they occur, dermatologists need to act fast. Marcia Ramos-e-Silva, M.D., Ph.D., professor and chair of the University Hospital and Federal University School of Medicine, Rio de Janeiro, Brazil, told colleagues at the European Academy of Dermatology and Venereology Congress in Paris on Friday.

Indeed, “most of the patients who go to the E.R. with skin diseases don’t need to go to the E.R., and only a limited number of diseases are responsible for most of the true dermatological emergencies,” she said. This is an international problem; “what we see is almost the same all over the world.”

According to Dr. Ramos-e-Silva, the role of dermatologists should be to provide a differential diagnosis and to distinguish a true emergency from a commonly presenting problem, and this should be taught starting in medical school and residency programs.

True dermatological emergencies are caused by allergic reactions or infections (bacterial or viral). Immediate management is required in the most severe cases. Consequently, “most of the patients who go to the E.R. with skin diseases don’t need to go to the E.R., and only a limited number of diseases are responsible for most of the true dermatological emergencies,” she said. This is an international problem; “what we see is almost the same all over the world.”

According to Dr. Ramos-e-Silva, the role of dermatologists should be to provide a differential diagnosis and to distinguish a true emergency from a commonly presenting problem, and this should be taught starting in medical school and residency programs.

True dermatological emergencies are caused by allergic reactions or infections (bacterial or viral). Immediate management may be required in the case of severe drug reactions, infections, allergic reactions and flares of inflammatory dermatoses. She reviewed some of the most severe cutaneous adverse reactions: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, Dress syndrome, and Staphylococcal Scalded Skin Syndrome. The first three are clinically similar as they are part of a spectrum.

ERYTHEMA MULTIFORME
This is an acute (onset usually 24 hours), self-limited, but potentially recurrent skin disease primarily affecting the limbs and face in young adults. Target lesions are symmetrical, fixed, erythematous and papular, with central clearing. Erythema multiforme minor (unlike major) does not usually have mucosal involvement, painful erosions, or systemic symptoms. The precipitating factor is usually infection, particularly by the herpes simplex virus (HSV) or Mycoplasma pneumoniae, Dr. Ramos-e-Silva notes. She advises to treat the cause (e.g., antivirals prophylactically for HSV).

STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS
Stevens-Johnson syndrome and toxic epidermal necrolysis are acute, potentially fatal adverse cutaneous drug reactions (primarily medication-related), with mortality rates of 5% and 25-50%, respectively. They are rare and mainly affect women. Risk factors include certain genotypes and immunosuppression.

Keratinocyte death via apoptosis leads to a scalded skin appearance and mucosal detachment; other signs and symptoms include high fever, stinging eyes, skin pain, irregular erythematous, dusky red, or purpuric macules. Dr. Ramos-e-Silva states that the extent of surface area involved is important to distinguish these two problems. Treatment includes discontinuing any and all possible drugs.

DRESS SYNDROME
Dress syndrome is an unusual, potentially life-threatening (2-10% mortality), multiorgan adverse reaction that develops two to six weeks after drug initiation. Fever and a morbilliform eruption, which involves the face, upper trunk and extremities, occur in 85% of patients. Treatment includes systemic corticosteroids and IV immunoglobulin.

STAPHYLOCOCCAL SCALDED SKIN SYNDROME
This is a hematogenous dissemination of the exfoliative toxins produced by *S. aureus*, mainly in infants and young children, involving malaise, fever, irritability, skin tenderness, erythema progressing to bullae within 48 hours, and fissures. The treatment is antibiotics with supportive care. Almost any bacterial infection can progress to an emergency situation, Dr. Ramos-e-Silva says.

These emergency conditions are best diagnosed by dermatologists, Dr. Ramos-e-Silva emphasizes, and emergency departments should involve these specialists when needed.

On the other hand, primary care practitioners should be ready to care for common dermatological conditions which should be treated as outpatient, and not in the E.R. ▲

Reference
Marcia Ramos-e-Silva, M.D., Ph.D. “Emergencies in dermatology” (abstract #D2T01.1G). EADV 2018 Meeting, Paris, France, September 14, 10-10:20 a.m.
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JAK trial effectively reverses alopecia areata

Two JAK inhibitors met their primary endpoints in a phase 2a study of alopecia areata. The study, presented at the European Academy of Dermatology and Venereology (EADV) Congress in Paris, focused on the safety and efficacy of PF-06651600, an oral Janus kinase (JAK) 3 inhibitor; and, PF-06700841, a tyrosine kinase (TYK) 2/JAK1 inhibitor.

Both JAK inhibitors met week 24 primary endpoints by improving hair regrowth scoring 33.6 of 100 points on the Severity of Alopecia Tool (SALT) scale and 49.5 of 100 points for JAK3 and TYK2/JAK1 respectively, according to Rodney Sinclair, M.D., of Sinclair Dermatology in Melbourne, Victoria, Australia, who shared the data.

The management of alopecia areata is complex. While spontaneous and treatment-induced recovery occurs in up to 50% of cases, this still leaves around 73 million people worldwide who suffer from chronic alopecia areata, or up to 25% whom have total hair loss.

“Given these figures, there’s an unmet need for a reliable and effective therapy in moderate-to-severe alopecia areata,” Dr. Sinclair said.

Alopecia areata is driven by cytotoxic T lymphocytes and reversed by JAK inhibition. An increasing number of case reports have demonstrated that oral JAK inhibitors effectively treat chronic alopecia areata. However, few randomized controlled trials have investigated the efficacy and safety of JAK inhibitors.

This trial investigated hair regrowth and adverse events. The study recruited an initial 145 adults with moderate-to-severe alopecia areata, which was defined as hair loss affecting more than 50% of the scalp that had persisted for more than six months. The trial included a handful of patients with areata totalis and areata universalis.

Subjects were randomly allocated to a PF-06651600 group (n = 48), PF-06700841 group (n = 47), or control group (n = 49). The PF-06651600 group received 200 mg/day during the induction period and 50 mg/day in the maintenance phase. The PF-06700841 group received 60 mg/day during the maintenance phase. The control group received a placebo.

At week 24 (vs. baseline), SALT-30 was achieved in 48% of the PF-06651600 group and in 36% of the PF-06700841 group.

“A number of subjects in the two treatment groups also achieved SALT-50 to SALT-75, and a significant proportion achieved SALT 90-100,” Dr. Sinclair reported.

The patients with areata totalis and areata universalis that received treatment also showed significant improvements in SALT scores and in eyebrow and eyelash scores.

Rhabdomyolysis was observed in two cases in the PF-06700841 group, and this was resolved after discontinuation. No other major adverse events were recorded.

“These JAK inhibitors are well-tolerated in patients, including those with areata universalis and areata totalis. Both treatments achieved the primary and secondary endpoints, and safety and tolerability, and I think that our patients with alopecia areata now have reason to be optimistic,” he said.

Disclosures: The featured study was funded by Pfizer.

Reference
Sinclair, R. (2018). A Phase 2a Randomized, Placebo-controlled Study to Evaluate Efficacy and Safety of Janus Kinase Inhibitors PF-06651600 and PF-06700841 in Alopecia Areata: 24-Week Results, The 27th European Academy of Dermatology and Venereology Congress, Paris, France, 15th September, 08:00 AM.
Even with the breadth of options available for patients with moderate-to-severe psoriasis ... Many don’t reach their treatment goals.”

Anne Robinson executive scientific director, AbbVie

Even with the breadth of options available for patients with moderate-to-severe psoriasis, there is still a high unmet need for these patients,” she said. “Many don’t reach their treatment goals.”

Patients were randomized to risankizumab in a head-to-head study with adalimumab, the psoriasis standard-of-care, and achieved greater skin clearance based on Psoriasis Area Severity Index (PASI) and Physician Global Assessment (PGA) scores at 16 weeks. After 16 weeks, patients with PASI scores of at least 50, but not 90, were randomized to continue with adalimumab or risankizumab and were re-assessed at week 44. Re-analysis revealed more risankizumab patients achieved PASI 90 scores than those receiving adalimumab.

Pooled data from the trials also revealed risankizumab is more effective than placebos in helping patients reach PASI 90 scores and PGA 0 or 1 scores at 16 weeks. In addition, patient information also showed risankizumab performed better in treating psoriasis that appears on the nails, hands, feet, and palms, as well as scalp sores.

“This pooled information is important to show the impact of risankizumab in those specific body areas,” Robinson said. “You really aren’t able to robustly assess individual results based on the relatively less-frequent occurrence in those particular areas of the body.”

Alongside revealing safety profiles comparable to adalimumab and other currently available psoriasis treatments, Robinson said, the trials also demonstrated that risankizumab performs consistently across patient groups. Researchers reviewed results for patients of all ages, weights, and geographic locations.

“It was reassuring to see that, regardless of the type of patient category analyzed, the patients were all very similar in the type of benefit they received with risankizumab treatment,” she said. “There wasn’t one category that was driving the benefits or one that wasn’t driving the benefits.”

Consequently, Robinson said, the comparable safety profile and the similar performance across all patient subgroups could increase dermatology confidence in how patients would respond to risankizumab, if given the opportunity.

Ultimately, she said, the results indicate that if risankizumab receives approval from the FDA, it will open the door for more patients to potentially experience a greater reduction in the impact of plaque psoriasis.

“Not every patient will respond to what’s currently available, and even those who do can lose response over time,” she said. “So, it’s important to look for new options for patients to achieve durable skin clearance and reach their treatment goals.”

Reference

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Dupilumab efficacy may extend to adolescents

NIA CASON | Staff Correspondent

Dupilumab (Dupixent, Sanofi Genzyme Regeneron) met its primary endpoints in a phase 3 study that focused on its use as a treatment for adolescents with moderate-to-severe atopic dermatitis. Data were presented at the European Academy of Dermatology and Venereology (EADV) Congress in Paris. “Dupilumab treatment showed clinically meaningful and statistically significant improvements in atopic dermatitis signs and symptoms and quality of life in adolescents,” said Eric Simpson, M.D., of Oregon Health and Science University, Portland, Ore., and the study’s principal investigator.

Atopic dermatitis in adolescence has an estimated prevalence of 8.6% in the United States and 5-15% in Europe. Adolescent atopic dermatitis affects mood, sleep and behavior, and the chronic relapsing nature of the condition severely affects quality of life. At present, there are limited treatment options for adolescents that have a good efficacy-safety ratio.

Dupilumab is a human monoclonal antibody directed against the interleukin-4 receptor subunit alpha (IL-4Rα) common to the receptors for interleukin-4 (IL-4) and interleukin-13 (IL-13), both of which are seemingly important in AD pathogenesis. Dr Simpson’s work follows previous work examining dupilumab in adults with atopic dermatitis in which it was shown to be safe and effective.

This randomized, placebo-controlled, double-blind, parallel-group study recruited 251 adolescents aged 12 to 17 years old (mean age: 14 years) with moderate-to-severe atopic dermatitis that was inadequately controlled by topical therapies. After a washout period, subjects were randomly allocated to a dupilumab Q4W treatment group (300 mg; n = 84), dupilumab Q2W treatment group (200 mg or 300 mg; n = 82), or a placebo group (n = 85). Endpoints were measured at baseline and at week 16.

The population had more severe atopic dermatitis than that of the previous study with adults, with higher mean Eczema Area and Severity Index (EASI) scores, a larger proportion exhibiting severe atopic dermatitis, and high allergic comorbidity (92%). The mean disease duration was 12 years.

Both dupilumab groups showed a significantly higher proportion of patients with IGA scores of 0 or 1 (clear or almost clear) than the placebo group at week 16, with slightly stronger responses seen in the Q2W group (Q4W group: 17.9%; Q2W group: 24.4%; placebo group: 2.4%). The proportion of patients reaching EASI-75 at week 16 was 38.1% in the Q4W group, 41.5% in the Q2W group, and 8.2% in the placebo group. All results were significant at p < 0.001.

“The effect sizes seen in the change in EASI scores from baseline were larger than those seen in the previous adult trial,” Dr Simpson said. Dupilumab treatment also enhanced quality of life as compared to placebo, as measured by the Children’s Dermatology Life Quality Index and the Patient Oriented Eczema Measure score.

Rates of conjunctivitis and injection-site reactions were higher in the dupilumab groups, but atopic dermatitis exacerbation and non-herpetic skin infections were higher in the placebo group. There was one serious adverse event in the placebo group (appendicitis).

“For most categorical endpoints, the Q2W regimen was numerically superior to the Q4W regimen,” Dr Simpson said. “Both placebo-corrected efficacy and safety of dupilumab in adolescents were similar to those observed in adults.”

Reference
Simpson, E. (2018). Dupilumab Efficacy and Safety in Adolescents with Moderate-to-Severe Atopic Dermatitis: Results from a Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Phase 3 Study, The 27th European Academy of Dermatology and Venereology Congress, Paris, France, 15th September, 10:45 - 11:00 AM
**INDICATION**

RETIN-A MICRO (tretinoin gel) microsphere is indicated for topical application in the treatment of acne vulgaris.

**IMPORTANT SAFETY INFORMATION**

- The skin of certain individuals may become excessively dry, red, swollen or blistered during the use of RETIN-A MICRO.
- Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.
- If warranted, patients should temporarily reduce the amount or frequency of application, or discontinue use temporarily or altogether. If a reaction suggesting sensitivity occurs, use should be discontinued.
- Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of RETIN-A MICRO, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight with the use of tretinoin.
- Patients should be encouraged to use a sunscreen with a SPF of 15 or higher and protective clothing over treated areas when exposure cannot be avoided.
- Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.
- The most common adverse events are mild to moderate irritation (erythema, peeling, dryness, burning/stinging, or itching of the skin).
- RETIN-A MICRO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and caution should be exercised in prescribing for nursing mothers. Safety and efficacy in patients under 12 have not been established.

