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For over five decades, the Foundation has funded innovative research that has paved the way for new and improved treatments in all aspects of the specialty.

Every disease seen in the practice of dermatology has new therapies, or even cures, awaiting development — that’s why the DF exists. It provides a simple and effective way for the entire dermatologic community to ensure continued advancements in care for patients everywhere.
Better laser resurfacing results

Future lies in drug delivery, postprocedural care

JOHN JESITUS | Staff Correspondent

The current complement of fractional ablative and nonablative lasers covers a wide variety of indications safely and satisfactorily, says Susan Van Dyke, M.D., a Paradise Valley, Ariz.-based dermatologist. However, she adds, skin tightening results often require adjunctive treatment modalities, and postprocedural regimens remain a puzzle.

Improving skin quality through resurfacing generally involves addressing superficial issues, such as dyschromias, precancerous lesions and rough, dull skin, along with crepiness and, with some lasers, mild laxity, according to Dr. Van Dyke. Additional roles for resurfacing include treating scars, freckles and pigment issues unrelated to aging, such as melasma and postinflammatory hyperpigmentation (PIH).

“I liken resurfacing to aerating your lawn — punching little holes in the tissue,” she says. Visible results include new surface skin, with collagen and elastin formation at deeper levels.

Laser success requires picking the right type of laser for the right indication in the right patient to get the right results, says Dr. Van Dyke, who presented on this topic at the Fall 2018 Cosmetic Bootcamp. Pigment problems reside in the superficial to mid-dermis, while mild and moderate rhytids reside in the mid-dermis and deep reticular dermis, respectively. Scers (acne and surgical) require even deeper remodeling.

Medical device regulation impacts patient care

WHITNEY J. PALMER | Staff Correspondent

Dermatologists and patients often rely on medications and topicalis to treat skin conditions, but some cases require the use of medical devices. Dermatologists can positively impact patient care by learning how these devices are developed.

The FDA’s Center for Devices and Radiological Health (CDRH) can help dermatologists better understand how the Food & Drug Administration (FDA) approaches, reviews and approves medical devices integral to dermatologic care. The CDRH’s main charge is to keep tabs on medical device innovations, evaluating them for safety and efficacy based on data submitted by manufacturers, according to Laura Marquart, M.D., FAAD, medical officer with the CDRH.

“Dermatologists should have a good grasp of our commitment to safe innovation and the types of products we review within the Center, as well as the regulatory pathways for these products,” she says. “They should understand the life cycle of the products and the recent dermatology-related advancements in CDRH over the last year.”

Some of these advancements include newly granted, cleared and approved devices, including...
Dermatology Times is guided by a core group of trusted physician experts who review meetings; suggest topics & sources; & conduct interviews.

our MISSION
Provide practical analysis of recent studies, regulatory updates, techniques, devices and business solutions; and facilitate discussion to optimize practice and improve patient care.

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.
Almost all dermatologists train in a clinical setting that accepts underinsured patients. Only a fraction of us continue to practice in an academic setting, and even fewer accept all patients, regardless of ability to pay. I chose this path for a decade after residency, left it for six years in a less inclusive private practice, then returned 10 years ago, for many reasons. A practice that does not exclude patients based on insurance is one that more dermatologists should consider, for many reasons.

The demand for dermatologic care far exceeds the workforce. Our seller’s market allows us the luxury to choose from a variety of practice settings. The American Academy of Dermatology (AAD) Practice Management Center is an online resource designed to help members with many aspects of managing a dermatology practice. The website portal includes a tutorial on emerging practice models to help inform dermatologists of the many workplace options.

The AAD Emerging Practice Models Committee advises this initiative. To date, the following models have been explored:
- Accountable Care Organization (ACO),
- Group Without Walls,
- Independent Practice Association,
- Joint Venture,
- Teledermatology,
- Concierge and Cash-only.

After reviewing the content created for the Concierge/Cash-only model, committee members voiced concerns about the ethical implications of this type of practice, the negative impact on access to care for patients with limited resources, our specialty’s comparatively low Medicaid acceptance rate and the need for formal AAD recognition of these issues.

So, as Deputy Chair and a committee member with practical experience in settings that include and exclude Medicaid, I was asked to create AAD Practice Management Center content about the pros and cons, as well as factors that support sustainability of a socioeconomically inclusive practice.

Job satisfaction is an obvious goal when choosing a practice setting.

Factors to help sustain a practice that includes the underinsured

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- Accept a salary comparable to that of your colleagues with primary appointments in Departments of Family Medicine, Internal Medicine or Pediatrics.
- Seek philanthropic support.
- Work at an ACO, where cost-savings are valued over fee-for-service revenue. These settings often include teledermatology.
- Implement a scheduling system to minimize no-shows (less than 4 weeks in advance; see Chaudhry SB et al. Improving Non-attendance Rates Among Medicaid-insured Patients. 2019; J Am Acad Dermatol. Accepted for publication).
- Make sure your organization provides administrative support for obtaining prior authorization and access to medications.
- Make sure your organization provides adequate nursing and case management support.
- Make sure your organization has adequate Social Service support.
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*Based on available 510(k) summaries as of October 2017.

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Although dermatologists constitute 1.4% of the total physician population, only 0.7% of claims are against dermatologists.

Settlement or litigation: What should I do?

Dr. Skin missed seeing a melanoma on his patient. It was present when he saw her, but he just did not see it. Two years after that visit, the lesion is biopsied by another physician. The depth 1.3mm and a sentinel lymph node is positive for metastatic disease. The former patient, now plaintiff, sues Dr. Skin for negligence. The plaintiff’s attorney offers to settle the case prior to going to court for $1 million dollars. Should Dr. Skin do so?

The first question to be asked is: “Was Dr. Skin negligent?”

If it can be argued that the duty of a reasonable physician would have been to diagnose the melanoma earlier and Dr. Skin did not do so, then he has breached his duty as a reasonable physician. If there is then a connection (nexus) between that breach and damages, then Dr. Skin would be considered negligent.

All would agree that metastatic disease would fall into the category of damages. There could be a significant economic loss to the patient, and if she dies, that economic value is established in terms of actuarial analysis of how long she might have lived. That might be much more than $1 million. The but is: Dr. Skin is not certain he was negligent. Should he settle or go to trial?

There is no question that the standard approach is one of “marching to trial.” However, the march to trial is a multi-year process that includes discovery, depositions, pre-trial hearings, various maneuvers and then trial. There are no guarantees. Dr. Skin, like most physicians, is not sure he has the emotional strength to go through this process. He had even been thinking of retiring.

In reality the majority of medical malpractice cases do settle out of court. One of the reasons for this is that cases are very expensive to investigate and prosecute. Litigation is very time consuming and victims often wait years to receive anything. The average in-court payout against all negligent physicians in the United States is $1 million to $4.5 million. The average settlement is for $500,000.

Since there are no guarantees, the decision becomes a balancing act. Of note, successful lawsuits against hospitals in the United States occur about 50% of the time; while successful lawsuits against physicians occur only 33%. Hospital payouts are often much higher than those against physicians.

The economic value of a case may also be determined by where it is brought. California and Texas have caps on pain and suffering. No state has a cap on medical expenses, lost income and lost future earnings. This could be a large number in this case.

If a case is settled, it should also settle all the plaintiff’s related bills ((Medicare, Workman’s Comp, ERISA, etc.). In addition, the settlement should be for total dollar amount without a breakdown of categories.

Having looked at the issues, it should be emphasized that the incidence of claims is still fairly low for dermatologists. Although dermatologists constitute 1.4% of the total physician population, only 0.7% of claims are against dermatologists. In addition, only 2% of truly negligent acts result in medical malpractice claims; while only 17% of all malpractice claims result from truly negligent acts.

Among dermatologists, the most common reasons for lawsuits are wrong site, functional outcome, post-procedure outcome, cosmetic outcome, recurrent tumor, improper consent, delayed diagnosis, and misdiagnosis.

Dr. Skin will ultimately need to make a decision as to whether to settle or not. There are no guarantees. Settlement will always be difficult, but sometimes is the best approach. Lastly, even if he retires, he will still have potential liability whether or not the case settles.
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In 2018, the FDA’s Center for Drug Evaluation and Research (CDER) approved 59 new novel drugs that represent products that have never before been used in clinical practice in the United States. This number includes new molecular entities (NMEs) that have an active moiety never approved before. In many ways, it was a banner year with the last record for novel approvals being 50 in 1996. Looking at the last three years, there was 45 approvals in 2015, 22 approvals in 2016, and 46 approvals in 2017.

Beyond the simple absolute number, further analysis suggests more encouraging news. First, 34 of these approvals (58%) were directed towards rare diseases or orphan indications. 32% (19/59) of these approvals are first-in-class therapies. Forty-one percent of these applications were designed as “Fast Track” medicines—this track is slated for new drugs that target unmet clinical needs and enable CDER to evaluate portions of the drug application ahead of the complete application to facilitate regulatory approval. Fourteen out of 49 drugs (24%) were further distinguished as a “Breakthrough Therapy” that addresses a serious or life-threatening disease for which there is an unmet clinical need and the new drug offers a potentially significant improvement over other available therapies. A breakthrough therapy designation leads to the commitment of additional regulatory resources and attention to shorten the development time between application and approval.1

Out of these 59 approvals, many have clear dermatological implications. In fact, 17% (10/59) have uses in dermatology and span infectious disease, oncology, and inflammatory conditions.

A summary is listed below organized by category.

**INFECTIOUS DERMATOLOGY**
- Omadacycline (Nuzyra) was approved for community-acquired, acute bacterial skin and skin structure infections (cellulitis).
- Tecovirimat (TPOXX) was approved to treat smallpox—it is the first drug to receive an indication for smallpox. While smallpox has been eradicated in 1980 as declared by the World Health Organization, it remains a biological weapon threat. TPOXX was approved under the FDA’s Animal Rule – which allows for efficacy to be established in animals when human trials are infeasible or unethical. A cohort of 359 healthy human volunteers demonstrated the drug’s safety. TPOXX was developed in collaboration with the U.S. Department of Health and Human Service’s Biomedical Advanced Research and Development Authority (BARDA).
- Moxidectin (moxidectin) was approved for the treatment of onchocerciasis in patients 12 years or older. In the pivotal trial, a single dose of moxidectin was superior to ivermectin in skin micro-filarial density in a clinical trial of more than 1400 patients.2

**CUTANEOUS ONCOLOGY**
- Cemiplimab-rwlc (Libtayo) was approved to treat cutaneous squamous cell carcinoma. Libtayo’s, a PD-1/PD-L1 checkpoint inhibitor, approval represents the first treatment for advanced cutaneous squamous cell carcinoma. In two open label clinical trials with 108 patients (33 with locally advanced disease, 75 with metastatic disease) showed that 47.2% of all patients had objective response with durability of response. The main side effects included immune-mediated reactions such as pneumonitis, colitis, hepatitis, and endocrinopathies. Libtayo was awarded both breakthrough therapy and priority review designations.
- Encorafenib (Braftovi) was approved for unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.
- Binimetinib (Mektovi) was another approved drug for unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.

**RARE / ORPHAN INDICATIONS**
- Lanadelumab-flyo (Takhzyro) was approved to treat type 1 and type II hereditary angioedema. Compared to placebo, patients receiving Takhzyro had an 87% reduction in mean number of angioedema attacks per month compared to placebo.3
- Cenegermin-bkhj (Oxervate) was approved to treat neutrophilic keratitis, which can be caused by herpetic infections along with other causes. Complete corneal healing in 8 weeks was demonstrated in 70% of patients treated with Oxervate compared to placebo. Oxervate was awarded priority review and an orphan drug designation.

**MEDICAL DERMATOLOGY**
- Sarecycline (seysara) was approved for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients nine years or older.
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PN99581EN-NA
Q. What is micellar water?
Micellar water cleansers are becoming a mainstay in most cosmetic and skincare company offerings, which attests to their consumer popularity. Micellar water is also a low-cost-of-goods item that fetches a premium price due its newness, providing an excellent profit margin.

Micelles are tiny cleanser droplets that are emulsified into a water vehicle. They usually contain surfactants that do not sting the eyes from the betaine group of detergents, also why these detergents are used in baby shampoos. Micellar water is a very dilute solution of surfactant that can be placed on a cotton pad and stroked over the eyes to remove eye makeup and other facial cosmetics. Formulations are available to remove both water removable and waterproof cosmetics.

Micellar water is an excellent cleanser for cosmetic removal and in persons with very dry and mildly soiled skin.

Q. What is the value of facial water sprays?
Facial water sprays are found in many upper end cosmetics as a way of renewing facial moisturization during the day without disturbing or removing facial cosmetics. The water is either aerosolized or sprayed from a pump and held about 8-12 inches from the face. However, spraying water on the face is not moisturizing. The face looks moisturized immediately after application with a dewy appearance, but the water rapidly evaporates. For this reason, many facial water sprays contain a humectant, such as sodium PCA, which holds the water longer on the skin surface and leaves behind a thin layer of humectant moisturization.

Some facial sprays contain water from special mineral or thermal springs. The water may contain minerals, such as silica and/or selenium that are felt to possess anti-inflammatory properties. This water is usually sprayed on clean skin followed by the application of a moisturizer to hold the water on the skin and colored cosmetics. The water is recommended for use in inflammatory skin conditions, such as eczema, atopic dermatitis, and rosacea.

Q. What is the best way to increase skin water content and moisturization?
The whole concept of skin moisturization is a misnomer. You cannot moisturize the skin, but you can control the loss of water from the skin, known as transepidermal water loss. When the amount of water the skin looses is decreased, the water content of the skin increases. This is the correct description of what happens via moisturization.

