WEARABLE DEVICE CONTINUES ON PAGE 19

POSITIVE RESULTS from a feasibility study investigating non-therapeutic Nano-Pulse Stimulation (NPS, Pulse Biosciences) for treating cutaneous non-genital warts have led to a larger multicenter study that aims to optimize the treatment parameters and hopefully replicate the early evidence of its efficacy and safety, says Gilly S. Munavalli, M.D., M.H.S.

The initial study enrolled 19 patients, of which a sizeable proportion had warts considered “difficult-to-treat” based on their location or failure to be cleared by other modalities. Even so, clinical and dermoscopic assessments showed that approximately 60% of treated lesions were cleared after one or two treatments with NPS.

Inlet
Outlet port
Microchannels

Technology targets cell death, immune response to treat non-genital warts

Wearable sensors might soon provide dermatologists and patients with unprecedented real-time information about skin health.

One such device in development, Epicore Biosystems’ wearable Discovery patch (Leo Pharma and Epicore Biosystems), aims to assess inflammatory biomarkers found in sweat and interstitial fluid in individuals with atopic dermatitis. The wearable technology will analyze cytokines in sweat to offer real-time objective assessment of the state of disease in adults with the chronic skin condition.

Leo Pharma’s innovation unit Leo Science and Tech Hub announced in early November 2019 that

How Do Recent Pathophysiological Findings in PUSTULAR PSORIASIS Have the Potential to Shape a New Treatment Paradigm?

How Do Recent Pathophysiological Findings in PUSTULAR PSORIASIS Have the Potential to Shape a New Treatment Paradigm?

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Can sweat indicate disease severity?

Investigational device aims to personalize atopic dermatitis care

Wearable sensors might soon provide dermatologists and patients with unprecedented real-time information about skin health.

One such device in development, Epicore Biosystems’ wearable Discovery patch (Leo Pharma and Epicore Biosystems), aims to assess inflammatory biomarkers found in sweat and interstitial fluid in individuals with atopic dermatitis. The wearable technology will analyze cytokines in sweat to offer real-time objective assessment of the state of disease in adults with the chronic skin condition.

Leo Pharma’s innovation unit Leo Science and Tech Hub announced in early November 2019 that...
By identifying the appropriate locally advanced basal cell carcinoma (laBCC) patients, the treatment journey starts with you.

INDICATION
ODOMZO® (sonidegib) is indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

• ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. ODOMZO is embryotoxic, fetotoxic, and teratogenic in animals
• Verify the pregnancy status of females of reproductive potential prior to initiating therapy. Advise females of reproductive potential to use effective contraception during treatment with ODOMZO and for at least 20 months after the last dose
• Advise males of the potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with ODOMZO and for at least 8 months after the last dose

Please see additional Important Safety Information on the back cover and Brief Summary of Prescribing Information, including Boxed WARNING, inside the front cover.
Brief Summary of Prescribing Information for ODOMZO® (sonidegib) capsules

This Brief Summary does not include all the information needed to use ODOMZO safely and effectively.

See full Prescribing Information for ODOMZO.

INDICATIONS AND USAGE
ODOMZO is a hedgehog pathway inhibitor indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.

WARNINGS AND PRECAUTIONS

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- Advise males of the potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with ODOMZO and for at least 8 months after the last dose.

Blood Donations: Advise patients not to donate blood or blood products during treatment with ODOMZO and for at least 20 months after the last dose.

Musculoskeletal Adverse Reactions: Obtain serum creatine kinase (CK) and creatinine levels prior to initiating therapy, periodically during treatment, and as clinically indicated. Temporary dose interruption or discontinuation of ODOMZO may be required based on the severity of musculoskeletal adverse reactions.

Premature Fusion of the Epiphyses: Has been reported in pediatric patients exposed to ODOMZO and other Hh pathway inhibitors. ODOMZO is not indicated for use in pediatric patients.

DOSAGE AND ADMINISTRATION
Recommended dosage: 200 mg taken orally once daily on an empty stomach, at least 1 hour before or 2 hours after a meal.

ADVERSE REACTIONS
The most common adverse reactions occurring in ≥10% of patients are muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus.

DRUG INTERACTIONS
CYP3A Inhibitors: Avoid strong CYP3A inhibitors. Avoid long-term (greater than 14 days) use of moderate CYP3A inhibitors.

CYP3A Inducers: Avoid strong and moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS
EMBRYO-FETAL TOXICITY: See boxed warning. ODOMZO can cause fetal harm when administered to a pregnant woman.

Report pregnancies to Sun Pharmaceutical Industries, Inc. at 1-800-406-7984.

LACTATION
Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with ODOMZO and for 20 months after the last dose.

PEDIATRIC USE
The safety and effectiveness of ODOMZO have not been established in pediatric patients.

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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PLR-00105
IMPORTANT SAFETY INFORMATION (continued)

Embryo-fetal Toxicity: ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Females of Reproductive Potential: Verify pregnancy status prior to initiating ODOMZO. Advise females to use effective contraception and not to breastfeed, due to the potential for serious adverse reactions in breastfed infants, during treatment and for at least 20 months after the last dose. Report pregnancies to Sun Pharmaceutical Industries, Inc. at 1-800-406-7984.

Males: Advise males to use condoms, even after a vasectomy, and to not donate semen during treatment and for at least 8 months after the last dose to avoid potential drug exposure in pregnant females or females of reproductive potential.

Blood Donation: Advise patients not to donate blood or blood products while taking ODOMZO, and for at least 20 months after the last dose because their blood or blood products might be given to a female of reproductive potential.

Musculoskeletal Adverse Reactions: Musculoskeletal adverse reactions, which may be accompanied by serum creatine kinase (CK) elevations, occur with ODOMZO and other drugs which inhibit the hedgehog (Hh) pathway. Obtain serum CK and creatinine levels prior to initiating therapy, periodically during treatment, and as clinically indicated. Temporary dose interruption or discontinuation of ODOMZO may be required based on the severity of musculoskeletal adverse reactions.

Premature Fusion of the Epiphyses: ODOMZO is not indicated for use in pediatric patients. Premature fusion of the epiphyses has been reported in pediatric patients exposed to ODOMZO and other Hh pathway inhibitors. In some cases, fusion progressed after discontinuation.

Drug Interactions: Avoid concomitant administration of ODOMZO with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, administer for less than 14 days and monitor closely for adverse reactions, particularly musculoskeletal. Avoid concomitant administration of ODOMZO with strong and moderate CYP3A inducers.

Geriatric Use: There was a higher incidence of serious adverse events, Grade 3 and 4, and events requiring dose interruption or discontinuation in patients ≥65 years compared with younger patients; this was not attributable to an increase in any specific adverse event.

Most Common Adverse Reactions: The most common adverse reactions occurring in ≥10% of patients were muscle spasms (54%), alopecia (53%), dysgeusia (46%), fatigue (41%), nausea (39%), musculoskeletal pain (32%), diarrhea (32%), decreased weight (30%), decreased appetite (23%), myalgia (19%), abdominal pain (18%), headache (15%), pain (14%), vomiting (11%), and pruritus (10%).

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ATOPIC DERMATITIS

Can sweat indicate disease severity?
Investigational device aims to personalize atopic derm care

LISETTE HILTON | Staff Correspondent

Wearable sensors might soon provide dermatologists and patients with unprecedented real-time information about skin health.

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ACNE SCARS

Adjunct PRP promising
Evidence increases, results still variable

JOHN JESITUS | Staff Correspondent

PLATELET-RICH PLASMA (PRP) shows promise as an adjunctive treatment for atrophic acne scarring, according to recent research. However, experts say that with all PRP combinations used in acne scarring, treatment regimens, research protocols and clinical results remain highly variable.

Lack of standardization has hindered dermatologists’ assessments of adjunctive PRP and platelet-rich products as a whole, says Michael Hesseler, M.D., founder of Arch Dermatology Institute in St. Louis, Mo.

“It’s been difficult to interpret the literature that’s available because of this lack of standardization,” he notes.

Many studies show that adding PRP to other modalities used to treat acne scars

DermatologyTimes.com
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**Increased Papanicolaou (Pap) smear changes** have been observed in women treated with topical tazarotene products. Advise patients to report any visual symptoms and changes, including promoters (tazarotene) may be associated with certain systemic toxicities. Due to the potential for systemic absorption, use of topical corticosteroids, including**:}

**Neonatal Depression**

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ATOPIC DERMATITIS

Device aims to personalize AD care

CLINICAL INSIGHT
Technology targets non-genital warts

ACNE SCARRING
PRP shows promise for acne scar Tx

columns

legal eagle
DAVID J. GOEBEL, M.D., J.D.

MY PATIENT BLED
Did I breach standard of care by not asking about my patient’s use of anti-coagulants?

profile
LISSETTE HILTON

DR. HONORED
Dr. Andrew Alexis recognized for work to close gaps for patients with skin of color.

irregular border
CAROL SOUTER, M.D.

MIND-BODY THERAPY
Evidence indicates benefit to disease management.

ATOPIC DERMATITIS

14 TOPICAL BOTANICALS EFFECTIVE
Study demonstrates botanical blend improves AD symptoms in kids.

15 BIOPSY ALTERNATIVE
Tape strips appear effective for skin sampling.

PSORIASIS

20 IL-17 TARGETED IN PUSTULAR PSORIASIS
Inhibiting IL-17 a potential method to manage GPP.

21 PALMOPLANTAR PUSTULOSIS PREVALENCE EXAMINED
Cohorts differed in co-occurrence with plaque psoriasis, but psoriatic arthritis risk linked to individuals with both.
Advances promise more personalized care

by MIKE HENNESSY, SR

IMPROVING QUALITY OF LIFE is one goal of dermatology care, especially for those with chronic disease. Atopic dermatitis, psoriasis, acne—these are all conditions that can significantly impact a patient clinically and psychologically. Advances in research and technology are hinting to a future of personalized diagnosis, management, and care.

One such device in development is Epicore Biosystems’ wearable discovery patch (Leo Pharma and Epicore Biosystems). The patch aims to assess biomarkers found in a patient’s sweat to assess the state of his or her atopic dermatitis (p.1). Another potential tool for better understanding disease state is a tape strip, which researchers are evaluating as an alternative to performing skin biopsies in children (p.18). Because there are different subtypes of atopic dermatitis, Dr. Emma Guttmann-Yassky says, “In the future, I think we’ll need personalized medicine in atopic dermatitis patients.”

In acne treatment, once scarring develops, evidence, while mixed, indicates that platelet-rich plasma may improve scars when combined with fractional laser treatment, microneedling, or dermabrasion. From a pathophysiology standpoint, it makes sense says Dr. Emil Tanghe, “What we’re doing is harnessing the body’s own wound-healing machinery and kickstarting that process,” says Michael Hesseler, M.D. (p.1).

However, some experts are finding that early, aggressive treatment may prevent acne scars — and the potentially resulting psychosocial scars (p. 23). They point to a study in which benzoyl peroxide plus adapalene improved scars approximately 30% at six months vs the untreated side in a split-face study. “Treatment not only prevented the development of new scars, but it also eradicated some of the pre-existing scars,” says Dr. Hilary Baldwin. She advises checking each acne patient carefully for early signs of scarring. The longer you wait, the more likely the condition is to cause physical scars, which she says, also result in emotional scars.

A case study involving a patient with extensive psoriasis (p. 22) illustrates a variety of socioeconomic factors that can create barriers to care. The authors note that it represents an extreme manifestation of a common, easily managed disease that went untreated. “In patients with limited access to healthcare, poor healthcare literacy and other socioeconomic barriers; the social support system, the cost-effectiveness of planned interventions and the burden on the patient must all be considered when designing an efficacious treatment plan,” the authors write.

In all, the advances and research insights reported in this month can serve as a reminder that personalizing treatment plans can optimize outcomes in a variety of conditions. We hope these insights and peeks at new developments will inspire, educate and support you in caring for each one of your patients.
He used to explain to his patients that they will have more post-surgical ecchymosis, but now he doesn’t even ask if they are on anti-coagulant therapy.

He recently performed a large excision. The patient did not take any prescription blood thinners but did take high daily doses of garlic and ginkgo. Unfortunately, the patient had progressive post-operative bleeding that led to volume loss and ultimate cardiovascular arrest. A lawsuit was brought against Dr. Surgery. Will he lose this case based on negligence?

Clearly a medication history is important for possible agents that may impair platelet function and increase risk of bleeding. The most common prescription agents that increase risk of hemorrhage or inhibit platelet function used on an outpatient basis include warfarin, low molecular weight heparin, fondaparinux, idraparinux, aspirin, clopidogrel, ticlopidine and dipyradomole.

Prescription and non-prescription non-steroidal anti-inflammatory drugs are also commonly used and inhibit platelet function. However, the intake of herbal and vitamin supplementation is also common. The four Gs: garlic, gingko, ginseng and ginger — along with vitamin E are commonly used agents that have been implicated in increasing risk of bleeding. Should Dr. Surgery have asked about the intake of such medications?

Complications from bleeding may or may not have legal significance. If the aggrieved patient is convinced his/her physician has been negligent, legal action may be taken against the dermatologist. Any analysis of physician negligence must first begin with a legal description of the elements of negligence. There are four required elements for a cause of action in negligence. They are duty, breach of duty, causation and damages. The suing plaintiff must show the presence of all four elements to be successful with such a claim.

The duty of a physician performing cutaneous surgery is to perform that procedure in accordance with the standard of care. Although the elements of a cause of action in negligence are derived from formal legal textbooks, the standard of care is not necessarily derived from some well-known textbook. It is also not articulated by any judge. The standard of care is defined by some, as whatever an expert witness says it is, and what a jury will believe.

In a case against any dermatologic surgeon whose patient has bled, the specialist must have the knowledge and skill ordinarily possessed by a specialist in that field, and must have used the care and skill ordinarily possessed by a specialist in that field in the same or similar locality under similar circumstances.

A failure to fulfill such a duty may lead to loss of a lawsuit by the dermatologist. If the jury accepts the suggestion that the dermatologist, by virtue of not asking about medicine intake, mismanaged the case and that the negligence led to damage of the patient, then liability will ensue.

The dermatologist is expected to perform cutaneous surgery in a manner of a reasonable physician. He need not be the best in his field. It is important to note that where there are two or more recognized methods of dealing with the same condition, a physician does not fall below the standard of care by using any acceptable method — even if one turns out to be less effective or more dangerous than another method.

Finally, in many jurisdictions, an unfavorable result due to an “error in judgment” by a physician is not in and of itself a violation of the standard of care if the physician acted appropriately prior to exercising his professional judgment.

In this situation, some experts may testify that patients should be taken off anti-coagulants; other experts will testify that one must look at the risk benefit ratio of stopping such treatment. The bigger question here is whether Dr. Surgery breached the standard of care by not ever asking about his patient’s medicine intake. A jury may determine that Dr. Surgery was negligent in not asking the question.

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

Dr. Goldberg is director of Skin Laser and Surgery Specialists of New York and New Jersey, past director of Mohs and Laser Research, Icahn School of Medicine at Mt. Sinai; and, adjunct professor of law, Fordham Law School in New York City.
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These were all very significant gaps early on in my career where I felt truly short-handed as a dermatologist ... I felt committed to narrow these gaps.

Dr. Andrew F Alexis, Mount Sinai St. Luke’s and Mount Sinai West, New York
handed as a dermatologist caring for these patients,” he says.

There were gaps in the literature in the early 2000s. Dr. Alexis says he quickly realized there were few published studies for understanding the pathogenesis or studying any treatments for many conditions that disproportionately affect patients with skin of color.

Still another gap: education, he says. Clinical images of patients with darker skin types were underrepresented in textbooks, which meant common dermatologic conditions impacting skin of color patients were few and far between.

“Early in my career, I felt committed to narrow these gaps,” he says.

The Skin of Color Center established in 1999 by Drs. Susan Taylor and Vincent Deleo gave Dr. Alexis and others a platform for making change, he says.

Driving innovation
The changes in the last 15 years have been remarkable, Dr. Alexis says.

“We’ve seen a very significant increase in the number of published studies that include patients with skin of color,” Dr. Alexis says.

That includes studies that address dermatologic disorders that are common throughout the population independent of one’s skin color or racial-ethnic background, as well as studies to better understand and improve treatment of conditions that are more prevalent in patients of color.

“As an example, we’ve seen more studies on products and treatments for hyperpigmentation, which is something that clearly disproportionately affects patients with skin of color,” he says.

On the educational front there has been tremendous growth in the number of educational resources available to help educate the dermatologic community and community at large about disorders that are prevalent in skin of color.

“Specifically, we see increased representation at multiple continuing medical education meetings, including the American Academy of Dermatology Annual Meeting. There’s lots of content that’s pertinent to skin of color. And there are more stand-alone meetings that focus just on disorders prevalent in skin of color, such as the Skin of Color Update annual meeting that I cochair with Eliot Battle, M.D.,” Dr. Alexis says.