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.
BRIEF SUMMARY OF PRESCRIBING INFORMATION
This Brief Summary does not include all the information needed to use RETIN-A MICRO safely and effectively. See full prescribing information for RETIN-A MICRO.

RETIN-A MICRO® (tretinoin) gel microsphere, 0.1%, 0.08%, 0.06% and 0.04%, for topical use
Initial U.S. Approval: 1971

INDICATIONS AND USAGE
RETIN-A Micro® is a retinoid indicated for topical application in the treatment of acne vulgaris.

CONTRAINdications
None.

WARNINGS AND PRECAUTIONS
Local irritation
The skin of certain individuals may become excessively dry, red, swollen, or blistered.

Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use altogether. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued.

To help limit skin irritation, patients must
• wash the treated skin gently, using a mild, non-medicated soap, and pat it dry, and
• avoid washing the treated skin too often or scrubbing it hard when washing.

Patients should apply a topical moisturizer if dryness is bothersome.

Exposure to Ultraviolet Light or Weather Extremes
Unprotected exposure to sunlight, including sunlamps (UV light) should be avoided or minimized during the use of Retin-A Micro and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have extended periods of UV exposure (e.g., due to occupation or sports), or those with inherent sensitivity to the sun, or those using medications that cause photosensitivity, should exercise particular caution.

In trials of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, and tretinoin cream, 0.1%, has now treated areas are recommended when exposure cannot be avoided [see Nonclinical Toxicology].

Weather extremes, such as wind or cold, also may be irritating to tretinoin-treated skin.

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

Clinical Trials in Subjects with Acne
In separate clinical trials for each concentration, acne subjects treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1% or 0.04%, over the twelve-week period showed that cutaneous irritation scores for erythema, peeling, dryness, burning/stinging, or fudging peaked during the initial two weeks of therapy, decreasing thereafter.

Approximately half of the subjects treated with Retin-A Micro, 0.04%, had cutaneous irritation at Week 2. Of effects, most of the subjects reported skin irritation, most with scores indicative of a mild irritation; 1% (3/225) of subjects treated with Retin-A Micro (tretinoin) Gel microsphere, 0.04%, discontinued treatment due to irritation, which included dryness in one patient and peeling and urticaria in another.

In trials of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, no more than 3% of subjects had severe irritation scores indicative of a severe irritation; 1% (3/225) of subjects treated with Retin-A Micro (tretinoin) Gel microsphere, 0.04%, discontinued treatment due to irritation, which included dryness in one patient and peeling and urticaria in another.

In a double-blind trial with 156 acne subjects comparing 12 weeks of treatment with Retin-A Micro (tretinoin) Gel, 0.04% or 0.1% (78 subjects each group), the most frequently reported adverse events affecting the skin and subcutaneous tissue were reported for doses of 10 mg/kg/day but none were observed at 5 mg/kg/day (95 times the MRHD based on BSA comparison).

In trials of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, no more than 3% of subjects had cutaneous irritation scores indicative of a severe irritation; 1% (4/122) of subjects treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1%, discontinued treatment due to irritation. Of these 14 subjects, four had severe irritation after 3 to 5 days of treatment, with blistering in one subject.

In a 21-day trial in 45 subjects with acne, most adverse events were mild in severity (severity was ranked on a 4-point ordinal scale: 0=none, 1=mild, 2=moderate, 3=severe). Less than 10% of patients experienced moderate cutaneous irritation and there was no severe irritation at Week 2.

In trials of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, 0.08%, 0.06% and 0.04%, over the twelve-week period treated areas were recommended when exposure cannot be avoided [see Nonclinical Toxicology].

Dermatologic findings and other adverse events consisted of skin irritation and were considered drug-related.

Trials in Subjects without Acne
In a half-face comparison trial conducted for up to 14 days in women with sensitive skin, but without acne, Retin-A Micro (tretinoin) Gel microsphere, 0.1%, was statistically less irritating tretinoin cream, 0.1%, but not compared to other agents 21-day trial in 25 women with normal skin showed that Retin-A Micro (tretinoin) Gel microsphere, 0.1%, had a lower irritation profile than tretinoin cream, 0.1%. The clinical significance of these irritation studies for patients with acne is not established.

Comparability effectiveness of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, and tretinoin cream, 0.1%, has now been established. The lower irritancy of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, in subjects with acne may be attributable to the properties of its vehicle. The contribution of decreased irritancy by the MICROSPONGE System has not been established. No irritation trials have been performed to compare Retin-A Micro (tretinoin) Gel microsphere, 0.04%, with either Retin-A Micro (tretinoin) Gel microsphere, 0.1%, or tretinoin cream, 0.1%.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of Retin-A Micro Gel.

Because these 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.

Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. Retin-A Micro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Thirty human cases of temporally associated congenital malformations have been reported during two decades of clinical use of tretinoin products. Although no definite pattern of teratogenicity and no causal association could be established from these cases, five of the reports describe the rare birth defects category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

For purposes of comparison of the animal exposure to systemic human exposure, the MRHD applied topically is defined as 1 gram of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, 0.1%, applied daily to a 60 kg person (0.017 mg tretinoin/kg body weight).

Pregnant rats were treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1%, at daily dermal doses of 0.001 mg/kg/day tretinoin (0.3% of the dermal maximally tolerated dose of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice.

There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.1 times the MRHD based on BSA comparison).

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Dermal carcinogenic testing has not been performed with Retin-A Micro (tretinoin) Gel microsphere, 0.1%, 0.08%, 0.06% or 0.04%.

In a 91-week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. These concentrations are near the tretinoin concentration of 0.04% and 0.1% clinical formulations. A dose-related incidence of liver tumors in male mice was observed at these same time of the maximum systemic exposures associated with the administered 0.017% and 0.035% formulations. These doses are two and four times the MRHD based on BSA comparison.

The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice.

Ovulation
Oral ingestion of large amounts of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.
ANGIOFIBROMA TREATMENT

Topical sirolimus shows positive results in two studies

WAYNE KUZNAR | Staff Correspondent

Topical sirolimus may offer a new treatment option for angiofibroma, a benign tumor most often appearing first during childhood. It is associated with tuberous sclerosis complex (TSC) in children. Angiofibromas can become more aggressive and more confluent as people get older. In some patients, it can be disfiguring. Current treatments include laser surgery, cryotherapy, dermabrasion, which, in addition to being painful and causing scarring, don’t prevent recurrence of lesions.

A recent large study led by researchers at The University of Texas Health Science Center at Houston, and published in the July issue of *JAMA Dermatology*, showed that 1% topical rapamycin appears effective and safe for treatment of TSC-related facial angiofibromas.

A smaller study published in the same issue of *JAMA Dermatology* by researchers at Osaka University in Japan supports the use of 0.1% topical tacrolimus (Protopic) for angiofibromas and other tuberous sclerosis complex lesions. The authors found that 0.2% sirolimus gel was clinically beneficial for treating TSC-related facial angiofibromas.

A consideration in the use of 1% topical sirolimus for angiofibromas is the likely need for long-term uninterrupted treatment, according to Thomas N. Darling, M.D., Ph.D., who authored an editorial that accompanied the rapamycin study. A study by Malissen et al (*J Am Acad Dermatol* 2017;77:464-72) showing that reducing the frequency of use to three times weekly was used off label.

Another consideration is when to initiate therapy; some reports suggest greater efficacy with treatment at early stages of tumor formation. While short-term studies suggest a low potential for adverse events, long-term studies are needed to better define the adverse event profile; although, “results from long-term oral administration in TSC and in transplant recipients provide some reassurance,” Dr. Darling wrote. Finally, the optimal topical formulation (ointment, gel, solution) needs to be defined, and whether or not surgery for thicker lesions before starting sirolimus would enhance efficacy should be determined, he wrote.

**RAPAMYCIN STUDY**

In the rapamycin study, 179 patients were randomized into one of three arms: a vehicle-only control, topical rapamycin 0.1%, or topical rapamycin 1%. The treatment or vehicle was applied nightly for six months. The group randomized to 1% rapamycin had a mean improvement of 16.7 points from baseline to visit seven on the AGS, which was statistically superior (overall and at every study visit) to the mean 2.1-point improvement in the patients randomized to vehicle only (P<0.001). Patients randomized to 0.1% rapamycin had a mean 11.0-point improvement on the AGS at visit seven, which was statistically superior to vehicle only overall (P<0.01), and at every individual visit except visit 2 (P=0.07). Use of 1% rapamycin was visually superior to 0.1% rapamycin but not statistically significantly superior.

The end-of-trial photo was rated better than the baseline photo in the 1% rapamycin group for 81.8% of patients compared with 65.5% in the 0.1% rapamycin group and 25.5% in the vehicle-only group.

“Over time, the lesions began shrinking and regions of the face became clearer. One of the things that we would like to see is whether the oral therapy in combination with the topical could produce further improved outcomes. We also think that further studies are needed to define the optimal dose or the optimal concentration. As we only used two concentrations we don’t know if perhaps 2% would be even better or maybe 0.5% would be enough,” said Mary Kay Koenig, Ph.D., department of pediatrics, The University of Texas Health Science Center at Houston.

**MORE TO EXPLORE**

Mary Kay Koenig, MD; Cynthia S. Bell, MS; Adekade A. Hebert, MD, et al. “Efficacy and Safety of Topical Rapamycin in Patients with Facial Angiofibromas Secondary to Tuberous Sclerosis Complex. A Randomized Clinical Trial,” *JAMA Dermatology* July 2018. DOI:10.1001/jamadermatol.2018.0464

Mari Watabe-Kaneda, MD, PhD; Yuuki Ohno, MD; Ysassiyuki Fujita, MD, PhD, et al. “Sirolimus Gel Treatment in Patients for Facial Angiofibromas,” *JAMA Dermatology* July 2018. DOI:10.1001/jamadermatol.2018.1408

Thomas N. Darling, M.D., Ph.D. “Topical Sirolimus to Treat Tuberous Sclerosis Complex (TSC),” *JAMA Dermatology* July 2018. DOI:10.1001/jamadermatol.2018.0465

**EVOLUTION OF THERAPEUTIC DEVELOPMENT**

Immunosuppressives that inhibit cell signaling pathways began to be tested in inflammatory skin diseases about 25 years ago. Topical tacrolimus, which inhibits calcineurin, was approved by the Food and Drug Administration in 2000 for the treatment of atopic dermatitis. Topical sirolimus, which interrupts the mammalian target of rapamycin (mTOR) pathway, was not showing the same efficacy as topical tacrolimus.

Later, the loss of TSC1 and TSC2 protein function in tuberous sclerosis complex tumors was found to lead to activation of mTOR, a regulator of cell growth and protein translation, and tumor formation. In 2006, the mTOR inhibitor sirolimus administered orally was shown to reduce the size of TSC subependymal giant cell astrocytomas, an indication for which it received FDA approval in 2010. While oral sirolimus was also found to lead to an improvement in angiofibromas and other tuberous sclerosis complex lesions, the rate of potentially serious adverse effects prevented its use for this indication. Study of topical sirolimus for the treatment of tuberous sclerosis complex skin lesions followed, and the documented efficacy in case reports and study participants led to compounding pharmacies making a topical version that was used off label.
The skin cracks associated with DFUs make these wounds particularly vulnerable to the introduction of fungus, the authors wrote.

“Fungal foot infections, although often overlooked, are dangerous in that they create a portal of entry for secondary bacterial infection through fissures and splits,” they said.

Existing research indicates the presence of fungi in the DFU wound microbiome often goes under-identified. According to one study, those who examined yeast and fungi in chronic wounds, 23% tested positive for fungi. But, nearly 41% of DFUs were fungal positive, and the predicted fungal bacterial ratio was more than 50%. Another study, focusing exclusively on DFUs found 28.6% were fungal-positive based on microscopic examination, but only 20% were positive by culture.

These findings, the authors say, suggest fungi is present, but standard microbiology laboratory protocols should detect more than 25% of DFUs, supporting the assertion that culture-dependent methods underestimate diversity and burden.

To get a better picture of how fungi impact wounds, the authors cited their own follow-up research using PCR-based amplicon sequencing of the fungal internal transcribed spacer region to more specifically pinpoint the prevalence and structure of fungal communities in DFUs over six months. They found highly diverse fungi were present in 71.6% of DFU specimens and in 79% of wounds within a 26-week study.

Importantly, researchers say patients who received systemic antibiotics had much higher fungal diversity in wounds than those who didn’t.

“This suggests that using antibiotics solely targeting bacteria may create an environment favorable to fungal colonization and expansion,” the authors wrote.

Increased fungal diversity was also linked to worsening wound environments, suspected bacterial infections, and an increase in prescribed antibiotics.

**Fungal Species**

Previous research indicates more than 75% of commonly isolated yeasts in DFUs were from the genus Candida. In fact, the same three species—Candida parapsilosis, Candida tropicalis, and Candida albicans—were present in more than 50% of fungal-positive wounds. The review authors also identified, using high frequency, a clear distribution of wounds with high proportions of pathogenic or allergenic fungi, such as Cladosporium spp. and Aspergillus spp. These fungi and others are linked to poor outcomes, including open wounds that remained after six months of treatment, the authors note. Fungal pathogens are also highly associated with wound necrosis which frequently leads to amputation.