Given this understanding, the best way to increase skin water content is to put an impermeable plastic wrap on the skin stopping all evaporation. This is not the solution because under these conditions the skin will become hyperhydrated and macerated. Thus, the optimal moisturizer should allow some water loss, but not too much.

The best products to maintain skin water content should contain an ingredient to stop water loss, known as an occlusive, and an ingredient to hold the water in the skin, known as a humectant.

The best occlusive moisturizers are mineral oils, silicone oils, and vegetable oils, such as grapeseed oil, hemp oil, jojoba oil, sesame oil, etc. The oils create a thin film over the skin surface reducing transepidermal water loss by 20-60%, depending on the combination of oils used. The mineral and vegetable oils are combined with silicone oils, such as dimethicone and cyclomethicone, to make the moisturizer less greasy.

Finally, a humectant must be added, such as hyaluronic acid, hydrolyzed collagen, sodium PCA, glycerin, sorbitol, etc. Hyaluronic acid, found naturally in the dermis and the substance used in facial filler injectables, is an expensive, but highly effective humectant. Hyaluronic acid is found in many of the higher end moisturizers for this reason. Lower end moisturizers use glycerin, which is less expensive.
Remembering
Vic Narurkar, M.D.

LISSETTE HILTON | Staff Correspondent

Beloved, brilliant, fun, giving, humble and a pioneer — these are among the words colleagues and friends use to describe Vic Narurkar, M.D., who died after a massive heart attack last month, days shy of his 51st birthday.

The unexpected loss of a cosmetic dermatology icon has left many thinking about Dr. Narurkar’s significant contributions to the subspecialty, the person he was and the void he left.

“Vic was a prodigy and a genius. He was the original Doogie Houser. He graduated from Brown University at 16 and graduated from Stanford Medical school at age 20. Vic was incredibly humble and didn’t talk much about his age and incredible accomplishments,” says Kathleen M. Welsh, M.D., who met Dr. Narurkar more than 30 years ago when they were first-year dermatology residents at Stanford.

Despite each launching aesthetic practices in San Francisco in the same year, Dr. Welsh says the two were friends and colleagues — not competitors.

“If Vic thought there was an innovative, new technology that was going to improve our cosmetic practices, he would call me and say, ‘Kathleen, you have to try/buy this. This is going to be big.’ Because of his counsel over the years, I have a very small laser graveyard!” Dr. Welsh says.

Spokane, Wash., dermatologist Wm. Philip Werschler, M.D., was performing demonstration injections at last month’s Maui Derm meeting when he got the news that his dear friend of nearly 25 years had passed. Dr. Werschler says he and Dr. Narurkar “grew up” together as dermatologists. They earned their stripes in the profession by speaking at meetings, conducting studies, publishing their work and, eventually, mentoring others.

“We’d often talk about how we had the best job in the world as dermatologists,” Dr. Werschler says.

LEGACY OF A LEGEND
Dr. Narurkar made immense scientific contributions in the field of aesthetic medicine. In the world of lasers and devices, he was legend. His interest in devices started early when he completed a fellowship in laser and cosmetic dermatologic surgery with laser pioneer Philip Bailin, M.D. As a fellow, Dr. Narurkar was involved in developing pulsed dye and alexandrite lasers used for birthmark and tat-
Consumer survey ranks top non-surgical procedures

RealSelf reports consumer feedback trends

NEW DATA related to consumer satisfaction trends soon to be released by RealSelf reveals the “Most Worth It” procedures for 2019.

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The online cosmetic information resource ranks more than 140 surgical and nonsurgical cosmetic procedures and brands based on consumer satisfaction scores generated from consumer reviews on the RealSelf platform. Making the “Most Worth It” list are 28 surgical and 23 nonsurgical treatments. To be recognized as a “Most Worth It” procedure, a treatment must have a cumulative Worth It Rating of 90% or more over the prior 12 months and meet the minimum review requirement during the same period, according to a RealSelf news release.


Retired Mayo Dermatology Chair dies at age 82

ARNOLD LEESCHROETER, M.D., died Thursday February 14, 2019, at the age of 82. Dr. Schroeter joined the Mayo Clinic Dermatology staff following his residency. In 1985, he became the Chairman of Dermatology at Wright State Medical School in Dayton, Ohio, but returned to Mayo Clinic in 1994 to become Chair of the Dermatology Department. He remained at Mayo until retirement in 2008.

As well as being an active teacher and mentor, Dr. Schroeter authored more than 200 publications over his career.

Nature-based skin care effective as adjunct to prescription rosacea therapy

BURT’S BEES skin care products may be an effective as an adjunct to prescription therapy in the management of rosacea, according to data published in the February issue of Journal of Drugs in Dermatology and which will be reported at the American Academy of Dermatology Annual Meeting this month.

Eighty female patients with rosacea between the ages of 25 and 70 years old were first treated with topical 0.75% metronidazole gel twice daily. Following baseline assessments, the patients were randomized to receive – in conjunction with the topical therapy - either a four-week regimen consisting of a cleanser containing natural oils, beeswax and witch hazel and day and night creams containing natural oils, glycerin, and botanical anti-inflammatories or a four-week control regimen of cetyl alcohol, sodium lauryl sulphate-containing cleanser, and glycerin, polyisobutene-containing lotion.

Blinded investigator global assessment of rosacea, investigator-rated, and subject-rated overall skin appearance was assessed again at two and four weeks. The investigational regimen clinically and statistically improved erythema by 28%, telangiectasia by 26% and papules/pustules by 34% (p<0.001) while the control regimen improved rosacea symptoms by 8 to 12%.

New drug targets A3AR

Can-Fite explores muscle tissue to fight psoriasis, cancer

WHITNEY J. PALMER | Staff Correspondent

Cancer and inflammation can metastasize and affect virtually every organ in the body, including the skin. However, there’s one part of the body that resists both conditions — the muscles.

Pnina Fishman, Ph.D., an immunology and oncology researcher, wanted to know why. And, she was curious to know if she could do something about it.

“I came across a very interesting question,” she said. “Why did cancer and inflammation go everywhere in the body, but not in the muscle tissue when it accounts for nearly 65 percent of body weight?”

That query launched Fishman, then a professor of life sciences and the head of the Lab of Clinical & Tumor Immunology at Felsenstein Medical Research Institute at Tel Aviv University, down a path with her colleagues that ultimately revealed muscles have a natural defense to cancer and inflammation assault. Her research showed muscles release small molecules that have inherent anti-cancer and anti-inflammation properties.

Muscles, she said, activate the A3 adenosine receptor (A3AR) that inhibits cell growth. Because A3AR is found in much higher quantities in cancer and inflammatory cells than in normal, healthy cells, targeting the receptor with specific drug therapies can cause cancer and inflammation cell death. More in-depth research also showed A3AR is a predictive biomarker that can identify individuals that are most responsive to these types of drugs.

With this knowledge, Fishman and a fellow faculty member, Ilan Kohn, Ph.D., founded Can-Fite Biopharmaceuticals Ltd., in 2000. Fishman has served as its chief executive officer (CEO) since 2005, and Kohn is the Chairman of the Board.

THE ROAD TO CEO
Since the beginning of her academic career as a student at Bar-Ilan University, Fishman has maintained an interest in the body’s cells and their functions. Her studies and research led her from microbiology to hematology to oncology and immunology.

“All of my academic career, I had been interested in the relationship between cancer disease and inflammatory disease,” she said. “And, when my lab made the discovery about muscles and the small molecules, I realized there was a chance to develop a drug or drugs out of this idea.”

At that point, she went to Kohn and asked him to draft a patent to protect the intellectual property. He agreed and also committed to contributing $1 million to start Can-Fite. In order to grow the company, however, Fishman stepped back from her professorship and devoted all her energies to the new venture, including forging partnerships with investigators at other institutions, such as the National Institutes of Health.

“As a result of our partnership, we have a very good framework and basis for drug development in place,” Fishman said.

Today, the company is publicly traded on the New York Stock Exchange.

FIRST DERMATOLOGY DRUG
With its first drug under development, piclidenoson, Fishman said, Can-Fite is looking to treat psoriasis. The same drug, currently in phase 3 clinical trials, also has an indication for rheumatoid arthritis. Although there are several existing treatment options for psoriasis, including acitretin, cyclosporine, and methotrexate, piclidenoson is designed to be different, she said.

Piclidenoson binds to the Gi protein associated with A3AR which is over-expressed in psoriasis patients. Instead of an injection or infusion, patients take piclidenoson orally twice a day, eliminating the need for them to schedule an outpatient clinic visit. According to clinical study data, based on approximately 1,200 participants, it causes no adverse
Natural extracts for acne
Plant-based therapy more effective than synthetic antibiotics

INGRID TORJESEN | Staff Correspondent

A cream containing natural extracts of propolis, tea tree oil, and Aloe vera has been found to be more effective in reducing mild to moderate acne than a cream containing the synthetic antibiotic erythromycin, research published in Clinical Pharmacology: Advances and Applications shows.1

Antibiotics that suppress Propionibacterium acnes are the standard treatment for acne but are becoming less effective due to the emergence of antibiotic-resistant bacterial strains. Clinicians are also encouraged to prescribe fewer antibiotics overall due to the rising threat of antimicrobial resistance.

Many plants are known to have innate antimicrobial action, so researchers are increasingly looking to see whether plant-based treatments might be an effective alternative to antibiotics. This study aimed to evaluate the efficacy of a new cream based on three natural extracts (propolis, “tea tree oil” and “Aloe vera”) in treating mild to moderate acne, comparing it to a cream based on 3% erythromycin and to its vehicle alone (placebo).

The study was conducted at the Skinlab, Department of Biomedical Sciences, University of Sassari, Italy where 60 patients with mild to moderate acne vulgaris were randomly divided into three groups of 20.

All patients were aged between 14 and 34 years; had no more than 20 comedones and 50 papules and pustules; no nodules, cysts, and no more than slight erythematous scarring presence; had not received topical or systemic acne treatments during the previous three months; and had previously been responsive to treatment used was not sufficient to obtain results.”

The study also showed that PTAC does not possess sebum-reducing properties, respected the hydrophilic film, and did not irritate the healthy skin as it did not change the superficial sebometry, the pH and the erythema index.

“Compounds, such as isoflavones, chalcone, and tannin, contained mainly in the propolis, have been reported to be effective in inhibiting 5-α-reductase enzymes in vitro,” said Mazzarello, but this was no such effects were observed with PTAC in the study, “perhaps because 1-month application or the concentration used was not sufficient to obtain results.”

Reference


Quick Takes

Clinicians are looking for alternatives to antibiotics due to the rise of antimicrobial resistance.

Many plants are known to have innate antimicrobial actions.

Patients that used cream containing natural extracts reported greater reduction in acne symptoms and scars.

“...cream containing propolis, tea tree oil, and A. vera is more effective in reducing acne compared to the preparation of synthetic origin...and has greater function in reducing erythema.” Vittorio Mazzarello, Skinlab, Department of Biomedical Sciences, University of Sassari, Italy.
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Topical retinoids prevent P. acnes biofilm

by ASHA GOWDA, M.S., M.D.1 & CRAIG G. BURKHART, M.P.H., M.D.2

1 Case Western Reserve University, Cleveland, Ohio, USA
2 Clinical Professor, University of Toledo College of Medicine, Toledo, Ohio, Ohio University College of Osteopathic Medicine, Athens, Ohio, USA

Quick Takes

P. acnes produces a biofilm that promotes comedone formation.

The biofilm acts as a glue, increasing the cohesiveness between follicular keratinocytes and debris.

Topical retinoids’ comedolytic properties counteract the biofilm and dislodge debris.

Comedonal acne is a therapeutic nuisance for many individuals. While mild cases are easier to treat, recalcitrant and untreated lesions can leave behind permanent scars and become difficult to manage later on.

The first line treatment for comedonal acne remains topical retinoids, such as adapalene, tretinoin, isotretinoin, and tazarotene.1 These unplugging agents normalize the hyperproliferation of keratinocytes, increase cell turnover, and enhance the desquamation of follicular keratinocytes.2,3 Not only do these topicals prevent the formation of microcomedones, the precursor lesion of acne, but they also have comedolytic properties that help expel the follicular debris and reduce the appearance of visible lesions.2,3

Given that the therapeutic effects of these agents are dose-dependent, the medication strength can be altered according to the severity of the disease. Additionally, the topical agents can be developed as different vehicles, such as gels or creams, that can offer different potencies. The range of concentrations and variety of formulations allow for treatment to be individually personalized. Recently, adapalene 0.1% gel, also known as Differin, became the first topical retinoid available over the counter, while all other agents still require a prescription.3 Of these topical agents, tazarotene is contraindicated in pregnancy, whereas other topical retinoids require extreme caution.3

Dermatologists preferentially prescribe topical retinoids as a fixed combination topical treatment with an antimicrobial agent due to its enhanced efficacy. For instance, adapalene frequently is combined with benzoyl peroxide or clindamycin.4,5 Similarly, tazarotene is used with clindamycin or as a triple combination therapy with benzoyl peroxide-clindamycin or benzoyl peroxide-erythromycin.6,7 Thus, these combined agents have mechanisms of action that target the microcomedone, and also the Propionibacterium acnes bacteria, which is known to be involved in the pathophysiology of acne.

P. acnes is regarded as a key player in acne vulgaris, however interestingly, the exact role of P. acnes in acne vulgaris is uncertain. The role of P. acnes appears to be diverse and contingent on other determinants like the environment and genetic influences. This brings into question, how exactly are therapeutic agents targeting this bacterium?