In the literature, there has been a spike in the number of review articles in peer review journals that focus on dermatologic disorders that are prevalent in skin of color and their management, as well as nuances to managing disorders in skin of color.

Same goes for textbooks, according to Dr. Alexis. There is much better representation of diverse skin types in the images in major reference books in dermatology that are used by the majority of residents and other trainees. And there are even textbooks that have focused specifically on dermatologic disorders in skin of color.

Dr. Alexis says that it’s particularly satisfying to witness increases in the number of trainees who early in their careers as dermatologists have developed a special interest in treating disorders of skin of color.

“I think the last area, which is particularly rewarding and helpful to patients, is that we’re seeing therapeutic advances for many of the prevalent conditions for patients of skin of color, such as melasma, as well as common disorders that can affect all patients that have nuances in skin of color, such as acne, atopic dermatitis and psoriasis, not to mention conditions that are specific to skin of color, such as pseudofolliculitis barbae, acne keloidalis nuchae,” he says.

“We’ve seen remarkable advances in the ability to use lasers and energy-based devices across the broad spectrum of patients with skin of color in ways that were unprecedented.”

Dr. Alexis says that today he is able to offer patients with skin of color positive outcomes.

“We’re making major gains in managing hyperpigmentation. We’re catching scarring alopecia, such as central centrifugal cicatricial alopecia (CCCA), earlier and are able to change its course through various therapies. We’re using lasers and devices to tackle previously very tough problems, such as acne scarring and pigmented disorders, and to really push the envelope and get better results using these devices. And we’re using laser hair removal for pseudofolliculitis barbae or ingrown hair,” he says. “It’s really transformative being able to do these things safely and reproducibly.”

But the work to advance skin of color dermatologic care is ongoing, and Dr. Alexis who today chairs the department of dermatology and directs the Skin of Color Center at Mount Sinai St. Luke’s and Mount Sinai West in New York City, says he plans to expand his involvement in training the next generation of leaders who will advance the field of dermatology, especially for the conditions that disproportionately affect skin of color.

“This is something that I experienced first-hand early in my career, which really was the spark that led me to focus on this area.”
“We now have a greater understanding of how ... MBTs can diminish some of the effects of the stress response.”

Mind-body therapies effective for skin disorders

by CAROL SOUTOR, M.D.

Dermatologists routinely see patients with stress-induced skin problems such as a child with a flare of atopic dermatitis on the first day of school, a teenager with an acne flare before final exams, an adult who develops urticaria before public speaking or the patient who cannot stop scratching and picking at their skin. We also see patients with significant anxiety and depression related to their chronic skin conditions.

Usually, we do not routinely recommend psychotropic medications or suggest psychotherapy for all patients with stress-related cutaneous disorders, and many patients do not follow through with these recommendations even when they are made.¹

Mind-body therapies (MBTs) offer a comprehensive approach to these problems, which may be as effective and safer than other management options. Mind-body therapies include treatments administered by practitioners and self-directed practices that patients do on their own. Examples of MBTs used to treat skin conditions include meditation, mindfulness, breathing techniques, hypnotherapy, acupuncture, yoga and tai chi.²

With recent advances in psychoneuroimmunology, we now have a greater understanding of how both acute and chronic stress can affect the skin and how MBTs can diminish some of the effects of the stress response. The effects of stress on the skin are primarily mediated by the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal medullary axis. Stress can trigger inflammation, dysregulate immune function, impair the skin’s barrier function, slow wound healing and alter blood flow to the skin.³

Mind-body therapies can mitigate many of these deleterious effects on the skin. The mechanisms by which they do this are complex and have not yet been fully investigated. However, it has been established that MBTs activate the parasympathetic nervous system and downregulate the sympathetic nervous system, which, in turn, can mitigate some aspects of the stress response. In addition, MBTs beneficially affect the areas of the brain that deal with emotional regulation and psychological response to stressors.⁴

Many MBTs have been standardized and have evidence for efficacy in a wide range of physical and mental disorders, especially depression and anxiety. They have been reported to be beneficial in many cutaneous disorders, including psoriasis, atopic dermatitis, ichthyosis, acanthosis nigricans, rosacea, herpes simplex, postherpetic neuralgia, verruca vulgaris, alopecia areata, trichotillomania, urticaria, pruritus, prurigo nodularis and hyperhidrosis.⁵

Mind-body therapies are also increasingly recommended by oncology colleagues for their patients who are frequently utilizing mind-body practitioners and may be a source for advice on referrals. Insurance coverage varies depending on location and patient’s specific policy. Self-directed therapies such as mindfulness and meditation are of no cost and many of the other therapies are relatively low cost compared to the alternatives. A recent study showed that people who use certain MBTs lowered their total health care utilization costs by 43%.⁶

In summary, many of our patients are already using MBTs for various reasons and many others would benefit from their use. Dermatologists should consider recommending MBTs as part of an integrative approach to managing skin disorders. ▶

References

Mind-body therapies are also increasingly popular with the general public. A survey of 2,055 adults showed that 18.9% had used at least one MBT in the previous year and at least one MBT in the previous year and 40-50% reported that these therapies were “very helpful for their condition.” Many people view MBTs as being central to their overall well-being and do not reserve their use just for times of illnesses.

Most clinic and hospital health care systems offer MBTs. Our oncology colleagues frequently utilize mind-body practitioners and may be a source for advice on referrals. Insurance coverage varies depending on location and patient’s specific policy. Self-directed therapies such as mindfulness and meditation are of no cost and many of the other therapies are relatively low cost compared to the alternatives. A recent study showed that people who use certain MBTs lowered their total health care utilization costs by 43%.⁶

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IMPORTANT SAFETY INFORMATION

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Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on the following pages of this publication.
Brief Summary of Prescribing Information for ODOMZO® (sonidegib) capsules

This Brief Summary does not include all the information needed to use ODOMZO safely and effectively.

See full Prescribing Information for ODOMZO.

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- Advise males of the potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with ODOMZO and for at least 8 months after the last dose.

Blood Donations: Advise patients not to donate blood or blood products during treatment with ODOMZO and for at least 20 months after the last dose.

Musculoskeletal Adverse Reactions: Obtain serum creatine kinase (CK) and creatinine levels prior to initiating therapy, periodically during treatment, and as clinically indicated. Temporary dose interruption or discontinuation of ODOMZO may be required based on the severity of musculoskeletal adverse reactions.

Premature Fusion of the Epiphyses: Has been reported in pediatric patients exposed to ODOMZO and other Hh pathway inhibitors. ODOMZO is not indicated for use in pediatric patients.

DOSAGE AND ADMINISTRATION

Recommended dosage: 200 mg taken orally once daily on an empty stomach, at least 1 hour before or 2 hours after a meal.

ADVERSE REACTIONS

The most common adverse reactions occurring in ≥10% of patients are muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus.

DRUG INTERACTIONS

CYP3A Inhibitors: Avoid strong CYP3A inhibitors. Avoid long-term (greater than 14 days) use of moderate CYP3A inhibitors.

CYP3A Inducers: Avoid strong and moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

EMBRYO-FETAL TOXICITY: See boxed warning. ODOMZO can cause fetal harm when administered to a pregnant woman.

Report pregnancies to Sun Pharmaceutical Industries, Inc. at 1-800-406-7984.

LACTATION

Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with ODOMZO and for 20 months after the last dose.

PEDIATRIC USE

The safety and effectiveness of ODOMZO have not been established in pediatric patients.

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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PLR-00105
For patients with locally advanced basal cell carcinoma (laBCC) who are not a candidate for surgery or radiation.

ODOMZO (sonidegib), is the latest FDA-approved hedgehog pathway inhibitor indicated for the treatment of adult patients with laBCC that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.

**IMPORTANT SAFETY INFORMATION (continued)**

**Embryo-fetal Toxicity:** ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. **Females of Reproductive Potential:** Verify pregnancy status prior to initiating ODOMZO. Advise females to use effective contraception and not to breastfeed, due to the potential for serious adverse reactions in breastfed infants, during treatment and for at least 20 months after the last dose. Report pregnancies to Sun Pharmaceutical Industries, Inc. at 1-800-406-7984.

**Males:** Advise males to use condoms, even after a vasectomy, and to not donate semen during treatment and for at least 8 months after the last dose to avoid potential drug exposure in pregnant females or females of reproductive potential.

**Blood Donation:** Advise patients not to donate blood or blood products while taking ODOMZO, and for at least 20 months after the last dose because their blood or blood products might be given to a female of reproductive potential.

**Musculoskeletal Adverse Reactions:** Musculoskeletal adverse reactions, which may be accompanied by serum creatine kinase (CK) elevations, occur with ODOMZO and other drugs which inhibit the hedgehog (Hh) pathway. Obtain serum CK and creatinine levels prior to initiating therapy, periodically during treatment, and as clinically indicated. Temporary dose interruption or discontinuation of ODOMZO may be required based on the severity of musculoskeletal adverse reactions.

**Premature Fusion of the Epiphyses:** ODOMZO is not indicated for use in pediatric patients. Premature fusion of the epiphyses has been reported in pediatric patients exposed to ODOMZO and other Hh pathway inhibitors. In some cases, fusion progressed after discontinuation.

**Drug Interactions:** Avoid concomitant administration of ODOMZO with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, administer for less than 14 days and monitor closely for adverse reactions, particularly musculoskeletal. Avoid concomitant administration of ODOMZO with strong and moderate CYP3A inducers.

**Geriatric Use:** There was a higher incidence of serious adverse events, Grade 3 and 4, and events requiring dose interruption or discontinuation in patients ≥65 years compared with younger patients; this was not attributable to an increase in any specific adverse event.

**Most Common Adverse Reactions:** The most common adverse reactions occurring in ≥10% of patients were muscle spasms (54%), alopecia (53%), dysgeusia (46%), fatigue (41%), nausea (39%), musculoskeletal pain (32%), diarrhea (32%), decreased weight (30%), decreased appetite (23%), myalgia (19%), abdominal pain (18%), headache (15%), pain (14%), vomiting (11%), and pruritus (10%).

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on previous pages of this publication.

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A recent study demonstrated that a clever combination of topical botanicals were effective for improving mild-to-moderate symptoms of atopic dermatitis (AD) in children.1 Topical preparations containing natural agents are needed in the treatment of AD and many other chronic inflammatory dermatoses, according to Leon H. Kircik, M.D., Icahn School of Medicine at Mount Sinai, New York, and co-author of the study.

“Botanicals are not new and have been used for thousands of years in traditional Chinese and Indian medicine,” he says. “However, what’s new is that the botanicals are now being evaluated in a more scientific fashion.”

Dr. Kircik and fellow colleagues conducted a multicenter randomized, blinded study to determine the efficacy of a novel botanical combination in the Kamedis Eczema Therapy Cream (Kamedis, Inc.) (the test product) for children and adults with mild-to-moderate symptoms of AD. The one-month-long clinical study included a subpopulation of children who were randomly divided into three treatment groups: test product, vehicle or comparator. A total of 39 children (female: n=24; male: n=15; age range 3 to 18 years) with uncomplicated, stable, mild-to-moderate AD were included. The vehicle used was the identical test product without the botanical combination, while the comparator was a leading over-the-counter brand moisturizer in the U.S. market. All three treatment groups used the same Kamedis body wash followed by one of three randomized treatment creams for the affected areas. Multiple parameters were assessed including improvements in pruritus, as well as the Investigator Global Assessment (IGA), extent of affected Body Surface Area (BSA), as well as SCORAD and EASI indexes.

Compared with vehicle, the test product achieved superior outcomes in all evaluated clinical parameters. Forty percent of subjects achieved 0 (clear) on IGA scale and 60% achieved 0 or 1  (clear or almost clear) compared with 8% or 38% of vehicle subjects, respectively. The BSA comparative outcomes and the SCORAD and EASI indexes also demonstrated the test product’s advantage over the vehicle.

In mild-to-moderate cases of AD, treatment is focused on reducing exposure to triggers with simultaneous topical application of emollients and steroid-free barrier creams, as well as topical corticosteroids. More severe cases are treated with systemic corticosteroids, immunosuppressive agents such as methotrexate, cyclosporine or azathioprine and, recently, with novel biologics. According to Dr. Kircik, the side effects are one of the limiting factors for using systemic agents long-term, particularly in young children.

Though topical therapies are effective and readily used for chronic dermatoses, these would be better reserved to quell the flares, he says. “Topical botanicals could be used as an adjunctive therapy to help reach and maintain disease clearance,” says Dr. Kircik.

Kamedis Eczema Therapy Cream is a non-steroidal homeopathic emulsion containing a special formulation of six botanicals known to have significant anti-inflammatory and potential antimicrobial effects.

A complimentary full skincare regimen is recommended for treating AD, Dr. Kircik says, as well as to maintain the remission results achieved.

“Topical botanicals could be used as an adjunctive therapy to help reach and maintain disease clearance.”

Leon H. Kircik, M.D. Icahn School of Medicine Mount Sinai, New York

Disclosures
Dr. Kircik is an advisor, consultant, and an investigator for Kamedis, Inc.

References
Tape strips appear effective as a non-invasive way to sample skin to determine disease severity, pruritis, and transepidermal water loss in pediatric patients with early onset atopic dermatitis (AD), according to a study published in *JAMA Dermatology*.

The strips may offer researchers an alternative to performing biopsies in kids enrolled in clinical trials and for longitudinal studies, according to the paper.

“In atopic dermatitis and in other skin diseases, biomarkers are important to understand the inflammatory and barrier phenotype of the disease. They’re important to frame how to treat these diseases and to understand what types of treatments may work and what molecules we should target in these diseases,” says the study’s lead author Emma Guttman-Yassky, M.D., Ph.D., professor of dermatology and immunology and vice chair of dermatology at the Icahn School of Medicine. “Up until recently, we couldn’t do biomarkers in children because it’s so difficult to obtain skin and blood in children.”

Researchers have used tape strips to identify AD biomarkers in adults with AD, but this method has not yet been applied to infants and young children. In fact, the authors write that researchers don’t currently have an available reproducible, minimally invasive way to track cutaneous disease in pediatric longitudinal studies or clinical trials. And most tape strip studies detected only a limited number of samples, which is not compatible with longitudinal studies or clinical trials, according to Dr. Guttman-Yassky.

**THE STUDY**

Dr. Guttman-Yassky and colleagues studied 51 children >5 years with and without recently diagnosed moderate-to-severe AD. They collected tape strips from nonlesional and lesional skin of those with the skin disease, as well as from the skin of unaffected children.

The tape strips take a small amount of the stratum corneum without leaving a scar. Researchers found the tape strips left mild redness that lasted only minutes, Dr. Guttman-Yassky says.

The researchers analyzed samples for RNA and found a very similar phenotype to what has been previously identified from skin biopsies in children, she says.

Specifically, they found the tape strips detected 77 of 79 immune and barrier gene products evaluated, with a 97% gene detection rate and 99% sample detection rate.

Only one sample in the study was not evaluable in comparison with much lower detection rates by other recently published studies in adults or older children, according to Dr. Guttman-Yassky. Fifty-three of the 79 markers were able to differentiate lesional and nonlesional skin in children with AD from healthy skin from healthy children.

“Many cellular markers of T cells (CD3), [AD]-related dendritic cells (Fc epsilon RI and OX-40 ligand receptors), and key inflammatory (matrix metalloproteinase 12), innate (interleukin 8 [IL-8] and IL-6), helper T cell 2 (TH2; IL-4, IL-13, and chemokines CCL17 and CCL26), and TH17/TH22 (IL-19, IL-36G, and S100A proteins) genes were significantly increased in lesional and nonlesional [AD] compared with tape strips from healthy normal skin,” according to the study.

The tape strips are better for tracking pediatric dermatitis than blood samples, according to Dr. Guttman-Yassky.

“In children we really need biomarkers of skin, and this is the only way to obtain such biomarkers,” she says.

The authors conclude that the tape strips could be useful for tracking pediatric dermatitis’ response to treatments and for predicting the disease’s future course and comorbidities.

“Eczema is not a disease where one size fits all,” she says. There are different subtypes of atopic dermatitis.

“In the future, I think we’ll need personalized medicine in atopic dermatitis patients. Tape strips can be valuable for such a personalized medicine approach,” she says.

Dermatologists and other specialists could, one day, use tape strips in clinical practice to help define skin diseases of all kinds, according to Dr. Guttman-Yassky.

For the purpose of her research, Dr. Guttman-Yassky used CUDERM tape strips, but says the expertise lies in the process because it is not easy to obtain the amount of RNA needed for reliable biomarkers from tape strips.

“Right now this is done in my lab, but in the future it may be possible to expand it,” she says.