Additionally, the investigators discovered chronic rhinitis, like DFUs, is associated with polymicrobial colonization and biofilm formation. The allergenic fungi were linked to larger and longer-lasting wounds, but they weren’t associated with hemoglobin A1C or white blood cell counts that impact foot ulcers. These findings further indicate fungi found in slow-healing wounds is underestimated and needs further investigation, they said.

“Exclusion of fungi from DFU microbiome analysis is short-sighted because the healthy skin microbiome comprises bacteria and fungi,” they wrote. “Moreover, the feet have been shown to exhibit the highest level of fungal diversity within the skin microbiome, with many species considered opportunistic pathogens. Culture-dependent and culture-independent studies focusing on fungi have consistently revealed that a significant portion of chronic wounds, such as DFUs, are colonized or infected with fungi.”

The researchers hypothesized that, as a mixed bacterial-fungal community, the wound microbiome would facilitate interactions between gram-positive and gram-negative bacteria and fungi to form multi-species biofilms. Existing data show fungi promotes adhesion to these surfaces and could give bacteria a substrate on which to bind, making it harder for antimicrobial medications to penetrate a wound.

Overall, the authors wrote, the evidence points to the need to expand the arsenal of medications used to fight these infections. Using only drugs that target bacteria can lead to the flourishing of fungi in wounds tissue and open the door for fungal infections to spread.

“Current treatments for wounds with suspected biofilm are primarily focused on targeting bacteria,” they said, recommending providers prescribe fluconazole to decrease the mean healing time for a DFU. They advocated for continued research into the wound microbiome to expand the knowledge base surrounding the relationship between microbial bioburden, wound progression, host response, and other individual characteristics.

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**References**

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Scarc formation ‘better’ in elderly

**Cellular-level findings provide clues about wound repair**

**WHITNEY J. PALMER | Staff Correspondent**

### Quick Takes

- Researchers sought to understand factors that influence scar formation.
- They noted that SDF1 is present in greater amounts in younger individuals leading to thinner scars.
- Findings may change how dermatologists treat hypertrophic and keloid scars.

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**Older skin might heal more slowly, but it heals with less scarring than younger skin.**

According to new research, published in *Cell Reports*, the secreted compound stromal-derived factor 1 (SDF1) is present in greater amounts in younger individuals, leading to thicker scars. Older individuals have lower SDF1 levels. This finding could explain why older patients have less significant scarring from surgery or wounds, said researchers from the Perelman School of Medicine at the University of Pennsylvania, Philadelphia.

To determine what factors might influence scar formation, researchers conducted several experiments with young and old mice. They confirmed younger mice are more prone to scarring and identified SDF1 as the differentiating compound.

### The Study

Using 2mm ear piercings in the ears of both 1-month-old and 18-month-old mice, the team showed how these groups heal differently. The mice had the equivalent human ages of 12 years old and 70 years old, respectively. Using H&E staining, they discovered the ears of older mice healed with normal tissue, hair follicles, sebaceous glands, and subcutaneous fat. They did not scar. Conversely, the opposing cartilage end plates in younger mice remained approximately 2mm apart, and they had visible scarring.

Results were duplicated by performing full-thickness excisional wounding assays to assess dorsal back skin. Younger mice healed with fibrotic scars and exhibited higher levels of α-smooth muscle actin (αSMA), a marker of myofibroblasts that are involved in scar formation. Older mice experienced less scarring, a return of hair follicles, and lower αSMA levels. Younger mice did heal faster, reaching 85% of their full healing within two weeks. Older animals only achieved 30% during that same time.

Additionally, the researchers tested whether a circulating factor in blood played a role in scarring and tissue regeneration. By mingling the blood of young and older mice, they created a heterochronic parabiosis pair (young:old), and they compared it to isochronic control pairs (young:young and old:old). When comparing 2mm ear piercings, the isochronic pairs behaved as previously demonstrated. The old:old group’s ears healed with smaller-sized holes, cartilage regeneration, and no scarring while the young:young pair experienced scar formation. However, in the heterochronic pair, the older mice adopted the healing process seen in younger mice, healing with larger holes and scars.

As a result, researchers concluded a circulating factor found in young blood does, in fact, promote scar formation and blocks skin tissue regeneration in older mice. Based on evidence from existing literature on tissue regeneration, they opted to focus on SDF1, a gene associated with regeneration, as a possible responsible factor. They hypothesized SDF1 suppression in older mice promoted tissue regeneration. With immunohistochemistry and cell isolation experiments, they localized the majority of SDF1 expression to wound edge keratinocytes, indicating that age suppresses SDF1 secretion from injured keratinocytes.

Using a generation of mice designed to limit keratinocytes-secreted SDF1, the investigators confirmed conditional SDF1 inactivation in keratinocytes. The modified mice experienced more healing of ear piercings, increased chondrocyte proliferation, diminished αSMA expression, and decreased scarring. In addition, serum SDF1 levels did not increase. Researchers, next, created a heterochronic parabiosis pair between young, modified mice and older, control-group mice, to confirm whether skin-specific SDF1 bolsters scar formation. Ear piercings in these modified mice saw reduced scar formation, the return of more hair follicles, and reduced αSMA levels.

These findings are not isolated to mice. They can also be applied to human skin, the researchers said. Similar to mice, wounded young human skin presented higher levels of SDF1 transcript compared to older wounded human skin. By depriving the tissue of nutrients, which mimics the loss of blood supply during injury, investigators revealed SDF1 increased in young skin, but not in older skin.

In addition, they created 3-dimensional organoid constructs with young (<1 year old) and older (>71 years old) human skin cells. Hole punch injuries, like the ear piercings, prompted SDF1 transcript and protein and downregulated the transcript of EZH2, an enzyme that silences gene function, in an age-dependent manner. They also treated these constructs with DZNep, a pharmacologic EZH2 inhibitor, and it restored SDF1 expression in older organoids. The results, they said, indicate inhibiting SDF1 or EZH2 could decrease scar formation in humans, but clinical trials would be necessary to validate those findings.

Overall, these results suggest the desire and need for tissue to heal and regenerate quickly fades over time. While controlling SDF1 expression can limit scar production, the researchers said more work is necessary to develop a better understanding of the compound’s impact on skin, as well as other organs.

“We speculate that, from an evolution perspective, a young injured animal favors fast and imperfect wound repair over slow and perfect tissue regeneration,” they wrote.

“Future studies are needed to assess the relationship between skin re-epithelialization speed and scar formation.”

---

Reference:
COULD THE SKIN LESION YOU’RE SEEING...

ACTUALLY BE A DEADLY BLOOD CANCER?

YOU PLAY A CRITICAL ROLE IN EARLY AND ACCURATE DIAGNOSIS OF BPDCN

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive and deadly hematologic cancer with skin lesions that may be mistaken for other skin disorders.¹ ²

WHO ARE PATIENTS WITH BPDCN?

- ~85-90% present with skin lesions²⁻⁴
- ~75% are men²⁻⁵
- Typically between 60-70 years of age, but all ages can be affected²⁻⁵

Plasmacytoid dendritic cells (pDCs) invade the dermis where they proliferate, resulting in skin lesions that take the form of¹⁻³⁻⁶:
- Nodular lesions (73%)
- Bruise-like macules (12%)

Research has uncovered key markers, including α123, that allow for the proper diagnosis of BPDCN.⁶ *

*BPDCN diagnosis can include other markers, such as α4, α56, TCL1, and α303 (BDCA2).⁷

For more information, visit BPDCNinfo.com.

WHEN BIOPSING SKIN LESIONS, ASK YOUR PATHOLOGIST TO TEST FOR α123. REFER PATIENTS EARLY.

REFERENCES:
Post-treatment pigmentation

Low-dose bleomycin injections result in curious side effect

LISETTE HILTON | Staff Correspondent

Low-dose bleomycin injections used to treat venous and venous lymphatic malformations might have an unanticipated side effect: curiously-shaped hyperpigmentation, researchers reported at the International Society for the Study of Vascular Anomalies’ (ISSVA’s) annual workshop in Amsterdam.

“One of the standards of care in the interventional radiology community for patients with venous and venous lymphatic malformations is to inject a very, very low dose of bleomycin,” said Bernard Cohen, M.D., professor of pediatrics and dermatology, Johns Hopkins University, Baltimore, who presented with colleagues on several case studies.

Providers tend to favor bleomycin treatment for patients with these malformations because of the low risks for intense inflammation or ulceration. The chemotherapy agent causes a clot to form, often making the malformation disappear. The treatment carries lower risk of scarring, pain and inflammation than with other agents, including alcohol according to Dr. Cohen.

However, pigmentation may appear in places where a patient’s skin experienced minor pressure or trauma. The pigment, for example, might be in the shape of electrocardiography (EKG) leads, tape or the neckline of a hospital gown.

Dr. Cohen tells patients to avoid putting pressure on their skin in the weeks following treatment and to use sunscreen to protect from darkening.

“It’s important to explain to these patients that while bleomycin injection for venous and venous lymphatic malformations is safe and not likely to make a scar or an ulcer, it may leave some pigmentation,” he said.

In most cases, the hyperpigmentation resolves with time, he said.

References
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- High satisfaction\(^1\)\(^-\)\(^5\)
- Usage across a wide range of skin types\(^1\)\(^-\)\(^5\)
- Low to no downtime\(^1\)\(^-\)\(^5\)

\(^*\)Based on available 510(k) summaries as of October 2017.


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Practical lessons learned with checkpoint inhibitors

GALADRIEL BONNEL, PH.D., FNP | Staff Correspondent

**Quick Takes**
Only a minority of patients with advanced melanoma have long-term survival.

Anti-PD-1/PD-L1 agents demonstrated less resistance and greater short-term benefit in survival.

Overall survival is not a reliable outcome to compare therapies. Progression-free survival is more appropriate.

**Immunological response to cancer comprises a series of complex steps — from antigen release to the killing of tumor cells. In cancer immunotherapy, the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathways are particularly targeted.**

Jean Jacques Grob, M.D., Ph.D., professor of dermatology at Aix-Marseille University, France, identifies two main objectives of immunotherapy: to take advantage of the inflammatory micro-environment in order to activate inhibited T cells (PD-L1 expression), and if this is not done spontaneously, to transform the tumor micro-environment into an inflammatory one.

Dr. Grob presented lessons learned in recent years, as well as future questions regarding the use of checkpoint inhibitors in advanced melanoma at the European Academy of Dermatology and Venereology (EADV) Congress in Paris.

**Survival and Resistance**
Dr. Grob reported that recent clinical studies of anti-CTLA-4 therapies show that only a minority of patients with advanced melanoma have long-term survival. The majority developed primary resistance. In contrast, anti-PD-1/PD-L1 agents demonstrated less resistance and greater short-term benefit in terms of survival (e.g. nivolumab vs. chemotherapy and pembrolizumab vs. ipilimumab). Nevertheless, approximately 40% of treated patients develop immediate primary resistance, and progressive secondary resistance also occurs. Overall survival, he says, is no longer a reliable outcome to compare therapies since it is the result of a strategy using multiple drugs, indicating that progression-free survival is more appropriate.

**Response Rate**
Checkpoint inhibitors may show a better response later, unlike targeted therapies. An immediate response, though, is not required for long-term survival. Dr. Grob notes that combining anti-PD-1 and anti-CTLA-4 treatments appears to augment the number of controlled patients as well as increase response rates (rapid impact) compared to anti-PD-1 alone.

**The Search for Answers**
Dr. Grob questioned the future of melanoma treatments and suggested the following responses:
- Why is there primary resistance to immunotherapy?
- Primary resistance to anti-PD-1 agents (and anti-PD-1 combined with anti-CTLA-4) may be associated with disease aggressiveness.
- Does the survival curve reach a plateau with anti-PD-1 agents? This has not been observed yet.
- Once the disease is under control, when can immunotherapy be discontinued?
- In patients who are progression-free at 2 years, this has been maintained in most patients after discontinuation. Complete responders have better outcomes.
- What are risks of treating too long?
- What about toxicity? The incidence of adverse events was not found to increase over two to three years of treatment with an anti-PD-1.
- Can immunotherapy be given again after stopping?
- Checkpoint inhibitors have clearly changed the prognosis of melanoma, yet the search for evidence-based answers to these and other questions regarding their use continues, he said.

Reference
Pr. Jean Jacques Grob, M.D., Ph.D. “Checkpoint inhibitors” (abstract # D1TS6-4A), EADV 2018 Meeting, Paris, France, September 13, 3-3:20p.m.
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

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 tretinoin.
- ONEXTON Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.
- Dizziness, 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.
- Oral 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 to 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/UVB 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 1-800-214-4576 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.


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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).

Collitis/Enteritis
ONEXTON Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis (see Warnings and Precautions).

WARNINGS AND PRECAUTIONS

Collitis
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 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 Clostridium 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 assays 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: Collitis (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 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 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 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)

<table>
<thead>
<tr>
<th>Before Treatment</th>
<th>Maximum During Treatment</th>
<th>End of Treatment (Week 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Mild</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Mild</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Severe</td>
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<td>Moderate</td>
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</tr>
<tr>
<td>Severe</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*Mild = 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 irritant 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/m², respectively) or subcutaneous doses of up to 200 mg/kg (80 and 40 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², 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 TOXICOLGY

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 aceton 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 950, 2700, and 15000 mg/kg/day (1.6, 4.8, and 16 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/m², 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 keratoacanthomas 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 1, 6, 4, 3, and 16 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m², 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/g/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/m²) 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
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By:
Valeant Pharmaceuticals International, Inc.
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Pregnancy does not induce changes in nevi

NIA CASON | Staff Correspondent

The lack of any hard and fast guidelines for best clinical practices means that the management of moles and melanoma during pregnancy is a challenge, says Professor Marie Aleth Richard reporting at the European Academy of Dermatology and Venereology (EADV) Congress in Paris.