The P. acnes bacteria reside on the skin as part of the microbiome.8 After colonization, P. acnes can synthesize a glycocalyx polymer made of polysaccharides and proteins that has adhesive properties.9,10 Therefore, this biofilm also functions as a biological glue that promotes comedone formation by increasing the cohesiveness between follicular keratinocytes and debris.10 Contents within the pilosebaceous unit accumulate and remain adhered within the follicle.10 We have previously described the role of this glue-like secretion in...
Acne vulgaris is an area of continued investigation, yet even with new studies elucidating the pathogenesis of this disease and identifying new targets for therapy, topical retinoids remain the first line treatment.

preventing the natural shedding of dead keratinocytes and giving rise to the microcomedone. In such a setting, the comedolytic properties of topical retinoids help to counteract the biological glue and dislodge the collection of debris. When this hyperkeratotic plug cannot be expelled through the epidermal surface, it expands beneath and can release its contents into the dermal tissue, where an inflammatory reaction ensues.

Fortunately, in addition to its action against the microcomedone, topical retinoids have anti-inflammatory effects, enabling them to remain the first line treatment for comedonal acne. Although irritant dermatitis is a common limitation to the use of topical retinoids, this can be minimized by reducing the medication concentration or frequency of application, and often subsides. For patients with contraindications, for cases that are resistant to treatment, or for patients whose disease has progressed into inflammatory acne, antibacterials and oral isotretinoin are beneficial.

Topical antimicrobials like erythromycin and clindamycin can also be used for acne, however, dual therapy with a bactericidal agent has become the standard to inhibit growth of resistant bacteria on the skin. Few of these combinations, such as 5% benzoyl peroxide and 0.5% erythromycin, and 5% benzoyl peroxide and 1% clindamycin have recently been shown to be active against the *P. acnes* biofilm. Some have suggested that even the addition of oral zinc salts to topical treatments like erythromycin may help with reducing erythromycin-resistant strains. Along with targeting the *P. acnes* bacteria, certain antibiotics like clindamycin have anti-inflammatory properties. Commonly used oral antibiotics include tetracycline, doxycycline, erythromycin, azithromycin, and minocycline. Collateral damage, however, is inevitable with long-term use of antibiotics. The associated risks of systemic effects, such as alteration of the body’s microbiome, limit the duration of oral antibiotic use to 12 weeks.

Sarecycline is a new antibiotic of the tetracycline family that is currently under investigation as a more precise and selective agent against *P. acnes*. Oral isotretinoin is another compelling option, especially for those with severe inflammatory acne, nodulocystic acne, or post-inflammatory scarring.

Despite the inconvenience of the monthly follow-ups with laboratory testing, the ability of isotretinoin to target all four pathophysiologic pathways of acne vulgaris makes it a very attractive therapeutic option. Acne vulgaris is an area of continued investigation, yet even with new studies elucidating the pathogenesis of this disease and identifying new targets for therapy, topical retinoids remain the first line treatment. We believe that the efficacy of topical retinoids is partly due to the unplugging action that counteracts the cohesive efforts of the *P. acnes* biofilm. Currently, there are few studies investigating the *P. acnes* biofilm as a target for therapy. We expect that a better understanding of the biological glue secreted by *P. acnes* bacteria will guide advancements in comedonal acne treatment in the future.

**References**

Heart disease risk high in atopic eczema

LISSETTE HILTON | Staff Correspondent

**Quick TAKES**

Research suggests that inflammation in severe atopic eczema increases heart disease risk.

Mild eczema, however, has a neutral impact on cardiovascular outcomes.

Prevention strategies are needed to reduce heart disease risk in patients with severe cases.

**BY THE NUMBERS: STROKE AND HEART DISEASE RISK IN ATOPIC ECZEMA**

- **20%** Increased stroke risk
- **40%-50%** Heightened risk of unstable angina, myocardial infarction, atrial fibrillation, cardiovascular death
- **70%** Increased heart failure risk

Adults with severe and predominately active atopic eczema are at higher risk for cardiovascular disease outcomes, including myocardial infarction, stroke and death, compared to adults without eczema, shows an observational population-based study published May 23 in the journal *BMJ*.

Results from studies assessing links between atopic eczema and cardiovascular outcomes have been mixed. But there’s increasing evidence that systemic inflammation associated with atopic eczema might increase cardiovascular disease risk. And, given that up to 10% of adults worldwide are affected by eczema, it’s important from a public health perspective to understand even a small uptick in cardiovascular risk among these patients, write authors who were led by Sinead Langan, Ph.D., of the London School of Hygiene and Tropical Medicine in London.

“We found higher risks of cardiovascular disease than expected among eczema patients relative to people without eczema, as well as consistent findings across the cardiovascular outcomes when assessing severe and persistently active eczema. If these results are robustly replicated, it would support targeted screening and a focus on primary prevention strategies to reduce cardiovascular disease among such patients,” wrote Dr. Langan and Richard Silverwood, Ph.D., the study’s first author.

The authors compared the medical records of 387,439 adults (mean age 43 years, 66% female) with atopic eczema to 1,528,477 matched controls.

They found that patients with severe atopic eczema had a 20% increased stroke risk; 40-50% heightened risk of unstable angina, myocardial infarction, atrial fibrillation and cardiovascular death; and, 70% increased heart failure risk.

Patients were classified as having moderate disease if they received at least two potent topical corticosteroid prescriptions in a single year or topical calcineurin inhibitor treatment. The authors defined severe disease in those who had received phototherapy, systemic immunomodulator therapies or a referral from their primary care provider for atopic eczema.

In a median follow-up of 5.1 years, they found adults with eczema were 10-20% more likely to experience non-fatal myocardial infarction, unstable angina, heart failure, atrial fibrillation or stroke than adults free of eczema.

The moderately increased risk of non-fatal cardiovascular outcomes had a dose-response relationship with atopic eczema severity and cumulative activity. Whereas previous studies have identified positive associations between severe atopic eczema and cardiovascular outcomes, mild eczema appears to have a slightly protective or neutral impact on cardiovascular outcomes, the authors wrote.

“This may suggest a dose-response effect, an alternative pathogenesis underlying mild compared with severe conditions, the effect of systemic therapies used to treat severe forms of atopic eczema or misclassification bias owing to the way in which patients with atopic eczema were classified,” they write.

This is one of the few longitudinal studies to have adjusted for traditional cardiovascular risk factors, including body mass index, smoking and alcohol consumption. One of the limitations is that it’s an observational study.

An important next step would be to develop prevention strategies aimed at building awareness and reducing cardiovascular disease risk among those with severe and very active atopic eczema, according to the authors.

In an accompanying editorial, John R. Ingram, D.M., of Cardiff University in the United Kingdom writes that eczema has joined the growing list of inflammatory conditions, including severe psoriasis, linked to cardiovascular risk.

“For patients with severe or more active eczema, the evidence from the study by Silverwood and colleagues makes the case for targeted screening of standard [cardiovascular] disease risk factors. We may need to rethink thresholds for primary prevention interventions in this patient group by factoring in severe eczema as an independent [cardiovascular] disease risk factor,” Dr. Ingram writes.

**References**


Ingram John R. “Atopic eczema and cardiovascular disease.” *BMJ*, May 23, 2018. DOI:https://doi.org/10.1136/bmj.k2504

The drug life cycle

How the FDA ensures safety, efficacy of dermatology drugs

WHITNEY J. PALMER | Staff Correspondent

In many ways, success in dermatology is measured by the efficacy of the medications used to treat skin conditions. Consequently, dermatologists should feel confident in the drugs and topical treatments they prescribe their patients.

To help providers have a greater understanding of the efforts of the Food & Drug Administration (FDA) to ensure all drugs are of pharmaceutical quality, Michael Kopcha, Ph.D., R.Ph., director of the FDA’s Office of Pharmaceutical Quality, offers insight into the drug life cycle and drug quality.

The concept of drug quality is vital to dermatologic treatment, he says, because of the impact it has on patients. “Quality is what ensures every dose of drug is of the appropriate strength — not too weak and not too strong — and free of contamination and defects,” Kopcha says.

The Office of Pharmaceutical Quality ensures that all marketed drugs consistently meet quality standards throughout their life cycle in all facilities internationally, he says.

THE DRUG LIFE CYCLE

The drug assessment process ensures manufacturers are capable of meeting established quality standards. To do so, the FDA evaluates data on the drug product, as well as drug manufacturing processes and facilities. In addition, the agency also inspects manufacturing facilities, monitors the state of quality of drugs on the market and encourages the use of modern manufacturing technologies. It also conducts science-based research that can support quality standards and policy development.

DRUG REGULATION

According to an FDA spokesperson, information on how the agency regulates approved drugs, as well as drugs under development, could have particular applicability to dermatologic indications where skin pathology might be assessed photographically over time to document response to investigational drugs.

The FDA Center for Drug Evaluation and Research (CDER) is responsible for evaluating new drugs before they are approved for sale. Before any human clinical trials, a CDER team of physicians, statisticians, chemists and pharmacologists determines whether the drug’s health benefits outweigh the risks by using the drug company’s safety and efficacy data.

Potential new drugs must also go through a three-prong approval process. First, the agency analyzes the target condition and currently available treatments as a reference point for the new drug’s risks and benefits. Second, the team assesses the drug’s actual risks and benefits based on data collected from at least two clinical trials. Third, the team also designs risk management strategies, including a drug warning label, to alert providers and patients to the possible negative outcomes associated with the drug.

THE IMPACT IT HAS

Ultimately, Kopcha says, ensuring drug quality means the medication can consistently meet the expectations of patients and dermatologists. Patients anticipate that any dermatologist-prescribed medication will safely perform as expected with the same efficacy and at the same dose every time.

Regulations that provide for consistent drug quality and performance can also affect how dermatologists view medications, he says. With these protocols and standards in place, providers can have greater trust in legally-marketed drugs.

“Hopefully, dermatologists will come away with a renewed appreciation for the medicine they prescribe or recommend to their patients,” Kopcha says. “They, too, can have more confidence in their patient’s next dose of medicine.”

WHEN QUALITY ISSUES ARISE

While the drug assessment process is designed to create dependable quality levels, problems can still occur, Kopcha says.

“When manufacturers submit an application to the FDA, we conduct a rigorous quality assessment to ensure the company can consistently produce a safe and effective product,” he says.

“However, even when manufacturers are very vigilant, sometimes quality issues arise after drug approval.”

If one such case presents, he says, dermatologists can report any suspected quality issues through the FDA’s MedWatch system via an online reporting form. The system also allows dermatologists to report any concerns their patients have about the quality of their medicine.

TAKE-AWAY MESSAGES

Overall, Kopcha emphasizes the importance of a pharmaceutical quality assessment system and asks dermatologists for help.

Pharmaceutical quality is the bedrock of providing patients with safe, effective drugs, and while the FDA is responsible for regulating the quality of medications in facilities worldwide, dermatologists can play an integral role in how well the systems works, he says.

“We need dermatologist to commit to the importance of pharmaceutical quality,” Kopcha says. “We need them to discuss potential drug quality issues with patients and report them.”
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Use in Specific Populations

- Pregnancy and Nursing Mothers: Otezla is Pregnancy Category C; it has not been studied in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether apremilast or its metabolites are present in human milk. Caution should be exercised when Otezla is administered to a nursing woman.

- Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information.

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severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued OTEZLA generally improved quickly. Consider OTEZLA dose reductions in patients with severe diarrhea, nausea, or vomiting.

Depression: Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur. During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (12/920) of patients treated with OTEZLA discontinued treatment due to depression compared with none in placebo-treated patients (0/506). Depression was reported as serious in 0.1% (1/1308) of patients exposed to OTEZLA, compared to none in placebo-treated patients (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) of patients while receiving OTEZLA, compared to 0.2% (1/506) in placebo-treated patients. In the clinical trials, one patient treated with OTEZLA attempted suicide while one who received placebo committed suicide.

Weight Decrease: During the controlled period of the trials in psoriasis, weight decrease between 5%–10% of body weight occurred in 12% (96/784) of patients treated with OTEZLA compared to 5% (19/382) treated with placebo. Weight decrease of 21% of body weight occurred in 2% (16/784) of patients treated with OTEZLA 30 mg twice daily compared to 1% (3/382) patients treated with placebo. Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered.

Drug Interactions: Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

ADVERSE REACTIONS

Clinical Trials Experience in Psoriasis: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial 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. Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.6%), diarrhea (1.0%), and headache (0.8%). The proportion of patients with psoriasis who discontinued treatment due to any adverse reaction was 6.1% for patients treated with OTEZLA 30 mg twice daily and 4.1% for placebo-treated patients.

| Table 3: Adverse Reactions Reported in 21% of Patients on OTEZLA and With Greater Frequency Than In Patients on Placebo; up to Day 112 (Week 16) |
|-----------------|-----------------|-----------------|
| Preferred Term  | Placebo (N=506) | OTEZLA 30 mg BID |
|                 | n (%)           | (N=920) n (%)    |
| Diarrhea        | 32 (6)          | 160 (17)        |
| Nausea          | 35 (7)          | 155 (17)        |
| Upper respiratory tract infection | 31 (6) | 84 (9) |
| Tension headache | 21 (4)          | 75 (8)          |
| Headache        | 19 (4)          | 55 (6)          |
| Abdominal pain  | 11 (2)          | 38 (4)          |
| Vomiting        | 8 (2)           | 35 (4)          |
| Fatigue         | 9 (2)           | 29 (3)          |
| Decrease appetite | 5 (1)          | 26 (3)          |
| Insomnia        | 4 (1)           | 21 (2)          |
| Back pain       | 4 (1)           | 20 (2)          |
| Migraine        | 5 (1)           | 19 (2)          |
| Frequent bowel movements | 1 (0) | 17 (2) |
| Depression      | 2 (0)           | 12 (1)          |
| Bronchitis      | 2 (0)           | 12 (1)          |
| Tooth abscess   | 0 (0)           | 10 (1)          |
| Folliculitis    | 0 (0)           | 9 (1)           |
| Sinus headache  | 0 (0)           | 9 (1)           |

*Two subjects treated with OTEZLA experienced serious adverse reaction of abdominal pain.

Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) patients following discontinuation of treatment with OTEZLA (apremilast).

DRUG INTERACTIONS

Strong CYP 450 Inducers: Apremilast exposure is decreased when OTEZLA is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** Pregnancy Category C: OTEZLA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972. Nursing Mothers: It is not known whether OTEZLA or its metabolites are present in human milk. Because many drugs are present in human milk, caution should be exercised when OTEZLA is administered to a nursing woman. Pediatric use: The safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age has not been established. Geriatric use: Of the 1257 patients who enrolled in two placebo-controlled psoriasis trials (PSOR 1 and PSOR 2), a total of 108 psoriasis patients were 65 years of age and older, including 9 patients who were 75 years of age and older. No overall differences were observed in the efficacy and safety in elderly patients ≥65 years of age and younger adult patients <65 years of age in the clinical trials. Renal impairment: Apremilast pharmacokinetics were characterized in subjects with mild, moderate, and severe renal impairment as defined by a creatinine clearance of 60-89, 30-59, and less than 30 mL per minute, respectively, by the Cockcroft–Gault equation. While no dose adjustment is needed in patients with mild or moderate renal impairment, the dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

**Hepatic Impairment:** Apremilast pharmacokinetics were characterized in patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

**OVERDOSAGE**

In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

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Device regulation impact on patient care FROM PAGE 1

ing dermal fillers and micro-needling devices. There has also been recent growth in point-of-care diagnostics, ablative technologies, skin-imaging devices, lasers and wound dressings.

Marquart also points to the current re-organization underway at the CDRH, which includes efforts to help increase information sharing and inform collective decision-making. Once complete, she says, the re-organization will greatly benefit the quality of services patients receive.

ABOUT CDRH

One of the most significant things dermatologists should understand about the CDRH, Marquart says, is how it oversees and approves Class III devices – the products that present the highest level of risk to patients. These devices also require pre-market approval (PMA) and must follow a specific application process.

According to Marquart, there are six ways new or modified Class III devices can apply for PMA.

1. NEW DEVICE: These products must submit an original PMA with manufacturer-provided clinical and pre-clinical data. This application also applies to significant changes to existing product design or patient populations for which new data would be necessary.

2. PANEL-TRACK PMA SUPPLEMENT: This application applies to significant device design or performance changes, as well as new indications for use. New clinical data is necessary.

3. PMA (180D) SUPPLEMENT: Devices that have significant changes in components, materials, design, specifications, software, color additives or labeling should pursue this application.

4. PMA REAL-TIME SUPPLEMENT: This application is for products the FDA has previously determined appropriate for the real-time supplement. It covers minor changes to device design, software, sterilization or labeling.

5. SPECIAL PMA SUPPLEMENT: This application covers device changes to labeling, quality control and manufacturing processes that enhance device safety or use.

6. PMA 30-DAY NOTICE: This application applies to changes in the manufacturing process or manufacturing method.

WHAT DERMATOLOGISTS CAN DO

A dermatologist’s role with medical devices can go beyond the clinic. Marquart offers several ways to impact medical device quality and safety.

First, dermatologists can apply to serve on an FDA Advisory Committee or opt to participate in a Network of Experts through a professional society.

Second, when a serious problem arises with a device, dermatologists should report it directly to the agency to ensure the FDA can act promptly.

Third, dermatologists can collaborate with the FDA to develop patient or device registries, and the National Evaluation System for Health Technology (NEST). NEST uses data from clinical registries, electronic health records and billing claims to generate evidence for device evaluation. Interested dermatologists should contact cdrhclinicalevidence@fda.hhs.gov, she says.

Overall, Marquart hopes dermatologists will gain a deeper understanding of what the CDRH does and how it impacts dermatological care.

Quick TAKES

The FDA’s CDRH focuses on evaluating medical device innovations for safety and efficacy.

CDRH oversees and approves Class III devices. Such devices require pre-market approval.

Dermatologists can collaborate with the FDA to positively impact medical device quality and safety.

Muscle tissue inspires drug to target posriasis, cancer FROM PAGE 20

side events, reactions, or events compared to the other psoriasis medications. Patients taking other therapies often experience nausea, vomiting, and fatigue, among other responses, Fishman said.

“This is a huge benefit for patients with the chronic condition psoriasis, for which they might take medication their entire lifetime,” she said.

“Taking a drug that has a large adverse effect profile isn’t a good thing for this patient population.”

Alongside piclidenoson, Can-Fite has two other drugs under development. Namodenoson, currently in phase 2 studies, is designed to target liver cancer and its preceding conditions — non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. A third, unnamed drug is also intended to combat inflammation in several arthritis conditions.

WHAT’S NEXT?

In addition to the three existing drugs, Fishman said, there are several indications the company would like to pursue in the future, including prostate cancer, breast cancer, and melanoma. At this point, however, she said, she and her colleagues are concentrating on bringing these three drugs through the pipeline with the help of the Food & Drug Administration and the European Medical Agency within the next five years.

Although there are no plans to market directly to patients, Can-Fite intends to secure licensing agreements. Several are already in place, she said, but the goal is to expand globally. They also plan for the price point to hit somewhere between existing biologics and methotrexate.

“We want to position ourselves as the small molecule, orally-available, affordable drug with the excellent safety profile,” she said.

Ultimately, Fishman said, rather than treating patients with biologics or methotrexate and waiting to see if they fail these therapies while experiencing adverse reactions, she would like to see piclidenoson be the go-to drug for patient suffering from psoriasis.

“We would like to be the first-line treatment so the patient will be able to get the drug for a lifetime without suffering adverse events and won’t need to go to the outpatient clinic,” she said. “They just need two tablets — one in the morning and one in the evening — and their skin will be clear without negative effects.”

†
Jeuneau takes aim at aesthetic market share

LISETTE HILTON | Staff Correspondent

Quick Takes

The FDA approved Jeuneau on February 1, 2019, and Evolus plans to launch this spring.

Jeuveau is the first 900 kDa molecule neurotoxin since Botox.

Aesthetic-only Jeuveau has no government reimbursement restrictions, giving it pricing flexibility.

Former Allergan executives who today oversee operations at Evolus say Jeuveau (prabotulinumtoxinA), a 900 kDa purified botulinum toxin type A complex, is poised to challenge Botox’s aesthetic dominance.

The FDA approved Jeuveau Feb. 1, 2019, and Evolus plans to launch Jeuveau in spring 2019.

Evolus Chief Executive Officer David Moatazedi spent 13 years at Allergan before joining Evolus in May 2018. Among his roles, Moatazedi ran Allergan’s facial injectable business, including Botox, Juvederm and Kybella.

He says there were a few things about Evolus that convinced him to make the career move. One is Evolus is an aesthetic company launching with a product that takes aim at the aesthetic market’s largest category: neurotoxins. Allergan has led the market for many years and today commands about 70% of the market share. Dysport (abobotulinumtoxinA, Ipsen) has about 20% market share, followed by Xeomin (incobotulinumtoxinA, Merz) with about 10%, according to Moatazedi.

“This market in the U.S. is probably a $1.2 billion category for neurotoxins. And it’s the number one aesthetic procedure done in the U.S.,” Moatazedi says.

Jeuveau has a strategic advantage, Moatazedi claims, because it’s aesthetic only. Since Evolus doesn’t have a reimbursed form of its neurotoxin, it has more pricing flexibility. Evolus analysts predict Jeuveau might be 20% to 30% less expensive than Botox, according to a January 2019 article by GlobalData Healthcare.

It affords Evolus a promotional edge, as well, according to Moatazedi. “Since we don’t have a therapeutic reimbursed form of our product, we’re not held to some of the standards, including Sunshine Act or other activities as they relate to how we promote our product.”

Jeuveau is the first 900 kDa molecule neurotoxin since Botox was introduced, according to Moatazedi.

“Scientifically all the other neurotoxins are formulated differently than Botox. Xeomin for example is 150 kDa molecule and Dysport is a range of molecular sizes. The 900 kDa has proven over the course of 20 years to represent the gold standard in this category,” Moatazedi.

Jeuveau, manufactured with Evolus’s proprietary Hi-Pure technology, has longevity, and more might be more evident when five-month results from a head-to-head study comparing Botox to Jeuveau are published. Moatazedi says he anticipates that study will come out in a peer reviewed journal around the time of the launch.

Evolus Chief Marketing Officer Michael Jafar, who was with Allergan for about 15 years, says the company has data on more than 2,100 patients and will share that data, which includes a multicenter phase III study of 540 patients comparing prabotulinumtoxinA (Jeuvea) to OnabotulinumtoxinA (Botox) for treatment of glabellar lines. Researchers, who presented the findings at the Cosmetic Bootcamp 2018 in June, found a single treatment of 20 U of prabotulinumtoxinA was non-inferior to 20 U of onabotulinumtoxinA and superior to placebo. Researchers followed subjects for up to 150 days.

Jafar says, before Jeuveau, there were no products that competed both in clinical studies and in its formulation makeup with Botox.

“The market always looks for a challenger brand to neutralize the monopoly that exists, and I knew this product would have a shot at that,” Jafar says.

Jeuveau isn’t the only potential newcomer to the neurotoxin market. Up-and-comer Revance is anticipating entering the market with its long-acting neuromodulator daxibotulinumtoxinA for Injection RT002 in 2020.
Online cosmeceutical sales

LISETTE HILTON | Staff Corrrespondent

Online shopping is integral to customers’ overall positive experience, according to dermatologist Missy Clifton, M.D., of Premier Dermatology in Bentonville, Ark., who shared her best practices for launching an online marketplace in October at the American Society for Dermatologic Surgery (ASDS) Annual Meeting in Phoenix, Ariz.

“For many of our patients seeking a skincare regimen, we’ll begin with an in-office complimentary skin analysis. This allows us to customize an effective regimen that addresses their unique concerns,” Dr. Clifton says. “Once a regimen is established, our patients enjoy the convenience of being able shop online to reorder products or even enroll in auto-ship. By custom designing a store, you get to determine how each click behaves for both the customer and staff... The fewer the clicks, the better. The better the integration with the practice as a whole, the better the integration with the rewards programs, the more successful you’ll be with the online store,” she says.

MANAGE YOUR OWN PLATFORM
First, find a reputable web developer to set up the platform. The goal is to create an integrated online store that office staff can easily update and manage, according to Dr. Clifton.

Online platforms that a third party manages, may require waiting days or weeks before being able to make updates for specials or promotions. “That’s the key: to be able to make changes in real time, without having to get in touch with an account executive at a subscription-based store.” It may cost more upfront, but “You get to quickly and easily make changes yourself,” she says.

CREATE SEAMLESSNESS
In a perfect world, a practice’s online store integrates with the practice management software. However due to personal health information, most practice management systems do not openly integrate with outside platforms. “When someone makes an online purchase, the order information is logged in our practice management software,” she says. As a result, Dr. Clifton’s staff manually log order information about store purchases to their PM system, thus enabling the office to accurately track each patient’s experience and progress and make suitable product recommendations.

When Dr. Clifton’s staff receives an order, they process it immediately. Not only that, but they also put the order in a beautifully branded box with matching tissue paper, according to Dr. Clifton.

Orders go out the same day the order is received. Orders that come through on the weekends go out on Monday, she says.

In addition to product use sheets, “We also give them a couple of samples of products that might complement the products that they’re using. We look in their history to see what they’ve used and then give them samples of things that would be complementary that they haven’t used. We also tell them how to use the samples. Very often, people will try those samples and love them, and then they’ll come back to purchase those products the next time.”

MAKE LIFE EASY FOR EVERYONE
Make sure that the online store’s setup makes it easy to go from shopping to payment, without too many click throughs.

“By custom designing a store, you get to determine how each click behaves for both the customer and staff... The fewer the clicks, the better. The better the integration with the practice as a whole, the better the integration with the rewards programs, the more successful you’ll be with the online store,” she says.

QuickTAKES

Selling cosmeceuticals online is a natural extention of in-office sales.

A reputable web developer can create an online platform that can be managed in-house for daily updates.

Collecting sales data can improve and enhance patient results.

“Having a web developer design the store that’s right for your practice costs more up front but allows more freedom in day-to-day functionality.”

Missy Clifton, M.D., Premier Dermatology in Bentonville, Ark.
Botulinum toxin injections may improve scarring

NADIA M. WHITEHEAD | Staff Correspondent

Long lauded for its ability to reduce the appearance of wrinkles, botulinum toxin is now being considered for reducing scarring. By using botulinum toxin to denervate underlying muscle and immobilize tension—which increases inflammation, fibrosis, erythema and scar size—scarring can potentially be reduced, say researchers in a review published in the Journal of Drugs in Dermatology.

The review, published in the September issue of the journal, highlights several success stories of the toxin’s use in improving scarring. Dr. Domenico Vitarella, Ph.D., author of the review and a researcher with Bonti, Inc., says that although the FDA has not approved botulinum toxin for this specific use, “the treatment seems to be gaining momentum among physicians.”

In 2006, researchers reported the first blinded, placebo-controlled, randomized study for scar reduction on 31 patients with forehead wounds. The patients either had traumatic forehead lacerations or were undergoing plastic surgery for the removal of a mass on the forehead.

Patients received a botulinum toxin or placebo injection in the musculature adjacent to lesions within 24 hours of surgery. Those who received botulinum toxin received a median Visual Analog Scar Score (VASS) of 8.9 while placebo recipients received a median score of 7.2.