**References**


**Disclosures**

Northwestern University Skin Disease Research Center and Regeneron Sanofi funded the study. Dr. Guttman-Yassky has received other research grants from AbbVie, Asano/Biologics, Celgene, Dermset, OSI Pharmaceuticals, Lilly, GlaxoSmithKline, Genentech/Pharmaceuticals, Innoderm Research, Janssen Biotech, Kyowa Kirin, Leap Pharma, Novus, Novartis, Pﬁ zer, Ralexar Therapeutics, Regeneron, Sanofi, and UNION Therapeutics. She has received personal fees from AbbVie, Allegan, Amgen, Asano/Biologics, Celgene, Cancer Pharmaceuticals, CRB Technologies, Dermset, OSI Pharmaceuticals, Lilly, ENO Sinos, Escelle, RAPT Therapeutics, GlaxoSmithKline, GlaxoSmithKline, Kyowa Kirin, Leap Pharma, Mitsubishi Tanabe, Novartis, Pﬁ zer, Regeneron, Sanofi, and UNION Therapeutics.

**Quick Takes**

Researchers found cellular markers were significantly increased in lesional and nonlesional atopic dermatitis compared with tape strips from healthy normal skin. Method could be useful for tracking treatment response, predicting disease course and comorbidities. Tape strips take a small amount of the stratum corneum without leaving a scar.
INTRODUCING SEYSARA, A NOVEL ORAL TETRACYCLINE DEVELOPED SPECIFICALLY FOR MODERATE TO SEVERE ACNE PATIENTS AS YOUNG AS 9.

For more information, visit SEYSARA.com

**INDICATIONS AND USAGE**
SEYSARA (sarecycline) tablet, is indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.

Limitations of Use: Efficacy of SEYSARA beyond 12 weeks and safety beyond 12 months have not been established. SEYSARA has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, SEYSARA should be used only as indicated.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**
SEYSARA is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

**WARNINGS AND PRECAUTIONS**

- **Central nervous system side effects,** including headache, blurred vision and papilledema. Although such as visual loss that may be permanent or severe exists.
- **Intracranial hypertension** has been associated with the use of tetracyclines. Clinical manifestations include headache, blurred vision and papilledema. Although signs and symptoms of intracranial hypertension resolve after discontinuation of treatment, the possibility for sequelae include headache, blurred vision and papilledema. Although central nervous system side effects, including headache, blurred vision and papilledema, although such as visual loss that may be permanent or severe exists.
- **Photosensitivity reaction** has been observed in some individuals taking tetracycline use. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery. These symptoms may disappear during therapy and may disappear when the drug is discontinued.
- **Superinfection** including fungi. If Clostridium difficile associated diarrhea (CDAD) occurs, SEYSARA should be discontinued and appropriate therapy instituted.
- **Bacterial resistance** to tetracyclines may develop in patients while using SEYSARA. Because of the potential for drug-resistant bacteria to develop during the use of SEYSARA, it should only be used as indicated.

**LIMITATIONS OF USE**

- As with other antibiotic preparations, use of SEYSARA may result in overgrowth of non-susceptible organisms, superinfection including fungi. If Clostridium difficile associated diarrhea (CDAD) occurs, SEYSARA should be discontinued and appropriate therapy instituted.
- **As with other antibiotic preparations, use of SEYSARA may result in overgrowth of non-susceptible organisms, superinfection including fungi. If Clostridium difficile associated diarrhea (CDAD) occurs, SEYSARA should be discontinued and appropriate therapy instituted.**

**STUDY DESIGN:** The safety and efficacy of SEYSARA was assessed in two identically designed, 12-week, multicenter, randomized, double-blind, placebo-controlled trials. In both studies, SEYSARA was administered orally once-daily for 12 weeks as 60 mg, 100 mg, or 150 mg tablets, based on patient weight.

**STUDY RESULTS:** Mean absolute reduction (co-primary endpoint) was 15.3 in study 1 (SC1401) and 15.5 in study 2 (SC1402) vs 10.2 and 11.1 in the placebo groups at Week 12, respectively. 21.9% of ITT patients in study 1 and 22.6% of ITT patients in study 2 achieved IGA success (co-primary endpoint; defined as ≥2-point improvement from baseline in IGA scale for inflammatory lesions of acne, and a score of 0 [clear] or 1 [almost clear]) at Week 12 vs 10.5% and 15.3% of patients with placebo, respectively (p<.0001 for study 1 and p=.0038 for study 2).

**INDICATORS OF FULL PRESCRIBING INFORMATION**

Most common adverse reaction (incidence ≥ 1%) is nausea.

**ADVERSE REACTIONS**

- **Gastrointestinal reactions:** Nausea, vomiting, diarrhea, abdominal pain, constipation
- **Hypersensitivity reactions:** Urticaria, urticarial rash, pruritus
- **Seizure activity** has been reported with nearly all antibacterial agents, and may range in severity from mild diarrhea to fatal colitis. If *Clostridium difficile* Associated Diarrhea (antibiotic associated colitis) occurs, discontinue SEYSARA.
WHAT DO I SAY TO PATIENTS FRUSTRATED WITH ACNE?

SEYSARA®

TOUGH ON ACNE.

- Significant inflammatory lesion count reduction at Week 12, and as early as Week 3

EASY ON PATIENTS.

- Convenient once-daily dosing, with 3 weight-based strengths; with or without food

With a demonstrated safety profile

• Central nervous system side effects, including light-headedness, dizziness or vertigo, have been reported with tetracycline use. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery. These symptoms may disappear during therapy and may disappear when the drug is discontinued.

• Intracranial hypertension in adults and adolescents has been associated with the use of tetracyclines. Clinical manifestations include headache, blurred vision and papilledema. Although signs and symptoms of intracranial hypertension resolve after discontinuation of treatment, the possibility for sequelae such as visual loss that may be permanent or severe exists. Concomitant use of isotretinoin and SEYSARA should be avoided because isotretinoin, a systemic retinoid, is also known to cause intracranial hypertension.

• Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using SEYSARA.

• Bacterial resistance to tetracyclines may develop in patients using SEYSARA. Because of the potential for drug-resistant bacteria to develop during the use of SEYSARA, it should only be used as indicated.

• As with other antibiotic preparations, use of SEYSARA may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, SEYSARA should be discontinued and appropriate therapy instituted.

ADVERSE REACTIONS

Most common adverse reaction (incidence ≥1%) is nausea.

PLEASE TURN THE PAGE FOR BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION.

IGA, investigator’s global assessment; reflects the investigator’s overall general assessment of the quantity and quality of inflammatory lesions (range 0-4 with 0 being clear and 4 being severe).

ITT, intent-to-treat.

Reference:

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USSEY0311a 05-2019
BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION FOR SEYSARA® (sarecycline)

This brief summary does not include all the information necessary to use SEYSARA safely and effectively. See full Prescribing Information for SEYSARA (sarecycline) tablets for oral use.

INDICATIONS AND USAGE
SEYSARA® (sarecycline) tablet, is indicated for the treatment of inflammatory lesions of non-nodular acne vulgaris in patients 9 years of age and older.

Limitations of Use: Efficacy of SEYSARA beyond 12 weeks and safety beyond 12 months have not been established. SEYSARA has not been evaluated in the treatment of infections.

To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, SEYSARA should be used only as indicated [see Warnings and Precautions].

CONTRAINDICATIONS
SEYSARA is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS AND PRECAUTIONS
Teratogenic Effects
• SEYSARA, like other tetracyclines, can cause fetal harm when administered to a pregnant woman. If SEYSARA is used during pregnancy or if the patient becomes pregnant while taking SEYSARA, the patient should be informed of the potential hazard to the fetus and treatment should be stopped immediately.

• The use of drugs of the tetracycline-class during tooth development (second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of these drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported.

• All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fetal growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated with SEYSARA during pregnancy in association with maternal toxicity [see Use in Specific Populations].

Clostridium difficile Associated Diarrhea (Antibiotic Associated Colitis)
Clostridium difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to potential overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to its pathogenicity. Hypertoxic producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD can be reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use is not directed against C. difficile should be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

Central Nervous System Effects
Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with tetracycline use. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery. These symptoms may disappear during therapy and may disappear when the drug is discontinued.

Intracranial Hypertension
Intracranial hypertension in adults and adolescents has been associated with the use of tetracyclines. Clinical manifestations include headache, blurred vision, and papilledema. Although signs and symptoms of intracranial hypertension resolve after discontinuation of treatment, the possibility for sequelae such as visual loss that may be permanent or severe exists. Patients of childbearing age who are overweight have a greater risk for developing intracranial hypertension.

Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines. Concomitant use of isotretinoin and SEYSARA should be avoided because isotretinoin, a systemic retinoid, is also known to cause intracranial hypertension [see Drug Interactions]. If visual disturbance occurs during treatment, patients should be checked for papilledema.

Photosensitivity
Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UV/A/B treatment) while using SEYSARA. If patients need to be outdoors while using SEYSARA, they should wear loose-fitting clothing that protect skin from sun exposure and discuss other sun protection measures with their physician.

Development of Drug Resistant Bacteria
Bacterial resistance to tetracyclines may develop in patients using SEYSARA. Because of the potential for drug-resistant bacteria to develop during the use of SEYSARA, it should only be used as indicated.

Superinfection/Potential for Microbial Overgrowth
As with other antibiotic preparations, use of SEYSARA may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, SEYSARA should be discontinued and appropriate therapy instituted.

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

A total of 1064 subjects and 1069 subjects with moderate to severe acne vulgaris were treated with SEYSARA and placebo, respectively, for 12 weeks in 3 controlled clinical trials. The only adverse drug reaction reported in at least 1% of subjects was nausea, SEYSARA 3.1% versus placebo 2.9%.

The following additional adverse drug reactions occurred in less than 1% of female SEYSARA subjects: vulvovaginal mycotic infection (0.8%) and vulvovaginal candidiasis (0.6%).

DRUG INTERACTIONS
Effect of Other Drugs on SEYSARA
Oral Retinoids: Tetracyclines may cause increased intracranial pressure as do oral retinoids, including isotretinoin and acitretin [see Warnings and Precautions]. Avoid coadministration of SEYSARA with oral retinoids.

Antacids and Iron Preparations: Coadministration with antacids containing aluminum, calcium or magnesium, bismuth subsalicylate, and iron-containing preparations may impair absorption of SEYSARA, similar to other tetracyclines, which may decrease its efficacy. Separate dosing of SEYSARA and these medications containing aluminum, calcium or magnesium, bismuth subsalicylate, and iron-containing preparations.

Effect of SEYSARA on Other Drugs
Penicillin: Similar to other tetracyclines, SEYSARA may interfere with the bactericidal action of penicillin. Avoid coadministration with penicillin.

Anticoagulants: Similar to other tetracyclines, SEYSARA may depress plasma prothrombin activity, which may increase the risk of bleeding in patients who are on anticoagulant therapy. Decrease anticoagulant dosage when coadministered with SEYSARA as appropriate.

P-Glycoprotein (P-gp) Substrates: Concomitant use of SEYSARA may increase concentrations of concomitantly administered P-gp substrates (e.g. digoxin). Monitor for toxicities of drugs that are P-gp substrates. May require dosage reduction when given concurrently with SEYSARA.

Oral Hormonal Contraceptives: There is no clinically significant effect of SEYSARA on the efficacy of oral contraceptives containing ethinyl estradiol and norethindrone acetate.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary: SEYSARA, like tetracycline-class drugs, may cause fetal harm, permanent discoloration of teeth, and reversible inhibition of bone growth when administered during pregnancy [see Warnings and Precautions and Use in Specific Populations]. The limited available human data are not sufficient to inform a drug-associated risk for birth defects or miscarriage. Tetracyclines are known to cross the placental barrier; therefore, SEYSARA may be transmitted from the mother to the developing fetus. In animal reproduction studies, sarecycline induced decreased fetal body weight in fetuses when orally administered to pregnant rats during the period of organogenesis at a dose 1.4 times the maximum recommended human dose (MRHD) of 150 mg/day (based on AUC comparison). When dosing with sarecycline continued through the period of lactation, decreases in offspring survival, offspring body weight, and implantation sites and viable embryos in offspring females occurred at a dose 3 times the MRHD (based on AUC comparison). The potential risk to the fetus outweighs the potential benefit to the mother from SEYSARA use during pregnancy; therefore, pregnant patients should discontinue SEYSARA as soon as pregnancy is recognized.

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

Lactation
Risk Summary: Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions on bone and tooth development in nursing infants from tetracycline-class antibiotics, advise a woman that breastfeeding is not recommended with SEYSARA therapy [see Warnings and Precautions].

Females and Males of Reproductive Potential
Infertility: Avoid using SEYSARA in males who are attempting to conceive a child. In a fertility study in rats, sarecycline adversely affected spermatogenesis when orally administered to male rats at a dose 8 times the MRHD (based on AUC comparison).

Pediatric Use
The safety and effectiveness of SEYSARA have been established in pediatric patients 9 years of age and older for the treatment of moderate to severe inflammatory lesions of non-nodular acne vulgaris. Safety and effectiveness of SEYSARA in pediatric patients below the age of 9 years has not been established. Use of tetracycline-class antibiotics below the age of 8 is not recommended due to the potential for tooth discoloration [see Warnings and Precautions].

Geriatric Use
Clinical studies of SEYSARA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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Northwestern University Feinberg School of Medicine Department of Dermatology researchers are starting a phase 2 proof-of-principle study using the patch on adult atopic dermatitis patients to track inflammatory biomarkers on different skin locations.

Northwestern dermatologists completed a study in 2019 testing the clinical utility of the Discovery platform showing the wearable technology quantified target cytokine concentrations in sweat in different skin locations.

Steve Xu, M.D., assistant professor of Dermatology at Northwestern and an advisor to Epicore, says sweat is the next frontier for biomarker discovery — one that will open new avenues for early intervention and precision therapy.

“Epicore is an exciting company because it’s really leveraging wearable devices for a biofluid that we’ve long ignored. Sweat offers a rich source of information that Epicore can collect noninvasively,” Dr. Xu says.

Research on the technology is an opportunity to see how sweat might serve as an indicator of disease severity.

“You’ll be able to measure biomarkers that could predict when a flare is coming on before it’s evident. It could also indicate how individual people respond to certain medications. There’s a lot of opportunity to explore sweat as a potential tool to manage and treat atopic dermatitis better,” he says.

The Discovery patch is in the research and development phase but could soon come to market.

“We have been working on some of these research projects in collaboration with Epicore and Leo Pharma. They’re using these patches and applying them on atopic dermatitis patients as well as healthy normal people and collecting sweat directly from these subjects. At this point, we’re still identifying and validating these signatures. But once we do that, I think it’s a relatively rapid path to clinical deployment,” he says.

Once on the market, the Discovery patch would offer a noninvasive technology that’s easy to apply and painless.

“What’s particularly exciting about this effort is the opportunity to map inflammation biomarkers around atopic dermatitis lesions locally and across the entire body from individual wearers. This foundational insight about local and global biochemical signals will inform new classes of wearable devices for tracking skin conditions continuously outside of clinical settings,” says A.J. Aranyosi, Ph.D., chief scientific officer and co-founder of Epicore Biosystems.

In the real world, Dr. Xu envisions that this wearable microfluidic device platform will be something patients and doctors use collaboratively, as well as a consumer health monitoring technology.

“Right now, we’re completely reactive. We wait for bad things to happen and we try to catch up. I think the opportunity here is to be able to get in front of the condition — in front of the disease — using biomarkers in sweat. And then hopefully reducing the pain and suffering that’s caused by this condition,” he says.

This isn’t the first wearable device that Dr. Xu has researched or helped to develop. He was among the developers of a UV sensor that tells wearers how much UV they’re getting. That technology is available at Apple stores worldwide through L’Oréal.

“It’s the world’s first battery-free sun powered sensor for UV. It helps people stay safe in the sun,” says Dr. Xu. “That product is one example of a wearable that certainly has permeated dermatology.”

L’Oréal and Epicore Biosystems introduced My Skin Track pH earlier in 2019. My Skin Track pH combines Epicore Biosystems’ wearable microfluidic sensor technology with L’Oréal’s expertise in skin care. It measures personal skin pH levels and creates customized skin care regimens and product recommendations.

“That’s pretty exciting and that has relevance obviously to patients with atopic dermatitis because it is a good marker of skin barrier function,” says Dr. Xu. “New technologies are coming online and measuring useful things. They’re affordable and applicable to a wide variety of skin conditions.”

Epicore Biosystems' wearable Discovery patch

Credit: Jeffrey Model, Roozbeh Ghaffari, Epicore Biosystems

Dr. Aranyosi

Dr. Xu

Quick TAKES

2019 study examined clinical utility of the Discovery platform.

Patch will measure inflammatory biomarkers in sweat that could predict a flare.

Researchers are starting a phase 2 proof-of-principle study.

FROM PAGE 1

Weearable device aims to predict skin health
IL-17 as a potential target for pustular psoriasis

CHERYL KRADER, B.S. PHARM | Staff Correspondent

Findings from published reports demonstrate a therapeutic benefit of interleukin (IL)-17/T-helper 17 (Th17) axis inhibitors in patients with generalized pustular psoriasis (GPP). Establishing a role of these biologic agents in the management of GPP, however, will require additional research to assess their efficacy and safety, according to Plachouri et al., who undertook a systematic review of the available evidence on this topic.