Pr. Richard, of Hôpital de la Timone, Marseille, France, said that melanoma is a hormonally responsive tumor. Increased levels of hormones such as estrogen, progesterone and beta endorphin can increase melanocyte stimulation and cause an increase in pigmentation. Some melanomas have progesterone and estrogen receptors. As well as altered hormone levels, pregnancy also induces a state of immunosuppression, which decreases tumor surveillance and allows tumor progression.

Changes in lesions should not be attributed to pregnancy, she said. This means that biopsies and excisions, which should be obtained promptly from any suspicious or changing mole in pregnant women, can be performed safely during pregnancy.

**CHANGES IN NEVI DURING PREGNANCY**

Many clinicians believe that pregnancy comes with common changes in moles. While there are slight transient dermoscopic changes in moles during pregnancy, normal nevi should only experience slight and non-significant clinical changes. Several studies have shown that changes in nevi size are only seen on the front of the body.

“Pregnancy does not induce significant physiologic changes in nevi besides those on the breasts and abdomen, which grow with skin expansion,” Pr. Richard said. There is also no evidence to show that there is a darkening of nevi during pregnancy, another common misconception.

“Changes that occur in the nevi of pregnant patients should not be disregarded as a physiologic consequence of pregnancy. Any histopathological features consistent with melanoma should be viewed as melanoma,” she said.

The risks of biopsies and mole excisions under local anesthetic during pregnancy remain theoretical, Pr. Richard said.

“The low doses of lidocaine and epinephrine that are used in dermatologic surgery are considered safe,” she said. “This means that biopsies and excisions, which should be obtained promptly from any suspicious or changing mole in pregnant women, can be performed safely during all stages of pregnancy.

**MELANOMA IN PREGNANCY**

Traditionally, clinicians have held the belief that women who are pregnant at the time of melanoma diagnosis have a poorer prognosis and a higher risk of progression than non-pregnant women. However, pregnancy-associated melanoma (PAM) prognosis does not appear to be worse than melanoma in non-pregnant controls. Nonetheless, measures should be taken to protect the fetus in the treatment and imaging of PAM.

“All surgical procedures can be done safely during pregnancy. Biopsy, excision and flap closure can all be done in the first trimester of pregnancy. Local anesthesia can be used in all these situations,” Pr. Richard said.

Sentinel lymph node (SLN) status is the most important prognostic factor in patients with greater than 1 mm melanoma, and SLN biopsy is generally considered safe in pregnant women. Patients should be made aware that SLN biopsy does not increase overall survival and that complications are more common in the second or third trimester.

When the risk of metastasis is low (e.g. at stages 1-2ab), there is no need for imaging. Imaging can be performed in later disease stages, and more extensively in stage three. Imaging modalities that use ionizing radiation and radionuclides should be limited in pregnant women.

“These treatments are associated with a risk of teratogenesis and miscarriage in the first trimester, as well as fetal injury and childhood cancer,” Pr. Richard said. Chest radiographs with appropriate shielding, ultrasonography and MRI are generally the techniques of choice in pregnant women, although CT scans without contrast and nuclear medicine studies can be performed if necessary. “Decisions about imaging should be made on a case-by-case basis, and the risk of lymph node involvement, for example, should be considered,” she said.

After a PAM, oral contraceptives and hormone replacement therapy do not seem to increase the risk for melanoma.

**Quick TAKES**

- Changes in lesions should not be attributed to pregnancy and should be biopsied and excised.

- Pregnancy-associated melanoma prognosis does not appear to be worse than in non-pregnant controls.

- SLN status is the most important prognostic factor in patients with greater than 1 mm melanoma.
Two views on best approach to actinic keratosis treatment

NIA CASON | Staff Correspondent

In a joint, interactive session at the European Academy of Dermatology and Venereology (EADV) Congress in Paris, two physicians discussed the pros and cons of treatment for actinic keratosis. David de Berker, M.D., of the University of Bristol, England, argued against treatment, while Günther Hofbauer, M.D., of Allergology and Dermatology, Switzerland, proposed another argument: Actinic keratosis is a precancerous growth that should be treated. This article summarizes their positions.

DON’T TREAT: “KEEP THINGS IN PROPORTION”
Dr. de Berker led the creation and rewriting of the actinic keratosis guidelines in the United Kingdom.

“Today, I’ve been asked to propose the case that you don’t treat actinic keratosis — which of course is an artificial thing — but the idea here is to keep things in proportion.”

Actinic keratosis can be viewed and presented to patients in one of two ways: As sun damage spots or as precancers. Differences according to geographical and socioeconomic factors are also evident, such as those seen in the slight differences between the European and United Kingdom actinic keratosis guidelines.

“The European guidelines are comprehensive and difficult to argue with,” Dr. de Berker said. “The UK guidelines tell you what the outcomes will be. Some will go away, they write, and some will possibly turn into cancer. [They] also take individual patient differences into account. You’re treating the patient and not the actinic keratosis.”

There may also be some issues with consent. Most actinic keratosis therapies, whether cryosurgery or cream application, have side effects and thus require consent, and most patients with actinic keratosis are elderly. Dr. de Berker presented an exemplary study in which 13% of patients with acute actinic keratosis were deemed to lack capacity for consent.

Patients aged 60-80 years old may also be less concerned about receiving treatment. Using insurance data from Kaiser Permanente, one study found that the vast majority of nearly 6,000 patients were middle-aged. This indicates that older patients are less likely to seek treatment than younger patients, Dr. de Berker said.

Cancer anxiety also influences treatment.

“The way we have this discussion with [patients] will influence their response in terms of whether they’re choosing treatment or not,” he said. When actinic keratosis is framed as a “precancer,” patients are more likely to choose treatment than if described as “spots” (Berry et al., 2017, JAMA Dermatology).

Grade and patient history should also be considered.

Medical concern is lower in patients aged over 80 years old with thin or lower-grade actinic keratosis and no previous skin cancer, and is higher in younger patients (younger than 60 years old) with multiple lesions, previous skin cancer, and a range of grades of actinic keratosis.

TREAT: “SCC AND AK ARE MISNOMERS”
Actinic keratosis cells should be considered as cancer cells, even if only a few will go on to invade, says Dr. Hofbauer.

“Biologically speaking, there is no difference between an actinic keratosis cell and an invasive squamous cell carcinoma cell,” he said.

Behind clinically normal-looking skin is an active struggle and a deli...

Quick TAKES

Older patients may be less likely to seek treatment than younger patients.

When AK is framed as “precancer,” patients are more likely to choose treatment than if it is described as “age spots.”
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MSL-163 Rev A
Surgery best bet for BCC

NIA CASON | Staff Correspondent

As a rule, surgery is the first choice for basal-cell carcinoma (BCC). However, for patients with low-risk superficial basal cell carcinoma, non-surgical medical therapy may be appropriate, said Eduardo Nagore, M.D., who presented at the at the European Academy of Dermatology and Venereology Congress in Paris.

Dr. Nagore, of the Instituto Valenciano de Oncología in Spain, led a discussion about non-surgical therapeutic modalities for low-risk BCC.

Non-surgical therapy is suited to tumors around the eyes, nose, mouth or ears where relapse can be devastating. The updated European guidelines for BCC treatment recommend imiquimod, photodynamic therapy, 5-fluorouracil, and cryosurgery as first-line treatments for superficial BCC, and all but imiquimod as second-line treatments for nodular BCC.

“While many people seem to be using non-surgical techniques, there has been a lack of good quality results from randomized controlled clinical trials,” Dr. Nagore said. Any new treatment should be compared against surgery, which has the highest cure rate and lowest rate of recurrence, he said.

IMIQUIMOD

Imiquimod is an immune response modifier that promotes the Th1 response. It activates the innate immune system enhancing cytotoxic T-cell activation, NK cell stimulation, and pro-apoptotic activity.

Its efficacy has been demonstrated in several trials and the optimal efficacy-safety balance is five times per week for six weeks. A clinical cure rate of 80-90% and a pathological cure rate of around 85% has been reported. There was a five-year sustained clearance in 85-87%. Five-year results of a large-scale trials reported imiquimod cure rates of 91% for superficial BCC and 85% for nodular BCC. The recurrence of superficial BCC was eight (84% success) and that of nodular BCC was six (81% success), and the overall difference in treatment success (surgery/imiquimod) was around 15%.

Imiquimod is generally well-tolerated and inflammatory reactions are not necessarily related to treatment outcomes.

“The immune response is very individual. There’s not a one-on-one relationship between the reaction and the outcome,” he said.

Rest periods do not affect the outcome.

PHOTODYNAMIC THERAPY (PDT)

PDT is a three-step procedure that involves application of a topical photosensitizer (such as aminolevulinic acid or methylaminolevulinate) and light exposure (LEDs/lasers). Activation of the photosensitizer by illumination causes a release of reactive oxygen species and consequent destruction of the target tissue by apoptosis or necrosis. Two treatment sessions with a one-week interval are recommended.

PDT is generally well-tolerated. Side-effects include tingling, burning and pain during illumination, and erythema and edema after treatment. For superficial BCC, efficacy can be reduced by the presence of pigment. A clearance rate of 79-97% at three months was reported in a recent systematic review.

“Imiquimod has a better efficacy, but some dermatologists prefer PDT,” Dr. Nagore said. PDT is quicker, only involving single treatments. Some patients prefer a fast resolution of the problem, whereas others may prefer to wait to have a better cosmetic outcome.

5-FU

On entering the cell, 5-FU is converted into active metabolites that interfere with normal nucleic acid functioning. This means that 5-FU can achieve targeted cell death of rapidly proliferating cells with a minimal effect on normal skin cells.

Published in early 2018 one clinical trial of 601 patients compared the efficacy of imiquimod cream (5% once daily for five consecutive days/week for six weeks), methylaminolevulinate PDT (two treatments, one-week interval), and 5-FU cream (twice daily for 4 weeks). This is the first and only study to report five-year recurrence rate data for 5-FU. Imiquimod was more effective than both PDT and 5-FU, and 5-FU was marginally superior to PDT.

“5-fluorouracil could be considered as second-line therapy,” he said.

CRYOSURGERY

Cryosurgery induces localized frostbite, resulting in necrosis and tissue destruction. Liquid nitrogen is the most effective cryogen for clinical use, and effective removal requires temperatures of -40°C to -60°C. The general principle of cryosurgery is “freeze fast, thaw slow,” and repeated freeze-thaw cycles (recommended for facial basal cell carcinomas) increase effectiveness. Recurrence rates vary from 8-40%.

“It could be considered as palliative treatment in cases not suitable for
topical treatment," Dr. Nagore said. Cryotherapy has been associated with delayed wound healing, non-precise tissue destruction, nerve damage, and scars, and more adverse effects are seen in patients with dark skin, Raynaud’s disease and diabetes.

"Until last year, there has been a lack of controlled trials for laser treatment for basal cell carcinomas," Dr. Nagore said.

A recent comparative trial of 240 patients with superficial BCCs found that cryotherapy had an efficacy (cure rate at three months), cosmetic outcome, and patient satisfaction that was comparable to pulsed CO₂ laser therapy. Patient satisfaction of laser therapy was similar to that of surgery.

Cryotherapy applied to imiquimod refractory basal cell carcinomas seems to sensitize the tumor to the effect of the drug, thus reducing the percentage of patients who need surgery after an incomplete response to imiquimod. This was shown in a pilot study by Dr. Nagore and colleagues and in a phase three interventional study. Further clinical research trials are required.

**INGENOL MEBUTATE**

Ingenol mebutate was reported to be a safe and efficient treatment for basal cell carcinomas in a phase two-A trial of 60 patients with optimal histological and pathological clearance at 0.05%.
Immunotherapy expands derm’s role in cancer Tx

GALADRIEL BONNEL, PHD, FNP | Staff Correspondent

DERMATOLOGISTS MAY NOT think their role involves managing adverse effects associated with immunotherapy because they don’t prescribe it. Furthermore, once cutaneous side effects have been evaluated, they may consider the job done and in the hands of the oncologist.

However, these are not convincing arguments for Jean Bolognia, M.D., professor of dermatology at Yale University School of Medicine. She suspects that, in the near future, dermatologists will not only be concerned with managing side effects from new systemic therapies for melanoma, but also for other types of cancer (e.g., lung or bladder cancer) where immunotherapy is being prescribed.

Dr. Bolognia presented compelling information at the 2018 European Academy of Dermatology and Venereology (EADV) Congress in Paris about the dermatologist’s expanding role in the differential diagnosis of cutaneous side effects, as well as their pharmacological management after immunotherapy treatment.

PATIENT EDUCATION
Dermatologists will need to become more involved with advising patients suffering from melanoma who receive immunotherapy, especially in the adjuvant setting, and what side effects they may experience.

Dr. Bolognia says patients with stage four melanoma may be more willing to accept rare side effects, but with stage three melanoma and no evidence of disease, rare life-threatening side effects become more about weighing a risk-benefit ratio.