A separate study reported in 2013 describes 24 patients with facial wounds who were randomized to receive no injection or the injection of botulinum toxin within 72 hours of surgery. At one-year follow-up, the group treated with botulinum toxin received a median Vancouver Scar Scale (VSS) score of 8.25, while the control group received median scores of 6.35.

In his review, Dr. Vitarella writes that despite these successes, much remains to be explored. For one, larger clinical trials are still needed to gain FDA approval. “Physicians are experimenting and using this product off-label for scar reduction [right now],” Dr. Vitarella says. “Bonti believes this is a great area of study and this can work and help [reduce scarring], but we are not able to advocate for physicians doing this until there’s official FDA approval.”

Optimal dosing is also to be determined to avoid causing functional problems, particularly when botulinum toxin is injected to the lower face. For example, in one case, a woman whose lip was crushed in a motor vehicle accident experienced reduced oral sphincter function resulting in spillage of liquids and mild dysarthria for four weeks after she received surgical repair and botulinum toxin to the perioral musculature. The patient was limited to a soft diet for 10 days after the procedure. She eventually returned to normal eating habits and at six months, a scar was hardly perceptible.

Dr. Vitarella believes such functional problems caused by the botulinum toxin may be avoided if the toxin can be reconfigured to have a shorter duration. His company is currently developing and testing the product EB-001 for optimized scar reduction.

References
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Cosmetic procedures more than vanity

WHITNEY J. PALMER | Staff Correspondent

Eventhough cosmetic procedures can be used to enhance a patient’s appearance, vanity isn’t the only motivator behind decisions to undergo treatments. According to recent research, the reasons patients might choose a cosmetic treatment are more complicated.

According to a 2017 American Society for Dermatologic Surgery survey, the patient population considering cosmetic procedures has more than doubled from 30% in 2013 to 70% in 2017. The most commonly requested dermatologist-performed treatments are light and laser therapy, facial rejuvenation injections, chemical peels and body sculpting.

But, rather than being fueled by a singular desire to be more physically attractive, the results of a new JAMA Dermatology study revealed patients report emotional, physical, social and professional reasons for seeking cosmetic procedures to enhance their appearance. Ultimately, study authors conclude, having a better understanding of these personal motivations can help dermatologists better counsel patients on which procedures might be most effective and what they can expect for realistic results.

In the first prospective, national, multi-center observational study, including two academic and 11 private dermatology practices, investigators surveyed 511 patients about their reasons for pursuing cosmetic procedures. This patient-centered approach assessed motives in six quality-of-life domains — cosmetic, emotional, physical, social, school and/or work success and cost and/or convenience.

THE STUDY

Approximately 23% attributed the decision to a physician’s recommendation and an additional 25% pointed to a family member’s or friend’s previous experience. Only 2.3% listed their spouse or partner.

“This finding highlights the importance of social norms and is in agreement with prior data,” the researchers write. “It indicates knowing someone who has undergone cosmetic treatment is suggestive of patients’ interest.”

Of the participants, 440 (86.1%) were female, 286 (56%) were age 45 and older, 386 (75.5%) were white and 469 (91.8%) had some level of college education. Additionally, 270 (52.8%) had at least two previous cosmetic procedures, 88 (17.2%) had one and 149 (29.2%) had none.

Botulinum toxin injections were the most popular, accounting for 165 procedures (32.3%). Soft-tissue fillers and lasers for brown spots and/or melasma ranked second and third with 94 procedures (18.4%) and 85 procedures (16.6%), respectively.

As anticipated, most patients (391; 78.4%) reported a desire to look younger and fresher, particularly in photographs. Many (382; 81.4%) wanted clearer skin. In fact, more than half (269; 56.6%) opted for a procedure to ensure they look good when encountering friends. This group gravitated toward skin tightening, wrinkle treatments, neurotoxins and injectables.

Others (261 patients; 54.8%) felt cosmetic procedures would improve their professional appearance and help them remain competitive. These patients, most interested in maintaining their current appearance or reducing brown spots or redness, leaned toward laser treatments.

But the additional, underlying reasons patients revealed for selecting cosmetic procedures were more complex.

Overall, researchers say, patients reported wanting to positively improve many aspects of their lives. Many patients (328; 69.5%) revealed the belief cosmetic procedures would improve their self-confidence or make them feel happier (314; 67.2%). Of this group, most pursued acne scar treatment, microdermabrasion, body contouring and laser hair removal.

Additionally, “health augmentation” was a substantial reason supporting cosmetic procedures. More than half of survey respondents (253; 52.3%) selected treatments to stave off any worsening of their existing conditions and symptoms. Other patients (180; 38.6%) believed a cosmetic treatment would provide future health protection.

According to results, the quest for tattoo removal could include a mental and emotional health component. Most cited a desire to improve their overall quality of life and return to their former appearance, as well as increase self-confidence and alleviate any tattoo-related stress.

Ultimately, investigators report, study results revealed patients’ reasons for pursuing cosmetic procedures are multi-factorial.

“This study shows patient seek aesthetic or cosmetic procedures for various reasons,” they write. “Often, the motivation is not simply to look attractive, but to address serious psychological and emotional issues.”

Reference

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Photos provided by Dr. Michael H. Gold, M.D., FAAD
Successful laser results require picking the right indication for the right patient.

Post procedural regimens remain a challenge.

with more aggressive lasers, she says, although treating the reticular dermis too aggressively can generate scars.

DEEP TREATMENTS

Deep ablative treatments generally address moderate-to-severe photodamage and scars, according to Dr. Van Dyke. In the past, fully ablative CO₂ lasers used with multiple passes at 50% overlap penetrated to the reticular dermis.

“Patients almost always lost their pigmentation, but the results were spectacular,” she says. Despite short procedure times with a single treatment, immediate tightening and long-term collagen stimulation, “...you had to do this procedure under general anesthesia.” Along with pigment loss, patients experienced weeks of skin oozing, weeping and crusting. Thus the procedure fell out of favor in the late 1990s.

“Therefore, we went from fully ablative treatments, destroying everything in sight, to fractional treatments,” which leave bridges of normal tissue between ablated columns to speed healing. “That’s why we’re getting healing in seven to eight days, even when I treat aggressively. And I’ve not seen anybody lose pigment with fractional CO₂ laser treatment.”

A single treatment provides improvements in tone and texture. “It’s rare for a patient to say, ‘I’m not happy with my results.’ You also get immediate tightening with the fractional CO₂ — you can see it while you’re doing it.” However, these results are less dramatic than with fully ablative CO₂. So she combines fractional CO₂ with other modalities such as Thermage (Solta Medical) or Ultherapy (Merz Aesthetics).

Incidence of adverse events (AEs) after deep ablative fractional resurfacing remains fairly significant, says Dr. Van Dyke. In a study of 490 treatments performed in 374 patients published in 2011, overall AE rate was 13.6%.

The most common AEs were infection (5.7%) and acneiform reactions to topical products (5.3%). “Even though all these companies make these fancy post-procedural care products,” she says, “I have yet to find one that I can use on a patient after CO₂ laser. Always go back to Aquaphor (Johnson & Johnson).”

Additionally, yeast infections and bacterial infections impact around five percent of the patients Dr. Van Dyke treats with CO₂ laser. She typically puts these patients on empirically guided antibiotics and prescribes vinegar soaks to soothe the skin and combat yeast infection.

“And I see these patients very frequently — on day one, day four and day seven. If they’re going to get an infection, it happens on day four or five. With minocycline and fluconazole, I’ve not had any scarring or antibiotic resistance in over 1,000 patients.”

MEDIUM-DEPTH RESURFACING

Nonablative fractional lasers can handle mild-to-moderate photodamage and scars, according to Dr. Van Dyke. With these lasers, optimal results usually require three to six sessions. Because the stratum corneum remains intact, she says, these treatments require no wound care or clinical downtime — just two to four days of social downtime. Although nonablative fractional treatments can approach the results of fully ablative resurfacing, Dr. Van Dyke adds, nonablative fractional treatments do not tighten skin.

The Fraxel Restore laser (Solta Medical) provides significant leeway in terms of aggressiveness, she says, depending on skin type. For acne scars, such as boxcar and ice-pick scars in African-American patients, Dr. Van Dyke says, repetitive nonablative fractional treatments provide better results than CO₂ laser.

SUPERFICIAL RESURFACING

Dr. Van Dyke’s low-power nonablative fractional laser of choice, the Clear + Brilliant (Solta Medical), offers 1,440 nm and 1,927 nm wavelengths and delivers about 1/10 the power of her workhorse Fraxel Restore. Treatment offers minimal discomfort with excellent outcomes, usually with six or more treatments. Additionally, she commonly performs low-energy nonablative fractional treatments every couple months after medium or deep laser resurfacing as maintenance therapy.

Low-energy nonablative fractional lasers require no downtime. “It’s like polishing an apple — to refresh, treat fine lines and remove pigment. This is my go-to treatment for melasma, combined with hydroquinone four percent at the time of treatment.” Rather than using hydroquinone between appointments, her patients typically use a non-hydroquinone brightener such as Lytera (SkinMedica/Allergan) or Even Tone Correcting Serum (SkinBetter Science).

Dr. Van Dyke has seen no adverse events with this laser. She uses the 1,440 nm wavelength for fine lines, texture and tone.

“The 1,927 wavelength has been shown to open micropores in tissue... a great drug-delivery system.” Applying topical medications such as hydroquinone or vitamin C immediately post-treatment allows them to penetrate the epidermis, she says.

As for the future, Dr. Van Dyke says that the lasers already available allow doctors to tailor treatments to individual patients. “The real future is in the drug-delivery area, with hydroquinone, antioxidants, platelet-rich plasma and post-procedural skincare regimens.”

Post-procedural regimens remain a bigger challenge, says Dr. Van Dyke, who tests some regimens for drug developers. Yet she remains optimistic that manufacturers will conquer this hurdle.

Disclosures: Dr. Van Dyke has been a speaker, investigator or advisor for Allergan, Goldnera, Merz and Valeant.

Reference

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DERMOSCOPY

Dermoscopy: The dermatologist’s stethoscope

ILYA PETROU, M.D. | Staff Correspondent

With the incidence of skin cancers still on a steady rise, the timely detection and appropriate treatment and management of melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) has never been more urgent.

Beyond the dermatoscope, the continued research and development of other noninvasive optical imaging techniques has led to a number of variably effective diagnostic approaches.

“Dermoscopy is a type of skin cancer screening technology that enables the physician to view the detailed structures of the lesion in question much more closely,” says Alexander Witkowski, M.D., Ph.D., of the department of dermatology at the University of Modena & Reggio Emilia.

“In addition to up to 10-20x magnification, the dermatoscope allows us to see both the surface and subsurface structures of lesions and is used as a basic filter to check the basic dermatoscopy criteria (i.e., asymmetry, round structures, and/or presence of blue-grey structures) of pigmented lesions,” he adds. He also works in the Veterans Hospital department of dermatology, Wroclaw, Poland, and Sportmedicus Skin Cancer Clinic, Krakow, Poland.

Although major technological advances in optical imaging techniques over the last two decades have resulted in significant improvement in the recognition of suspicious pigmented lesions, experts say that the dermatoscope remains an irreplaceable tool in the armamentarium of dermatologists to more closely view and accurately assess the pigmented lesion under scrutiny.

“For the foreseeable future, I do not anticipate anything to be able to replace dermoscopy as the dermatologist’s stethoscope,” says Eric Tkaczyk, M.D., Ph.D., F.A.A.D., director of the Vanderbilt Translational Skin Imaging Clinic.

“The dermatoscope offers an immediate image that provides much more information than you can get with your standard physical exam, enabling physicians to dramatically increase both their sensitivity and specificity when evaluating suspicious pigmented lesions,” he adds. Dr. Tkaczyk also is assistant professor of dermatology at Vanderbilt University Medical Center, assistant professor of Biomedical Engineering at Vanderbilt University, and attending Dermatologist at the Nashville VA Medical Center, Nashville, Tenn.

As more advanced imaging and other noninvasive diagnostic techniques continue to emerge, Dr. Tkaczyk believes that there will be an increase in the utilization of these other innovative techniques including some that interface with dermoscopy, such as non-dermatologist assessment of dermoscopic lesions (i.e. artificial intelligence and Tele-Health).

To date, the strongest data gathered from clinical studies is on RCM. Compared to other emerging techniques, this data has significantly helped the technology overcome once challenging issues including reimbursement from Medicare, Medicaid, and other insurances, as well as expedite the process of the technology’s widespread implementation and integration into practice.

In the right hands, the specificity and sensitivity of RCM are both very high at approximately 70% and 95-97%, respectively, in dermoscopically equivocal lesions. Compared to RCM, all of the other technologies currently available do not approach such high specificity and sensitivity.

“RCM gives you a full view of the suspect lesion, up to 50mm x 50mm, with submicron resolution so you can see individual details of individual cells,” Dr. Tkaczyk says.

Apart from past reimbursement issues, another pivotal barrier that has kept RCM away from the average dermatologist in the United States and has hindered the technology from moving forward and being readily available was that there weren’t any appropriate training programs in place that would teach dermatologists how to use the technology properly. According to Dr. Witkowski, using the device is relatively easy but correctly interpreting the images can take some time to learn and master.

“Striping” is a recent major development in RCM technology that allows for a much quicker generation of images, up to 50% faster than the previous software used. This would save valuable time for both physician and patient, Dr. Witkowski says.

OCT is another technology that has also proven to be useful in diagnosing some lesions. Having a depth view of approximately 1 mm to 2 mm (many times deeper than RCM) and generating images at lower resolution, OCT technology is helpful in identifying BCC but less appropriate for detecting melanoma amongst melanocytic nevi. The imaging process works very quickly, accurately diagnosing BCC within 30 seconds. Viewing the depth of a lesion can help the clinician quickly determine whether the lesion is a superficial BCC or a deeper lesion such as...
an early stage nodular BCC.