In their report, the investigators stated that other conventional systemic therapies (i.e., retinoids, cyclosporine and methotrexate) and other biologics (i.e., tumor necrosis factor inhibitors and IL-12/23 inhibitors) have been associated with variable results when used to treat GPP.

They noted the pathogenesis of GPP is not fully understood, but mutations in the IL36RN gene that encodes the IL-36 receptor antagonist protein and in CARD14 (caspase recruitment domain-containing protein) are thought to be associated.

Interest in IL-17 inhibition relates to reports that serum and mRNA levels of IL-17 are significantly higher in patients with pustular psoriasis than in patients with nonpustular disease.

WHAT’S IN THE LITERATURE?

To examine the evidence for IL-17 blockade as a treatment for GPP, the authors performed a review following recommendations of the Preferred Reporting Items for Systemic Reviews. They searched the Embase, MEDLINE (PubMed) and Scopus databases for English language articles published between 2012 and 2019 to identify papers relating to GPP and the use of secukinumab (Cosentyx, Novartis), ixekizumab (Taltz, Eli Lilly) and brodalumab (Siliq, Valeant Pharmaceuticals). The search identified 88 articles; 38 fit the inclusion criteria for review, and the authors summarized their findings.

Secukinumab was evaluated in a Japanese open-label phase 3 study enrolling 12 adult patients, of which only three received secukinumab as monotherapy. Treatment with secukinumab was associated with early benefit, significant improvement at the week 16 endpoint, durable responses through week 52 and no unexpected adverse events.

Other articles describing secukinumab included one case series composed of six patients, eight reports of single adult cases, and four case reports describing pediatric patients. Overall, these reports showed rapid remission of GPP with the use of secukinumab, and authors of the case series noted that it could be an effective therapeutic option independent of IL36RN mutation status.

Ixekizumab was evaluated in two Japanese open-label, phase 3 trials, each including five adult patients. Follow-up duration was 24 weeks in one trial and extended to over three years in the other study. In both cohorts, ixekizumab was well-tolerated and associated with early benefit that was sustained in most patients. Three other published reports were identified that also described rapid improvement of GPP in single patients treated with ixekizumab.

Only a single paper was identified that described brodalumab treatment for patients with GPP. The article reported on a Japanese open-label, phase 3 study that included 12 adults. Significant improvement or remission was obtained in 83.3% of patients at week 12 and in 91.7% of patients at week 52.

Plachouri et al. also identified a single case report of a patient deemed to have possible secukinumab-induced paradoxical pustular psoriasis. Two papers were found that described a total of 22 patients who developed pustular disease after discontinuing brodalumab treatment for plaque psoriasis. Authors of one paper postulated that abrupt withdrawal of TH17/IL-17 axis suppression could be the underlying mechanism.

They further noted that, compared with secukinumab and ixekizumab, development of pustular lesions may be more likely after discontinuing brodalumab because it has a broader spectrum of action for suppressing the TH17/IL-17 pathway. They explained that whereas secukinumab and ixekizumab target the IL-17A ligand, brodalumab targets the IL-17 receptor A and blocks the action of multiple members of the IL-17 family, including IL-17A, F, E, C, and A/F.

References
Researchers recently undertook an epidemiologic study to investigate the prevalence of palmoplantar pustulosis (PPP) and co-existing plaque psoriasis.1

Palmoplantar pustulosis is characterized by recurrent sterile pustular dermatosis and erythematous plaques on the palms of the hands and soles of the feet, and often occurs alongside plaque psoriasis.2 As a result, some dermatologists actually consider the condition to be a subtype of psoriasis. This is still debated, however, due to evidence pointing towards differences between the genetic characteristics of PPP and those of plaque psoriasis.1,2,3

Although some research has connected PPP to tobacco use, cardiometabolic disease and/or autoimmune disease,4 little is known about the prevalence of palmoplantar pustulosis or patients who suffer from the condition. The authors of the study, published in the British Journal of Dermatology in February 2019, aimed to fill this gap in research by collecting data from administrative healthcare registries and databases across the United States, Denmark and Germany.

THE STUDY
Researchers pulled data for the U.S. cohort from the Truven Health MarketScan database; the Danish Nationwide Registries for the Danish cohort; and the nationwide data set from Statutory Health insurance for the German cohort.

The authors gathered information on the sex and age of participants, which were similar across the three groups. They also used the Carlsen Comorbidity Index to estimate a weighted comorbidity score between 0 and 6. Psoriatic arthritis, hypertension, diabetes, thyroid disease and inflammatory bowel disease were also identified using ICD-10 coding.

Of the total 1,435,751 patients identified through the U.S., Danish and German databases, investigators found 1,832 patients had palmoplantar pustulosis. The one-year prevalence of palmoplantar pustulosis was estimated at 0.009% in the U.S. cohort; 0.005% in the Danish cohort; and 0.08% in the German cohort. In patients with palmoplantar pustulosis, 61.3% had co-occurring plaque psoriasis across the three cohorts.

PREVALENCE, CO-OCCURRENCES
The differences in prevalence of PPP and its co-occurrence with plaque psoriasis across the three cohorts might be due to a variety of factors, according to the study authors.

“The prevalence and co-occurrence of PPP and plaque psoriasis are higher in the German cohort compared to the U.S. and Danish cohorts, which may be due to differences in diagnostic criteria and/or patient reporting,” say the researchers, led by Alexander Egeberg, M.D., Ph.D., department of dermatology and allergy, Copenhagen University Hospital Gentofte, Gentofte, Denmark. “Diagnostic challenges may therefore have caused some misclassifications of the disease.”

The authors also suggest there may be nuances in the way physicians identify and diagnose PPP across the three countries, which could explain the differences in PPP prevalence (0.005 – 0.08%). Other types of psoriasis, such as guttate psoriasis and/or nail psoriasis, were also not included in the study, which could have affected the reported disease prevalence.

Additionally, the authors note, some cases of PPP may have been recorded as psoriasis, inflating the prevalence estimate in the U.S. cohort as there is no ICD-9 code for PPP in the U.S. and ICD-10 codes were not available until October 2015.

COMORBIDITIES
Investigators found that individuals with PPP and plaque psoriasis were also more likely to experience psoriatic arthritis, researchers found.

While PPP typically presents with pustules on neutral colored skin, it may resemble psoriasis as erythematous and hyperkeratotic plaques may occur.”

Alexander Egeberg, M.D. Ph.D., Copenhagen University Hospital Gentofte, Gentofte, Denmark
A case involving a 35-year-old patient with extensive psoriasis illustrates the variety of socioeconomic factors that can create barriers for adequate healthcare. It should also remind physicians that they have a responsibility to act as patient advocates and should strive to provide patients with personalized treatment plans that can optimize outcomes given their unique circumstances. According to the physicians from the University of Missouri School of Medicine in Columbia, MO, who reported the case:

The patient had erythematous plaques with adherent hyperkeratotic silvery scales covering his scalp, face, limbs, and trunk. He reported progressive worsening of the rash and fatigue over the previous two months. The patient had a past medical history of schizoaffective disorder, limited exposure to healthcare, and was not being seen regularly by a primary care physician.

The patient developed the rash at age 21 and then was diagnosed with plaque psoriasis. Previous treatments included topical corticosteroids — triamcinolone and dexamethasone — and systemic therapies — methotrexate and cyclosporine — but they were minimally effective. Recently, the patient started treatment with apremilast (Otezla, Celgene), and he reported it was effective. However, the cost of the medication and his limited access to healthcare resulted in poor adherence.

Because of the severity and extent of the rash, the physician who saw the patient questioned whether it was plaque psoriasis. A skin biopsy was performed, and the results confirmed the diagnosis. The patient was prescribed topical triamcinolone, and the rash markedly improved.

The authors of the case report note that it represents an extreme manifestation of a common, easily treatable disease that went untreated because of multiple systemic and socioeconomic barriers. Citing the trend of rising overall costs of healthcare, they cautioned that it will become exceedingly difficult to find ways to provide patients with optimal and affordable care. The authors also pointed out that higher out-of-pocket costs for patients are another consequence of rising healthcare costs. As occurred in the reported case, medication cost can limit treatment adherence.

Medication non-adherence may be an unintended result of advocating for patients with chronic medical conditions to assume more independent disease management. Referring again to the reported case, the authors note this type of treatment paradigm is inherently flawed for some individuals and can doom them to failure.

Citing another published paper on factors underlying medication nonadherence, the authors of the case stated, “In patients with limited access to healthcare, poor healthcare literacy and other socioeconomic barriers; the social support system, the cost-effectiveness of planned interventions and the burden on the patient must all be considered when designing an efficacious treatment plan.”

References
Quick TAKES
Topical retinoid, antibiotic combined treatment helps prevent later acne scarring. Data suggest topical retinoids should be included in treatment plan early. Device-based treatment outcomes improve with increased visits, less aggressive settings.

Aggressive, early treatment prevents scarring

JOHN JESITUS | Staff Correspondent

Treating all acne early with a topical retinoid and an antibiotic can help patients avoid scarring and its psychosocial consequences, experts say. The aggressive approach also may help stave off medicolegal concerns, they add.

Medical dermatology can address subtle scars, says Hilary Baldwin, M.D., director of the Acne Treatment and Research Center in Morristown, N.J. In this regard, the OSCAR study showed that benzoyl peroxide plus adapalene improved scars approximately 30% at six months versus the untreated side in a split-face study.

“Treatment not only prevented the development of new scars, but it also eradicated some of the pre-existing scars,” Dr. Baldwin says.

Mechanistically, the retinoid adapalene is more likely than benzoyl peroxide to explain these effects. Tretinoin has shown similar effects in reducing and preventing scars. A recent study by Loss showing that treating early and effectively can stop acne and scarring, and possibly improve some pre-existing scars.

“With lasers and lights, you can go so far. But having an extra tool that can work in concert makes eminent sense,” he says.

The new research allows him to tell patients with active acne, “we’re not only going to treat your acne, but you’re also going to improve the scars, which is a big deal.”

Furthermore, says Dr. Tanghetti, patients with existing scars can afford and use adapalene gel on their own.

Even mild acne can scar. An international survey of dermatologists and health records revealed that the proportion of patients with mild acne who experienced scarring ranged from 22 to 28%. Accordingly, Dr. Baldwin says that when first seeing a patient, check carefully for early signs of scarring.

“I don’t think we look carefully enough at our patients with acne, because we don’t ‘need’ to. They walk in the door, and it takes five seconds to know how, other things being equal, you would treat that patient,” she says.

“With lasers and lights, you can go so far. But having an extra tool that can work in concert makes eminent sense,” he says.

The rest of the visit is spent ensuring that the treatment plan suits the patient.

“I suggest you haul out your magnifying glass and look carefully for any signs of scarring. That’s important for medical as well as medicolegal reasons,” Dr. Baldwin adds.

Medically, she explains, pointing out early signs of scarring to patients and parents supports one’s recommendation for aggressive therapy.
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The data suggest that we ought to be treating with topical retinoids from the very beginning in every patient with acne.”

Hilary Baldwin, M.D., Morristown, N.J.

Scarring prevention best achieved with early, aggressive treatment FROM PAGE 23

for things later on,” she says. Along with acne severity, scarring risk factors include male gender, high body mass index (BMI) and a family history of acne.

“The BMI link is not strong enough to say, ‘If you just lost some weight, your acne would improve.’ And you can’t change your family or gender. So the only thing you can do is to make sure that you’re adequately treated,” Dr. Baldwin says.

In the recent past, she says, dermatologists have begun recognizing that the longer they wait to treat acne well, the more likely patients will scar. “And this seems to be most true in the first three years of acne development,” she says.

Parents sometimes wait to treat acne until children are older because they fear giving young girls oral contraceptives, or they fear using isotretinoin altogether.

“The longer you wait, the more likely you are to create scars,” says Dr. Baldwin. However, she says, many dermatologists have not yet embraced this philosophy. Concerned about irritation, they start with other drugs and add topical retinoids later.

“The data suggest that we ought to be treating with topical retinoids from the very beginning in every patient with acne,” she says.

Tactics to reduce retinoid irritation include every-other-day application and moisturizing first.

“And then just grin and bear it. After the first two weeks, it generally doesn’t irritate anymore,” Dr. Baldwin adds.

Acne scars also can cause emotional scars, Dr. Baldwin says. When children say that peers stare or talk about their acne and scars, she says, patients and physicians often downplay these concerns.

“The tendency is to say, ‘Oh sweetie, that’s not true. Maybe they’re talking about something else,’” she notes. However, research shows that people indeed judge others with acne scars to be less attractive, confident, happy and successful.

Still, Dr. Tanghetti says that he finds quality-of-life studies difficult to put into perspective.

“I always want to do the best I can for patients. Het the patient be the judge of what to treat. Who am I to judge how acne affects someone?”

Provided the acne is under control (and the patient does not have body dysmorphic disorder), he says, mild-to-moderate scars are often highly amenable to topical and device therapy.

“We can get outstanding results with those,” he says. “The deeper, more severe scars are always going to be a bigger challenge.”

In treating moderate-to-severe scars with devices, says Dr. Tanghetti, practitioners used to swing for “home runs” using fully ablative CO, aggressive fractional CO and aggressive nonablative fractional processes.

“But we’re seeing now that patients want to preserve their activities. So rather than trying to do it in one or two treatments, we’re doing it in three to five, with less aggressive settings and less downtime, and getting modest to good results,” he says.

He avoids lasers and lights with keloids because patients usually have a combination of lesions. He typically avoids subcision and fillers until seeing how laser therapy, and possibly radiofrequency microneedling (RFMN), perform.

“There’s an incredible number of devices available for acne scars,” Dr. Tanghetti says. Rather than creating days to weeks of downtime with aggressive resurfacing, he adds, there are ways to use devices such as the SmartXide Tetra CO (DEKA), which has high-pulse, low-wattage settings that ablate the epidermis and cause minor dermal wounding.

“There’s virtually no downtime,” Dr. Tanghetti says. “We even do it without anesthesia.”

After treatment, patients can apply moisturizer and light makeup and return to work immediately.

Combining lasers with microneedling allows deeper treatments. If combining laser treatments with RFMN, Dr. Tanghetti suggests applying topical anesthetic before microneedling, followed by the laser.

Dr. Tanghetti also uses a 755 nm fractional picosecond laser in various skin types.

“We’ve found that with the less arrays that are used with picosecond technology, I can even treat very dark African-American skin and get some improvement of acne scars with relatively superficial treatment.” Epidermal injuries promote release of cytokines that cause rejuvenation and scar remodeling over time, he explains.

Based on the success of adapalene with and without benzoyl peroxide, he adds, many developers are exploring whether other retinoids can achieve similar results.

“The leading contenders would be tretinoin and tazarotene. Altreno (tretinoin, Ortho Dermatologics) would be a great fit because it’s very tolerable and spreadable,” he says.

Additionally, Ortho Dermatologics recently received FDA approval for its tazarotene lotion (Arazelot) that uses the same polymeric mesh vehicle, which Dr. Tanghetti says includes humectants and emollients that dramatically boost tolerability.

Disclosures:

Dr. Tanghetti is a consultant for Cynosure, DEKA, Quanta, Corneal and Aesthetics. He has no financial interest in a laser under development for active acne. Dr. Baldwin is a consultant and researcher for Sideluma and Ortho Dermatologics.

References:

PRP shows promise as adjunct treatment for scarring FROM PAGE 1

can be helpful. A meta-analysis of seven studies that was published online in Aesthetic Plastic Surgery showed that adding PRP to fractional laser treatment, microneedling or dermabrasion often provides significantly better improvement in acne scars.1 Due to the small number of studies that met inclusion criteria, however, these authors could draw no conclusions about specific combinations.

Conversely, a review by Hesselet al. concluded that adding PRP to fractionally ablative CO2 laser improves acne scars, patient satisfaction and postprocedural symptoms.2 However, results regarding PRP with microneedling were mixed, and significant between-study heterogeneity precluded further analysis of microneedling or laser combinations. The review appeared online in the Journal of the American Academy of Dermatology.

“The literature regarding adjunctive PRP with laser for acne scarring is better compared to PRP with microneedling,” Dr. Hesseler says. “That’s not to say that PRP is ineffective with microneedling. But we’re seeing mixed results in the setting of a relatively lower quality of evidence.”

STUDY DESIGNS

While laser-PRP studies used fairly consistent PRP types and regimens, says study co-author Nikhil Shyam, M.D., the variability of microneedling study designs made it much more difficult to draw meaningful conclusions from them. He is a New York-based dermatologist in private practice.

Microneedling-PRP studies reviewed by Drs. Hesseler and Shyam included topical and intradermal application, although most of these evaluated adjunctive topical PRP.