SIDE EFFECTS
When giving antibodies as immunotherapy, you are inhibiting an inhibitory signal, and this leads to immune stimulation.

In the case of vitiligo, you are already aware that autoimmune endocrinopathies can occur. Dr. Bolognia recommends that instead of memorizing a list of side effects, you need to make links to what you already know. Therefore, it is not surprising that patients may experience adrenal sufficiency, uveitis, and thyroid disease, among other problems.

Pulmonary and cardiac side effects can be fatal, and so these potential side effects need to be considered, particularly in the adjuvant setting.

Patients who develop cutaneous sarcoidosis may present, and so dermatologists can advise other physicians caring for the patient regarding the differential diagnosis if pulmonary lesions occur (i.e., sarcoidosis rather than metastatic disease).

As Dr. Bolognia advises, it is important that dermatologists realize they will likely see more patients for cutaneous side effects following immunotherapy, both in melanoma and beyond.

Reference
Jean Bolognia, M.D. “Adverse effects of immunotherapies” (abstract # D1T06.4D), EADV 2018 Meeting, Paris, France, September 13, 4-4:20p.m.

Dermatologists should be prepared to treat cutaneous side effects. Advise patients about potential side effects. When evaluating patients, make connections to what you already know.
Pregnancy does not induce significant physiologic changes in nevi besides those on the breasts and abdomen, which grow with skin expansion.”

Marie Aleth Richard, Hôpital de la Timone, Marseille, France

Melanoma in pregnant patients at stages 1-3 can be treated as in non-pregnant patients FROM PAGE 57

Pregnancy is an actinic keratosis growth from the bottom. There is no increased risk of melanoma after ovarian stimulation for in vitro fertilization, no effect of a subsequent pregnancy after a diagnosis of melanoma or PAM, and no need to defer pregnancies in women with localized or low-risk melanoma.

“Women with an increased risk of melanoma recurrence should be advised to wait for two to three years before becoming pregnant again,” she said. This is when recurrence is most common. PD-1 and PD-L1 play a key role in maintaining fetal tolerance, and PD-1 and PD-L1 inhibitors for the treatment of melanoma may therefore affect pregnancy. In animal studies, anti-PD-1/PD-L1 significantly increased the risks of spontaneous abortions.

“The use of an anti-PD-1/PD-L1 like pembrolizumab before a future pregnancy, such as an adjuvant setting in a young woman with a melanoma with high risk of recurrence, might also increase the risk of spontaneous abortion due to a decrease of the maternal immune tolerance to allo-antigens expressed by the fetus in future pregnancy,” she said.

In terms of best practice, Pr. Richard concludes that treatment of thin melanoma in stage one through three should be the same in pregnant and non-pregnant patients. In PAM with a low risk for nodal involvement, re-excision under local anesthesia is necessary, and it is reasonable to postpone the SLN biopsy until after delivery. In PAM with a high risk of recurrence or of nodal involvement, decisions for SLN biopsy or extensive imaging should be made on a case-by-case basis. Individual patient management should be based on the mother’s wishes, and she should receive enough information to make informed decisions about treatment, she said. ▲

Reference

Debate: Two physicians discuss whether all AKs should be treated FROM PAGE 58

cate balance between mutated cells and normal differentiation. One publication (Martincorena et al., 2015, Science) found that about one quarter of skin on the upper eyelids harbours mutations in middle-aged people.

“I believe separating actinic keratosis from other skin cancers is fictitious because we don’t yet know which actinic keratosis are those that carry risks,” said Dr. Hofbauer referring to the treatment of mild hypertension. About 100 patients are treated to prevent just one myocardial infarction. “I realize if we call actinic keratosis ‘cancer,’ we may trigger fear and cost, but we should not obscure the terms by fearing the implications of it,” he said.

It is possible that actinic keratosis size and grade cannot, in fact, tell us which cells will progress to squamous cell carcinoma. Using these features to inform treatment was also called into question. While the common view is that there is an actinic keratosis growth from the bottom to the top and an increasing disruption to the epidermal architecture, Dr. Hofbauer suggests that growth towards the bottom may be the important factor in the transition from actinic keratosis to squamous cell carcinoma, regardless of the actinic keratosis size. One recent publication found that proliferation towards the bottom was mainly by thin, mild, ‘innocent-looking’ actinic keratosis (Schmitz et al., 2018, JDDG).

“This would lead me to treat more actinic keratosis than fewer actinic keratosis,” he said.

Field treatment could be adopted to catch all early atypical cells, Dr. Hofbauer said. Actinic keratosis treatments typically have good cosmetic outcomes and longer remission.

Treatments such as soft radiotherapy for field cancerization result in younger-looking skin and effects that last for 10-20 years. Photodynamic therapy effects last around three years and treatment can be repeated. Medication such as nicotinamide can also be beneficial; nicotinamide reportedly repairs DNA damage, prevents squamous cell carcinoma and basal cell carcinoma, and reduces actinic keratosis (Chen et al., 2015, New England Journal of Medicine).

“One provocation would be to say: ‘Treat it before it happens,’” Dr. Hofbauer said. He explains that it is not the actinic keratosis itself that is of interest, but the damage it represents, and that symptoms are not singular events but are linked together by an underlying driving force.

“The point is that we try to correct these risk factors in order to reduce the occurrence of these major events down the road,” he said. Early treatment is also cost-effective. Once squamous cell carcinoma occurs the cost of care remains high, said Hofbauer. ▲

References
Combining lasers may improve tattoo removal

NIA CASON | Staff Correspondent

While nano-second Q-switched lasers (ns-lasers) are still considered the gold standard for tattoo clearance, newer methods such as picosecond lasers (ps-lasers) and combination therapies might hold more promise in effectively removing tattoos, particularly in more complicated indications, researchers reported at the European Academy of Dermatology and Venereology (EADV) Congress in Paris.

Agneta Troilius Rubin, M.D., of Skane University Hospital in Sweden, reviewed advances in vascular and pigmented lasers at the meeting.

The last few decades have seen significant advances in dermatologic laser surgery, she said. These developments have revolutionized the treatment of skin alterations and have brought with them greater precision and efficacy. In parallel to these technological advances, the increase in tattoos being acquired means there is a greater demand for their removal.

After recognition of the clinical application of ns-lasers in the early 1990s, their use in tattoo removal became increasingly common. While effective, certain colors may be resistant to ns-lasers, pigmentary changes and blistering can occur, and the need for multiple treatments results in long treatment durations with significant intervals between laser sessions.

**PICOSECOND LASERS**

The clinical efficacy of ps-lasers was first reported in the late 1990s, with a more efficient and faster removal of pigmented lesions than ns-lasers. Despite this, the first commercially available ps-laser for tattoo removal and treatment of pigmented lesions (the 755-nm alexandrite laser, PicoSure) was approved by the FDA in 2012. In a separate talk, Klaus Fritz, M.D., said that the shorter pulse duration of just $10^{-12}$ seconds makes this a revolutionary laser technology in tattoo removal.

“The picosecond laser has been reported to achieve removal in fewer sessions than the nanosecond laser, and with less in the way of unwanted side effects,” said Dr. Rubin, M.D.

The ps-laser also limits damage precisely to the pigment target, which gives a greater efficacy. It is a good option for tattoos that are not responsive to ns-lasers, as well as for multicolored tattoos. That said, true color blind lasers have not yet been achieved. The ps-laser also causes less induction of post-inflammatory hyperpigmentation in susceptible skin types, such as Asian skin. It also works well for dermal melanocytosis, but is less effective for melasma.

**CO₂ LASER TREATMENT**

The removal of cosmetic tattoos is complicated not only by their aesthetically sensitive location, but also in that they often contain white metallic compounds that darken on pigment-specific laser treatment. Ablative CO₂ laser treatment can be effective in these cases, because it does not target specific tattoo inks and thus causes no paradoxical tattoo ink darkening. One review, published in June, reported that CO₂ laser treatment of cosmetic tattoos carries no risk of paradoxical pigmentation and CO₂ laser vaporization significantly improved removal of eyeliner and lip liner tattoos. There were no reports of infection or scarring, and side effects included erythema, edema, and serosanguinous drainage.

**MULTIPLE-PASS METHODS**

A major limiting factor of ns-laser treatment is the development of cavitation bubbles and vacuoles within the epidermis and dermis that result from the rapid heating of tattoo ink particles. Q-switched lasers also have no effect on deep-intradermal pigment. Enhanced tattoo removal through epidermal clearance can be achieved through multiple-pass meth-
Safety recommendations for tattoo removal

By DERMATOLOGY TIMES STAFF

Investigators from the Health Hazard Evaluation Program of the Centers for Disease Control and Prevention visited a Massachusetts hospital in 2017 to assess healthcare workers’ exposure to hazardous materials associated with plumes created arising from laser tattoo removal. They assessed exposures to metals, volatile organic compounds (VOCs), particles, bacteria, carbon monoxide, and hydrogen sulfide, plus work practices and airflow patterns. They issued recommendations for improvements that may interest other centers.

RECOMMENDATIONS

1. Have laser technology manufacturers provide specific information on shelf life, storage conditions, and appropriate cleaning methods for laser safety eyewear as described in the American National Standards Institute (ANSI) standard Z136.3 Section 4.6.2.
2. Utilize the signs indicating “laser in use” only when lasers are being used.
3. Use smoke evacuators to help control nuisance odors. Use the existing smoke evacuators in a manner consistent with how it is used during laser hair removal.

PERSONAL PROTECTIVE EQUIPMENT

1. Discontinue use of the laser masks and molded surgical masks for respiratory protection. If employees want to use respirators on a voluntary use basis, use NIOSH-approved filtering facepiece respirators (such as an N95).
2. Contact your local Department of Environmental Health and Safety officials to ensure that your office is in compliance with the voluntary use provisions of the OSHA respiratory protection standard (29 CFR 1910.134) for wearing filtering facepiece respirators during tattoo removal. We found no evidence that respiratory protection should be required.
3. Ensure that all LPE is clearly labeled with the optical density and wavelength that the eyewear protects against as described in ANSI standard Z136.3 Section 4.6.2.3. Any eyewear with a faded or missing information should be discarded.
4. Only purchase and provide respirators certified by NIOSH. The list of NIOSH-approved N95 respirators can be found here: http://btt.ly/NIOSHRespirators

References

Characterizing Exposures During Laser Tattoo Removal in a Hospital Dermatology Center, JEME Report No. 2017-0016-3319, May 2018
Low exposure to cosmetic ingredients still risky

Even low-level exposure to mixtures of chemicals commonly used in cosmetic and personal care products is associated with changes in women’s reproductive hormones, according to a new study in Environmental International.

The study of reproductive-aged women, led by George Mason University researchers, suggests exposure to bisphenol A, chlorophenols, benzophenones and parabens often used in sunscreens and other cosmetic and personal care products could impact women’s lifetime risk of hormonally mediated diseases.

Researchers studied 509 urine samples from 143 healthy premenopausal women, who were not using birth control. They measured levels of these environmental chemicals, including antimicrobial preservative parabens and UV filtering benzophenones.

The novel component of this study the report on mixtures of chemicals widely used in personal care products, using multiple measures of exposure across the menstrual cycle. This improves upon research that relied on one or two measures of chemicals, author Anna Pollack, Ph.D., M.P.H., George Mason University assistant professor of Global and Community Health, said in a study-related press release.

Dr. Pollack and colleagues not only found that mixtures of chemicals might impact reproductive hormone levels, but also that the relationship between these chemicals and hormones is complicated. Certain chemicals and UV filters seem to decrease reproductive hormones in multi-chemical exposures, whereas exposure to others appear to increased reproductive hormones.

Taking a closer look at the findings: While paraben metabolites were associated with hormones in single chemical models, results from single chemical models did not consistently reach statistical significance.

In the multi-chemical approach, researchers uncovered statistically significant associations between the chemicals and hormone changes. For example, paraben factors, paraben metabolites, and UV filters seem to interact in ways that affect hormones.

Seven in-demand cosmeceutical categories

COSMECEUTICAL PRODUCTS aim to do more than moisturize skin. Depending on their active ingredients, cosmeceuticals can help rejuvenate, regenerate, exfoliate, lessen inflammation, heal skin and more.

Cosmeceutical categories, based on important ingredients and their mechanisms of action, can help aesthetic physicians match products to ideal patient candidates, according to dermatologist Zoe Diana Draelos, M.D., who practices in High Point, N.C., and founded Dermatology Consulting Services, a company that works with cosmeceutical firms to develop formulations and conduct product testing.

According to Dr. Draelos, seven of the most popular cosmeceutical categories are:

1. **Moisturizers, including emollients, occlusives and humectants, help to RELIEVE dry aging skin, atopic dermatitis, pruritus, and more.**

2. **Retinols have been shown to have a diminished but real retinoid effect on skin without the irritation associated with prescription topical retinoic acid (tretinoin) use, Dr. Draelos says.**

   Boston, Mass., dermatologist Ranella Hirsch, M.D., adds retinoid-containing cosmeceuticals are vitamin A derivatives with many uses in dermatology practice. They can help patients with acne to aging concerns.
5. Use of exfoliants, including products with salicylic acid, glycolic acid or lactic acid—things that peel off the outer layers of skin, according to Dr. Draelos. “These are best matched to specific skin concerns. Beta-hydroxy acid (salicylic acid) is well suited to help with acne breakouts, while alpha hydroxy acids are very useful to brighten skin and help with mild discoloration,” Dr. Hirsch says.