“Technologies such as RCM and OCT can be ideally used in those cases that are not crystal clear upon first assessment with a dermatoscope and can help to differentiate morphologically between the telltale characteristics of borderline lesions with a very high sensitivity and specificity,” Dr. Witkowski says.

Other techniques such as multi-spectral imaging or Raman spectroscopy provide different information. They give information about the biochemistry of the viewed lesion. According to Dr. Tkaczyk, spectroscopy techniques yield valuable information on the chemical changes that occur well in advance of any structural changes that one would see with histopathology sections. However, the data on existing devices shows the specificity to be around 10-40%, depending on the publication. Well-designed large multicenter clinical studies on these spectroscopies are few and far between, underscoring the tendency for popularity of RCM.

“One current focus of industry is to combine the strengths of technologies to overcome each of their individual weaknesses, as well as making these devices cheaper and more portable. Very soon, we will see the advent of combination devices integrating OCT and RCM, or dermoscopy and RCM in one single device. I believe the symbiosis of multi-modal imaging is really where the future lies in optimal skin cancer screening technology,” Dr. Tkaczyk says.

Disclosures. Neither Dr. Tkaczyk or Dr. Witkowski report any relevant disclosures.
Targeted therapy for skin malignancies

INGRID TORJESEN | Staff Correspondent

The past decade has seen significant advances in the understanding of molecular pathogenesis of skin cancer leading to the development of targeted treatments and immunotherapies that have dramatically improved progression free survival and even overall survival in melanoma, basal cell carcinoma (BCC) and even some rarer cutaneous carcinomas.

Until 2011, the standard of care for metastatic melanoma was chemotherapy with dacarbazine (DTIC) as monotherapy or part of a combination regimen which was associated with response rates of only 5–28% and no significant increase in survival duration. At that time median survival of patients with non-resectable metastatic melanoma was 6–10 months, with only 4–6% of patients surviving to five years.

Since 2011 targeted therapy with BRAF (BRaf proto-oncogene serine/threonine kinase) inhibitors and MEK (mitogen-activated protein kinase) inhibitors, and immunotherapy with checkpoint inhibitors against CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) inhibitors and PD-1 (programmed cell death protein 1) and its ligand L1 (PD-L1) has become available. All are associated with increased response rates and extended progression-free survival and overall survival compared with dacarbazine.

Melanomas can be classified into four large genomic subtypes: mutant BRAF, mutant NRAS, mutant NF1 and triple wild-type (i.e., without mutations in these 3 genes), and types of mutation vary according to sun damage and tumor type, says Eggert Stockfleth, M.D., Klinik für Dermatologie, Venerologie und Allergologie, St. Josef-Hospital, Ruhr-Universität Bochum, Bochum, Germany. For example, melanomas from chronically sun-exposed skin have most often NF1, NRAS mutations and occasionally BRAF mutations, whereas melanomas from intermittently sun-exposed skin tend to have BRAF mutations (50%) or NRAS mutations (15–20%). Significantly mutated genes in cutaneous melanoma include BRAF, NRAS, CDKN2A and TP53 and although the specific mutation will not influence outcome, it will determine which is the most appropriate therapy.

Oncogenic mutations in BRAF and NRAS induce overstimulation of the RAS/RAF/MEK/ERK signalling pathway (also known as the MAPK [mitogen-activated protein kinase] pathway), which is central to the pathogenesis of cutaneous melanoma. Most BRAF mutations (89%) involve the kinase activation loop at the p.V600 position (BRAF V600), and the most common BRAF V600 mutation (80%) is a valine to glutamic acid mutation at codon 600 (V600E), which is associated with a 500-fold increase in the kinase activity of BRAF. This leads to cascade activation of MEK and ERK.

Mutations of BRAF V600 are an important target in recently developed molecular targeted therapy for melanoma and three BRAF inhibitors are available for treatment of BRAF V600-mutated advanced melanoma: vemurafenib, dabrafenib and encorafenib. The current first-line treatment is a combination of a BRAF inhibitor and MEK inhibitor.

“BRAF/MEK combined therapy which produces response rates around 20% higher than BRAF inhibitor monotherapy, median progression free survival exceeds one year and overall survival reaches approximately two years,” Dr. Stockfleth says.

A combination of targeted therapy and immunotherapy may be a future potential therapeutic option for BRAF V600 mutant advanced melanoma, as BRAF V600 mutation in melanoma increases production of immunosuppressive factors, leading to an immune-suppressive phenotype, he adds.

“Mutated BRAF may induce T-cell suppression via secretion of inhibitory cytokines or by membrane suppression of co-inhibitory molecules such as PD-1 and PD-L1, suggesting that a combination strategy targeting BRAF, MEK and PD-L1 signalling could be effective,” he says. Clinical trials are producing promising results with these triple combinations.

Basal cell carcinoma (BCC) is the most common type of skin cancer and most cases result from mutations in key receptors in the Hedgehog (HH) signaling pathway, which controls cell proliferation, cell fate specification, tissue patterning and tissue homeostasis. In 85–90% of cases of BCC this involves inactivation mutations in the PTCH1 (Patched 1) transmembrane receptor and in 10% of cases activating mutations in SMO (smoothened) transmem-

Quick Takes

Combination of targeted therapy, immunotherapy may be potential therapeutic option for BRAF V600 mutant advanced melanoma.

Vismodegib and sonidegib show efficacy in clinical trials, receive regulatory approval for BRAF V600 mutant advanced melanoma.

Clinical trials show high frequency of durable responses in patients with MCC treated with PD-1 inhibitors who had not received prior chemotherapy.

“Until 2011, the standard of care for metastatic melanoma was chemotherapy with dacarbazine (DTIC) … which was associated with response rates of only 5–28% and no significant increase in survival duration.”

Eggert Stockfleth, M.D., St. Josef-Hospital, Ruhr-Universität Bochum, Bochum, Germany
brane receptor, a cell-associated signal transmitting component. Two agents that inhibit SMO in the HH pathway — vismodegib and sonidegib — showed efficacy in clinical trials and have received regulatory for treatment of locally advanced BCC and, for vismodegib only, metastatic BCC. Other HH pathway inhibitors are in development.

Over the last ten years the incidence of the Merkel cell carcinoma (MCC), a rare but aggressive neuroendocrine tumor of the skin, has increased worldwide. The Merkel cell polyomavirus (MCPyV) is clonally integrated in approximately 80% of MCC tumors, and the remaining 20% have large numbers of ultraviolet radiation associated mutations.

Merkel cell carcinoma is characterized by high tumor expression of PDL1 in the tumors, which led to recent clinical trials involving PD-1 pathway blockade in advanced MCC and clinical trials have shown a high frequency of durable responses in patients treated with PD-1 inhibitors who had not received prior chemotherapy. The PD-1 blocker avelumab has recently become the first agent to be approved for metastatic, relapsed/refractory MCC.

However, approximately 50% of patients with MCC do not benefit long term from PD-1 pathway blockade.

Dermatofibrosarcoma protuberans (DFSP) is a rare intermediate- to low-grade soft tissue neoplasm malignancy that rarely metastasizes. Activating mutations in the genes for PDGF or PDGF receptors have been recorded which led to the approval of molecularly targeted therapy with imatinib, which inhibits tyrosine kinases as well as PDGF receptors, in unresectable cases and as neoadjuvant therapy.

Potential new therapies for advanced or metastatic DFSP include multikinase inhibitors pazopanib and regorafenib.

References
As only patients whose tumors harbor the ‘druggable’ mutation will benefit from a targeted treatment, there is strong need for reliable, fast, and easy-to-use detection of mutations.”

Marius Ilie, from the Laboratory of Clinical and Experimental Pathology, Pasteur Hospital, Nice

Tool to assess tumor genotype

Routine tumor mutation detection may be feasible in pathology lab

INGRID TORJESEN | Staff Correspondent

**Quick Takes**

Detecting BRAF and NRAS mutations via PCR-based techniques requires a dedicated infrastructure, which isn’t always present in pathology labs.

Cell-free circulating DNA (cfDNA) can provide a useful snapshot of the BRAF and NRAS genotype of melanoma patients’ tumor tissue and act as a useful surrogate to assessing tissue biopsies for the markers, a study published in Oncotarget suggests.¹

Detection of BRAF mutations is a pre-requisite for treatment with BRAF inhibitors, and detection of a mutated NRAS oncogene is a biomarker of poor outcome and resistance to treatment with BRAF inhibitors.

Several methods to detect BRAF and NRAS mutations in formalin-fixed paraffin embedded (FFPE) samples are currently available in molecular pathology laboratories worldwide, but polymerase chain reaction (PCR) based techniques require a dedicated infrastructure, which is not always present in pathology laboratories.

Liquid biopsy in metastatic melanoma has emerged as an alternative tool that is complementary to tumor biopsies for detection of ‘druggable’ molecular alterations, with several studies demonstrating that circulating cell-free DNA (cfDNA) represents genetic information from the whole tumor genome and can provide evidence of the clonal evolution and tumor heterogeneity in several types of cancer, including melanoma.

Researchers at the Université Côte d’Azur in France assessed the sensitivity and specificity of the fully automated ready-to-use Idylla™ PCR-based system in identifying BRAF V600 and NRAS mutations in plasma samples from 19 patients with stage IV metastatic melanoma at baseline and during the course of treatment.

The cfDNA genotype obtained with Idylla was compared to the results obtained with matched-tumor tissue obtained via FFPE and to clinical outcome.

At baseline, nine (47%) of the 19 patients harbored a BRAFV600 mutation in their cfDNA and a NRAS mutation was detectable with plasma in 15% of patients before treatment. Two months after targeted treatment with a BRAF inhibitor the BRAFV600 mutant cfDNA was undetectable in all patients and three were disease-free. Sensitivity and specificity were 80% and 89% for BRAF status, and 79% and 100% for NRAS status in pretreatment cfDNA assessed using the Idylla™ PCR-based system compared to results obtained with a tissue test.

Marius Ilie, from the Laboratory of Clinical and Experimental Pathology, Pasteur Hospital, in Nice, says: “As only patients whose tumors harbor the ‘druggable’ mutation will benefit from a targeted treatment, there is strong need for reliable, fast, and easy-to-use detection of mutations. Furthermore, a personalized treatment scheme requires monitoring of the tumor’s genomic status.”

He adds: “We demonstrated that the detection of the BRAF and NRAS cfDNA status with the Idylla™ assay is feasible in a routine manner in a pathology laboratory, before and after systemic treatment of patients with metastatic melanoma. The assay reached acceptable concordance when compared with standard molecular analyses with matched tumor tissue.”

The Idylla™ system offers a fast and easy-to-handle integrated “sample-to-result” approach with results available in less than 2 hours after blood taking, including plasma, preparation, whereas other sequencing approaches requiring samples to be manually handled can have turnaround times of several days, he explains.

The Idylla™ system could also be implemented in a standard pathology laboratory, Ilie says, and the approach “could offer a good alternative to a surgical biopsy in fragile patients or patients with inaccessible metastatic sites to assess ‘druggable’ molecular alterations,” and “would be of particular interest for patients with a new metastatic melanoma, which often evolve rapidly and require urgent identification of the mutation status.”

“Large prospective clinical studies are needed to evaluate the medical impact of cfDNA-guided decisions,” he says.

**Reference**

Dual therapy approaches

Genetic targets might be relevant in treating cutaneous melanoma

INGRID TORJESEN | Staff Correspondent

Genes such as ERBB2, KIT, FGFR3, and RET, which are targets of approved pharmacologic therapies in other cancer types but are considered atypical for cutaneous melanoma, might be relevant in the treatment of individual patients, a study published in Cancer suggests.1

The BRAF/MEK inhibitor combination is a recognized treatment option for patients with activating BRAF mutations at position 600, but for patients with melanomas with other oncogenic genetic aberrations, effective signaling pathway inhibitors have not yet been approved.

Patients who respond to BRAF/MEK inhibitors usually develop resistance within nine to 12 months, so identifying additional, potentially actionable genomic alterations, allowing the individualization of inhibitor combinations as treatment, would be beneficial by enabling them to receive a dual therapy regime.

German researchers analyzed 45 primary melanomas and 91 metastatic melanomas from 92 patients receiving treatment at the University Hospital in Würzburg. They used a self-designed melanoma panel including more than 50 genes focused on the most relevant genetic alterations in melanoma and on genes that affect signaling pathways and thus can be targeted by pharmacologic inhibitors.

The panel was developed based on information derived from the previous analyses of the exomes and genomes of several hundred melanomas to identify the most frequently mutated genes and potentially relevant melanoma oncogenes and tumor suppressors. Genes that are atypical for melanoma were also included to detect alterations with high therapeutic relevance for patients with unknown driver mutations.

The comprehensive approach was based on targeted DNA sequencing and supported by RNA and protein analysis.

Comparison with patient-matched blood samples allowed the researchers to detect actionable somatic mutations, copy number variations (CNVs), and germline variants.

Among all patients, CNVs were identified in one-third of samples and contained amplifications of druggable kinases, such as CDK4, ERBB2, and KIT.

Considering single nucleotide variants (SNVs) and CNVs, 60% of patients with metastases exhibited co-occurring activations of at least two pathways, thus providing a rationale for individualized combination therapies. Alterations in the CDK4 pathway were seen in more than 40% of patients who had metastases, including the majority of those with NRAS-mutant tumors.