“Again,” Dr. Hesseler says, “this comes back to not having a consensus in regard to processing or delivering the PRP, and there are many different researchers testing this independently from one another.”

Nevertheless, Dr. Hesseler says, the dermatology community is beginning to organize its thoughts further about platelet-rich products—how to use them and for what dermatologic conditions they appear effective. For example, five of the seven laser studies he and Dr. Shyam reviewed used leukocyte-rich PRP (L-PRP). Unlike pure or leukocyte-poor PRP, L-PRP involves including the buffy coat of leukocytes and higher-density platelets that settle above the layer of red blood cells after centrifugation.

The physiology behind platelet-rich products makes sense, Dr. Hesseler says.

“Platelets are the first cells that show up in our wound-healing cascade. So, what we’re really doing is harnessing the body’s own wound-healing machinery and kickstarting that process with PRP,” he explains.

However, Emil Tanghetti, M.D., questions the longevity of that kickstart. He is director of the Center for Dermatology and Laser Surgery in Sacramento, Calif.

“Think of the pathophysiology. You’re putting a platelet-derived growth factor on the skin after performing a procedure,” he says. However, he says, it’s unclear if PRP works without some sort of access channels, or how long growth factors last once applied.

“The laser seems to work a little better—that’s the suggestion from the data. The problem is, most of my patients don’t want aggressive fractional ablative laser treatments,” Dr. Tanghetti says. “There’s too much downtime.”

Instead, he typically uses fractional radiofrequency (RF) microneedling for acne scars, followed by a secondary therapy to enhance efficacy with relatively minimal downtime.

“For some of our darker-skinned patients, we sometimes use picosecond technology, or fractional nonablative technology, in particular the thulium laser. Or we can add to the RF microneedling with a very superficial CO2 fractional laser with low energies. We have a unit (SmartXide Tetra, DEKA) that gives a high peak-power pulse, so it creates a thulium-like injury.”

Dr. Hesseler says, “We’re still learning a lot about PRP and other platelet-rich products. The real value of this treatment option is that it’s been shown to be beneficial, yet also quite safe.” With adjunctive PRP for acne scarring, he says, several studies reflect not only better acne scar improvements, but also less postprocedural symptoms and higher patient satisfaction.

Dr. Tanghetti counters that good postprocedural wound care might work at least as well as PRP in reducing downtime. Without knowing all the nuances of whether and how researchers optimized wound care in each study, he says, he doubts the efficacy of PRP in this regard.

One day, says Dr. Hesseler and Shyam, dermatologists may use adjunctive PRP in additional treatment combinations and for additional therapeutic targets. If there were more of a consensus regarding PRP terminology and techniques, says Dr. Hesseler, “then platelet-rich products would certainly be investigated with other procedures as well.”

All sources agree that more research is needed. Recently, Huang et al. performed a meta-analysis of 11 acne-scarring studies involving PRP, including eight studies analyzed by Hesseler et al. The meta-analysis showed that in aggregate, the risk ratio (RR) of achieving at least 50% improvement with adjunctive PRP was 1.93 (microneedling: 3.6; CO2 laser: 1.3), and the RR of achieving at least 75% improvement was 3.21 (microneedling: 3.9; CO2 laser: 3.3).2

Based on the meta-analysis and Hesseler et al., meta-analysis lead author Yu-Chen Huang, M.D., says she believes adjunctive PRP is a good choice for acne scarring, although the ideal PRP regimen and combination needs further clarification. Dermatologists in Asia generally believe that PRP promotes cell differentiation, proliferation and regeneration and enhances wound recovery, adds Dr. Huang. She is assistant professor of dermatology at Taipei Medical University, Taipei, Taiwan.

Dr. Hesseler says that because people have begun noticing what PRP can do for acne scars, he foresees further research with other techniques such as subcision. Dermatologists use many of these same procedures for hypertrophic scars, he says, and these procedures also may show augmented benefits with PRP.

“Although most of literature has looked at atrophic scars,” adds Dr. Hesseler, “it would be interesting to see additional research focused on other types of acne scars, as well as other types of scars altogether.”

He also believes there is still value in combining PRP with microneedling or other minimally invasive procedures for acne scarring.

“This still has to be investigated further,” Dr. Hesseler says.

Dr. Shyam says that although microneedling has been around awhile, its popularity for acne scarring has grown recently. Accordingly, he foresees that increasing numbers of microneedling-PRP studies with larger sample sizes and more detailed descriptions of PRP processing will be published.

Dr. Tanghetti says, “I’d love to see more data, but good luck getting it.” In the rush to capitalize on the latest “in” treatment, he says, research often lags behind.

“And as with all fads, if it’s real, it will survive. If not, it will die,” he says.

Disclosures

Drs. Hesseler, Shyam and Huang report no relevant financial interests. Dr. Tanghetti is a consultant to Cygnaa, REMA, Suneva, Carrioso and Aesthetics Biomedical but owns no stock in these companies.

References


Underdiagnosis common

Lack of ‘typical’ presentation requires diagnostic savvy

JOHN JESITUS | Staff Correspondent

The multifaceted, waxing and waning nature of rosacea requires physicians to be able to distinguish its many manifestations from those of similar conditions, according to a recent review.1

“The typical patient suffering with rosacea has been stereotyped as a 30- to 60-year-old white woman of Northern European ancestry who gets red-faced while drinking alcohol and often has pimples on her cheeks,” says lead author Sandra Marchese Johnson, M.D. She is a Fort Smith, Arkansas-based board-certified dermatologist in private practice.

“We now know not everyone is typical.” Modern textbooks reflect a more nuanced understanding, says Dr. Johnson; although, perhaps not all dermatologists are reading them.

Rosacea is common and affects up to 10% of the population; however, its true prevalence is unknown, she says, because the condition is often underdiagnosed. Dr. Johnson says in her clinical experience, rosacea is most underdiagnosed in darker skin types because it is more difficult to appreciate erythema or telangiectasias.

Decker-skinned patients may have a lower genetic propensity for rosacea, write Johnson et al., and/or melanin may protect against ultraviolet light as a rosacea trigger. Whatever the reasons, says Alexis et al. in a separate publication, rosacea in Fitzpatrick types IV to VI often presents in women previously misdiagnosed with late-onset acne.2 In diagnosing such patients, Alexis et al. suggest focusing on history of exacerbating factors, sensitivity to topical products, episodic facial flushing and ocular symptoms.

Rosacea’s complexity also contributes to underdiagnosis, as does the fact that symptoms often occur transiently and independently. The four main presentations of rosacea can overlap, adds Dr. Johnson.

Determining the source of redness helps set management and patient-education strategies. A treatment that targets lesions, for example, may have minimal effect on persistent erythema or telangiectasias. Conversely, a treatment only targeting to diffuse erythema may create the perception that lesions have worsened, when, in fact, reducing background redness makes the lesions stand out more.

Regarding differential diagnosis, factors that can help distinguish lesional rosacea from acne vulgaris include the presence of telangiectasias and eye symptoms, and absence of comedones, with rosacea. Regarding primarily erythematous presentations, pustules rarely occur in the malar rash of lupus, while the characteristic lesions of discoid lupus are coin-like, red and scaly, appearing on the cheeks, nose, ears and scalp.

Red, scaly lupus lesions may also resemble those of seborrheic dermatitis. “On dermoscopy,” write Johnson et al., “rosacea has linear vessels arranged in a polygonal network, while seborrheic dermatitis has dotted vessels in a patchy distribution.” Miscellaneous rosacea mimics can include erythromesic psoriasis, pustular psoriasis, impetigo and erysipelas.

For the past decade, treatment decisions have been driven by rosacea subtype classification. However, experts now advise a phenotype-based approach, which allows better treatment targeting. The growing array of therapies allows increasing individualization, study authors add.

For papules and pustules, topical treatments include metronidazole 0.75% cream, ivermectin 1% cream, azelaic acid 15% gel and foam and sodium sulfacetamide 10% with or without sulfur. Topical treatments that target erythema include brimonidine 0.33% gel and oxymetazoline 1% cream. Commonly used oral treatments for rosacea include tetracycline-type agents in antibiotic and subantimicrobial doses.

For best results, Johnson et al. advise combining treatments. For example, the MOSAIC study showed that ivermectin plus brimonidine achieved superior efficacy versus vehicle.3 Additionally, an analysis of four randomized topictreatment trials showed that patients with complete clearing had five more relapse-free months than those who did not clear completely. Based on quality-of-life scores, this study showed that earlier effective treatment and longer remission times also may delay disease progression.

Researchers continue to discover more about rosacea. Many years ago, she notes, researchers began discussing the association between Helicobacter pylori infection and rosacea symptoms. “Now we are learning more about other gut issues and rosacea symptoms.”

References


Disclosures

Dr. Johnson is or has been a consultant, speaker and investigator for Galderma.

For more information, visit: https://www.jdrugsdermatol.com/105/11/1888/894
Distinguish characteristics among differentials

JOHN JESITUS | Staff Correspondent

A paucity of studies and case reports has contributed to the misconception that rosacea rarely afflicts patients with skin of color (SOC), says authors of a recent review.

“Rosacea in SOC patients is grossly under-recognized and underdiagnosed,” says senior author Susan C. Taylor, M.D. “This is because it is often difficult for dermatologists and other providers to appreciate the erythema that is diagnostic.” She is associate professor of dermatology at the University of Pennsylvania’s Perelman School of Medicine, vice president-elect of the American Academy of Dermatology and founder of the Skin of Color Society.

In a separate publication, investigators using the search term “rosacea” found 3,786 articles indexed for MEDLINE, versus just 32 for the terms “rosacea” and “skin of color.”

The true prevalence of rosacea in SOC remains unknown. While a 2018 meta-analysis estimated global rosacea prevalence in all adults to be 5.46%, estimates of rosacea prevalence in SOC patients in individual studies range from 0.4% (Angola) to 12.4% (Colombia).

Underdiagnosis and misdiagnosis of rosacea in SOC lead to increased morbidity.

“Symptoms of burning, stinging, erythema, papules and pustules negatively impact patient quality of life, and patients may suffer needlessly,” says Dr. Taylor.

Undiagnosed rosacea moreover may progress to disfiguring rhinophyma. Likewise, the fact that the granulomatous variant of rosacea has been predominantly reported in black patients may stem from increased susceptibility in these patients.

To highlight erythema and telangiectasias in SOC, Taylor et al. recommend using adequate lighting, skin blanching and dermatoscopy.

“When you apply pressure to the skin with a slide or dermatoscope,” explains Dr. Taylor, “the blood will drain from the skin, and the skin appears white beneath the slide or dermatoscope. Then when you release the pressure, the blood comes back into the skin, and you can then appreciate the redness.”

Similarly, photographing the affected area against a dark blue background provides a contrast that makes identifying redness easier, she adds.

In the differential diagnosis of rosacea, systemic lupus erythematosus (SLE) occurs particularly more commonly in SOC. Dr. Taylor says, “The malar or butterfly rash of SLE can appear similar to rosacea, but the malar rash typically spares the nasolabial folds, while rosacea does not. Conversely, papules and pustules rarely occur in SLE.”

To confirm or rule out SLE, Taylor et al. suggest performing a complete physical examination and a skin biopsy with hematoxylin and eosin and direct immunofluorescence, as well as checking serologies including antinuclear antibody (ANA).

Although elevated ANA has been reported in patients with rosacea, it is lower than what is typically seen in SLE. If ANA is elevated, Dr. Taylor advises checking more specific SLE antibodies; for example, the double-stranded DNA test is positive in lupus. SLE also can be differentiated histologically by a considerably lower CD4:CD8 ratio, fewer CD4+CD25+ regulatory T cells and more CD123+ plasmocytoid dendritic cells versus rosacea.

Rosacea and seborrheic dermatitis can present concurrently. Symptoms of seborrheic dermatitis include erythematous patches and plaques involving the scalp, anterior and posterior hairlines, pre- and post-auricular areas and medial eyebrows. Both rosacea and seborrheic dermatitis may impact the nasolabial folds, but the presence of scale distinguishes the latter.

Additionally, the erythematous lesions of seborrheic dermatitis are often annular, and the post-inflammatory hypopigmentation (and to a lesser extent, hyperpigmentation) common to this condition are relatively uncommon in rosacea.

The heliotrope rash that marks dermatomyositis differs from rosacea in its dusky, violaceous hue and its periorbital involvement. Other signs that indicate dermatomyositis, which is four times more common in African-American versus Caucasian patients, include edema of the face and extremities, Gottron papules and poikiloderm.

Cutaneous sarcoidosis may present with multiple morphologic features, most typically firm yellow, brown, violaceous, red or flesh-colored monomorphic papules or nodules affecting the perioral, perioscular, medial and/or lateral face. However, plaques, lupus pernio, subcutaneous infiltrates and infiltrates of scars also have been reported. Sarcoid papules typically measure 1 to 5 mm on the face, neck and periorbital skin. They are initially orange or yellow-brown, then turn brownish-red or violaceous before involving to form faint macules. Papular lesions also may evolve into plaques, particularly on the extremities, face, scalp, back and buttocks.

Unlike sarcoidosis, granulomatous rosacea lacks plaques, lupus pernio, subcutaneous infiltrates and infiltration of scars. Although patients with granulomatous rosacea may report pain, pruritus or burning, these patients do not experience the flushing and erythema seen in more typical rosacea presentations.

Distinguishing features of steroid dermatitis may include full-facial involvement, versus rosacea’s centrifacial predilection. Regarding acne vulgaris, patients with this condition do not experience telangiectasias and flushing, while those with rosacea do not experience comedonal lesions but can have hyperpigmented macules.

References

Disclosures
Dr. Taylor has been an investigator, speaker and advisory board member for Aladina (maker of isometasone) and an advisory board member for Galderma (maker of flornoxime).
Foamix is a specialty pharmaceutical company working to solve some of today’s most difficult therapeutic challenges in dermatology and beyond. With expertise in topical medicine innovation as a springboard, the company is working to develop and commercialize solutions that were long thought impossible. Its proprietary Molecule Stabilizing Technology (MST™) is being utilized in the company’s investigational dermatology products in late stage development.

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Topical minocycline shows treatment efficacy in PPR

MORGAN PETRONELLI | Assistant Editor

Recently published results from a phase 2b study demonstrated the therapeutic efficacy of a novel topical minocycline gel (HY01, Hovione) on patients with papulopustular rosacea (PPR). The results are significant, because it could potentially lead to a topical alternative to oral minocycline or oral doxycycline, for reducing inflammatory facial lesions in papulopustular rosacea, according to the authors.

Minocycline has been proven to be an effective treatment for PPR in an oral formulation; however, oral minocycline carries risk of side effects, says George Macgrath, M.D., medical director at Hovione, which sponsored the study. A topical option may concentrate the drug at the site of action, while decreasing systemic exposure substantially and may lead to fewer side effects, write the authors of the phase 2 study, which was published online January 6, 2020, in the British Journal of Dermatology.

“Minocycline is an oral antibiotic that’s been used in both acne and rosacea effectively, and the new formulation now takes this oral pill and puts it into a gel that can be applied to the face. And because, orally, minocycline is effective in rosacea, there was a good chance it might also be effective topically,” says Zoe Diana Draelos, M.D., High Point, N.C., who was an investigator and author of the study.

The phase 2 study was a double-masked, parallel group, randomized, multicenter, vehicle-controlled trial that enrolled 270 patients with papulopustular rosacea located in 26 sites across the United States. Researchers compared the therapeutic efficacy among patients receiving 1% minocycline gel (n=92), 3% minocycline gel (n=96) or vehicle (n=82) applied to the face once nightly for 12 weeks. The primary endpoint was the mean decrease in inflammatory lesion count at week 12. The secondary endpoint was measured by the number of patients achieving “clear” or “almost clear” and a 2-grade improvement on the Investigator Global Assessment (IGA) and IGAe (including erythema) scales.

At baseline, the mean lesion count among patients was 24.6 in the 1% minocycline arm, 25.1 in the 3% minocycline arm, and 24.3 in the vehicle arm. Mean decrease in lesion counts were significantly higher in the 1% and 3% arms (12.64, p=0.0147, 95% CI -7.930—0.871 and 13.09, p=0.0073, 95% CI -8.319 to -1.310) compared with the vehicle arm (7.93). At four weeks following the completion of the study, patients in the 3% arm maintained a significant reduction in inflammatory lesions compared with vehicle.

Additionally, the study met its secondary endpoint with 38.9% of subjects achieving IGA success in the 1% minocycline arm (p=0.34, OR 1.396 and OR 0.708 to 2.751 vs. vehicle), 46.2% in the 3% arm (p=0.04, OR 2.028 and OR 95% CI 1.040 to 3.952 vs. vehicle) and 30.8% in the 1% minocycline arm (p=0.34, OR 1.396 and OR 95% CI 0.708 to 2.751 vs. vehicle). The results of the study demonstrate that topical minocycline is safe, well tolerated and potentially efficacious, the authors note. This could lead to an alternative option to oral doxycycline and oral minocycline with potentially fewer side effects, they add.