6. Use of anti-inflammatories and cosmeceuticals. Anti-inflammatory cosmeceuticals include salicylic acid, glycolic acid, lactic acid and, sometimes, retinoids, like resveratrol, according to Dr. Draelos. Anti-inflammatory-containing cosmeceuticals overlap into other categories, as antioxidants in many cosmeceutical types. These ingredients, according to Dr. Hirsch, can work synergistically with sun protection products to reduce environmental skin damage. "This is a category we try to incorporate on some level into the majority of regimens from a preventative standpoint," Dr. Hirsch says.

7. Use of stem-cell containing cosmeceuticals. These agents help with dryness and restoration of the skin barrier and tend to be useful for those with dry skin and eczema, especially when those patients experience seasonal skin changes, Dr. Hirsch says.

References


Disclosures: Dr. Hirsch is a member of the Atolla founding team. Dr. Draelos works with many companies that manufacture cosmeceuticals.
Stem cell-derived peptide improves epidermal thickness

LISETTE HILTON | Staff Correspondent

There’s scientific evidence that a topical facial regimen containing defensin peptides rejuvenates facial skin much like topical retinoic acid but without associated irritation and inflammation, according to San Antonio, Texas, dermatologist Vivian Bucay, M.D., clinical assistant professor, University of Texas Health Science Center, San Antonio. She was among the researchers to conduct a double-blind, vehicle-controlled study, including histologic analysis, of the DefenAge (Progenitor Biologics, a division of MediCell Technologies) skincare regimen. Researchers looked at whether the defensins-containing regimen would improve the structure and function of aging facial skin.

Defensins’ skin healing and potential rejuvenating effects can be traced to a type of stem cell. Defensins, which are antimicrobial peptides, activate an LGR6-positive stem cell locus in the hair follicle. LGR6-positive stem cells generate new epidermal cells during acute post-trauma wound healing.

Aesthetic physicians might use peels, laser procedures, and more to traumatize skin and activate these stem cells.

“The idea was can we use defensins in a topical to activate the stem cells without having to traumatize the skin — without having to do a peel or laser procedure. We showed, that’s exactly what happened,” says Dr. Bucay who is part owner of MediCell Technologies.

Researchers studied 44 females, ages 41 to 70 years, with skin types I through V. Subjects used either the active regimen, including a serum, cream and mask containing alpha-defensin 5 and beta-defensin 3, or identical looking vehicle-only products. The women applied the cream and serum to the face and neck twice daily for 12 weeks and could use the mask twice a week. Researchers evaluated results using histopathology and immunohistochemistry in seven of the women. For all subjects, researchers evaluated pore size, clinically, and evaluated superficial and deep wrinkles based on Griffiths scale and high-resolution photography. Researchers also analyzed 15 patients using 3-dimensional imaging and skin care scores for evenness, pores, oiliness, as well as high-resolution skin ultrasound to determine trans epidermal water loss, elasticity, color and hydration.

Comparing the active and placebo groups’ baseline evaluations to results at six and 12 weeks, the researchers found that the active group’s epidermal thickness increased significantly, without inflammation, irritation or dryness.

“Specifically, this regimen increases epidermal thickness, reduces appearance of pores, reduces wrinkles, and reduces melanin,” they write in the study published April 2018 in the Journal of Drugs in Dermatology. “This data is consistent with the hypothesis that a defensin-containing skincare regimen activates the body’s own dormant stem cells to generate healthy new epidermal cells.”

**STEM CELL STRAIGHT TALK**

Claims that skincare products contain skin rejuvenating stem cells are misleading, according to Dr. Bucay.

“You can’t put a stem cell on the skin and expect it to do something. It’s not going to be alive,” she says.

Furthermore, it’s often a mystery if putting growth factors on the skin does anything at all to improve skin function or structure, she says.

“We hypothesize about the signaling cascade with growth factors. We know growth factors don’t penetrate the skin — they’re too big. So, even if they’re turning something on, they’re going to send signals to all kinds of stem cells, including stem cells that already have damage in them. It could also be a completely different set of stem cells that the growth factors are targeting,” Dr. Bucay says.

Defensins are peptides, not growth factors, which are small enough to easily penetrate into the pores, she says.

A RETINOL ALTERNATIVE, ADJUNCT

Doctors typically recommend gold standard retinol or retinoic acid to reduce typical signs of aging. But not all patients are good candidates for these topicals, according to Dr. Bucay.

Dr. Bucay says that ideal candidates for the DefenAge regimen include women who are or are thinking about getting pregnant because the topicals are not contraindicated in those patients. She also uses it for patients with sensitive or dry skin, who can’t tolerate retinoids.

“For patients who live in sunny areas, this is a good option because it’s not photosensitizing,” she says.

Dr. Bucay says she uses only the serum for patients with oily skin. And for acne patients already on retinoids, Dr. Bucay might combine DefenAge with topical retinoids to further improve skin appearance and function.

“The results we found in the study are comparable to what we find with retinoic acid,” she says.

**Disclosures:** Dr. Bucay is part owner of MediCell Technologies, serves on its medical advisory board, is a speaker and investigator for the company.
Dr. Brian Biesman and Dr. Michael Gold invite you to the 2019 Music City SCALE Meeting. The meeting is for all physicians and clinicians interested in enhancing their practice and learning more about the latest procedures in aesthetic medicine. In addition to the educational sessions, there are live patient workshops and an exhibit hall with the leading members of the industry.

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- Non-Invasive Body Contouring
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Must-know physician liability issues with medspas

Lisette Hilton | Staff Correspondent

Quick Takes

If you’re going to own a medical spa business, you should have experience in medical aesthetics.

If you’re going to delegate treatments, you should be sure that the practitioner is authorized to perform the delegated treatments.

Be sure you know your state’s interpretation of the Corporate Practice of Medicine doctrine.

There are three high-risk areas for physicians who own or are medical directors of medspas, and they include supervision, delegation and noncompliant ownership structure, according to attorney Renee E. Coover with ByrdAdatto, a law firm specializing in healthcare and business law.

**SUPERVISION**

Physician supervision becomes risky when non-core cosmetic doctors, including OB/GYNs, emergency room physicians and pediatrics, who become medspa directors or own these facilities don’t have experience in medical aesthetics.

“To be a supervisor or medical director of a medical spa, it’s really important that the physicians, themselves, have the appropriate experience and training. At the end of the day, if the medical board opens an investigation based on a disgruntled patient, employee or even a vindictive ex-spouse, that physician has to be able to defend himself or herself in front of the medical board as to why certain treatments were performed in the ways that they were. If that physician doesn’t have appropriate training and experience in the medical treatments and services that are being offered at that medical spa, it is not appropriate for the physician to be supervising and delegating those treatments.”

**DELEGATION**

Second, a physician should ensure that the medical spa practitioners on staff can legally perform the treatments the physician plans to delegate.

Physicians can avoid investigations by only delegating treatments to providers that are authorized to perform them.

**NONCOMPLIANT OWNERSHIP STRUCTURE**

The issue of noncompliant ownership structure depends on whether a state follows the Corporate Practice of Medicine doctrine, which dictates if medical facilities can be non-physician owned, according to Coover. Even states that abide by the Corporate Practice of Medicine doctrine might have allowable exceptions.

“In a state that follows the Corporate Practice of Medicine doctrine strictly, that state may say that only physicians can own a practice that provides medical services, which would include a medspa. A handful of states follow the Corporate Practice of Medicine doctrine but have some exception where the physician can own in conjunction with a midlevel provider, like a PA or NP, or there’s a loose interpretation of the Corporate Practice of Medicine doctrine that may have been the case five years ago, but now we’re seeing an increase in enforcement,” she says. “It’s really important that physicians look into their state laws and talk to a health care attorney that is well versed in this area before signing on to be medical director.”

This might be a severe example of what can happen to physicians who are involved in medspas that are operating illegally, but it’s reality, according to Coover.

“I think there’s the belief that no one is going to get caught because of the lack of enforcement. That may have been the case five years ago, but now we’re seeing an increase in enforcement,” she says. “It’s really important that physicians look into their state laws and talk to a health care attorney that is well versed in this area before signing on to be medical director.”

Real-life Example

**BREAKING THE RULES**

In non-compliant ownership, says Renee E. Coover with ByrdAdatto. She notes a recent scenario in which an OB/GYN practiced in a state that required physician ownership of a medical spa. The OB/GYN had no history of reprimand or discipline when she decided to affiliate with a medical spa, where she had been contracted to perform liposuction.

“She was asked to be the medical director of the medspa but had no ownership,” Coover says. “A patient scheduled liposuction with her and cancelled that liposuction before the doctor ever saw that patient. The patient asked for a refund. When the medical spa refused to give the person a refund, that potential patient turned the medical spa to the medical board. They opened an investigation and found the physician was not the owner of the medical spa. They stripped the doctor of her license and reprimanded her. She was reported to the National Practitioner Data Bank. Basically, she was blacklisted. When they reported her to the national databank, they found that she also had a license in New York as a physician, so, New York opened an investigation on her. That’s still pending.”

**REAL-LIFE EXAMPLE**

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How physicians can join forces to remain independent

JAMES F. SWEENEY | Staff Correspondent

Quick Takes
A number of factors are making it difficult for physicians to succeed in solo practice.

Several options have developed that allow physicians to share in administrative support, tools and negotiating leverage.

The physicians who want to stay independent are joining together in a variety of practice models and corporate structures they hope will give them a better chance of survival.

The move to value-based care, consolidation among healthcare providers, and an emphasis on finding efficiencies is making it difficult for smaller practices to succeed alone. So they’re turning to organizations that help practices transition to value-based care by providing the administrative support, tools and negotiating leverage that come with size.

“I think (independent) practices are looking for a way to survive. There are a lot of practices that would like to try to make it on their own and they want to find the model that lets them do that,” says Kenneth Hertz, F.A.C.M.P.E., principal consultant with Medical Group Management Association (MGMA).

Though the organizations have common goals, there are differences among them, and practices should do their homework to find the best fit, says Hertz.

“The key to it is knowing what you want and what you want for your patients,” Hertz says. You’ve got to think it through very well and you’ve got to ask a lot of questions.”

Six options are highlighted below:

#1 ACOS LED BY PRIVATE FIRMS

Jonathan Lilly, M.D., an internist in Dunbar, W. Va., knew his practice would need help negotiating value-based care if it wanted to remain independent.

That’s why Dunbar Medical Associates, which has seven physicians and five non-physician practitioners in two offices, has contracted since 2016 with Aledade, a Maryland-based company that forms ACOs with independent practices. Dunbar is an Aledade-led ACO with 16 other practices.

Aledade uses data from the practice to track patient care and identify where practices can provide better service. Among other things, it identifies high-risk patients, flags emergency department visits, tracks immunizations and wellness visits, manages specialist referrals, and alerts the practice to cases in which chronic care management is needed, says Dr. Lilly.

“They help us to identify (patients) who are more fragile and who need additional attention,” he says.

Aledade, which works with 275 practices in 18 states, uses its proprietary population health and workflow tools to analyze practice and ACO data and recommend the correct action for them to take, says Dan Bowles, M.B.A., M.P.P., vice president of provider networks.

“Having the data is good, but you need to know what to do with the data. You’ve got to mine the data in an efficient way,” he says.

Aledade takes a share of practice reimbursements earned through the Medicare Shared Savings Program (MSSP).

Dunbar earned shared savings reimbursement for 2016, the first year it worked with Aledade, and expects to earn it for 2017 as well, says Dr. Lilly. (The reimbursements for 2017 have not been announced yet.)

Dr. Lilly says his practice plans to stay in the ACO because it’s not sure it could remain independent without that assistance. “Anyone who is going to do (value-based care) on their own is taking on a lot,” he says.

#2 HOSPITAL-LED ACOs

Some independent practices that want to avoid being bought by large healthcare systems are instead joining ACOs led by those same systems.

THE PHYSICIAN’S ROLE IN MEDICAL LEGAL WORK

By HEIDI MOAWAD, M.D.

WHEN COMPLICATED medical-related legal issues arise, physicians are often asked to provide expert opinions. Physicians who have worked in a consultative capacity in the medical legal field are good resources for insight about how to look for opportunities, the anticipated time commitment and reimbursement, how the process works and whether medical legal work is stressful for physicians.

GETTING STARTED

Timothy Wiebe, M.D., a neurosurgeon in Bakersfield, Calif., was not looking for medical legal work when he was first asked to provide his expert opinion about a patient. Subsequently, parties familiar with his work contacted him with additional requests for consultations.

Dr. Wiebe suggests that doctors who are interested in medical legal consulting maintain board certification, attend continuing medical education (CME) courses, and participate in meetings and presentations to highlight their professional abilities to the community. In addition to being qualified, the way a physician expert manages time and availability is an important aspect of getting and keeping clients.

Nancy Hammond, M.D., a neurologist in Kansas City, Mo., who received a cold call when an expert was needed for a case, suggests that one way to get started as an expert witness is to reach out to contacts.

Sharon Peach, M.D, a critical care specialist in Missoula, Mont., started in expert witness work by attending a conference to learn about expert witness practice. She had her name listed in a directory, but her first case was obtained through networking, not through the directory.

WHAT A PHYSICIAN MEDICAL EXPERT DOES

Dr. Hammond explains that the bulk of medical legal consultation consists of examining medical records and writing a well-annotated report specific to the case, with the possibility that a physician may be asked to give a deposition and testify at trial. A core part of the work involves understanding the medical benchmarks and identifying deviations from the norm.