Unexpectedly, 9% of patients were found to carry potentially protumorigenic germline mutations frequently affecting receptor tyrosine kinases. Two-thirds of BRAF/NRAS wild-type melanomas were found to harbor activating mutations or CNVs in receptor tyrosine kinases such as ERBB2 and KIT.

ERBB2 expression is uncommon in melanomas, but in breast and stomach cancers, high ERBB2 levels are associated with rapid tumor growth and metastatic spread and provide the rationale for targeting ERBB2 by treatment with trastuzumab and lapatinib.2

KIT can be targeted by small-molecule inhibitors, such as imatinib, which are approved for the treatment of gastrointestinal sarcomas with mutations in exon 11, encompassing the juxtamembrane region with amino acids 550 through 591.3

“The combination of CNVs with activating or deleterious mutations enabled us to create a pathway matrix, which illustrates the predicted activated signaling pathways for each patient,” said Silke Appenzeller, Comprehensive Cancer Center, Mainfranken, University of Würzburg, Würzburg, Germany. “Importantly, the majority of our patients harbored genomic changes, which led to at least two pathway alterations.

“We propose that a targeted, deep-sequencing approach with careful consideration of oncogenic and deleterious SNVs and CNVs will help to identify patients who might benefit from a combination of BRAF/MEK inhibitors with an individually determined “inhibitor X” from the very beginning of their treatment.”

Different dual-therapy regimens have been tested in preclinical mouse models with promising results.

References


“..."The combination of CNVs with activating or deleterious mutations enabled us to create a pathway matrix, which illustrates the predicted activated signaling pathways for each patient.”

Silke Appenzeller, Comprehensive Cancer Center, Mainfranken, University of Würzburg, Würzburg, Germany.
Benchmarking improves financial performance

BOB KRONEMYER | Staff Correspondent

In order for a dermatology practice to advance to the next financial level, it is important that you identify needed areas of improvement.

“This is where benchmarking comes into play,” says George Smaistrla Jr., FHFMA, CMPE, CPC, who serves as secretary/treasurer of the board of directors of the Association of Dermatology Administrators and Managers (ADAM) and chair of their benchmarking committee.

“Benchmarking are those sets of statistics that the practice deems relevant regarding its operations which can be used for trending purposes,” he says.

Statistics can range from something as simple as the number of patient visits in a day, week or month, to the amount of charges being generated or the amount of dollars being collected.

“Typically, what a practice will do when it starts to take on a process improvement or tries to maximize its ability to improve its overall operations is select some key statistics or some key metrics to track,” Mr. Smaistrla tells Dermatology Times.

For example, by tracking the number of daily appointments and the number of kept appointments, the practice is able to determine the amount of unused time capacity and consider ways to potentially fill those slots.

“Where are your appointments coming from or where might you better target to increase the volume of appoint-
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George Smaistrla Jr., FHFM, CMPE, CPC
Association of Dermatology Administrators and Managers

Benchmarking helps a practice monitor key metrics to improve overall performance. FROM PAGE 54

Tracking the number of hours that staff cover a clinic (10 staff members, each normally working 40 hours a week for a total of 400 weekly hours) might all of a sudden spike to a 150 hours of overtime which is paid at time and a half. “This probably indicates that you are understaffed and therefore you could save some money by hiring an additional few more employees and reduce some of that overtime expense,” Smaistrla says. “Better yet, look at why you have the overtime in the first place. Does it make sense or not? Perhaps one of your employees are playing with the clock and not giving you real work for the hours being paid.”

One reliable benchmark is the number of full-time equivalent (FTE) staff to FTE providers. “For a busy Mohs surgeon, you might require three FTE staff to one FTE surgeon,” Mr. Smaistrla says. “However, these ratios are all directly dependent on the amount of work being provided by the physician. A new doctor performing fewer cases will not need as high a ratio of staff.”

Employee benefits, though, are not really cost controllable, according to Smaistrla. “You may be able to tweak costs one year to the next, but you are likely only going to achieve a single, one-year saving,” he says.

Finally, Mr. Smaistrla recommends that a practice consistently looks at key metrics and constantly ask what can be done better. “The only way you can know what you can do better is to know what you have done,” he says.

Disclosure: George Smaistrla Jr. reports no relevant financial disclosures.
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A physician’s guide to preventing data breaches

Debra A. Schute | Medical Economics

During each of the past three years, covered entities paid more than $20 million in HIPAA fines. While a handful of major breaches made headlines—most notably Anthem’s $16 million mistake—small practices can’t afford to be complacent about security.

The more negligent a healthcare organization is found to be at the time of a HIPAA violation, the higher the penalty. According to the U.S. Department of Health and Human Services, fines can range from $100 to $50,000 per violation or record, with a maximum penalty of $1.5 million per year for each violation.

For physician practices, even minor penalties can take a major financial toll. And that’s where the trouble just begins. “More importantly for practices, a breach could impact their business continuity,” says Robert Tennant, director of health information technology (HIT) policy for the Medical Group Management Association. The loss of one month’s worth of claims data, for example, could cause significant disruption and potential loss of revenue, he notes.

Another significant risk to medical practices is damage to their reputations, says Matthew Fisher, J.D., a partner with Mirick, O’Connell, DeMallie & Lougee LLP, in Massachusetts. Once you’ve had a HIPAA breach, the name of your practice is listed permanently on the Office for Civil Rights’ Wall of Shame—including the offense, date, and number of individuals affected. “It does have an impact in terms of patients wanting to continue with the provider,” Fisher says.

There’s also the ongoing cost of providing credit monitoring to affected patients for at least a year, as required by HIPAA, as well as the mental anguish of having to respond to a government investigation, whether a fine is issued or not, adds Fisher.

As a result, preventing breaches of protected health information should be viewed by practices as a business imperative, says Tennant, adding that security depends on continually asking the question, “What if?”

The list of scenarios to consider is nearly infinite: a phishing attack, sending a fax to the wrong number, losing an unencrypted thumb drive, as well as threats that have yet to evolve.

CONDUCT A RIGOROUS RISK ASSESSMENT

The best way to identify a practice’s key vulnerabilities is by conducting a baseline risk assessment, which has been required of practices since the HIPAA Security Rule went into effect. HHS is vague as to when and how often covered entities must conduct risk assessments—they recommend it be done ‘regularly’—but experts suggest performing this assessment at least annually.

“The risk analysis is going to give you a pretty comprehensive overview of your weaknesses, and is really going to help frame out how you’re going to implement all the different security policies,” says Fisher. Nonetheless, it’s a step practices often skip. “For incidents that result in a settlement of monetary fine, almost every time, there’s either a missing risk assessment or an inadequate risk analysis,” he says.

For practices that don’t have the necessary in-house technical expertise, it can be worth the cost to outsource at least part of the project, experts say. A third party may also give a more accurate assessment by looking at a practice’s systems with true objectivity, notes Fisher. He recommends getting an outside perspective every three to four years.

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And if a breach does occur, a thorough risk assessment as well as written policies and procedures will help the practice defend itself against penalties, Fisher says.

EMPHASIZE SECURITY FUNDAMENTALS

While major cyberattacks involving ransomware or other external hacks draw headlines, many breaches result from mistakes made within the practice.

“The human component is the most difficult to secure,” says Michael Yamamoto, chief information security officer for Beth Israel Deaconess Medical Center in Boston. “We have 23,000 employees. If a hacker asked everybody what their passwords are, then there’s probably somebody who’s going to tell them.”

Yamamoto recommends that healthcare organizations of all sizes focus cybersecurity training around the basics of everyday work life. “Fundamentally, a lot of security comes down to people’s passwords,” he says. “If somebody gets that password, they’re in.”

To keep hackers at bay, he recommends using long passwords with at least 12 characters, and different passwords for every place a user logs in. To keep track of them all, he advises using a password manager, which is a software application that stores and manages a user’s passwords for all their various online accounts and security features. This tool stores the passwords in an encrypted format, which the user accesses with a master password.

Fisher also recommends that practices require multi-factor authentication, such as a password and a fingerprint, whenever possible.

Another best practice is to instruct individuals not to access medical records they don’t need to perform their job. “People probably don’t realize they’re perpetuating data breaches when they enter a record that they really have no clinical reason to be in. We tell people they can’t look in their own medical records or those of family members outside of the due course of their jobs,” Fisher says.

Finally, physicians must take cybersecurity training seriously and keep their knowledge up to date by really listening to the education their employers provide, says Rebecca Grochow Mishuris, M.D., M.P.H., associate chief medical information officer for Boston Medical Center and an assistant professor of medicine at Boston University School of Medicine.

“There are new threats coming out all the time that we have to address,” she says. “It’s not enough to say you learned it three years ago. Three years ago, things were very different than they are now from a data security standpoint.”

For example, phishing attacks have become much more sophisticated in recent years. “It’s not like the email from the prince in Nigeria anymore. It’s an email that looks like it came from your institution,” says Dr. Mishuris, a general internist at Boston Medical Center. So anyone using the practice’s email system needs to be aware that the practice will never ask for a password over email, or a link that requires the user to sign in, without verbal warning.

A strong spam filter will catch most emails falsely claiming to be from the practice or other trusted entities, but it’s critical that all users learn to recognize a potentially dangerous email and what to do about it.

REQUIRE REPORTING

Practices must make it clear to all clinicians and staff that if they click on a bad link, open a suspicious attachment, or make another security-related mistake that they will not be disciplined—and that reporting incidents is crucial, Dr. Mishuris says.

The sooner a potential breach is discovered, the sooner an organization can take steps to stop or minimize the damage, such as securing the employee’s password and sending a blast email to describe the threat to the rest of the staff and instruct them on what to do if they receive it. To that end, individuals must be trained in reporting procedures, which typically involve notifying IT via a dedicated email address of phone number, she explains.

“It’s important that the practice culture not penalize reporting, but promote behaviors that help find gaps and make improvements,” Dr. Mishuris says. Early detection that allows time to intervene in a breach is essential to limiting a practice’s liability when security incidents occur, she says.

COMMUNICATE CREATIVELY

Security and privacy officials at Beth Israel Deaconess employ several tactics to instill good security habits throughout the organization, but a common thread is an effort to make messaging memorable, says Yamamoto.

For example, the organization has distributed bags of Swedish Fish candy with accompanying information about phishing, he says. Yamamoto has also been filmed holding a fishing pole in an educational video about the same topic.

“We try to use a story-based approach, using funny or [silly] things that will help people stop for a moment and think about what they’re doing,” he says. “When you’re so busy pushing things out, it’s really easy to perpetuate a major problem.”

GIVE HIT SOME TLC

Finally, HIT systems themselves need regular attention to operate securely, using outside help if necessary, says Yamamoto. It is especially important to install software updates when they are released and make sure antivirus software is adequate and up-to-date.

“Keep those things up with some tender loving care, and you’ll be in pretty good shape,” he says.
Dr. Brian Biesman and Dr. Michael Gold invite you to the 2019 Music City SCALE Meeting. The meeting is for 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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FDA oversights for dermatology devices

STEVE XU MD FAAD | Contributing Columnist

The Food and Drug Administration (FDA) plays a critical role in the oversight of many medical devices used commonly in dermatology that range from high-risk to low-risk products. Within the FDA, the Center for Devices and Radiological Health (CDRH) is the responsible Center for the regulation of medical devices. Overall, the FDA’s CDRH has grouped 1,700 different generic types of devices into 16 medical specialties referred to as panels. Dermatological devices are often (but not always) regulated under the General and Plastic Surgery panel.

Ultimately, the FDA regulates medical devices by categories of risk. The first is the determination of whether a product is a medical device or not. There is a long legal definition to what constitutes a device. But, in summary, a product is considered a medical device if the intended use is to diagnosis, cure, mitigate, treat or prevent disease in man or animals. Importantly, a medical device achieves its primary intended purpose through non-chemical action within or on the body of man. An example of a device used in dermatology that is not considered a medical device are new and emerging UV sensors. By simply reporting external exposure of UV, these sensors do not meet the FDA’s definition of a medical device and can be sold to consumers directly without FDA clearance.

Class I medical devices are considered the lowest risk devices and subject largely to only general controls. These general controls include requirements for the company to follow appropriate labeling rules, and good manufacturing practices. The majority of Class I devices are exempt from premarket notification of the FDA prior to market entry. Bandages, examination gloves, and most handheld surgical instruments (e.g. punch biopsy tools) fall in this category.

Class II devices are considered moderate risk and represents the broadest range of medical devices. Typically, Class II devices undergo clearance by the FDA through the 510(k) pathway where a new medical device can cite a predicate (already approved) device as substantially equivalent. Often, no clinical data is needed to obtain this clearance. There are several prescription moisturizers that are actually regulated as medical devices cleared through the 510(k) pathway. The manufacturers have argued that these moisturizers provide benefit via non-chemical means in order to obtain FDA clearance as a medical device rather than a drug. Certain fractional non-ablative lasers also obtain 510(k) clearance as a Class II medical device. Narrow band phototherapy systems are another example of Class II medical devices cleared via the 510(k) pathway.

Class III medical devices pose the highest risk. These devices usually support or sustain life, are implanted, or present a significant potential risk of illness or injury. These devices must follow the strictest regulatory pathway known as the pre-market approval pathway. The device typically requires clinical data demonstrating safety and efficacy prior to FDA approval. The most well-known examples of Class III devices in dermatology are soft tissue fillers.

Dermatology is a specialty that employs a wide range of medical devices that range from cosmetic applications to medical dermatology. The FDA plays a critical role in the regulation, approval, and post-marketing surveillance of the safety and efficacy of these devices. Practicing dermatologists should be made aware of the ability to submit adverse event reports related to medical devices to MedWatch, the FDA’s Safety and Information and Adverse Reporting Program. A MedWatcher mobile app is now also available. By reporting adverse events directly to the FDA including near misses, dermatologists can play an important role in surveillance of emerging public safety issues related to medical devices in our field. Reporting adverse events to the manufacturer directly is also another option—but law, they are required to forward such reports to the FDA. My suggestion is to do both.