Up next for Hovione: Based on this phase 2 data, the company announced plans to move into its MARS-2 and MARS-3 (Minocycline Against Rosacea Study) phase 3 trials to further investigate efficacy of 3% minocycline gel. The trials will enroll 750 patients to assess absolute reduction of inflammatory lesions at week 12 compared with baseline and clearance on the IGA scale, according to a company press release. If results from the phase 3 trials can replicate the clinically significant improvements observed in the phase 2 study, the drug will move toward FDA marketing approval, the company says.

“We don’t really have a good treatment for rosacea in all patients who experience the disease. So, the addition of topical minocycline offers a treatment alternative dermatologists can use in treating rosacea,” Dr. Draelos tells Dermatology Times.

References

“The recognition that oral minocycline is effective in rosacea led to the development of topical minocycline.”

Zoe Draelos, M.D., High Point, NC
Gene expression profiling tests may soon be used for squamous cell carcinoma.

A recent study found positive using gene expression profiling test results optimized patient management.

Gene expression profiling tests can be a very useful adjunct tool in separating the high-from low-risk cSCC lesions, helping clinicians offer their patients more appropriate and measured treatment and management options,” says Graham Litchman, D.O., M.S., clinical research fellow at the National Society for Cutaneous Medicine, New York, N.Y., and co-author of the study.

Researchers found that the GEP results significantly influenced the decision-making process of dermatologists for the evaluated cases. Data showed that in the majority of vignettes, a lower risk cSCC-GEP test result led to a statistically significant decrease in the proportion of dermatologists who would recommend radiation, chemotherapy/immunotherapy, SLNB or quarterly follow-up. Conversely, a higher-risk cSCC-GEP result significantly shifted the management toward an increased intensity of these recommended measures in all vignettes.

The most commonly relied upon cancer staging tools today are the American Joint Committee on Cancer (AJCC) and Brigham Women’s Hospital (BWH) staging systems. However, even these widely used and accepted staging tools have their limitations, Dr. Litchman says, including having a low sensitivity and low positive predictive value for predicting metastasis. According to Dr. Litchman, GEP testing represents an opportunity to educate and improve the process by which dermatologists go through and figure out how to more accurately categorize and manage these challenging SCC patients.

“Appropriately choosing a GEP test for further assessing the risk of a lesion under scrutiny can be challenging. Whenever clinicians are starting to incorporate new technologies, Dr. Litchman says it is important to use them with regularity. In this way, clinicians learn and get comfortable with GEP tests, and when and when not to order them for their patients. According to Dr. Litchman, novel cSCC-GEP tests can increase the clinician’s confidence in questionable lesions and, when successful, lower morbidity, hopefully the mortality and the economic burden of some of these cancers. “Augmenting the way that you’ve done things for years can ultimately benefit your patients and your practice. I think that as we move into this new age of advanced medicine, the management of cSCC will evolve to significantly improve the way we diagnose and treat our patients,” Dr. Litchman says.

**Disclosures**

Dr. Litchman participated in a research fellowship, which was partially funded by Castle Biosciences Inc.

**Reference**

Nano-pulse stimulation promising for skin lesions

CHERYL GUTTMAN KRADER, B.S. PHARM | Staff Correspondent

Nano-Pulse Stimulation (NPS) causes selective damage to cellular structures in the epidermis and dermis without affecting the integrity of dermal tissue and stimulates an immune response.

“The specificity of NPS suggests it could be used to treat cellular targets in the epidermis and dermis with good cosmetic results. The studies to date have shown excellent results using NPS to treat seborrheic keratosis (including macular lesions), warts and sebaceous hyperplasia,” says Dr. Rohrer.

“Early feasibility studies are in development or underway to investigate this modality in the treatment of cherry angiomas, common nevi, syringoma, acne, tattoos and nodular basal cell carcinomas.”

BENIGN LESION APPLICATIONS

Results have been published from a study investigating NPS for treatment of sebaceous hyperplasia [Munavalli GS, et al., Oct 4. Epub ahead of print]. The paper reported outcomes for 222 treated lesions, of which 90% were rated as clear and 9.5% were judged mostly clear at 60 days post-treatment. Mild hyperpigmentation and slight volume loss were each noted at approximately one-third of the treated sites. Therefore, a dose-response study was launched to evaluate whether use of a lower energy level could maintain efficacy but avoid the pigmented and volume changes.

“Interim results from the ongoing dose-response study show that the lowest energy level tested resulted in a 95% clearance rate with improved cosmesis,” he says.

A recently published study investigating NPS for treatment of raised, off-facial seborrheic keratosi reported 82% clearance efficacy. Emerging data from an ongoing study of macular SK lesions suggest comparable efficacy clearance.

“The ability of NPS to target sebaceous glands prompted interest in investigating it as a treatment for acne. A feasibility study is now underway investigating that application in patients with back acne [See “Nonthermal energy shows promise as ‘Tx for back acne’ online at bit.ly/energybackacne]. Initial results showed an 89% lesion reduction.

Positive results were also achieved in a feasibility study investigating NPS for treating cutaneous non-genital warts, and a larger multicenter study is underway to further explore this application. [See “New therapeutic perspective for non-genital warts,” page 1].

“In the wart study, untreated control warts also cleared after NPS, supporting the idea that the procedure stimulates an immune response,” Dr. Rohrer says.

MALIGNANT TARGETS

A pilot study was conducted to investigate NPS for treatment of nodular basal cell carcinomas. Seven patients with nodular BCCs located on the chest, forearm, back or shoulder received a single session of NPS. All post-treatment (3-7 weeks) biopsies of the NPS treatment zone were devoid of nodular BCCs. There was no clinical or histologic evidence of dermal scarring. An ongoing study is further investigating NPS for BCC, and there is also interest in its use for treating nevi and melanoma, says Dr. Rohrer.

“Preclinical studies performed in animal models of melanoma showed that NPS treatment eliminated the primary tumor and stimulated a lasting immune response with reduction in metastases and increased animal survival,” he says.

“The potential for NPS to treat melanoma and stimulate an immune response that can target metastases holds major interest for me as a dermatologic surgeon specializing in skin cancer and aesthetic dermatology.”

Disclosure: Dr. Rohrer is an investigator and member of the scientific advisory board for Pulse Biosciences.
Study supports evidence on indoor tanning risk

Results show harm increases with number of exposures

CHERYL GUTTMAN KRADER, B.S., PHARM | Staff Correspondent

The results showed a statistically significant increased risk for high users (+83%), medium users (+60%), and low users (+29%).

Analyses of potential interactions suggest that it is the total amount of indoor tanning that matters, not the duration of use or age at initiation.

Dose-response relationship between indoor tanning use and development of cSCC was investigated by categorizing women into four groups by total number of lifetime sessions: 0 (never), 1-38 (lowest use), 39-240 (medium use), and >240 (highest use). The analysis found that compared with never users, the risk for cSCC development was significantly increased by 29% among lowest users, 60% among medium users, and 83% among women in the highest use group.

Compared with never users, women with a ≤10-year history of indoor tanning and those with a longer history of use had similar significantly increased risks of cSCC (41% and 43%, respectively). Women who started indoor tanning at age 30 or older had a 36% increased risk of cSCC relative to never users, and the risk for women who started indoor tanning at a younger age was increased significantly by 51%.

No association was found between age at initiation of indoor tanning and age at cSCC diagnosis. “We believe ours is the first study to investigate an association between age at initiation of indoor tanning and age at cSCC diagnosis,” Mr. Lergenmuller says.

The findings of the study are consistent with previous meta-analyses linking use of indoor tanning devices with an increased risk of cSCC. The meta-analyses included between three and six previous meta-analyses linking use of indoor tanning and age at cSCC diagnosis.
Study: Daxi safe, effective

CHERYL GUTTMAN KRADER, B.S. PHARM. | Staff Correspondent

Collective results from the SAKURA phase 3 clinical trial program investigating daxibotulinumtoxinA for injection (“DAXI”, Revance Therapeutics) for the treatment of moderate-to-severe glabellar lines show that the neuromodulator provides generally safe and long-lasting benefit with one treatment consisting of five injection points, each in one corrugator muscle and one in the procerus muscle.

SAKURA 3, which was an open-label phase 3 safety study investigating DAXI for treatment of moderate-to-severe glabellar frown lines, enrolled 2691 patients who received up to three repeat treatments at an interval of 36 weeks. Overall, patients received a total of 3830 injections of DAXI 40 U (8 U per point).

“This is the largest clinical trial ever conducted investigating aesthetic treatment with a neuromodulator,” says Sabrina Fabi, M.D., who was an investigator. “The efficacy results paralleled those seen in the randomized, placebo-controlled SAKURA 1 and SAKURA 2 clinical trials showing that DAXI was very effective at one month and was associated with prolonged benefit, typically persisting five to six months post-injection,” says Dr. Fabi, associate research director, Cosmetic Laser Dermatology, San Diego.

SAKURA 3 was a prospective, 84-week study. Eligible patients had moderate-to-severe glabellar lines judged using the four-point Investigator Global Assessment-Frown Wrinkle Severity Scale; baseline severity was rated “moderate” in approximately two-thirds of the enrolled cohort. Approximately 12% of patients enrolled in SAKURA 3 had been previously treated with DAXI in SAKURA 1 or 2. A total of 40% of all subjects had been treated previously with another botulinum toxin product.

Patients received DAXI 40 U. Subjects selected for retreatment could receive it no sooner than 12 weeks later and once their frown severity score had returned to baseline. These patients were eligible for a third injection using the same criteria. Follow-up visits were scheduled at weeks 1, 2, 4 and every four weeks through week 36 after the first and second injections and through week 12 following a third injection. A total of 2,380 patients received a first DAXI injection, 882 patients were treated with a second cycle, and 568 patients received a third DAXI injection in SAKURA OLS.

A ≥2-point composite response at maximum frown at week four was achieved by 73% of patients after the first treatment cycle, which was nearly identical to the results in SAKURA 1 and 2. In SAKURA 3, the response rates were 78%, after cycle two and 80% after cycle three.

“The majority of patients in SAKURA 3 were rated prior to treatment as having either moderate or severe glabellar lines. That means they would have to improve to “none” to achieve a ≥2-point composite response, and that is a very high bar to cross,” Dr. Fabi says.

At week 24 after DAXI injection, approximately one-third of patients had a wrinkle severity score of none to mild. Using a Kaplan-Meier time to event analysis, the median time to loss of none or mild rating was 24 weeks. Median time to return to baseline severity was approximately 28 weeks. Patient satisfaction was high, she says.

Adverse events were mild, transient and mostly limited to local reactions that would be expected with any needle injection, (eg, injection site pain and erythema), as well as headache that is widely reported with neuromodulator injections for treatment of glabellar lines. The rates of injection site pain, erythema and headache in SAKURA 3 were all <6%.

Overall, 1.3% of patients experienced eyelid ptosis, and the rate of eyelid ptosis per treatment was 0.9% per treatment.

Results from SAKURA 1 and SAKURA 2 were reported in articles published online in Plastic and Reconstructive Surgery and the Journal of the American Academy of Dermatology. The two identically designed studies included a total of 405 patients who received a single treatment with DAXI 40 U.

The primary endpoint analysis showed that 73.8% of DAXI patients but only 0.5% of controls achieved a two-point composite response at week 4. The responder rate in the DAXI group was the same whether patients had moderate or severe glabellar lines at baseline. At week 4, 97.3% of subjects were rated as None or Mild by the investigator, and 91.1% when rated by the subjects at the 24-week follow-up visit. The median time to return of baseline severity was approximately 27 weeks.

The incidence of eyelid ptosis associated with DAXI in SAKURA 1 and 2 was 2.2%.

DAXI has unique characteristics compared with other neuromodulators that are approved for aesthetic use. Although all of the products contain the same 150 kDa core neurotoxin protein (botulinum toxin type A), unlike onabotulinumtoxinA (Botox Cosmetic) and abobotulinumtoxinA ( Dysport), DAXI is highly purified and free of accessory proteins. In contrast to both the latter two competitors and incobotulinumtoxinA (Xeomin), DAXI is formulated with a patented stabilizing peptide excipient and is free of animal-derived components and human serum albumin.

Disclaimer
Revance Therapeutics submitted a Biologics License Application for DAXI to the US FDA in the treatment of moderate-to-severe glabellar lines in November 2019. Dr. Fabi is an investigator for Allergan, Croma, Goldamera, Merz, and Revance and has stock in Allergan and Revance.
GETTING OTEZLA GETS EVEN EASIER

8 out of 10 commercially insured lives in the US have preferred access with no biologic step required for Otezla.1

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Indicates no DMARD or biologic step-edit required.

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*Basic, Standard, and Advanced Control Formularies.
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DMARD, disease-modifying antirheumatic drug.

Please see accompanying Brief Summary of Full Prescribing Information.

RESULTS

the way

THEY WANT THEM

With a proven efficacy and safety profile, oral dosing, and no label-required lab monitoring, Otezla is a treatment experience patients can respond to.*†

INDICATIONS

• Otezla® (apremilast) is indicated for the treatment of adult patients with active psoriatic arthritis
• Otezla is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

Otezla: the ONLY ORAL treatment indicated for psoriatic arthritis and plaque psoriasis

IMPORTANT SAFETY INFORMATION

Contraindications
• Otezla® (apremilast) is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

Warnings and Precautions
• Diarrhea, Nausea and Vomiting: Cases of severe diarrhea, nausea, and vomiting were associated with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases patients were 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; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting
• Depression: Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on Otezla. Patients, 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 they should contact their healthcare provider if such changes occur
  – Psoriasis: Treatment with Otezla is associated with an increase in depression. During clinical trials, 1.3% (12/920) of patients reported depression compared to 0.4% (2/506) on placebo; Depression was reported as serious in 0.1% (1/1308) of patients exposed to Otezla, compared to none in placebo-treated patients (0/506). Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. One patient treated with Otezla attempted suicide; one patient on placebo committed suicide
  – Psoriatic Arthritis: Treatment with Otezla is associated with an increase in depression. During clinical trials, 1.0% (10/998) reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. Suicidal ideation and behavior was observed in 0.2% (3/1441) of patients on Otezla, compared to none in placebo treated patients. Depression was reported as serious in 0.2% (3/1441) of patients exposed to Otezla, compared to none in placebo treated patients (0/495). Two patients who received placebo committed suicide compared to none on Otezla
• Weight Decrease: Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla
  – Psoriasis: Body weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla and in 5% (19/382) of patients treated with placebo. Body weight loss of ≥10% occurred in 2% (16/784) of patients treated with Otezla compared to 1% (3/382) of patients treated with placebo
  – Psoriatic Arthritis: Body weight loss of 5-10% was reported in 10% of patients taking Otezla and in 3.3% of patients taking placebo
• Drug Interactions: Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended
PSORIATIC ARTHRITIS

**Significant joint improvement**

In PALACE™ 1

38% ACR20 response with Otezla® (apremilast) 30 mg twice daily (n = 168) vs 19% with placebo (n = 168) at week 16 (primary endpoint; \(P = 0.0001\))

*The efficacy and safety of Otezla in psoriatic arthritis was evaluated in 3 multicenter, randomized, double-blind, placebo-controlled phase 3 trials in adult patients with active psoriatic arthritis (N = 1493). Patients were randomized 1:1:1 to either Otezla 30 mg twice daily, Otezla 20 mg twice daily, or placebo for 24 weeks, after a 5-day titration period.*

In PALACE 1, Otezla significantly increased ACR20 response (n = 168) at week 16 (primary endpoint) vs placebo (n = 168) (38% vs 19%; \(P = 0.0001\)).

**Safety profile:** The most common adverse reactions (≥5%) were diarrhea, nausea, and headache.

**PALACE 1-3 clinical development program**

• Otezla was studied in 3 randomized, double-blind, placebo-controlled trials of similar design
• Adult patients (N = 1493) with psoriatic arthritis for at least 6 months, now with active psoriatic arthritis (≥3 swollen joints and ≥3 tender joints) despite prior or current DMARD therapy, were randomized 1:1:1 to placebo, Otezla 30 mg, or Otezla 30 mg given twice daily, after an initial 5-day titration
• Patients who were therapeutic failures of ≥3 agents for psoriatic arthritis (small molecules or biologics) or >1 biologic TNF-α inhibitor were excluded
• Placebo-controlled efficacy data were collected and analyzed through week 24. Placebo nonresponders at week 16 were re-randomized to either 20 mg twice daily or 30 mg twice daily Otezla. At week 24, all remaining patients receiving placebo were re-randomized to either 20 mg twice daily or 30 mg twice daily. Patients treated with Otezla remained on their initial treatment. Patients entering a long-term extension phase could be treated through 5 years
• 65% of patients received concomitant therapy with at least one DMARD, including 55% methotrexate

ADVERSE REACTIONS

• **Psoriasis:** Adverse reactions reported in ≥5% of patients were (Otezla%, placebo%): diarrhea (17, 6), nausea (17, 7), upper respiratory tract infection (9, 6), tension headache (8, 4), and headache (6, 4)

**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

**REFERENCES**


MODERATE TO SEVERE PLAQUE PSORIASIS

**Significant skin improvement**

In ESTEEM® 1

33% PASI-75 response with Otezla 30 mg twice daily (n = 562) vs 5% with placebo (n = 282) at week 16 (primary endpoint; \(P < 0.0001\))

*The efficacy and safety of Otezla in plaque psoriasis was evaluated in 2 multicenter, double-blind, placebo-controlled trials of similar design. Patients with moderate to severe plaque psoriasis (N = 1257) were randomized 2:1 to Otezla 30 mg twice daily or placebo for 16 weeks after a 5-day titration.*

In ESTEEM 1, Otezla significantly increased PASI-75 response (n = 562) at week 16 (primary endpoint) vs placebo (n = 282) (33% vs 5%; \(P < 0.0001\)).