According to Dr. Wiebe, doctors who provide expert opinions need to consider multiple explanations that could conceivably explain a clinical scenario, stay up to date with relevant literature...
Many healthcare networks, such as Deaconess Health System in Evansville, Ind., are forming ACOs that offer primary care practices tools and resources to help them realize the benefits of value-based care. The Deaconess system includes five regional healthcare facilities and more than 160 primary care providers in Indiana, Illinois, and Kentucky.

“The practices understand the pressures they’re up against and they know they have to seek some outside help,” says Fredrick Wallisch, M.D. He owned his own practice before joining Deaconess where he recruited members for the healthcare system ACOs. Now working for Evolent Health, a consulting firm that works with Deaconess and other organizations on the transition to value-based care, Dr. Wallisch says hospital-led ACOs offer easy integration with and access to a healthcare system, in addition to the usual service sharing, back office, population management, and data services support. In addition, many practices were already affiliated with Deaconess before joining the ACO, which gives them a level of familiarity, he says.

The Deaconess ACO is attractive to many practices, Dr. Wallisch says, because, as a CMS Next Generation ACO, its members are exempt from penalties on malpractice insurance, network wide contracting with payers, a medical school loan repayment program, and more, says Dr. Reiss. “It’s a difficult situation, no doubt, but the IPA definitely helps us hang onto our independence,” he says.

**#3 CLINICALLY INTEGRATED NETWORKS**

CINs can give physicians the advantages of practicing integrated medicine within a large network of providers, but without becoming employees of a healthcare system.

A CIN is a collection of healthcare providers, such as physicians and hospitals, that work together to improve care and reduce costs. They generally share record systems, track data and rely on evidence-based care. CINs were created by the Federal Trade Commission (FTC) to serve the commercial or self-insured market while ACOs treat Medicare patients.

The FTC requires a CIN to include: clinical practice guidelines to improve performance, financial incentives for achieving goals, physician leadership and commitment, and development of infrastructure and technology. CINs can jointly negotiate contractual fees if the primary purpose of the negotiation is to improve care. CINs can support ACOs or patient-centered medical homes as part of the network by acting as a mechanism for sharing infrastructure and development costs.

Independent practices can reap substantial benefits from CIN membership, says Gene Good, J.D., C.P.A., chief executive officer of Doctors Management, a Knoxville, Tenn.-based practice consulting firm. He cites the potential for higher negotiated rates with private payers, help with care quality reporting, and a harmonious relationship with local hospitals that belong to the CIN.

Practices that join CINs should retain an escape clause if physicians are unhappy with the results, including the right to opt out of the negotiated rates and to do quality care reporting on their own, if necessary, he says, adding that practices must guard against any infringement on their judgement.

“Make sure there are no onerous restrictions on your clinical protocols, including restrictions on patient treatment or physician referral options for your patients,” Good says.

**#4 INDEPENDENT PRACTICE ASSOCIATIONS**

An IPA is a business entity owned by a network of independent physicians formed to share services, improve care, reduce overhead and negotiate with other healthcare organizations, such as insurers, HMOs, ACOs and hospitals regarding payments. Though originally formed to focus on fee-for-service rates, they are transitioning to negotiating value-based contracts.

IPAs typically charge a membership fee, which varies according to size and services provided. There is no limit to the number of practices that can belong to an IPA, though they usually are located in the same area. The larger the association, the greater its negotiating clout.

A collection of independent practices in Vermont formed IPA Health First after two previous tries as ACOs failed to produce the hoped-for savings, says Chief Medical Officer Paul Reiss, M.D.

Bandaging together is necessary in Vermont because the state is particularly challenging for independent practices, says Dr. Reiss. “It’s small (pop. 623,000), consistently ranks among the healthiest states and is dominated by a single healthcare system, the University of Vermont Health Network, which gives it the upper hand when negotiating with small practices.

The IPA, which includes about 150 physicians and non-physician practitioners in 74 practices, offers members group purchasing, negotiated premiums on malpractice insurance, network-wide contracting with payers, a medical school loan repayment program, and more, says Dr. Reiss.

“It’s a difficult situation, no doubt, but the IPA definitely helps us hang onto our independence,” he says.

**#5 DIVISIONAL MERGERS**

In a divisional merger, two or more practices form a single corporate entity that, due to its larger size, can have greater clout in negotiating with private payers, healthcare systems, vendors, and others, Glaser says. It differs from an IPA in that it requires the practices to become a single legal entity with centralized decision-making, consolidated billing with accounting and financials and other services.

Divisional mergers are an increasingly popular option for internal medicine and other primary care practices that want to become larger with
Medicare’s Chronic Care Management (CCM) program looked like a big opportunity for some physicians when it was launched in 2015. The Centers for Medicare & Medicaid Services (CMS) offered to pay practices about $40 per patient per month (now $45) for between-visit management of Medicare patients with two or more chronic conditions. But relatively few practices have taken on CCM, partly because meeting the expansive requirements of CCM appeared difficult, and most groups have not been able to justify hiring extra nurses or outside services to perform the care management interactions.

Medical practices that want to keep their patients healthier while also tapping into this new revenue stream are looking for ways to make CCM more efficient and less costly—which is where mobile-enabled remote patient monitoring (mRPM) comes in. This type of technology, which typically includes a dashboard for the physician practice and a patient-friendly mobile app for check-ins between appointments, can greatly enhance communication between providers and patients. In addition, patients become more aware and engaged in their own care without overburdening the practices.

Remote monitoring is an expanding element of modern care. CMS recently unbundled another level of remote patient monitoring, using a different CPT code, unrelated to CCM, allowing providers to bill separately for these broader services. CMS also increased the weighting of remote monitoring as a practice improvement option under the Merit-based Incentive Payment System (MIPS). So there are plenty of reimbursement opportunities to use mobile monitoring in practice.

WILL BOOMERS USE THE TECHNOLOGY? Though the percent of people 65 years or older who now have smartphones is growing, adoption is not uniform and has been influenced by many factors, including age, location, and race.

According to a Pew Research Center survey, 42% of people aged 65 or older own a smartphone, translating to 34 million older adults. However, adoption varies by race and age. In 2017, 59% of non-Hispanic white adults, 48% of Hispanic adults, and 38% of non-Hispanic black adults over age 65 owned a smartphone.

HOW THE TECHNOLOGY WORKS Mobile remote patient monitoring is convenient for both physicians and patients and uses few resources to reach a large population and gather their data consistently and efficiently. An automated schedule uses push notifications to prompt the patient to send in specific information at a time and place convenient for them. Once the data has been received, a clinician assesses the information and, if necessary, escalates to a face-to-face visit or phone conversation. So, from the viewpoint of meeting the CMS requirements, mobile-enabled monitoring is more cost effective and more likely to meet patients’ needs than other communication methods.

The technology typically includes some type of biometric data collection that can be transmitted to the patient’s physician and automatically analyzed for concerns. This process can be done automatically: the information can be directly entered by the patient and shared with the care team via mobile technology.

But biometric data alone isn’t enough. In order for the physician to gain a full picture of the patient’s health, these quick mobile-enabled check-ins should also include subjective and objective questions about their health, including details on medication adherence, care transitions, new doctors, and social determinants of health that could be affecting their treatment plan adherence.

Of course, no care team needs or wants to be inundated with data every five minutes—it’s important to know if a patient is sleeping well over time, not if he or she had one night of good or bad sleep. So, for mobile monitoring to be effective and actionable, it’s important that the frequency of data collection and reporting be guided and standardized via predetermined schedules based on the patient’s condition, clinical guidelines, and provider preferences. As that data arrives, certain algorithmic flags can create alerts for intervention—such as a patient who wants her doctor to contact her, or one whose biometric readings have been creeping up, or one who reports he hasn’t taken his meds for a few days. The doctor can then call these patients or ask to see them in the office.

WILL BOOMERS USE THE TECHNOLOGY?

There is evidence that seniors are increasingly taking advantage of mobile technology in their everyday lives, whether for texting, Facebook-sharing, FitBit-tracking, or other purposes. According to a 2017 survey by Pew Research Center, 42% of people who are 65 years or older now have smartphones—with higher usage among more affluent and more educated seniors. Sixty-seven percent of seniors use the internet, and 34% use social media.

Based on the Pew survey, it’s safe to assume that many of the two-thirds of Medicare patients who suffer from chronic conditions also use smartphones or other mobile devices. That means practices can leverage mobile monitoring to track these patients’ chronic conditions at regular intervals.

42% of people 65 years or older who now have smartphones, according to a Pew Research Center survey.
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Practicing physicians have to make ancillary services more efficient—and profitable—because of the larger combined patient base. Also, practices in a divisional merger can add complementary ancillary services, as well as share such things as EHRs, IT, and other back office support, Glaser says.

Though the combined entity is governed by a supervisory board with directors from each member, each practice retains a great deal of financial and operational independence, Glaser says. For example, member practices do not need to be in the same building or even the same city and revenue flows are kept largely separate. Of course, being farther apart can make it more difficult to coordinate and share services.

The divisional merger must be structured carefully to avoid Stark law violations, Glaser says. Also, a divisional merger between two small practices might not deliver the desired leverage in negotiations. And, like in many marriages, frictions can arise between partners.

Nonetheless, it can work, Glaser says: “Doctors are an independent lot and, structured correctly, the divisional merger lets them stay that way.”

**INSURER-LED ACOs**

Given the many points of friction between independent physicians and private payers, it might be surprising that practices are joining ACOs led by insurance companies. But several health plans, including some of the largest in the country, such as Aetna and United Healthcare, have formed ACOs. They emphasize that they have the patient data and resources to evaluate patient outcomes.

Brown & Toland Physicians, a San Francisco-based IPA, says it has achieved shared savings working with a variety of insurer-led ACOs. The network of 210 Bay Area physicians, most of them in small practices, cares for more than 335,000 HMO and PPO patients, says John Long, M.D., vice president of external relations.

The ACOs have been successful in helping member practices stay independent largely by cutting costs and earning shared savings by demonstrating improvement in the various value-based care programs, Long says. The private insurers’ expertise in identifying lower-cost treatment options has been helpful in that regard, he says.

**Mobile monitoring carries potential to help improve outcomes and generate revenue**

Mobile monitoring makes patients feel like they are doing something to support their own health, which engages them and can lead to greater adherence to treatment plans. In addition, the technology can:

- Provide consistent, automated monitoring of patient progress with the current treatment plan
- Inform providers about patient status during pivotal periods, such as transitions of care
- Enable providers to intervene early on emerging issues, which can improve patient outcomes
- Reduce costs and prevent readmissions
- Flag social determinants of health issues that require early intervention (ex: the patient no longer has someone who can pick up a prescription refill or take them to a doctor’s appointment), which can be particularly important with elderly patients.

**CMC REGULATIONS MENTION RPM**

CCM reimbursement requires the use of one of three CPT codes—99490, 99487, and 99489—that reflect increasing levels of time and complexity. The lowest level requires that at least 20 minutes be provided to eligible patients outside the office under the supervision of a physician or other qualified health professional each month. The second code entails 60 minutes, and 99489 is an add-on code for 99487, indicating additional 30-minute increments.

CMS requires practices to furnish a number of non-visit services in order to bill for CCM reimbursement. Among other things, they must “provide enhanced opportunities for the patient and any caregiver to communicate with the practitioner regarding the patient’s care by telephone and also through secure messaging, secure internet, or other asynchronous non-face-to-face consultation methods (for example, email or secure electronic patient portal).”

Mobile-enabled monitoring is one type of non-face-to-face asynchronous communication. The cost-benefit ratio of mobile monitoring is much more favorable than phone-based patient monitoring.

**OTHER CMS INITIATIVES**

Meanwhile, CMS is starting to reimburse for remote patient monitoring in other ways. To start with, the agency unbundled CPT code 99091, effective Jan. 1, 2018. This change allows a provider to be reimbursed separately for time spent on collection and interpretation of health data that is generated by a patient remotely, even if the provider also bills for reimbursement under the CCM or the Transitions of Care codes.

In addition, the agency recently updated its scoring regulations for MIPS, granting a higher weight to patient engagement efforts within the Improvement Activities category. The CMS guidance specifically calls out the use of patient-generated health data through digital platforms.

When used in conjunction with other CMS strategies, mobile-enabled remote patient monitoring can not only increase physician revenue but also help providers achieve the value-based care goals of improving the patient experience of care, improving the health of populations, and reducing the per capita cost of healthcare. At the same time, this technology allows practices to advance care in a way that is efficient and convenient both for them and their patients.

**Disclosures:**

Harry Soza is CEO of CAREMINDr, a health IT company focused on creating mobile technology to enable effective remote patient monitoring that gives doctors the ability to check in on patients between office visits.

Irina Yermilov, M.D., MPH, MS, CAREMINDr’s chief medical officer, has more than 10 years of experience measuring costs and quality related to chronic conditions.
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Burnout rate not as bad as we think

Quick Takes

Existing data does not compare the same parameters.

One data set says that 5% of doctors are burnout-out.

The definition of burnout is as vast as its presumed prevalence.


Of the 182 studies, the authors noted at least 142 different definitions for what constituted “burnout,” and they noted that overall burnout prevalence among the studies ranged from 0% to 80.5%.