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Remembering Dr. Vic Narurkar

FROM PAGE 13

too removal. Afterwards Dr. Narurkar was appointed dermatology director, assistant professor at UC Davis Laser Center, where he was the original investigator for laser hair reduction with alexandrite and diode lasers; cosmetic vascular lesion treatment with pulsed dye and KTP lasers; and skin resurfacing with CO2 lasers, according to his Bay Area Laser Institute website.

He was a board member of the American Society of Dermatologic Surgery (ASDS), a past president of the American Society of Cosmetic Dermatology and Aesthetic Surgery and co-director of the Cosmetic Boot Camp. An author of some 200 scientific papers, Dr. Narurkar was a lead clinical investigator for just about the entire spectrum of common cosmetic devices and treatments — from CoolSculpting to Juvéderm (Allergan).

“I believe his greatest impact in the field of dermatology was the fact that he was very focused on evidence-based medicine. He always needed proof of what worked and how it worked,” according to Montclair, N.J., dermatologist Jeanine B. Downie, M.D., who knew Dr. Narurkar for 20 years. “Vic was absolutely brilliant, with a photographic memory. He made me reach higher…. ”

Dr. Narurkar was a captivating speaker and a connector of people, Dr. Welsh says. “He loved to teach and freely shared his time with others,” Dr. Welsh says. “I think that for many, many dermatologists, when they had a complication or problem with a device they would go out: Who yo’ gonna call? Vic Narurkar!”

Dr. Narurkar wasn’t afraid to challenge long-held beliefs if they weren’t backed by rigorous study, says Dr. Welsh. “His biggest contribution may be that for years he has been the conscience of our rapidly changing specialty, always putting science and patient safety at the forefront.”

HONEST AND AUTHENTIC (#NOPosers)

Dr. Narurkar never claimed to be something he wasn’t and was proud to be a dermatologist, according to Dr. Werschler. To help drive aesthetic education among the specialty, Dr. Narurkar helped to cofound the Cosmetic Boot Camp meeting.

Kenneth Beer, M.D., professor of dermatology at the University of Miami and Cosmetic Bootcamp founder, says Dr. Narurkar was the spirit of the Bootcamp. “Although I started it, I recognized my limitations early and sought out people who could add to the meeting. [Vic] was selfless and made me a better speaker and person, always kidding me that some of my strategies were not approved by the ‘Narurkar Charm School,’ ” Dr. Beer says.

Dr. Narurkar would disagree using data to substantiate his perspective. In essence, he increased the knowledge without increasing the volume, according to Dr. Beer.

“He was a passionate educator who demanded accountability and no baloney in our specialty — not from colleagues and not from industry,” says New Orleans-based dermatologist and Cosmetic Bootcamp Founder Mary Lupo, M.D.

That no-baloney mentality might have also been the impetus that led to Dr. Narurkar’s favorite #noposers hashtag, which was based on Dr. Narurkar’s belief that self-promotion should be honest and authentic—not misleading, according to Dr. Werschler.

RESILIENCE AND JOY

Heidi Waldorf, M.D., a dermatologist in Nanuet, N.Y., says she was taken by her colleague’s resilience and joy right from the start, when they met in 1993.

“I was interviewing for Mohs fellowship at Cleveland Clinic and Vic was already the senior fellow…,” Dr. Waldorf writes on social media pages.

Her image of Dr. Narurkar is of him smiling, waving his hand and telling her not to worry about what other people do or think.

Dr. Narurkar learned about resilience the hard way. He was harassed during his residency because of his sexual orientation, according to Dr. Welsh.

“This experience affected him profoundly and he turned the experience into a positive over the years by becoming a mentor and protector for others who suffered similarly because of their race, sex or gender differences,” Dr. Welsh says.

Dr. Downie says she and Dr. Narurkar were “brown people” in the dermatology world and saw things from their unique skin of color perspectives.

“We would validate each other’s concerns and support each other through unpleasant incidences. Vic and I were the same, but we were different and that was one of our many significant bonds,” Dr. Downie says.

Dr. Werschler says he’ll miss not only the dermatologist and physician that Dr. Narurkar was, but also the countless memories Dr. Werschler and his long-time partner Mike Hirner laughing, being foodies together and having ridiculous fun.

“Vic and Mike were like surrogate parents to my son John,” Dr. Werschler says.

Dr. Narurkar’s close friend Patti Pao, founder and CEO of the skincare line Restorsch, says Dr. Narurkar didn’t need the money. He practiced for the love of dermatology and in a way that made him proud.

“When you don’t need the money, you make different kinds of decisions. It left him very free to practice the way he wanted to practice. He didn’t have to be beholden to industry; he didn’t have to do all these studies; he didn’t have to be on the podium; he didn’t have to be famous,” Pao says. “What it enabled him to do was completely focus on the things that were important to him, which were giving his patients the best possible care. He performed all of the procedures himself only using products and devices that passed rigorous third-party clinical studies published in major medical journals. I admired him greatly because he just kept his head down, did the best job he could and did what he thought was right — all day every day.”

Dr. Narurkar leaves behind his parents, who live in Palo Alto; his husband Mike Hirner of San Francisco; and his dachshund Mavis.
diminishing returns beyond that limit.

A recent North American Gallup Poll documented an income threshold for happiness at $105,000. (Jebb AT et al. Happiness, income satisfaction and turning points around the world. Nature Human Behaviour; 2:33-38.) Average physician incomes far exceed the lower threshold for happiness, but span and often far exceed the upper limit. Some disadvantages associated with higher incomes are higher demands on time, heavier workloads and greater spectrum of responsibility. This may help explain why many studies have not recognized salary as among the most important sources of physician satisfaction.

For some clinicians, bypassing third party payors with a cash-only or concierge practice is an appealing model. Others value the capacity to serve patients without regard to their ability to pay. Both settings have advantages and disadvantages.

The economic advantages of a cash-only practice are obvious while the disadvantages of serving the socioeconomically disadvantaged have been more well-recognized than the rewards. These include lower reimbursement and high no-show rates. In my practice, restricted access to medications and the number of either grateful or entitled patients has been comparable across socioeconomic groups. But it should be noted that the benefits of serving the needy more closely align with the most important factors that contribute to physician job satisfaction, and also minimize burnout.

For clinicians without these additional resources, or those who would like enjoy the benefits of caring for underinsured patients on a part-time basis, volunteer to see them at an understaffed hospital or clinic.

With these thoughts in mind, the AAD Emerging Practice Models Committee and Task Force on Drug Pricing will be considering programs to promote some of these initiatives, including recommendations to help guide institutions in the creation and maintenance of programs to facilitate volunteer physician service and creation of a centralized database for free or low-cost access to dermatologic medications.

Advantages of a practice that includes the underinsured

- Patient interaction
- Autonomy in making medical decisions
- Varied, interesting patients
- Complex medical problem-solving
- High demand
- Patients who are less dissatisfied with the need to wait for an appointment
- A higher proportion of persistent problems that require medical intervention, rather than reassurance-only
- Ability to focus on medical, more than business-related issues
- No need to market services, sell products or maintain an on-line reputation
- Gratification associated with service to patients and support of burdened colleagues
- Contribution to improved patient outcomes and decreased overall cost of healthcare with fewer misdiagnoses and unnecessary treatments from emergency room and urgent care providers
- Opportunity to provide early intervention, especially for children, who are disproportionately Medicaid insured
- Adherence to the physician professional code-of-conduct
- Enhanced public perception
- Job security
- Like-minded, collaborative colleagues
- Opportunity for interacting with residents and students
- Access to large organization benefits for staff

Innovation: Novel drugs in 2018

- Tildrakizumab (Ilumya) was approved for adults with moderate-to-serve plaque psoriasis. Ilumya is a IL-23 inhibitor demonstrating 64% and 61% PASI-75 at week 12 in their two Phase-3 pivotal trials.
- Glycopyrronium (Qbrexza) was approved for primary axillary hyperhidrosis in adult and pediatric patients nine years and older in a topical formulation.

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If you are interested in learning more about these opportunities, please contact:
Drea Rosko, Physician Recruiter, St. Luke’s University Health Network, PhysicianRecruitment@sluhn.org.
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Qosmedix expands glass packaging collection

**Qosmedix**, a certified cosmetic, skincare, spa and salon supplier, recently announces that it has expanded its collection of glass packaging to include 3 ml, 5 ml and 15 ml as a result of increased demand. The bottles are meant for sampling and packaging liquid cosmetics and cosmeceuticals, such as serums, oils and lotions.

FOR MORE INFORMATION: qosmedix.com

DefenAge eye cream fights signs of aging

Progenitor Biologics® recently announced the launch of **3D EYE RADIANCE CREAM**, a new addition to the DefenAge skincare collection. This product contains the company’s proprietary Age-Repair Defensins and is designed to improve skin health and appearance around the eyes.

“Scientific and clinical data show that defensins reprogram skin to turn younger every day, reversing aging. Basically, whenever you need to refresh or normalize your skin, just activate the skin’s reprogramming mechanism,” said Progenitor Biologics’ CEO, Nikolay Turovets, PhD.

According to the company, the eye cream lifts, firms and smooths upper eyelids, addresses dark circles and puffiness and diminishes the appearance of crow’s feet and fine lines. The eye cream’s metal applicator allows for gentle and soothing application directly onto the delicate skin around the eyes.

The eye cream is free from parabens, fragrance, animal- and human-derived ingredients. It has also been tested by ophthalmologists and dermatologists and is safe for contact lens wearers.

FOR MORE INFORMATION: defenage.com

Harvard-trained dermatologist creates hair care line

**SEEN** is a clinically proven non-comedogenic and non-irritating hair care line developed by board certified dermatologist, Dr. Iris Rubin. The hair care collection was created to combat breakouts caused by shampoos, conditioners and other styling products that touch the skin.

The line includes a shampoo, conditioner and blow-out creme.

“I like to fix things – and this needed fixing. Rather than throwing prescriptions at the problem, we wanted to find a better way. With SEEN we’ve created a line that’s truly good for skin while bringing the real everyday joys of gorgeous hair, luxury beauty and increase confidence,” said Dr. Rubin.

The products aim to promote shiny, smooth and healthy hair with a patented formula that includes hemisqualane, bisabolol, shea butters and cetyl esters, squalene, ceratonia silqua and moringa oleifera. **SEEN** products do not contain clogging oils or silicones, phthalates, sulfates, parabens, dyes or gluten.

All products are safe for all skin and hair types, including color-treated hair.

FOR MORE INFORMATION: helosexual.com

NuFACE offers skincare on-the-go

**NUFACE FIX™** is an anti-aging product that uses FDA-cleared microneedling technology, which firms and tightens skin in two steps. Created by **NUFACE**, this duo includes a smoothing serum and a smoothing device that addresses fine lines and wrinkles around the eyes, lips and forehead.

**NUFACE FIX™** Line Smoothing Serum contains magnesium gemstone and hyaluronic acid, which hydrate and brighten skin. The **NUFACE FIX™** Line Smoothing Device is a portable, pen-sized applicator that comes with a micro USB cable for charging on-the-go. After applying the serum to the device, individuals should turn on the device on and use a feathering technique for up to three minutes.

According to data from a single center, non-randomized, single arm trial, 100% of participants said their skin felt instantly hydrated after using the product. 97% said their skin felt instantly tighter around the eyes and 95% said their eyes appeared less puffy.

FOR MORE INFORMATION: mynuface.com
Energy-based device facial rejuvenation options

By Lisette Hilton

LASERS

ENERGY USED:
- Ablative: Carbon Dioxide (CO2)
- Fractionated ablative: CO2 Erbium Yttrium aluminum garnet (Erbium: YAG), ablative fractional laser (AFL)
- Nonablative fractional laser (NAFL)
- Combined fractionated lasers: Er:YAG/Nd: YAG combinations

INDICATIONS:
- Full-face, including mild to moderate wrinkles, and acne scarring

ADVERSE EFFECTS:
- Hyperpigmentation and prolonged recovery (CO2 ablative).
- Ablative non-fractionated lasers are contraindicated in Fitzpatrick type V and VI skin types.

TAKEAWAYS:
- Full-field ablative resurfacing offers superior results for moderate photaging, but patients must be counseled about longer downtimes and higher risk of AEs. Fractionated lasers offer shorter downtimes with modest results and are a promising option for scar remodeling.

LIGHT THERAPY

ENERGY USED:
- Intense pulsed light (IPL)
- Light-emitting diodes (LED)

INDICATIONS:
- To induce dermal remodeling without epidermal ablation. Often combined with other lasers to improve skin clarity or improve mild photaging.

ADVERSE EFFECTS:
- Small dyschromia risk with IPL use in patients with history of dyschromia.

TAKEAWAYS:
- IPL and nonablative fractionated lasers are safe and effective for melasma and in combination with bleaching agents and superficial chemical peels. But melasma has a high propensity for recurrence.

NON-LASER-BASED THERMAL TIGHTENING

ENERGY USED:
- Bipolar radiofrequency (RF)
- Monopolar (RF)
- Intense focused ultrasonomography (IFUS)
- Microfocused ultrasonomography (MFU)

INDICATIONS:
- Mild to moderate skin laxity and photaging, extrinsic skin aging (without notable underlying structural ptosis)

ADVERSE EFFECTS:
- Minimal erythema, edema and discomfort.

TAKEAWAYS:
- Ultrasound and RF energy-based therapies are promising for mild improvement of skin laxity with less downtime, but more research is needed on the long-term benefit.