**Safety profile:** The most common adverse reactions (≥5%) were diarrhea, nausea, upper respiratory tract infection, tension headache, and headache.

**ESTEEM clinical development program**

• Evaluated in a multicenter, double-blind, placebo-controlled trial. Patients with moderate to severe plaque psoriasis (N = 844) were randomized 2:1 to Otezla 30 mg twice daily or placebo for 16 weeks after a 5-day titration
• At week 16, all patients originally assigned to placebo transitioned to Otezla 30 mg twice daily. At week 32, some patients originally randomized to Otezla were, based on clinical response, re-randomized to Otezla or placebo. Those re-randomized to placebo restarted Otezla 30 mg twice daily at loss of response, but no later than week 52
• Selected inclusion criteria: Age ≥18 years, BSA involvement ≥10%, sPGA ≥3, PASI score ≥12, candidates for phototherapy or systemic therapy
• Patients entering a long-term extension phase could be treated through 5 years

ACR, American College of Rheumatology; BSA, body surface area; DMARD, disease-modifying antirheumatic drug; ESTEEM, Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; PALACE, Psoriatic Arthritis Long-Term Assessment of Clinical Efficacy; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment; TNF, tumor necrosis factor.

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OTEZLA® (apremilast) tablets, for oral use

The following is a Brief Summary of the Prescribing Information; see Full Prescribing Information for complete product information.

CONTRAINDICATIONS
OTEZLA® is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation [see Adverse Reactions (6.1)].

WARNINGS AND PRECAUTIONS
Diarrhea, Nausea, and Vomiting: There have been postmarketing reports of severe diarrhea, nausea, and vomiting occurring within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hydration 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 reduction or suspension if patients develop 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 or to promptly report any evidence of worsening or emergence 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 for any patient.

Psoriatic Arthritis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.0% (10986) of subjects treated with OTEZLA reported depression or depressed mood compared to 0.8% (4445) treated with placebo. During the clinical trials, 0.3% (4/1441) of subjects treated with OTEZLA discontinued treatment due to depression or depressed mood compared with none in placebo treated subjects (0/495). Depression was reported as severe in 0.2% (2/1441) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/495). Instances of suicidal ideation and/or behavior have been observed in 0.6% (2/1441) of subjects after receiving OTEZLA, compared to none in placebo treated subjects (0/495). In the clinical trials, 2 subjects who received placebo committed suicide compared to none in OTEZLA-treated subjects.

Psoriasis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (12501) of subjects treated with OTEZLA reported depression compared to 0.4% (2556) treated with placebo. During the clinical trials, 0.1% (1/1038) of subjects treated with OTEZLA discontinued treatment due to depression compared with none in placebo-treated subjects (0/332). Depression was reported as severe in 0.2% (1/1038) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/332). Instances of suicidal ideation and/or behavior have been observed in 0.3% (3/1038) of subjects while receiving OTEZLA, compared to 0.2% (1/506) in placebo-treated subjects. In the clinical trials, 1 subject treated with OTEZLA attempted suicide while one who received placebo committed suicide.

Weight Decrease: During the controlled period of the studies in psoriatic arthritis (PsA), weight decrease between 5%-10% of body weight was reported in 10% (48491) of subjects treated with OTEZLA 30 mg twice daily compared to 3.3% (16459) treated with placebo [see Adverse Reactions (6.1)]. During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (66184) of subjects treated with OTEZLA compared to 5% (31932) treated with placebo. Weight decrease of 0.1% of body weight occurred in 2% (10764) of subjects treated with OTEZLA 30 mg twice daily compared to 1% (3362) subjects 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 Interaction: 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 [see Drug Interactions (7.1)].

Adverse Reactions Reported in ≥2% of Patients on OTEZLA 30 mg Twice Daily and ≥1% in Patients on Placebo on Day 1-16 (Placebo %, OTEZLA %):

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>Placebo %</th>
<th>OTEZLA %</th>
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<tr>
<td>Nervous System</td>
<td>2%</td>
<td>4%</td>
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<tr>
<td>Gastrointestinal</td>
<td>17%</td>
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<tr>
<td>Metabolism</td>
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<tr>
<td>Immune System</td>
<td>5%</td>
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Adverse Reactions Reported in ≥2% of Patients on Placebo on Day 0-112 (Week 16) (Placebo %, OTEZLA %):

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<tr>
<th>CATEGORY</th>
<th>Placebo %</th>
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<tr>
<td>Immune System</td>
<td>5%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Other adverse reactions reported in patients on OTEZLA in clinical studies including extension studies:

- Infections and Infestations:
  - Urinary tract infection: 0.4% (21/5069) treated with OTEZLA, none in placebo treated subjects (0/5069)

- Dermatologic:
  - Rash: 0.6% (32/5069) treated with OTEZLA, none in placebo treated subjects (0/5069)

- Respiratory, Thoracic, and Mediastinal Disorders:
  - Cough: 0.6% (32/5069) treated with OTEZLA, none in placebo treated subjects (0/5069)

- Nervous System Disorders:
  - Dizziness: 0.6% (32/5069) treated with OTEZLA, none in placebo treated subjects (0/5069)

- Gastrointestinal Disorders:
  - Nausea: 1.4% (74/5069) treated with OTEZLA, none in placebo treated subjects (0/5069)

- Gastrointestinal Disorders:
  - Diarrhea: 1.2% (61/5069) treated with OTEZLA, none in placebo treated subjects (0/5069)

- Metabolic and Nutritional Disorders:
  - Dyslipidemia: 0.4% (21/5069) treated with OTEZLA, none in placebo treated subjects (0/5069)

- Mental Health Disorders:
  - Depression: 0.2% (3/1441) of subjects treated with OTEZLA reported depression compared to 0.4% (2/506) treated with placebo [see Adverse Reactions (6.1)].

- Reproduction Disorders:
  - Erectile dysfunction: 0.6% (32/5069) treated with OTEZLA, none in placebo treated subjects (0/5069)

Based on APRPI.006_OTZ_PaPaJ_HCP_BSM_006_36_2017

RX Only
Toxin results vary
Study examines differences to inform best clinical practice

WHITNEY J. PALMER | Staff Correspondent

Different preparations and dilutions of botulinum toxin type A can produce different results for relaxing facial muscles, as well as improve skin elasticity, pliability and re-organize facial collagen. Understanding those differences could have implications for improved clinical practice, according to industry experts.

The ability to use botulinum toxin type A to relax facial muscles and improve skin elasticity and pliability make it a highly sought-after treatment among patients. However, clinical evidence indicates not all types and concentrations provide the same results overall or in the same time frame.

In fact, a recent study published in the Journal of Cosmetic Dermatology revealed that using various botulinum toxin dilutions already actively employed in patient care can allow dermatologists to control and change the outcome for individual patients. But, for the best results, similar to a mild midfacial lift, providers should opt for less diluted toxins.

According to Rungsima Wanitphakdeedecha, M.D., lead study author, dermatologist and dermatologic surgeon based in Bangkok, Thailand, physicians should use this information in planning treatment and managing patient expectations.

“Although more diluted toxins may seem to produce better and faster fibroblast contraction,” she says, “in reality, more diluted toxins deliver lower total toxin dosages, thereby reducing toxin efficacy and longevity in clinical practice.”

The team posited that it was the fibroblast contraction itself that could be a potential mechanism for the positive lifting effect patients experience.

TYPES AND DILUTIONS
Prior to this study, it was unknown how intradermal botulinum toxin A injections prompt fibroblast contraction. It was also unclear which toxin or dilution ratio could be used to achieve the maximum satisfactory outcome for the individual patient. This is the first study to tackle this question, Dr. Wanitphakdeedecha says.

To determine how different botulinum toxin types and dilutions affect normal human dermal fibroblasts, her team tested various dilutions of botulinum toxins routinely used in practice, including onabotulinumtoxin (ONA), abobotulinumtoxin (ABO), prabotulinumtoxin A (PRABO), incobotulinumtoxin A (INCO) and letbotulinumtoxin A (LETI). Each toxin was tested in multiple dilutions, ranging from 1:2.5 to 1:10, and the team tested 50 fibroblasts per solution. Photographs and measurements taken every two hours from baseline 0 to 12 hours post-treatment revealed how much each fibroblast contracted over time.

Based on study data analysis, she says, INCO, PRABO, LETI and ABO produced a decrease in fibroblast length at multiple dilutions. ONA was the only botulinum toxin A type that didn’t prompt a significant decrease in length at any time point or dilution ratio.

“Different botulinum toxin A types induce fibroblast contraction to different extents and at different speeds.”

Rungsima Wanitphakdeedecha, M.D.
Bangkok, Thailand

Among botulinum toxin A types, INCO was the only toxin that significantly shortened fibroblasts at all dilution levels examined. That result equates an almost-immediate lifting effect that is sustained for the length of time the toxic remains active, and the preferred INCO dilution ratio, she says, is 1:6.

While PRABO and LETI did cause fibroblast shortening at various dilution ratios from 1:7 and above, the impacts were interpreted to have short-term clinical effectiveness. ABO also instigated a significant fibroblast contraction at the 1:7 dilution, but the effect was seen only after 10 to 12 hours. ABO didn’t produce fibroblast shortening at any other dilution ratio or time period.

These results highlight the varying degrees of impact and efficacy patients experience with each type of botulinum toxin.

“We, therefore, conclude that different botulinum toxin A types induce fibroblast contraction to different extents and at different speeds,” she says.

CLINICAL SIGNIFICANCE
Ultimately, Dr. Wanitphakdeedecha says, the study findings indicate botulinum toxin type A could be used effectively with no cytotoxic effect on fibroblasts. This finding supports what previous investigators have found in their evaluations and observations.

“Of clinical significance was our finding that, while the fibroblasts displayed a measurable decrease in length, their overall size did not change, and they did not disappear from the field of view,” she says. “Physicians should carefully consider the speed at which they hope to achieve an outcome, especially if fibroblast contraction may produce a visual tissue lifting.”

Consequently, for the best possible outcomes, dermatologists should use the data surrounding the efficacy of botulinum toxin type A dilutions and results to select the best product and dilution level for intradermal injections for face lifting.

Despite these results showing significant fibroblast contraction with many botulinum toxin types, Dr. Wanitphakdeedecha says further investigations are needed to determine the full extent and mechanism of this impact. Not only is a larger sampling of cells required, but a larger number of dilution levels should also be evaluated.

“An in-depth profile of these changes can provide botulinum toxin users with an understanding of the molecular mechanism behind the outcomes of different toxin-based aesthetic interventions and, also, to clarify why different commercial preparations product different results,” she says.

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Body toning technologies

LISETTE HILTON | Staff Correspondent

The latest evolution in nonsurgical body contouring began last year with muscle-toning technology Emsculpt (Ems). Two other similar devices entered the market soon after to claim some of that noninvasive market share: Cooltone by Coolsculpting (Allergan) and truSculpt flex (Cutera).

The muscle stimulating devices noninvasively tone and stimulate muscle just enough to give reasonably fit patients a more sculpted look and feel.

Unlike volume reduction devices, such as Coolsculpting (Allergan), TruSculpt ID (Cutera) or SculptSure (Cynosure), muscle stimulating technology works to tone and shape by hyper stimulating the underlying muscle. The ideal candidate — one that is fit with minimal body fat — will likely by most satisfied from the investment, according to experts.

But results are temporary and treatments expensive, often in the range of $750 to $1,000 per treatment area. And having one of these devices is a sizeable investment for an aesthetic practice.

So, how does an aesthetic practice decide whether to invest in one of these technologies?

We asked several aesthetic physicians to share what they’ve learned about what differentiates the technologies and more.

A QUESTION OF ROI

Plastic surgeon Christie Prendergast, M.D., Santa Monica, Calif., says Emsculpt has the advantage of being the first muscle-building and sculpting device on the market. That means it has more brand recognition to consumers than the others. However, adding Emsculpt to a practice comes at a hefty price.

“CoolTone… in terms of value can be more cost effective for those who already own a Coolsculpting machine,” says Dr. Prendergast.

One of the differentiators with Cooltone is that Allergan claims its technology has a higher intensity than competitors’ devices. That could mean fewer sessions and time to see the same results, but the jury remains out on that until there’s more data, according to Dr. Prendergast.

“For truSculpt flex one of the things that Cutera is marketing, which I think has some clinical significance, is that truSculpt flex has multidirectional electromagnetic therapy,” says Dr. Prendergast.

In theory, truSculpt flex might result in a more even, balanced result because instead of stimulating superficial muscle, like Emsculpt and Cooltone, it stimulates the superficial and deep muscle fibers. That, too, remains to be seen with more data, she says.

Best candidates for all muscle sculpting or toning technologies are generally physically fit and should be counseled that results are not permanent and need to be maintained with diet and exercise. Treatment enhances what patients have at baseline and is ideal for busy professionals who cannot dedicate the amount of time in the gym needed to achieve their body goals, according to Dr. Prendergast.

The temporary boost in muscle tone and function comes at a pretty steep price, so proper patient selection and counseling patients on what to expect is very important.

“I don’t think patients will see good ROI if they’re using this as a substitute for diet and exercise,” she says.

DEFINING MAINTENANCE PROTOCOLS

Dermatologist Dan Belkin, M.D., who practices in New York City and South Hampton, N.Y., uses Cooltone. He says the technology is attractive to patients, offering more defined abs and rounder buttocks without the work, by stimulating “supramaximal” contractions that one cannot (and need not) muster on one’s own.

Benefits beyond aesthetics

COSMETIC PHYSICIAN Tahl Humes, D.O., Denver, Colo., describes the market for these devices as broad and going beyond purely cosmetic indications.

“This can be a new treatment for aesthetic practices. Muscle toning technology offers a noninvasive solution for patients who want to tone their bodies, but do not want (and need not) muster on one’s own.

Compared to traditional aesthetic procedures such as Ultherapy or Emsculpt, this technology can be used as a stand-alone treatment or in combination with other noninvasive technologies.

Dr. Humes recommends that doctors who are considering investing in one of these devices do the following:

Speak with other doctors who have the technology and see not only how they like it, but how their patients and staff like the treatment.

Look at before and after photos from peers and other doctors, not just company studies.

Ask their peers’ questions, such as: What kind of results are you seeing? What has your patient feedback been like? How does your staff like performing the treatment?

Do research and look at the studies that are out there.

“Compare them and make the ultimate decision on your own,” Dr. Humes says. 

Disclaimer: Dr. Humes reports no conflicts of interest.
NPS study targets non-genital warts

Performed under local anesthesia, the NPS treatment was well-tolerated and associated with generally favorable cosmetic results. Impressively, clearance was also noted for many untreated, non-contiguous warts, reported Dr. Munavalli, assistant clinical professor of dermatology, Wake Forest University School of Medicine, Winston-Salem, N.C., and founder and medical director, Dermatology, Laser and Vein Specialists of the Carolinas, Charlotte, N.C.

“Patients seek treatment for non-genital warts because they can cause discomfort and, if visible, carry a social stigma. Some warts, particularly plantar warts, can be very refractory to our currently used treatment approaches,” he says.

“The results from the first human investigation of NPS treatment for non-genital warts are encouraging. Now we look forward to analyzing data from the larger study and the possibility of having another option to treat what can be a bothersome problem.”

Dr. Munavalli and Vic Ross, M.D., Scripps Clinic, San Diego, Calif., were co-investigators in the initial feasibility study. Eligible patients could have up to two warts treated and needed to have a third wart that could be left untreated as a control. They were seen for follow-up after seven, 30 and 60 days.

Reduction in wart size was often seen at the 30-day visit, and tissue recovery at sites of cleared warts was rapid and complete. The treatment was associated with immediate pinpoint bleeding and swelling and sometimes hemorrhagic blisters and crust formation.

“These local reactions were all self-limited and similar to what we see with other destructive technologies,” says Dr. Munavalli.

“However, because the treatment zone with other options, such as cryotherapy, is not very controllable, they can cause damage to surrounding skin. In contrast, the effect of NPS is very specific to the area covered by the treatment tip, and in this study, we had positive patient reports of a minimal pain recovery period.”