The strictest criteria to define burnout used by a subset of studies included in Rotenstein and Mata’s systematic review required individuals to have an emotional exhaustion level of over 27 (on a scale of 0 to 54), a depersonalization level of over 10 (on a scale of 0 to 30), and a personal accomplishment level of less than 33 (on a scale of 0 to 48) on the Maslach Burnout Inventory (MBI). These criteria resulted in only about 5% of doctors as having burnout.

Conversely, the loosest criteria to define burnout used by another subset of studies considered individuals to be burnt out if they surpassed a minimal score on either the exhaustion or the depersonalization subscale of the MBI, translating into spuriously high burnout prevalence estimates of 50% or even greater.

Ranges for the prevalence of emotional exhaustion, depersonalization, and low personal accomplishment varied from 0% to 86.2%, 0% to 89.9%, and 0% to 87.1%, respectively, they wrote.

Dr. Mata says there are no agreed-upon criteria for labeling someone experiencing burnout. “Because of that, it is very difficult, if not impossible, to say how many people have burnout,” Dr. Mata tells Dermatology Times. “Researchers need to take a step back and think about the important methodologic issues that surround the measurement and definition of burnout, before they state how prevalent the condition is.”

OCCUPATIONAL STRESS VS DEPRESSION

Dr. Mata says feelings of burnout are certainly something a lot of physicians experience.

“Feeling emotionally drained from your work once a week or once a month could simply be attributed to having a bad day at work,” Dr. Mata says. “It does not mean you have a syndrome. Everyone experiences emotional drain from work to some extent, particularly people who work very hard.”

Dr. Mata was principal investigator of two previous reviews on physician depressive symptoms in JAMA in 2016 and 2015, respectively.2,3 The 2016 study found that approximately 20% of medical students screened positive for depression when assessed with high-specificity inventories, that only 15% of depressed students sought psychiatric treatment, and that 11% of students reported suicidal ideation. The 2015 study also showed that roughly 20% of resident physicians screened positive for depression when assessed with high-specificity inventories.

“The goal of the current study and these two past studies is, in part, to measure the response of physicians to exposure to chronic occupational stressors,” Dr. Mata says.

Occupational stressors encompass everything from working very long hours to being exposed to extremely ill or dying patients in an emotionally fraught situation. For younger physicians and medical students, in particular, having a substantial amount of debt and/or not having money can also cause stress.

Resident physicians also may work up to 80 hours a week, in which case there is not much time for self-care and spending time with friends and family, again factors that can lead to stress.

“Burnout is often cited as being secondary to bureaucratic tasks at the hospital,” Dr. Mata says. “Doctors are spending less time than ever at the patient’s bedside and more time on computer-related tasks.”

But the downside of using depression rather than burnout as an outcome, according to Dr. Mata, is that the doctor’s emotional response to his or her job becomes pathologized by considering it within the framework of depression.

“The nice thing about burnout is that it is not the doctor’s fault that they are burned out, but rather it is due to the environmental and cultural factors at their workplace,” he says.

WHAT THE DATA MEANS

Remedies to reduce burnout need to be addressed at the systems level as opposed to the physician level, according to Dr. Mata.

“Solutions need to be coming from hospital administrators to correct the structural problems in the workplace that are affecting doctors. But before getting carried away with solutions and ‘treatments,’ a better understanding of how to define and measure burnout is badly needed,” he says.

In an accompanying editorial in JAMA entitled “Physician Burnout – A Serious Symptom, But of What?”14, authors Thomas Schwenk, M.D., of the University of Nevada in Reno, and Katherine Gold, M.D., of the University of Michigan Health System in Ann Arbor, share their suspicion in being able to define the term burnout:

“There is no grounded understanding of the pathophysiology of burnout or agreement on how it should be measured,” they wrote.

In addition, the study authors are unable to make conclusions about the prevalence of burnout or its effects, according to the editorial writers, because of excess heterogeneity in the study design and the methods used to measure burnout across a host of cultures and health systems.

The editorial writers also point out that the MBI was originally intended to assess burnout in the social service professions from the stress of caring for clients, which may not be applicable for evaluating physicians.

Rottenstein et al write that their review calls into question whether prevalence estimates can be meaningfully interpreted. In addition, they note the necessity of developing a consistent definition and improved assessment tools for burnout.

Disclosures: Dr. Mata reports no relevant financial disclosures.

References


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Often utilized as a treatment modality for non-melanoma skin cancer, this session will explore the impacts & effects of superficial radiation therapy as a treatment modality for cutaneous oncology.

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With a focus on essential strategies specific to running dermatology practices, this specialty session includes the fundamentals of compliance, coding and reimbursement, MACRA, and legal advice. Lectures will further highlight various tools for growing medical practices through additional revenue streams, optimizing social media channels, and discovering supplementary tactics.

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This advanced track will provide the most recent clinical updates in hair restoration, supplemented by scientific research, topical treatments, and procedural innovations including PRP.

**Anti-Aging & The Dermatologist:**
This track will review hormonal practices & protocols, the implications of the microbiome in dermatology, integrative protocols for dermatologic procedures, and new advances in Regenerative Medicine all through the lens of clinical dermatology.
Verrica working with practitioners

As seen in Dermatology Times, page 19

Verrica Pharmaceuti
cal Clinical Trials

RECRUITING CLINICAL TRIALS:

NCT03487549: Cantharidin and Occlusion in Verruca Epithelium (COVE-1)
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NCT03377803: Cantharidin Application in Molluscum Patients (CAMP-2)
This study is a phase three, randomized, double-blind, placebo-controlled, pivotal study to evaluate the safety and efficacy of VP-102 topical film-forming solution in subjects with molluscum contagiosum. VP-102 will be applied once every 21 days for up to four applications to treatable lesions on subjects 2 years and older. Efficacy will be assessed as the proportion of subjects achieving complete clearance (baseline and new) on day 84.

COMPLETED CLINICAL TRIALS

NCT03186378: Evaluation of Systemic Exposure to VP-102 in Subjects with Molluscum Contagiosum
This was a phase two, open-label study to evaluate the safety, efficacy and systemic exposure of VP-102 topical film forming solution [0.7% (w/v) cantharidin] in subjects 2 years and older with molluscum contagiosum.

NCT03017846: Safety and Efficacy of Topical Cantharidin for the Treatment of Molluscum Contagiosum, Phase 2
The objective of this trial is to see if commercially-viable cantharidin formulation (VP-102) has a comparable safety and efficacy profile as formulations previously studied under conditions which most closely match the what has been historically done in the clinic.

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Verrica is always looking to work with practitioners who have identified unmet needs in dermatology, ” Dr. Davidson said.

Verrica is also in a phase two trial for common warts using the same drug device product. And, next year, a phase two clinical trial for plantar warts is expected to commence. “Because plantar warts are much tougher to treat, we will use a more potent formulation of cantharidin and perhaps a different applicator,” White says.

“If our trials are successful, we expect to be the first FDA-approved therapy for the treatment of molluscum contagiosum and anticipate becoming the standard of care,” White said.

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<tr>
<th>ADVERTISER</th>
<th>PRODUCT</th>
<th>WEBSITE</th>
<th>PAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEIERSDORF</td>
<td>ECZEMA RELIEF</td>
<td><a href="http://www.eucerinus.com">www.eucerinus.com</a></td>
<td>31</td>
</tr>
<tr>
<td>BEIERSDORF</td>
<td>AQUAPHOR HEALING OINTMENT SPRAY</td>
<td><a href="http://www.aquaphorus.com">www.aquaphorus.com</a></td>
<td>43</td>
</tr>
<tr>
<td>CANFIELD SCIENTIFIC</td>
<td>VECTRA</td>
<td><a href="http://www.canfieldscl.com">www.canfieldscl.com</a></td>
<td>61</td>
</tr>
<tr>
<td>CONSERVATION EASEMENT ADVISORS</td>
<td></td>
<td><a href="http://www.conservationeasements.net">www.conservationeasements.net</a></td>
<td>37</td>
</tr>
<tr>
<td>EPIPHANY DERMATOLOGY</td>
<td></td>
<td><a href="http://www.epiphanydermatology.com">www.epiphanydermatology.com</a></td>
<td>33</td>
</tr>
<tr>
<td>INDUCTION THERAPIES</td>
<td>COLLAGEN P.I.N</td>
<td><a href="http://www.inductiontherapies.com">www.inductiontherapies.com</a></td>
<td>49</td>
</tr>
<tr>
<td>MERZ AESTHETICS</td>
<td>ULTHERAPY</td>
<td><a href="http://www.ultherapy.com">www.ultherapy.com</a></td>
<td>39</td>
</tr>
<tr>
<td>NEWSURG,INC</td>
<td>KTP</td>
<td><a href="http://www.NewSurg.com">www.NewSurg.com</a></td>
<td>27</td>
</tr>
<tr>
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<td>Q &amp; PICO</td>
<td><a href="http://www.newsurg.com">www.newsurg.com</a></td>
<td>13</td>
</tr>
<tr>
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<td>CORPORATE</td>
<td><a href="http://www.ortho-dermatologics.com">www.ortho-dermatologics.com</a></td>
<td>11</td>
</tr>
<tr>
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<td>ATRENO</td>
<td><a href="http://www.ATRENO.com">www.ATRENO.com</a></td>
<td>15 - 16</td>
</tr>
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<td>45 - 46</td>
</tr>
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<td><a href="http://www.ortho-dermatologics.com">www.ortho-dermatologics.com</a></td>
<td>55 - 56</td>
</tr>
<tr>
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<td>INSTALIFT</td>
<td><a href="http://www.Instalift.com">www.Instalift.com</a></td>
<td>59</td>
</tr>
<tr>
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<td>STEMLINE</td>
<td><a href="http://www.bpdcninfo.com">www.bpdcninfo.com</a></td>
<td>51</td>
</tr>
<tr>
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<td>PICOWAY</td>
<td><a href="http://www.syneron-candela.com">www.syneron-candela.com</a></td>
<td>53</td>
</tr>
<tr>
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<td>VBEAM</td>
<td><a href="http://www.syneron-candela.com">www.syneron-candela.com</a></td>
<td>8 - 9</td>
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<tr>
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<td></td>
<td><a href="http://www.verrica.com">www.verrica.com</a></td>
<td>29</td>
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</tbody>
</table>

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ALASTIN SkinCare unveils body sculpting treatment

ALASTIN SkinCare launched its body sculpting product TransFORM Body Treatment with TriHex Technology at the American Society for Dermatologic Surgery (ASDS) Annual Meeting in October.

The TransFORM product is designed to enhance the effects of non-surgical body fat reduction and energy-based skin tightening procedures by supporting the production of elastin and collagen. TransFORM can also be used daily as a standalone treatment.

The product contains a blend of peptides, including Hexapeptide-11, that penetrate the dermal fat around the hair follicle to naturally stimulate the removal of fat debris. ALASTIN says that the treatment also improves skin crepiness and texture by hydrating the skin and boosting the body’s natural production of hyaluronic acid.

Initial split-body evaluations showed subjects that used the TransFORM product alongside non-surgical fat reduction procedures experienced enhanced results. Subjects that used the product as a standalone treatment saw an improvement in skin roughness and crepiness by an average of 11% at week 4 and 38% by week 8.

FOR MORE INFORMATION: www.alastin.com
The basics of wound care include reducing bioburden, reducing edema and maintaining a moist wound environment. In this table, we revisit a 2014 article from the journal, Plastic Surgical Nursing, in which Marcia Spear, DNP, ACNP-BC, CWS, GPN, addressed the “Principles of Wound Care—Back to the Basics.”

**BIOBURDEN** An overabundance of bacteria in wounds can cause biofilms to spread, which can prompt antimicrobial resistance that inhibits wound healing of both acute and chronic wounds. Antimicrobials and debridement are usually the first go-to treatments for biofilms, but these are not without possible adverse events. Topical agents, such as antibiotic ointments or creams, can lead to contact dermatitis, narrow antimicrobial spectrum, unequal moisture balance and antimicrobial resistance. So, in these cases, dressings or debridement may be preferred.

Bacterial bioburden may be high in cases of increasing exudate, delayed healing, discolored granulation tissue, friable granulation tissue, pocketing at the base of the wound, foul odor, increasing pain, and wound breakdown.

Signs of an infected wound include erythema, localized pain and heat, cellulitis, and edema.

**TREATMENTS FOR BIOBURDEN**

- Silver, combined with foams, alginates, contact layers, hydrogels, collagen have potential for anti-inflammatory action.
- Iodine, such as a cadexomer molecule for absorption and cytolytic debridement, allows slow release of the antimicrobial.
- Chlorhexidine, polyhexamethylene biguanide, in a gauze or foam packing.
- Honey, combined with alginites or hydrogel, produces a slow release of peroxide as an antibacterial dressing.
- Methylene blue and gentian violet bound to a foam that is slowly released on the basis of the amount of exudate provides antimicrobial coverage.
- Debridement: surgical, mechanical, sharp, or enzymatic as appropriate.

**MOIST WOUND HEALING**

- Achieving moisture balance is essential in wound healing. “Allowing the wound to dry out decreases fibroblast proliferation and inhibits epithelial cell migration.” Dressings can maintain moisture which can aid in removing excessive exudate and debris. When too much moisture is present, use dressings that absorb moisture.
- Change dressings as necessary to maintain the moisture balance.
- For wounds that are too dry, select dressings that add moisture, such as hydrogels.

**EDEMA**

- The presence of edema can inhibit wound healing by causing cell death and creating a toxic wound environment. Edema is a sign of disease, so experts recommend identifying the cause and treating accordingly.