The NPS treatment was associated with some residual erythema that tends to fade over time, as well as a low incidence of hyperpigmentation, which may be reduced through future refinement of the treatment parameters.

“Overall, patient satisfaction has been very high, which is not surprising considering that our cohort included patients who were probably frustrated after failing other therapies,” says Dr. Munavalli.

**BIOLOGICAL BASIS FOR EFFICACY**

NPS involves the delivery of low energy, high voltage, ultra-short (nanosecond) electrical pulses to the targeted lesion that ultimately results in regulated apoptotic cell death. It is postulated that the destruction of the lesion cells is accompanied by extracellular release of human papilloma viral specific antigens that subsequently trigger an immune response.

The observed resolution of untreated warts – a phenomenon that Dr. Munavalli refers to as a bystander effect – supports the idea that the mechanism of action of NPS for clearing warts involves activation of the host immune system.

“This immunomodulatory mechanism of action has been reported in the literature and through clinical observation with other destructive technologies and may not be unique to NPS. With NPS, however, there is a clear basis for understanding how immune activation can occur,” says Dr. Munavalli.

He adds that another important feature of NPS is that it is specific to cellular targets.

“NPS does not affect the dermal connective tissue, hair follicles, or blood vessels, and that is why we generally see good cosmetic results.”

**EXPANDING THE EVIDENCE**

Three more dermatologists are joining Dr. Ross and Dr. Munavalli as investigators in the second study investigating NPS for the treatment of non-genital warts. They aim to enroll 60 subjects across their five sites. Patients will be able to receive a total of four NPS treatments with a 30-day interval between treatments.

As of October 2019, 33 patients were enrolled, and the majority of their warts had been refractory to prior treatments.

The treatments are being performed with one of five tip sizes, depending on wart size. A range of treatment settings are being evaluated with the aim of finding parameters that provide the best benefit-risk ratio.

**Disclosures**

Dr. Munavalli and Ross are investigators and members of the scientific advisory board for Pulse Biosciences.
Investigational drug for keloids

Patient treated for atopic dermatitis leads investigators to explore potential

INGRID TORJESEN | Staff Correspondent

The atopic dermatitis treatment dupilumab (Dupixent, Sanofi) could offer a therapeutic option for keloids, according to data reported in the Journal of European Academy of Dermatology and Venereology that demonstrated a patient given the drug for severe atopic dermatitis also experienced a dramatic reduction in the size of their keloids.

Atopic dermatitis is an independent risk factor for keloids, which are benign growths that appear as result of abnormal collagen proliferation due to disrupted wound healing. These growths can greatly impact quality of life and are most likely to occur in African American and Asian populations.

The patient in this particular case report was a 53-year-old African American man with severe atopic dermatitis (Body Surface Area/BSA 70%; SCORing of AD/SCORAD, 50; Eczema Area and Severity Index/EASI, 33) who also presented with two keloids: one a large prominent exophytic nodule with raised borders, the other a smaller nodule on the right pectoral fossa that had been present for more than two years. The patient had previously received more than six intralosional triamcinolone injections to treat the keloids, but these injections had little impact on the size of the keloids.

In August 2018, he began a course of dupilumab 300mg subcutaneous injections every two weeks for his atopic dermatitis, and seven months later his condition had improved significantly (BSA 8%; SCORAD, 16; EASI, 10). It was also apparent there had been significant improvement in his keloids: the amount of surrounding borders and the smaller keloid had completely disappeared.

Current treatments for keloids including intralesional steroids, bleomycin and surgical excision, are of limited benefit. Keloids that resolve frequently reoccur, and there is a need for new treatment approaches.

Lead researcher Emma Guttman-Yassky, M.D., of the department of dermatology and Laboratory of Inflammatory Skin Diseases, Icahn School of Medicine at Mount Sinai, New York, says, “We now have a few more patients without atopic dermatitis that responded to dupilumab as well, so I believe it is going to work on all keloid patients regardless of atopic dermatitis.”

The New York researchers also used real-time PCR to evaluate Th2 gene expression (IL-4R, IL-13, CCL18) in lesional and non-lesional keloid skin taken from three female African American patients with severe chronic keloids but no atopic dermatitis and compared the results with those from skin samples taken from five African American patients with healthy skin. They found that IL-4R, directly targeted by dupilumab, was highly up-regulated in keloid lesions versus controls, IL-13 was significantly increased in lesional and non-lesional keloid skin taken from three female African American patients with healthy skin.

Genes involved in cartilage/bone development and highly expressed in keloids, such as cadherin 11 and fibrillin 2, were all significantly increased in keloid lesions compared with non-lesional skin and controls.

The researchers point out that their case report “is the first report of keloid improvement with dupilumab that blocks type 2-driven inflammation via IL-4/IL-13 signaling.”

“This study has the potential to revolutionize the way we are thinking of the pathogenesis of keloids, which were primarily thought of as abnormal wound healing response and not as having an immune-based etiology,” Dr. Guttman-Yassky says.
Body toning technologies FROM PAGE 40

At his practice, Cooltone is an adjunct to other body contouring techniques like noninvasive fat reduction, such as Coolsculpting (Allergan); biostimulatory fillers, like Sculptra (Galderma) and Radiesse (Merz); and subcision, or Cellfina (Merz).

“Cooitone is FDA-cleared for buttocks, thighs and abdomen. It is at a lower price point than Emsculpt, which is important given any muscle stimulation device is going to require maintenance. It also delivers 50% more magnetic intensity than Emsculpt at both of their maximal operating strengths, which is typically how they are applied,” says Dr. Belkin. “It has not yet been established, however, whether this makes a difference in outcome.”

Coollone has fewer cleared treatment areas than the other devices, and, as with the entire class of these devices, an optimal protocol for maintenance has not been established, he says.

“All muscle stimulation device will need some sort of maintenance protocol that is yet to be well defined. It seems effects from this technology last at least a month, but patients may require a treatment every few months for them to persist,” according to Dr. Belkin.

Dr. Belkin practices at the Laser & Skin Surgery Center of New York, which was one of the research facilities that tested Cooltone.

Dr. Green reports no conflicts of interest.

LEARN TO CONNECT!

New York City cosmetic dermatologist Michele Green, M.D., says having a muscle stimulating device can boost a practice’s bottom line but that’s not a given.

“The HIFEM magnetic field technology (electromagnetic energy) is similar to that of an MRI machine,” she says. “Having Emsculpt as a part of your treatment offerings can boost a practice’s revenue, as patient’s need approximately four treatments two to three days apart. The cost per treatment ranges from $750 to $1000 per treatment area. In addition, treatment can be done by a trained technician under the supervision of the physician.”

Cooitone, uses magnetic muscle stimulation to penetrate deep into the muscle layers, but Cooltone is only FDA approved for the abdomen, thigh and buttck area, according to Dr. Green.

“Emsculpt is the gold standard body sculpting device. It is FDA approved to treat the calves, biceps, triceps, abdomen and buttck areas with good results,” she says. “One thing for practices to think about before taking the body toning device plunge is that the overall body sculpting market is saturated. Medspas offer services in this category at prices that can make it hard for physicians to compete, according to Dr. Green.

And these machines are expensive to maintain. While Dr. Green says the Emsculpt does not use consumables, practices pay $10,000 to change the applicator pads after 300 to 450 treatments.

“The deciding factor is the open-ended question of ongoing maintenance treatments and how many treatments are needed after the initial treatment on an ongoing basis. Also, there are no studies that have been published analyzing the long-term efficacy of the treatments,” she says.

Disclaimer:

Dr. Green reports no conflicts of interest.

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</tr>
</tbody>
</table>

**AD INDEX**

<table>
<thead>
<tr>
<th>ADVERTISER</th>
<th>PRODUCT</th>
<th>WEBSITE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AACS</td>
<td></td>
<td>cosmeticsurgery.org</td>
<td>44</td>
</tr>
<tr>
<td>Almirall</td>
<td>Seysara</td>
<td>seysara.com</td>
<td>16–18</td>
</tr>
<tr>
<td>Amgen</td>
<td>Otezla</td>
<td>otezlopro.com</td>
<td>35–38</td>
</tr>
<tr>
<td>ASLMS</td>
<td></td>
<td>aslms.org</td>
<td>43</td>
</tr>
<tr>
<td>Foamix Pharmaceuticals</td>
<td>Amzeeq</td>
<td>foamix.com</td>
<td>29</td>
</tr>
<tr>
<td>Galderma</td>
<td>Aklief</td>
<td>aklief.com/NCP</td>
<td>CV3–CV4</td>
</tr>
<tr>
<td>Janssen Biotech Inc.</td>
<td>Tremyfa</td>
<td>tremyfa.com</td>
<td>insert 14–15</td>
</tr>
<tr>
<td>NewSurge</td>
<td></td>
<td>newsurg.com</td>
<td>7</td>
</tr>
<tr>
<td>Ortho Dermatologies LLC</td>
<td>Duobrii</td>
<td>duobrii.com</td>
<td>CV2–3</td>
</tr>
<tr>
<td>PER</td>
<td></td>
<td>gotoper.com/go/AAD20SD</td>
<td>outer1</td>
</tr>
<tr>
<td>Rohrer Aesthetics</td>
<td></td>
<td>rohreraesthetics.com</td>
<td>24</td>
</tr>
<tr>
<td>Sun Odomzo</td>
<td></td>
<td>cover wrap &amp; 11–13</td>
<td></td>
</tr>
</tbody>
</table>

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IMPORTANT INFORMATION ABOUT

AKLIEF®
(trifarotene) Cream, 0.005%

BRIEF SUMMARY
This summary contains important information about AKLIEF Cream. It is not meant to take the place of your doctor’s instructions. Read this information carefully before you start using AKLIEF Cream. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about AKLIEF Cream. For full Prescribing Information and Patient Information, please see the package insert.

WHAT IS AKLIEF CREAM?
AKLIEF Cream is a prescription medicine used on the skin (topical) to treat acne vulgaris. Acne vulgaris is a condition in which the skin has blackheads, whiteheads, and pimples.

WHO IS AKLIEF CREAM FOR?
AKLIEF Cream is for use in people 9 years of age and older. It is not known if AKLIEF Cream is safe and effective in children younger than 9 years old.

Do not use AKLIEF Cream for a condition for which it was not prescribed. Do not give AKLIEF Cream to other people, even if they have the same symptoms you have. It may harm them.

WHAT SHOULD I TELL MY DOCTOR BEFORE USING AKLIEF CREAM?
Before you use AKLIEF Cream, tell your doctor if you:

- have skin problems, including eczema, cuts or sunburn.
- are pregnant or planning to become pregnant. It is not known if AKLIEF Cream will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if AKLIEF Cream passes into your breast milk.
- should use AKLIEF Cream on the smallest area of skin and for the shortest time needed while breastfeeding.
- Do not apply AKLIEF Cream to the nipple and areola to avoid contact with your baby.
- Talk to your doctor about the best way to feed your baby if you use AKLIEF Cream.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you use any other medicine for acne.

WHAT SHOULD I AVOID WHILE USING AKLIEF CREAM?

- Minimize exposure to sunlight. You should avoid using sunlamps, tanning beds, and ultraviolet light during treatment with AKLIEF Cream. If you have to be in sunlight or are sensitive to sunlight, use a sunscreen with SPF (sun protection factor) of 15 or more, and wear protective clothing and a wide-brimmed hat to cover the treated areas.
- You should avoid using AKLIEF Cream on skin areas with cuts, abrasions, eczema, or on sunburned skin.
- You should avoid using skin products that may dry or irritate your skin such as medicated or abrasive soaps and cleansers, cosmetics that have strong skin drying effects and products containing high levels of alcohol.
- You should avoid using “waxing” as a hair removal method on skin treated with AKLIEF Cream.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF AKLIEF CREAM?
The most common side effects of AKLIEF Cream include:

- Application site (skin) irritation, itching and sunburn.

AKLIEF Cream may cause serious side effects including:

- Local skin irritation. Local skin reactions are common with AKLIEF Cream. They are most likely to happen during the first four (4) weeks of treatment and may decrease with continued use of AKLIEF Cream. Signs and symptoms of local skin reaction include:
  - Redness
  - Dryness
  - Scaling
  - Stinging or burning

To help reduce your risk of developing these local skin reactions, when you begin treatment with AKLIEF Cream, you should begin applying a moisturizer on your skin as often as needed.

Tell your doctor if you develop symptoms of a local skin reaction. Your doctor may tell you to use AKLIEF Cream less often, or temporarily, or permanently stop your treatment with AKLIEF Cream. These are not all of the possible side effects of AKLIEF Cream. For more information, ask your doctor or pharmacist.

You are encouraged to report negative side effects of prescription drugs to the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088. You may also contact GALDERMA LABORATORIES, L.P. at 1-866-735-4137.

HOW SHOULD I USE AKLIEF CREAM?

- Use AKLIEF Cream exactly as your doctor tells you to use it. Apply a thin layer of AKLIEF Cream over the affected areas one (1) time each day, in the evening.

HOW SHOULD I STORE AKLIEF CREAM?

- Store AKLIEF Cream at room temperature, 68° to 77° F (20° to 25° C).

- Keep AKLIEF Cream away from heat.

- If you received a sample tube of AKLIEF Cream from your doctor, keep the tube tightly closed.

- Keep AKLIEF Cream and all medicines out of the reach of children.

WHAT ARE THE INGREDIENTS OF AKLIEF CREAM?
Active ingredient: trifarotene
Inactive ingredients: allantoin, copolymer of acrylamide and sodium acryloyldimethyltaurate, dispersion 40% in isohexadecane, cycloheximide, 5% ethanol, medium-chain triglycerides, phenoxethanol, propylene glycol, purified water.

WHERE SHOULD I GO FOR MORE INFORMATION ABOUT AKLIEF CREAM?

- Talk to your doctor or pharmacist.
- Visit www.AKLIEF.com or call 1-866-735-4137.

References:

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Galderma Laboratories, L.P., Fort Worth, Texas 76177 USA

Revised: 9/19
ACNE DOESN’T HAVE TO RUIN THEIR MOMENTS.

The first new retinoid molecule for the treatment of acne in 20+ years.¹

The power of precision

Specifically targets RAR-γ, the most common retinoic acid receptor in the skin.²,³

Powerful efficacy* & well-tolerated

In PIVotal Study 1,† >50% fewer inflammatory lesions on face and trunk at Week 12.‡ Favorable tolerability on both the face and trunk areas, across 4 different parameters.²

Most common adverse reactions (incidence ≥ 1%) in patients treated with AKLIEF Cream were application site irritation, application site pruritus (itching), and sunburn.⁴

IMPORTANT SAFETY INFORMATION

Indication: AKLIEF® (trifarotene) Cream, 0.005% is a retinoid indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

Adverse Events: The most common adverse reactions (incidence ≥ 1%) in patients treated with AKLIEF Cream were application site irritation, application site pruritus (itching), and sunburn.

Warnings/Precautions: Patients using AKLIEF Cream may experience erythema, scaling, dryness, and stinging/burning. Use a moisturizer from the initiation of treatment, and, if appropriate, depending upon the severity of these adverse reactions, reduce the frequency of application of AKLIEF Cream, suspend or discontinue use. Avoid application of AKLIEF Cream to cuts, abrasions or eczematous or sunburned skin. Use of “waxing” as a depilatory method should be avoided on skin treated with AKLIEF Cream. Minimize exposure to sunlight and sunlamps. Use sunscreen and protective clothing over treated areas when exposure cannot be avoided.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

* The exact process by which trifarotene ameliorates acne is unknown.

† PIVotal Studies 1 & 2 Design — First large-scale, multicenter, randomized Phase 3 clinical trials evaluating the efficacy and safety of topical therapy vs vehicle in both facial and truncal acne over 12 weeks. Patients: Screened and randomized to once-daily trifarotene cream 50 µg/g (n=1,214) or vehicle (n=1,206). Primary endpoints: 1) absolute change in inflammatory and non-inflammatory lesion counts on the face from baseline to Week 12; 2) Investigator Global Assessment (IGA)§ success rate on the face. Secondary endpoints: 1) absolute change in inflammatory and non-inflammatory lesion counts on the trunk from baseline to Week 12; 2) Physician Global Assessment (PGA)§ success rate on the trunk. Success rate: Percentage of patients achieving IGA face rating of clear (0) or almost clear (1) and PGA trunk rating of clear (0) or almost clear (1) and at least a 2-grade change in IGA or PGA rating from baseline at a particular study visit. Safety endpoints: Incidence of adverse events and local tolerability (erythema, scaling, dryness, and stinging/burning). vs 44.6% reduction with vehicle; P=0.001 for face and vs 50% reduction with vehicle; P=0.001 for trunk.⁵

§ The definitions of severity for the 5-point IGA (face) and PGA (trunk) scales were the same: 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate) and 4 (severe).⁶

Please see brief summary of full Prescribing Information on the next page.